Professional self-determination of future doctors: priorities in conditions of the war in Ukraine

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ABSTRACT BOOK

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ORIGINAL ARTICLE

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Using a chatbot as a digital tool at the primary health care level

Hlib D. Aleksandrenko, Maryna V. Shevchenko
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ABSTRACT

Aim: To analyze the feasibility of utilizing a digital tool such as a chatbot at the primary health care level as part of a health program.

Materials and Methods: With the involvement of a general practitioner and the use of a digital tool, a chatbot, a three-month health program was conducted for employees of an IT company. The chatbot was used to collect information, monitor the health status of participants and provide personalized health recommendations. To evaluate the program's effectiveness survey was conducted to compare participants answers before and after using standardized evaluation scales. A questionnaire based on the Evaluation and Management Services Guide was created to collect medical information on the health status of participants before and after the program.

Results: After the program, the average total score of participants' health complaints and symptoms decreased (from 27.1 to 16.1, p=0.019). The average severity of the chief complaint on a scale of 0 to 10 decreased from 5.08 to 2.27, or by 55.3% (p=0.00676). The frequency of individual complaints such as eye pain, decreased concentration, increased fatigue and irritability also dropped.

Conclusions: The chatbot enabled the primary care physician to respond promptly to participants' health complaints. The results demonstrated the potential of chatbots as innovative and accessible digital tools at the primary health care level for providing recommendations, monitoring health, and contacting a primary care physician in a timely manner.

KEY WORDS: primary health care, preventive health services, digital health, mental health, health informatics

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INTRODUCTION

Primary health care (PHC) is the foundation of health systems as it provides citizens with their first point of contact for health services, offering preventive, curative, and rehabilitative care. However, PHC faces challenges that can reduce its effectiveness and accessibility [1]. The introduction of digital technologies presents new opportunities to transform and modernize PHC, improving its quality and accessibility [2].

Digital health is an interdisciplinary field that uses digital technologies and solutions to enhance healthcare quality, improve health outcomes, and promote public health [3]. Digital health interventions have the potential to improve PHC services, increase quality, coverage, and efficiency, and contribute to achieving universal health coverage (UHC) [4]. Recent publications have emphasized the increasing importance of digital tools in PHC and their potential to enhance access to services, healthcare quality, and efficiency [5]. A systematic review of digital health technologies during COVID-19 [6] found that telemedicine and mobile applications played a crucial role in maintaining PHC during the pandemic. It is also noted that the COVID-19 pandemic further accelerated the digital transformation of PHC. The consensus report of the US National Academies of Sciences, Engineering, and Medicine [7] also emphasizes the importance of developing digital tools to support the work of primary care physician (PCP). In particular, it refers to clinical decision support systems, the integration of data from different sources, and the use of analytics, artificial intelligence, and machine learning to identify risks and predict treatment outcomes.

Digital tools are being implemented in PHC to address challenges such as improving mental health, treating chronic diseases, promoting physical activity, and enhancing communication between healthcare professionals and patients [8]. It is important to note that the widespread use of mobile technologies has led to the development of various diabetes-related and health promotion applications [9].

Special attention should be given to the potential of chatbot implementation in healthcare. Precedence Research estimates the global healthcare chatbot market to be worth $196.9 million as of 2022, with projected size of $944.7 million in 2032 (17% annual growth). According to Grand View Research, the healthcare system

is one of the top three verticals for the use of chatbots, following online trading and the financial sector [10].

At the PHC level, chatbots have shown promise for improving service delivery through personalized service, improving diagnosis and prevention of chronic diseases, collecting patient feedback, and managing health during global pandemics. Some chatbots have also proven effective in providing information and engaging in conversations. Users can ask a chatbot for additional information about symptoms, conditions, complications, or methods of treatment and self-help methods. This allows for and leads to wider access to important and verified information [11].

Therefore, it is imperative to identify the most effective methods for integrating digital tools into PHC, such as utilizing chatbots to gather and analyze data, customize communication, and promptly address patient inquiries and concerns.

AIM

To analyze the feasibility of using a digital tool as a chatbot at the primary health care level as part of a health program.

MATERIALS AND METHODS

This study describes the development and implementation of a health program for employees of a Ukrainian IT company.

The study participants were 16 IT specialists from one company with offices in three cities in Ukraine: Kyiv, Zhytomyr, and Chernihiv.

The study was conducted from October 2020 to March 2021.

The program utilized a chatbot as a digital tool to collect, exchange, and interpret health information of participants. Additionally, it provided continuous feedback to the general practitioner (GP) involved in the program. The chatbot was developed using a low-code platform, enabling the programming and transfer of patient care processes through a graphical interface. The chatbot algorithm collected real-time information on the health status of program participants, monitoring their complaints, requests, and questions, which were addressed by the GP.

The health program was created using the author's model [12]. The development process followed the principles of information security and data confidentiality. Additionally, the platform used to create the digital tool complied with the General Data Protection Regulation (GDPR).

To collect medical information about the participants' health status before and after the program implementation, a questionnaire was created based on the Evaluation and management services guide developed by the U.S. Centers for Medicare & Medicaid Services [13]. These guidelines provide a framework for documenting various aspects of patient care. This questionnaire contains 4 main components:

1. Chief complaint: main symptoms, problem, condition, or diagnosis that the participant is concerned about. The severity of the main complaint is rated by the participant from 0 (There is no CC) and 1 (minimum) to 10 (maximum).
2. History of Present Illness: details and chronological description of the development of the existing problem or disease from the first signs and/or symptoms.
3. Review of Systems: an inventory of body systems obtained through a series of questions seeking to identify signs and/or symptoms (health complains) which the patient may be experiencing or has experienced. These types of review have been defined for general multi-system and the following single organ systems: constitutional symptoms (eg, fever, weight loss); eyes; ears, nose, mouth, and throat (ENT); cardiovascular; respiratory; gastrointestinal; genitourinary; musculoskeletal; integumentary (skin and/or breast); neurological; psychiatric; endocrine; hematologic/lymphatic/immunologic (HLI).
4. Past, Family, and/or Social History: experience of diseases, surgeries, injuries, previous treatment regimens; family history (review of medical events, diseases or hereditary conditions), social history (information about professional activities, living conditions, work environment, etc.).

The results of the survey were mainly used to obtain information about the presence of diseases and to assess the health complaints of each participant for further consultation with PCP. The main components of the questionnaire for analysis were the chief complaint and the review of systems. These were used for comparative analysis before and after.

The chatbot collected and analyzed information in real-time regarding complaints and needs from program participants. It provided personalized health recommendations and tracked the health status of program participants. Daily questions and requests were transmitted to the PCP in an anonymous form, with the possibility of further individual consultation. To maintain anonymity throughout the collection and processing of information, each participant was assigned a unique identifier (UID).

The data was analyzed using descriptive statistics, as appropriate for this study's purpose. The statistical significance level was determined using the Wilcoxon test, with a critical level of significance of 0.05 or less. Data

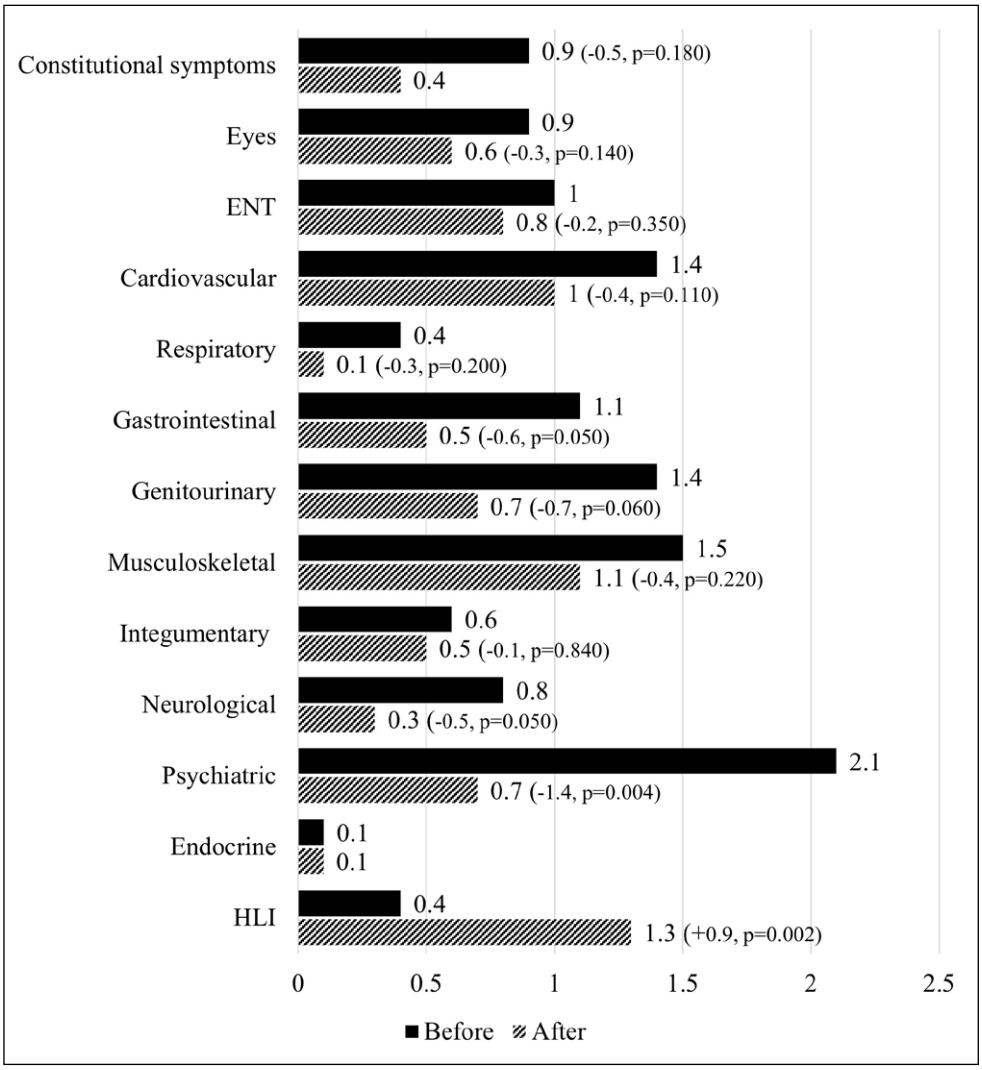

Fig. 1. Comparison of the average number of health complaints in review of systems (n=16).

analysis was performed using the Statistical Package for the Social Sciences (SPSS).

The study was conducted in compliance with ethical principles. Participation in the program was voluntary and based on the potential participants' own motivation. The corporate program developers and participants signed agreements on non-disclosure and confidentiality of information. Information was collected, processed, and visualized anonymously using UIDs to identify information about a particular participant.

RESULTS

After implementation of the health program, there was a significant average decrease in the total score of the chief complaint and health complaints in review of systems among the participants. At the beginning of the project, the average total score was 27.1 points, while at the end, it was 16.1 points, indicating a decrease of -10.9 points (p=0.019).

The average score of chief complaint decreased significantly from 5.08 to 2.27 (p=0.00676), representing a reduction of 55.3%. Furthermore, the number of participants who reported the chief complaints decreased from 12 (75%) to 8 (50%), with a general reduction of 33.3%. The most common chief complaints at the beginning of the program were headaches, weakness, and dizziness (reported by 6 participants), pain in various parts of the back (reported by 4 participants), and symptoms of depression, anxiety, and fatigue (reported by 3 participants). At the end of the program, the types of health complaints shifted. Four participants reported experiencing headaches, three participants reported back and lumbar pain, one participant reported issues with the ENT, and one participant reported fatigue.

The total number of health complaints in review of systems among participants decreased by 57.0% (from 198 to 113, p=0.00776). The average number of complaints in review of systems per individual body system also decreased (Fig. 1). The psychiatric system experienced the largest decrease in the number of health complaints, from an average of 2.1 to 0.7 complaints per person (p=0.004). There was a decrease in the number of health complaints related to diseases or problems with

the genitourinary (from 1.4 to 0.7, p=0.060), gastrointestinal (from 1.1 to 0.5, p=0.05), and neurological (from 0.8 to 0.3, p=0.0505) systems. Simultaneously, there was a decrease in the number of constitutional symptoms (from 0.9 to 0.4, p=0.180), diseases or problems with the cardiovascular system (from 1.4 to 1.0, p=0.110), respiratory system (from 0.4 to 0.1, p=0.200), and eyes (from 0.9 to 0.6, p=0.140), although these decreases were not statistically significant. Additionally, the number of complaints related to the ENT, musculoskeletal, integumentary, and endocrine systems was not statistically significant (p>0.050). However, there was a significant increase in the number of health complaints related to the HLI (from 0.4 to 1.3 complaints, p=0.002).

After implementing the program, the frequency of complaints from participants in many areas decreased. Specifically, there has been a decrease in the number of complaints regarding fatigue (from 8 to 3), eye pain (from 4 to 0), eye redness (from 3 to 0), shortness of breath during nervous exertion (from 2 to 0), moist cough (from 2 to 0), sputum production (from 2 to 0), nausea (from 4 to 2), abdominal pain (from 5 to 2), menstrual irregularities (from 6 to 0), and limb numbness (from 3 to 0). There was a significant decrease in the frequency of complaints related to psycho-emotional symptoms. For example, the number of reported frequent headaches decreased from 6 to 3, unreasonable anxiety - from 4 to 1, decreased concentration - from 5 to 1, problems falling asleep - from 5 to 3, increased irritability - from 6 to 1, and mood swings - from 5 to 3.

DISCUSSION

This study analyzed the feasibility of using a chatbot as a digital tool in PHC to track health complaints or deterioration among participants. The results showed that the GP could track information about health complaints of participants and respond promptly to their needs through online or offline counseling. The results suggest that a chatbot can serve as an efficient digital tool to enhance access to PHC. The combination of a chatbot with the traditional model of PHC provision resulted in a positive impact, as evidenced by the decrease in the number of complaints among program participants.

The study's findings align with the overall trend of increasing reliance on digital tools in PHC. Specifically, the study confirms the efficacy of digital solutions in mental health [1], chronic disease monitoring [8], medical staff-patient communication improvement [9], and timely healthcare service access [11]. Also, the results of this study are consistent with the findings of other researchers, on the potential of using chatbots for screening and remote monitoring of patients. It was demonstrated the effectiveness of a chatbot for COVID-19 screening of healthcare workers, reducing wait times, enabling physical distancing, and providing real-time data for staffing decisions [14]. Similarly, another study developed a preventive care chatbot that offers information, advice, and monitoring to patients undergoing home treatment for COVID-19 and dementia, showcasing the potential of chatbots for personalized care [15].

At the same time, data on the use of chatbots in PHC indicate their potential for managing chronic diseases, supporting diagnostic processes [3], and preventing non-communicable diseases. However, the issue of ensuring the ethical and safe implementation of such technologies, in particular with the use of large language models, remains relevant [6].

The study had limitations, including a small sample size and limited observation period, which prevent further extrapolation of results. To draw more solid conclusions, expanding the study in terms of participants and duration is advisable.

Nevertheless, the preliminary findings indicate that further exploration of the role of chatbots and other digital tools in PHC is necessary. It is important to note the lessons learned, particularly the need to develop the digital literacy of health professionals to effectively use digital tools such as chatbots in clinical practice. Integrating digital health into education and training programs is crucial for developing a digitally literate health workforce [16]. The introduction of digital tools should be accompanied by training for both healthcare providers and users to enhance their digital skills. It is important to address the global issue of the digital divide, which refers to the gap in access to and ability to use digital tools, in order to prevent inequalities in access to digital health. Efforts to implement digital tools at the PHC level should include initiatives to bridge the divide between those who have access to technology and those who do not [17].

In addition, in order to realize the potential of digital tools to improve PHC services delivery and outcomes globally, the development of digital health policies is critical [18].

CONCLUSIONS

The utilization of a digital tool such as a chatbot for health programs involving a general practitioner indicates that the physician can respond promptly to participants' health complaints. For instance, after analyzing the frequency of health complaints related to a particular body system among program participants, the general practitioner involved in the program provided online counseling and recommendations for prevention and treatment.

The study results show that chatbots have potential as innovative and accessible digital tools for primary health care. They can provide individualized health recommendations, monitor, and control health, allow patients to contact a doctor, and provide timely assistance. However, it is important to ensure appropriate levels of cybersecurity and personal data protection when implementing these digital tools - they must be regulated and comply with national or internationally adopted standards.

Future research could focus on digital divide, developing and implementing specialized digital tools tailored to specific user groups, taking into account their psychological, physical, professional, and other characteristics. Combining chatbots with other digital tools may be effective and warrants further investigation. Furthermore, the implementation of chatbot algorithms that utilize artificial intelligence methods shows promise. However, it is important to consider ethical, privacy, regulatory, and other issues when implementing them.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Comparison of the clinical effectiveness of hepaticojejunostomy and self-expanding metal stents for bypassing the bile ducts in patients with unresectable pancreatic head cancer complicated by obstructive jaundice

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ABSTRACT

Aim: To improve treatment outcomes of patients with unresectable pancreatic head cancer complicated by obstructive jaundice by improving the tactics and techniques of surgical interventions.

Materials and Methods: Depending on the treatment tactics, patients were randomised to the main group (53 people) or the comparison group (54 people). The results of correction of obstructive jaundice by Roux-en-Y end to side hepaticojejunostomy (main group) and common bile duct prosthetics with self-expanding metal stents (comparison group) were compared.

Results: The use of self-expanding metal stents for internal drainage of the biliary system compared to hepaticojejunostomy operations reduced the incidence of postoperative complications by 29.9% ($\chi2=13.7$, 95% CI 14.38-44.08, $p=0.0002$) and mortality by 7.5% ($\chi2=4.16$, 95% CI -0.05-17.79, $p=0.04$). Within 8-10 months after biliary stenting, 11.1% (6/54) of patients developed recurrent jaundice and cholangitis, and another 7.4% (4/54) of patients developed duodenal stenosis with a tumour. These complications led to repeated hospitalisation and biliary restentation in 4 (7.4%) cases, and duodenal stenting by self-expanding metal stents in 4 (7.4%) patients.

Conclusions: The choice of biliodigestive shunting method should be selected depending on the expected survival time of patients. If the prognosis of survival is up to 8 months, it is advisable to perform prosthetics of the common bile duct with self-expanding metal stents, if more than 8 months, it is advisable to perform hepaticojejunal anastomosis with prophylactic gastrojejunal anastomosis.

KEY WORDS: pancreatic head cancer, obstructive jaundice, cancerous pancreatitis

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INTRODUCTION

Due to late diagnosis, up to 80% of patients with pancreatic head cancer (PHC) undergo only palliative surgical treatment aimed at eliminating complications such as obstructive jaundice and impaired gastric evacuation [1, 2]. Correction of biliary obstruction is performed by biliodigestive bypass or transpapillary stenting of the common bile duct with self-expanding metal stents (SEMS). The use of SEMS is characterised by a lower number of postoperative complications, lower mortality and shorter hospital stay [3]. However, due to the high efficiency of modern polychemotherapy regimens, the life expectancy of patients after palliative interventions has increased from 9 to 12-16 months. During this period, biliodigestive shunts retain their drainage function, and SEMS can be bypassed by the tumour, bile acid salts, and bacterial biofilms. As a result, recurrent jaundice and cholangitis develop, requiring repeated hospitalisations and reconstructive interventions [4, 5].

AIM

To improve the outcome of treatment of patients with unresectable pancreatic head cancer complicated by obstructive jaundice by improving the tactics and techniques of surgical treatment.

MATERIALS AND METHODS

The randomised prospective study included 107 patients with locally advanced and unresectable pancreatic head cancer without signs of duodenal obstruction treated at the clinics of the Department of Surgery #2 of the Bogomolets National Medical University in

2016-2022. Exclusion criteria were: verified duodenal obstruction, liver gate cancer, carcinomatosis. Pancreatic head cancer was verified in accordance with the recommendations of the European Society for Medical Oncology (ESMO, 2019, 2022), the National Comprehensive Cancer Network (NCCN, 2015-2022) and the classification of the American Joint Committee on Cancer (AJCC, editions VI, VII, VIII, 2002-2017). Based on these documents, the patients were diagnosed with stage III-IV pancreatic head cancer. In all patients, the cancer was histologically identified as ductal adenocarcinoma (WHO, 2000). The resectability of pancreatic head tumours was determined based on comparisons of clinical, laboratory and radiological examination data, according to the NCCN (2019-2022) and ESMO (2019, 2022) guidelines.

Depending on the treatment tactics, patients were randomised to the main group (53 people) or the comparison group (54 people). At the time of hospitalisation, patients in both groups did not differ significantly in age and gender characteristics, hyperbilirubinemia, indications for surgical treatment, comorbidities, and histological characteristics of tumors ($p>0.05$) (Table 1).

It is important to note that patients in both groups were elderly or senile and all had comorbidities (from one to three diseases).

Patients in the main group underwent correction of obstructive jaundice by biliodigestive bypass using the Roux-en-Y end to side hepaticojejunostomy technique with a 50 cm Roux limb. A prophylactic side-to-side gastrojejunostomy was performed in all patients. Patients in the comparison group underwent transpapillary stenting of the common bile duct with SEMS after endoscopic retrograde cholangiopancreatography. The decision to perform endoscopic stenting vs. surgery was based on the suggestion of our interdisciplinary discussion with due regard to the patient's general health status, and the cancer staging. In addition, all options of palliative treatment were extensively discussed with the patient. Boston Scientific WallSTENT Biliary Uncovered 10mm-60mm stents were used. In cases of duodenal stenosis, HANAROSTENT Duodenum/Pylorus NDSL20-140-230 stents were used. Histological diagnoses were confirmed intraoperatively.

After surgical treatment in the study groups, the incidence of postoperative complications, mortality and survival were analysed. Postoperative mortality and morbidity were recorded according to the "Accordion Severity Grading System of Surgical Complications" by Steven M. Strasberg, 2009, which is a variant of the Clavien-Dindo scale (1992, 2004, 2018) [6, 7]. Additionally, the duration of stent functioning without recurrence of mechanical jaundice and/or cholangitis and the frequency and timing of duodenal stenosis were analysed in patients of the comparison group.

STATISTICS

The normality of data distribution was determined by the Shapiro-Wilk test. The difference between the groups was determined using Student's t test for independent samples in the case of parametric and Kruskal-Wallis test in the case of nonparametric data distribution. Differences in sample distribution were assessed using the $\chi 2$ test criterion. Differences between indicators were considered significant at $p<0.05$. Statistical analysis was performed using Statistica 10 (Serial Number: STA999K347150-W) and MEDCALC® (open access Internet resource, https://www.medcalc.org/calc/). Median survival time (together with 95% CI) was calculated via the Kaplan-Meier method and the data were analyzed by means of the log-rank test.

RESULTS

In a comparative analysis of the results of surgical treatment of patients, the specific weight of postoperative complications in patients of the main group was 37.3% versus 7.4% in the comparison group ($\chi 2=13.7$, 95% CI 14.38-44.08, $p=0.0002$) (Table 2).

Among the patients in the main group, complications developed in 20 (37.7%) patients, in 14 (26.4%) patients they were classified as Grade I-III (Minor complications: postoperative wound suppuration, gastrostasis, urinary retention), in 6 (11.3%) patients - as Grade IV-VI (Major complications: hepaticojejunoanastomosis suture failure, acute liver failure, myocardial infarction, pulmonary thrombosis). In the comparison group, complications (cholangitis) were observed in 4 (7.4%) patients and were classified as Grade II and required only pharmacological treatment. The mortality rate among patients in the intervention group was 7.5% (4/53), and there were no deaths in the comparison group ($\chi 2=4.16$, 95% CI -0.05-17.79, $p=0.04$). It is important to note that complications in the comparison group were mild and were effectively managed with pharmaceuticals. All re-hospitalisations within 90 days after surgery occurred among patients in the main group (6 patients, 11.3%) ($\chi 2=6.4$, 95% CI 2.33-22.55, $p=0.01$). Of these patients, 2 (3.8%) were readmitted for percutaneous abdominal drainage, 2 (3.8%) for intravenous antibiotic therapy for cholangitis, and 2 (3.8%) for nonspecific hypogastric pain due to urinary tract infection.

Out of 4 (7.5%) in-hospital deaths (30 days after surgery), all deaths occurred among patients in the main group and were due to the development of the

Table 1. Demographic characteristics and serum bilirubin content at the time of hospitalization in the studied groups

Indexes	Main group (n=53)	Comparison group (n=54)	p
Median age (years)	67.3±5.4	68.1±4.9	0.42
Sex			
men	34 (64%)	32 (59.2%)	0.61
women	19 (36%)	22 (40.8%)	0.61
Bilirubin content in blood serum, μmol/l	204.4±49.3	216±38.1	0.17
Indication for palliative surgery			
Tumor locally advanced	53 (100%)	54 (100%)	–
Liver metastasis	12 (22.6%)	15 (27.8%)	0.53
Peritoneal metastasis	2 (3.8%)	3 (5.6%)	0.66
Histological diagnosis	Pancreatic adenocarcinoma 53 (100%)	Pancreatic adenocarcinoma 54 (100%)	–
Comorbidities			
Hypertension	53 (100%)	53 (98.1%)	0.31
Diabetes mellitus	19 (35.8%)	16 (30.2%)	0.53
COPD	2 (3.8%)	2 (3.7%)	0.97
CVA	3 (5.6%)	2 (3.7%)	0.64
IHD	27 (50.9%)	29 (53.7%)	0.77

Abbreviations: COPD – chronic obstructive pulmonary disease; CVA – cerebrovascular accident; IHD – ischemic heart disease.

Table 2. Post-operative complications and outcomes

Indexes	Main group (n=53)	Comparison group (n=54)	p
Surgical complications (Accordion Severity Grading System scale, ASGS)			
Total number of complications	20 (37.3%)	4 (7.4%)	0.0002
Grade I	8 (15.1%)	–	0.002
Grade II	4 (7.5%)	4 (7.4%)	0.98
Grade III	2 (3.8%)	–	0.15
Grade IV	2 (3.8%)	–	0.15
Grade V	–	–	–
Grade VI	4 (7.5%)	–	0.04
Management of complications			
Surgical revision of hepaticojejunostomy	2 (3.8%)	–	0.15
Radiological procedures	4 (7.5%)	–	0.04
Intravenous antibiotics	4 (7.5%)	4 (7.4%)	0.98
Hospital stay (days)	14 ±2,1	3 ±0,8	<0.0001
Hospital readmission with 90 days	6 (11.3%)	–	0.01
In hospital-mortality	4 (7,5%)	–	0.04

following complications: acute liver failure, myocardial infarction, thromboembolism of the pulmonary artery, abdominal sepsis.

After surgical correction of obstructive jaundice, according to the recommendations of the chemotherapist, 51.7% (28/49) of patients in the main and 66.7% (36/54) of patients in the comparison group received adjuvant chemotherapy. The time to start chemotherapy was not different (42±9.8 days vs. 39±6.7 days) in the study groups (p=0.06). Overall, the survival rate of patients in the main group was 8.5±1.7 (range 6-11) months versus 7.9±1.9 (range 5-10) months for patients in the experimental group, with no significant difference in survival between the two groups (p=0.08). However, among the 21 patients in the experimental group and 18 patients in the comparison group who did not receive chemotherapy, the survival rate was 7.5±0.6 and 6.8±0.7 months, respectively. After surgical correction of jaundice, chemotherapy treatment of 28 out of 49 patients in the main group and 36 out of 54

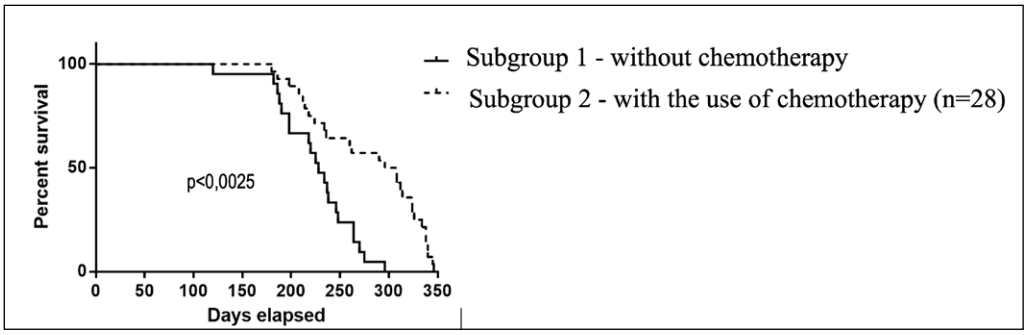

Fig. 1. Survival of patients in the main group depending on chemotherapy.

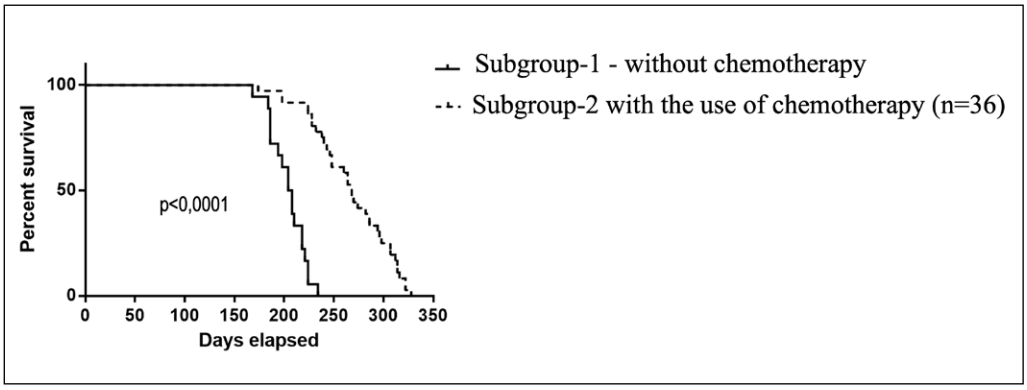

Fig. 2. Survival of patients in the comparison group depending on chemotherapy.

patients in the comparison group ensured survival in the main group and the comparison group of 9.3±0.98 and 8.9±0.81 months, respectively. Thus, chemotherapy treatment contributed to an increase in survival by 24.0% (p=0.007) of patients in the main group and by 30.8% (p=0.01) of patients in the comparison group. All patients in both groups were under medical supervision until death. The survival rates of patients in the two groups, depending on the method of correction of obstructive jaundice and chemotherapy, are shown in Figures 1 and 2.

When analysing the results of treatment of patients in both groups in the period from 4 to 11 months after surgical correction of jaundice, it was found that during this period biliodigestive and gastrojejunal shunts in patients of the main group functioned without complications. However, in 6 (11.1%) patients who underwent SEMS biliary prosthesis, recurrent jaundice and cholangitis developed in the period from 8 to 10 months after stenting. In these cases, 4 patients underwent biliary system replacement, and in 2 cases, jaundice and cholangitis were eliminated by endoscopic stent rehabilitation and antibiotic therapy, taking into account the sensitivity of the bile microflora to antibiotics. In another 4 (7.4%) patients in the comparison group, the course of the disease was complicated by nausea, vomiting, a feeling of heaviness in the epigastrium, and progression of cachexia. According to the results of fluoroscopy and fibrogastroduodenoscopy, patients were diagnosed with duodenal stenosis due to a tumour of the pancreatic head. This complication was eliminated by duodenal stenting with duodenal SEMS. No complications were observed after the procedure, and the evacuation of gastric contents was restored.

DISCUSSION

Meta-analyses of other studies show that surgical bypass is associated with a higher rate of postoperative complications and mortality, but some authors report that in the long-term postoperative period, the incidence of jaundice recurrence in patients after surgical bypass is lower [8, 9]. At the same time, the issues of postoperative outcomes in the correction of jaundice with the use of modern SEMS models and the latest chemotherapy protocols remain unclear. Our study demonstrates that the use of SEMS is associated with a 29.9% reduction in the incidence of early postoperative complications ($\chi2$=13.7, 95% CI 14.38-44.08, p=0.0002) and a 7.5% reduction in mortality ($\chi2$=4.16, 95% CI -0.05-17.79, p=0.04) compared to surgical bypass. At the same time, Ying-bin Liu (2020), Beger H.G., Büchler M.W. (2023) report that SEMS effectively drain the biliary system for 6 months, and later, due to obstruction of the stent by a tumour, salts, bacterial films, recurrent jaundice and cholangitis may develop [2]. Therefore,

it becomes clear that patients whose life expectancy after jaundice correction exceeds 8 months should be given preference for biliary bypass surgery. In 2020, Fabian et al. published a meta-analysis comparing palliative double stenting for malignant duodenal and biliary obstruction with surgical double bypass [10, 11]. The clinical success of endoscopic biliary stenting was higher than that of surgical bypass, and double stenting was associated with fewer complications but more frequent need for reintervention than surgical bypass. The recurrence rate of jaundice in surgical patients was consistently lower than in stented patients [12].

Our study demonstrated that, taking into account medical indications and contraindications (comorbidities, multiorgan dysfunction/insufficiency), adjuvant chemotherapy could be performed in 57.1% of patients in the main group and 66.7% of patients in the comparison group. As a result, the survival rate of patients in the main and comparison groups increased by 24.0% and 30.8%, respectively. At the same time, no recurrence of jaundice and cholangitis was observed among the patients in the main group and there were no signs of impaired gastric evacuation. At the same time, in the SEMS group, in the period from 8 to 10 months after stenting, 6 (11.1%) patients developed recurrent jaundice and cholangitis, and another 4 (7.4%) patients developed duodenal stenosis by a tumour. These complications of the late postoperative period led to re-hospitalisation of 10 (18.5%) patients, intensive care and biliary system replacement in 4 (7.4%) patients and duodenal stenting with duodenal SEMS in 4 (7.4%) patients. No complications were observed after these procedures. The results obtained are in line with the results of the meta-analysis of five randomised controlled trials by Scheufele F. and Friess H. (2018), which showed that surgical bypass is associated with a reduction in recurrence of jaundice compared to biliary stent placement [13].

The results of the study show that the two analysed treatment strategies are successful. Surgical bypass, compared to SEMS placement, ensures no recurrence of jaundice and no development of duodenal obstruction in the long-term postoperative period. The use of SEMS demonstrates better results in the early postoperative period, but more than 8 months after stent placement, 18.5% of patients develop complications: recurrent jaundice with cholangitis or duodenal obstruction. An important factor in the choice of surgical treatment technology is the selection of an effective palliative polychemotherapy regimen. Currently, there is a debate in the literature about the individual choice of chemotherapy protocols, as there is no biomarker that can predict its effectiveness. However, the experience of the study shows that if the cancer tumour is sensitive to the drugs of the chosen polychemotherapy regimen, survival can increase up to 12 months, and then the value of surgical bypass, given its better long-term results, becomes relevant.

CONCLUSIONS

The use of self-expanding metal stents for internal drainage of the biliary system compared to hepaticojejunostomy operations reduced the incidence of postoperative complications by 29.9% ($\chi2=13.7$, 95% CI 14.38-44.08, p=0.0002) and mortality by 7.5% ($\chi2=4.16$, 95% CI -0.05-17.79, p=0.04).

Within 8-10 months after biliary stenting, 11.1% (6/54) of patients developed recurrent jaundice and cholangitis, and another 7.4% (4/54) of patients developed duodenal stenosis with a tumour. These complications led to repeated hospitalisation and biliary restentation in 4 (7.4%) cases, and duodenal stenting by self-expanding metal stents in 4 (7.4%) patients.

The choice of biliodigestive shunting method should be selected depending on the expected survival time of patients. If the prognosis of survival is up to 8 months, it is advisable to perform prosthetics of the common bile duct with self-expanding metal stents, if more than 8 months, it is advisable to perform hepaticojejunal anastomosis with prophylactic gastrojejunal anastomosis.

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CONFLICT OF INTEREST
The Authors declare no conflict of interes

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ORIGINAL ARTICLE

CONTENTS

Traceability and control as levers to prevent leakage from legal circulation when legalizing medical cannabis

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ABSTRACT

Aim: To reveal traceability and control as levers to prevent leakage from legal circulation when legalizing medical cannabis.

Materials and Methods: The methodological basis of this research work is based on a systematic approach. Methods of structural and logical analysis, bibliosemantic, abstraction and generalization were used in this article.

Results: The analysis of the regulatory framework and regulatory initiatives in the field of circulation of narcotic drugs, in particular, cannabis (in total 56 documents) demonstrated repeated attempts to reform it in Ukraine in order to increase the availability and efficiency of medical and pharmaceutical services. Recently adopted law on the legalization of medical cannabis pays special attention to the traceability of the circulation of medical cannabis and cannabis-based medicines (CbMs) by digitalization and creation of the appropriate electronic information system.

Conclusions: With the adoption of the law on the legalization of medical cannabis Ukraine became the 57th country in the world to legalize such cannabis. The study and analysis of the regulatory framework of Ukraine, taking into account the best world practices, showed that the legalization of medical cannabis will allow for providing more effective care to many patients including wounded defenders.

KEY WORDS: cannabis, medical cannabis, traceability, drug policy, narcotic drugs, control

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INTRODUCTION

Over the past decade, drug policies at the global level have prioritized decriminalization and human rights, harm reduction, and innovative and voluntary treatment. An important role is given to regulating the legal circulation of cannabis, primarily for medical use. Currently, the world has collected enough scientific data that confirm the effectiveness of the use of cannabinoids in the treatment of over 50 pathological states, primarily in the treatment of pain, PTSD, epilepsy and seizure disorders, and multiple sclerosis [1-3]. The integration of Ukraine into the European Union, and the need for modern, affordable, and effective methods of pain relief and treatment of PTSD require, in particular, the updating of the legal framework regarding the circulation of medical cannabis in accordance with the best world normative practices.

Many countries around the world have already legalized the medical use of cannabis. These countries include Albania, Argentina, Australia, Barbados, Brazil, Canada, Chile, Colombia, Costa Rica, Croatia, Czech Republic, Cyprus, Denmark, Ecuador, Finland, Georgia, Germany, Great Britain, Greece, Israel, Ireland, Italy, Jamaica, Lebanon, Luxembourg, Malawi, Malta, Mexico, Netherlands, New Zealand, North Macedonia, Norway, Panama, Peru, Poland, Portugal, Rwanda, Saint Vincent and the Grenadines, San Marino, South Africa, Spain, Sri Lanka, Switzerland, Thailand, Uruguay, Vanuatu, Zambia, Zimbabwe. Some of them have more restrictive laws that only allow the use of certain medicinal products derived from cannabis. In the United States, 38 states, 4 territories, and the District of Columbia have legalized the medical use of cannabis, but at the federal level, its use remains forbidden [3,4].

Clear rules for the circulation of cannabis for medical purposes are being worked out in Ukraine, taking example of such countries as Austria, Belgium, Czech Republic, Great Britain, Denmark, Finland, France, Germany,

Slovakia, Sweden, Switzerland, and others. However, the experience of these countries is recent and, given the development of modern information technologies in Ukraine, our state can, under certain conditions, become one of the best in ensuring the proper legalization of cannabis and preventing its illicit traffic.

AIM

In the light of the adoption of the law on the legalization of medical cannabis, the issue of the scientific justification of ensuring control through traceability in general and, in particular, of the problems of proper control in the sphere of circulation of narcotic drugs, psychotropic substances, and precursors, are becoming especially relevant. Therefore, the purpose of this article is to reveal traceability and control as levers to prevent leakage from legal circulation when legalizing medical cannabis.

MATERIALS AND METHODS

The methodological basis of research work is based on a systematic approach. Methods of structural and logical analysis, bibliosemantic, abstraction, and generalization were used in this article. An analysis of the current legal framework of Ukraine for the years 1991-2024 was carried out on the subject of regulation of the circulation of cannabis and its derivatives, as well as relevant draft laws and subordinate legislation (in total 56 documents from the official websites of the Verkhovna Rada of Ukraine, the Cabinet of Ministers of Ukraine, the Ministry of Health of Ukraine, the State Service of Ukraine on Medicines and Drugs Control).

RESULTS

At the international level, the circulation of cannabis is regulated by UN conventions [5,6,7]. In accordance with World Health Organization (WHO) recommendations, in December 2020, the United Nations Commission on Narcotic Drugs removed cannabis and its derivatives from Schedule IV of the Single Convention on Narcotic Drugs of 1961, which includes strictly controlled drugs. At the same time, it kept it in Schedule I - the list of all drugs subject to international control [8].

Until now, the main documents regulating the status of cannabis in Ukraine were the Law of Ukraine "On narcotic drugs, psychotropic substances and precursors" [9] and the Resolution of the Cabinet of Ministers of Ukraine "On approval of the list of narcotic drugs, psychotropic substances and precursors" [10]. The circulation of cannabis and tetrahydrocannabinol in Ukraine was prohibited. In April 2021, the government resolution added nabilone and nabiximols to the list of psychotropic substances whose circulation is restricted [11]. However, these drugs were never submitted for the state registration of medicinal products and, accordingly, they did not enter real circulation in Ukraine.

On December 21, 2023, the Verkhovna Rada of Ukraine adopted the Law "On amendments to certain laws of Ukraine regarding the state regulation of cannabis plants for use in educational purposes, educational, scientific and scientific-technical activities, production of narcotic drugs, psychotropic substances, and medicinal products with the purpose of expanding patients' access to necessary treatment" (hereinafter - the Law) [12].

According to the academic dictionaries, legalization is "the act of allowing something by law, e.g. the legalization of drugs" [13], "the process of making something legal when it was previously illegal" [14]. Full legalization is that is limited only by the quality of the product itself, and low-quality products are prohibited for sale [15]. Therefore, we can only talk about full and incomplete legalization or its absence. Incomplete legalization has its own characteristics depending on what is being legalized. In the case of cannabis plants, the latter are a kind of "case", which, with more than a hundred different cannabinoids in terms of their pharmacological effect on the human body, contains one that needs restrictions in its distribution - tetrahydrocannabinol (hereinafter - THC). Depending on its content, hemp varieties, and their circulation usually differ in different countries.

Traceability is a concept that originates from the food industry and is used to ensure the quality of the respective products. Yes, in accordance with clause 15 of Art. 3 of a Regulation of the European Parliament and of the Council (of the EU) No. 178/2002, "traceability" means the ability to trace and track at all stages of production, processing and distribution of food products, fodder, productive animals or substances that are intended to be included or expected to be included in food or feed [16]. The traceability of medical cannabis is necessary not so much to ensure quality, but to limit the leakage of tetrahydrocannabinol from legal circulation.

In the adopted Law it is stated that the circulation of hemp for medical purposes, products of its processing, the plant substance of cannabis, medicinal products produced (made) from them is allowed in medical practice, educational purposes, educational, scientific and scientific and technical activities on condition of control and traceability ensured at all stages of such circulation. Thus, it is traceability and control that must become necessary conditions of circulation. Proper control over

the circulation of medical cannabis can be qualitatively organized only on the basis of appropriate traceability from the seed to the sale to the consumer. The Law also states that circulation traceability is ensured by implementing a number of measures that should be considered [12].

The procedure of purchase of hemp for industrial purposes is currently provided by the relevant Resolution of the Cabinet of Ministers of Ukraine of December 27, 2008 No. 1129 [17], which states that the purchase is carried out by economic entities from entities of production of seeds and planting material entered in the State Register of Seed Producers. This procedure is clarified by clause 33 of the Resolution of the Cabinet of Ministers of Ukraine of April 6, 2016 No. 282 [18], since not any economic entity, but only a properly licensed one specifically for sowing and growing, can purchase industrial hemp today. In general, the Law of Ukraine " On narcotic drugs, psychotropic substances and precursors", adopted in 1995, actually equated technical hemp with drugs, applying the corresponding legislative regulation on licensing, which excessively complicated conducting economic activity of growing hemp [9].

DISCUSSION

With the adoption of the Law, the actual launch of the medical hemp market will take place and industrial hemp should move to the plant market, and medical hemp should be regulated in the similar way to the current one regarding industrial hemp, with the condition of increased traceability and control. Such an increase should first of all be ensured by proper digitalization, because the latter can simplify all legal procedures with hemp and at the same time increase the traceability of these processes. Modern artificial intelligence programs are able to use video cameras to calculate the number of seeds for planting and record them. Then, the number of labeling units and further stages of the procedures regarding the plant will be determined by the number of seeds. Thus proper digitalization is also ensured by appropriate labeling of each plant, each batch of products of medical cannabis processing and each unit of packaged products, which is further specified in the Law [12].

All relevant transactions will be included in a common database, including the date of manufacture and series of medicines in which medical cannabis is used. In this way, both the leakage of medical cannabis from legal circulation and attempts to sell a falsified drug will be prevented. This will allow tracking of the entire production and supply chain of medicines containing tetrahydrocannabinol contained in hemp for medical purposes, including sale to a patient specifically defined by a doctor's prescription. Traceability of circulation for educational, scientific purposes as well as scientific and technical activities should also be ensured through the labeling of each hemp plant and each derivative thereof containing THC.

According to the order of the Ministry of Health of Ukraine [19], since October 13, 2023, the dispensing of narcotic (psychotropic) medicinal products in pharmacies began to be carried out exclusively based on an electronic prescription throughout Ukraine. In our opinion, electronic accounting should also be applied to extemporaneous narcotic medicinal products, which are appropriately manufactured directly in pharmacies and now may be one of the exceptions from the rule.

The Law provides to create an electronic information base for further analysis in order to determine the demand and quotas for the cultivation of medical cannabis [12]. Such base should become a component of the unified state electronic system for managing the circulation of narcotic drugs, psychotropic substances and precursors.

The system must contain information on all elements related to circulation, except for personal data, which can be disclosed only to supervisory and law enforcement authorities.

That is, the system must contain all possible information that can confirm the chain of traceability of the origin of medical cannabis and its derivatives and the legality of the corresponding products. The processing and protection of personal data in the system must be carried out in accordance with the Laws of Ukraine "On protection of information in automated systems"[20] and "On protection of personal data" [21].

The results of manipulations with hemp plants and their derivatives must be entered into the system by the relevant entities and the employee responsible for the state not later than a day after receiving the relevant information, which must also be recorded by the electronic system.

It is advisable to use artificial intelligence (AI) to ensure control and traceability of circulation at all stages.

According to the adopted law, the cultivation of hemp for medical purposes is carried out in accordance with the requirements of the proper practice of cultivation and collection of raw materials of plant origin. In Ukraine, the proper practice of cultivation and collection of raw materials of plant origin was put into effect by order of the Ministry of Health of Ukraine [22]. This practice, taking into account its multifactorial nature, can also, in the future, be controlled using AI technologies, but this is already a prospect for further research into traceability and control over the circulation of relevant plants and substances.

CONCLUSIONS

With the adoption of the Law "On amendments to certain laws of Ukraine regarding the state regulation of cannabis plants for use in educational purposes, educational, scientific and scientific-technical activities, production of narcotic drugs, psychotropic substances, and medicinal products with the purpose of expanding patients' access to necessary treatment", Ukraine became the 57th country in world legalizing medical cannabis. Among them, there are the USA, Canada, EU countries, etc. The study and analysis of the regulatory framework of Ukraine, taking into account the best world practices, showed that the legalization of medical cannabis will give an opportunity to provide more effective care to many patients including wounded defenders.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Cytokine profile in multiple sclerosis patients with and without Covid-19

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ABSTRACT

Aim: To investigate the possible effect of COVID-19 disease on cytokine profile and some circulating growth factors in patients with multiple sclerosis (MS).

Materials and Methods: Serum cytokine levels as well as growth factors content were assessed be means of a solid phase enzyme linked-immunosorbent assay in 97 MS patients of which 41 had and 56 did not have confirmed COVID-19 in the past 4-6-month period, and 30 healthy individuals who were age-, and gender-matched.

Results: Some proinflammatory cytokine (such as TNFα, IFNγ) levels were higher while anti-inflammatory cytokine, namely IL-4, was lower in MS patients compared to controls indicating Th1/Th2 imbalance. Our findings revealed that the imbalance of circulating Th1/Th2 cytokines in MS patients after SARS-CoV-2 infection became even more pronounced, thus, might be a reason for the disease deterioration. Furthermore, nuclear factor κB level in MS patients after COVID-19 was found significantly elevated from that with no history of SARS-CoV-2 infection, and could be the cause of proinflammatory cytokines overexpression.

Conclusions: Our findings revealed that immunopathology of MS is associated with a Th1/Th2 imbalance, furthermore, SARS-CoV-2 infection can lead to the deterioration of this condition in MS patients, causing even more pronounced overexpression of proinflammatory cytokines and decrease in anti-inflammatory cytokines. Our results also indicated that studied growth factors can be involved in MS development but exact mechanism is not clearly understood and requires further research.

KEY WORDS: multiple sclerosis, coronavirus disease, SARS-CoV-2, Th1/Th2 cytokines, growth factors, NFκB, HIF-1α

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INTRODUCTION

Multiple sclerosis (MS) is one of the most frequent disabling neurological diseases affecting millions worldwide. Since the global prevalence of MS is rising every year and today 2.8 million people are living with this diagnosis around the globe [1], it has become a trending research topic and area of considerable interest to the science community. MS is characterized by multifocal and scattered lesions through the grey and white matter of the central nervous system (CNS) originating from an autoimmune disturbance [2]. In MS, a person's immune system attacks the protective covering (myelin sheath) of nerve fibers in the brain and spinal cord often leading to spasms, pain, muscle weakness, different organs disfunction, and sometimes, decline in cognitive ability, coordination and vision loss [3].

It has been generally accepted that MS is a chronic immune-mediated disorder in which demyelination and tissue injury is driven and amplified by the inflammatory process throughout all stages of the disease [4]. Since pathogenesis of MS is accompanied by the blood brain barrier (BBB) disruption [5], macrophages and lymphocytes can migrate freely into the CNS consequently initiates an inflammatory cascade followed by sclerotic plaques formation, demyelination, and neurodegeneration [2, 6]. During the past few decades, major progress has been made in understanding the relationship between inflammatory process and MS pathogenesis [7]. Autoreactive T cells, namely, T helper (Th)-1 CD4+ T cells and Th17 cells, are involved into the MS pathogenesis, primarily, through their secretion of pro-inflammatory cytokines and chemokines that trigger microglia activation and chronic oxidative injury [8]. Macrophages and microglial cells also release different immunomodulators which may harm oligodendrocytes and are crucial for recruitment of inflammatory cells into the CNS [9].

Due to the multi-faceted autoimmune nature of MS,

immunomodulating therapy are crucial for patients with MS [4, 10]. Because of that it has been speculated that patients with MS are at higher risk for a severe course of infection diseases [11]. One the other hand, infections can result in an increased severity of MS-related symptoms and may trigger clinical relapses [12, 13]. Given the rapid rate of spread of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [14, 15], it is important to focus the current studies on the identification of the clinical characteristics and outcomes of COVID-19 among patients with MS. Preliminary results from recent studies have shown that pathogenetic mechanisms of COVID-19 and MS largely overlap [16]. In particular, there are several potential crossroads of MS and COVID-19 immunological pathways: the type-1 IFN (IFN-I) response, the T-helper 17 (TH-17) axis, and the inflammasome pathway. Thus, pinpointing the biomodulators of neurodegenerative and inflammatory events associated with both COVID-19 and MS could help extend knowledge on the etiopathogenesis of these conditions.

AIM

Taking into consideration the important role of cytokines in the neuroinflammatory processes, the aim of the present study was to evaluate the pro-inflammatory (including tumor necrosis factor (TNF)-α and interleukin (IL)-1β, -6 and -12), Th 1 (interferon (IFN)-γ), and Th 2 (IL-4 and -10) cytokine serum levels in MS patients without or with COVID-19 disease confirmed in the period of the past 4-6 months. Additionally, the levels of some important growth factors such as fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF) as well as hypoxia-inducible factor 1alpha (HIF-1α) and *nuclear factor kappa B* (*NF-κB*) were also estimated in the serum of patients with MS previously suffered or did not from COVID-19.

MATERIALS AND METHODS

The study was conducted by means of collaboration between ESC "Institute of biology and medicine" of Taras Shevchenko National University of Kyiv (Kyiv, Ukraine) and the University Clinic of the Bogomolets National Medical University (Kyiv, Ukraine) from January 2021 to August 2022. Ethical approval was obtained from the both Institutional Ethical Committees. The written informed consent was acquired from all patients and healthy volunteers.

The study comprised a group of 127 people; 97 were MS patients of which: 41 were diagnosed with COVID-19 disease in the past 3-6-month period (MS, Covid-19$^+$ group) and 56 did not suffer from COVID-19 previously (MS, Covid-19$^-$ group), and 30 were healthy volunteers (control group) who were well matched to the group of MS patients by age and gender. A diagnosis of MS was confirmed if individuals have evidence of CNS damage that is disseminating in space and in time according to the 2017 McDonald criteria [17]. We excluded all those MC patients who had an active malignancy (either metastatic or nonmetastatic); were on immunosuppressive medications; had one of the following: advanced renal failure, chronic lung disease or liver cirrhosis. At the time of blood sampling, all participants did not have any symptoms of infection disease. The recruitment was also limited to patients aged from 35 to 45 years.

Blood samples were taken, and serum was obtained by centrifugation at +4°C and 1300 g for 20 min. Serum was collected and frozen at –20 °C until analysis. The serum samples of all participants were also used to determine anti-SARS-CoV-2 IgG titers. To measure the titers of anti-SARS-CoV-2 IgG in samples, a chemiluminescent microparticle immunoassay (Abbott Laboratories, USA, Cat. No 06R86-20) was performed according to the manufacturer's instructions. Results from the anti-SARS-CoV-2 IgG assay are given as index values (S/C). The S/C value less than 1.40 was considered negative while the S/C value of 1.40 or greater was classified as positive per the manufacturer's recommendation.

The levels of cytokines (TGFα, IFNγ, *IL*-1β, -4, -6, -8, -10, and -12) and growth factors (FGF-2, EGF, VEGF, PDGF) as well as factors such as HIF-1α and *NF-κB* were measured in serum by enzyme-linked immunosorbent assay (ELISA), following the standard protocols. Primary antibodies were purchased from *Santa Cruz Biotechnology,* Inc., USA (Dalas, TX, USA). Corresponding secondary antibodies conjugated to horseradish peroxidase were purchased from Sigma-Aldrich (Saint Louis, MO, USA). Substrate solution (0.04 % *o*-phenylenediamine and 3.5 mM H_2O_2 in 100 mM *acetate buffer*, pH 5) was used for detection. The reaction was stopped after 20 min by the addition of 100 µL of a stop solution and the absorbance was determined at 492 nm with ELISA reader (BioTek Instruments, USA). All the values were recorded in duplicate. The concentrations of cytokines as well as growth and transcription factors in the serum of healthy volunteers were set at 100%, and *changes* in their concentrations were given as *percentage* of *controls*.

Statistical analysis was performed with STATISTICA Package version 12.0 (StatSoft. Inc.). The arithmetic mean (M) and mean squared deviation (SD) indicators were calculated. To clarify the normal distribution of quantitative data, the Kolmogorov-Smirnov test or

Table 1. Basic characteristics of the MS patients and healthy controls

Indicator (unit of measurement)	Patients' groups		
	Control (n = 30)	MS, Covid-19$^+$ (n = 41)	MS, Covid-19$^-$ (n = 56)
Age (years)	41 ± 4	40 ±5	41 ± 5
Sex (male/female)	10/20	14/27	20/36
Time since MS diagnosis (years)	-	4.6 ± 1.3	4.4 ± 1.5
Current anti-SARS-CoV-2 IgG titer (S/C index)	< 1.40 (negative)	70 ± 8 (positive)	< 1.40 (negative)

Shapiro-Wilk test was used. Data between two groups were compared using the Mann-Whitney U-test. Kruskal-Wallis H-test was performed to compare data among multiple groups. A $p<0.05$ was considered statistically significant.

RESULTS

Some basic characteristics of the MS patients and healthy individuals are shown in Table 1. MS patients consisted of 34 males and 63 females, and their age ranged from 35 to 46 years. In the aggregate, 42% of MS patients had COVID-19 disease in the past 3-6-month period, while the others had no COVID-19 previous history. MS patients were age and gender matched to a control group (Table 1).

Since MS is a progressive immune-mediated disorder, and cytokines play an important role in the disease progression, we wondered whether pro- and anti-inflammatory cytokine levels were changed in MS patients after COVID-19. Thuse, serum cytokine levels were compared between both groups of MS patients (with or without confirmed COVID-19) and healthy controls (Fig. 1).

MS is considered a Th 1 lymphocyte-mediated disorder, and it was quite expected that serum levels of IFNγ, Th1-related molecules, were increased in MS patients, however, it should be noted that IFNγ level was significantly higher in the group of MS patients after COVID-19 compared with MS patients with no COVID-19 history (Fig. 1).

With regards to the pro-inflammatory cytokine profile, TNF-α levels did not differ significantly among both groups of MS patients but were higher compared with the control. Serum IL-12 level was higher in MS patients after COVID-19 compared with the control value but in the group of MS patients with no COVID-19 history it was at the control level. At the same time, serum IL-6 levels observed among both MS groups did not differ from that of the control group. Finally, IL-1β levels were higher among healthy subjects compared with MS patients (Fig. 1).

In the Th 2 anti-inflammatory cytokine profile, IL-4 levels were higher in control subjects compared with both groups of MS patients. Although, the IL-10 levels did not differ between MS patients with no history of COVID-19 and controls, its level in MS patients after COVID-19 was significantly elevated (Fig. 1).

Since growth factors comprised an important group of cytokines playing a crucial role in the pathways of cell proliferation, differentiation and activation, we hypothesized that among them also could be risk factors for the initiation and progression of MS. Thus, in the present study, we also examined the circulating levels of some important growth factors, namely FGF-2, VEGF, EGF, PDGF.

As can be seen from the Figure 2, no difference was detected in FGF-2 levels between MS patients with no COVID-19 history and controls while in the group of MS patients after COVID-19 the level FGF-2 was significantly elevated. The levels of EGF and PDGF were remarkedly lower in the serum of both MS patients' groups compared with control subjects, however, there were no difference between their values in MS patients with or without COVID-19 history. The serum VEGF levels were higher among MS patients of both groups than those of controls but they did not differ between MS patients with or without COVID-19 history (Fig. 2).

In this study we also estimated the circulating levels of hypoxia-inducible factor 1alpha (HIF-1α) as it is a key regulator in hypoxic and ischemic brain injury. Higher HIF-1α level was observed among MS patients with no COVID-19 history compared with control subjects. However, no difference was detected between HIF-1α levels of MS patients after COVID-19 and control individuals.

The transcription factor NF-κB is a central mediator of inflammation with strong contribution to inflammasome pathway during MS development. In this study, we compared serum levels of NF-κB in MS patients with or without COVID-19 history (Fig. 2). Our results revealed that NF-κB levels were increased in MS patients either with or without COVID-19 history compared with controls. However, it should be noted that NF-κB level was significantly higher in MS patients after COVID-19 compared with value of MS patients with no COVID-19 (Fig. 2).

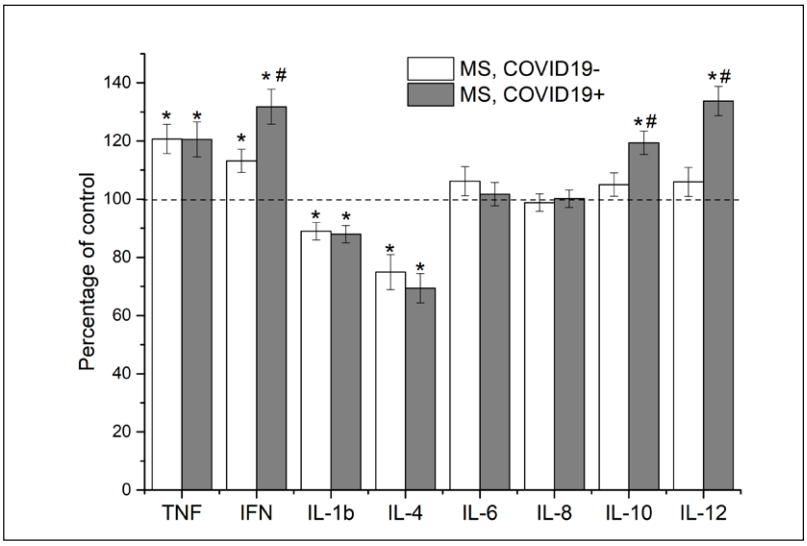

Fig. 1. The serum cytokine profile of MS patients with or without COVID-19 history. Cytokine TNFα, IFNγ, IL-1β, IL-4, IL-6, IL-8, IL-10, and IL-12 contents were expressed as percentage of control (100 %).
*p<0.05 significantly different from the control group; # p<0.05 significantly different from the MS, COVID19- group.

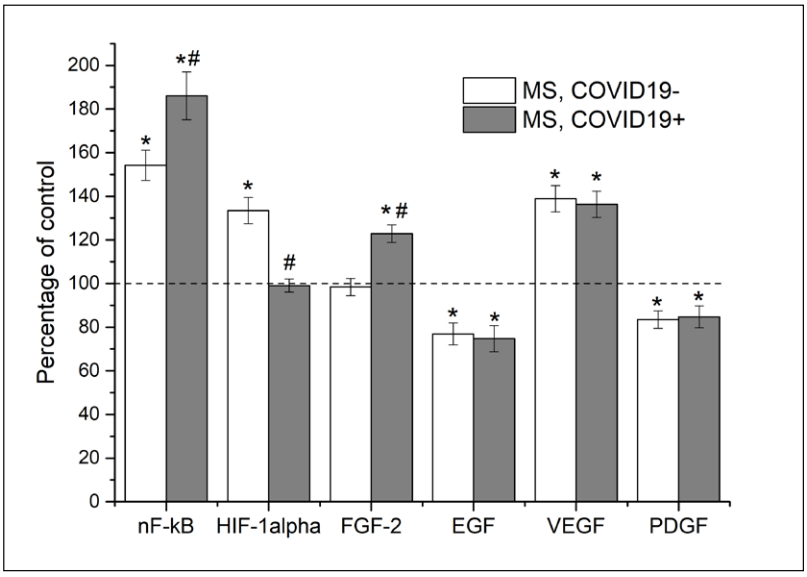

Fig. 2. The serum growth factor profile of MS patients with or without COVID-19 history. The contents of growth factors (FGF-2, EGF, VEGF, PDGF) as well as nF-κB and HIF-1α were expressed as percentage of control (100 %).
*p<0.05 significantly different from the control group; # p<0.05 significantly different from the MS, COVID19- group.

DISCUSSION

Previously, it has been shown that infections can trigger MS exacerbations [12, 13, 18] but an association between COVID-19 and increased risk of infection-related MS exacerbations has not been conclusively improved. Since immune mediators have a crucial role in the development of MS lesions, and pro- and anti-inflammatory cytokine levels have been found to correlate with MS progression [7, 8, 19], in the current study we aimed not only to evaluate the changes in serum cytokine profile of MS patients but also to elucidate the impact of COVID-19 on the circulatory cytokine levels. The study enrolled 97 MS patients from the University Clinic of the Bogomolets National Medical University (Kyiv, Ukraine). Among them there were 41 individuals who had been diagnosed with COVID-19 in the past 4-6-month period. To understand the impact of COVID-19 on serum cytokine profile laboratory data from MS patients with COVID-19 were compared with corresponding data from patients with MS but without COVID-19 history.

With regards to the serum cytokine profile in MS patients with no COVID-19 history, the findings from the current study are consistent with results of previous studies [19, 20] and supported the generally accepted immune-mediated mechanism underpinning MS disease [2, 4]. Hence, MS is considered a Th1 lymphocyte-mediated disease, and it was expected to find enhanced levels of Th1-related molecules, namely IFN-γ and TNF-α, in MS patients. On the other hand, anti-inflammatory cytokines produced by Th2 cells (IL-4, IL-10, etc.) act as negative feedback regulators on proliferation and differentiation of Th1 cells, and have anti-inflammatory effect, thereby, inhibiting MS progression. Our results revealed that immunopathology of MS is associated with a Th1/Th2 imbalance related to overexpression of proinflammatory cytokines and decrease in anti-inflammatory cytokines. According to our findings, SARS-CoV-2 infection in MS patients can lead to the deterioration of the condition of patients. As could be seen from the results obtained (Fig. 1), Th1/Th2 imbalance in MS patients after COVID-19 became even more pronounced. Overproduction of proinflammatory cytokines while decreasing the anti-in-

flammatory cytokines could lead to acute inflammatory lesions in MS patients, and, consequently, to more severe course of the disease.

It is well known that the nuclear factor NF-κB pathway enhances the expression of proinflammatory genes and is involved in MS development [21]. Our results revealed increased level of circulating NF-κB in MS patients (Fig. 2) which might be one of the reasons of proinflammatory cytokines overproduction under the disease development. Furthermore, NFκB level in MS patients after COVID-19 was found significantly different from that with no history of SARS-CoV-2 infection (Fig. 2) and might indicate a more severe disease prognosis.

Previously, it was shown that HIF-1α could be implicated in neuronal apoptosis, and disruption of BBB [22], and, contrarily, some other studies demonstrated protective effect of HIF-1α against neurologic dysfunction and neuronal apoptosis [23]. Since, HIF-1α seems to be involved in the cell's response to brain injury, in a current study, we investigate its levels in MS patients with and without COVID-19. The elevated serum HIF-1α level was shown in MS patients with no COVID-19 history, while in MS individuals after SARS-CoV-2 infection its level was decreased and did not defer from control (Fig. 2).

Here, we also hypothesized that growth factors may also have an essential role in the MS development, thus establishing the causal relationship between circulating levels of growth factors in MS patients before and after COVID-19 could be important from clinical perspective. Our results highlight that MS patients either with or without COVID-19 history have elevated levels of VEGF and, simultaneously, decreased EGF and PDGF content compared to controls. However, no differences were observed among MS patients of both groups (Fig. 2). We hypothesized that VEGF, which is also known as vascular permeability factor, could be involved in the MS development due to its ability to regulate vascular permeability, and to contribute to BBB breakdown [24]. Overall, growth factors might be important mediators linked to MS lesion progression however, exact relation and mechanism are not clearly understood and require further research.

CONCLUSIONS

In summary, the results of the present study suggest a Th1/Th2 balance shift in favor of a Th1 cytokine profile in patients suffering MS. Furthermore, SARS-CoV-2 infection in MP patients associated with even more pronounced overexpression of proinflammatory cytokines and decrease in anti-inflammatory cytokines. The increase of circulating Th1 cytokines can lead to the deterioration of symptoms in MS patients. Our results also indicated that studied growth factors may be involved in MS development but exact mechanism is not clearly understood and requires further research.

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ORIGINAL ARTICLE

CONTENTS

Dental treatment of children under general anesthesia during the period of matrial law

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ABSTRACT

Aim: To summarize the experience of providing dental medical care under general anesthesia to children from different regions of Ukraine during the martial law, taking into account the factors affecting the choice of optimal conditions for dental treatment.

Materials and Methods: Dental treatment under general anesthesia of 1,258 children from different regions of Ukraine has been performed since March 2022. The condition of the teeth (df, df+DMF, DMF) and hygienic state of the oral cavity (OHI-S) were determined. The level of awareness of parents regarding the preservation of children's dental health was studied through a questionnaire.

Results: An unsatisfactory oral hygiene, a high level of caries were found in the vast majority of children. The highest df was observed in the group of children aged 3 to 6 years (7.14±0.33), which is significantly higher than in the group of children under 3 years of age (4.32±1.04, $p \leq 0.05$). The worst oral hygiene was observed in children aged 6-12 years (OHI-S 2.62±0.32). An insufficient level of awareness of parents and children regarding dental health was revealed. A total of 1,712 operations under general anesthesia were performed. The majority of patients could not regularly appear for follow-up examinations due to the forced departure from the country.

Conclusions: The organization of dental treatment under general anesthesia allows solving a number of problems of dental care for children during the war.

KEY WORDS: Dental caries, general anesthesia for children, organization of dental care, martial law, dentistry during the war

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INTRODUCTION

The dental health of Ukrainian children is deteriorating, it is largely due to the large-scale invasion of Russia and the introduction of martial law in Ukraine (Decree of the President of Ukraine dated February 24, 2022). In connection with the hostilities, many Ukrainian families were forced to leave their homes and did not have access to either medical or dental care for a long time [1-3]. Therefore, one of the urgent issues in the conditions of martial law is the issue of organization and provision of dental care to children.

AIM

To summarize the experience of providing dental medical care under general anesthesia to children from different regions of Ukraine during the Martial Law, taking into account the factors affecting the choice of optimal conditions for dental treatment.

MATERIALS AND METHODS

For 21 months, starting from March 17, 2022, on the basis of the Dental Medical Center of the Bogomolets National Medical University (SMC of NMU) performed dental examination and treatment under general anesthesia of children from different regions of Ukraine (a total of 1,258 people under the age of 18 were examined and treated) [4,5]. Examination of the oral cavity included an assessment of the hard tissues of the teeth (df, df+DMF, DMF) and the hygienic state of the oral cavity (according to the OHI-S). The level of awareness of parents regarding the preservation of children's dental health was studied through a questionnaire. When choosing a method of dental treatment in children, their general somatic, psycho-emotional condition was taken into account, as well as the real possibility of regular visits to the dentist in order to continue treatment, check-ups and preventive measures was assessed. Information about each examined person, including social factors (belonging to privileged categories, internal and external movements due to the introduction of martial law, etc.), was entered into the Medical Card of the dental patient [6,7]. The obtained data were processed by generally accepted variational statistical methods using a personal computer and the R-Statistics (2001) statistical software package. The reliability of the difference in the dental examination data in different age groups was assessed using the Student, Mann–Whitney, $\chi 2$.

Table 1. Region of registration and transfer of children who received dental care during the period of martial law in Ukraine

Place of residence	The number of persons who received dental treatment	Movement of persons who have received dental care	
		Movement of persons who have received dental care	The number of children returned to Ukraine from among those who went abroad after treatment
Kyiv	759	521 *(68,64%)*	43 *(8,25%)*
Kyiv region	362	187 *(51,66%)*	37 *(19,79%)*
Chernihiv	27	9 *(33,33%)*	2 *(22,22%)*
Chernihiv region	32	14 *(43,75%)*	4 *(28,57%)*
Kherson	5	5 *(100%)*	-
Kherson region	7	7 *(100%)*	-
Zhytomyr	6	3 *(50%)*	1 *(33,33%)*
Zhytomyr Region	12	5 *(41,67%)*	1 *(20,00%)*
Rivne	11	6 *(54,55%)*	2 *(33,33%)*
Volyn region	13	8 *(61,54%)*	2 *(25%)*
Zaporizhzhia	6	6 *(100%)*	-
Zaporizhzhia region	8	6 *(75%)*	-
Kharkiv	4	4 *(100%)*	-
Kharkiv region	3	3 *(100%)*	-
Mykolayiv	2	2 *(100%)*	-
Mykolayiv region	1	1 *(100%)*	-
In total	**1258**	**787 *(62,55%)***	**92 *(11,69%)***

RESULTS

Dental care for children was provided on the basis of the SMC of Bogomolets NMU in the period from 17.03.2022 to 24.02.12.2024. Dental examination was carried out and dental treatment was provided to 1258 persons under the age of 18 from different regions of Ukraine (Table 1).

As can be seen from Table 1, residents of Kyiv and Kyiv region, as well as residents of the regions that were most affected by the war, turned to the SMC of NMU. A third (34.82%) of the children who sought help during the period of martial law live in rural areas.

It is worth noting that almost two-thirds of the treated children (787 families - 62.55%) were later taken abroad by their parents with a plan to save them from the war; of them: city residents – 556 (44.2%), rural areas – 231 (18.36%). Subsequently, 92 families returned to Ukraine, which is only 11.69% of the total number of those who came.

During the dental examination, an unsatisfactory state of oral hygiene, a high level of caries and the prevalence of its complicated forms were found in the vast majority of children (Table 2).

The highest df was observed in the group of children aged 3 to 6 years (7.14±0.33), which is significantly higher than in the group of children under 3 years of age (4.32±1.04) $p \leq 0.05$. The worst indicator of oral hygiene is observed in children aged 6-12 years (OHI-S 2.62±0.32), this indicates poor hygiene.

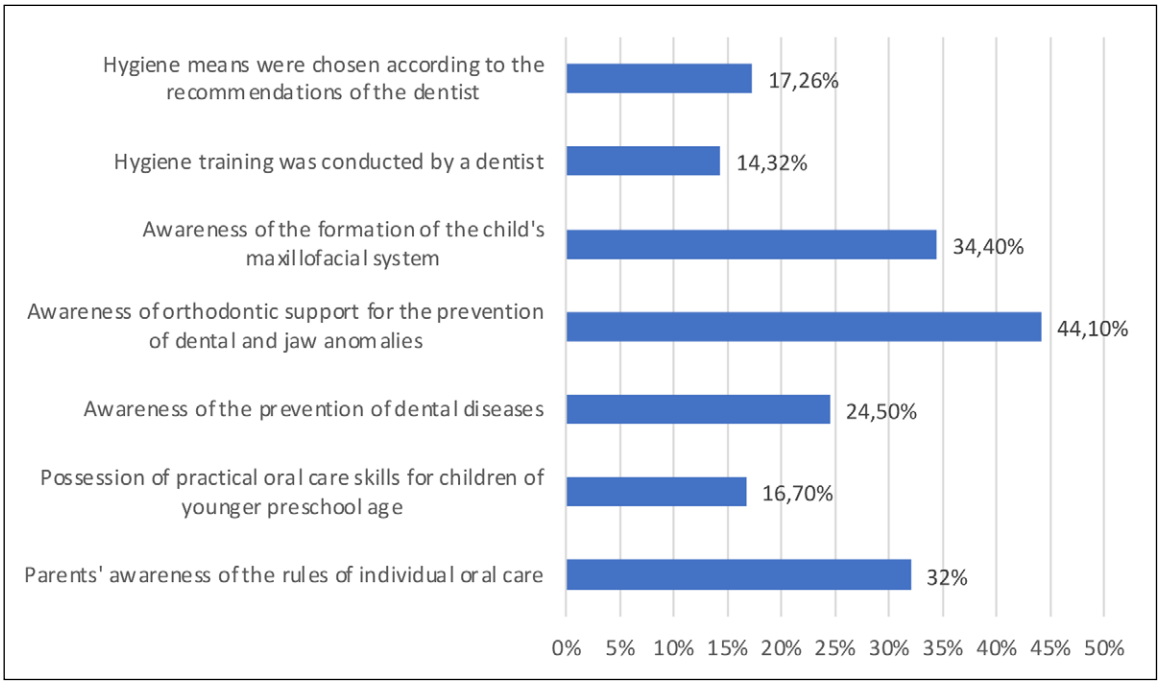

Fig. 1. Awareness of parents of examined children regarding children's dental health.

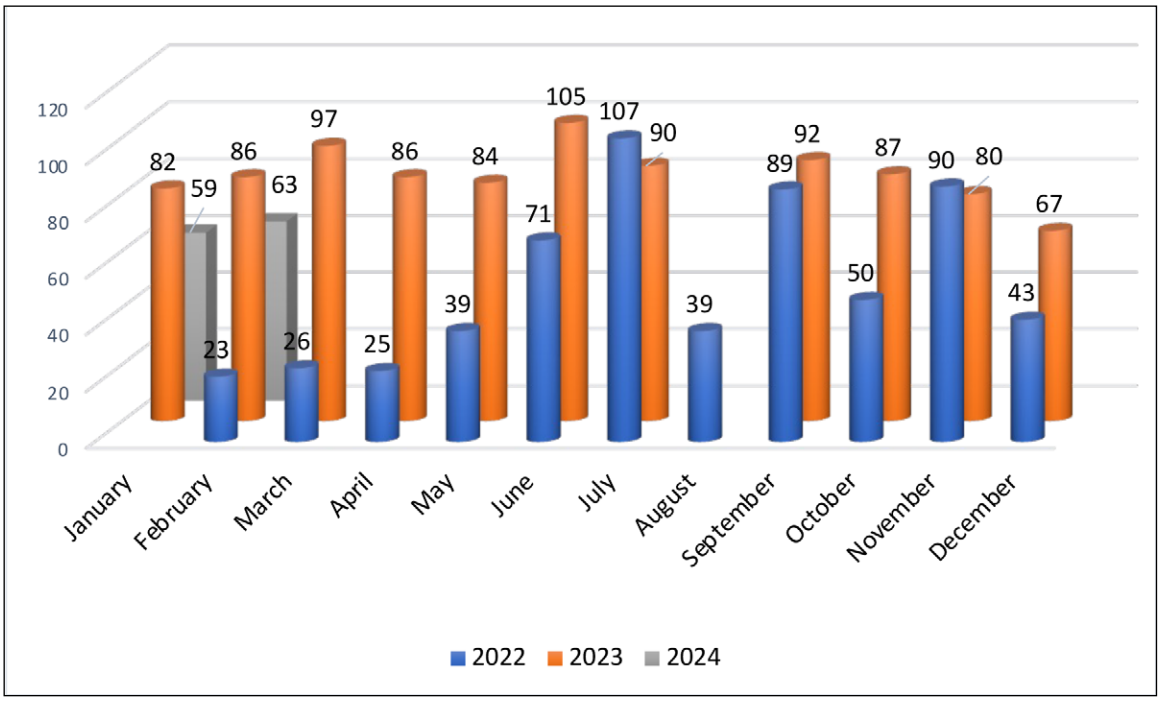

Fig. 2. Distribution of operations performed on children under general anesthesia in different months of 2022 and 2023/2024.

For the primary and secondary prevention of the main dental diseases, it is important to have a sufficient level of sanitary literacy of parents. The awareness of parents and children regarding the preservation of dental health acquires special importance in the conditions of martial law with limited access to a dentist. The results of the study of the parents awareness regarding the maintenance of dental health are shown in fig. 1.

Dental treatment of children under general anesthesia was carried out taking into account the clinical situation in each individual case in one or more visits according to the regulations for the dental treatment under general anesthesia [8]. A total of 1,712 operations were performed, of which 781 were urgent interventions (surgical); planned – 931 (therapeutic direction – 583; therapeutic along with planned surgical interventions – 348) (Fig. 2).

Table 2. Dental status of children of various ages examined during the period of martial law in Ukraine

Age (number of children)	Oral hygiene (OHI-S)	df, df+DMF, DMF
0-3 (229)	-	4,32±1,04
3-6 (541)	-	7,14±0,33*
6-12 (420)	2,62±0,32	5,98±1,28
12-18 (68)	2,38±0,15	6,79±0,24*

* The reliability of the difference of the results from the data in the group of 0-3 years $p \leq 0.05$.

The choice of the method of dental treatment under general anesthesia in the examined children was determined by a number of reasons, the main ones of which were:

- A significant need for dental treatment, the need to treat caries complications.
- The need for immediate emergency care.
- Labile psycho-emotional state, high level of stress.
- Young age of the child (up to 3 years).
- Technical complexity of treatment of complicated dental caries in molars in children with insufficient level of cooperation.
- The need for simultaneous treatment of all teeth due to the impossibility of planning several visits because of forced migration or the unavailability of dental care in the near future for various reasons.

As can be seen in fig. 2, the number of patients who needed dental treatment was the highest in July 2022 (107 operations were performed), which was mostly due to the need for treatment before forced departure abroad.

It should be noted that due to the forced departure from the country, the vast majority of patients could not regularly appear for follow-up examinations, ant this fact made it impossible to determine the effectiveness of treatment.

DISCUSSION

The data we received regarding the unsatisfactory state of dental health of the population of Ukraine during the war coincide with the results of other studies both in Ukraine [9,10], as well as in other countries affected by military operations. In particular, in a study conducted in Libya during the military operations of 2016/2017 and after them, a certain dependence was found between the education of parents (which indirectly indicates their awareness, in particular, of sanitary culture) and the intensity of caries in their children, including refugees [10]. Thus, the importance of sanitary literacy for the prevention of dental diseases during the war and in the post-war period was noted. The results of our research also demonstrated the low level of dental literacy of the population, which makes it difficult to maintain the dental health of children in extreme conditions.

The difficulty of obtaining dental care during the Wartime period is justified by objective reasons of a technical nature (lack of medical care, migration of the population, departure of doctors from abroad, destruction of dental buildings/offices/equipment [11]. At the same time, issues related to the organization, the treatment and management planning of children in the conditions of martial law has not been sufficiently studied and illuminated to date, since more attention was paid to military dentistry in the world dental literature [12-14].

In our opinion, dental treatment under general anesthesia is a priority choice for the treatment of the oral cavity during the period of martial law. Choosing this method makes it possible to provide a large amount of care in a short period of time without additional stress for the child [15,16]. At the same time, dental treatment under general anesthesia cannot provide guarantees without regular preventive measures [17]. So, children affected by wars should be identified as target groups for oral health promotion programs.

Therefore, our experience of work during the war can be useful for the organization of dental care in medical institutions of our country.

CONCLUSIONS

The implementation of martial law in the country significantly affects the state of dental health of children and the organization of their dental treatment. It is necessary to take into account the high need for the treatment of complicated and uncomplicated caries, the unsatisfactory state of oral hygiene, the low level of sanitary literacy of parents (especially among residents of rural areas), as well as population migration, which greatly complicates the possibility of regular control of the dental status of children. The organization of dental rehabilitation under general anesthesia allows solving a number of problems of dental care for children during the war, provided that parents and children are properly educated about health.

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ORIGINAL ARTICLE

CONTENTS

Ghrelin attenuates the inflammatory response induced by experimental endotoxemia in mice

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ABSTRACT

Aim: The aim of this research is to assess the anti-inflammatory effect of ghrelin in mice models of polymicrobial sepsis.

Materials and Methods: 35 male albino Swiss mice, ages 8-12 weeks, weighing 23-33g, were randomly separated into five groups n = 7; normal group was fed their usual diets until time of sampling, the sham group subjected to Anaesthesia and laparotomy, sepsis group subjected to cecal ligation and puncture, vehicle group was given an equivalent volume of intraperitoneal saline injections immediately after cecal ligation and puncture, and the ghrelin group was treated with 80 µg/kg of ghrelin intraperitoneal injections immediately following cecal ligation and puncture. Twenty hours after cecal ligation and puncture, mice were sacrificed; myocardial tissue and serum samples were collected. Serum IL-1β, NF-κB, and TLR4 levels were measured, and inflammatory response's effects on cardiac tissue were evaluated.

Results: The mean serum IL-1β, NF-κB, and TLR4 levels were markedly elevated in the sepsis and vehicle groups than in the normal and sham groups. The mean serum levels of IL-1β, NF-κB, and TLR4 were considerably lower in the ghrelin-treated group than in the vehicle and sepsis groups. Myocardium tissue of the normal and sham groups showed normal architecture. The sepsis and vehicle groups had a severe myocardial injury. The histological characteristics of ghrelin-treated mice differed slightly from those of the normal and sham groups.

Conclusions: Our study concluded that ghrelin exerts anti-inflammatory effects in polymicrobial sepsis, as indicated by a considerable decrease in the IL-1β, NF-κB and TLR4 serum levels.

KEY WORD: Ghrelin, NF-κB, CLP, IL-1β, sepsis, TLR4

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INTRODUCTION

Sepsis is an unregulated systemic inflammatory reaction, which could lead to death from multiple organ failure. The fundamental cause of a poor prognosis in sepsis is an imbalance between the pro- and anti-inflammatory responses. About 31 million individuals worldwide suffer from sepsis yearly, leading to more than 5 million deaths. Due to the lack of data from numerous low-income areas, these results likely underestimate the true worldwide impact of sepsis [1]. In sepsis, signal transduction is triggered by the binding of damage-associated molecular patterns (DAMPs) derived from injured tissues or pathogen-associated molecular patterns (PAMPs) derived from microbes to toll-like receptors (TLRs) on monocytes and antigen-presenting cells [2], resulting in the migration of nuclear factor kappa B (NF-κB) from the cytoplasm into the nucleus of the cell. After that, NF-κB stimulates the synthesis of proinflammatory cytokines such as interferon, interleukin (IL)-1, IL-18, and tumour necrosis factor-alpha (TNF-α) [3]. Even though there is an increase in knowledge about the pathophysiology of sepsis, therapeutic control of sepsis has advanced slowly.

Ghrelin is a polypeptide hormone comprising 28 amino acids, primarily released in the stomach [4]. It is responsible for increasing both the release of growth hormone (GH) and the appetite. Numerous studies demonstrated that some mammalian peptide hormones have promising effects against sepsis, including vasopressin, oxytocin, human chorionic gonadotropin, ghrelin, and glucagon [5]. The hormone ghrelin has anti-inflammatory effects in disorders affecting many body systems, including the endocrine, immune, digestive, skeletal, respiratory, metabolic, and central nervous systems. Treatment with ghrelin reduces inflammation, which in turn reduces the severity of many conditions such as inflammatory bowel disease, arthritis, sepsis, diabetic nephropathy, obesity, pancreatitis, cachexia, and some rodent models of chronic inflammation [6-9]. Ghrelin suppresses proinflammatory cytokine expres-

sion by macrophages, T lymphocytes, and monocytes [10]. Numerous investigations have verified that ghrelin has an immunomodulatory effect on sepsis. Ghrelin prevents lipopolysaccharide (LPS) stimulated microglia from releasing inflammatory cytokines [11], moreover, it inhibits IL-6 release by LPS-stimulated dopaminergic nerve cells [12]. Exogenous ghrelin significantly reduce LPS-induced synthesis of proinflammatory cytokines in mice [13]. Even 12–24 hours after cecal ligation and puncture (CLP), ghrelin reduced mortality and markedly lowered both pathological scores and clinical parameters of sepsis in mice. IL-1β is a major proinflammatory cytokine responsible for the modulation of hosts' innate immune system response [14]. IL-1β is a cardio-depressant proinflammatory mediator that increases markedly in both human and animal models during sepsis. TLR4 is a unique pattern recognition receptor expressed on the surface of immune cells [15, 16]. TLR4 stimulates the host immunological response towards bacterial, fungal, viral, and malaria infections. NF-κB is a rapid-acting transcription factor that modulates diverse cellular processes and is involved in septic shock syndrome, chronic inflammatory conditions, multiple organ dysfunction, and viral infections. NF-κB augments the synthesis of proinflammatory cytokines, such as TNF-α, IL-12, and IL-1β [17-20].

AIM

The aim of this research is to assess the anti-inflammatory effect of ghrelin in mice models of polymicrobial sepsis.

MATERIALS AND METHODS

ANIMALS PREPARATION

Thirty-five male albino Swiss mice were acquired from the Iraqi Center for Cancer Research. They were maintained at the Faculty of Pharmacy/University of Kufa animal house. They were housed in cages with a 12-hour light/12-hour dark cycle, temperatures ranging from 22-24°C, humidity levels ranging from 60-65%, and unrestricted access to water and food. The study was conducted in the Laboratory of Clinical laboratory department/Faculty of Pharmacy, University of Kufa from December 5, 2022, until February 25, 2023.

STUDY DESIGN

The mice were acclimatized for a week and then randomly divided into five groups of 7 animals each:

- Normal group: Mice were fed their usual diets until the time of sampling.
- Sham group: Mice were subjected to Anaesthesia and laparotomy; the sham group was the negative surgical control group.
- Sepsis group: Mice were subjected to the CLP procedure; it was the positive surgical control group.
- Vehicle group: An equivalent volume of normal saline intraperitoneal injections was given immediately following CLP.
- Ghrelin-treated group: Mice were treated with 80 µg/kg of recombinant human ghrelin intraperitoneal injections immediately following CLP.

Twenty hours after CLP, mice were sacrificed; myocardial tissue and serum samples were collected.

EXPERIMENTAL MODEL OF SEPSIS

According to recent research, this study chose mice to induce polymicrobial sepsis using the CLP model [14]. Briefly, 0.01 mg/g xylazine and 0.1 mg/g ketamine were injected intraperitoneally to mice to induce anesthesia. [21-26]. An abdominal midline incision of 1.5 cm was made. The cecum was ligated beneath the Bauhin valve, double perforated with a 22-gauge needle, and slightly squeezed to force a small stool out of the puncture. Then, the cecum returned to its anatomical position, and a 4-3 surgical suture was used to close the abdominal incisions.

PREPARATION OF GHRELIN

Recombinant pure human ghrelin 95% (Elabscience, USA) was dissolved in normal saline. Then, 80µg\kg ghrelin was administered intraperitoneally immediately after CLP.

SAMPLES COLLECTION

BLOOD SAMPLES

The blood samples were gathered by heart puncture before sacrificing mice. It was placed in a gel tube and left at room temperature for 1 hour. Serum was separated by centrifuging blood for 20 minutes at 4000 rpm. The enzyme-linked immunosorbent assay (ELISA) technique measured serum IL-1β, NF-κB, and TLR4 levels.

TISSUE SAMPLES

The cardiac tissue was fixed in a 10% formaldehyde solution for 20 hours. After dehydration and clearing, cardiac tissue was embedded in a paraffin block, and a 5 µm thick section was sliced using a microtome. Hematoxylin and eosin were employed to stain the tissue slices before being examined under a light microscope.

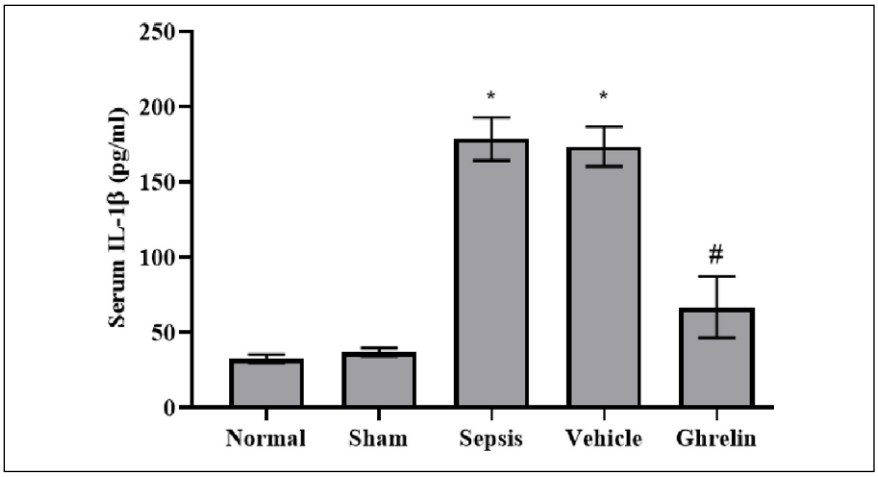

Fig. 1. Serum IL-1β level in the experimental groups: * significant, p<0.001 *vs*. normal or sham groups; # significant, p<0.001 *vs*. sepsis or vehicle groups.

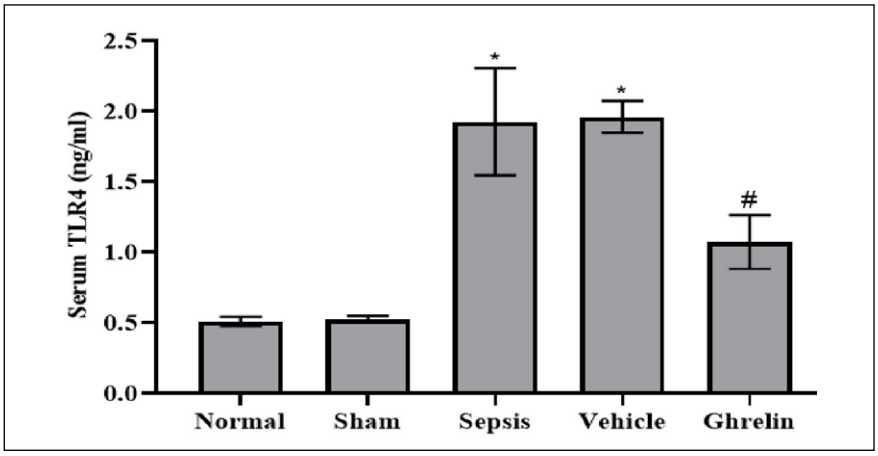

Fig. 2. Serum TLR4 level in the experimental groups: * significant, p<0.001 *vs*. normal or sham groups; # significant, p<0.001 *vs*. sepsis or vehicle groups.

HISTOLOGICAL EXAMINATION

The extent of cardiac damage was evaluated for each cardiac section using an optical microscope, and photographs of the sections were obtained. Histological sections of the heart were scored according to the Zingarelli protocol (36). The criteria for this scoring system were:

- Score 0: There is no damage.
- Score 1: Localized necrosis with interstitial oedema.
- Score 2: Diffused swelling of the cardiomyocytes.
- Score 3: Leukocyte infiltration and contraction band.
- Score 4: Contraction band, neutrophil infiltration, and haemorrhage.

STATISTICAL ANALYSIS

Version 8.1 of GraphPad Prism was employed to conduct the statistical analysis. Mean ± standard error mean (SEM) was used to display the data, and all groups were compared by one-way the analysis of variance (ANOVA) test. The Bonferroni method for multiple comparisons was subsequently employed to conduct post-hoc tests. Histopathological changes were compared between groups by a non-parametric test followed by Dunn's post hoc test. All analyses were considered statistically significant if $P < 0.05$.

RESULTS

EFFECT OF GHRELIN TREATMENT ON IL-1B AFTER POLYMICROBIAL SEPSIS

Serum IL-1β levels were markedly elevated in the sepsis group than in the normal and sham groups (p<0.001). There were no statistically significant variations in serum IL-1β levels between the vehicle and sepsis groups or between the normal and sham groups. Compared to the sepsis and vehicle groups, ghrelin administered immediately after the CLP procedure considerably lowered serum IL-1β levels (p<0.001) (Fig. 1.).

EFFECT OF GHRELIN TREATMENT ON TLR4 AFTER POLYMICROBIAL SEPSIS

Serum TLR4 levels were markedly elevated in the sepsis group than in the normal and sham groups (p<0.001). There were no statistically significant variations in serum TLR4 levels between the vehicle and sepsis groups or between the normal and sham groups. Compared to the sepsis and vehicle groups, ghrelin administered immediately after the CLP procedure considerably lowered serum TLR4 levels (p<0.001) (Fig.2).

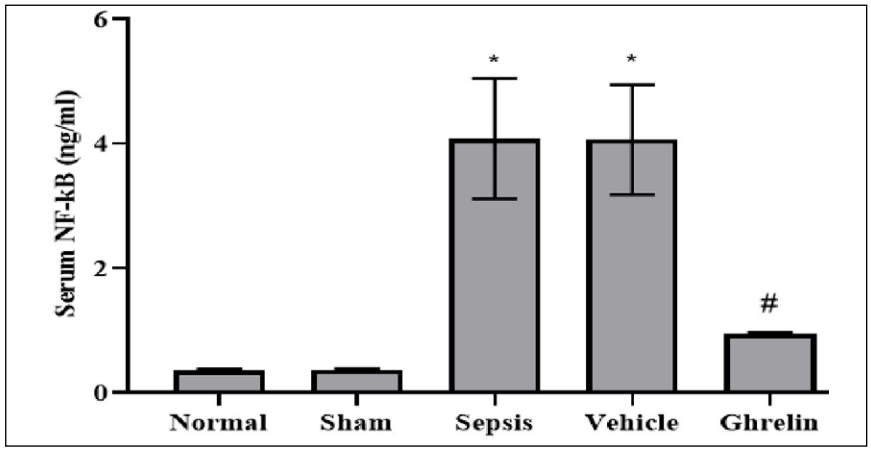

Fig. 3. Serum NF-kB level in the experimental groups: * significant, p<0.001 *vs*. normal or sham groups; # significant, p<0.001 *vs*. sepsis or vehicle groups.

EFFECT OF GHRELIN TREATMENT ON NF-KB AFTER POLYMICROBIAL SEPSIS

Serum NF-κB levels were markedly elevated in the sepsis group than in the normal and sham groups (p<0.001) (Fig.3).

There were no statistically significant variations in serum NF-κB levels between the vehicle and sepsis groups or between the normal and sham groups. Compared to the sepsis and vehicle groups, ghrelin administered immediately after the CLP procedure considerably lowered serum NF-κB levels (p<0.001) (Fig.3).

HISTOPATHOLOGICAL CHANGES OF MYOCARDIAL TISSUE AFTER POLYMICROBIAL SEPSIS

Myocardium tissue of the normal and sham groups showed normal architecture with distinct myocyte boundaries and without erythrocyte leakage and leukocyte infiltration (Fig.4. A-B).

All mice in these groups have normal histopathological findings (score 0), as shown in (Fig.5). The sepsis and vehicle groups had a highly severe myocardial injury (score 4), characterized by the appearance of contraction bands, interstitial oedema, leukocyte infiltration, and erythrocyte extravasation (Fig.4 C-D). The mean histological score was significantly higher in the vehicle and sepsis groups than in the normal and sham groups (p<0.001) (Fig.5). The ghrelin-treated group had a mild myocardial injury (score 1) (Fig.4 E). The mean histological score was markedly lower in the ghrelin-treated group than in the sepsis and vehicle groups (p<0.01) (Fig.5).

DISCUSSION

Sepsis is an unregulated systemic inflammatory reaction that could lead to death from multiple organ failure. This study found significantly higher serum levels of IL-1β in vehicle and sepsis groups compared to the normal and sham groups. In contrast, the ghrelin-treated group had markedly lower serum IL-1β levels than the vehicle and sepsis groups. Yousif et al. (2020) [27] found that IL-1β levels in heart tissue and plasma were elevated in septic mice, which was related to reduce cardiac contractility and induced myocardial damage. Similarly, Zigam et al. (2023) [22] demonstrated that serum IL-1β levels increased significantly 24 hours after CLP surgery compared to the sham group. In contrast, Corrêa da Silva et al. (2019) [28] showed that ghrelin has an immunoregulatory effect on LPS-activated macrophage, as demonstrated by stimulation of IL-12 expression and suppression of IL-1β release. Moreover, Shao et al. (2020) [29] found that ghrelin injection decreased the synthesis of IL-1β in the lung tissues in a mouse model of acute lung injury. Qiu et al. (2022) [30] showed that ghrelin administration had a considerable suppressive action on the expression of IL-1β compared to the rat model of subarachnoid haemorrhage. According to our results, it is evident that the studies mentioned above all support the results we obtained. This study found a significantly higher serum level of TLR4 in sepsis and vehicle groups compared to the normal and sham groups. By contrast, the ghrelin-treated group had markedly lower serum levels of TLR4 compared to the vehicle and sepsis groups. According to Wang et al. (2019), CLP-induced sepsis stimulates the NF-κB phosphorylation and TLR4 activation in the lung tissue of rats. In contrast, Sun et al. (2016) [24] demonstrated that ghrelin inhibited the protein expression of TLR4 in mice after myocardial ischemia/reperfusion injury. Wang et al. (2019) revealed that the ability of ghrelin to reduce apoptosis and inflammation could be related to the inhibition of TLR4/NF-κB in the testes of mice subjected to immobilization stress. Liu et al. (2023) show that the TLR4 pathway was activated in response

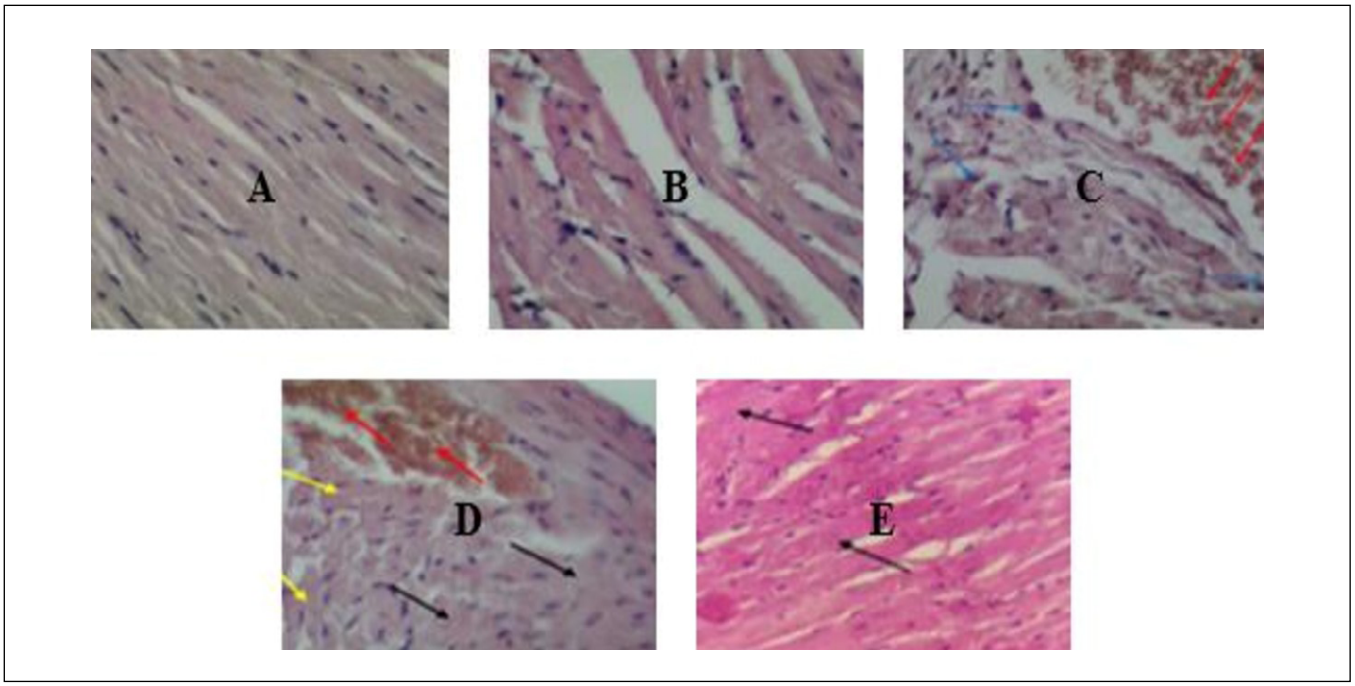

Fig. 4. Photograph of the heart section stained with H&E (X400). A: normal group showed normal architecture (score 0); B: sham group showed normal architecture (score 0); C: sepsis group, showed haemorrhage (red arrows) and leukocyte infiltration (blue arrows); D: vehicle group showed haemorrhage (red arrows), cell swelling (yellow arrows), and necrosis (black arrows); E: ghrelin group showed mild necrosis (black arrows).

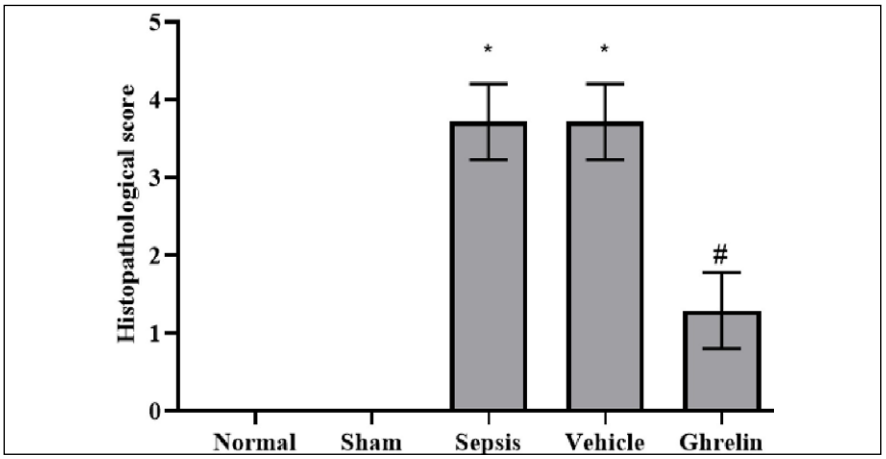

Fig. 5. Histopathological score in the experimental groups: * significant, $p<0.001$ *vs*. normal or sham groups; # significant, $p<0.01$ *vs*. sepsis or vehicle groups.

to high glucose or hyperglycemia and significantly suppressed by ghrelin administration in vitro and in vivo. The current study revealed a significantly higher serum NF-κB level in sepsis and vehicle groups compared to the normal and sham groups. However, the serum NF-κB level decreased substantially in the ghrelin-treated group compared to the sepsis and vehicle groups. Yousif et al. (2020) [27] found that activation of NF-κB and phosphorylation of mitogen-activated protein kinase (MAPK) are increased in septic mice and cause a decrease in left ventricle function. In addition, it was reported that MAPK/NF-κB pathway activation is associated with increased plasma TNF-α, IL-6, and IL-1β levels, causing a further decrease in left ventricle function. Yildiz et al. (2021) revealed that the NF-κB expression was substantially increased in the lung tissue of CLP rats. While Liu et al. (2019) demonstrated that ghrelin administration significantly reduced NF-κB expression in rats' autoimmune encephalomyelitis models, suggesting its Neuroprotective effects. Qu et al. (2019) demonstrated that ghrelin treatment reduces NF-κB activation in mouse models of psoriasis. Moreover, Zheng et al. (2017) [14] showed that ghrelin inhibited the translocation of NF-κB in alveolar macrophages obtained from septic rats. Song et al. (2021) reported that ghrelin suppresses inflammation and autophagy associated with chronic obstructive pulmonary disease by blocking the NF-κB signalling pathways. In polymicrobial sepsis, oxidative stress and excessive production of proinflammatory cytokines result in myocardial histological abnormalities. These mediators cause cardiac tissue necrosis, pycnosis, karyolysis, and karyorrhexis.

This study showed that vehicle and sepsis groups had substantially higher cardiac tissue injury than normal and sham groups. The histopathological damage scores were mostly highly severe (score 4) for sepsis and vehicle groups. While ghrelin administration significantly reduces cardiac tissue injury compared to sepsis and vehicle groups. The ghrelin-treated group had mild (score1) histopathological damage scores. Topcu et al. (2022) indicated that elevated proinflammatory cytokine and oxidative stress in septic cardiac tissue result in severe injury manifested as degenerative cardiomyocytes, vascular congestion, and oedema. However, Topcu et al. (2022) demonstrated that ghrelin could protect rats against septic-induced cardiotoxicity by reducing the inflammatory response and apoptosis. A recent study showed that ghrelin ameliorates thyroxin-induced myocardial injury in rats through anti-inflammatory effects, antioxidant effects, and decreased expression of heart renin-angiotensin system components.

CONCLUSIONS

Our study concluded that ghrelin exerts anti-inflammatory effects in polymicrobial sepsis, as indicated by a considerable decrease in proinflammatory cytokines levels, including IL-1β, NF-κB and TLR4.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Evaluation of cardiovascular complaints in higher education students experiencing elevated level of situational anxiety during the martial law and peacetime

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ABSTRACT

Aim: To calculate the average score of situational anxiety level and compare the risk of developing cardiovascular complaints in higher education students from the country in the martial law and the country in peacetime according to the respondents' level of situational anxiety. To analyze the impact of place of residence on the frequency of complaints among students with an elevated level of situational anxiety in both countries.

Materials and Methods: Descriptive and inferential statistics: cluster method, qualitative analysis method; exploratory observational analytical short-term case-control study. The State-Trait Anxiety Inventory (STAI) [1] questionnaire was used to calculate the situational anxiety level indicator. Calculations were conducted using Excel and MedStat software.

Results: The research results demonstrated higher level of situational anxiety among students who belonged to higher educational institutions in the country under the martial law. The odds ratio is 0,42 (95% CI 0,27-0,66), indicating that the elevated level of situational anxiety was encountered more frequently in the study group compared to the control group of students.

Conclusions: The average score of situational anxiety level was found to be higher among students from a country where the martial law has been implemented. The presence of the martial law in the country was identified as a factor associated with an increased risk of complaints from the cardiovascular system among students. The risk of developing cardiovascular complaints in the context of elevated situational anxiety is confirmed.

KEY WORDS: Armed Conflict, Cardiovascular Diseases, Public Health, Stress Disorders

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INTRODUCTION

Two years into the martial law in Ukraine are ongoing; the multifaceted repercussions of this period on the nation's well-being cannot be overlooked. Beyond its immediate impact on political and social structures, the prolonged state of military preparedness has cast a shadow over the health of the population, particularly the younger generation. Hans Selye emphasized several key stress pathogenesis concepts, with particular distinction given to the following three:

- The type of individual (species of animal) experiencing stress does not determine the physiological response to it.
- The general adaptation syndrome encompasses three specific stages representing the defensive reaction when exposed to a recurring stressor.
- The likelihood of developing an adaptation disease increases with the strength and duration of the body's defensive response to stress [1].

The data collected from respondents regarding the emergence of cardiovascular complaints during the martial law suggest a confirmation of the third proposition. This confirmation gradually becomes evident, aligning with Selye's main purpose for this proposition, which is to identify risk factors for stress-related psychosomatic illnesses, particularly cardiovascular diseases [2].There are the various adverse effects that the martial law has influence on the health of Ukrainians, shedding light on the implications for the well-being of the country's youth. As we navigate through the intricate web of factors influencing health in times of conflict, it becomes imperative to understand the nuanced interplay between the declared the martial law and the overall health landscape, with a specific focus on the well-being of the younger demographic [3].

AIM

To calculate the average score of situational anxiety level and compare the risk of developing cardiovascular complaints in higher education students from the country in the martial law and the country in peacetime according to the respondents' level of situational anxiety. To analyze the impact of place of residence on the frequency of complaints among students with an elevated level of situational anxiety in both countries.

MATERIALS AND METHODS

Descriptive and inferential statistics: cluster method, qualitative analysis method; exploratory observational analytical short-term case-control study. Information was collected by distributing surveys with Google Forms online. Online survey distribution was preferred due to the method's accessibility, speed of dissemination and respondent pool expansion. Additionally, we considered ecological considerations to preserve forests and reduce carbon dioxide emissions. The study group consisted of the students who were exposed to the conditions of the martial law for a period of two full years; exposure included stress due to massive missile strikes, attacks by unmanned aerial vehicles, experience of incursions into the territory they lived, forced displacement/residence in an occupied area and so on. In an anonymous online survey, 102 participants from various age groups in Ukraine took part, including 70 female respondents (68.6%) and 32 male respondents (31.4%). The age distribution of respondents included: 17-18 years (2.9%), 19-20 years (18.6%), 21-22 years (27.5%), 23-24 years (24.5%), 25-26 years (14.7%), 27-28 years (4.9%), 29-30 years (3.9%), and over 30 years (3%). The first section of the questionnaire included general questions about the respondents' characteristics and questions from The State-Trait Anxiety Inventory (STAI) [1] questionnaire. The last question in the first section of the survey clarified whether respondents reported cardiovascular system complaints from 24.02.22 until the time of the survey (February, 2024). In case of a positive response, the second section of the questionnaire opened, focusing on detailing the complaints. The control group comprised higher education students from a country where the martial law has not been declared, no armed conflicts were recorded. At the same time 94 students from higher education institutions in Poland participated the survey, comprising 66 female respondents (70.2%) and 28 male respondents (29.8%). The age distribution of respondents included: 17-18 years (4.3%), 19-20 years (17%), 21-22 years (17%), 23-24 years (43.6%), 25-26 years (12.8%), 27-28 years (4.3%), and 29-30 years (1%). The first section of the questionnaire was identical to the first section of the survey for students from Ukraine. The second section of the questionnaire was dedicated to detailing complaints, but it also analyzed domestic factors during peacetime that students associated with the mentioned complaints. This survey format is validated from the previous studies [4,5]. Calculations were conducted using Excel and MedStat software.

RESULTS

From the entire sample of students from Ukraine, the situational anxiety level indicator for 20 of them remained within the normal range - up to 30 points, for 39 students, the indicator ranged from 30 to 45 points, indicating a moderate increase in situational anxiety. In the majority, 43 individuals had this indicator at 46 points or higher, indicating a significant increase in the level of situational anxiety. The vast majority of the Polish students – 44 people – scored 30 points or less, indicating a situational anxiety level within the normal range; 28 students scored between 30-45 points, and the minority, consisting of 22 students, scored 46 points or more, suggesting a higher level of situational anxiety (Table 1).

Upon detecting the influence of residing in Ukraine on the elevation of the situational anxiety level indicator, it was found that the risk ratio is 0.42 (95% CI 0.27-0.66). In the experimental group, the event occurs more frequently than in the control group (Table 2). In those students who lived in Ukraine during the period of martial law at the time of the study, an elevated level of situational anxiety was more common compared to the control group of students from Poland.

An investigation was carried out to examine the odds of developing cardiovascular complaints in the presence of elevated anxiety, separately for Ukrainian and Polish students. It was found that for Ukrainian students with the elevated level of situational anxiety the odds ratio is 2.29 (95% CI 1.05-5.01). The risk of developing complaints from the cardiovascular system is higher in Ukrainian students whose level of situational anxiety was moderately or significantly elevated than in students who don't have it. Furthermore, for Polish students, the odds ratio is 3.52 (95% CI 1.82-6.81). It means the event occurs more rarely in the group of students without any changes in their anxiety level.

Analysis was conducted to assess the influence of residing in Ukraine on the development of complaints from the cardiovascular system («Pathology») among students who had an elevated level of situational anxiety, compared to students from Poland (Table 3).

Table 1. Data on the level of situational anxiety and complaints from the cardiovascular system among students obtained from the survey

The anxiety level indicator	Amount of students	Ukraine (Case)	Amount of students	Poland (Control)
The normal range (up to 30 points)	20	15 did not report complaints	44	36 did not report complaints
		5 reported complaints		8 reported complaints
Moderately elevated (30-45 points inclusive)	39	17 did not report complaints	28	11 did not report complaints
		22 reported complaints		17 reported complaints
Significantly elevated (46 points or more)	43	18 did not report complaints	22	7 did not report complaints
		25 reported complaints		15 reported complaints
Total	102		94	

Table 2. Table of calculations on the impact of residing in Ukraine on the elevation of the situational anxiety level indicator (OR=0.42 [95% CI 0.27-0.66])

	Ukrainian students (Case)	Polish students (Control)
The level of situational anxiety within the normal range	20	44
The level of situational anxiety is elevated (moderately + significantly)	82	50

Table 3. Comparison of the number of students in two countries who experienced elevated level of situational anxiety

	Ukrainian students	Polish students
Pathology	47	32
Without pathology	35	18
Total	82	50

Table 4. Table of comparative risk of pathology amid elevated levels of situational anxiety in Ukrainian and Polish students

The indicator	Ukrainian students (n=102)	Polish students (n=94)	The significance level, p
Risk of pathology	52 (51,0%)	40 (42,6%)	<0,001

The normality of the distribution was checked using the Shapiro-Wilk test for both indicators. For both, the distribution differs from normal, $p < 0,05$. Percentage of «Pathology» (D_1) for Ukrainian students (determination of the confidence interval; Fisher's angular transformation method; Sample size: N=102) was 51.0% with interval estimate $41.2\% <= D_1 <= 60.7\%$ at a significance level of p=0.05. Percentage of «Pathology» (D_2) for Polish students (determination of the confidence interval; Fisher's angular transformation method; Sample size: N=94) was 42.6% with interval estimate $32.7\% <= D_2 <= 52.8\%$ at a significance level of p=0.05 (Table 4, Fig. 1.).

The two groups were compared using the chi-square test with a two-sided critical region. Variables have 2 levels. Chi-square = 0.98, degrees of freedom k = 1. The difference is not statistically significant at the significance level, p = 0.323. Therefore, under conditions of elevated levels of situational anxiety, there is a risk of developing cardiovascular complaints for students in higher education institutions, regardless of the country they are in. However, for students in the both countries, the risk of developing cardiovascular complaints in the context of elevated situational anxiety has been confirmed: for Ukraine, the odds ratio is 2.29 (95% CI 1.05-5.01); for Poland, the odds ratio is 3.52 (95% CI 1.82-6.81).

For students from Ukraine, an additional question was separately added: «How has the condition of your cardiovascular system changed based on subjective feelings compared to the previous year?» This question was included because the questionnaire was distributed among students who participated in the survey for our previous research. The responses to this question were as follows: 26 students (50%) chose the answer «Remained identical, without changes»; 24 students (46.2%) selected the answer «Deteriorated, the number of complaints increased»; 2 students (3.8%) chose the answer «Improved, the number of complaints decreased» (Fig. 2.).

Students from Poland were offered options for responses regarding domestic reasons during peacetime, which could be associated with the increase in situational anxiety and corresponding complaints from the cardiovascular system. The reasons were distributed

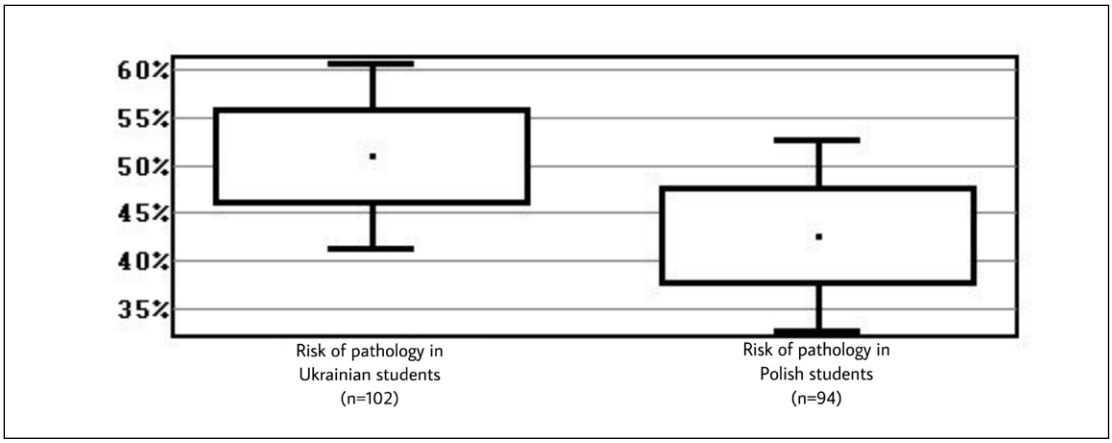

Fig. 1. Comparative risk of pathology amid elevated levels of situational anxiety in Ukrainian and Polish students, standart error and 95% CI.

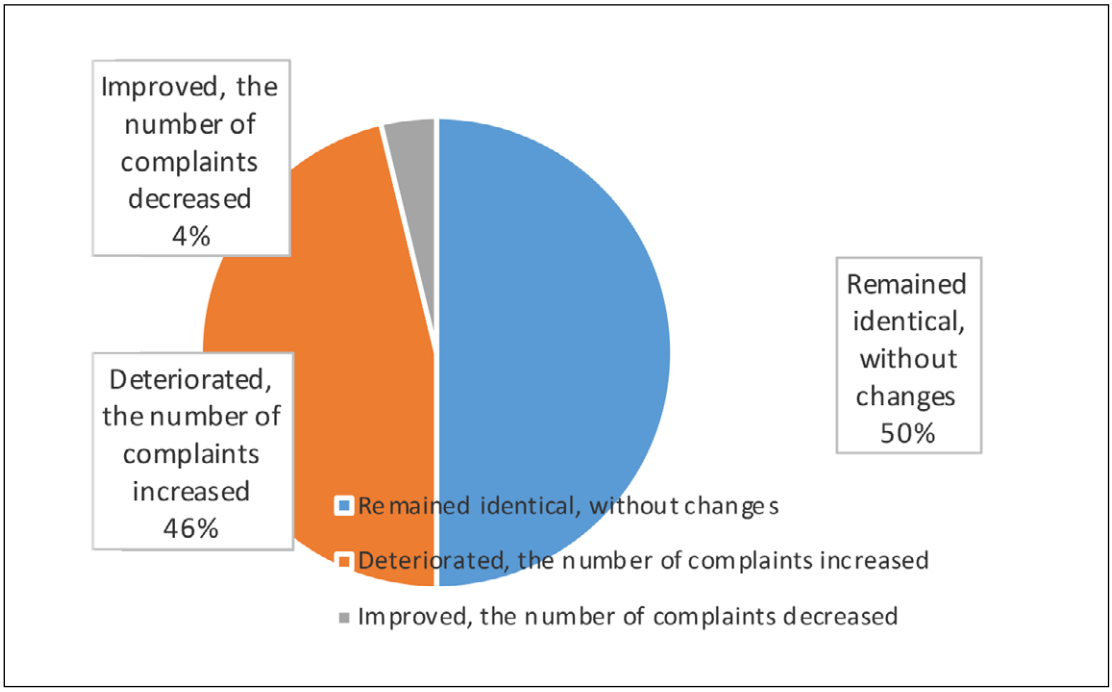

Fig. 2. Subjective Assessment of the Cardiovascular System State among Higher Education Students in Ukraine.

as follows: «Studying or working» - 43 students (78,2% of 55 Polish students with correspondent complaints), «Family relationship» - 17 (30,9%), «International news» - 12 (21,8%) students, «Global ecological conditions» - 3 (5,5%) students, «Inherent anomalies» - 3 (5,5%) students.

DISCUSSION

The issue of predicting cardiovascular diseases in the context of elevated anxiety levels has been studied for a long time. In 2011 a study focusing on the correlation between the level of C-reactive protein and depression and anxiety in patients with ischemic heart disease was published [4]. This research demonstrated a connection between depression, anxiety, and an increase in the level of C-reactive protein - a marker of systemic inflammation, which has been consistently shown to predict the risk of ischemic heart disease: «The research was performed in 80 patients (n = 80), mean age 60 ± 15 years. These patients have no high cholesterol level, high body mass index and n = 64 (80%) of them are no smoker. To evaluate depression we used Beck depression scale. Anxiety was assessed by the Spilberger State-trait anxiety scale. CRP was measured in venous blood. Results show that increased level of C-reactive protein was found in aorto-coronary bypass graft surgery group n = 28 (70%), in angioplasty group C-reactive protein n = 12 (30%); $\chi^2 = 6.40$ p = 0.012. In angioplasty group patients who had increased level of CRP had high degree of depression p = 0.001. In these group was revealed high degree of trait anxiety

$p < 0.001$ too. In aorto-coronary bypass surgery group elevated level of CRP was associated with high degree of depression $p = 0.001$» [4].

The topic of the emergence of complaints from the cardiovascular system among students in the context of a state of war in the country has been studied since the beginning of the full-scale invasion. The results of this research confirm the hypotheses formed during previous studies[5, 6]. The first survey was conducted among students of higher education institutions from all regions of Ukraine and included 411 individuals in the sample[4]. About 296 individuals (72%) of the 411 respondents reported manifestations of complaints from the cardiovascular system after February 24, 2022 (September 16, 2022). At that time, respondents most often associated the appearance of complaints from the cardiovascular system with emotional exhaustion (243 individuals or 79.7%), news (210 individuals or 68.9%), lack of sleep and sleep disturbances (201 individuals or 65.9%), sounds of explosions/air defense operations (189 individuals or 62%), as well as the sound of air raid sirens (165 individuals or 54.1%). In 2022, another study was conducted on students from Ukraine. At that time, 123 students from higher education institutions were surveyed, resulting in the hypothesis that there is an increased risk of complaints from the cardiovascular system among students during a state of war due to the factor of increased anxiety. In the surveyed individuals, the odds ratio was 5.08 (95% CI 2.39-7.76)[5]. The most common complaints reported by students then included episodes of tachycardia, pronounced sensation of palpitations, dizziness, pain in the chest area, shortness of breath during physical exertion. About 87% of the surveyed students who reported the appearance of complaints from the cardiovascular system or exacerbation of pre-existing ones associated them with the wartime situation in the country. In our current study, the hypothesis formed in previous works has been confirmed. Data collection took place during the second half of February, a period when some students in Poland were undergoing exam sessions, including LEK exam. The obtained data on anxiety levels among students from Warsaw and Olsztyn are likely associated with this, as one of the leading causes of anxiety chosen by students was «Studying or working.» However, overall indicators were less pronounced when compared to students who assessed their stress from the perspective of living in the martial law. Consequently, we also obtained data indicating that under any external conditions, if the anxiety level is elevated, there is a risk of developing complaints from the cardiovascular system in students. At the same time, the level of situational anxiety is higher among students from Ukraine, so we can assume that for them, these risks may be somewhat higher. Anxiety holds direct relevance for uncovering mechanisms of cardiopathogenesis, developing novel therapeutic strategies, and initiating clinical interventions in the population at risk of developing heart disease [7]. The topic of this work requires further development and analysis.

CONCLUSIONS

The average score of situational anxiety level was found to be higher among students from a country where the martial law has been implemented. The presence of the martial law in the country was identified as a factor associated with an increased risk of complaints from the cardiovascular system among students. The risk of developing cardiovascular complaints in the context of elevated situational anxiety is confirmed.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

New training, new attitudes: non-clinical components in Ukrainian medical PHDs training (regarding critical thinking, academic integrity and artificial intelligence use)

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ABSTRACT

Aim: The paper studies the attitude to critical thinking, academic integrity and the Artificial Intelligence use of the Ukrainian medical PhD students.

Materials and Methods: In 2023, 56 medical PhD students from the Bogomolets National Medical University, Kyiv, Ukraine, underwent the survey. The participation was voluntary, upon the oral consent. The data included in the survey questions include various aspects related to critical thinking, analysis skills, and attitudes towards plagiarism.

Results: A significant majority of the medical PhD students (75%) place high importance on critical thinking. While a majority (89.29%) apply analysis and critical thinking skills in their English studies, there's a notable percentage (7.14%) that is uncertain. Although most are aware of the unacceptability of cheating and plagiarism (75%), a small proportion admit to having plagiarized (12.5%). Only 30.4% of the respondents reported using GPT Chat for study. Responses to witnessing peers plagiarize or using Artificial Intelligence show a varied attitude, with many expressing unwillingness to report such incidents (30.36%).

Conclusions: The survey highlights the recognized importance of critical thinking in academic study among medical PhD students, while also points to areas where attitudes and practices regarding these skills could be improved. The study shows a vast area for improvement regarding academic integrity, as almost one-third of respondents need more defined standards. This definitely puts some questions before the present medical postgraduate education, and requires change of the educational paradigm, clear rules of academic conduct, and a system of control.

KEY WORDS: Postgraduate education, integrity, Ukrainian PhDs

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INTRODUCTION

In the medical education today, the introduction of non-clinical components (such as critical thinking and academic integrity) into medical PhD (Doctors of Philosophy) training programs is becoming increasingly important. This article studies the reform Ukrainian medical PhD programs, since 2017, and particularly focuses on the integration of these essential skills into the curriculum. The push to this reflects a global trend, not only in Ukraine, and it acknowledges the significance of physician training, beyond the traditional clinical competencies.

Nowadays, Ukraine, with its rich history in medical education, is at the forefront of redefining medical PhD training. Reforming the postgraduate education has not just responded to the requirements of modern healthcare, it represented active training approach. In the article we are going to study the attitude of the medical PhDs and perception of critical thinking and academic integrity in their curricula, which originally aimed to train clinically and intellectually effective medical researchers. We suppose that the need for such medical education changes may be explained for the progressing medical environment, its technological progress, ethical issues, and evidence-based practice. Critical thinking is the basis for academic and professional performance, as it helps us manage challenges. Academic integrity, on the other hand, provides a sense of ethical responsibility, and ensures that the future medical PhDs will keep to the highest standards of honesty and professionalism. Present technology, including the AI, tremendously re-formats the real efforts of the academicians, and requires a new educational philosophy.

In order to study the current perception by medical PhDs of the non-clinical components in their curricula, we have held the survey at Bogomolets National Medical University, Kyiv, Ukraine. It evaluates the current state of non-clinical training among Ukrainian medical PhD students, focusing on their attitudes towards critical thinking and academic integrity. By this, we meant to study the effectiveness of the current teaching PHD strategies, and propose improvements.

AIM

The aim of the article is to study the views on such significant issues of postgraduate education as critical thinking and academic integrity, to learn the perception of these significant academic notions by the Ukrainian medical PhD students, and to offer the possible ways of the education perfection.

MATERIALS AND METHODS

In 2023, 56 medical PhD students from the Bogomolets National Medical University, Kyiv, Ukraine, underwent the survey. The participation was voluntary, upon the oral consent, which explains the small size of a sample, as many medical PhD students preferred not to answer the questions. Furthermore, it needs mentioning, that all the respondents are the Ukrainian citizens, experiencing war attacks of Russia, which may explain their stressed mood and absence of will to engage in any survey.

The data included in the survey questions include various aspects related to critical thinking, analysis skills, and attitudes towards plagiarism. The respondents stated their gender, age, rated the importance of critical thinking ("very important", "important". "undefined", "not very important" and "insignificant"), the necessity of teaching critical thinking in universities(" it is necessary", "it is not necessary", " it is not necessary", "It is classified", or the free choice), experience of application of analysis in the English classes and working with the texts("I do it often", "I do it sometimes", "I don't do it", "I rarely do it", "I never do it"), experience of critical analysis of published sources ("Yes, I do it", "It depends", " NO, I don't do it"), critical evaluation of teachers ("Yes, always", "More yes than no", "It depends", "More no than yes", "No"), necessity of critical thinking ("Yes,", "No", "It depends"), and acceptability of using someone's work from Internet("It is acceptable", "It is more acceptable than unacceptable", "It is not acceptable", "It is more unacceptable than acceptable", "I don't know"), awareness of unacceptability of plagiarism(" I have been told about it", ?I haven't been told about it", " I don't recollect being told about it"), personal experience with plagiarism(" I have plagiarised", " I have never plagiarised", " I can't recollect any cases"), and the reaction to peers plagiarism("I would report such issues", "I wouldn't report such issues", "I don't care about such issues"). The last set of questions was related to the AI (Artificial Intelligence) use: the experience of the AI use in preparation for studies, the experience of making the AI write something for them, and attitude to the AI ("Is the AI use acceptable?", with answers "Acceptable", "Somewhat acceptable", "It's hard to say", "More unacceptable", "Unacceptable").

RESULTS

A close analysis of the data shows several trends and perspectives. The cohort exhibits a near-even gender distribution, with 51.79% male and 48.21% female respondents, which generally corresponds to distribution of male and female medical PhD students in Bogomolets National Medical University. Regarding age, the largest group comprises younger individuals (20-30 years old), representing half of the respondents. Those aged 30-40 years make up 30.36%, while 19.64% are older than 40 years, highlighting a diverse age range among the students.

A substantial majority (75%) of the medical PhD students consider critical thinking skills to be 'Very important'. An additional 21.43% find these skills more important than not, suggesting a strong overall recognition of the value of critical thinking in their academic journey. Only a small fraction view critical thinking as non-important (1.79%) or express indifference (1.79%).

As for teaching critical skills in the medical universities, an overwhelming 89.29% of the students advocate for the inclusion of critical thinking and analysis skills in university curricula across all specialties. A minority (7.14%) believe these skills should not be taught in all specialties, and an even smaller group (3.57%) deems them unimportant, indicating a predominant belief in the necessity of these skills in higher education.

Nearly half of the respondents (48.21%) often apply analysis skills in their academic and medical English classes, and a similar proportion (46.43%) do so sometimes, which suggests a widespread application of these skills in postgraduate humanities studies. However, a small group either rarely applies (1.79%) or does not apply (1.79%) these skills, with an equal percentage unsure about what analysis skills include.

The application of critical thinking skills while working with medical English texts is also significant, with 50% trying to apply them and 44.64% confidently doing so. A small percentage (5.36%) of the respondents sees no point in applying these skills in this context, which reflects varied approaches to critical thinking in academic exercises. This trend is reflected also in answers about critical evaluation of ANY materials published, where 75% stated they did it often, and 23.2% stated "It depends". An important trend is shown in critical attitude of the respondents to the teachers, as 48.2% always evaluate their teachers' words, and 32.1% are more likely to do it, which overall forms the majority of critically thinking cohort. Only 14.3% stated "It depends", which could also be added, under the appropriate circumstances, to those who critically evaluate everything.

As for the plagiarism and cheating unacceptability, three-quarters of the medical PhDs acknowledge the

unacceptability of cheating and plagiarism, and this indicates their high level of awareness of academic integrity. However, 23.21% do not share this view, and a small fraction (1.79%) provided non-specific responses. While most PhD students (87.50%) did not report plagiarizing during their PhD studies, 12.50% admit to it, which highlights ongoing challenges in ensuring academic honesty. The PhD students' responses to peers plagiarizing are varied. A significant portion is uncertain (32.14%) about how they would react, and 30.36% are more likely to not complain. Those who would definitely not report such incidents make up 25%, while only a minority would likely (7.14%) or definitely (5.36%) report plagiarizing peers, which illustrates a variety of attitudes towards academic misconduct.

While artificial intelligence has been introduced in the Ukrainian web space, and has been active for nearly a year, its adoption among Ukrainian PhD students appears limited. Only 30.4% of these students reported using GPT Chat for study, and a smaller fraction, 17.9%, acknowledged using GPT (or any other AI application) for writing essays or abstracts. This modest acknowledgement might not necessarily reflect a reluctance to apply AI technologies but rather a delayed adjustment to technological progress. Interestingly, opinions on the use of GPT for academic purposes are divided: 32.1% of respondents view it as unacceptable, equating it to cheating, 25% see it as somewhat acceptable under certain conditions, and 33.9% remain undecided, possibly due to a lack of understanding of its full capabilities and implications. However, we should mention that the age distribution of the group means a huge share of young students, who should be prone to use all newest technological advanced. Due to this, the retarded acceptance by the PhDs of AI technologies seems more than strange.

DISCUSSION

We justify the obtained results, comparing it to the similar studies in the world, as the issue of non-clinical component of the medical training has been raised by authors abroad. Most authors agree to the significance of critical thinking and academic integrity in undergraduate medical education, although the theme remains unleashed regarding the postgraduate education. Shirazi & Heidari [1] have studied the relationship between critical thinking skills, learning styles, and academic achievement in nursing students. Their work puts emphasis on importance of critical thinking in nursing education, it highlights how different learning styles can affect academic success. Similarly, Sullivan et al. [2] have discussed methods of improving clinical teaching of critical thinking, high-quality care, and equity. The authors focused on the importance of integrating these elements into CME, and they emphasize effective training strategies. Also, Hanlon et al. [3] have assessed critical thinking in dental students, as they use the Health Sciences Reasoning Test, where they compare critical thinking abilities across different levels of dental education and practice. Additionally, Borglin [4] supports critical thinking, as well as academic writing skills as the crucial in nurse education. The author underscores the significance of these skills in nursing practice, he suggests methods how to integrate them into nursing curricula. Also, Mitchell & Carroll [5] have dealt with academic and research misconduct in PhD education, as they are focusing on issues with students and supervisors. The paper describes ethical doctoral challenges, and suggests ways to improve the academic integrity. Regarding other countries, Rajovic et al. [6] have examined attitudes to plagiarism among PhD medical students in Serbia, while Rokni et al. [7] have investigated the prevalence of plagiarism in Iran, where a broad perspective on academic integrity issues in the region has been presented. Cerdà-Navarro et al. [8] have analyzed academic integrity policies against academic misconduct in postgraduate studies, and focuses on Spanish universities. Ng et al. [9] have explored the integration of clinical and research training in MD-PhD programs, Bonham [10] studies the history of MD-PhD training and discusses its future prospects. Overall, the papers could be grouped into three categories: those who talk about the critical thinking and academic achievement (Shirazi & Heidari [1] and Hanlon et al. [3], Borglin [4]); about academic integrity and misconduct: Mitchell & Carroll [5] and Rajovic et al.[6], Rokni et al. [7] and Cerdà-Navarro et al. [8]; and about the structure and effectiveness of medical training programs (Sullivan et al.[2], Ng. et al. [9] and Bonham [10]. Overall, all authors admit significance of the critical thinking skills. And most authors admit the problem of academic misconduct, plagiarism and cheating which is growing among the PhDs. In fact, no foreign study has been dedicated to the perception by the PhDs of certain significant aspects of their study, such as critical thinking necessity, or the AI use, and the theme is found to be extremely fascinating.

Our study reflects attitude of the Bogomolets PhD students to two most important issues of education: critical thinking and academic integrity, including the AI. From this analysis, it is evident that a significant majority of the medical PhD students place high importance on critical thinking and believe it should be taught in universities. While a majority apply analysis and critical thinking skills in their English studies, there's

a percentage that is uncertain or does not see the point in doing so, particularly in language studies. This indicates potential gaps in understanding or valuing these skills among some PhD students and puts challenges before the curriculum of the PhDs training. The course "Critical thinking" is not taught directly, though the medical PhDs study other numerous courses, such as "Philosophy of Science", "Methods of Research", and, anyway, a certain proportion of the surveyed does not regard critical thinking as a significant skill for an academician, which means necessity for transformation of curriculum, or more thorough selection of the applicants at enrolment.

A vivid example of application of the critical skills is their use at a certain course class: English, where almost a half stated use of skills "sometimes", which means mechanical uptake of the knowledge and material. So, by transitioning from the overall understanding of the critical skills necessity by majority, and narrowing the issue to certain courses, with decreasing group of those who find them necessary, we realize that emphasis on integration of critical skills in teaching EVERY course should be done, and it should be done long before the Postgraduate course, but not only during the undergraduate studies.

Critical thinking skills, taught during the undergraduate education, will lead to the development of the critical perception of any information, including that reproduced by medical teachers. Of the surveyed, almost one third stated they were more likely to critically evaluate their teachers' words, and a small portion hesitated, which, under the authoritative circumstances and absence of academic school will lead to poor critical thinking skills after graduation. So, we would like to stress upon the necessity of application of critical skills, starting from the first university years, which would motivate both students and their teachers. But this requires a thorough change of educational paradigm, on the state level.

In terms of academic integrity, while there is a high level of awareness of the unacceptability of cheating and plagiarism, a worrying proportion of Medical PhD students admit to having plagiarized. Additionally, the varied responses to witnessing peers plagiarize suggest a reluctance or uncertainty in addressing academic misconduct among peers. All this necessitates several steps required by the educational institutions. Firstly, during the undergraduate education, the unacceptability of plagiarising should be taught, and this should be supported on the state level, incorporated into practice of checking the students' papers by anti-plagiarism software and adopting punishments for plagiarising. Secondly, to prevent plagiarising, extra courses should be introduced, teaching how to write their own texts, analyze the sources, review the works and cite them properly. This should compose the education component, the same as a set of theoretical medical or clinical courses. Thirdly, the model of academic integrity should be adopted on the state educational level (which has not been done in Ukraine yet), with clear rules of game, awards and punishments. The absence of such regulation, and undefined rules lead to not serious attitude of the students to academic integrity.

A separate issue is the AI use, regarding the academic integrity. Being a newly introduced software, it has not gained popularity among the Ukrainian PhDs yet, although its use may break all rules of academic conduct, and, both the Ukrainian students and teachers need clarification on what it represents, how it could be used without breaking the academic conduct rules and cheating. All this requires changes of the curriculum for the undergraduate students, introduction of the AI use into their study, and a separate course for the medical PhD courses teachers, to clarify the AI application use and prevent misconduct manifestations.

CONCLUSIONS

The significance of critical thinking for the Ukrainian medical PhD students is undeniable, although there are evident areas where practices regarding these skills could be improved or studied thoroughly. The survey shows high importance which the medical PhDs place on the critical thinking.

Regarding the academic integrity, the study shows a vast area for improvement, as a certain percentage of the surveyed medical PhD students need more defined standards of academic integrity, particularly regarding the AI. All this necessitates for a deeper introduction of critical thinking skills, both during the undergraduate and postgraduate studies, and the academic integrity course. Altogether, this requires a defined state policy, introduction of critical thinking course within the educational curricula, together with the professional courses, introduction of academic integrity policy, system of awards and punishments, and a deeper understanding of the AI capabilities, both for the Ukrainian teachers and PhD students.

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ORIGINAL ARTICLE

CONTENTS

Studying of psycholinguistic features of doctors' professional communication under war conditions

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ABSTRACT

Aim: Studying of psycholinguistic features of doctors' communication competence in Ukraine under war conditions.

Materials and Methods: Bibliosemantic method; method of system analysis, comparison and generalization; empirical methods – direct observation of the doctors' and patients' living language, typology of empirical data according to socio-demographic indicators.

Results: Within the study, 286 dialogues were collected. With voluntary consent, they were recorded in video and audio formats in compliance with ethical, bioethical, and legal norms. Next, initial typology of dialogues, their lexical and semantic analysis with identification of typical positive and negative communicative strategies were carried out. With the help of the «Textanz» specialized computer software, 48 dialogues were subjected to the content analysis procedure for two separate «Doctors» and «Patients» samples.

Conclusions: The results of the analysis of «Doctor-Patient» dialogues enabled identifying and describing psycholinguistic markers of typical physiological, mental, social, and spiritual states of individuals seeking medical help under martial law. Thus, the markers of positive emotional states (optimism, confidence, empathy, etc.) and affective, negative emotional processes (anxiety, fear, anger, aggression, sadness, depression, etc.) were identified.

KEY WORDS: Higher medical education, psychilinguistics, doctors, communication competence, numbing, martial law

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INTRODUCTION

FORMULATION OF THE PROBLEM

The war waged by the russian federation affected the physical and mental well-being of every individual in Ukraine. The number of patients with inclusion, chronic psychotraumatization, the consequences of physical and mental injuries, the manifestation and exacerbation of mental and chronic non-infectious diseases, and other issues that require systematic psychological support, assistance, and rehabilitation is steadily rising.

Participating in hostilities, being under occupation or in an area with constant rocket and artillery fire significantly increases vulnerability to psychosocial stress, leads to chronic distress, and contributes to the spread of such mental disorders as depression, anxiety and post-traumatic stress disorders. Different mental health disorders can be also caused by moving to other regions or countries with the associated loss of work and a familiar, comfortable environment; household troubles; financial difficulties; social isolation; uncertainty about the future and anxiety for family and friends; distress due to lack of sleep, separation from close people (death, moving, etc.)

There is a noticeable problem of the psychological retraumatization risk of the patient when contacting a doctor. This problem is caused by a combination of numbing (avoidance of trauma reminders) and increased vulnerability to the quality of medical communication.

Therefore, the communication competence of future masters of medicine acquires new features and the status of a socially significant problem.

AIM

The focus of our research is aimed at creating a catalog of «Doctor-Patient» dialogues and their psycholinguistic processing in order to develop the strategies and tactics aimed at the formation of professional communication of doctors in the conditions of martial law.

MATERIALS AND METHODS

To accomplish the tasks set, the following methods were used: theoretical (biblio-semantic, system analysis, comparison and generalization) for substantiating approaches to lexical and semantic analysis; empirical (direct observation of the doctors' and patients' live language, typology according to socio-demographic indicators: gender, age, level of education, marital status, type of professional employment, presence of physical and mental injuries in history, etc.); statistical processing by the «Textanz» specialized software.

RESULTS

In order to study the psycholinguistic features of the doctors' professional communication under the war conditions, we have organized the collection of materials to create a database of «Doctor-Patient» dialogues. The dialogues were recorded through collaboration with doctors who work in war conditions and patients who have experienced stressful situations. Currently, the collection consists of 286 dialogues recorded with voluntary consent in video and audio formats in compliance with ethical, bioethical, and legal norms. Each dialogue is accompanied by information about gender, age, education, marital status, region of permanent residence, professional employment, presence of physical and mental injuries in the anamnesis.

After the initial typology of dialogues (medical, patient; age categories; gender categories; regions of material collection, etc.), they were transcribed with maximum preservation of all the features of «live speech». Then, we held the lexicaland semantic analysis of dialogues with the identification of typical positive and negative communication strategies and tactics, analysis of the structure of sentences and features of the certain grammatical constructions usage for different types of messages, recommendations, and questions.

With the help of the «Textanz» (v. 2.3) specialized computer software, 48 dialogues were subjected to the content analysis processing for two separate samples: «Doctors» (sample 1) and «Patients» (sample 2). For further semantic analysis, generalization and interpretation, only the words with the recorded frequency of 3 or more were taken [1, 2], as it is a statistically significant indicator within the framework of the psychosemantic approach. The obtained results are summarized in Table 1.

The obtained results were analyzed in more detail using a noun as the main part of speech. Based on the results of the content analysis of the transcribed texts, 1,781 nouns were singled out; namely, 1,272 nouns are in the «Doctors» sample, and 509 are in the «Patients» one (as already mentioned above).

DISCUSSION

In works [3-11], typical recommendations regarding the interaction of a doctor with patients in various clinical situations are considered. Next the effectiveness of using modern technologies in the process of forming the communication competence of the future medical worker; mechanisms that reduce the impact of distress on the emotional state of medical workers aiming at restoring the psychosomatic and psychosocial health of the population are also studied.

Now, let us analyze the results given in the table I. First of all, we noticed that in sample 1, a total of 7,697 statistically significant words were recorded against 4,296 in sample 2. This means that doctors communicate almost twice as actively as their patients. This fact can be explained, in particular, by the presence of doctors in a mostly predominant role in the situation of an official reception. Then, it can also imply the reaction of a certain psychophysiological depression of patients considering their situation coupled with the need to consult a doctor.

Pronouns were the most frequent among the main parts of speech in both samples, and their relative number is slightly higher among doctors (32.18%) compared to patients (28.44%). All in all, if the «You» category clearly dominates in «Doctors» sample (44.42% of the total number of recorded pronouns), the «I» category dominates in «Patients» sample (50.42%). Such a result is also natural regarding the positions and tasks of various communicators in the «Doctor-Patient» system. The main task of a doctor is to find out the true reason for a visit and to develop mechanisms for optimal treatment of a probable disease through an appeal to the patient. The task of a patient, respectively, is to tell as much as possible about their complaints and problems.

The second largest number of recorded words consists of nouns, and again, its relative representation is slightly higher in sample compared to sample 2. We can see the differences between the samples according to the leading category: it is «Diseases and their symptoms» for doctors (19.89%), and «Temporality» for patients (27.70%). Thus, in this context, the professional orientation of doctors was revealed – to identify a specific disease or diseases based on their symptoms in this case. Instead, as we can assume according to the obtained data, the patients are aimed at restoring the usual rhythm of life, which was obviously

Table 1. Dominant categories and lexemes of different parts of speech

Part of speech (total word count)	«Doctors» sample			«Patients» sample		
	Total count	Basic category (absolute/relative number)	Basic lexemes	Total count	Basic category (absolute/relative number)	Basic lexemes
I. Main parts of speech (7519)	5037			2482		
Pronoun (2327)	1621 (32,18%)	«You» (720 / 44,42 %)	«You», «Your»	706 (28,44%)	«I» (356 / 50,42 %)	«I», «me», «my»
Noun (1781)	1272 (25,25 %)	«Diseases and symptoms» (253 / 19,89 %)	«problems»,»pain», «illness, disorder»	509 (20,51 %)	«Temporality» (141 / 27,70 %)	«day», «time», «years»
Verb (1595)	1099 (21,82 %)	«Communication and its components» (335 / 30,48 %)	«talk, speak», «think, understand», «move in space»	496 (19,98 %)	«Being» (137 / 27,62 %)	«was, be», «last», «continue»
Adverb (1472)	834 (16,56 %)	«Temporality» (249 / 29,86 %)	«after, then», «now», «often»	638 (25,71 %)	«Temporality» (196 / 30,72%)	«sometimes, seldom», «after, then», «now»
Adjective (294)	174 (3,45 %)	«Neutral» (99 / 56,90 %)	«that», «possible, «general»	120 (4,83 %)	«Neutral» (55 / 45,83 %)	«last», «that», «previous»
Numeral (50)	37 (0,73 %)	–	«once, several», «one, first», «two, second»	13 (0,52 %)	–	«once, several», «three», «one, first»
II. Additional parts of speech	2660		The most frequent part	1814		The most frequent part
Conjunction (1853)	1220 (45,86 %)	–	«and»	633 (34,90 %)	–	«and»
Preposition (1516)	987 (37,11 %)	–	«in, on»	529 (29,16 %)	–	«in, on»
Particle (876)	331 (12,44 %)	–	«no, not»	545 (30,04 %)	–	«no, not»
Exclamation (216)	109 (4,10 %)	–	«please»	107 (5,90 %)	–	«well»
Interjection (13)	13 (0,49 %)	–	«for example»	–	–	–

disturbed by the disease and accompanying factors.

The verb ranked third in terms of its representativeness in general (however, not for both samples, which we will later focus on separately). In sample 1, 1099 relevant words were recorded within the «Communication and its components» dominant category (30.48%), while 494 verbs were within the «Being» basic category in sample 2 (27.62%). Such a result is also completely natural, since the doctor at work is a representative of the socionomic profession, in which communication is the main means of its effective implementation. Instead, an ill person worrying not only for their health but also life, generally begins to be more deeply and fully aware of their existence. This was clearly evidenced by the results of the content analysis.

The adverb is fourth in total number, but it is the second most recorded part of speech in sample 2 (25.71% vs. 16.56% in sample 1). Although in both samples «Temporality» category turned out to be the dominant one (20.86% and 30.72% respectively), the significant predominance of adverbs in the sample of patients demonstrates the need for a more detailed description of their own conditions than it is offered by the doctor, who, obviously, communicates according to more abstract and generalized cognitive options. Certain trends are also proved by a deeper analysis of the content of these leading categories. Particularly, the questions of doctors usually start with: «How often...», but the answers of patients – «Sometimes, rarely...». In other words, doctors focus on specific indicators, while patients give often not so specific answers. This can be associated, among other things, with the functioning of the mechanisms

of psychological protection (the displacement of traumatic experiences into the unconscious and other mechanisms).

The adjective is significantly less significant in terms of its quantitative representation (174 of them are in sample 1 and 120 – in sample 2). The characteristic of the recorded data implies the following: although the relative number of this part of speech differs slightly in both samples (3.45% and 4.83% respectively), doctors use «neutral» adjectives significantly more often (56.90%) than their patients (45.83%). This fact illustrates the greater affective «charging» of patients, with whom the doctors remain more neutral: on the one hand, they should not provoke the patient to probable affective «outbreaks», and, on the other hand, prevent their own emotional «burnout».

Finally, the least frequent among all recorded main parts of speech are numerals. The total count of numerals is 37 in sample 1 (0.73%) and 13 –in sample 2 (0.52%). Here, the following fact is significant: both doctors and patients sometimes count different events and phenomena (some number of «times») and talk about what happened «for the first time». However, only the doctors use the lexemes «two, second» in their speech. This all is connected with the need to remind the patient about a probable second (next) appointment.

Let us now move on to the additional parts of speech. In both samples (1220 and 633 words respectively), such a part of speech as a conjunction became dominant among them. Also, the conjunction «and» prevails in both samples; however, despite this, its relative share is significantly higher in the statements of doctors (45.86%) compared to patients (34.90%). This indicates a greater semantic coherence of the verbal communication of doctors: they, unlike patients, are (as already mentioned) mostly in a dominant position and in a more balanced psycho-emotional state.

The second most frequent additional part of speech (though not for both samples – we will focus on it below) was the preposition (1516 words). Its representation is 987 words in sample 1 (37.11%), and 529 – in sample 2 (29.16%). In both samples, the preposition «in» turned out to be dominant. In particular, this happened due to the fact that while describing the symptoms, the examples of their specific localization are often given («... in the back», «... in the tooth», etc.).

The participle was the third official part of speech in terms of the total number of words (876), but it is the second in sample 2, and its absolute quantitative indicator significantly exceeds the one in sample 1 (545 against 331). In addition, the relative indicator of the dominant share of «no, not» in both samples is also significantly higher in sample 2 (30.04% and 12.44% respectively). This result can be explained by the fact that in response to the specialist's numerous questions, the patients deny, if, for example, the mentioned symptoms do not apply to them or, at least, are not recognized by them.

The fourth official part of speech is an exclamation (total count is 216). Its relative presence in both samples turned out to be approximately the same: 109 in sample 1 (4.10%) and 107 – in sample 2 (5.90%). Nevertheless, the most frequent word is «please», in doctors' exclamation count, and «well» – in patients' one. This fact indicates the manifestations of the necessary politeness in the professional communication of the specialists and everyday vocabulary of the patients. With such words, the latter show their expectation for continued communication and for consistent professional help.

Lastly, such an interjection as «for example» was found only in the statements of doctors (13 words). Thus, while communicating, they try to explain the essence of a certain issue as understandably as possible to patients using specific examples. Instead, patients do not use this interjection, although they also explain something to doctors (in particular, their symptoms).

It is also worth paying attention to those lexemes that are found either only among doctors or, on the contrary, only among patients in various contexts. This fact is a characteristic from the point of view of doctors' professional communication. In particular, it is necessary to mention the differences in the semantic content of the «Physiological and mental processes, states, qualities» category. For example, there are such lexemes as «thoughts», «attention», «memory», «wisdom» only in the sample of doctors. This fact indicates the efforts of specialists to transfer communication with the patient to rationalistic notions, to appeal to the intellectual abilities of the recipients, to stimulate their reflection on their own conditions. Instead, the concepts of «irritability» and «panic» are found only in a sample of patients. This testifies to their efforts to convey the negative psycho-emotional states caused, in particular, by the conditions of military operations. The doctors, however, avoid such words in order not to retraumatize their patients.

CONCLUSIONS

The results of the analysis of «Doctor-Patient» dialogues made it possible to identify and describe psycholinguistic markers of typical physiological, mental, social, and spiritual states of people seeking medical help under martial law conditions; single out the markers of

positive emotional states (optimism, confidence, empathy) and affective and negative emotional processes (anxiety, fear, anger, aggression, sadness, depression).

The results of the study can be used in the development of scientifically based recommendations regarding the content of both mandatory questions and precedent textual and event allusions, which should not be mentioned during the collection of anamnesis and performed physical examination. They also should be avoided when discussing sensitive and taboo topics with the patient during the collection of anamnesis and further observation.

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CONTENTS

Characteristics of the mental health of employees of healthcare facilities in the conditions of war

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ABSTRACT

Aim: To study the state of mental health of staff of healthcare facilities (HCFs) of different categories (managers, doctors, nurses) 2 years after the beginning of the Russian invasion of Ukraine.

Materials and Methods: The study, using valid psycho-diagnostic methods, was conducted in 3 stages: studying the frequency of mental states, Mental Health Continuum, and occupational self-efficacy. Using descriptive and analytical statistics, we analyzed the results obtained from 114 respondents.

Results: It was found that in the majority of the study group, regardless of the position held (manager, doctor, nurse), the levels of anxiety, frustration, aggressiveness, and rigidity were low (64.0%-50.9% of respondents); flourishing and high development of occupational self-efficacy were recorded in 59.6% and 61.0%, staff of HCFs respectively. A small proportion of specialists (10.5%-4.4%) revealed a high level of manifestation of mental states; languishing and a low level of professional self-efficacy were practically absent. In other study participants, all indicators were at the borderline level.

Conclusions: Almost 2 years of functioning in the context of the war has led to the development of a certain adaptation and resilience in all categories of healthcare employees, which allows them to fulfill their professional duties. At the same time, there is a significant number of healthcare professionals who have moderate and high levels of mental stress, and problems with mental health stability, which requires systemic decisions to be made at the sectoral level to ensure the mental health of staff of healthcare facilities.

KEY WORDS: mental health, healthcare facilities, Russian-Ukrainian war

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INTRODUCTION

The global experience of the psychological consequences of war shows that military events are a significant threat to the deterioration of the population's mental health. [1]. After the outbreak of the full-scale Russian-Ukrainian war, the situation with mental health in the country deteriorated sharply, due to several factors: a sense of danger to themselves and their families as a result of constant shelling of the country's territory; migration to other regions or countries and related material and domestic problems [2].

According to the Minister of Health, the demand for psychological assistance in Ukraine in 2023 almost doubled compared to the previous year [3]. Ukrainian and international researchers call the condition of mental health of refugees who left Ukraine en masse as a result of the Russian invasion of Ukraine, catastrophic [4].

The materials of the All-Ukrainian study of the mental health of the population, conducted by the Gradus research company in September 2022, testify to the prevalence of several negative mental states among Ukrainians during the full-scale war [5].

Medical staff, who play a significant role in addressing both mental and general health issues in wartime, experience a double mental burden due to similar circumstances and systematic contact with victims in need of assistance. There is evidence that healthcare workers who constantly deal with patients who have suffered various kinds of losses as a result of war suffer from symptoms of depression, anxiety, and stress [6].

In Ukraine, research on mental health staff of healthcare facilities (HCF) is practically absent.

AIM

To study the state of mental health of staff of healthcare facilities of different categories (managers, doctors, nurses) 2 years after the beginning of the Russian invasion of Ukraine.

MATERIALS AND METHODS

Mental health was studied using a set of standardized methods professionally adapted to the Ukrainian context by the H.S. Kostiuk Institute of Psychology of the National Academy of Pedagogical Sciences of Ukraine: «Self-assessment of anxiety, frustration, aggression, and

rigidity»; «The mental health continuum - short form» «Short occupational self-efficacy scale» [7].

The cross-sectional study was conducted in January 2024. A total of 114 employees of 16 HCFs (primary health care centers, general and specialized hospitals) in the Dnipropetrovsk oblast were involved, of whom managers made up 17.5% (20.5; 24.5), doctors - 55.3% (46.2; 64.4), nurses - 27.2% (19.0; 35.4); average length of service - M±SD=20.5±12.2 years. Out of the total number of respondents, 26.3% (18.2; 34.4) were men, 73.7% (65.6; 81.8) were women; the average age of the respondents was 47.3±12.3 years; 72.8% (64.6; 81.0) had higher and 27.2% (19.0; 35.4) had secondary education. Of all respondents, 93.5% (89.0; 98.0) reported that some of their patients were victims (both civilian and military) as a result of military conflict, and the remaining 6.5% (2.0; 11,0) stated that such patients constitute the majority.

Statistical processing of the results was carried out using the software program STATISTICA 6.1 (StatSoftInc., serial number AGAR909E415822FA) and Excel-2010 using methods of parametric and non-parametric statistics. For relative values, 95.0% confidence intervals (95% CI) were calculated based on the corrected Wald method. The assessment of the validity of the differences in relative indices was carried out according to Pearson's Chi-square test (Chi-square test – $\chi 2$). The critical value of the level of statistical significance was accepted at the level of $p<0.05$ (5%).

Compliance with the principles of bioethics and medical deontology was confirmed in the conclusion of the biomedical ethics commission of the Dnipro State Medical University (protocol No. 16 of February 21, 2024).

RESULTS

The study of the mental health of HCF employees was conducted in 3 stages. At the first stage, the frequency of various mental states (anxiety, frustration, aggression, rigidity) was studied using the "Self-Assessment of Mental States" methodology.

It was found that in general, in the study group, the levels of anxiety and frustration were low in almost 2/3 of the respondents (63.2%, 95% CI 54.3-72.1 and 64.0%, 95% CI 55.2-72.8, respectively) (Fig. 1).

More than a quarter of the respondents (26.3%, 95% CI 18.2-34.4 and 31.6%, 95% CI 22.8-40.4) had medium levels of anxiety and frustration, meaning that their actions can be influenced by circumstances and emotions. A small proportion of respondents (10.5%, 95% CI 4.9-16.1 and 4.4% 95% CI 0.6-8.2, respectively) had high levels of both mental states.

Among the various symptoms characterizing these mental states, the most prevalent, not related to level characteristics, were: anxiety symptoms such as restless sleep (47.4%; 95% CI 38.2-56.6); and signs of frustration, described as «troubles make me very upset" - 54.4% (95% CI 45.3-63.5) and periodic despair - 31.6% (95% CI 23.1-40.1).

According to the aggressiveness scale, more than half of the respondents (54.4 %; 95%CI 45.3-63.5) had a low level of this mental state, and 39.5% (95%CI 30.5-48.5) had an average level of aggressiveness. Only 6.1% (95%CI 2.1-10.1) of respondents had a high level of aggression (see Fig. 1). In the total number of study participants, the most common symptoms characterizing aggression were: «I am easily angered» - 35.1% (95% CI 26.3-43.9); «I have the last word» - 32.5% (95% CI 23.9-41.1); «I am not satisfied with little, I want much more» - 50.9% (95% CI 41.7-60.1).

The results of the study of rigidity show that 50.9% (95% CI 41.7-60.1) of respondents have a low level of this mental state; 44.7% (95% CI 35.6-53.8) of respondents have an average level of rigidity; only 4.4% (95% CI 0.6-8.2) of the study group have severe rigidity.

Among the respondents, the most common signs of rigidity were: difficulty changing habits - 40.4% (95% CI 31.4-49.4) of respondents; intrusive thoughts - 37.7% (95% CI 28.8-46.6); lack of desire to take any risk - 49.1% (95% CI 39.9-58.3); and wariness of everything new - 31.6% (95% CI 23.1-40.1).

The correlation analysis revealed a weak connection between: anxiety and the position ($rs = 0.20$; $p=0.03$), i.e. a slight increase in anxiety along the trajectory of manager - doctor - nurse; frustration and gender ($rs = 0.20$; $p=0.03$) - women are slightly more frustrated than men; aggression and age ($rs = 0.19$; $p=0.03$) - in older age groups, the level of aggression increases slightly; rigidity and education ($rs = 0.22$; $p=0.04$) - people with higher education have less rigidity compared to average medical staff.

When analyzing the levels of manifestation of mental conditions in HCF employees working in different positions, the following trends were found in managers compared to doctors and, in turn, in doctors compared to nurses: 1) to a higher frequency of low anxiety; 2) to a lower frequency of low aggressiveness, which may be due to the peculiarities of the work of managers, which consist in the need to keep their feelings under control and be an authority for subordinates for successful management. However, there were no significant differences in the levels of manifestation of any of the analyzed mental states between the groups of employees (Table 1).

The second stage of the study examined the Mental Health Continuum of HCF employees. The overall level for the entire sample was 49.5±10.3 (M±SD) points on a

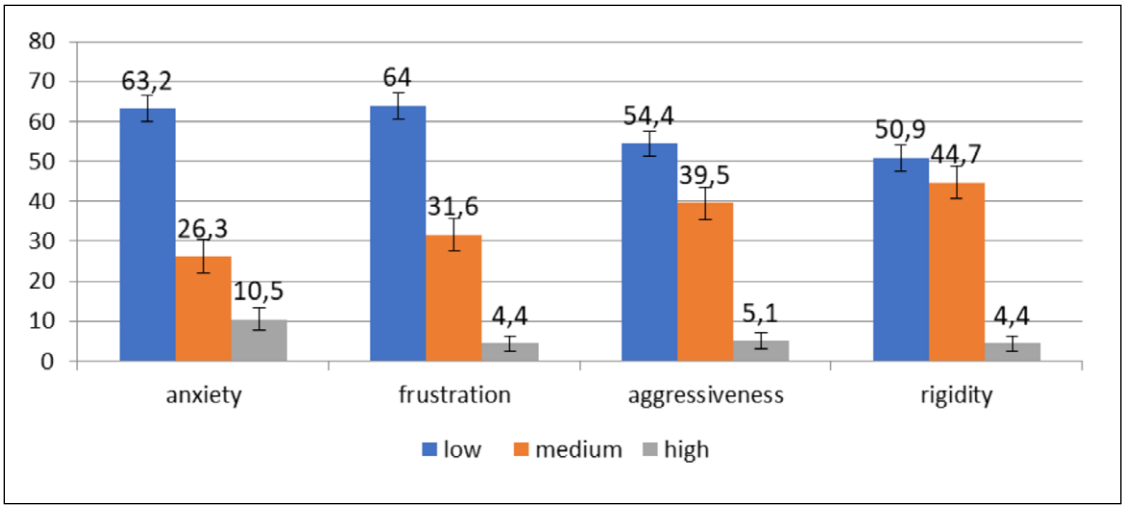

Fig. 1. Distribution of levels of manifestation of mental conditions in healthcare employees, in %.

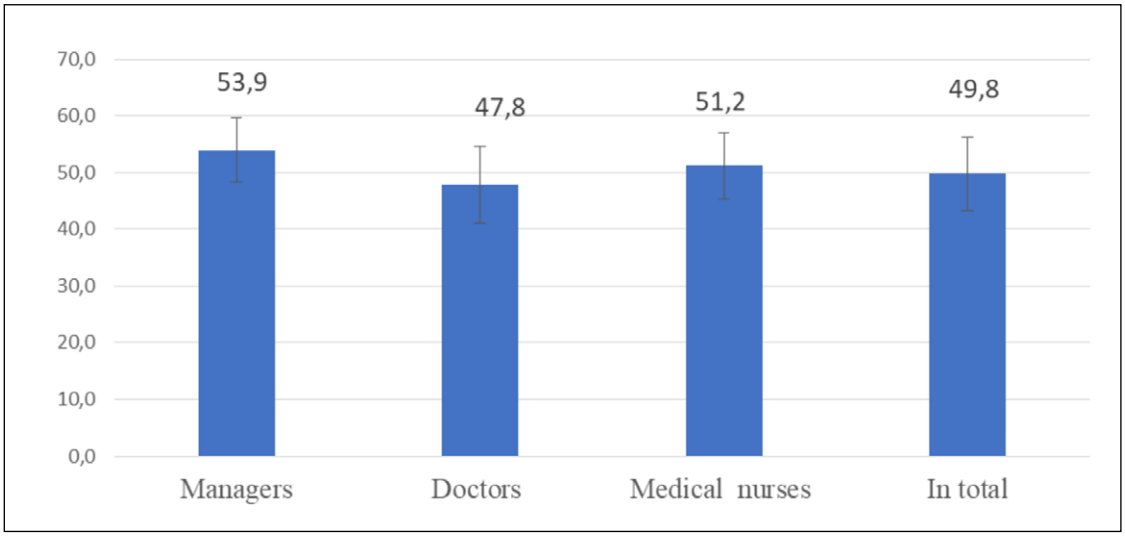

Fig. 2. Mental Health Continuum in different groups of HCF employees (scores).

70-point scale, which corresponds to the average level of this indicator. No significant differences were found between the groups of subjects (Fig. 2),

The in-depth examination of the Mental Health Continuum is based on the Mental Health Status categories, which integrate the characteristics of the subjective, social, and psychological well-being of staff. This analysis results in 3 categories: Flourishing - high level of well-being, Moderately Mentally Healthy, and Languishing or low level of well-being [7].

When analyzing the levels of mental health of HCF employees by Mental Health Status categories, it was found (Table 2) that 59.6% (95% CI 50.6-68.6) of the study participants have a harmonious level of well-being – Flourishing; 38.6% (95% CI 29.7-47.5) - Moderately Mentally Healthy, and 1.8% (95% CI -0.6-4.8) - Languishing. No significant differences were found between the groups, although there is a certain tendency to a higher level of well-being of HCF management staff. There was no association Mental Health Continuum with age, gender, education, or length of service.

At the same time, several statements indicating social disadvantage in certain positions are quite common, including doubts about their ability to make an important contribution to society (22.8%, 95% CI 15.0-30.6); about the ability of society to become better for HCF workers (48.2%, 95% CI 39.0-57.4). Symptoms of psychological distress are much less common: from the maximum value of 16.7% (95% CI 9.8-23.6) of respondents who are not satisfied with themselves as a person to 4.4% (95% CI 0.6-8.2) of respondents who do not see the purpose and meaning of life.

In the third stage, we studied occupational self-efficacy, the level of development of which on average among the staff of healthcare organizations was Me (25%;75%)=28.0 (25.0;31.0); no significant differences were found between the groups of managers, doctors and nurses ($p>0.05$). According to the levels of occupational self-efficacy development, the respondents were

Table 1. Distribution of levels of manifestation of mental conditions among HCF employees working in different positions, in %

Level	Managers of HCF n=20	Doctors n=63	Medical nurses n=31	p between groups
Anxiety				
Low	80,0 (62,5-97,5)	65,1 (53,3-76,9)	48,4 (30,8-66,0)	p>0,05
Medium	10,0 (-3,1-19,4	25,4 (14,6-36,2)	38,7 (21,6-55,9)	
High	10,0 (-3,1-19,4)	9,5 (2,3-16,7)	12,9 (1,5-24,3)	
Frustration				
Low	65,0 (44,1-85,9)	65,1 (53,3-76,9)	61,3 (44,2-78,5)	p>0,05
Medium	35,0 (14,1-55,9)	30,2 (19,5-42,7)	32,3 (15,8-48,8)	
High	0	4,8 (-0,5-10,3)	6,5 (-2,2-15,2)	
Aggressiveness				
Low	45,0 (23,2-66,8)	50,8 (38,4-63,2)	67,7 (51,2-84,2)	p>0,05
Medium	50,0 (28,1-71,9)	39,7 (27,6-51,8)	32,3 (15,8-48,8)	
High	5,0 (-4,6-14,6)	9,5 (2,3-16,7)		
Rigidity				
Low	55,0 (33,2-76,8)	42,9 (30,2-55,0)	64,5 (47,7-81,3)	p>0,05
Medium	45,0 (23,2-66,8)	49,2 (36,7-61,8)	35,5 (27,5-52,3)	
High	0	7,9 (1,3-15,1)	0	

Table 2. Mental Health Continuum in different groups of HCF employees by category (%)

Position	Mental Health Status		
	Flourishing	Moderately Mentally Healthy	Languishing
Managers	70,0 (49,9-90,1)	30,0 (9,9-50,1)	0,0
Doctors	57,1 (44,9-69,3)	39,7 (27,6-51,8)	3,2 (-1,2-7,6)
Medical nurses	58,1 (40,7-75,5)	41,9 (24,5-59,3)	0,0
All employees	59,6 (50,6-68,6)	38,6 (29,7-47,5)	1,8 (-0,6-4,8)

Notes. Level of intergroup differences p>0.05.

distributed as follows: 61% (52;70) of HCF staff had a high level of occupational self-efficacy; 38% (29;47) - an average, and 1 % (-0,8;2,8) - a low level.

DISCUSSION

Conducted using valid methods of studying mental health in employees HCF. The results of the study show that the vast majority of the study group (64.0%-50.9% of respondents), regardless of their position (manager, doctor, nurse), had low levels of anxiety, frustration, aggression, and rigidity. That is, these professionals are characterized by balance, the ability to bring things to a logical conclusion; they are resistant to failure, able to perform complex tasks in any conditions, and can easily switch from one attitude to another. More than ¼ of the

respondents have intermediate (average), and a small proportion of professionals (10.5%-4.4%) have high levels of relevant mental states. The latter is characterized by feelings of tension, nervousness or inability to relax, easy excitability, difficulties in relationships with people, as well as low self-esteem, a tendency to avoid difficulties in difficult situations, difficulty adapting to new conditions, which in general can be a significant obstacle to effective professional functioning [8].

When comparing individual symptoms of various mental conditions identified in HCF employees in our study and in the general population, obtained within the framework of the All-Ukrainian Mental Health Survey [5], despite the differences in methodological approaches, it was found that several signs in both groups occurred with almost the same frequency: Restless sleep in 47.4% of employees HCF and 41% of the population, intrusive negative thoughts - 37.7% and 35.0%; irritation - 35.1% and 38%; emotional instability - 31.6% and 29.6%, respectively. At the same time, such characteristics as indifference or apathy and pessimistic views of reality as a sign of depression were significantly less common among HCF workers than among the general population (15% vs. 35% and 11.4% vs. 24%, respectively), which is evidence of the faster formation of protective and adaptive mechanisms in people performing responsible work that allow them to adequately accept the challenges of war - Resilience, which is confirmed by the results of other studies [9].

This thesis is supported by the data obtained on the prevalence of HCF employees' Flourishing and high levels of development of self-efficacy occupational and the practical absence of Languishing and low occupational self-efficacy. It should be emphasized that high professional self-efficacy means that the personnel of medical organizations, even in the conditions of war and certain psychological stress associated with it, believe in their ability to successfully perform tasks related to professional activity [1]. At the same time, it is alarming that about 40% of respondents were characterized as Moderately Mentally Healthy and had borderline characteristics of the development of occupational self-efficacy.

The findings of a large international study «Insights in Public Mental Health» demonstrate the need for comprehensive, evidence-based measures to protect the mental health and well-being of healthcare workers so that they can properly perform their important work to maintain public health [10]. At the same time, psychodiagnostics is an important step in maintaining their mental health and, if necessary, restoring it [11].

Our study has several limitations, including the following:

1) Since the study was conducted as a cross-sectional study, it is impossible to assess the dynamics of mental health indicators of HCF employees during the war.
2) It is difficult to predict how long-term the adaptation of HCF staff will be and what consequences of chronic overstrain can be expected in the future.

CONCLUSIONS

The prolonged operation in the context of the Russian-Ukrainian war for almost 2 years has led in almost all categories of HCF employees to the development of certain adaptations, such as the ability to adjust to changing situations and expectations; and resilience, as the ability to overcome difficulties, which allows them to fulfill their professional duties.

At the same time, there is a significant number of healthcare facilities professionals who have a moderate to high degree of mental stress or its symptoms; and problems with mental health stability, which requires systemic decisions to be made at the sectoral level to ensure the mental health of healthcare facilities staff, on which both the mental and physical health of the population to some extent depends.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Non-communicable diseases and their risk factors in Ukraine: analysis of the global burden of disease 2019 study

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ABSTRACT

Aim: To analyse the burden and risk factors of Non-Communicable diseases (NCDs) in Ukraine to determine the ways to prevent them.

Materials and Methods: Using a statistical method, NCDs DALYs (Disability-Adjusted Life Years) in Ukraine were analyzed in dynamics for 1990-2019 and in comparison, with European and EU countries based on the data from "Global Burden of Disease, 2019" research.

Results: The burden of NCDs in Ukraine is 1.5 time higher than in European and EU countries. The most negative dynamic trends and significant differences between indicators in Ukraine and EU countries (with an excess of 2 or more times) were identified for DALYs due to cardiovascular diseases, digestive diseases and substance use disorders. In Ukraine the burden of NCDs can be reduced on 25.9% by normalization of systolic blood pressure, on 21.2% by optimizing diet, on18.5% by quitting smoking, on 17.6% by lowering LDL cholesterol, on 16.5% by normalizing body weight and on 9.2% by quitting alcohol abuse.

Conclusions: Ukraine should develop and implement a modern system for monitoring and assessing the NCDs burden and their risk factors; strengthen the capacity of public health institutions and their ability to attract communities to implement interventions to control NCDs modified risk factors, increase awarnes and the population's responsible attitude towards their health; strengthen the ability and motivate primary health care to provide quality primary prevention, screening and timely diagnosis and treatment of chronic NCDs.

KEY WORDS: Non-Communicable diseases, DALYs, risk factors, prevention, health care managment

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INTRODUCTION

Non-Communicable diseases (NCDs) are one of the most urgent global public health problems. According to the World Health Organization data, NCDs kills 41 million people in the world every year, including 17 million (41.5%) people under the age of 70. NCDs is the cause of 74% of all deaths in the world [1,2].

NCDs is not only a medical, but also a socio-economic problem. The program of global actions until 2030 in the field of sustainable development, adopted by the UN, sets one of the goals of reducing premature mortality from non-communicable diseases by a third [3].

This goal can be achieved through the effective implementation of population strategies for leading risk factors modifying and timely detection and effective treatment of NCDs. And if in the countries of the European Union (EU), thanks to the successful provision of programs for primary, secondary and tertiary prevention, have achieved a significant reduction in age-standardized mortality due to NCDs, then Ukraine, like other countries of Eastern Europe, remains one of the European and world leaders in NCDs premature mortality [2,4,5].

To develop an effective policy in the field of public health, including the strategy for the prevention of NCDs in Ukraine, it is necessary to rely on scientifically based comprehensive data on the impact of NCDs and their risk factors on the health of the population [6,7,8]. A modern approach that allows for such an assessment is a comprehensive analysis of the burden of disease, which is measured by the indicator of years of healthy life lost due to premature mortality and disability. In the context of the transformation of the public health system in Ukraine, which was initiated in Ukraine, using the DALYs indicator due to NCDs instead of simply measuring the number of deaths and diseases, as well as quantifying the factors that lead to the loss of years of healthy life, will allow to obtain a more accurate epidemiological picture of NCDs, and due to a reasonable assessment, form an evidence base for strategy of NCDs prevention [6, 9,10].

The use of data from the international study Global Burden of Disease (GBD) to analyze the burden of NCDs

in Ukraine is especially relevant in the absence of a national information base for a comprehensive analysis of the epidemiology of NCDs and their risk factors [6].

AIM

To analyse the burden and risk factors of Non-Communicable diseases (NCDs) according to the DALYs indicator in Ukraine in dynamics for 1990-2019 and in comparison with Europe and the European Union in order to determine the ways of prevention.

MATERIALS AND METHODS

The assessment of the burden of NCDs in Ukraine was based on the analysis of statistical information obtained from the database of the international epidemiological study Global Burden of Diseases (GBD), coordinated by the Institute for Health Metrics and Evaluation, University of Washington, USA [10].

The burden of NCDs was estimated in DALYs (Disability-Adjusted Life Years). One DALY is one year of healthy life lost. DALYs are calculated by adding Years of Life Lost (YLLs) and Years Lived with Disability (YLDs).

The statistical analysis used data on the absolute number of DALYs, YLLs and YLDs due to NCDs; crude rates of NCDs DALYs per 100,000 population, age-standardized rates of NCDs DALYs (the direct method of standardization according to the world standard of age composition of the population was used). The analysis was carried out over the period 1990-2019; the growth rate indicator (% change) was used to assess the intensity of dynamic changes. The comparative analysis was carried out using a comparison index, for the calculation of which the age-standardized rates of NCDs DALYs in Europe and EU countries were taken as 1.0. The analysis was performed for all NCDs, as well as according to the level 2 and level 3 causes of DALYs presented in the GBD database.

The analysis of environmental, behavioral and metabolic risk factors for the NCDs burden in Ukraine was carried out based on an assessment of their contribution (in %) to the formation of NCDs DALYs, as well as by comparing the NCDs DALYs rates caused by the influence of a specific factor in 1990 and 2019.

RESULTS

In 2019, the population of Ukraine lost 17,610,060.4 years of healthy life, or 39,984.3 per 100,000 population, due to disability and premature mortality caused by NCDs. Throughout the observation period, NCDs were consistent leaders in the structure of DALYs: their specific weight among all causes of DALYs was 78.2% in 1990 and 81.6% in 2019.

Among all years of life lost due to NCDs disability and mortality, 47.2% were caused by cardiovascular diseases, 15.3% - neoplasms, 6.7% - digestive diseases, 5.6% - musculoskeletal diseases, 4.6% - mental disorders, 4.4% - neurological diseases (Fig. 1).

73.2% of years of healthy life of the population were lost due to NCDs premature mortality, and 26.8% - due to NCDs disability. Predominance of years lost due to premature mortality over years lived in a state of disability is characteristic of such groups of NCDs as: cardiovascular diseases (95.9%), neoplasms (97.2%), digestive diseases (87.2%), chronic respiratory diseases, substances use disorders (63.5%). The predominance of years lived in a state of disability over years lost due to premature mortality occurred for: nevrological diseases (60.6%), diabetes and kidney diseases (63.5%). Almost 100% of DALYs are caused by years lost due to disability in the case of mental disorders, sense organs diseases, skin and subcutaneous diseases, and musculoskeletal diseases.

The analysis of the dynamics of the age-standardized NCDs DALYs, carried out for 1990-2019, revealed its wave-like fluctuation at a sufficiently high level in Ukraine with the maximum values of the indicator in 1995 and 2007. The dynamics of NCDs DALYs in Ukraine is fundamentally different from Europe and the European Union, where throughout the entire period there was a stable and pronounced trend towards a decrease in the burden of NCDs. (Fig. 2). As a result, over 30 years it decreased by 20.9% in European countries, and by 23.6% in EU countries, while in Ukraine in 2019 the NCDs DALYs was 3.4% higher than in 1990. Dynamic changes led to a growing gap in the levels of DALYs in Ukraine and Europe, if in 1990, the indicators in Ukraine were close to the European ones, then in 2019, the Ukrainian NCDs DALYs exceeded the similar indicator in Europe by 1.4 times, and in EU countries – 1.6 times.

The problem of high loss of years of healthy life due to premature mortality and disability caused by NCDs in Ukraine primarily concerns the male population. Over 30 years of observation, the gap in NCDs DALYs in men and women increased from 1.4 to 1.6 times.

A comparative analysis of the causes of DALYs in Ukraine and Europe revealed that the first 2 ranking positions in all territories are consistently occupied by cardiovascular (CVD) and neoplasms, while the ranking of other NCDs groups in Ukraine differs from the European one. (Table 1).

The levels of age-standardized DALYs rates per 100,000 population for groups of NCDs and their dynamic trends in Ukraine also differed from European ones.

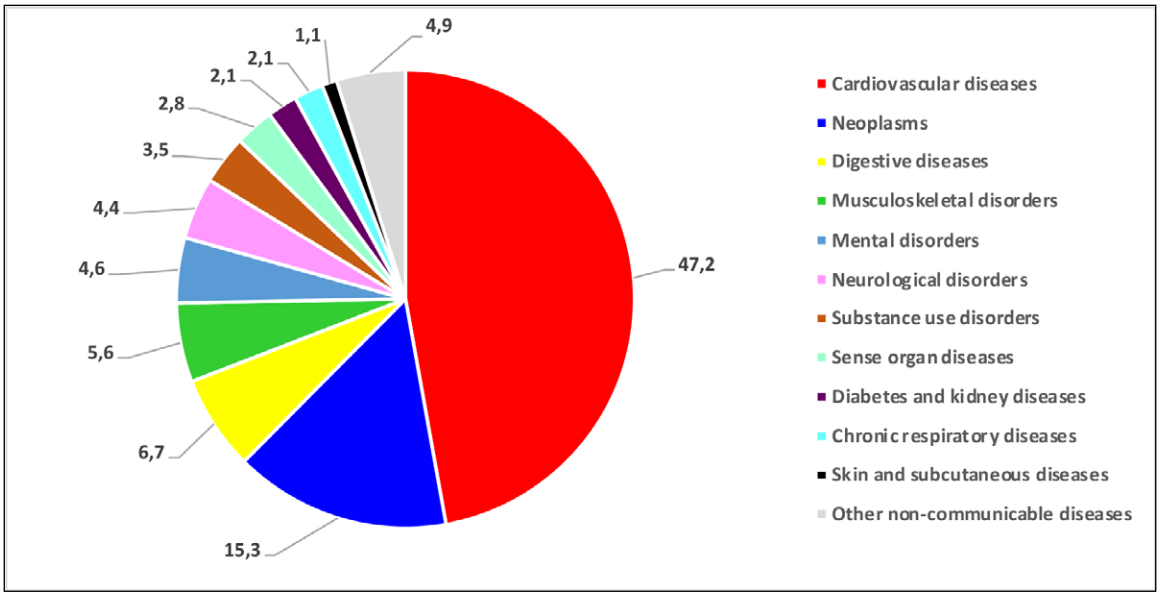

Fig. 1. Composition of DALYs due to NCDs in Ukraine, 2019 (%).

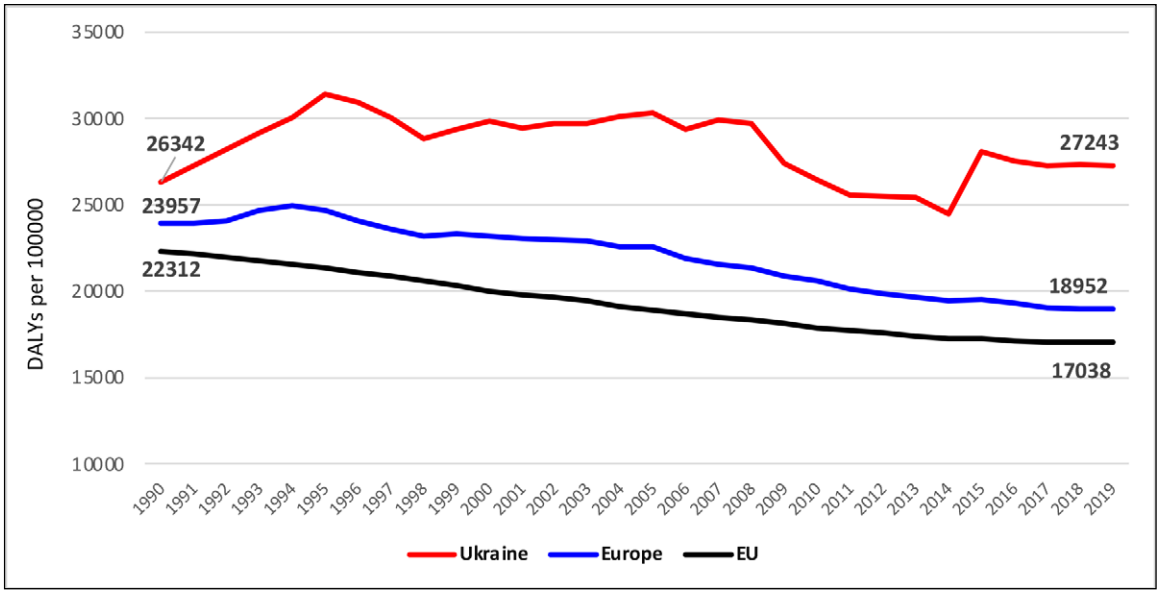

Fig. 2. Dynamics of age-standardized NCDs DALYs rates in Ukraine, Europe and the EU in 1990-2019 (per 100,000 population).

The most significant differences, which almost fully explain the gap in the burden of NCDs in Ukraine and Europe, are determined for CVD. In 2019 the population of Ukraine lost 2.6 times more years of healthy life due to CVD than residents of Europe and 4.1 times more than in EU countries (Table 1). Compared to 1990, the gap increased due to multidirectional trends in the levels of CVD DALYs: in Ukraine, the indicator increased by 16.0%, while in European countries it decreased by 39.5%, and in the EU - by 53.9%. Ukrainians, like Europeans in general, lose the greatest number of years of healthy life due to ischemic heart disease (IHD), strokes and cardiomyopathies. In Ukraine, IHD accounts for 25.9% of DALYs from all causes, strokes - 8.6%, cardiomyopathia and myocarditis - 2.3%, respectively. IHD takes Ukrainians 3.3 times more years of healthy life than the average in Europe and 5.8 times more than in the EU. Losses due to strokes are 2.1 and 3.3 times higher, due to cardiomyopathies and myocarditis 2.7 and 6.6 times, respectively.

Compared to CVD, the situation with neoplasms DALYs in Ukraine was closer to the European one: the level of DALYs from this cause decreased by 17.0% over 30 years (in Europe by 21.9%, in the EU by 22.4%) and exceeded similar European indicators only in 1.2 times. The main losses of years of healthy life are due such Neoplasms as cancer of the trachea, bronchi, and lungs (2.1% of DALYs from all causes), colorectal cancer (1.6%), stomach cancer (1.2%), and breast cancer (1.1%).

The burden of chronic respiratory diseases in Ukraine at the beginning of the observation period

Table 1. Comparative characteristics of the NCDs DALYs* in Ukraine, Europe, and EU in 1990, 2019

Years	Ukraine		Europe		EU		Comparison index Ukraine/ Europe	Comparison index Ukraine/ EU
	DALYs per 100 000	Rank	DALYs per 100 000	Rank	DALYs per 100 000	Rank		
All non-communicable diseases (DALYs per 100 000)								
1990	26341.5		23957.1		22312.4		1.1	1.2
2019	27243.2		18951.6		17038.3		1.4	1.6
% change	+3.4		-20.9		-23.6			
Cardiovascular diseases (DALYs per 100 000)								
1990	9753.9	1	7275.7	1	5983.2	1	1.3	1.6
2019	11316.7	1	4401.1	1	2758.8	1	2.6	4.1
% change	+16.0		-39.5		-53.9			
Neoplasms								
1990	4881.2	2	4368.0	2	4304.7	2	1.1	1.1
2019	4049.7	2	3411.9	2	3342.4	2	1.2	1.2
% change	-17.0		-21.9		-22.4			
Chronic respiratory diseases								
1990	1347.4	8	1086.6	6	1047.1	7	1.2	1.3
2019	575.4	9	729.6	8	754.5	8	0.8	0.8
% change	-57.3		-32.9		-27.9			
Digestive diseases								
1990	1005.7	8	1054.1	7	1077.9	6	1.0	0.9
2019	2007.2	3	977.3	6	764.8	7	2.1	2.6
% change	+99.6		-7.3		-29.0			
Neurological disorders								
1990	1272.4	6	1383.0	5	1397.4	5	0.9	0.9
2019	1324.3	6	1372.6	5	1407.5	5	1.0	0.9
% change	+4.1		-0.7		+0.7			
Mental disorders								
1990	1643.7	3	1746.7	4	1865.9	4	0.9	0.9
2019	1575.6	5	1750.2	4	1873.5	4	0.9	0.8
% change	-4.1		+0.2		+0.4			
Substance use disorders								
1990	1013.2	7	715.9	9	537.8	10	1.4	1.9
2019	1171.3	7	718.9	9	602.8	10	1.6	1.9
% change	15.6		0.4		12.1			
Diabetes and kidney diseases								
1990	435.0	11	770.8	8	751.4	8	0.6	0.6
2019	572.6	10	829.1	7	796.8	6	0.7	0.7
% change	+31.6		+7.6		+6.0			
Skin and subcutaneous diseases								
1990	435.1	10	602.4	10	673.9	9	0.7	0.6
2019	444.8	11	614.8	10	683.9	9	0.7	0.7
% change	+2.2		+2.1		+1.5			
Sense organ diseases								
1990	747.0	9	595.8	11	515.3	11	1.3	1.4
2019	720.1	8	554.7	11	483.5	11	1.3	1.5
% change	-3.6		-6.9		-6.2			
Musculoskeletal disorders								
1990	1543.1	4	1876.8	3	2012.5	3	0.8	0.8
2019	1593.4	4	1895.9	3	2019.8	3	0.8	0.8
% change	+3.3		+1.0		+0.4			
Other non-communicable diseases								
1990	2263.9		2481.2		2145.4		0.9	1.1
2019	1892.1		1695.4		1550.1		1.1	1.2
% change	-16.4		-31.7		-27.7			

*2-nd level cause of DALYs in GBD study.

exceeded the similar indicator in Europe by 1.2 times, and in EU countries by 1.3 times. Due to the higher rates of reduction of DALYs in Ukraine (by 57.3%, against 32.9% in Europe and 27.9% in the EU), the burden of these diseases in 2019 was 80.0% of European. The main losses of years of healthy life are due to such respiratory diseases as chronic obstructive pulmonary diseases.

The most unfavorable dynamic trend is established for the burden of digestive diseases, which increased in Ukraine by 2 times over 30 years and in 2019 exceeded similar indicators in Europe by 2.1 times, in the EU by 2.6 times. This trend in Ukraine is caused by liver cirrhosis and other liver diseases.

Substance use disorders are another group of NCDs, the burden of which in Ukraine significantly exceeds the European one and has a negative trend over time. For this cause DALYs in Ukraine increased by 16.3% over 30 years and in 2019 exceeded the average in Europe by 1.6 times and in the EU countries by 1.9 times. Alcohol use disorders caused the most DALYs in this groop.

The comparative analysis revealed that due to sense organs diseases Ukrainians lose 1.3 times more years of healthy life than Europeans and 1.5 times more than residents of EU countries. Age-related hearing loss and blindness are the main cause of DALYs among all sense organs diseases in Ukraine.

According to the materials presented in Table 1, the loss of years of healthy life due to the remaining groups of NCDs does not exceed the average indicators in Europe and EU countries and has dynamic trends close to European ones.

During further analysis of the NCDs burden in Ukraine, we identified the leading diseases and pathological conditions from level 3 causes in the GBD database, which together account for half (52.5%) of DALYs from all causes (Table 2). These include (in ranking order): IHD, strokes, liver cirrhosis, lower back pain, cardiomyopathy, cancer of the trachea, bronchi, and lungs, alcohol use disorders, depressive disorders, colorectal cancer, headaches.

Over 30 years, age-standardized DALYs due liver cirrhosis increased (2.4 times), IHD (by 32.0%), cardiomyopathies (by 53.3%), alcohol use disorders (by 4.3%). Age-standardized DALYs decreased due to bronchial cancer, lung trachea (by 42.6%), strokes (by 20.0%), and colorectal cancer (by 11.7%). All (apart from lung cancer) crude indicators of DALYs had an upward trend, most pronounced for those diseases whose increase was revealed by the analysis of standardized indicators.

At the next stage of the research the role of behavioral, metabolic, and environmental risk factors on the formation of the burden of NCDs in Ukraine was estimated and it was determined how many years of healthy life can be saved if the effects of these factors are eliminated.

It was found that normalization of systolic blood pressure can reduce NCDs DALYs by a quarter (25.9%), optimizing diet - by 21.2%, smoking cessation - by 18.5%, lowering LDL cholesterol - by 17.6%, normalizing body weight - by 16.5%, refusal to drink alcohol - by 9.2%, normalization of glucose level in plasma - by 8.4%, elimination of air pollution - by 5.6%, kidney dysfunction - by 4.9%, optimization of the temperature regime - by 3.7% (Table 3).

The dynamic analysis of the risk factors contribution to the formation of NCDs DALYs revealed that alcohol abuse caused an increase in DALYs by 1143.5 years (per 100,000 population) in 2019 compare to1990, high body-mass index - by 910.7 years, high systolic blood pressure - by 649.6, high LDL cholesterol - by 646.7, irrational diet - by 558.6, respectively. Negative dynamic changes in NCDs DALYs were also caused by such risk factors as high glucose level, substance use, and kidney function. Reduced exposure to air pollution, occupational hazards and smoking led to lower NCDs DALYs in 2019 compared to 1990 (Table 3).

DISCUSSION

The study found that the NCDs burden in Ukraine is 1.5 times higher than in European and EU countries. Its dynamics is characterized by a wave-like fluctuation at a sufficiently high level, in contrast to a stable and pronounced decline in Europe. The most significant differences between indicators in Ukraine and EU countries (with an excess of 2 or more times) are discovered for DALYs due to CVD, digestive diseases, substance use disorders. High body-mass index and alcohol abuse were the risk factors that most determined the increase in NCDs DALYs over 30 years in Ukraine.

The revealed trends are consistent with the results of other studies, which showed an increase in the burden of NCDs in the countries of Eastern Europe since 1991 (with a peak in 2005) against the background of its decrease in the countries of Western Europe [4, 12]. The reason for such dynamics in the east of Europe is socio-economic transformations in the countries of the former socialist camp and the Soviet Union. Socio-psychological stress experienced by the population as a result of the protracted socio-economic crisis and the extremely high prevalence of behavioral risk factors, a significant part of which (tobacco smoking, abuse of alcohol and other psychoactive substances, poor nutrition), correlating with socio-economic situation of the population, as well as the lack of access to quality health care for patients with NCDs, have been identified

Table 2. 10 main causes of DALYs due to Non-Communicable diseases in Ukraine, 1990, 2019

Cause of DALYs (3-rd level in GBD)	% of total DALYs	Age -standardize DALYs rate per 100 000		% change	Crude DALYs rate per 100 000		% change
		1990	2019		1990	2,019.00	
Ischemic heart disease	25.9	5604.9	7400.2	32.0	7305.7	12674.5	73.5
Stroke	8.62	3165.4	2533.5	-20.0	4183.2	4217.9	0.8
Cirrhosis liver	3.52	382.1	1305.3	241.6	479.4	1724.8	259.8
Low back pain	2.99	1096.9	1086.1	-1.0	1291.0	1463.3	13.3
Cardiomyopathy	2.32	563.8	864.5	53.3	665.2	1137.7	71.0
Lung cancer	2.09	1099.2	631.2	-42.6	1494.1	1025.8	-31.3
Alcohol use disorders	2.04	764.8	797.7	4.3	851.7	999.4	17.3
Depressive disorders	1.79	756.6	683.4	-9.7	871.5	876.4	0.6
Colon and rectum cancer	1.69	549.4	485.3	-11.7	735.7	795.8	8.2
Headache disorders	1.5	641.1	641.0	0.0	695.4	737.0	6.0

Table 3. The contribution of individual risk factors in the formation of NCDs DALYs in Ukraine, 1990, 2019

Risk factors	1990			2019			$DALYs_{2019}$ - $DALYs_{1990}$ (per 100 000)
	DALYs per 100 000	%*	Rank	DALYs per 100 000	%	Rank	
High systolic blood pressure	5533.0	22.8	1.0	6182.6	25.9	1.0	649.6
Dietary risks	4522.3	18.5	3.0	5080.9	21.2	2.0	558.6
Tobacco use	4748.0	20.0	2.0	4575.7	18.5	3.0	-172.3
High LDL cholesterol	3575.8	14.6	4.0	4222.5	17.6	4.0	646.7
High body-mass index	3136.4	13.1	5.0	4047.0	16.5	5.0	910.7
Alcohol use	1679.4	6.1	8.0	2822.9	9.2	6.0	1143.5
High fasting plasma glucose	1520.1	6.2	7.0	1983.1	8.4	7.0	463.1
Air pollution	2061.2	8.6	6.0	1365.7	5.6	8.0	-695.5
Kidney dysfunction	875.8	3.6	10.0	1173.7	4.9	9.0	297.9
Non-optimal temperature	972.8	4.0	9.0	866.7	3.7	10.0	-106.1
Drug use	315.7	1.1	12.0	632.4	1.8	11.0	316.7
Occupational risks	481.2	1.9	11.0	343.1	1.2	12.0	-138.1

*The DALYs due to Non-communicable in Ukraine, which is caused by the influence of each individual risk factor, includes the individual contribution of each risk factor, as well as its interaction with other risk factors.

as the main reasons for the significant gap that currently exists in the NCDs burden in Western and Eastern Europe [4, 12, 13].

The greatest territorial variability in the burden of disease in the European region was found, as in our study, for CVD, digestive, respiratory diseases, substance use disorders and diabetes [4].

The analysis of the experience of the countries of Western Europe proves that the success of these countries in reducing the NCDs burden is due, first of all, to a reduction in premature mortality caused by CVD, which by 50% is the result of improving control over modified risk factors through a successful combination of population and individual (for high-risk groups) approaches and by 40% - improvement of timely diagnosis and treatment of CVD [14].

It has been proven that the most effective preventive strategies are those that lead to lifestyle changes regarding diet, physical activity, quitting smoking, alcohol and controlling metabolic disorders [7, 15].

Particularly encouraging is the success of the North Karelia Project in Finland, which aimed to control the main modifiable risk factors for cardiovascular disease (hypertension, smoking and hypercholesterolemia) through a population-based lifestyle intervention strategy and which achieved a reduction in mortality from cardiovascular diseases by 82% in Finland [16].

To date, the economic effectiveness of interventions in the field of prevention of NCDs has been proven. It has been shown that for every US$1 spent on scaling up control of NCDs in low- and lower-middle-income countries, society will receive a benefit of at least US$7

due to growth in employment, productivity, and life expectancy. Implementation of effective measures to prevent NCDs in low-income and lower-middle-income countries requires an additional cost of only US $1.27. USA per person per year [17].

The Ukrainian strategy aimed to reduce the NCDs burden should based on a modern system for monitoring and assessing the NCDs burden and their risk factors; be comprehensive, interdisciplinary, rationally combine population and individual approaches to primary prevention with modern methods of secondary and tertiary prevention of NCDs and consider the experience of European countries, which have achieved significant success in this field over the past 30 years [5,6].

CONCLUSIONS

In 2019, NCDs took 17,610,060.4 years of healthy life from the population of Ukraine (39,984.3 per 100,000 population), which accounted for 81.6% of all years lost due to disability and premature mortality. The main classes of diseases that formed the structure of the NCDs burden in Ukraine are cardiovascular diseases (47.2%), neoplasms (15.3%), digestive diseases (6.7%), musculoskeletal diseases (5.6%), mental disorders (4.6 %), neurological diseases (4.4%).

During the entire observation period (1990-2019), the Ukrainian age-standardized NCDs DALYs exceeded the similar indicators in Europe and EU countries. Due to the significant decrease over 30 years of the NCDs burden in Europe, against the background of its high value in Ukraine, in 2019 this excess reached 1.4 and 1.6 times. The most negative dynamic changes and a significant excess of Ukraines indicators compared to European ones were founded for DALYs caused by CVD, digestive diseases and substance use disorders.

The study shows that it is possible to reduce NCDs DALYs in Ukraine by normalizing systolic blood pressure (by 25.9%), optimizing diet (by 21.2%), quitting smoking (by 18.5%), lowering LDL cholesterol (by 17.6%), normalizing body weight (by 16.5%), quitting alcohol use (by 9.2%), normalization of the level of glucose in the plasma (by 8.4%).

Taking into account global experience and the experience of European countries, which have already achieved significant success in controlling NCDs, Ukraine should develop and implement a modern system for monitoring and assessing the NCDs burden and their risk factors as a component of the electronic health care system; strengthen the capacity of public health institutions and their ability to attract communities to implement interventions to control NCDs modified risk factors, increase awarnes and the population's responsible attitude towards their health; strengthen the ability and motivate primary health care to provide quality primary prevention, screening and timely diagnosis and treatment of chronic NCDs.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Levels of anxiety and depression in patients with endometrial hyperplastic processes and extragenital pathology in the perimenopausal period

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ABSTRACT

Aim: The aim of the study was to determine the level of anxiety and depression in patients with endometrial hyperplastic processes and somatic pathology in the perimenopausal period.

Materials and Methods: Overall, 150 women who were split into 2 groups, participated in this study and answered on questionnaires that were conducted according to the Hospital Anxiety and Depression Scale (HADS) to assess the degree of anxiety and depressive symptoms in patients. PHQ-2 and PHQ-9 questionnaires were used to study the level of anxiety and depression.

Results: Analysis of the results obtained using the HADS scale revealed that both anxiety and depressive symptoms in patients of the main group were more pronounced than in women of the control group. Identification of psycho-emotional disorders is the result of adverse effects of somatic diseases and gynecological pathology.

Conclusions: The results of the study indicate the need to correct psycho-emotional disorders and take them into account when choosing a method of treatment in such patients

KEY WORDS: gynecological pathology, depressive symptoms, psycho-emotional disorders, perimenopause

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INTRODUCTION

The results of our own research and data from scientific sources indicate that patients of the perimenopausal period make up 50.0–55.0% of all patients with pathology of the endometrium and myometrium, aimed at scraping the tissue lining the uterine cavity (endometrium). The frequency of combination of hyperplastic processes of the endometrium and adenomyosis in them is 40.0–46.6%. Such patients should be included in the risk group of endometrial cancer, as more than a third of them (33.0%) show a complex atypical form of hyperplasia (endometrial adenomatosis) and in 65.6% of cases of uterine polyps. In the presence of a clinical diagnosis of "uterine leiomyoma with hemorrhagic syndrome" during perimenopause there is a high coefficient of diagnostic load, as well as a high frequency of detection of severe atypical hyperplasia (adenomatous endometrial hyperplasia — 38.6%) and uterine polyps — 71.3% [1-4].

Perimenopausal period of a woman's life is quite complex in terms of physiological restructuring of the body, which in the case of pathological course is manifested by neurovegetative, psychoemotional and metabolic-endocrine symptoms [4-6]. The pathological course of physiological reorganization of the body of women in this period can be provoked by existing extragenital diseases (in 57.0–90.0% of women) and hyperplastic processes of the endometrium and myometrium (in 17.0–35.0%). That is why the attention of many researchers is drawn to the medical problems of these age groups and of particular importance are the issues of corrective therapy, which ensures the adaptation of a woman's body to the new metabolic balance after attenuation of ovarian function [6-8].

According to Kornienko et al. [6], hyperproliferative processes of the endometrium significantly worsened the full range of indicators of quality of life, subjectively assessing their psychological well-being, patients rated it lower than physical. Patients feel social activity disorders highly than the body dysfunction. The psychopathic personality structure of a woman with endometrial pathology is characterized by neuroticism, depression, emotional lability, and shyness. Moreover, neuroticism significantly reduced not only the psychological but also the physical component of patients' health and had a significant impact on all parameters of life quality [5, 6, 9-12].

By the period of perimenopause, the frequency of endometrial pathology increases significantly and is characterized by the appearance of somatoform disorders which significantly limit women's social and physical capabilities [8, 10, 14, 15]. Existing gynecological pathology has a negative impact on a woman's life-quality and unfortunately, this fact is rarely paid attention in choosing a treatment or rehabilitation methods [10, 16, 17].

Taking into account previously noted, we can sum up that timely, effective, un-recurrent, and safe cure of the uterus and endometrium combined pathologies in women of the perimenopausal period with somatic pathology is actual and has to be studied deeply. Moreover, timely diagnosis and adequate therapy, taking into account the existing somatic pathology in perimenopause patients, is the key to successful prevention of uterus cancer development.

Thus, the analysis of the literature data indicates the need to determine the level of anxiety and depression in patients with the endometrium hyperplastic processes in the perimenopausal period.

AIM

The research aim was to determine the level of anxiety and depression in patients with endometrial hyperplastic processes and somatic pathology in the perimenopausal period.

MATERIALS AND METHODS

3-5 days before the expected surgery, we conducted a survey of 100 patients of the perimenopausal period with hyperplastic processes of the endometrium and myometrium (main group). The survey data of 50 healthy women in perimenopausal period without disorders in myometrium and endometrium served as a control. The control and the main groups were representative by the age: the age was from 46 to 60; the average age was 54.2±6.7 in the main group and 53.1±5.9 in the control ($p>0.05$).

To study the anxiety and depression level in patients with endometrial hyperplastic processes in the perimenopausal period, we used questionnaires PHQ-2 and PHQ-9 according to the requirements of the Ministry of Health of Ukraine from 25.12.2014 No. 1008. Questionnaire PHQ-2 consisted of two points. If answered yes to at least one question, the survey was conducted using the PHQ-9 questionnaire, a nine-point depression self-assessment scale that is effective in diagnosing major depressive disorder (MDD). Criteria for assessing the severity of depression were performed in points: 0-4 points no depression; 5-9 points mild "subclinical" depression; 10-14 points moderate depression; 15-19 points moderate-severe depression; 20-27 severe depression.

In order to objectively assess of the anxiety and depressive symptoms' degree, a questionnaire was conducted according to the Hospital Anxiety and Depression Scale (HADS). The HADS scale [18] was subjective and designed to screen for anxiety and depression in somatic hospital patients.

Objectification of the results was achieved through statistical processing of materials using the Microsoft Excel analysis package and with the help of computer software products included in the Microsoft Office Professional 2000 package, Russian Akademik OPEN No Level license. The obtained results were processed by the methods of variation statistics: absolute values using Student's t-test, relative values (%) the non-parametric Fisher's test angular transformation (f). The probability level of an error-free forecast was limited by the t-criterion ($t\geq2$; $P\geq95\%$) or evaluated the probabilistic characteristics of the results of any of the used statistical methods $0.001 < p < 0.05$.

RESULTS

The frequency of extragenital pathology in our examined patients is shown in Table 1.

We drew attention to the fact that the frequency of the main types of extragenital pathology in patients of the control group was a little lower. However, we have not found significant differences between the groups ($p>0.05$). This indicated the representativeness of the groups in terms of the frequency of extragenital pathology.

Analysis of the main types of extragenital pathology frequency in the examined patients showed that the structure of extragenital pathology was dominated by varicose veins in the lower extremities, arterial hypertension of the second and third stages; ischemic heart disease, angina pectoris; obesity, liver, gall bladder, and pancreas pathologies. It has been noted, that 78.0% of patients had somatic pathology represented by two or more diagnoses.

In our study, the following disorders were observed in the psycho-emotional state of the examined women according to the PHQ-9 questionnaire, of the main group: feeling of fatigue and exhaustion 64.0±4.8%; sleep disorders 64.0±4.8%; appetite problems 46.0±4.98%; depressed mood and low interest in ordinary affairs 54.0±4.98%; difficulty concentrating 33.0±4.7%; hypodynamia 26.0±4.4%; 4% of patients intended the possibility do to themselves (Table 2).

Table 1. Frequency of extragenital pathology in the examined patients, (P ± m)

Extragenital pathology	Main group n=100	Control group n=50
Anemia	25.0±4.36*	2.0±1.98
arterial hypertension of 2-3 stages	46.0±4.98*	20.0±5.66
coronary heart disease	8.0±2.7*	4.0±2.8
varicose veins of the lower extremities	61.0±4.9*	8.0±3.8
Adiposity	43.0±4.95*	14.0±469
diffuse euthyroid goiter	17.0±3.76*	6.0±3.36
diseases of the gastrointestinal tract	42.0±4.93*	16.0±5.2
Diabetes	13.0±3.36*	4.0±2.8

Note: * - p <0.05 between indicators in the main and control groups; difference is statistical valuable.

Table 2. The results of the survey on the questionnaire PHQ-9, (P ± m)

Indicator	Main group (n=100)	Control group (n=50)
Very low interest or satisfaction from ordinary things	54.0±4.98*	10.0±4.2
Bad mood, depression or feelings of helplessness	52.0±4.99*	18.0±5.4
Difficulty falling asleep, intermittent or too long sleep	64.0±4.8*	28.0±6.3
Feeling tired or exhausted	64.0±4.8*	14.0±4.9
Poor appetite or vice versa - overeating	46.0±4.98*	18.0±5.4
Bad thoughts about yourself	5.0±2.2*	0
Difficulty concentrating	33.0±4.7*	20.0±5.6
Your movements or speech are so slow that others may notice	26.0±4.4*	4.0±2.8
Thoughts about harming yourself	4.0±1.95*	0

Note: * - p <0.05 between indicators in the main and control groups; difference is statistical valuable.

Table 3. Levels of anxiety and depression by the HADS scale (P±m)

HADS scale	Control group (n=50)	Main group (n=100)
The range of anxiety		
Norm (0–7 points)	70.0±6.5*	28.0±4.5
Subclinical anxiety (8–10 points)	22.0±5.8*	50.0±5.0
Clinical anxiety (over 11 points)	8.0±3.8*	22.0±4.1
The depression level		
Norm (0–7 points)	84.0±5.2*	26.0±4.4
Subclinical depression (8–10 points)	12.0±4.6*	54.0±4.98
Clinical depression (over 11 points)	4.0±2.8*	20.0±4.0

Note: *- p<0.05 between indicators in the main and control groups; difference is statistical valuable.

The results of the survey revealed a fairly high level of psycho-emotional stress in the surveyed women of the main group. Table 3 presents the results in assessment of the frequency rate and depression that was get in our research.

The analysis of the survey's data showed that anxiety symptoms were most often represented by complaints of a feeling of tension, inner anxiety, restlessness, and a feeling of panic. In patients with endometrial and myometrial pathology (main group), complaints were realized in subclinical (50.0±5.0) and clinical (22.0±4.1) anxiety. And the indexes of the main group were significantly higher (p<0.05) frequent than in women from the control group respectively, 22.0±5.8 and 8.0±3.8%. We have to note that pathological symptoms were found in 72.0% of patients with uterine pathology, which significantly exceeds this indicator in patients of the control group (30.0%).

The depressive syndrome was manifested by indifference, apathy, excitability, hypodynamia, negativism during the assessment of events, and complaints about the lack of perspective in the future. We have fixed both subclinical and clinical depression in both groups. So, for the main group, these indicators were established

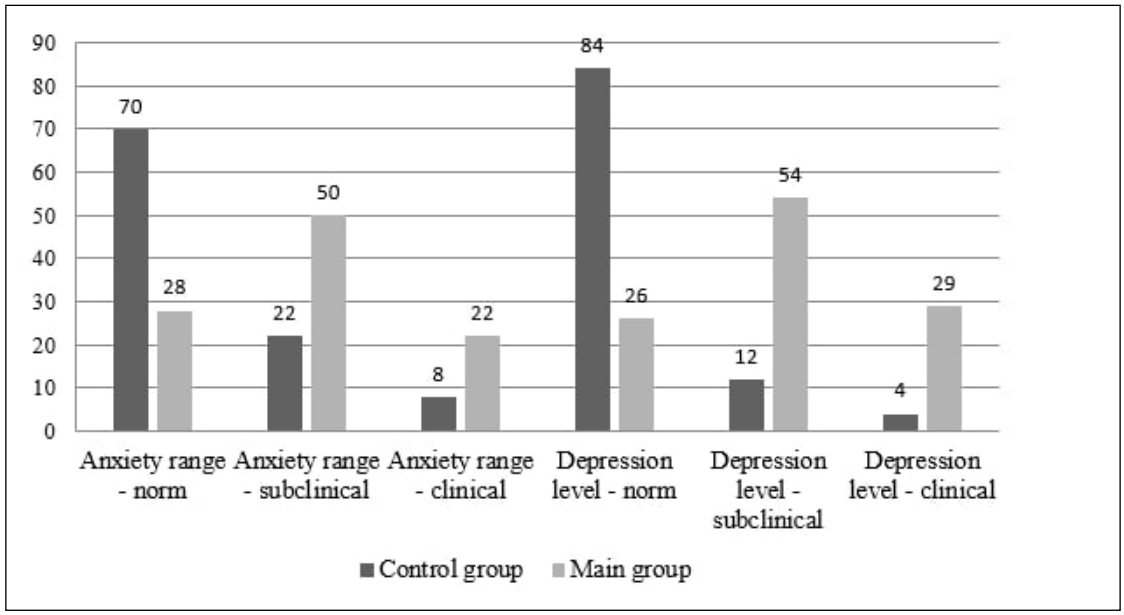

Fig. 1. The levels of anxiety and depression in the examined patients of the main and control groups.

in 54.0±4.98% and 20.0±4.0%. And for the control - in 12.0±4.6% and 4.0±2.8%. The differences between groups were significant ($p<0.05$). We can conclude that pathological symptoms, that were characteristic of the depressive syndrome, were found in 74.0% of patients in the main group and only in 16.0% of women in the control.

DISCUSSION

Despite many studies on the endometrium inflammatory etiology and pathogenesis, the mechanisms of the process, the causes of its recurrence, and the lack of effecti0veness of conventional diagnostic, treatment-and-prophylactic measures are not fully understood. The high frequency of recurrences of endometrial pathology (29.5%) remains. It indicates the lack of effectiveness of the treatment-and-prophylactic and rehabilitation measures system for this category of patients [15]. It is an important task – to improve the effectiveness of the treatment and the life quality of premenopausal women with pathological endometrial processes. In this, we need to talk about taking care of the psychological state of the patients because of the impact of the behavior features on the treatment efficiency [14]. So, we were care of the task that remains an urgent problem in modern gynecology and its resolving makes it possible to improve the health of women in menopause.

As a result of our research, we can note that patients with the hyperplastic processes in the endometrium had a high level of concomitant somatic pathology and emotional stress. This indicates the presence of chronic stress, emotional instability, and anxiety. The obtained results on the frequency and combination of extragenital pathology in patients of perimenopausal age can show us a significant role of vascular and endocrine pathology in the development of hyperplastic processes of the endometrium [2, 3, 9].

We fixed, 78% of patients of this age had a combined extragenital pathology. In the analysis of literary sources according to our research topic, we need to note data from Kornienko (2017) [13, 19] regarding the frequency of extragenital pathology and pathological changes of the endometrium in the premenopausal period. According to the author's data, endometrium pathologies in the premenopausal period are accompanied by vegetative disorders, sleep disorders, and neuroticism, which correlated with our data.

Conducted research gives us possible to detect the character dysfunctional personal features of patients perimenopausal age with the endometrial pathologies [20, 21]. We had an opportunity to detect the neuroticism, decreased balance, and severe autonomic dysfunction syndrome manifested by various sleep disorders. The levels of anxiety and depression in the studied groups were compiled in Fig. 1.

These results may indicate the presence of constant stress in the examined patients, as well as emotional instability and anxiety. And our data is confirmed by Onya and Otorkpa [22] who note that the range of the depression disorders is 45.67% in the postmenopausal period. We noted that the range of depression behavior in women with extragenital pathology was over 70% and significantly higher than in control group of patients.

We can note that the preference in behavior disorders is in difficulties with sleeping and, as a result, in feeling tired or exhausted (Table 2). This significantly reduces immunity defense and lowers regeneration proprieties [23]. This fact is indirectly confirmed by the fact of low interest in life flowing (over 50% of persons with gynecological disorders) (Table 2).

The obtained by us results regarding the psychical and emotional state of women suffering from endometrial hyperplastic processes are confirmed by the research results of Boychuk, et al. [2, 9]. Also, our data is complement to the Gambadauro, et al. (2018) [12] research. The authors traced the relationship between endometrial pathology and depressive symptoms, which are mainly determined by chronic pain. Moreover, individual vulnerability factors for such patients were fixed in their research. According to Laganà et al. [20] as well as to Singh and Puckett [21], the presence of severe autonomic, anxiety-depressive, and neurotic disorders in patients with hyperplastic processes of the endometrium was due to disorders in the hypothalamic-pituitary-adrenal-ovarian axis of hormonal regulation. The increased secretion of gonadotropic, steroidal, and tropic was detected.

CONCLUSIONS

In patients with hyperplastic processes in endometrium and myometrium against the background of extragenital pathology, a high level of somatic pathology and psycho-emotional stress is found, which indicates the presence of chronic stress, emotional instability, and anxiety.

We have fixed that the group of women with hyperplastic processes of the endometrium and myometrium had significant increased levels of clinical and subclinical anxiety and depression levels: 72% of patients in the main group had anxiety signs and 83% of this group had depressive signs. However, these parameters in the control group were 30% and 16% respectively. So, based on the results of our study, we can note the demand to manage and, if it is a requirement, correct psychological and emotional disorders in patients with hyperplastic processes of the endometrium and myometrium to improve treatment efficiency.

The obtained psychological and emotional disorders are the result of adverse effects of somatic diseases and gynecological pathology. However, the timely diagnostics and correct cure of fixed behavior disorders will affect the physiological state and can improve the treatment efficiency because of improving the psycho-somatic state of the patient's body.

Medicals can easily use the proposed scale for checking anxiety and depression. So, we can recommend using it in common practice for the initial detection of anxiety and depression in patients.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Landscape therapy: rehabilitation potential in patients with post-infarction cardiosclerosis

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ABSTRACT

Aim: To evaluate the rehabilitation potential, effectiveness and safety of landscape therapy in the complex rehabilitation treatment of patients with post-infarction cardiosclerosis (PC) complicated by chronic post-infarction cardiac aneurysm (CPCA) at the sanatorium stage.

Materials and Methods: We examined 62 patients with PC complicated by CPCA aged 38 to 65 years. Patients were randomized into two groups: the 1st group was undergoing the "Progressive gait" physical activity protocol in the city, and the 2nd group - in the rehabilitation department in a sanatorium. Survey, six-minute walk test, electrocardiography, echocardiography, coronary angiography were performed.

Results: The average distance that 2nd group patients walked in 6 minutes increased from 301.00 ± 17.00 to 467.00 ± 32.00 m ($p<0.05$). Only in patients of 2nd group during 3 weeks of complex rehabilitation there was a decrease in body mass index from 23.70 ± 1.60 to 18.90 ± 1.50 and the diameter of the calf muscle significantly increased from 33.90 ± 2.30 cm to 38.10 ± 3.10 cm ($p < 0.05$). Ejection fraction in the 2nd group was 51.00 ± 4.50% compared to the 1st group - 44.70 ± 3.60% ($p < 0.05$), which was accompanied by a decrease in the functional class of heart failure in patients of the 2nd group.

Conclusions: The rehabilitation potential of landscape therapy in the complex rehabilitation treatment of patients with complicated PC at the sanatorium stage is determined by a significant improvement in myocardial contractility and physical endurance of patients, and improving the quality of life.

KEY WORDS: landscape therapy, rehabilitation potential, post-infarction cardiosclerosis

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INTRODUCTION

Restorative treatment is a modern direction of medicine, the task of which, in addition to clinical and preventive, consists in increasing the adaptive capabilities of a person, increasing the health potential and maintaining the body at a high level of functioning [1-5]. Climate therapy and landscape therapy occupy a special place in the large arsenal of rehabilitation methods. It is these important components that are concentrated in sanatorium-resort treatment facilities in Vinnytsia, which is geographically located on the territory of Eastern Podillia of Ukraine, the 320-kilometer-long valley of the Southern Bug, which is rich in picturesque landscapes, mineral springs, historical, cultural and architectural heritage. The components of recreational areas of Vinnytsia are climate, natural landscape, objects of garden and park art, and anthropomorphic architecture. An exceptional part of this heritage is the ancient palace and park estates, many of which are adapted into sanatorium-type medical institutions, where patients of all ages and nosological categories are treated annually. The components of landscape art in rehabilitation treatment include dendrological, floristic and landscape compositions (alpine slides, terracing, parterres, lawns), sculpture and water features (fountains, ponds, waterfalls) [1].

The problem of real implementation of physical rehabilitation in everyday clinical practice of treating patients with post-infarction cardiosclerosis (PC) is extremely multifaceted. On the one hand, the rapid development of heart failure (HF), high mortality, low quality of life, and negative attitude towards others are characteristic of this clinically severe contingent of patients [6]. On the other hand, physical training of patients who have suffered a myocardial infarction (MI), thanks to an increase in tolerance to physical exertion, increases the maximum consumption of oxygen by the heart muscle, reduces the demand of the myocardium for the latter and contributes to a more economical consumption of oxygen. At the cellular level, the

functional failure of the muscle is characterized by the restructuring of mitochondria [7, 8].

The above-mentioned processes are manifested, first of all, by the inability to develop sufficient effort. Kiilavori K. et al. [9] found that the maximum effort of the transverse striated muscle in patients with III-IV functional classes of HF is 2.8 times less than in a healthy person, i.e. the value of the maximum effort developed by the transverse striated muscles is inversely proportional to the HF class, and the feeling of fatigue that occurs in a patient with HF during dosed physical activity is directly correlated with the degree of functional muscle failure [10, 11].

Thanks to improved methods of treating acute MI, it is now possible to rehabilitate patients even with complicated forms of PC. Post-infarction cardiac aneurysm (CPCA) is one of the variants of post-infarction cardiac remodeling, and patients with this pathology require comprehensive rehabilitation measures. A prerequisite for the comprehensive rehabilitation of patients with CPCA, especially in view of the deficit of the muscle component [1], is physical rehabilitation at different stages of complex treatment. In this regard, it is at the sanatorium and resort stage of rehabilitation of patients with CPCA that a successful combination of drug correction and physical training aimed at the main links in optimizing the provision of exercise programs becomes possible. One of the current areas of development of methods for rehabilitation of patients with PC is the study of the influence of individual patient characteristics on the optimal rate of activation.

AIM

The aim of our study was to evaluate the rehabilitation potential, effectiveness and safety of landscape therapy in the complex rehabilitation treatment of patients with PC complicated by CPCA at the sanatorium stage.

MATERIALS AND METHODS

We examined 62 patients with PC complicated by CPCA aged 38 to 65 years. The diagnosis was verified according to international criteria [1]. All patients underwent coronary angiography at the pre-sanatorium stage. All patients received conventional therapy for chronic HF [12]. Patients in both groups were activated according to the first stage of the "Progressive gait" physical activity protocol [1], which included: frequency of training - 5 times a week, distance - 10 km per week, speed - 1 km in 13 minutes. During the study, patients were randomized into two representative groups. The 1st group - 32 patients who were undergoing the "Progressive gait" physical activity protocol in the city under the supervision of the National Pirogov Memorial Medical University clinic specialists, and the 2nd group - 30 patients who were undergoing physical rehabilitation according to the "Progressive gait" protocol in the rehabilitation department of the Khmilnyk sanatorium in Vinnytsia region. The components of landscape therapy include climate, mineral springs, natural landscape, dendrological, floristic and landscape compositions (alpine slides, terracing, parterres, lawns), sculpture, water features (ponds, waterfalls) and anthropomorphic architecture [13].

Time since the last MI till the start of the rehabilitation program in patients of both groups was on average 2.34 ± 1.70 years. The majority of patients (90% of patients) were diagnosed with HF class III. Patients of both groups were in a stable condition (body weight fluctuations not exceeding 0.5 kg) for 60 days before being included in the study. All patients before the development of MI, which was complicated by CPCA, worked in their profession in full. All examinations were performed at the beginning of the comprehensive rehabilitation program and at the end of the third week of follow-up.

Electrocardiographic examination in 12 standard leads was performed on a Hungarian electrocardiograph "Heart Screen 112 D". Daily ECG monitoring was performed using a Hungarian-made Cardio Tens monitor complex. The day before the examination, the patients were discontinued all antianginal drugs, except for the sublingual form of nitroglycerin in angina attacks.

Exercise tolerance was assessed based on the results of a six-minute walk test. This test was performed according to the recommendations of the European Society of Cardiology and the Society of Heart Failure Specialists (2001) [14].

The test scores correlate well with the NYHA HF functional class. Each functional class corresponds to its own walking distance, and each class is significantly different from the others, with differences in walking distance reaching 100 meters between "neighbouring" classes.

The type of motor activity of the aneurysm, geometric, structural and hemodynamic characteristics of the heart muscle were determined by echocardiography, which was performed in standard positions on an ultrasound system manufactured by Aloka SSD-630 (Japan) with a mechanical transducer with a frequency of 3.5 MHz.

The quality of life of patients was determined using the Medical Outcomes Study 36-Item Short Form health survey (SF-36) [15]. To ensure the reliability of the results, a control group of 20 healthy volunteers was formed. The SF-36 reflects patients' satisfaction with their physical and

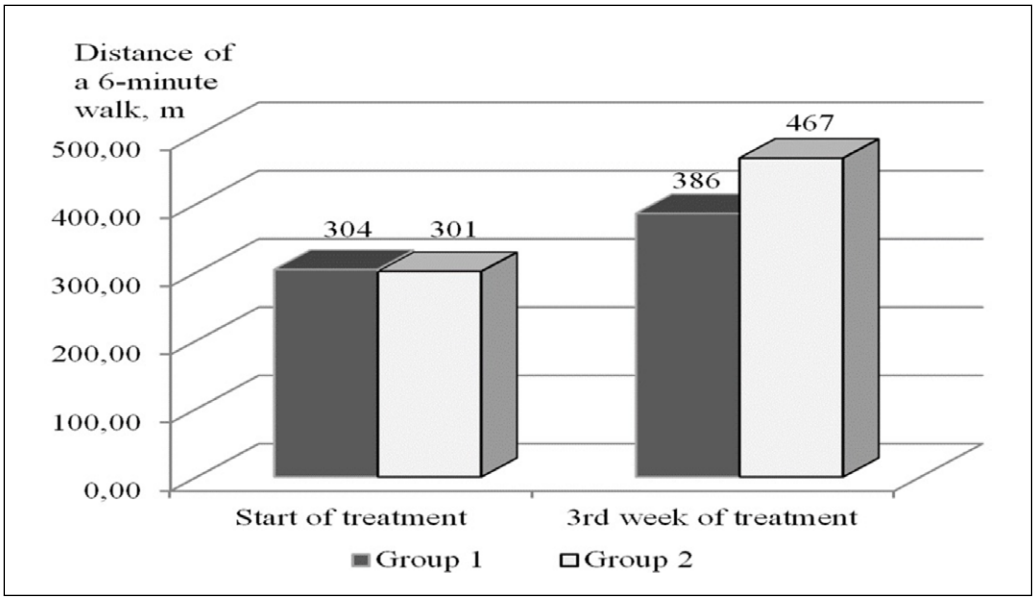

Fig. 1. Dynamics of the 6-minute walk test in patients with post-infarction cardiosclerosis complicated by chronic post-infarction cardiac aneurysm at the stage of physical rehabilitation.

mental state, social functioning, and self-assessment of pain severity. A higher score indicates better health. The following indicators were quantified:

PF - physical functioning, which reflects the extent to which health limits the performance of physical activities, as well as the tolerance of significant physical activity;

RP - the impact of the physical condition on role functioning;

BP - pain intensity and its impact on the ability to perform daily activities, including work in and outside the home;

GH - general health status - the patient's assessment of their current health status and treatment prospects, resistance to the disease;

VT - vitality - feeling full of strength and energy or, opposite, being exhausted;

SF - social functioning, is determined by the degree to which the physical and emotional state limits social activity;

RE - the impact of the emotional state on role functioning, involves assessing the degree to which the emotional state interferes with work or other usual daily activities, including large time expenditures, reduced workload, and reduced quality of work;

MH - is a characteristic of mental health.

Final value of the indicator = [(sum of final values of the items - the lowest value)/possible range of values] x 100.

Data analysis was performed in SPSS Statistics v.23. Summary statistics of mean, standard deviation and percentiles were used for quantitative measurements. The association between measures was assessed using the correlation test and t-test. The probability value was estimated at 0.05 confidence level (P=0.05).

RESULTS

The duration of coronary artery disease before the development of transmural infarction, which led to the formation of CPCA, ranged from several hours to 6 years in patients of both groups, with an average of 1.67 ± 1.59 years. The average functional class of angina in group 1 was 2.97 ± 0.13, in group 2 - 2.87 ± 0.11. The mean left ventricular ejection fraction in group 1 was 42.58 ± 3.39 %, in group 2 - 42.90 ± 3.10 %.

During the 3-week rehabilitation course, all patients significantly improved their health: shortness of breath, the number of angina attacks decreased, and a subjective impression of increased endurance of physical activity appeared. However, only in patients of 2nd group, who underwent physical rehabilitation in a sanatorium surrounded by a landscape park, these changes were accompanied by an improvement in the six-minute walk test.

The average distance that these patients walked in 6 minutes increased from 301.00 ± 17.00 to 467.00 ± 32.00 m ($p<0.05$) (Fig. 1).

Among the patients of the 1st group, 12 patients avoided the physical training protocol (irregular performance, violation of the duration of the training regimen). In the process of communicating with these patients, it was found that the monotony of covering the required meters according to the protocol every day was perceived primarily by these individuals as a heavy burden in the psychological aspect.

The maximum distance according to the test with a six-minute walk among these 12 patients was 325.00 ± 12.00 m compared to the baseline of 304.00 ± 14.00 m. Among the other patients of group 1 who followed the Progressive Gait protocol, only a tendency to increase the volume of loads was registered, the increase in the

Table 1. The effect of physical rehabilitation on the quality of life of patients with PC complicated by CPCA in the dynamics of complex rehabilitation treatment (M ± m)

Quality of life indicators	Control group of healthy volunteers (n=20)	1st group (n=32)		2nd group (n=30)	
		Before treatment	After 3 weeks of treatment	Before treatment	After 3 weeks of treatment
PF	96,1 ± 20,1	41,20 ± 6,20	48,00 ± 7,80*	41,00 ± 6,40	52,40 ± 6,30*
RP	91,0 ± 18,9	20,10 ± 4,10	26,10 ± 8,40*	19,90 ± 4,30	33,10 ± 8,70*#
BP	88,9 ± 19,3	41,30 ± 6,50	47,30 ± 8,70*	40,90 ± 6,70	55,60 ± 7,40*#
GH	74,3 ± 18,4	33,50 ± 7,60	35,40 ± 9,60	32,30 ± 7,80	45,30 ± 10,30*#
VT	64,2 ± 15,1	45,70 ± 3,50	45,40 ± 9,20	44,30 ± 3,70	54,10 ± 6,20*#
SF	86,0 ± 19,0	59,30 ± 5,00	60,20 ± 5,30	58,90 ± 5,20	66,30 ± 6,70*#
RE	67,0 ± 14,8	40,80 ± 9,50	42,60 ± 9,80	39,90 ± 9,70	49,70 ± 10,10*#
MH	68,3 ± 15,1	53,00 ± 5,40	54,70 ± 5,10	52,20 ± 5,60	64,10 ± 4,40*#

Notes:

1. * - the difference is significant compared to the indicators before treatment, $p < 0.05$.
2. # - the difference is significant compared to the indicators of the 1st group, which underwent physical rehabilitation in the city after 3 weeks of treatment, $p < 0.05$.

maximum distance in the six-minute walk test was 385.00 ± 27.00 m.

Due to the stimulating effect of landscape therapy on extracardiac mechanisms of compensation for hemodynamic disorders, patients in group 2 showed a greater degree of increase in the tolerance to physical activity, less severity of unpleasant subjective sensations compared to patients in group 1.

Only in patients of 2nd group during 3 weeks of complex rehabilitation there was a decrease in body mass index from 23.70 ± 1.60 to 18.90 ± 1.50 ($p < 0.05$), first of all, due to a decrease in the thickness of the fat layer at the level of the belly button from 3.90 ± 0.70 cm to 2.10 ± 1.30 cm. In patients with initially low body weight (less than 90% of the ideal), no decrease in body weight was observed during physical activity. Thus, regular physical activity does not lead to the progression of cachexia, but modifies the patient's body weight by reducing fat content and increasing muscle mass.

Only in patients of 2nd group, as a result of the program of complex rehabilitation, the diameter of the calf muscle significantly increased from 33.90 ± 2.30 cm to 38.10 ± 3.10 cm ($p < 0.05$).

The dynamics of the clinical picture, morphometric parameters and physical endurance fully corresponded to the changes in Echo-CG parameters characterizing the contractile function of the heart. A significant ($p < 0.05$) increase in cardiac contractile function was observed in patients of group 2 compared with baseline and group 1.

Thus, at the end of the 3rd week of treatment in the rehabilitation department of the Khmilnyk sanatorium, the ejection fraction in the 2nd group was 51.00 ± 4.50% compared to the 1st group - 44.70 ± 3.60% ($p < 0.05$), which was accompanied by a decrease in the functional class of HF in patients of the 2nd group. Regular physical activity resulted in a decrease in heart rate, ST depression depth decreased from 2 mm to 1 mm, and the duration and frequency of painless ischemia decreased by an average of 71.00% ($p < 0.05$).

Clinical and instrumental data were fully consistent with reliable quantitative changes in the quality of life of our patients: there was an increase in vitality (surge of vitality), social activity, energetic state, mental state and general health assessment compared to the group of patients who mastered the "Progressive gait" physical rehabilitation protocol in urban settings (Table 1).

Indicators of physical functioning, its impact on role functioning; pain intensity and its impact on the ability to engage in activities of daily living were significantly increased in both the 1st and 2nd groups of patients.

However, such components of quality of life as indicators of the impact of physical condition on role functioning; pain intensity and its impact on the ability to perform daily activities at the end of 3 weeks of rehabilitation were significantly higher than the same indicators in patients of the 2nd observation group.

At the end of the stay in the rehabilitation department for all patients of group 2, according to the protocol, a scheme of gradual increase in physical activity at the outpatient stage was developed, which included physical activity in accordance with the first stage for another 3 weeks and the transition to the second stage (6 weeks) - a gradual increase in distance to 21 km per week, walking speed of 1 km in 11.5 minutes. In case of poor exercise tolerance during this period, patients are recommended to return to the first stage regimen, which should be followed for life. In case of good exer-

cise tolerance within 16 weeks - lifetime preservation of the proposed regimen.

DISCUSSION

The results of our study proved that the positive dynamics of the six-minute walk test was reliable only in the 2nd group of patients at the end of the rehabilitation course. The component of a favourable psychological microclimate played an important role in this process, in particular, it was specifically the patients of the 1st group who, in their explanations of the reasons for avoiding the physical training protocol, complained about the monotony of the visual picture during exercise.

The creation of visual, psychological and climatic comfort, which is important for the rehabilitation of any directions, is directly related to the architectural environment, which is organized according to the artistic system of humanistic orientation, in which the main dimension of composition, function and imagery is a "human being".

Such architecture is built and perceived as anthropomorphic, everything in it is proportional to a real person, everything in it is understandable to a person, which ultimately creates a favourable psychological microclimate.

Mass loss is one of the processes that determine the condition of the transverse striated muscles. Its loss of more than 10% leads to a clinically significant decrease in maximum oxygen consumption [2, 16], i.e., a decrease in maximum effort and progression of functional failure. The study of peripheral muscle function [17] in patients with HF has revealed that their condition may be associated with two processes - dysfunction and weight loss. Regular physical activity leads to an increase in volumetric blood flow in the muscle group to be trained [18, 19]. The dysfunction of the transverse striated muscles is caused by a decrease in the number of active capillaries per unit volume; the formation of a predominantly anaerobic pathway of energy production [18]. An equally important problem of transverse striated muscle dysfunction is the progression of fibrosis, which is caused by a significant increase in collagen synthesis [20]. With an excessive amount of collagen, the muscle bundle moves away from the capillary, this impairs its nutrition and contributes to functional muscle failure.

It should be noted that the effectiveness of rehabilitation programs is determined by the positive results of not only the hemodynamics of the heart muscle, but also by the functional adaptation of the skeletal muscles. A significant increase in the diameter of the calf muscle, which was found only in patients of the 2nd group, correlates with the studies of E. Hambrecht, who found that 24-week training leads to a significant increase in volumetric blood flow in the calf muscles, maximum oxygen consumption, that is, to the maximum increase in the developed force [21].

A distinctive feature of our study was the intention to improve not only physical functioning but also the quality of life of patients, as the main paradigm of modern medicine.

Harmonization of the body's condition is impossible without unity with the natural environment, of which the human being remains a part at all times. Greek sculptors were well aware of the correspondence of the correct proportions of the human body to the number 0.618. Ancient architects used it in their immortal creations. For example, the ratio of the height of the Parthenon temple in Athens (5th century BC) to its length is 0.618. The Renaissance genius Leonardo da Vinci called this ratio the "golden ratio". However, the connections between medicine, architecture, and landscape art are not only historical, but also purely scientific. In the early 40s of the nineteenth century, garden and park planning and floristry were an integral part of medical education at leading German universities. Future doctors were taught to choose samples so that the garden and park compositions they created would not only bring aesthetic pleasure but also benefit health. Today, the rehabilitation of patients surrounded by picturesque nature gives amazing results not only in the subjective plane of the patients' feelings, but also in the objective plane of evidence-based medicine. The therapeutic effect of landscape therapy is associated with the harmonization of the environment and human perception of the world, the ability to create a psychological microclimate for life and treatment, and to inspire and motivate patients to physical rehabilitation [21]. Thus, landscape therapy as a stage of treatment is an optimal opportunity to initiate physical rehabilitation of patients with PC and to successfully combine physical training and drug correction [22-24].

The proposed scheme of complex rehabilitation of patients with CPCA at this stage of treatment is effective and safe; all patients of group 2 adequately withstood the regimen of the first stage of physical activity according to the "Progressive gait" protocol [25].

CONCLUSIONS

The rehabilitation potential of landscape therapy in the complex rehabilitation treatment of patients with complicated PC at the sanatorium stage is determined by a significant improvement in myocardial contrac-

tility and physical endurance of patients, overcoming myocardial detrainability, reducing the duration and frequency of painless ischemia, reducing HF and angina, and improving the quality of life.

The therapeutic effect of landscape therapy is associated with climatic comfort combined with the humanistic orientation of anthropomorphic forming, harmonization of the environment with natural objects and design tools, and the ability to create both a positive psychological microclimate and motivate patients to physical rehabilitation.

Continuation of comprehensive rehabilitation in the next stages of the program will significantly improve the prognosis and global quality of life of patients with PC, including its complicated course.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Long-term trends (compared to the pre-war period) and public health impact of surface ozone in Ukraine

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ABSTRACT

Aim: To analyze the dynamics of ambient air pollution by surface O_3 (in pre-war and wartime periods) and assess its impact on public health in order to provide proposals aimed at developing preventive programs.

Materials and Methods: Physical and chemical methods of analysis (O_3 – gas analyzers APDA-370 HORIBA, meteorological sensor WS-600); health risk assessment (AirQ+); statistical data processing methods (StatSoft STATISTICA 10.0 portable, Microsoft® Excel).

Results: Air quality monitoring in peak season 2021 and 2022 detected exceedances of the daily maximum 8-hour ozone (O_3) concentration. This resulted in a health risk for the exposed population during 70 % (174 days) and 84 % (181 days) of observations, respectively. The maximum exceedance levels were 1.7 and 2.1 times higher than the recommended limit. Estimated number of excess cases of natural and respiratory mortality in the population over 30 years due to long-term O_3 exposure: 227 (95 % CI: 0; 450) and 22 (95 % CI: 0; 54), respectively. Predictive assessments of ozone (O_3) air pollution's impact during wartime activities suggest an average increase of 40 % in additional deaths from non-communicable diseases.

Conclusions: Obtained results can serve as a basis for development of medical and environmental measures aimed at implementing adaptation proposals for public health in conditions of global climate change and wartime.

KEY WORDS: air pollution, O_3, war actions, risk assessment, mortality

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INTRODUCTION

A recent study published by the Institute for Health Metrics and Evaluation (IHME) in their "Global Burden of Disease" report identified Ukraine as one of the European countries most affected by air pollution. This pollution is estimated to contribute to 10 % of the population's social health burden, resulting in approximately 43,000 premature deaths and nearly one million lost disability-adjusted life years (DALYs) [1]. At the same time, continuous russian aggression (rocket attacks, fires in ecosystems, residential and non-residential premises, etc.) has extremely increased ambient air pollution on the territory of Ukraine [2-4]. Surface ozone (O_3) exposure is a major concern for scientists and health experts. This gas can linger in the atmosphere for extended periods and travel long distances, even across borders (transboundary) [5]. Since the photochemical processes of the O_3 formation (from precursors – nitrogen compounds, volatile organic compounds, carbon oxide, etc.) occur under the influence of solar radiation and take several hours, and the winds can carry the plume of pollution before it is formed, this makes O_3 sensitive to meteorological indicators as well (including humidity and temperature) [6, 7].

According to expert estimates, the number of population affected by O_3 concentrations, above the 2021 WHO short-term guideline value (the maximum daily eight-hour mean of 100 μg/m^3), ranged between 93 % and 98 % in the period of 2013-2020, with no downward trend over time [6]. According to epidemiological studies O_3 could cause respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, pneumonia and cardiovascular diseases [8-11]. In addition, O_3 can cause irritation, dryness of the skin and mucous membranes, lead to DNA damage of keratinocytes of the epidermis, thereby leading not only to a violation of their cellular function, but also to mutations, which as a result can lead to skin cancer development [12, 13].

Asian countries suffer most from global ozone-related respiratory deaths, contributing an estimated 79 % of the one million deaths worldwide. India and China alone account for a staggering number of these

deaths, with approximately 400,000 and 270,000 fatalities respectively. In contrast, Africa, Europe, and North America each have reported between 50,000 and 60,000 ozone-attributable deaths, while Latin America and Oceania had fewer cases [14]. In 2020, an estimated 24,000 people in the 27 EU Member States died prematurely due to acute exposure to O_3 levels exceeding 70 μg/m³ [15]. A study by Orru et al. (2019) and Selin et al. (2009) suggests that mortality linked to acute ozone exposure is expected to rise in Central and Southern Europe by 2050. Economic welfare losses encompassing mortality costs and leisure losses, resulting from ozone-related health impacts due to climate and precursor emission changes, could accumulate to 9.1 billion EUR between 2000 and 2050 [6].

AIM

This study aims to analyze changes in ambient air pollution caused by surface ozone (O_3) during both prewar and wartime periods. We will assess the impact of these changes on public health to develop proposals for preventive programs.

MATERIALS AND METHODS

In accordance with the assigned tasks, field studies of chemical pollution of ambient air O_3 in the surface layer of the atmosphere (SLA) were continuously conducted round the clock at air quality monitoring stations (AQMS) which are located in Kyiv city. Instrumental measurements of O_3 concentration levels were made using gas analyzers APOA-370 (Horiba), which use the method of non-dispersive ultraviolet absorption with cross-modulation (NDUV). Measurement range: 0 – 1 mln^{-1}; measurement error $\delta = \pm 1$ % [16]. Measurement of meteorological parameters (temperature, humidity and wind speed) using a meteorological sensor WS-600 with the meteorological rod of the automatic meteorological station Meteo system-Vaisala.

Measurement of mass concentration levels O_3 (one-hour and 30-minute mass concentrations) and meteorological parameters (speed, humidity and temperature indicators) was performed in the time intervals from January to December 2021-2022. This study assesses health risks associated with ambient ozone (O_3) air pollution. We compare measured O_3 concentrations to the air quality standards recommended by Ukraine's National Ambient Air Quality Standards (NAAQS) with a daily limit value of 30 μg/m³, as well as recommendations from the World Health Organization (WHO) [17, 18]. Meanwhile, health impacts were also assessed based on the average daily maximum 8-hour ozone (O_3) concentrations during peak season. Peak season is defined as the six consecutive months with the highest running average O_3 concentration, typically from March to August [19].

The software AirQ+ v.2.2 was used to estimate the long-term health effects, in terms of mortality by using in Kyiv air quality data, city-specific relative risk (RR) values and baseline incidence [20]. The effects of O_3 on natural and respiratory mortality in the population over 30 years of age (estimated attributable proportion (AP) and estimated number of excess cases) were estimated. In this investigation, the utilization of default values for the relative risk (RR) index in the AirQ+ model was necessitated by limitations, including a lack of adequate prior studies establishing RR values specific to the target areas. These default values are derived from meta-analysis studies. In this study, RR values for the natural mortality and respiratory mortality were 1.00 (1.01–1.02) and 1.00 (1.02–1.05), respectively. Information on the number and health indicators of the exposed population was used according to the State Statistics Service of Ukraine data [21]. In addition, all absolute values of mortality were converted to 100 thousand, and the obtained results were determined with 95 % confidence interval (CI).

Statistical analyses were performed using software tools Microsoft® Excel 2019 and STATISTICA 10.0. Descriptive statistics included calculation of minimum (min), maximum (max), mean, standard deviation (SD), and standard error of the mean (SEM). Spearman's rank correlation coefficient (rs) was used to assess relationships between variables.

RESULTS

It was determined that in 2021 and 2022, the average daily mass concentrations of O_3 at AQMS ranged from (min-max): 6.5 μg/m³ – 68.6 μg/m³ and 5.7 μg/m³ – 90.4 μg/m³ (Table 1, Fig. 1). In addition, the average annual concentration of O_3 in 2021 was at the level 39.8 μg/m³; in 2022 – 48.6 μg/m³. The conducted studies showed an increase in the average mass concentrations of O_3 in 2022 compared to 2021 in terms of maximum values by almost 1.2 times.

Generally, number of days with an average daily O_3 concentration above 30 μg/m³ (NAAQS) amounted to 228 (68 % of measurements) in 2021, and 241 (77 % of measurements) in 2022 [17].

Comparative analysis of interseasonal variability of O_3 pollution in the SLA showed that the highest mean values (M±m) were observed in 2021 and 2022, respectively, in (Fig. 2): spring (44.8 ± 1.2 μg/m³ and 62.0 ± 1.2 μg/m³) and summer periods (57.3 ± 1.3 μg/m³ and

Table 1. Annual average O3 concentrations (μg/m3) in 2021 and 2022 (January-December)

Year	mean	median	min	max	SD	SEM
2021	39.8	38.3	3.8	80.8	17.3	0.9
2022	48.6	50.9	5.7	90.4	19.0	1.1

Table 2. Average of peak season daily maximum 8-hour means O3 concentrations (μg/m3) in 2021 and 2022

Peak season (March-August)	mean	median	min	max	SD	SEM
2021	70.28	68.82	21.36	106.38	16.497	1.25
2022	77.74	78.60	30.91	124.78	15.29	1.14

Table 3. Attributable proportion (AP) expressed as number of excess cases of mortality due to long-term O3 exposure, Kyiv (2021)

Health outcome	Estimated AP (95 % CI)	Estimated number of excess cases (95 % CI)
natural mortality	1.02 % (0 – 2.02)	227 (0 - 450)
respiratory mortality	2.02 % (0 – 4.89)	22 (0 - 54)

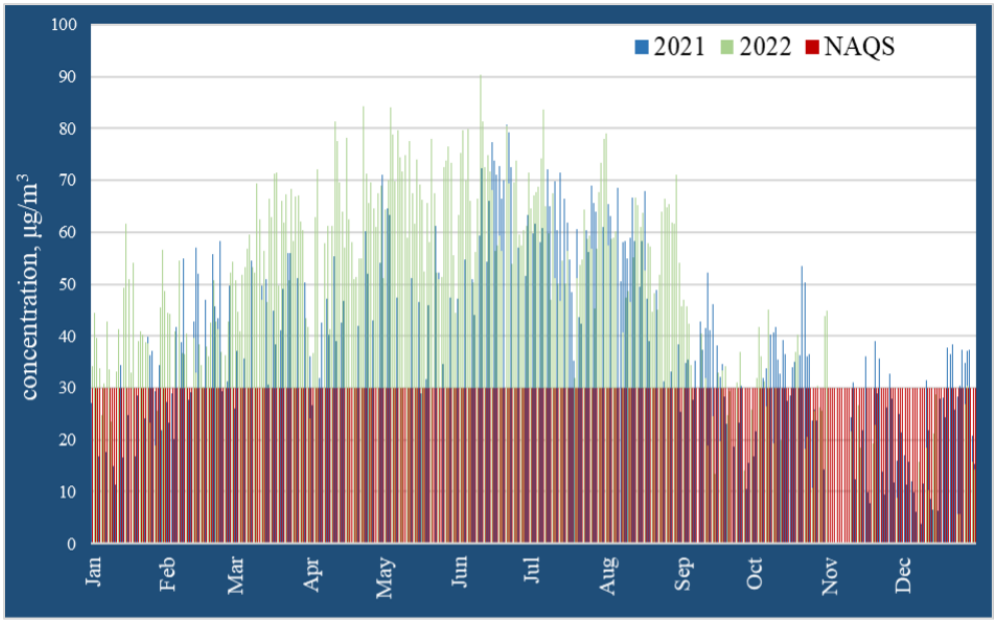

Fig. 1. Daily average O3 concentrations (μg/m3) in 2021 and 2022 (January-December). The red line corresponds to NAAQS.
*(the transfer of air masses from equatorial latitudes), as well as in June, July and the first half of August – high air temperatures (over 30 °C) [6, 22].

61.5 ± 1.1 μg/m³); the lowest – in winter (27.6 ± 1.3 μg/m³ and 33.7 ± 1.4 μg/m³) and fall periods (28.2 ± 1.4 μg/m³ and 2022 – not assessed due to lack of sufficient data (only 68 %) available due to emergency and rolling blackouts AQMS due to russian attacks on critical infrastructure), which is completely reasonable and justified for the climatic conditions of Ukraine.

In this work, was also studied the correlation between O_3 concentrations and meteorological indicators (air temperature (°C), relative humidity (%) and wind speed (m/s)). Due to non-normal data distribution, Spearman's rank correlation coefficient was employed to assess the strength of the relationship.

The findings indicate the existence in 2021 and 2022 of moderate negative correlations between O_3 and humidity (r_s = - 0.59; $p<0.0001$; r_s = - 0.68; $p<0.0001$, respectively), while the relationship between O_3 and temperature is found to be statistically significant and positive

($r_s = 0.55$; $p<0.0001$; $r_s = 0.48$; $p<0.0001$, respectively). This, in turn, is due to the fact that an increase in humidity reduces the extinction coefficient and inhibits the flow of photochemical reactions associated with the formation of O_3, contributing to its wet deposition and increasing dry deposition (absorption by trees) [5, 22]. At the same time, an increase in O_3 concentrations during an increase in air temperature leads to a temperature inversion and acceleration of photochemical reactions of O_3 formation from precursors [5]. The Spearman correlations between O_3 and wind speed in 2021 and 2022 were of weak positive correlations ($r_s = 0.33$; $p<0.0001$; $r_s = 0.39$; $p<0.0001$, respectively).

Assessment of the health effects of ozone was carried out with based on an average of peak season daily max-

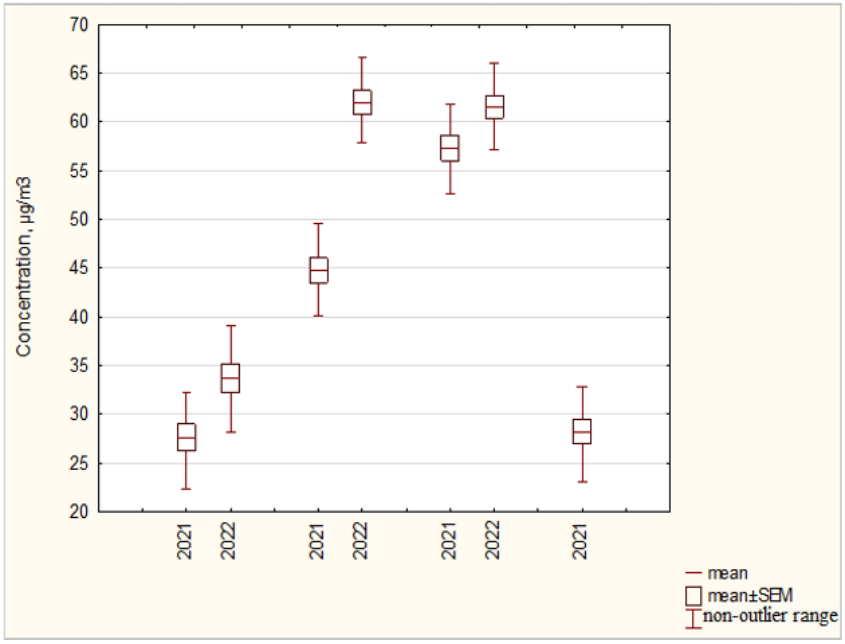

Fig. 2. Box plot daily average O3 concentrations (µg/m3) in 2021 and 2022 (different seasons).

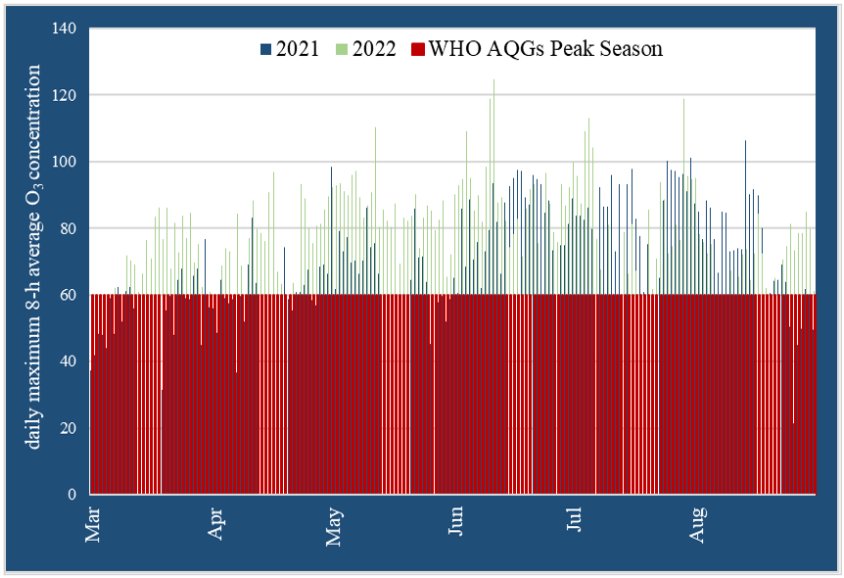

Fig. 3. Maximum daily 8-hour O3 concentrations (µg/m3) in 2021 and 2022 (March-August). The red line corresponds to the WHO limit value in peak season.

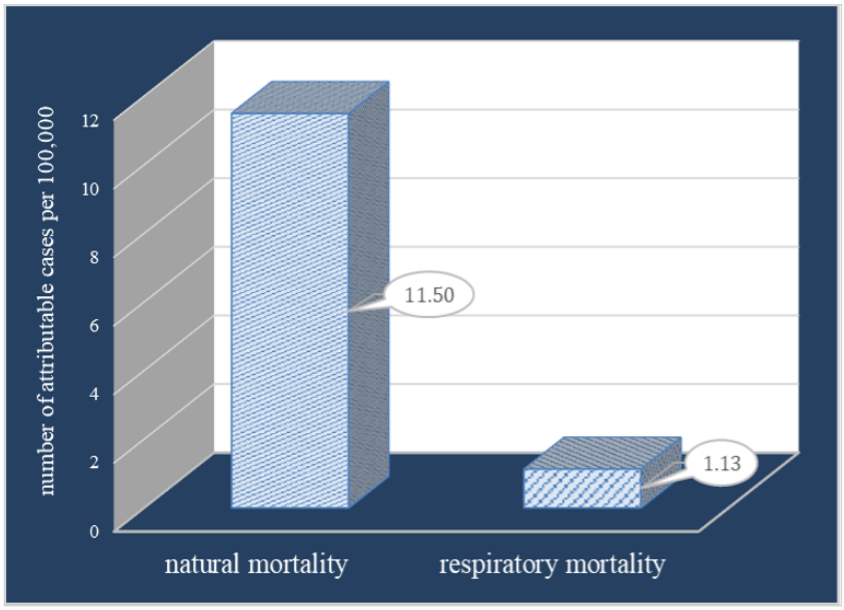

Fig. 4. Additional mortality per 100,000 population due to long-term O3 exposure, Kyiv (2021).

imum 8-hour means O_3 concentrations. For the years 2021 and 2022, the peak season mean concentrations of O_3 are shown in Table 2.

In peak season in 2021 and 2022 daily maximum 8-hour average O_3 concentrations ranged from (min-max; M±SEM): 21.36 – 106.38 μg/m³; 70.28 ± 1.25 μg/m³ and 30.91 – 124.78 μg/m³; 77.74 ± 1.14 μg/m³, respectively. Figure 3 shows the time series of the daily maximum 8-hour O_3 concentrations in 2021 and 2022 (March-August) (Fig. 3).

Air quality monitoring in peak seasons of 2021 and 2022 detected exceedances of the daily maximum 8-hour ozone (O_3) concentration set by the WHO (60.0 μg/m³). This resulted in a health risk for the exposed population during 70 % (174 days) and 84 % (181 days) of observations, with maximum exceedances reaching 1.7 and 2.1 times the recommended level, respectively [18].

During the development and implementation of medical and environmental measures to address air pollution, quantitative assessments of its health impacts are crucial. These assessments, employing epidemiological studies, to help estimate the reduction in life expectancy and premature (additional) mortality. The AirQ+ software complex was used to estimate the long-term health effects of O_3 exposure on the population. The software considered average daily maximum 8-hour ozone concentrations during peak season (March-August) for 2021 (70.28 μg/m³) and 2022 (77.74 μg/m³). Due to the lack of official statistical data on the number, health indicators and mortality of Kyiv residents in 2022, quantitative risk assessments were conducted only for 2021, including a probabilistic forecast of possible consequences in the wartime period of 2022.

The health effects as described by estimated AP and estimated number of excess cases of natural and respiratory mortality in the population over 30 years of age in due to long-term exposure of O_3 is shown in Table 3.

Overall, we estimate that in 2021: 227 (95 % CI: 0; 450) and 22 (95 % CI: 0; 54) of deaths due to all (natural) causes and respiratory diseases were attributable to long-term exposure to O_3 in Kyiv, respectively.

The risk assessment also revealed an increase in the estimated number of attributable cases per 100,000 people at risk from long-term O_3 exposure in 2021. Natural causes saw an increase of 11.50 cases, and respiratory diseases increased by 1.13 cases (Fig. 4).

DISCUSSION

Ozone pollution poses a significant global threat to public health. The persistent acts of russian aggression, including rocket attacks and fires affecting ecosystems as well as residential and commercial buildings, have substantially heightened the levels of air pollution across Ukraine's territory [2-4]. O_3 formation through photochemical processes depends on solar radiation and wind movement and sensitive to humidity and temperature. Higher humidity reduces extinction coefficient, slowing O_3 formation and increasing wet deposition. Elevated temperatures accelerate photochemical reactions, converting precursors into O_3 faster. [5-7, 22, 23].

The highest peaks of maximum and average daily mass O_3 concentrations (> 30 μg/m3; Fig. 1) in 2021-2022 were recorded in April-May during the periods of the highest solar activity, which is associated with meteorological features in this period of the year in Ukraine (the transfer of air masses from equatorial latitudes), as well as in June, July and the first half of August – high air temperatures (over 30 °C) [6, 23].

Meanwhile March 2022 saw atypical surges in O_3 mass concentrations coinciding with moments of intense wartime activities. These activities, including rocket attacks, triggered widespread biomass burning, particularly wildfires, which likely caused the ozone increase; April and May saw burning of peatlands and forests in the Chernobyl Exclusion Zone, but ozone levels were almost at the same level in July, when high air temperatures (over 30 °C) were recorded on the territory of Ukraine and a more or less calm situation on the part of war-related factors [17].

Research results align with studies (Vicedo-Cabrera, A.M. et al, 2020) from 20 countries showing a 0.2 % rise in total mortality in areas with high ozone concentrations. Additionally, the APHEA2 project reported a seasonal increase in mortality: 1.13 % from respiratory diseases and 0.45 % from cardiovascular diseases during warm months [24]. Predictive assessments suggest that wartime activities likely caused higher ozone (O_3) air pollution compared to pre-war periods. Daily maximum 8-hour O_3 concentrations in 2022 reached 77.74 μg/m³. This increase is expected to lead to an average rise of 40 % in additional deaths from non-communicable diseases. Further research is needed to confirm these findings and justify the selection of appropriate adaptation measures to protect public health during wartime conditions.

CONCLUSIONS

The highest peaks of mass concentrations of O_3 were definitely associated with meteorological features of Ukraine in certain periods of the year (transportation of air masses from equatorial latitudes) and high air temperatures (above > 30 °C). "Atypical" increases in O_3 concentrations were observed during periods of

active war actions and massive rocket attacks, which led to the ignition of large areas of biomass burning (in particular, forest fires, peat bogs, etc.) and additional emissions of a large number of pollutants (precursors) that are responsible for the formation of surface O_3. This proves the fact that the conduct of active war actions on the territory of Ukraine is the reason for the increase in ground-level O_3 concentrations, and its ability to be transported over long distances across national borders, and ultimately, to climate change on a global scale.

The assessments of the effects of O_3 on public health confirms that a number of premature deaths could be prevented if O_3 levels were reduced in accordance with the values given in the WHO Air Quality Guidelines. This analysis has a number of limitations, especially related to the continuation of the military conflict and its impact on the demographic, medical, ecological and economic development of Ukraine. However, the results of this analysis provide insight into the scope and processes of how improving air quality can affect people's health, quality of life, and ultimately well-being in a wartime environment.

The obtained results can serve as a basis for the development of medical and environmental measures (in particular, implementation of preventive programs; emergency notification of the population during the unfavorable meteorological conditions; educational campaigns, etc.) aimed at implementing adaptation measures for public health in conditions of global climate change and wartime.

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CONFLICT OF INTEREST
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ORIGINAL ARTICLE

CONTENTS

Spiritual health under the wartime: existential aspects

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ABSTRACT

Aim: To study the spiritual health in existential dimensions, as well as the meaning, value, and emotional components of spiritual health of Ukrainians under the wartime.

Materials and Methods: The theoretical and methodological framework of the paper is represented by the works of scholars in classical existentialism, contemporary philosophers, psychologists, medical psychologists, theologians, sociologists, etc. The complex nature of the issue necessitated the use of interdisciplinary approaches, philosophical, general scientific and special sociological methods of gathering, processing and analyzing information.

Results: The article analyzes the perception of spirituality and spiritual health related to mental and social aspects in the philosophy of classical existentialism and existential-humanistic psychology. The paper justifies the heuristic potential of these approaches for maintaining spiritual health of Ukrainians, which is based on holistic approaches to human beings and their spiritual frames. The article represents the results of sociological research by the Institute of Sociology of the National Academy of Sciences of Ukraine, the Scientific Research Institute of Social and Economic Development of the City, and a survey of the PhD students of the Bogomolets National Medical University (N=103) made by the authors, representing the results of statistical treatment of the spiritual health characteristics: emotional, value and meaning components.

Conclusions: The study has shown that the deterioration of mental health indicators of Ukrainians during the war is not accompanied by corresponding negative trends in their spiritual health. However, further research on this issue is necessary, including studies among respondents from other age groups (faculty, staff of the Bogomolets National Medical University).

KEY WORDS: Human, spirituality, spiritual health, existentialism, mental health

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INTRODUCTION

The full-scale Russian aggression against Ukraine is accompanied not only by numerous human casualties among both military personnel and civilians, enormous material losses, but also by significant changes in the internal subjective world of Ukrainians, as well as their mental and spiritual health. Modern scientists emphasize that "not all wounds of war are visible, but all require healing...," because "war is always a tragedy. Death, blood, pain, suffering – this is the true face of war. And in addition to physical wounds, visible consequences of injuries from weapons, there are invisible wounds – psychological, which require healing" [1].

A serious challenge here is Ukraine's ability to ensure the psychological, mental, and spiritual health of its citizens under martial law. There are numerous discussions, studies, and methodologies for medical and psychological assistance in the healthcare sector [2], regarding psychological [3] and mental health [1, 4] on theoretical and practical levels. At the same time, spirituality and spiritual health are often neglected or considered within the psychological, mental, or social health.

However, the study of spiritual health issues and its relationships with psychological, mental, and physical health has practical and theoretical significance, as the Ukrainian people under the wartime need both spiritual healing and spiritual strengthening.

AIM

To study the spiritual health in existential dimensions, as well as the meaning, value, and emotional components of spiritual health of Ukrainians under the wartime.

MATERIALS AND METHODS

The theoretical and methodological framework of the paper is represented by the works of scholars in classical

existentialism, contemporary philosophers, psychologists, medical psychologists, theologians, sociologists, etc. The complex nature of the issue necessitated the use of interdisciplinary approaches, philosophical, general scientific and special sociological methods of gathering, processing and analyzing information.

RESULTS

Since the onset of full-scale Russian invasion into Ukraine, almost all people of Ukraine have experienced collective trauma [2]. As a result of daily threats of missile and other attacks, they have been thrust into "borderline situations," where the lottery between life and death is determined by a few minutes or seconds. The National Institute for Strategic Studies, as of 2023, provides the following data: "According to experts' estimates, 40-50% of the population of Ukraine will need psychological assistance. After the war, at least every fifth person will experience negative consequences for mental health. WHO predicts that by 2025, every second Ukrainian may face problems in mental health" [4].

However, the authors question: is the deterioration of mental health characteristics among Ukrainians under the war accompanied by corresponding changes in their spiritual health? To answer this question, we will turn to the approaches of representatives of classical existentialism, existential-humanistic psychology, most of whom experienced the tragic events of the First and Second World Wars, and had personal experience of existence in borderline situations.

Søren Kierkegaard is considered a precursor to existential philosophy, as he filled the concept of "existence" with profound meaning. He began to consider the existence of human beings primarily as spiritual existence, and spirituality itself as inseparably linked to the psycho-emotional complex of human beings, as an existence reproduced not only in the philosophical-logical dimension but primarily in the dimension of the psycho-emotional characteristics of the individual.

Kierkegaard regarded fear as the fundamental characteristic of human existence – a means that pulls a person out of the captivity of mindless existence and awakens them to true being. For Kierkegaard, fear is an expression of the perfection of human nature, and its intensification (dread and despair) preserves and enhances this positivity. Fear, reaching the state of despair as a borderline state of the human self, reveals the possibilities of the human to rise to the level of spiritual existence. The measure of such a rise becomes faith, faith in the miracles. Kierkegaard emphasizes the transcendental origin of the miracle, showing, through examples from the Holy Scriptures, how existential misfortunes, illnesses, etc., were averted due to miraculous events. Through fear, dread, anxiety, and spiritual tension, the average person's aim towards existential search for the authenticity of their own existence is awakened.

The Danish philosopher was one of the first to raise the question of the "authenticity of existence" of a person, which can be interpreted through the contrast between the categories of "spiritual" and "non-spiritual." Kierkegaard's "sickness unto death" is a critical point in measuring the inauthenticity of existence.

Kierkegaard reinterpreted existence as a dialectic interrelation between the "spiritual" and "non-spiritual" aspects of existence in the feelings, evaluations, and conscious awareness of an individual's own purpose, role, and calling as a spiritual being. The main intention of Kierkegaard's philosophical thought was to provide people with a vision of their existential situation and alternatives available to them, while simultaneously urging them to choose, realize themselves, and become truly "existing individuals," without abandoning the spiritual meaning of their existence. Therefore, in Kierkegaard's view, the human spirit is an expression of its existentiality.

In the papers of the German philosopher, psychiatrist, and physician Karl Jaspers, the problem of existence arose "...primarily as a need for the treatment of mentally ill people and the creation of new clinical treatment methods. And the criticism of their ineffectiveness was essentially a critique of various philosophical principles that carried a certain way of understanding human existence in the world" [5]. "Because, as the German thinker proves, a person is not just a creature driven by instincts, not just a chamber of reason, but a creature that, by magnifying itself, seems to exceed its limitations. Its essence is not limited to being a subject for physiological, psychological, or sociological research. It is correlated with the all-encompassing, which transforms it into itself. We call this an idea because a person is spirit; we call it faith because it is existence" [6].

Thus, it is about the spiritual essence of the human being, the transcendent dimensions of human existence that need to be regarded in clinical medicine. Notably, Karl Jaspers specifically addressed the problem of creating a new variant of the philosophy of psychology that would correspond to the realities of up-to-date human existence, and provide the possibility of a credible determination of psychoneurological and psychopathological problems arising in such existence.

Gabriel Marcel, one of the founders of French existentialism, like Søren Kierkegaard, explored the problem of authentic existence as the "mystery" of the individual's existence: it is in this mystery that a person possesses

true (intimate) reality, and it is in this way that the entire world is revealed to the subject; true existence is not the soulless world of possession, where relationships between people are verbalized and fetishized, but the authentic world of existence, where the dualism of the individual and the world is overcome in the very act of existence, in the synthesis of the spiritual and the physical, in close contact not only with God and other people but also with the surrounding existence. Marcelian philosophy postulates the affirmation of faith, love, and hope for salvation in existential thought (and thus can be defined as "positive existentialism"), which open the doors for a person from the world of verbalized possession into the world of authentic existence, which Gabriel Marcel refers to as "being-against-death," that is, "being-against-non-being," advocating a refusal to submit to the dictates of Non-being.

Thus, at the core of authentic existence in Gabriel Marcel's philosophy lies spiritual communication, the interaction of the relationship of existence with being connected through people, through the "you," primarily through love as the purest, transcendent form of intersubjectivity. The issue of participation in the being of another person is closely related in Marcel's philosophy to the problem of death. It is Gabriel Marcel who, among existential philosophers, singled out the death of the neighbour as the main, true fact of the tragedy of human participation, rather than the intellectual experience of one's own end, or the awareness of one's own mortality, which accompanies a person throughout life.

The philosophy of the German thinker O.F. Bollnow was aimed at critically rethinking the ideological legacy of existentialism, overcoming pessimism and nihilism in human and cultural worldview, and returning a sense of "trust in being" to humanity.

In our research, philosopher's understanding of the uniquely human value experience, which arises not from gnoseology but from the involvement of all the manifestations of its existence with being, is of fundamental importance. This dimension of subjectivity determines the primacy of philosophical anthropology and the axiology constructed on its principles over the values of gnoseology. Secondly, this is the justification of understanding as a universal intellectual activity that extends to the spiritual life of the individual and the external world [7].

The question of spirituality and the relationship between mental and spiritual health occupies a prominent place in existential-humanistic psychology (L. Binswanger, C. Rogers, A. Maslow, R. May, R. Laing, V. Frankl, etc.).

Viktor Frankl, relying on the ideas of the "classic representatives" of existentialism, developed his own psychological (in many ways philosophical) theory called "logotherapy." By borrowing the method from existential analysis, he attempted to adapt it to the needs and create a new, applied philosophy of psychological sciences [5].

The foundation of Frankl's logotherapy undoubtedly lies in his philosophical-anthropological approaches. According to V. Frankl, "spirituality, freedom, and responsibility are the three existentials of human existence ... the spiritual is not just inherent to humans alongside the physical and the psychological, which are also common to animals. The spiritual is what distinguishes humans, what is inherent to them and them alone ... a person begins to behave as a human when they are able to transcend the level of psycho-physical-organic givenness ... constantly transcending oneself" [8]. "A human is more than just psyche, a human is spirit" [9].

V. Frankl insists that the primary intentional ability of humans is related to their turning toward meaning, the sense of existence, and values that require realization. Unlike animals, humans live by ideals and values. It is precisely this essence of human existence that is expressed by the concept of "self-transcendence".

V. Frankl identified three groups of values: creative values, experiential values (love), and relational values. The greatest achievements in Frankl's logotherapy are associated with the third group, as it concerns finding meaning in the most difficult, seemingly hopeless situations.

Therefore, in his psychotherapeutic practice, V. Frankl distinguished between psychological and spiritual problems, the so-called "noogenic neuroses", which are caused by a loss of sense of life. The goal of his method of logotherapy is to expand the patient's ability to see the full spectrum of potential meanings contained within any specific situation [8].

Notably, A. Längle, in his presentation "Spirituality and Existence", referred to V. Frankl as an advocate of spirituality in psychotherapy. Developing Frankl's ideas, he argued that spirituality influences a person's mental health [10].

Thus, the spiritual health of a person in existentialist philosophy is associated with concepts such as "authentic existence", "true being", and "being-against-death" (G. Marcel), and primarily characterizes the meaningful value-transcendent dimensions of human existence. At the same time, spiritual health is inseparably linked to various layers and levels of the psyche, particularly to the value-based, i.e., spiritual experiences of the individual. Therefore, in studying issues of spiritual health, we differentiate its emotional and meaning-life value components.

Table 1. What feelings do you experience when you are thinking of your future?

Feelings		
	Yes	**No**
Hope	65.3%	
Faith	75.2%	
Compassion	5.0%	
Optimism	26.5%	
Anxiety	28.4%	
Confusion	14.9%	
Fear	14.7%	
Confidence	10.9%	
Fatigue	32.7%	
Hopelessness	2.0%	
Pessimism	5.9%	
Interest	9.9%	
Joy	3.0%	
Indifference	2.0%	
Satisfaction	2.0%	
Other		
It's hard to answer/ I don't know		

Comparison of the data from the All-Ukrainian Monitoring of the Institute of Sociology of the NAS of Ukraine in 2021 [11], which reflected the prevailing moods among the Ukrainians, and the data of survey of the Kyivites in 2023, allows us to conclude on the ongoing trend towards the predominance of such positive moods as "hope" (40.5%), "optimism" (28.1%), altogether with the negative ones: "anxiety" (17.9%) and "confusion" (9.2%). Research indicates that the feeling of "hope" is characteristic of the youngest age group, aged 18 to 29 (49.8%) [12].

For comparison, let's present the results of a study conducted among representatives of the same age group – PhD students of the Bogomolets National Medical University, held by members of the NMU sociological group (N = 103).

The second group of questions in the study pertained to the assessment of the value significance for the postgraduate students, such questions (Table 2).

Based on the survey findings, we can suggest a ranking of current issues based on their importance to the respondents. In Group 1 (unconditional value), all respondents gave maximum importance to the issues of «Ukraine's victory terminating the war,» «Safety of family and loved ones,» and «Happiness and well-being in family life.» In Group 2 (maximum value), the majority of respondents assigned maximum importance to the suggested questions, but other response options were also present, including «Adhering to personal moral principles and norms» and «Kindness, mutual support, and assistance among people.» Group 3 (significant) comprised questions that most respondents rated with 4 out of 5 points, including «Success in professional self-realization,» «Dignified financial security,» and «High level of material prosperity and comfort.» The least important issue from the proposed list for the respondents was «Implementing effective measures to combat corruption and misconduct».

DISCUSSION

The existential aspects of interpreting spiritual health in borderline states also directly relate to the traditions of studying existentialism in Europe. We agree with the approach of the contemporary researcher K. Raidi, who, based on J. Maritain's scheme, divides classical existentialism into existential and existentialist (M. Heidegger and J.-P. Sartre), which, unlike existential existentialism (S. Kierkegaard, K. Jaspers, N. Berdyaev), "turned away" in the logic of its reasoning from the world of spirituality, from the world of psychoemotional. Therefore, within existentialism itself, two trends can be distinguished: existential (Kierkegaard, Jaspers, Marcel, Berdyaev, etc.), in which the concept of "existence" is paramount, and "existentialist" (Heidegger, Sartre), in which "existence" becomes a derivative concept of "being," "nothing," "body," etc [13-17]. The intentions of S. Kierkegaard, M. Unamuno, and other representatives of "existential existentialism," unfortunately, are not taken into account in modern studies of defining and understanding spirituality and spiritual health in crisis situations. In particular, today the following questions are a priority: volunteering as a tool for emotional awareness, the influence of social communications on mental health, the importance of sleep in ensuring mental health, the impact of combat stress on mental health, modern warfare, spiritual health, and the role of artificial intelligence, spiritual health as an integral component of human well-being. Even touching on the ontological security of personality during information-sense war, modern researchers do not utilize the heuristic potential of the classical existentialism legacy. In our opinion, the interpretation by representatives of classical existentialism (S. Kierkegaard, M. Unamuno) of spirituality as a peculiar psychoemotional expression of the inherent essence of a person can become a worldview guide for the theoretical and practical solution of the problem of preserving not only mental and mental but also spiritual health in wartime conditions. And such

Table 2. Value and meaning priorities

№	Question	1	2	3	4	5
1.	Ukraine's victory which will terminate the war	-	-	-	-	100%
2.	Implementing effective measures to combat corruption and misconduct	2.90%	5.90%	22.50%	34.30%	34.30%
3.	Adherence to personal moral principles and norms	-	-	2.00%	29.40%	68.6%
4.	Safety of family and beloved ones	-	-	-	-	100%
5.	Happiness and well-being in family life	-	-	-	-	100%
6.	Kindness, mutual support, and mutual assistance among people	-	-	-	22.50%	77.50%
7.	Success in professional self-realization	-	-	19.60%	58.80%	21.60%
8.	Appropriate financial security	-	-	5.90%	64.70%	29.4%
9.	High level of financial comfort	-	1.00%	4.90%	69.60%	24.50%

a path mainly lies through the experience of negative, tragic states in human existence (grief, anxiety, horror, suffering, death, absurdity, paradox), which transform into the opposite experience - positive (happiness, well-being, peace of mind, finding meaning, faith, love, victory, peace).

CONCLUSIONS

Thus, the deterioration of mental health indicators among Ukrainians during the war is not accompanied by corresponding negative trends in their spiritual well-being, as evidenced by the survey of Kyivites (September 2023) and PhD students of the Bogomolets National Medical University (February 2024). The respondents who participated in both studies demonstrate prevailing positive feelings. So, the majority of NMU PhD students (75.2%) expressed feelings of faith when thinking about the future. The concept of faith was included in the list of questions in a broad sense, namely, as the quintessence of morality and emotional sensitivity in humans, as one of the leading indicators of their spiritual well-being.

Among the value and meaning priorities of maximum importance to NMU PhD students were spiritual values (public, family, empathy, communicative, moral ones). Less significant were values of professional self-realization and material values, which are largely influenced, in our opinion, by the peculiarities of wartime. Considering that PhD students represent the age group of 18 to 29 years, which, according to sociological research among Kyivites (September 2023), exhibits more optimistic feelings than other age groups, it is advisable to conduct surveys among other groups of respondents, including students, faculty, staff of NMU, and so on.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Predicting fertility, neonatal and perinatal mortality, and stillbirths for evaluation of the needs for perinatal care in the future post-war reconstruction of Ukraine

Tatiana A. Vezhnovets, Oleksandr V. Korotkyi, Vitalyi G. Gurianov, Valentin D. Paryi, Tetiana M. Orabina, Andrii O. Pysariev, Yurii V. Marushko

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ABSTRACT

Aim: To predict trends in fertility, neonatal and perinatal mortality, and stillbirth rates to ascertain future perinatal care requirements during the post-war reconstruction in Ukraine.

Materials and Methods: The study uses the data from the Centre for Medical Statistics of the Ministry of Health of Ukraine, covering the years 2012 to 2022. The data analysis was by a univariate linear regression model. The quality of these models was evaluated using the coefficient of determination, R^2.

Results: In 2022, the birth rate in Ukraine had declined to 2.5 times lower than that of 2011. The period was characterized by a notable increase in the incidence of premature births and in neonates with birth weights under 1000 grams and between 1000 to 2499 grams. While the neonatal mortality rate decreased by 3.7 times, there remains a statistically significant ($p<0.05$) increase in the mortality rates of premature infants and neonates weighing less than 1000 grams. The stillbirth rate in Ukraine remains constant; however, it exceeds that of the European Union. Predictions indicate a rise in antenatal mortality and a reduction in both intranatal and perinatal mortality. As of 2022, the perinatal mortality rate in Ukraine made up 7.72 per 1000 live births, which is significantly higher than the rate in the European Union.

Conclusions: The optimization of the network of healthcare facilities and resources should be prioritized, in response to the reliable decline in the birth rate. This necessitates improvements in the medical care for premature and low birth weight infants, and efforts for preventing stillbirths.

KEY WORDS: fertility, stillbirth, neonatal mortality, perinatal mortality, perinatal care

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INTRODUCTION

Ensuring the availability and quality of health care is vital in Ukraine, even during health emergencies caused by russian aggression. Throughout more than 23 months of war, the Government Portal reports damages of 1523 health care facilities by russia, and destructions of 195 of them [1].

The joint commission of the Government of Ukraine, the World Bank and the European Commission estimated the preliminary damage to the health sector as of June 1, 2022, at $1.4 billion [2]. The estimated cost for the total health sector recovery totals $15.1 billion, including restoration of damaged infrastructure, covering for losses within the health sector, as well as enhancement of the access to critical health services [3]. In addition, the destruction of health care facilities and the occupation of the territories, have reduced access to medical care for women and children. This is expected to lead to increase in premature births, stillbirths, intrauterine infections among newborns, and the incidence of underweight children, as the displaced women from the war zone experience stress, trauma, inadequate nutrition and limited access to specialized health care facilities. Sometimes they are forced to deliver in non-medical settings. The stillbirth rate is closely related, on the one hand, to the level of medical and economical development in the country, and the overall function of the health care system. Though, it is affected by the health of parents and maternal behaviour during pregnancy [4, 5].

In order to achieve the Sustainable Development Goals declared by the United Nations by 2030 [6], even under the challenges produced by russian aggression, and during the period of post-war recovery, Ukraine is tasked with its healthcare transformation. This includes optimal structure and healthcare services reorganization, to provide the population with high-quality, safe, affordable healthcare, according to the population needs.

Therefore, the post-war reconstruction of the healthcare Ukraine requires optimal infrastructure, as well

as identification of necessary human, financial, and technical resources to achieve accessibility, safety, and quality of this service. This needs mathematical model prediction.

AIM

The aim of the study was to predict trends in fertility, neonatal and perinatal mortality, and stillbirths, to determine the needs for perinatal care in the future postwar period of Ukraine's reconstruction.

MATERIALS AND METHODS

The article examines the statistical data of Ukrainian healthcare institutions that provided perinatal care in 2012-2022, according to the reporting form 21 "Report on medical care for pregnant women, women in labour and women in childbirth in 20_". The analysis includes the following characteristics: fertility rate per 1000 inhabitants, percentage growth (decline) rate from 2012 to 2022 (%), neonatal mortality rate per 1000 births (0-28 days), early neonatal mortality rate (0-6 days) per 1000 births, stillbirth rate per 1000 births.

The calculation of the intensity coefficients was using resources of the State Statistics Service (http://db.ukrcensus.gov.ua), the Centre for Public Health of the Ministry of Health of Ukraine (http://medstat.gov.ua), the World Bank (https://data.worldbank.org), and UNICEF (https://data.unicef.org).

We developed a univariate linear regression model to analyze the data, and assessed its performance by the coefficient of determination, R^2. The data were treated by the MedCalc® Statistical Software version 22.009 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

RESULTS

Between 2012 and 2022, Ukraine experienced a significant reduction in the number of births, from 521,425 to 199,619. The period faced a significant decrease in the fertility rate, from 11.43 to 4.85 per 1000 people ($p<0.001$) (Fig. 1).

The fertility rate decrease in Ukraine made up 57.6% over these years. In comparison, the World Bank data indicates that the global fertility rate decrease was 15% (from 20 to 17 births per 1,000 population), and within the European Union, the decrease was 10% (from 10 to 9 births per 1,000 population) during the same period [7]. A catastrophic decline in the birth rate was observed in Ukraine, especially when compared to global and EU averages, primarily attributed to the war with russia that began in 2014. Moreover, projections from a linear regression model suggest that by 2027, Ukraine's fertility rate could have been reduced by an additional 48.5% from its 2022 level, reaching as low as 2.5 births per 1,000 population ($R^2=0.98$, $p<0.001$).

The perinatal care is provided in Ukraine through a network of municipal, private, or other (departmental) healthcare facilities. Between 2012 and 2021, the proportion of births in private and other (department) facilities increased from 1.42% to 2.11%. However, 2022 met a sharp decline to 1.41%, due to russia's full-scale military aggression.

A significant indicator for perinatal care planning is the rate of preterm births. Between 2012 and 2022, the proportion of preterm births in Ukraine increased significantly from 4.5% in 2012 to 5.5% in 2022 ($p<0.001$).

The regression analysis foresees that the proportion of preterm infants among newborns will climb to 5.97% by 2027.

The period from 2021 to 2022 was characterized by a significant decline in the percentage of full-term births of children with a birth weight of 3500 g, decreasing from 40.7% to 38.07%. Respectively, there was an increase in the proportion of neonates with a birth weight of up to 1000 g, from 0.25% to 0.33%. As for the newborns weighing 1000-2499 g, the proportion increased from 5.12% to 5.8% ($p<0.001$, with statistical significance confirmed by the chi-square test).

In the period from 2012 to 2022, Ukraine showed a downward trend in neonatal deaths among newborns, dropping from 1545 to 414 cases (decrease -73.2%). The neonatal mortality rate also significantly decreased from 2.96 to 2.07 per 1000 births ($p=0.003$) (Fig. 2).

According to the World Bank in 2021, the neonatal mortality rate in the European Union stood at 2.0 per 1,000 births, whereas in Ukraine, it was 2.24‰ [7]. Linear regression analysis projects a further significant reduction in the neonatal mortality rate in Ukraine by 17.4% by 2027, with a projected rate of 1.71 per 1,000 births ($R^2=0.81$, $p=0.003$).

During the same decade, we observed an increase in the mortality rate of preterm infants (0-28 days) from 71.97% to 77.78% ($p=0.014$). Additionally, the percentage of preterm infants weighing less than 1,000 g who died within the first 28 days rose from 33.8% in 2012 to 50.1% in 2022.

The period faced a decrease in the number of early neonatal deaths (0-6 days after birth) from 1,330 to 344 children, with a reduction rate of 74.1%. The early neonatal mortality rate significantly decreased from 2.55 to 1.72 per 1,000 births ($p=0.003$) (Fig. 3).

According to the World Bank, in 2019, the early neonatal mortality rate within the European Union member states stood at 1.8 per 1,000 births, which marked a

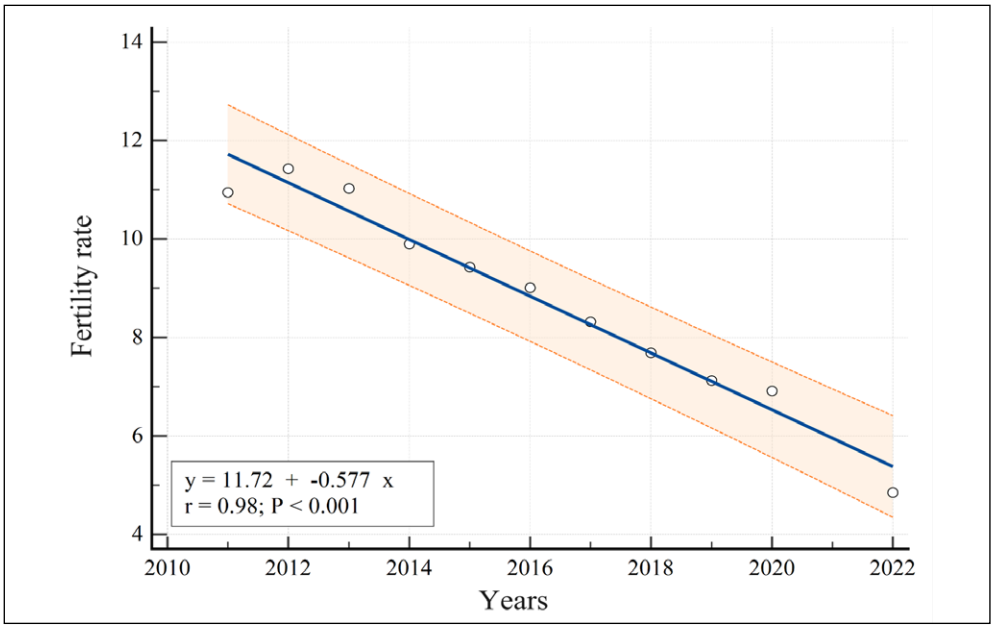

Fig. 1. Dynamics of the fertility rate per 1000 population in Ukraine in the period 2012-2022 (‰).

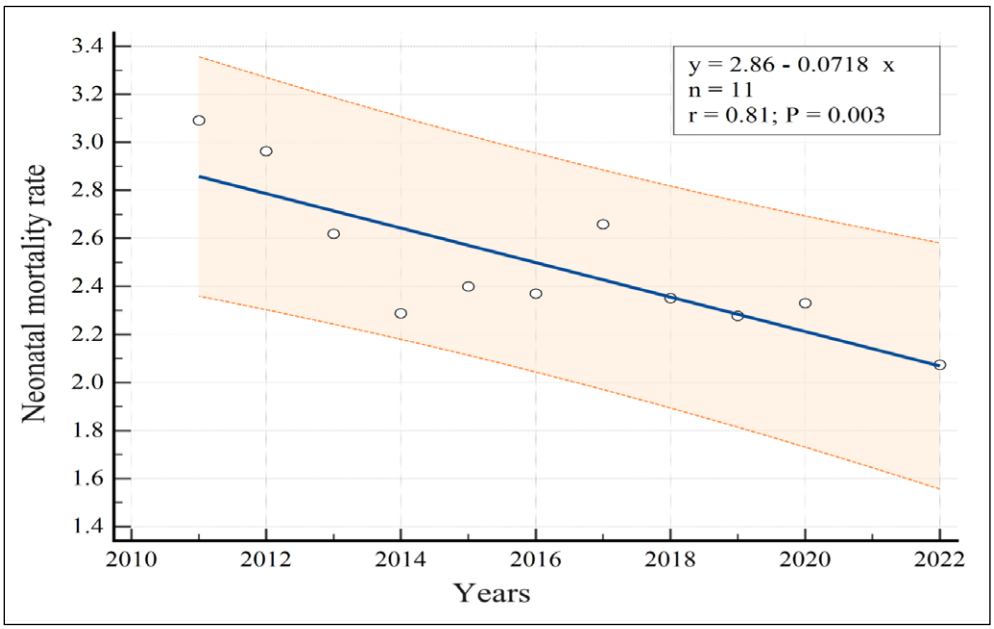

Fig. 2. Dynamics of the neonatal mortality rate per 1,000 births in Ukraine in the period 2012-2022 (‰).

decrease of 2.17% from 1.84 per 1,000 births in 2012 [7]. In Ukraine, the early neonatal mortality rate in 2019 was 1.91 per 1,000 births, which is 5.8% higher than that in the European Union member states. According to Liisa Lehtonen at all., the deaths of newborns within the first 0-6 days makes up 73% of all newborn mortality [8]. In Ukraine, this proportion was higher, at 86.72% in 2012 and 84.36% in 2022, which exceeds the global averages.

Predictions from the linear regression model suggest that by 2027 the early neonatal mortality rate in Ukraine will decrease to 1.4 per 1,000 births (R2 = 0.8, $p<0.05$), which represents a 18.6% reduction compared to 2022.

From 2012 to 2022, the proportion of preterm infants who died within the first 0-6 day period increased significantly from 70.1% to 74.7% (R^2 =0.65, $p<0.05$).

Over the same period, Ukraine observed a 2.6-fold decrease in stillbirths, from 3,163 to 1,201 cases. Consequently, the stillbirth decreased by 16.7% from 6.03 to 5.98 per 1,000 births (Fig. 4), with the rate calculated per 1,000 live births and stillbirths. The significant decrease in the infant mortality rate in Ukraine was not observed in the period ($p>0.05$).

According to UNICEF data in 2021, the global stillbirth rate was 13.9 per 1,000 births. At the same time, the European Union reported this rate in 2020 as 2.7 per 1,000 births. So, the coefficient in Ukraine is 2.3 times higher, compared to the countries of the European Union,

Projections from the linear regression model show that by 2027 Ukraine will have a steadily high stillbirth rate of 5.92 per 1,000 births (R^2 =0.09, $p>0.05$).

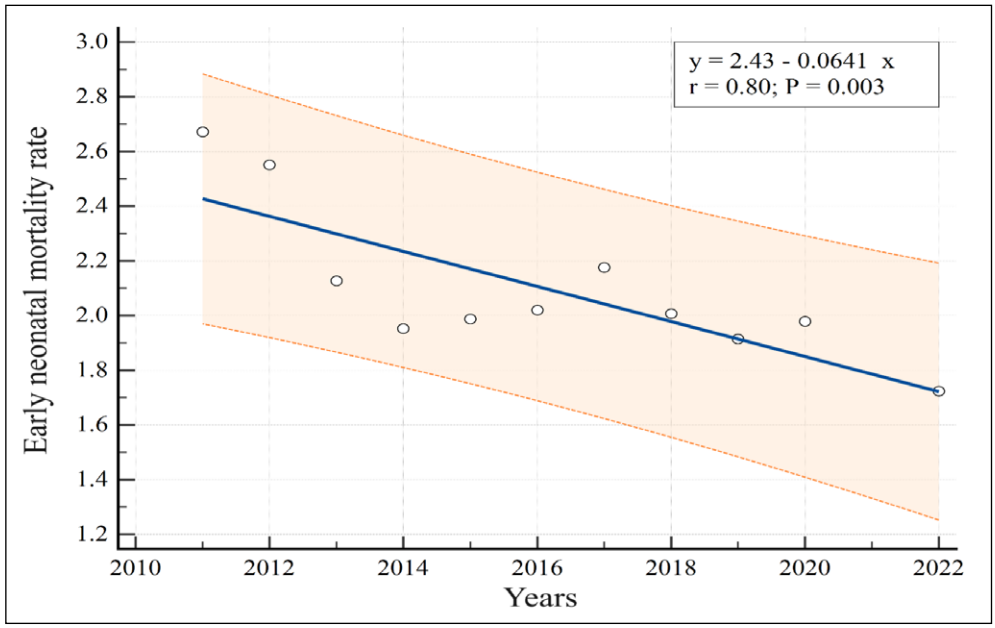

Fig. 3. Dynamics of the early neonatal mortality rate (0-6 days) per 1,000 births in Ukraine in the period 2012-2022 (‰).

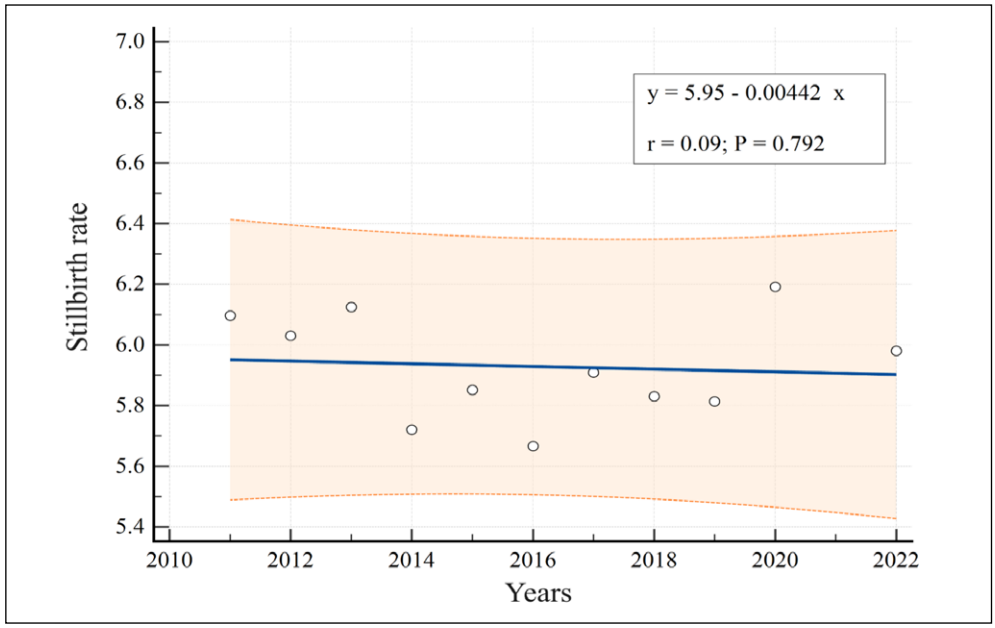

Fig.4. Dynamics of the stillbirth rate per 1,000 births in Ukraine in the period 2012-2022 (‰).

From 2012 to 2022, the proportion of premature stillbirths increased from 58.1% to 65.4%. According to the linear regression model, by 2027 Ukraine is expected to see a significant increase in the proportion of preterm stillbirths to 71.2% (R^2=0.95, p<0.001).

From 2012 to 2022, the number of fetal deaths in Ukraine from 22 weeks of gestation up to the labour diminished by 2.5 times, from 2,760 to 1,120 cases. However, during the same period, the antenatal mortality rate increased by 5.7%, from 5.26 to 5.58, per 1.000 live births and stillbirths (Fig. 5).

Further linear model analysis predicts, that by 2027, the antenatal mortality rate in Ukraine will increase by 23.6% to 7.3 (R^2=0.7, p<0.05).

In the period from 2012 to 2022, fetal deaths during childbirth in Ukraine decreased, dropping 5-fold, from 403 to 81 cases. During the same period, the intrapartum mortality rate, which includes live and stillborn births, decreased by 48.1%, from 0.77 to 0.4 per 1,000 births (Fig. 6).

According to the predictions from a linear regression model, by 2027, the intrapartum mortality rate in Ukraine is expected to decrease by 55.0%, to 0.18 (R^2 =0.91, p<0.001).

From 2012 to 2022, the perinatal mortality rate in Ukraine fell from 8.59 to 7.72 per 1,000 live births and stillborn births, or by 10.1% (Fig. 7).

According to the linear regression model, the perinatal mortality rate in Ukraine is expected to drop by 5.4%, to 7.3‰ by 2027 (R^2=0.63, p<0.05).

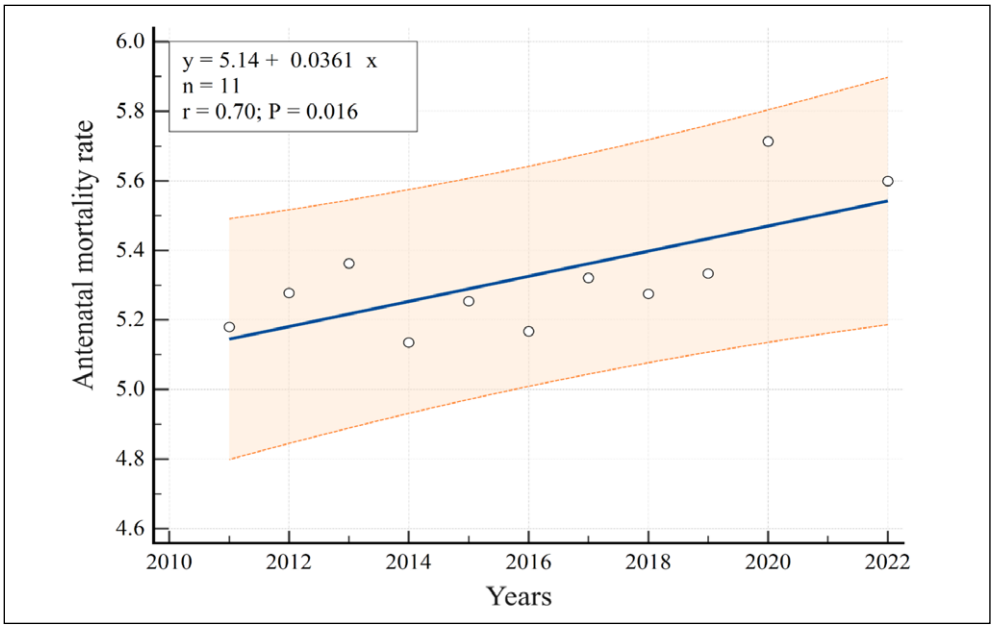

Fig. 5. Dynamics of the antenatal mortality rate per 1,000 live births and stillbirths in Ukraine in the period 2012-2022 (‰).

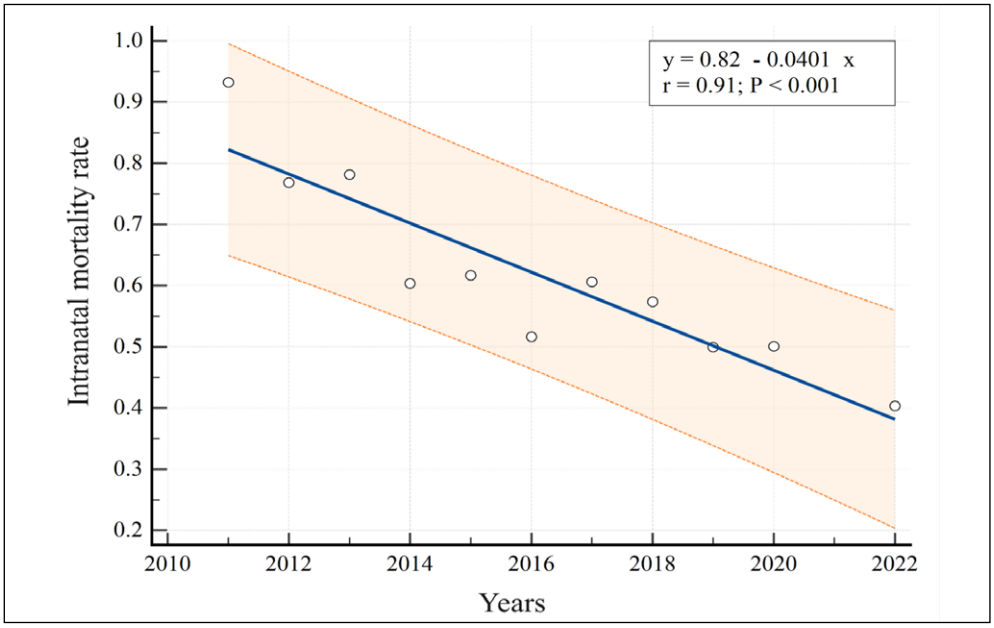

Fig. 6. Dynamics of the intrapartum mortality rate per 1,000 live births and stillbirths in Ukraine in the period 2012-2022 (‰).

DISCUSSION

The analysis of the presented research results indicates significant challenges to the structuring and implementation of perinatal care in Ukraine.

Ukraine is experiencing a significant decrease in the fertility rate, with the births in 2022 dropping by 2.5 fold, compared to compared to 2011. Two years of war have further exacerbated the birth rate. It is predicted that Ukraine might have the lowest birth rate in the European Union. At the same time, the proportion of premature babies and newborns weighing less than 1,000 grams, and those weighing 1,000-2,499 grams is significantly increasing among newborns. The characteristics of newborns by weight and gestational birth age reflect the conditions of fetal development, and serve an integral indicator of the woman's reproductive health, the progression of pregnancy, and the mother's quality of life. This value is objective by nature, and can be determined at the population level [4]. According to our study, a further increase in the number of these newborns is predicted, which requires special attention of pediatricians-neonatologists and certain technologies to ensure the high-quality perinatal care.

In Ukraine, between 2011 and 2022, there was a notable reduction in neonatal mortality, with a 3.7-fold decline. The neonatal mortality rate is projected to further decrease to 1.71 per 1,000 newborns in 2027. By this, Ukraine will comply with the UN Sustainable Development Goals, which stipulate no more than 12 deaths per 1,000 newborns by 2030 [7]. However,

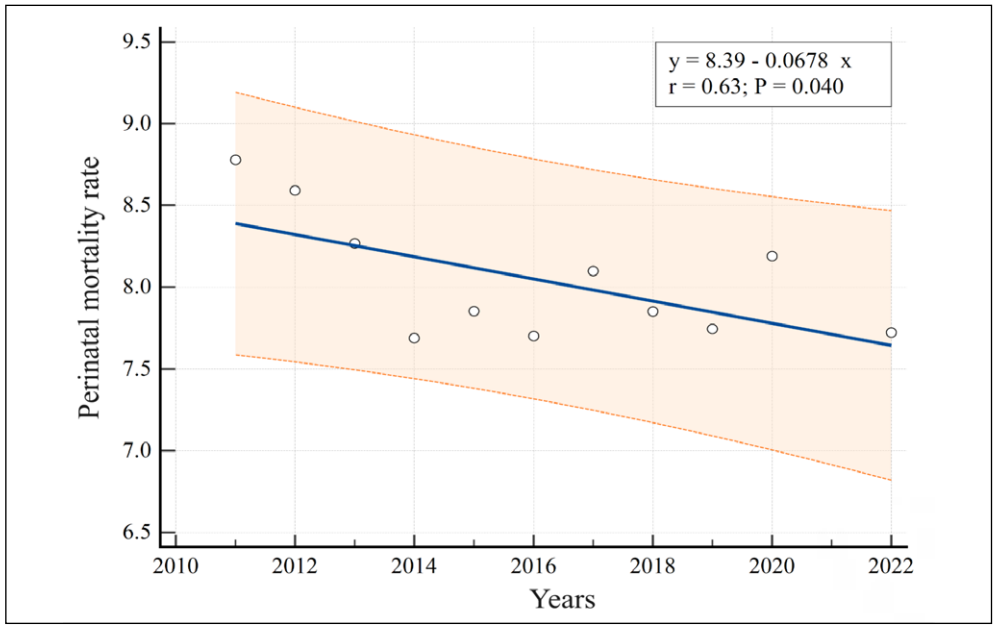

Fig. 7. Dynamics of the perinatal mortality rate per 1,000 live births and stillbirths in Ukraine in the period 2012-2022 (‰).

in Ukraine, there is still a significant upward trend in mortality of premature infants and those weighing less than 1,000 grams ($p<0.05$).

According to our prognosis, the stillbirth rate remains stable in Ukraine, but exceeds that in the European Union. The main cause of stillbirth is preterm birth [9].

Approximately 15 million preterm infants are born worldwide every year, which indicates 11% of all births [10]. With about 1 million children dying before the age of five due to complications from preterm births, , it makes a leading cause of death among children under 5, accounting for 18% of this age group deaths, and 35% of all neonatal deaths [10]. In addition, survivors of preterm birth may have lifelong disabilities, such as hearing and vision loss or learning disabilities [9, 11, 12]. The issue of preterm birth is of crucial importance for achieving the UN Sustainable Development Goals, which aim to eradicate all preventable deaths of newborns and children under the age of 5 by 2030 [7]. Various clinical, biological, environmental, and demographic factors affect the pregnancy outcomes. Maternal genetics, environmental exposure, stress level, nutrition quality, medical history, socioeconomic status, race and ethnicity, all play a role in determining the success of pregnancy [13]. However, the organization of perinatal care should be aimed at timely detection of threatening conditions during pregnancy in women. Addressing the issue of preventing preterm birth requires the perinatal service to emphasize the course of pregnancy by providing effective pregnancy support, including at the primary care [14, 15].

Our study predicts a rise in antenatal mortality in Ukraine. Therefore, OBGYNs need to perform a timely assessment of antenatal risk during pregnancy management. The high rates of antenatal mortality risk are definitely associated with the mother's age, history of stillbirth, male sex of fetus, congenital anomalies, etc.

The study shows that intrapartum and perinatal mortality is expected to decrease in Ukraine. As of 2022, the perinatal mortality rate in Ukraine stood as 7.72 per 1,000 newborns, which is significantly higher than in the European Union. Among the EU member states, this figure was 5.3 per 1000 newborns in 2021 [16]. The perinatal mortality is a critical measure of quality of perinatal services in a country.

Therefore, during the post-war reconstruction period in Ukraine, emphasized increase in the birth rate, and improvement of the perinatal care are required.

CONCLUSIONS

The findings indicate the need to refine the health care infrastructure and resources of perinatal care, considering the steady decline in fertility, improving medical care for preterm and low birthweight infants, preventing stillbirths in women through effective monitoring of pregnancy, involving screening programs for the timely detection of congenital anomalies and prevention of extragenital pathology.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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CONTENTS

A comprehensive analysis of anthropometric indicators in preschool children suffering from recurrent respiratory infections

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ABSTRACT

Aim: To determine the state of relationship between anthropometric indicators and susceptibility to recurrent respiratory infections in preschool children.

Materials and Methods: A total of 143 children (73 boys and 70 girls) aged 12-59 months, undergoing inpatient treatment on acute respiratory infection, were involved in the clinical study. The number of acute respiratory infection episodes during a previous year of their lives was taken into account. Besides, the basic indicators of physical development were assessed in the children, including: 1) body weight; 2) body length; 3) chest circumference; 4) body mass index; 5) body surface area; 6) Vervek's index.

Results: Cross-tabulation and rank correlation analysis did not demonstrate any interdependence between the susceptibility of the children examined to recurrent respiratory infections and their anthropometric indicators. Simultaneously, linear regression analysis showed that in the children aged 12-23 months, resistance index depended on their age and body length. The relative importance of the combined effect of the two above-mentioned indicators among all other potential risk factors for recurrent respiratory infections was 32.2%.

Conclusions: The detailed analysis of the findings outlined the methodological basis for further studies of the association between the incidence of acute respiratory infections in preschool children and their physical development. Multivariate statistical calculations of various risk factors for recurrent respiratory infections, including abnormal anthropometric indicators, are likely to increase the informational value of subsequent examinations.

KEY WORDS: preschoolers, physical development, repeated acute respiratory diseases

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INTRODUCTION

Acute respiratory infections (ARI), commonly diagnosed in preschool children, are considered to be one of the most pressing health challenge worldwide [1-3]. Characteristically, high incidence rates of ARI are directly and closely correlated with low levels of economic well-being in the population [2,4]. It is also worth noting that ARI is the leading cause of child mortality [5]. Globally, about 20% of all deaths among patients aged under 5 years are caused by ARI, most often in the form of severe pneumonia [6].

Parents and doctors, especially pediatricians, infectiologists and immunologists, are concerned when a child suffers from repeated or recurrent respiratory infections (RRI). Children with RRI pose a serious socio-economic burden for their families and society as a whole [7,8]. According to data published by G. Pasternak et al., RRI is diagnosed in 10-15% of child population [9].

Numerous reports were published on a large number of different factors (perinatal, individual, family, household, environmental, socioeconomic, etc.) contributing to frequent ARI episodes, especially in preschoolers [7,10-12]. In particular, these factors include significant deviations in their physical development from normal values. Specifically, it was reported that malnutrition is an important predictor of the increased incidence of lower respiratory tract infections in the children aged under 2 years [2]. Also, there was an evidence of relationship between ARI incidence in the children and their growth retardation frequency [13]. On the other hand, obesity in the pediatric patients also increases the likelihood of ARI [14]. However, the other findings showed no association between overweight or obesity in the children and the increased risk of hospitalization due to ARI [15].

Summing up all the above, further studies of the combination of abnormal anthropometric indicators and increased susceptibility of children to RRI are quite reasonable.

AIM

To determine the state of relationship between anthropometric indicators and susceptibility to recurrent respiratory infections in preschool children.

MATERIALS AND METHODS

The observational case-control study was undertaken in the pediatric somatic departments of the multi-field hospitals in the cities of Rubizhne, Kreminna and Sievierodonetsk, Luhansk region (Ukraine) in 2019-2021. An examination of 143 children (73 boys and 70 girls) aged 12-59 mos. hospitalised with ARI was carried out. According to the patients' anamneses, they had 1 to 15 ARI episodes during a previous year of their lives, including the current case.

The criteria for including children in the observation group were as follows: 1) gender - male and female; 2) age - from 12 completed mos. to 59 mos. 29 days; 3) ARI diagnosed with involvement of upper or lower respiratory tract; 4) body weight (BW) and body length (BL) of the patients examined were within (1-99)% range according to the current WHO standards [16]; 5) the absence of any diagnosed chronic disease; 6) the presence of informed parental consent to scientific study on a child; 7) children were not enrolled in other clinical trials.

Two integral clinical indicators were calculated for each patient: 1) modified infection index (InI) as the ratio of the number of ARI episodes during a previous year to a child's age, expressed in mos.; 2) resistance index (RI), representing the average number of ARI episodes per 1 mo. of a previous year. Apart from that, the basic anthropometric indicators of the children examined were measured and computed: 1) BW; 2) BL, 3) chest circumference (CC), 4) body mass index (BMI) by Ketle; 5) body surface area (BSA) by Dubois; 6) body proportion index by Vervek.

The recorded anthropometric indicators (BW, BL, BMI) were compared with standard percentile ranges [16]. The attribution of the integral anthropometric parameters (BW/BL, BW/age, BL/age, BMI/age) to particular standard deviation intervals or Z-intervals was determined with special software - "WHO Anthro" [17].

The study was conducted in accordance with the principles of the Declaration of Helsinki (2013). The local ethics committees of Bogomolets National Medical University (Kyiv, Ukraine) and Luhansk State Medical University (Rubizhne, Ukraine) approved the study protocol.

The statistical processing of the digital data was performed using the IBM SPSS Statistics 28 licensed software (USA). The Shapiro-Wilk test was used to verify whether the interval indicators complied with the normal distribution law. After that, such non-parametric characteristics as median (Me), Q_1 (25%) and Q_3 (75%) quartiles, quartile variation (V_q), minimum (X_{min}) and maximum (X_{max}) values of the indicator were used to describe the variation series.

Besides, the statistical computations included Kruskal-Wallis H-test, rank correlation analysis with the Spearman's coefficient (ρ) calculation, cross-tabulation with the Cramer's coefficient (φ_c) calculation, and linear regression analysis. In rank correlation and regression analyses, 95% confidence interval (CI) for the main coefficients was taken into account. The results obtained were considered significant if their asymptotic significance was less than 0.05 ($p<0.05$).

RESULTS

Initially, all the children examined were divided into four age subgroups: I - 12-23 mos., II - 24-35 mos., III - 36-47 mos., IV - 48-59 mos. (Table 1). As shown in this table, the total number of boys and girls in the observation group was almost equal. However, there were significant differences regarding the ratio between them in the age subgroups. Also, for all the patients examined, 6 ARI episodes per year was chosen as the threshold number to divide them into 2 frequency subgroups. Children who experienced 1-6 ARI episodes (subgroup A) in a previous year dominated over those who had more ARI episodes (subgroup B). The total number of patients with more frequent ARI episodes was almost 2.6 times lower as compared to those with less frequent ARI episodes. In children of subgroup I, the current episode of ARI was most often in the form of obstructive bronchitis (35.5%). Among the patients from the other age subgroups, community-acquired pneumonia was the most common diagnosis (Table 1).

The basic descriptive statistics for the anthropometric indicators taken into consideration are presented in Table 2. It was noteworthy that in all the age subgroups, low values of quartile variation were found for all these indicators, not exceeding 12%. With that, the V_q values for InI and RI in the children of different ages were significantly higher ranging from 24.22% to 39.93%. This evidenced a significant differentiation of the patients from all the age subgroups by the number of ARI episodes in their cases history (Table 2).

The Kruskal-Wallis H-test showed a difference between the age subgroups on InI ($H=35.013$; $p<0.001$) and RI ($H=10.072$; $p=0.018$). It was notable that for InI the average rank of its values decreased from subgroup I to subgroup IV. For RI, on the contrary, this rank decreased from subgroup IV to subgroup I.

Table 1. General characteristics of the examined children

Characteristic	Examined children				Total, n (%)
	Subgroup I, n (%)	Subgroup II, n (%)	Subgroup III, n (%)	Subgroup IV, n (%)	
Gender:					
- male	17 (54,8)	17 (44,7)	17 (41,5)	22 (66,7)	73 (51,0)
- female	14 (45,2)	21 (55,3)	24 (58,5)	11 (33,3)	70 (49,0)
ARI episodes p.a.:					
- 1-6 (subgroup A)	26 (83,9)	28 (73,7)	28 (68,3)	21 (63,6)	103 (72,0)
- 7 and ↑ (subgroup B)	5 (16,1)	10 (26,3)	13 (31,7)	12 (36,4)	40 (28,0)
Current diagnosis:					
- rhinopharyngitis	3 (9,7)	4(10,5)	3 (7,3)	5 (15,2)	15 (10,5)
- laryngopharyngitis	-	-	2 (4,9)	1 (3,0)	3 (2,1)
- laryngotracheitis	-	2 (5,3)	1 (2,4)	1 (3,0)	4 (2,8)
- acute bronchitis	7 (22,6)	14 (36,8)	11 (26,8)	14 (42,4)	46 (32,2)
- acute obstructive bronchitis	11 (35,5)	3 (7,9)	2 (4,9)	2 (6,1)	18 (12,6)
- community-acquired pneumonia	10 (32,2)	15 (39,5)	22 (53,7)	10 (30,3)	57 (39,8)

The distribution of the children examined by classification of their BW, BL and BMI into the percentile ranges according to the current WHO standards [16] is given in Table 3. It should be noted that most of the values of these physical development indicators in all the age subgroups were within the "central" combined range – 15-85% (Table 3).

Table 4 provides the data on the belonging of their 4 integral anthropometric parameters, namely: BW/BL, BW/age, BL/age, and BMI/age, to Z-intervals. This belonging was determined using the "WHO Anthro" software [17]. As with the percentile ranges, Z-scores for all these integral parameters in the children examined from all the age subgroups fell within the middle combined interval – ((-2Z)-(+2Z)).

Beforehand, the chosen categories for the patients' characteristics were coded in all the subgroups, namely: 1) gender, 2) the number of ARI episodes in a previous year (subgroups A and B), 3) the current clinical diagnosis, 4) the percentile range for BW, BL and BMI; 5) the Z-interval for BW/BL, BW/age, BL/age, BMI/age. Subsequent cross-tabulation carried out in the age subgroups between children with less and more frequent ARI episodes, on the one hand, and separately with all the other above-mentioned characteristics, on the other hand, did not demonstrate any interdependence between them in any case.

Rank correlation analysis conducted in all the age subgroups also revealed no association between InI and RI, on the one hand, and the anthropometric indicators studied (BW, BL, CC, BMI, BSA, and Vervek's index), on the other hand. Only a high or very high correlation degree between InI and RI should be noted for the children from all the subgroups. For instance, it was the lowest in subgroup I (ρ=0.880, p<0.001, CI: 0.759-0.942), and the highest in subgroup III (ρ=0.974, p<0.001, CI: 0.951-0.987).

Using linear regression analysis with stepwise inclusion of independent factors, an attempt was made to identify those that have a significant impact on the considered indices of ARI recurrence. In the children, 7 potential predictors were tested: BW, BL, CC, BMI, BSA, Vervek's index and their age. It was demonstrated that only in subgroup I, when using RI as a dependent variable, the prognostic model with 2 independent factors, specifically the patients' age and their BL, was obtained (Formula). The modelling was unsuccessful for the other age subgroups.

Formula:

$RI(p) = 1.474^{*} + 0.049^{**} \times \text{age (mos.)} - 0.024^{***} \times \text{BL (cm)}$,

where RI(p) - predicted RI; * - constant B (p=0.028; 95% CI: 0.170-2.778);

** - coefficient b_1 (p=0.001; 95% CI: 0.021-0.077);

*** - coefficient b_2 (p=0.023; 95% CI: (-0.045)-(-0.004)).

According to the mathematical algorithm presented, in children aged 12-23 mos., the predicted RI rises with increasing age and reduces with increasing BL. It should be added that the value of determination coefficient (R^2), taking into account the constant and both predictors, was 0.322. This means that for the children from subgroup I, the influence of these predictors on RI was quite high, accounting for 32.2% among all other possible predictors.

DISCUSSION

Thus, cross-tabulation and rank correlation analysis did not demonstrate any interdependence between the basic indicators of physical development in the

Table 2. Descriptive statistics of basic indicators in the examined children

Indicator	Me	Q_1–Q_3	V_q,%	X_{min}	X_{max}
Subgroup I, n=31					
Age, mos.	18,0	14,0–21,0	19,44	12,0	23,0
BW, kg	11,0	10,0–12,0	9,09	9,0	14,5
BL, cm	80,0	77,0–86,0	5,63	72,0	92,0
CC, cm	50,0	47,5–51,5	4,00	43,0	55,0
BMI, kg/m^2	17,19	15,60–19,20	10,47	14,18	21,33
BSA, m^2	0,482	0,454–0,522	7,05	0,422	0,566
Vervek's index, RU	1,12	1,07–1,18	4,91	1,01	1,24
InI, RU	0,250	0,167–0,333	33,20	0,056	0,563
RI, RU	0,333	0,250–0,500	37,54	0,083	0,917
Subgroup II, n=38					
Age, mos.	31,5	28,8–34,0	8,25	24,0	35,0
BW, kg	13,0	12,0–15,0	11,54	10,5	17,0
BL, cm	93,0	90,0–96,0	3,23	82,0	102,0
CC, cm	52,0	49,0–54,0	4,81	46,0	57,0
BMI, kg/m^2	15,66	14,47–16,39	6,13	13,01	18,14
BSA, m^2	0,571	0,544–0,620	6,65	0,476	0,685
Vervek's index, RU	1,18	1,14–1,24	4,24	1,07	1,32
InI, RU	0,169	0,111–0,220	32,25	0,029	0,577
RI, RU	0,417	0,250–0,583	39,93	0,083	1,250
Subgroup III, n=41					
Age, mos.	42,0	37,5–44,0	7,74	36,0	47,0
BW, kg	14,7	13,4–16,0	8,84	11,0	20,0
BL, cm	99,0	96,0–102,0	3,03	92,0	108,0
CC, cm	54,0	52,0–55,0	2,78	48,0	59,0
BMI, kg/m^2	14,71	14,15–15,89	5,91	11,53	19,22
BSA, m^2	0,626	0,594–0,667	5,83	0,528	0,765
Vervek's index, RU	1,20	1,15–1,25	4,17	1,04	1,38
InI, RU	0,128	0,094–0,156	24,22	0,053	0,256
RI, RU	0,417	0,333–0,583	29,98	0,167	0,917
Subgroup IV, n=33					
Age, mos.	54,0	50,0–56,0	5,56	48,0	59,0
BW, kg	17,0	16,0–19,5	10,29	14,0	22,5
BL, cm	107,0	103,5–112,0	3,97	95,0	119,0
CC, cm	56,0	54,0–57,6	3,21	50,0	67,0
BMI, kg/m^2	15,42	14,65–16,49	5,97	10,77	18,69
BSA, m^2	0,702	0,679–0,771	6,55	0,617	0,863
Vervek's index, RU	1,17	1,13–1,22	3,85	1,06	1,32
InI, RU	0,111	0,081–0,147	29,73	0,018	0,260
RI, RU	0,500	0,333–0,667	33,40	0,083	1,083

Note: RU - relative unit

different age subgroups of the children aged 12-59 mos. and their susceptibility to RRI. On the one hand, this is in line with the data from Pieniawska-Śmiech et al. according to which BW, BL and BMI in the patients aged 4 weeks to 18 years with RRI did not differ from the same indicators in the control subjects who did not have any history of frequent ARI episodes [18]. On the other hand, there are the current scientific publications that confirm

Table 3. Distribution of the examined children by their BW, BL and BMI belonging to percentile ranges

Percentile range*	Anthropometric indicator		
	BW, n (%)	BL, n (%)	BMI, n (%)
Subgroup I, n=31			
1-3%	-	1 (3,2)	-
3-5%	-	1 (3,2)	-
5-15%	-	7 (22,6)	1 (3,2)
15-25%	2 (6,4)	1 (3,2)	2 (6,5)
25-50%	5 (16,1)	3 (9,7)	4 (12,9)
50-75%	8 (25,8)	7 (22,6)	9 (29,0)
75-85%	6 (19,4)	4 (12,9)	1 (3,2)
85-95%	6 (19,4)	3 (9,7)	4 (12,9)
95-97%	1 (3,2)	1 (3,2)	2 (6,5)
97-99%	3 (9,7)	3 (9,7)	4 (12,9)
higher 99%	-	-	4 (12,9)
Subgroup II, n=38			
1-3%	-	-	1 (2,6)
3-5%	-	1 (2,6)	2 (5,3)
5-15%	5 (13,2)	3 (7,9)	6 (15,8)
15-25%	1 (2,6)	2 (5,3)	2 (5,3)
25-50%	8 (21,1)	9 (23,7)	8 (21,0)
50-75%	13 (34,2)	9 (23,7)	10 (26,3)
75-85%	3 (7,9)	3 (7,9)	3 (7,9)
85-95%	7 (18,4)	6 (15,8)	5 (13,2)
95-97%	1 (2,6)	1 (2,6)	1 (2,6)
97-99%	-	4 (10,5)	-
Subgroup III, n=41			
lower 1%	-	-	1 (2,4)
1-3%	1 (2,4)	-	3 (7,3)
5-15%	5 (12,2)	5 (12,2)	4 (9,8)
15-25%	4 (9,8)	5 (12,2)	8 (19,6)
25-50%	14 (34,2)	9 (21,9)	10 (24,4)
50-75%	8 (19,5)	9 (21,9)	7 (17,1)
75-85%	5 (12,2)	4 (9,8)	3 (7,3)
85-95%	1 (2,4)	6 (14,7)	3 (7,3)
95-97%	3 (7,3)	-	-
97-99%	-	3 (7,3)	1 (2,4)
higher 99%	-	-	1 (2,4)
Subgroup IV, n=33			
lower 1%	-	-	1 (3,0)
1-3%	1 (3,0)	1 (3,0)	-
3-5%	-	1 (3,0)	-
5-15%	3 (9,1)	3 (9,1)	1 (3,0)
15-25%	-	3 (9,1)	4 (12,1)
25-50%	9 (27,3)	7 (21,2)	8 (24,2)
50-75%	8 (24,2)	5 (15,2)	9 (27,3)
75-85%	4 (12,1)	5 (15,2)	5 (15,2)
85-95%	6 (18,2)	2 (6,1)	3 (9,1)
95-97%	2 (6,1)	2 (6,1)	-
97-99%	-	4 (12,0)	2 (6,1)

Note: * - only the percentile ranges including at least one indicator were shown.

Table 4. Distribution of the examined children by their integral anthropometric parameters belonging to Z-intervals

Z-interval*	Integral anthropometric parameter			
	BW/BL, n (%)	BW/age, n (%)	BL/age, n (%)	BMI/age, n (%)
Subgroup I, n=31				
(-3)-(-2) Z	-	-	1 (3,2)	-
(-2)-(-1) Z	1 (3,2)	-	8 (25,8)	1 (3,2)
(-1)-0 Z	10 (32,3)	6 (19,4)	5 (16,1)	6 (19,3)
0-(+1) Z	6 (19,4)	15 (48,4)	10 (32,3)	10 (32,3)
(+1)-(+2) Z	9 (29,0)	9 (29,0)	5 (16,1)	10 (32,3)
(+2)-(+3) Z	5 (16,1)	1 (3,2)	2 (6,5)	3 (9,7)
↑(+3) Z	-	-	-	1 (3,2)
Subgroup II, n=38				
(-3)-(-2) Z	-	-	-	1 (2,6)
(-2)-(-1) Z	8 (21,1)	5 (13,2)	4 (10,5)	8 (21,1)
(-1)-0 Z	11 (28,9)	10 (26,3)	11 (28,9)	11 (28,9)
0-(+1) Z	13 (34,2)	15 (39,5)	12 (31,6)	12 (31,6)
(+1)-(+2) Z	6 (15,8)	8 (21,0)	8 (21,1)	6 (15,8)
(+2)-(+3) Z	-	-	3 (7,9)	-
Subgroup III, n=41				
↑(-3) Z	1 (2,4)	-	-	1 (2,4)
(-3)-(-2) Z	2 (4,9)	-	-	3 (7,3)
(-2)-(-1) Z	5 (12,2)	8 (19,5)	5 (12,2)	6 (14,6)
(-1)-0 Z	17 (41,5)	17 (41,5)	14 (34,1)	16 (39,0)
0-(+1) Z	10 (24,4)	12 (29,2)	13 (31,7)	9 (22,0)
(+1)-(+2) Z	5 (12,2)	4 (9,8)	6 (14,7)	4 (9,8)
(+2)-(+3) Z	1 (2,4)	-	3 (7,3)	2 (4,9)
Subgroup IV, n=33				
↑(-3) Z	1 (3,0)	-	-	1 (3,0)
(-3)-(-2) Z	-	-	1 (3,1)	-
(-2)-(-1) Z	2 (6,1)	4 (12,1)	4 (12,1)	1 (3,0)
(-1)-0 Z	11 (33,3)	9 (27,3)	10 (30,3)	12 (36,4)
0-(+1) Z	14 (42,4)	12 (36,4)	10 (30,3)	13 (39,4)
(+1)-(+2) Z	4 (12,2)	8 (24,2)	4 (12,1)	5 (15,2)
(+2)-(+3) Z	1 (3,0)	-	4 (12,1)	1 (3,0)

Note: * - only the Z-intervals including at least one parameter were shown.

the higher susceptibility of children to RRI if they have substantial deviations in anthropometric indicators [13,14]. It should also be taken into consideration that in all the age subgroups, the total number of children with physical development indicators belonging to the extreme percentile ranges and Z-intervals was relatively small. This could be the main reason for the ineffectiveness of the above-mentioned correlation analyses. Nevertheless, linear regression analysis performed in the children aged 12-23 mos. was effective, demonstrating the dependence of RI on their age and BL. This suggests planning and conducting further studies on the relationship between anthropometric indicators and the frequency of ARI episodes in preschool children.

Several limitations of the study should be acknowledged. First, the study involved only those children who were undergoing hospital treatment, and outpatients were not included. Second, there are still some doubts about the accuracy of anamnestic data on the frequency of ARI episodes taken into account. Third, the number of subjects in the age subgroups was relatively small. Fourth, the informativeness regarding the impact of anthropometric indicators on children's susceptibility to RRI may be reduced, as the simultaneous combined effect of many known RRI risk factors [10-12] was not considered. Finally, the findings probably cannot be entirely

extrapolated to all children of the same age from different countries due to certain differences in the physical development of child's body, which are determined by geographical or even regional lifestyle conditions.

CONCLUSIONS

In the children aged 12-59 mos., cross-tabulation and rank correlation analysis showed no association between their susceptibility to recurrent respiratory infections and anthropometric indicators. At the same time, among the children aged 12-23 mos., linear regression analysis revealed significant dependence of resistance index on their age and body length. The methodological grounds for further studies of the relationship between preschoolers' susceptibility to frequent acute respiratory infections and the state of their physical development were outlined.

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CONFLICT OF INTEREST
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ORIGINAL ARTICLE

CONTENTS

Effectiveness of rifaximin and probiotics for the correction of intestinal permeability in patients with metabolic-associated fatty liver disease in combination with type 2 diabetes mellitus

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ABSTRACT

Aim: To investigate the effectiveness of rifaximin and probiotics for the correction of intestinal permeability in patients with metabolic-associated fatty liver disease (MAFLD) in combination with type 2 diabetes mellitus.

Materials and Methods: The prospective interventional randomized investigation included 68 patients with MAFLD in combination with type 2 diabetes, who were examined and divided into the 2 groups of treatment.

Results: The serum levels of interleukin (IL) - 6, IL-10 and zonulin, indicators of liver functional activity, liver attenuation coefficient between treatment group vs. control group after 2 weeks, 1 month, 3 and 6 months of therapy were significant differed. The serum levels of IL-6 and zonulin significantly decreasing and increasing of IL-10 in the treatment group after 2 weeks, 1, 3 and 6 months of combined therapy. When comparing of stool short-chain fatty acids concentration between treatment group vs. control group after 2 weeks, 1 month, 3 and 6 months of therapy the levels of acetic, butyric and propionic acids significantly differences and increase in their levels were established.

Conclusions: The results of the study in dynamics during 6 months show that the additional appointment of rifaximin, multispecies probiotic and prebiotic to metformin in patients with MAFLD and type 2 diabetes led to the elimination of subclinical inflammation, modulation of the permeability of the intestinal barrier and lowering increased intestinal permeability, as well as to the lower serum activity of liver aminotransferases and decrease the stage of steatosis.

KEY WORDS: inulin, multispecies probiotic, pectin, rifaximin, short-chain fatty acids, zonulin

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INTRODUCTION

Metabolic-associated fatty liver disease (MAFLD) is the most common multisystem chronic liver disease worldwide, which is closely related to obesity, insulin resistance, type 2 diabetes, and atherogenic dyslipidemia, and includes a wide spectrum of diseases from hepatic steatosis to steatohepatitis (NASH), fibrosis and cirrhosis of the liver, and may progress to hepatocellular carcinoma [1]. MAFLD and type 2 diabetes are pathophysiologically interconnected by insulin resistance and lipotoxicity. In recent years, there has been a growing interest in the intestinal-liver axis, the dysfunction of which leads to intestinal dysbiosis, bacterial overgrowth syndrome, and increased intestinal permeability [2].

The results of experimental and clinical studies revealed an increase in the number of gram-negative bacteria of the Bacteroidetes type compared to the number of gram-positive bacteria of the Firmicutes type in patients with MAFLD and type 2 diabetes [3]. Violation of intestinal bacterial homeostasis and changes in the content and distribution of bacteria in the intestine and their metabolic functions in patients with MAFLD and type 2 diabetes lead to increased permeability of the intestinal barrier, bacterial translocation and endotoxemia, which is a trigger for increased synthesis of zonulin, a protein that is one of the regulators of intestinal permeability [4]. Bacterial components of intestinal microbiota are ligands of Toll-like receptors. Intestinal dysbiosis and impaired intestinal barrier permeability contribute to increased hepatic expression of Toll-like receptors (TLRs) (TLR2, TLR4, TLR5, and TLR9) that recognize lipopolysaccharide (LPS), peptidoglycan, flagellin, and bacterial DNA [5]. This leads to the stimulation of Toll- and Nod-like receptors, which trigger a cascade of signaling reactions and the stimulation of excessive production of pro-inflammatory cytokines and chemokines by Kupffer cells, which initiate the process of chronic subclinical inflammation, which leads to inflammatory-destructive changes in the liver with subsequent progression to fibrosis [6].

The modulation of the intestinal microbiota with the help of antibiotics, probiotics, and prebiotics is a mod-

ern promising therapeutic direction for the correction of intestinal dysbiosis and impaired intestinal barrier permeability.

AIM

The aim of the study was to investigate the effectiveness of rifaximin and probiotics for the correction of intestinal permeability in patients with MAFLD in combination with type 2 diabetes mellitus.

MATERIALS AND METHODS

The study was conducted at Bogomolets National Medical University, Department of Internal Medicine № 1 (Kyiv, Ukraine) in accordance with Ukrainian laws, requirements of Good Clinical Practice and ethical principles of the Declaration of Helsinki. Written informed consent for participation in the investigation was obtained from all participants before the trial began. The protocol was approved by the Bioethical Committee of Bogomolets National Medical University (Ref. № 150/18.10.2021). The prospective interventional randomized investigation included 68 patients with MAFLD in combination with type 2 diabetes mellitus, who were examined and divided into the 2 groups of treatment. The control group included 34 patients with MAFLD in combination with type 2 diabetes, who were prescribed metformin monotherapy 500 mg 2 times a day. The treatment group - 34 patients with MAFLD in combination with type 2 diabetes, who were prescribed combined therapy - in addition to metformin, rifaximin 1200 mg/day was prescribed, i.e. in a dose of 200 mg 2 tablets 3 times a day for 14 days, multispecies probiotic containing live lyophilized bacteria (Lactobacillus, Bifidobacterium, Saccharomyces boulardii) 1 capsule 2 times a day and prebiotic containing lyophilized concentrates of Jerusalem artichoke (inulin) and apples (pectin) 1 sachet 2 times a day for 6 months.

Investigational drugs:

1. Metformin 500 mg prolonged-release tablets.
2. Rifaximin 200 mg tablets.
3. Capsules containing live lyophilized bacteria 10.0×10^9 CFU (Lactobacillus acidophilus — 2.0×10^9 CFU, Lactobacillus rhamnosus — 1.5×10^9 CFU, Lactobacillus plantarum — 1.5×10^9 CFU, Lactobacillus reuteri — 1.0×10^9 CFU, Lactobacillus casei — 1.0×10^9 CFU, Bifidobacterium bifidum 1.0×10^9 CFU, Saccharomyces boulardii — 2.0×10^9 CFU).
4. Powder 6 g per sachet containing lyophilized concentrates of Jerusalem artichoke (inulin) and apples (pectin).

The inclusion criteria were men and women aged 25-78 years, patients with MAFLD in combination with type 2 diabetes, whose diagnosis was established by determining the degree of steatosis based on the results of ultrasound steatometry performed on the scale of ultrasound attenuation (coefficient of ultrasound attenuation ≥2.2 dB/cm) and diagnostic criteria disorders of carbohydrate metabolism: 1) HbA1c > 6.5%; 2) fasting plasma glucose (FPG) test ≥ 7.0 mmol/l; 3) 2-hour plasma glucose during 75-g *oral glucose tolerance test* (*OGTT*) ≥ 11.0 mmol/l. The exclusion criteria included viral hepatitis, alcoholic liver disease, autoimmune hepatitis, drug-induced liver damage, Wilson-Konovalov disease, type 1 diabetes, decompensated type 2 diabetes, cancer, pregnancy, refusal to participate in the study.

For the diagnosis of MAFLD in patients, ultrasound steatometry was performed using the Ultrasign soneus P7 device with a 1–6 MHz convex sensor to determine the degree of liver steatosis according to the ultrasound attenuation coefficient scale proposed by M. Sasso et al. Type 2 diabetes mellitus (DM) was diagnosed according to the 2023 American Diabetes Association guidelines [7].

The general clinical examination included collection of complaints, history of illness and life, physical examination. During the physical examination of the patient, anthropometric indicators were measured, including height, body weight, body mass index (BMI) according to the Quetelet formula. Blood samples were collected to evaluate indicators of liver functional activity (alanine aminotransferase (ALT), aspartate aminotransferase (AST)). Analyses were performed using a biochemistry analyzer Cobas 6000 with appropriate reagent kits (Roche Diagnostics, Switzerland). The content of serum zonulin was determined by ELISA using test systems IDK Zonulin ELISA, KR5601 (Immunodiagnostic AG, Germany). The concentration of Human Interleukin 6 (IL-6) and 10 (IL-10) in serum was determined by the ELISA method using the Human Interleukin 6 and 10 ELISA Kit test systems (Elabscience, USA). The content of short-chain fatty acids in feces was determined by gas chromatography with mass spectrometry in Gas Chromatograph Perkin Elmer Clarus 680 GC (manufacturer USA).

The primary outcome measures were the changes in serum levels of interleukins (IL-6, IL-10), zonulin and evaluation of stool short-chain fatty acids (SCFAs) concentration after therapy. Secondary outcomes were the evaluation of indicators of liver functional activity (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and ultrasound attenuation coefficient after therapy.

Table 1. Baseline clinical-diagnostic characteristics of the treatment and control group participants

Parameter	Control group* (n=34)	Treatment group* (n=34)	P**
Sex (female/male) n (%)	20 (59%) / 14 (41%)	18 (53%) / 16 (47%)	0.169
Age, years	58.6 ± 2.9	59.8 ± 3.4	0.178
BMI, kg/m2	31.6 (28.8 – 35)	31.7 (29.3 – 34.6)	0.993
ALT, U/L	57.6 ± 1.1	57.8 ± 1.1	0.851
AST, U/L	49.9 ± 0.8	50.4 ± 0.9	0.566
Serum zonulin, ng/ml	69.6 ± 1.7	68.2 ± 1.5	0.292
IL-6, pg/ml	8.5 ± 0.3	8.6 ± 0.3	0.614
IL-10, pg/ml	3.6 ± 0.1	3.7 ± 0.1	0.723
Butyric acid, μmol/g	24,5 (16,9 – 25)	24,6 (17,2 – 25,7)	0.451
Acetic acid, μmol/g	74,6 (60,3 – 82,1)	74,7 (61,1 – 82,3)	0.654
Propionic acid, μmol/g	23,2 (21,1 – 26,3)	23,3 (21,4 – 26,6)	0.897
LAC, dB/cm	2.93 ± 0.04	2.94 ± 0.03	0,835

BMI: Body mass index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Interleukin 6: IL-6; Interleukin 10: IL-10; LAC : Liver attenuation coefficient

* Normally and non-normally distributed data were presented as mean ± standard deviation (SD) and median (Q1-Q3), respectively.

** For normal and non-normal distribution, t-test and Wilcoxon two-sample test were used, respectively.

Table 2. Comparison of indicators of liver functional activity between treatment group *vs*. control group throughout the study

Parameter	Time-Point	Control group* (n=34)	Treatment group* (n=34)	P**
ALT, U/L	Baseline	57.6 ± 1.1	57.8 ± 1.1	0.851
	After 2 weeks of therapy	57.5 ± 1.1	55.6 ± 1.1	0.023
	After 1 month of therapy	56.4 ± 1.2	54.3 ± 1.2	0.159
	After 3 months of therapy	53.1 ± 1.3	51.4 ± 1.3	0.014
	After 6 months of therapy	49.6 ± 1.2	47.5 ± 1.2	0,016
	P#	<0.001	<0.001	
AST, U/L	Baseline	49.9 ± 0.8	50.4 ± 0.9	0.566
	After 2 weeks of therapy	49.7 ± 0.9	47.4 ± 0.8	0.025
	After 1 month of therapy	48.2 ± 0.6	45.1 ± 0.7	0,031
	After 3 months of therapy	46.6 ± 0.5	43.2 ± 0.6	0.018
	After 6 months of therapy	44.7 ± 0.9	40.1 ± 0.8	0.022
	P#	<0.001	<0.001	

ALT: alanine aminotransferase; AST: aspartate aminotransferase

* Normally and non-normally distributed data were presented as mean ± standard deviation (SD) and median (Q1-Q3), respectively.

** For normal and non-normal distribution, t-test and Wilcoxon two-sample test were used, respectively.

For normally and non-normally distributed data, one-way repeated measures ANOVA and the Friedman test were used, respectively.

The GraphPad Prism Version 9.5.1.733 program was used for statistical processing of the obtained results. When checking the distribution of the obtained data for normality, the Shapiro-Wilk test was used. In the case of a normal distribution, quantitative variables were described by the arithmetic mean value with a standard deviation (Mean±SD), if different from the normal distribution, by the median with the first and third quartiles (Median (Q1-Q3)). In the case of a normal distribution of the data, the unpaired Student's t-test was used to check the probability of the difference between the mean values, and in the case of a non-normal distribution, the Wilcoxon test was used.

In the case of a normal distribution, using one-way repeated measures analysis of variance (ANOVA) with a preliminary implementation of the Mockley test of sphericity, or in the case of a non-normal distribution, the Friedman test was used to analyze the difference between the values at different time points of the study. In case of repeated measurements, the probability of difference between three or more mean values in the case of a nor-

Table 3. Comparison of serum levels of interleukins (IL-6, IL-10) and zonulin between treatment group *vs*. control group throughout the study

Parameter	Time-Point	Control group* (n=34)	Treatment group* (n=34)	P**
Serum zonulin, ng/ml	Baseline	69.6 ± 1.7	68.2 ± 1.5	0.292
	After 2 weeks of therapy	69.2 ± 1.2	35.2 ± 1.5	<0.001
	After 1 month of therapy	67.9 ± 1.5	30.3 ± 1.2	<0.001
	After 3 month of therapy	62.8 ± 1.4	19.7 ± 1.1	<0.001
	After 6 month of therapy	58.5 ± 1.0	10.1 ± 1.6	<0.001
	P#	<0.001	<0.001	
IL-6, pg/ml	Baseline	8.5 ± 0.3	8.6 ± 0.3	0.614
	After 2 weeks of therapy	8.4 ± 0.1	6.2 ± 0.1	<0.001
	After 1 month of therapy	8.2 ± 0.2	5.7 ± 0.2	<0.001
	After 3 month of therapy	7.9 ± 0.1	4.6 ± 0.1	<0.001
	After 6 month of therapy	7.6 ± 0.2	3.5 ± 0.2	<0.001
	P#	<0.001	<0.001	
IL-10, pg/ml	Baseline	3.6 (2.9 – 5.0)	3.7 (4.7 – 7.6)	0.723
	After 2 weeks of therapy	3.7 (2.8 – 5.1)	5.8 (4.9 – 7.8)	<0.001
	After 1 month of therapy	4.0 (2.7 – 5.2)	6.2 (5.0 – 8.5)	<0.001
	After 3 month of therapy	4.3 (3.2 – 5.2)	7.1 (6.0 – 8.6)	<0.001
	After 6 month of therapy	4.5 (3.2 – 5.4)	8.2 (7.1 – 9.7)	<0.001
	P#	<0.001	<0.001	

* Normally and non-normally distributed data were presented as mean ± standard deviation (SD) and median (Q1-Q3), respectively.

** For normal and non-normal distribution, t-test and Wilcoxon two-sample test were used, respectively.

For normally and non-normally distributed data, one-way repeated measures ANOVA and the Friedman test were used, respectively,

mal distribution was checked by the repeated measures ANOVA method, in the case of a non-normal distribution - by the Friedman test. The difference between the study groups was considered statistically significant at $P < 0.05$.

RESULTS

The baseline clinical-diagnostic characteristics of the treatment and control group participants are shown in Table 1. There were no statistically significant differences between the treatment and control groups at baseline. In patients of the control and treatment groups were established to increase of hepatic aminotransferases, serum zonulin and IL-6. Increased levels of serum IL-6 and zonulin indicate chronic subclinical inflammation and increased intestinal permeability in patients with MAFLD and type 2 diabetes. The results of steatometry established severe stage of steatosis (S3). The concentration of short-chain fatty acids in feces were reduced.

In the treatment group was significant decrease of ALT, AST activity in serum between baseline and after 2 weeks, 1, 3 and 6 months of therapy and significant differences between after 2 weeks, 1, 3 and 6 months of therapy. In the control group was significant decrease of liver enzymes in serum between baseline and after 3 and 6 months of therapy, but not between baseline and after 2 weeks and significant differences between after 2 weeks, 1, 3 and 6 months of therapy (Table 2).

When comparing of indicators of liver functional activity between treatment group vs. control group after 2 weeks,1 month, 3 and 6 months of therapy the levels of ALT and AST significant differences and decrease in their levels was established. The comparison of liver aminotransferases between the groups showed that ALT and AST levels were significantly lower in the treatment group after 2 weeks, 1, 3 and 6 months of combined therapy (Table 2).

In the treatment group was significantly lower serum levels of IL-6, zonulin and increase concentration of IL-10 between baseline and after 2 weeks, 1, 3 and 6 months of therapy and significantly differences between after 2 weeks, 1, 3 and 6 months of therapy. In the control group was significantly decrease of serum levels of IL-6, zonulin and increase concentration of IL-10 between baseline and after 1, 3 and 6 months of therapy, but not between baseline and after 2 weeks and significantly differed between after 2 weeks, 1, 3 and 6 months of therapy (Table 3).

The serum levels of interleukins (IL-6, IL-10) and zonulin between treatment group vs. control group after 2 weeks, 1 month, 3 and 6 months of therapy were significantly differed. The serum levels of IL-6 and zonulin were significantly decreasing and increasing of IL-10 in the treatment group after 2 weeks, 1, 3 and 6 months of combined therapy (Table 3).

Table 4. Comparison of stool SCFAs concentration profiles between treatment group *vs*. control group throughout the study

Parameter	Time-Point	Control group* (n=34)	Treatment group* (n=34)	P**
Acetic acid, μmol/g	Baseline	74,6 (60,3 – 82,1)	74,7 (61,1 – 82,3)	0.654
	After 2 weeks of therapy	74,8 (61.0 – 82,7)	80,8 (69,2 – 86,9)	0.002
	After 1 month of therapy	76,2 (62.0 – 83,1)	85,3 (75,4 – 92)	0.011
	After 3 month of therapy	79,4 (69,1 – 80,2)	93,1 (83,6 – 93,8)	0.033
	After 6 month of therapy	81,3 (80,7 – 82,9)	98,6 (95,4 – 100,2)	0.004
	P#	<0.001	<0.001	
Butyric acid, μmol/g	Baseline	24,5 (16,9 – 25)	24,6 (17,2 – 25,7)	0.451
	After 2 weeks of therapy	24,7 (17,6 – 25,3)	30,9 (21,5 – 33,6)	0.003
	After 1 month of therapy	26,3 (18,2 – 27,8)	33,7 (23,9 – 38,2)	0.024
	After 3 month of therapy	29,1 (19,6 – 30,2)	38,5 (25,9 – 39,3)	0.016
	After 6 month of therapy	33,2 (20,5 – 34,1)	41,8 (26,7 – 42,6)	0.001
	P#	<0.001	<0.001	
Propionic acid, μmol/g	Baseline	23,2 (21,1 – 26,3)	23,3 (21,4 – 26,6)	0.897
	After 2 weeks of therapy	23,5 (22,5 – 27,8)	29,5 (24.0 – 30,1)	0.013
	After 1 month of therapy	25,7 (23,6 – 28)	30,7 (26,1 – 31,5)	0.011
	After 3 month of therapy	28,2 (25,7 – 29,3)	35,6 (30,4 – 36,8)	0.003
	After 6 month of therapy	29,1 (27,7 – 30,1)	39,2 (35,5 – 40,9)	0.017
	P#	<0.001	<0.001	

* Normally and non-normally distributed data were presented as mean ± standard deviation (SD) and median (Q1-Q3), respectively.
** For normal and non-normal distribution, t-test and Wilcoxon two-sample test were used, respectively.
# For normally and non-normally distributed data, one-way repeated measures ANOVA and the Friedman test were used, respectively·

Table 5. Comparison of liver attenuation coefficient between treatment group *vs*. control group throughout the study

Parameter	Time-Point	Control group* (n=34)	Treatment* group (n=34)	P**
LAC, dB/cm	Baseline	2.93 (2.86 – 2.96)	2.94 (2.85 – 2.98)	0.835
	After 2 weeks of therapy	2.93 (2.86 – 2.96)	2.92 (2.84 – 2.97)	0.663
	After 1 month of therapy	2.93 (2.86 – 2.96)	2.91 (2.82 – 2.96)	0.607
	After 3 month of therapy	2.92 (2.85 – 2.94)	2.89 (2.80 – 2.94)	<0.001
	After 6 month of therapy	2.91 (2.83 – 2.92)	2.87 (2.79 – 2.91)	<0.001
	P#	>0.05	<0.001	

* Normally and non-normally distributed data were presented as mean ± standard deviation (SD) and median (Q1-Q3), respectively.
** For normal and non-normal distribution, t-test and Wilcoxon two-sample test were used, respectively.
# For normally and non-normally distributed data, one-way repeated measures ANOVA and the Friedman test were used, respectively.

In the treatment group was significantly increase of stool SCFAs concentration between baseline and after 2 weeks, 1, 3 and 6 months of therapy and significantly differences between after 2 weeks, 1, 3 and 6 months of therapy. In the control group was significantly increase levels of acetic, butyric and propionic acids between baseline and after 1, 3 and 6 months of therapy, but not between baseline and after 2 weeks and significantly differed between after 2 weeks, 1, 3 and 6 months of therapy (Table 4).

When comparing of stool SCFAs concentration between treatment group vs. control group after 2 weeks, 1 month, 3 and 6 months of therapy the levels of acetic, butyric and propionic acids significantly differences and increase in their levels were established. The comparison of stool SCFAs concentration between the groups showed that levels of acetic, butyric and propionic acids were significantly increase in the treatment group after 2 weeks, 1, 3 and 6 months of combined therapy (Table 4).

In the treatment group was significantly decrease of liver attenuation coefficient between baseline and after 2 weeks, 1, 3 and 6 months of therapy and significantly differences between after 2 weeks, 1, 3 and 6 months of therapy. In the control group was no statistically significant differences of liver attenuation

coefficient between baseline and after 2 weeks, 1, 3 and 6 months of therapy (Table 5).

When comparing of liver attenuation coefficient between treatment group vs. control group after 2 weeks, 1 month, 3 and 6 months of therapy the LAC significantly differences and decrease were established. The comparison of liver attenuation coefficient between the groups showed that liver attenuation coefficient were significantly decrease in the treatment group after 2 weeks, 1, 3 and 6 months of combined therapy (Table 5).

DISCUSSION

Numerous studies indicate that modulation of the intestinal microbiota with rifaximin and probiotic bacteria, yeast (Lactobacillus, Bifidobacterium, Saccharomyces boulardii) and prebiotics provides lowering permeability of the intestinal barrier and promotes its integrity, reduces bacterial translocation and endotoxemia [8]. It was established that rifaximin with probiotics and prebiotics leads to decrease in the level of endotoxin, liver transaminases, indicators of carbohydrate and lipid profile, pro-inflammatory cytokines (IL-6), and decrease in the stage of liver steatosis [9]. According to scientific data, rifaximin has a wide spectrum of antimicrobial action against gram-negative and gram-positive aerobic and anaerobic bacteria, has eubiotic properties and increases the relative amount of Lactobacillus and Bifidobacterium in the intestine. Rifaximin directly upregulates the expression of tight junction proteins, mainly zonula occludin-1 (ZO-1), thus lowering intestinal permeability [10].

Probiotics contain live bacteria that have the potential to strengthen the intestinal barrier layer as well as modulate the immune system. Lactobacillus and Bifidobacterium produce short-chain fatty acids in the colon by bacterial anaerobic fermentation of indigestible polysaccharides and have anti-inflammatory, immunomodulatory, antioxidant, antibacterial properties. The minimum necessary dose suitable to ensure a therapeutic effect should ranges between 8 and 9 log colony forming units (cfu)/mL [11].

SCFAs consist of butyric, propionic and acetic acids, which are an energy substrate for intestinal epithelial cells and regulate the condition of the intestinal barrier and affect the immunity of the intestinal mucosa [12].

Prebiotics are indigestible fermented compounds that induce the growth and activity of some genera of microorganisms in the colon, generally Lactobacillus and Bifidobacterium. Due to their chemical structure, prebiotics are not absorbed in the small intestine, but are fermented and used in the colon by endogenous bacteria as metabolic substrates, including short-chain fatty acids (SCFAs) [13]. The occurrence of prebiotics may inhibit pathogen adhesion, modulate lipid metabolism. Inulin and pectin are two of the most used prebiotics. Inulin is one of the best known prebiotic oligosaccharides with recognized specific and different functional attributes, such as modulation of the gut microbiota, prevention of adhesion and colonization by pathogens, stimulation of anti-inflammatory effects, reduction of food intake, modulation of bowel movements, regulation of alterations in lipid and glucose metabolism. Pectins are complex polysaccharides that exhibit bifidogenic and generally prebiotic properties on different strains of probiotic microorganisms [14].

As a result of our 6-months of treatment, dynamic changes in the level of interleukin 6 and 10, serum zonulin, short-chain fatty acids in feces and liver aminotransferases were noted in patients of both groups.

Already after the 2nd week of treatment, in patients, who received combined therapy were detected decrease level of serum zonulin and IL-6 and reached their reference values, as well as an increase in the concentration of serum IL-10 and short-chain fatty acids (acetic, butyric and propionic acids) in feces. This indicates an anti-inflammatory reaction in the intestinal mucosa, elimination of subclinical inflammation and reduced increased intestinal permeability, as well as restoration of the intestinal microbiota and stabilization of the intestinal barrier function.

In our study, in patients with MAFLD in combination with type 2 diabetes, who were prescribed combined therapy were showed significant lower serum activity of liver aminotransferases and decrease stage of steatosis from severe (S3) to moderate (S2), indicating reduced fatty infiltration in the liver compared to the control group after 6 months of treatment.

CONCLUSIONS

The results of the study in dynamics during 6 months show that the additional appointment of rifaximin, multispecies probiotic containing live lyophilized bacteria (Lactobacillus, Bifidobacterium, Saccharomyces boulardii) and prebiotic containing lyophilized concentrates of Jerusalem artichoke (inulin) and apples (pectin) to metformin in patients with MAFLD and type 2 diabetes led to the elimination of subclinical inflammation, modulation of the permeability of the intestinal barrier and lowering increased intestinal permeability. It was established that the prescribed combined therapy for the treatment of patients with MAFLD and type 2 diabetes contributed lower serum activity of liver aminotransferases and decrease the stage of steatosis from severe (S3) to moderate (S2), which indicates decrease in fatty infiltration in the liver.

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ORIGINAL ARTICLE

CONTENTS

Peculiarities of local immunity in dry eye disease on the background of hormonal dysfunction

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ABSTRACT

Aim: to determine the state of local immunity in DED on the background of hormonal dysfunction.

Materials and Methods: Of 32 women, 17 patients with diagnosed SM and 15 women of the control group were examined. The Ocular Surface Disease Index and the state of local immunity were defined by determining Ig As in lacrimal fluid (LF) by radial immunodiffusion in Mancini agar.

Results: During the OSDI questionnaire, a mild degree of DED was detected in 21 (65.6%) women, and an average degree was observed in 11 (34.4%) patients with SM. On average, OSDI was 34.54 ± 2.01. As a result of studies of the state of local immunity in patients with SM, a tendency to increase Ig As was noted, compared with the control group. An increase in Ig As in the lacrimal fluid in patients with SM to 0.34 ± 0.09 g/l was found, compared with the control group (0.24 ± 0.03 g/l).

Conclusions: Using the OSDI questionnaire, the presence of DED was detected in women with SM, mainly mild and moderate degree. The obtained results of the state of local immunity indicate in favor of a nonspecific inflammatory process, accompanied by a decrease in local immune protection and leading to further changes in the ocular surface.

KEY WORDS: dry eye disease, tear film, surgical menopause syndrome, hormonal dysfunction, secretory Ig A

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INTRODUCTION

Dry eye disease (DED) is a multifactorial disorder in which insufficient quantity or quality of tears does not provide proper moistening of the surface of the eye, characterized by impaired tear film homeostasis (TF). Today, there is a tendency to increase patients with DED, and ranges from 5% to 70%. The correlation of patients diagnosed with DED increases towards women over the age of 45. According to WHO, by 2030 this number will increase to 1 billion 200 million people [1-4].

Dysfunction of the ocular structures that create and regulate components of TF, including the tear glands, meibomian glands, cornea and conjunctiva, causes qualitative and/or quantitative tear deficiency, leading to instability and hyperosmolarity of TF. Violations of the structure of TF are accompanied by an inflammatory reaction and secretion of inflammatory factors, which leads to the involvement of immune cells and clinical pathology. As a result, there is a "circulus vitiosus" of inflammation and damage of the surface of the eye, which impairs the quality of life, causing symptoms such as discomfort, eye pain and deterioration of visual acuity of patients suffering from DED [5-8].

There are several risk factors that contribute to the development of DED. One of them is changes in the balance of sex hormones (estrogens, progesterone and androgens) that occur in perimenopausal women and affect the functioning of the tear, meibomian glands, as well as goblet cells of the conjunctiva on the production of components of the tear film, which leads to the development of DED. It is known that the resulting deficiency of sex steroids causes systemic changes in the tissues of the eyelids and the development of atrophic processes in the conjunctiva due to a disorder of hormonal homeostasis [9,10].

A special place among the estrogen deficiency states of women, which can lead to changes in the eye surface, is occupied by the surgical menopause syndrome (SM), which differs from age menopause by the simultaneous cessation of the functions of the uterus and ovaries. This, in a certain way, affects the rapid development of menopausal disorders. SM occurs after total and subtotal hysterectomy for benign neoplasms, as well as as as radiation treatment for malignant formation [11-13].

The sudden shutdown of ovarian function creates a deficiency of estrogen, testosterone and progesterone,

which increases the risk of the onset and subsequent progression of postovariectomy syndrome (POES).

According to the modern definition, POES is a complex of symptoms that manifests itself as vegetative-vascular, psycho-emotional, exchange-endocrine disorders and is observed in 60-80% of patients after complete removal of the ovaries. The resulting deficiency of sex steroids causes systemic changes in organs and tissues due to a disoder of hormonal homeostasis. Some researchers believe that symptoms of estrogen deficiency may appear in the first weeks after ovariectomy in 72.3-89.6% of women [14-16].

On the background of deficiency of sex hormones, there are vasomotor disorders, psycho-emotional disorders (40-60%), urogenital disorders and changes in the skin, nails and hair (30-50%), osteoporosis and diseases of the cardiovascular system (25-40%) [17,18].

The effect of hypoestrogenia on connective tissue can be manifested as an increase in pain in the joints, dryness and fragility of hair and nails and "dry" eyes. It should be emphasized that in this period patients often experience discomfort when using contact lenses [19,20].

On the background of hormonal dysfunction, changes in the indicators of cellular, humoral and local immunity are revealed. When studying the immune status in women of fertile age, 30-33% of the examined were found to have initial premorbid abnormalities of some immunogram parameters [21,22].

The local representations of the immune system are located in various tissues, organs and systems of the body. These factors can be found in suitable biological material. The concentration of individual products, for example immunoglobulins, may depend on the level of local synthesis and/or on the increased permeability of histohematic barriers [23,24].

An important marker of tear gland function is the content of immunoglobulins that are synthesized by plasma cells: secretory IgA is the main immunoglobulin in TF, IgG and IgE are present in lower concentrations.

There is evidence that one of the possible reasons for the decrease in immunological protection is hypoestrogen, because estrogens are hormones that increase the activity of non-specific resistance factors [25,26].

Secretory IgA is the main secretory immunoglobulin contained in the secrets of the body, namely tears. Secretory IgA is distinguished by the presence of an additional secretory component (S), synthesized by epithelial cells of the mucous membranes and attached to the IgA molecule at the time of its passage through epithelial cells. The main functions of secretory IgA are the binding of microorganisms on the surface of the mucous membranes, the activation of an alternative complement pathway and the activation of inflammatory reactions.

Ig As deficiency leads to repeated infections and autoimmune disorders. On the mucose surface the Ig As antibodies are usually concentrated directly in the mucus due to their interaction with the cystine contained in mucin. Thus, Ig As antibodies can participate in the process of immune defense [25,27].

An increase in the level of Ig As in LF relative to the norm, which may indicate a defect in local immunity and a tendency to nonspecific inflammatory processes on the mucous membranes. Compared with the norm of 0.165 ± 0.02 g/l, a decrease in the level of Ig As in LF is manifested by a tendency to allergic diseases and recurrent local viral infections with a prolonged course [23,28].

In case of defects of local immunity for verification of immunodeficiency, it is advisable to conduct an immunological study of those biological secrets that correspond to the localization of clinical lesions, and not to blood serum. With a defect of local immunity, because selective Ig As deficiency, changes in this immune factor in the lacrimal fluid are noted at normal or even increased Ig A content in serum [27,29].

AIM

To determine the state of local immunity in DED against the background of hormonal dysfunction.

MATERIALS AND METHODS

The study involved 32 women, from 36 to 59 years old - 17 patients with diagnosed SM from 2 months to 4.5 years old, and 15 women of the same age group who did not make complaints indicating DED and the pathological course of the perimenopausal period (control group).

An examination was performed that included the determination of the Ocular Surface Disease Index using the OSDI questionnaire and the state of local immunity, by determining Ig As in lacrimal fluid (LF).

A micropipette with a dispenser was used for LF sampling. LF was collected in sterile Eppendorf tubes using a plastic nozzle from the lower conjunctival sac of both eyes (approximately 1 ml) for 7-15 minutes. Previous epibulbar anesthesia of conjunctiva and eyeball was not performed. The biological material was delivered to the immunological laboratory no later than 2 hours after obtaining. The concentration of Ig As in LF was determined by radial immunodiffusion in Mancini agar. The method is based on the reaction of the formation of an insoluble complex of immunoglobulin with specific

antibodies to it in a thin layer of agar. The precipitate has the shape of a ring, the diameter of which is directly proportional to the logarithm of the concentration of the antibody (Ig As) determined.

RESULTS

The Ocular Surface Disease Index (OSDI) is a questionnaire used to assess the severity of patients' dry eye symptoms. It provides a quantitative assessment of the condition and can also be used to monitor the dynamics of symptoms over time and assess the effectiveness of treatment.

An OSDI questionnaire of 32 women with DED on the background of SM was conducted. The obtained data showed a mild degree of DED was detected in 21 (65.6%) women, and an average degree was observed in 11 (34.4%) patients with SM. Severe DED was not determined by the OSDI questionnaire. On average, OSDI was 34.54 ± 2.01, suggesting the presence of moderate DED symptoms in patients with SM.

The results of the OSDI survey indicate that DED is a common problem in women with SM. Symptoms of DED can range from mild to severe, and can significantly affect the quality of life of patients.

But should be considered that OSDI is a subjective research method that depends on the patient's indications and sensations. This may lead to an underestimation or overestimation of the severity of DED. Therefore, it is more appropriate to use this study in combination with objective methods for diagnosing a violation of the ocular surface.

The immune system controls the stability of the cellular and humoral composition of the body. Changes in Ig As lead to a decrease in immunological protection. It is known that with age, the reactions of cellular immunity decrease, the amount of Ig A in the secretions decreases, which increases the sensitivity of the mucous membranes to infections. The absolute number of lymphocytes decreases, the ability to antibody formation and the proliferative activity of T cells decreases, suppressor activity begins to prevail.

Local immunity of the cornea and conjunctiva plays an important role in protecting the eyes and is represented by various cells of the immune system that produce cytokines and immunoglobulins. IgA is a type of immunoglobulin that is secreted by the mucous membranes, including the conjunctiva. A number of studies have shown that patients with DED have a change in the state of local immunity, namely a decrease in IgA production in the lacrimal fluid and an increase in the concentration of pro-inflammatory cytokines.

The study compared the level of IgA in the tear fluid in patients with SM and in the control group. As a result of studies of the state of local immunity in patients with SM, a tendency to increase Ig As was noted, compared with the control group. An increase in Ig As in the lacrimal fluid in patients with SM to 0.34 ± 0.09 g/l was established, compared with the control group (0.24 ± 0.03 g/l). This fact may be related to the activation of local immunity. An increase in IgA levels in the lacrimal fluid in patients with SM may be associated with an increase in IgA production by conjunctival plasma cells and an increase in the permeability of conjunctival vessels, which leads to the release of IgA from the blood into the lacrimal fluid.

DISCUSSION

Previous DED studies have shown that at the present time, the incidence of the disease ranges from 5% to 70% and there is a tendency to increase such patients [1-4]. Violations of the TF structure are accompanied by a specific reaction and secretion of inflammatory factors, which leads to the involvement of immune cells and clinical pathology that impairs the quality of life, causing symptoms such as discomfort, eye pain and deterioration of visual acuity of patients suffering from DED [5-7]. As you know, one of the risk factors that contribute to the development of DED are changes in the balance of sex hormones (estrogens, progesterone and androgens), which occur in women in perimenopause and affect the functioning of the tear, meibomian glands, as well as goblet-shaped cells of the conjunctiva on the production of components of the tear film. On the background of hormonal dysfunction, changes in the indicators of cellular, humoral and local immunity are revealed. An important marker of tear gland function is the content of immunoglobulins that are synthesized by plasma cells: secretory IgA is the main immunoglobulin in TF, IgG and IgE are present in lower concentrations. Hypoestrogenia causes changes in the amount of Ig As, which leads to a decrease in immunological protection, because estrogens are hormones that increase the activity of non-specific resistance factors [23,28]. There are single works that indicate that with a defect of local immunity, because of selective Ig As deficiency, changes in this immune factor in the lacrimal fluid are noted at normal or even increased Ig A content in serum [27,29].

The results of the study of determining the ocular surface disease index (OSDI) and the state of local immunity, by determining Ig As in the lacrimal fluid (LF) by radial immunodiffusion in the Mancini agar, indicate the presence of dry eye syndrome (DED) in women with surgical menopause (SM), mainly mild and moderate degree. In these patients, there are pronounced disor-

ders in the state of local immunological protection of the eyes, which are manifested in a decrease in S-Ig A in the tear, which indicates a non-specific inflammatory process and leads to further changes in the surface of the eye, which is expedient for the diagnosis and correction of changes in the eye surface.

CONCLUSIONS

DED is a significant problem for women with hormonal disorders. Researches show that it can significantly affect the quality of life and needs attention and correction. Total ovariectomy performed in women of reproductive age is accompanied by a complex of complicated reactions of the neuroendocrine system, characterizing the process of adaptation of the female body to new conditions.

The OSDI test is a useful instrument for assessing ocular surface conditions in patients with DED. The data obtained using the OSDI questionnaire are informative and indicate the presence of DED in women with SM, mainly mild and moderate.

The immune system is a complex network of organs, tissues and cells that work together to keep the body healthy and protect it from external factors. Hypoestrogen can lead to changes in the amount of immunoglobulins, in particular secretory IgA, which is important for protecting the surface of the eye.

The obtained results of the state of local immunity evidence in favor of a nonspecific inflammatory process, accompanied by a decrease in local immune protection and leading to further changes in the ocular surface.

Determination of ophthalmic and immunological changes in patients with DED against the background of SM is expedient, because it helps to predict the further development of the disease, the possibility of influencing individual links of pathogenesis and, thereby, improving the quality of life of this category of patients.

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CONTENTS

Study of axiography changes in patients with temporo-mandibular joint dysfunction

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ABSTRACT

Aim: To determine the effectiveness of treatment of temporomandibular joints muscle and joint dysfunction with occlusive splints based on the analysis of axiography data.

Materials and Methods: 274 (two hundred and seventy-four) patients aged 18 to 44 years with a diagnosis of temporomandibular joints dysfunction before and after treatment.

Results: All patients with signs of temporomandibular joints dysfunction before treatment had a violation of the movement trajectory of the lower jaw: deviation – 68.7%, diflexion – 31.3%. When opening and closing the mouth, asymmetric shifts of the lower jaw of more than 2 mm were observed. After treatment with occlusive splints, the correct trajectory of opening and closing the mouth was noted: the number of patients with a trajectory violation decreased by 89.1%, and the amount of displacement of the lower jaw during opening and closing the mouth in 92.4% of patients decreased on average to 0.9 mm. When analyzing the movements of the lower jaw in the sagittal plane, deviations of the trajectory of the lower jaw were found in 79% of clinical cases. After the treatment using occlusive splints, 93.4% of cases of mandibular movement trajectory violations in the transversal plane were eliminated, and 78.1% of patients had a reduction in displacement volume to 0.9 mm. When analyzing the movements of the lower jaw in the sagittal plane, deviations of the trajectory of the lower jaw were found in 79% of clinical cases. After the treatment using occlusive splints, 93.4% of cases of mandibular movement trajectory violations in the transversal plane were eliminated, and 78.1% of patients had a reduction in displacement volume to 0.9 mm.

Conclusions: Movement trajectories of the lower jaw in the sagittal plane improved in 80.1% of patients, normalization of the position of the lower jaw in relation to the neuromuscular trajectory was achieved in 93.4% of clinical cases. According to the analysis of the parameters, this treatment should be considered effective.

KEY WORDS: dysfunction, prosthetic dentistry, clinical index of dysfunction, axiography, movement trajectories

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INTRODUCTION

The prevalence of temporomandibular joint (TMJ) dysfunction, especially in persons aged 18-45 years, reached 95-98% among all dental referrals. The course of the pathology is hidden, with periodic relapses and has a long-term nature, which is accompanied by a decrease in the overall quality of life. From the analysis of world scientific sources: the true prevalence of this pathology is uncertain due to the variety of diagnostic criteria [1-3].

According to modern scientific literature, the prevalence of this pathology is up to 95% [4, 5]. Patients with symptoms of TMJ dysfunction most often complain of impaired movement of the lower jaw, the appearance of sounds when opening and closing the mouth, discomfort and periodic pain in the joint area [3]. TMJ dysfunction is a polyetiological disease. According to domestic and foreign authors, the occurrence and development of disorders of the temporomandibular joint are influenced by genetically determined disorders of the development of bone, cartilage and connective tissues, as well as stress factors. At the same time, other authors [6-8] indicate that TMJ dysfunction is always accompanied by muscle pathology. Violation of the tone of the masticatory and temporal muscles is one of the main etiological factors of the TMJ function disorder in musculo-articular forms of manifestation, which are confirmed by the data of clinical and instrumental research methods [9,10].

Reatment of joint dysfunction is a multi-complex of complex therapeutic, orthopedic and psychological measures. In the literature, many methods of treating TMJ dysfunction are described, one of the modern ones is the use of occlusive splints, which allow you to change the position of the lower jaw, diagnose and eliminate TMJ muscle and joint dysfunction.

AIM

To determine the effectiveness of treatment of TMJ muscle and joint dysfunction with occlusive splints based on the analysis of axiography data.

MATERIALS AND METHODS

At the department of orthodontics and propaedeutics of orthopedic dentistry of the Bogomolets National Medical University, an examination of 274 patients aged 18 to 44 with a diagnosis of temporomandibular joint dysfunction was conducted. According to the research algorithm, all patients included in the examination groups were subject to diagnosis before and after treatment. At the time of the initial consultation, all patients had complaints of pain in the area of one or two temporomandibular joints, masticatory muscles, and clinical manifestations of TMJ dysfunction. We used axiography as a method that allows us to obtain accurate graphic data about the trajectory of the movement of the articular head during movements of the lower jaw.

This research method was used by us for the purpose of functional diagnosis of TMJ, as well as for adjusting articulators according to the individual parameters of the patient. This individual setting of the articulator eliminates the need to use additional methods of registering the position of the lower jaw and allows for maximum occlusal accuracy. We used the electronic device «Axioquick-recorder» of the company «SAM» - a device whose principle of operation consists in the interaction of ultrasonic sensors and receivers-registers, concentrated on the facial and dental arches.

For ease of work and to study changes in the neuromuscular component, which is pathogenetically and symptomatically key in the development of TMJ muscle-articular dysfunctions, patients were divided into clinical groups according to the severity of clinical dysfunctional manifestations of neuromuscular disorders:

1. TMJ dysfunction (h=5-10) with clinical manifestations only in the main masticatory muscles (79 people);
2. TMJ dysfunction (h=11-15) with clinical manifestations in the main and auxiliary masticatory muscles (106 people);
3. TMJ dysfunction (h=16-25) with clinical manifestations in the main, auxiliary masticatory and mimic muscles (89 people).

Treatment of all patients was carried out using an occlusive myorelaxant splint. The splint was made individually, thanks to the «EXOCAD» system, or manually in an analog articulator using an interocclusal register in a neutral neuromuscular position of the lower jaw. Setting the manufacturing parameters was necessarily based on axiography data. The average duration of treatment was six months with monthly adjustments of the occlusive splint. After treatment, all patients were re-examined.

The research results obtained by us belonged to statistical processing. The analysis was carried out using the author's MedStat package [2]. To compare pretreatment and posttreatment data, we used the appropriate comparison criteria for related samples. Comparison of qualitative features was carried out using the Chi-square test. In the case of comparison of data from more than two clinical groups, for quantitative indicators we used univariate analysis of variance (if the distribution law was normal) or the Kruskal–Wallis test (if the distribution law was different from normal).

RESULTS

All patients with signs of TMJ dysfunction before treatment had a violation of the movement trajectory of the lower jaw (deviation - 68.7%, diflexion - 31.3%). When opening and closing the mouth, asymmetric shifts of the lower jaw of more than 2 mm were observed (deviation from the middle line - more than 2 mm). After the treatment with occlusive splints, an improvement in the trajectory of opening and closing the mouth was noted: the number of patients with a trajectory violation decreased by 89.1%, and the volume of displacement of the lower jaw during opening and closing the mouth in 92.4% of patients decreased on average to 0.9 mm. When analyzing the movements of the lower jaw in the sagittal plane, in 79% of cases deviations of the trajectory of the lower jaw (change in the symmetry of the release and raising of the lower jaw) were detected. After treatment with occlusion splints, the trajectory of movement of the lower jaw in the sagittal plane improved in 89.1% of patients.

An example of a clinical case. Patient M., 38 years old, complained of pain, discomfort and clicking in the TMJ region. Medical history: no previous orthodontic treatment. At the time of consultation, the patient had been experiencing pain in the left TMJ area for about eight months, clicking in both joints for about three years. Tooth 26 was removed six years ago. Analysis of occlusion: closure of molars and canines according to Engle class II, incisal overlap in the sagittal direction - 2.7 mm, in the vertical direction - 2.4 mm. Analysis of cone-beam computed tomography (CPCT) of the TMJ: the distal displacement of the articular heads is determined, morphological changes in the TMJ area are not detected. Axiography of the movements of the lower jaw: a deviation of the lower jaw in the transverse plane was noted (displacement of the lower jaw during open-

Table 1. Analysis of axiography data in patients of the studied clinical groups before treatment

Indicators	I clinical group, degree	II clinical group, degree	III clinical group, degree	0 clinical group, degree
ASCI	47,1±0,9	45,9±1,3	45,1±1,4	48,1±1,1
BA	10,7±1,2	12,2±1,4	13,6±1,2	8,9±1,1
ASII	46,8±1,1	44,3±1,7	43,8±1,4	53,5±1,1

* Note: the Mann-Whitney test was used when comparing indicators.

Table 2. Analysis of axiography data in patients of the studied clinical groups after treatment

Indicators	I clinical group, degree	II clinical group, degree	III clinical group, degree	0 clinical group, degree
ASCI	48,1±1,3	47,9±1,3	46,7±1,4	48,1±1,5
BA	10,9±1,4	11,1±1,4	12,8±1,2	8,9±1,4
ASII	48,8±1,4	46,9±1,5	46,9±1,3	53,5±1,5

* Note: the Mann-Whitney test was used when comparing indicators.

Table 3. Assessment of axiography indicators

Clinical group	Me (Q_I – Q_{III})		Level importance differences p	Growth ACSI indicator, (95% CI)
	ACSI to treatment	ACSI after treatment		
I, (n=79)	47,3 (46,9 – 47,9)	49,1(48,5 – 49,5)	<0,001	1,7 (1,5 – 1,8)
II, (n=106)	47,3 (46,9 – 47,6)	48,1 (47,4 – 49,3)	<0,001	1,2 (0,9 – 1,4)
III, (n=89)	45,2 (44,9 – 46,4)	47,6 (47,3 – 47,9)	<0,001	2,2 (2,0 – 2,5)

Note: comparisons are made using the Wilcoxon T-test for paired samples.

ing of the mouth by 2.1 mm to the right and 3.1 mm to the left), the trajectories of movements of the lower jaw in the sagittal plane when opening and closing the mouth do not coincide.

We carried out the treatment: setting the lower jaw in a therapeutic position with the help of an individual myorelaxation splint. Wearing mode - 16-18 hours a day. After three months of using the splint with monthly corrections of the device, the patient indicated the absence of pain, clicking in the TMJ area, comfortable and even teeth closing. After treatment, a re-examination was carried out.

Axiography: the improvement of the trajectory of the movement of the lower jaw in the transverse (presence of deviation of the position of the lower jaw by 2.3 mm when opening the mouth) and sagittal planes was determined. As a result of the treatment, the trajectories of the movements of the lower jaw in the sagittal and transversal planes improved, the spatial position of the lower jaw was normalized and the neuromuscular position was achieved. We carried out quantitative calculations for the indicators of the angles of the sagittal condylar snclsnation wave (ASCI), transverse articular path, sagittal incisal path, determined changes in qualitative indicators, namely: symmetry of movements according to both sides, trajectory of movements. All results were compared with the control group. Comparative research results are shown in Tables 1-2.

The obtained results made it possible to establish that in individuals of clinical group 0 (control group) the average values of ASCI were 48.1±1.1 degrees, in patients of the I clinical group - 47.1±0.9 degrees, in the II clinical group - 45.9±1.3 degrees, III clinical group - 45.1±1.4 degrees. Comparisons of the studied clinical groups according to the KSSS indicators revealed statistically significant differences between them ($p<0.005$). A comparison of the average indicators of ASII of individuals of clinical group 0, I, II and III clinical groups determined significant statistically significant differences between them ($p<0.05$). The determined average values of Bennett's angle (BA) were equal to: in clinical group 0 - 8.9±1.1 degrees, in Ia clinical group - 10.7±1.2 degrees, in Ib clinical subgroup - 11.2 ±1 ,1 degree

The determined average indicators of BA in patients had the following indicators: in clinical group 0 - 8.9±1.1 degrees, in clinical subgroup I - 10.7±1.2 degrees.

When analyzing the trajectories of the angles of the sagittal incisal path in the clinical groups we studied, the following indicators were obtained: In the clinical group 0 - 53.5±1.1 degrees, in the I clinical group -46.8±1.1 degrees. It is a well-known fact that there is a dependence of the ASCI indicators and the angle of the sagittal incisal path (ASII) on each other. The difference in parametric data between ASCI and ASII should be equal to 5-10 degrees. The decrease in this difference is a reflection of overloading of the frontal teeth in static

and dynamic occlusion, which indicates an adaptive pathological ratio of the structural elements of the TMJ.

The determined average indicators of BA in patients had the following indicators: in clinical group 0 - 8.9±1.1 degrees, in clinical subgroup I - 10.7±1.2 degrees.

Based on the analysis of the difference in the above indicators, we obtained the following results: in clinical group 0 - 4.4 ± 1.1 degrees, in clinical group Ia - (-)0.3 ± 1.1 degrees, in clinical group II - (-)3.1±1.1 degrees, in clinical group III –(-) 1.7±1.2 degrees. Considering the obtained results, it should be noted the existing mechanism of overload and pathological redistribution of pressure in all, without exception, patients of the studied groups.

In clinical group 0, the general average parameters of the movements of the articular heads of the TMJ corresponded to the established standards for the length of the path during protrusion and latetrusion movements, when opening the mouth, the trajectories were formed clearly, synchronously. The beginning of mouth opening and the end of closing corresponded to each other, which is a sign of normal functioning of intra-articular elements. In the horizontal plane, the symmetry of the lateral trajectories and also the shape of the mouth opening trajectory were determined.

Therefore, in all patients with muscle-joint dysfunctions in the studied clinical groups, the trajectories of TMJ articular heads were asymmetric in shape and path length during protrusion, laterotrusions, and when opening the mouth. Signs of curved trajectories, inconsistencies between the starting point of opening the mouth and the end of closing it were revealed. This is an existing sign of disc pathology and degenerative changes that have already occurred with the surfaces of the joints.

The obtained results made it possible to establish that the treatment of the studied patients of the main clinical groups had the following results: in patients of the 1st clinical group - 48.1±1.3 degrees. The analysis of the obtained indicators of the characteristics of the transverse movements of the lower jaw - Bennett's angle - was as follows: in clinical group 0 - 8.9±1.4 degrees, in clinical group 1 - 10.9±1.3 degrees, in clinical group II 11 ,1±1.3 degrees. Significant statistical differences ($p<0.005$) were determined by comparison of ASII indicators in the groups.

A correlative relationship between the ASCI and ASII indicators has been determined: yes, under the conditions of a change in the ASCI parameters by 0.5-1 degrees, the ASII value also naturally changes by 0.5-0.8 degrees. The presence of registered relevant changes indicates a natural change and positive dynamics of patient treatment results. Thus, according to the results obtained during treatment: in patients of clinical group 1, this difference was 0.5-0.7±0.05 degrees, in patients of clinical group II – 0.3-0.5±0.05 degrees, in patients of the III clinical group - 0.2-0.4±0.03 degrees. Under the conditions of a decrease in the ASII index in relation to the ASII or the absence of changes in the patients, the treatment was subject to correction precisely at the expense of the articulation-occlusion component of the TMJ biosystem, since this was evidence of overloading of the corresponding groups of teeth in static and dynamic occlusion and had a pathological effect on the ratio of intra-articular structural elements.

In order to analyze the effectiveness of treatment of patients with TMJ muscle and joint dysfunction, an assessment of axiography indicators was also carried out. The indicator that characterizes the sagittal movements of the lower jaw is the most significant in terms of diagnostic value. For a reliable assessment, we selected the index of ASCI and performed its analysis before and after treatment in three groups. Table 3 shows the results of the analysis.

DISCUSSION

Thus, for all three clinical groups, after treatment, an increase ($p<0.001$) of the ASCI index was found on average, by more than 1 degree, which indicates a change in the trajectory of the movement of the articular head and the cancellation (absence) of spastic blocks due to the restructuring of the usual neuromuscular reflex with clinical dysfunctional manifestations of neuromuscular disorders. According to the analysis of the results of the treatment: for patients of the 1st clinical group, the ASCI h indicator was changed by 1.5-1.6 degrees. which is evidence of the alignment of the trajectory and the change in the vector of the direction of the movement of the jaw, for patients of the II clinical group, the index of ASCI increased by 0.9-1.4 degrees, which indicates the positive dynamics of treatment, however, such a change in parameters is due to the time of development of the pathology. For patients of the III clinical group, the ASCI index was increased by 2.0-2.5 degrees, which indicates significant changes in the ratio of structural elements of the TMJ biosystem, a corresponding increase in the articulatory movements of the jaw, and the qualitative dynamics of treatment and restoration of the TMJ biosystem.

Our study is important because it provides an opportunity to compare and analyze axiography data before and after treatment. The experience of world scientists, in whose works the analysis of occlusion-articulation parameters is given [8-10], shows us how thorough our approach to this research is. The new data obtained by

us as a result of the research make it possible not only for the convenience of the doctor's work, but also to increase the level of providing dental care as a whole.

In the future, it is planned to delve more and more into the study of the articulating component of the dental and jaw apparatus, including the functional biomechanical component of the TMJ. Practical recommendations: it is advisable to carry out research not only as an initial diagnosis, but also every three months during treatment: in order to detect changes and adjust treatment measures. Improvement of the diagnostic algorithm of patients with TMJ dysfunction will allow detection of pathology in the early stages, which will certainly improve the quality of dental care provided to patients.

CONCLUSIONS

After the treatment with the use of occlusive myorelaxation splints, the elimination of violations of the movement pattern of the lower jaw in the transverse plane was noted in 93.4% of cases, the volume of shifts was reduced to 0.9 mm in 78.1% of patients. The trajectory of movement of the lower jaw in the sagittal plane improved in 80.1% of patients, normalization of the position of the lower jaw in relation to the neuromuscular trajectory was achieved in 93.4% of clinical cases. According to the analysis of the parameters, this treatment should be considered effective.

According to our observations: the use of myorelaxing occlusive splints made according to a digital protocol for the treatment of temporomandibular joint dysfunction is more appropriate, compared to the use of splints made in an analog mechanical articulator (the effectiveness of therapy is, respectively, 92.8 and 85.7% of clinical cases).

The use of electronic axiography and a virtual articulator for the manufacture of myorelaxing splints allows you to shape them in strict accordance with the patient's individual parameters. Thanks to its application, a new opportunity appears to model myorelaxant splints taking into account individual trajectories of mandibular movements, which increases the effectiveness of treatment of patients with intra-articular disorders of the temporomandibular joints.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Treatment of patients with crowding of the anterior group of teeth by circumferential supracrestal fiberotomy

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ABSTRACT

Aim: To evaluate the effectiveness of the use of circumferential supracrestal fiberotomy in the treatment of tortoanomalies to improve the effectiveness of treatment, prevent recurrence and increase the stability of the achieved result.

Materials and Methods: Our study consists in determining the effectiveness of the use of methods that prevent the recurrence of tortoanomalies - circumferential supracrestal fiberotomy (CSF) in patients over the age of 16 years and the effect of CSF on the gingival junction in the treatment of tortoanomalies with fixed orthodontic multibonding equipment.

Results: The high level of stability of results proves expediency operations circumferential supracrestal fiberotomy and papilla splitting at orthodontic treatment of frontal teeth density at patients older 16 years and for increasing stability of results of treatment by prevention of relapse tortoanomalies. Efficiency of the offered ways of treatment is proved clinically and anthropometrically on the early and remote terms of supervision (1, 6, 12 months).

Conclusions: The high level of stability of results proves expediency operations circumferential supracrestal fiberotomy and papilla splitting at orthodontic treatment of frontal teeth density at patients older 16 years and for increasing stability of results of treatment by prevention of relapse tortoanomalies. Efficiency of the offered ways of treatment is proved clinically and anthropometrically on the early and remote terms of supervision (1, 6, 12 months).

KEY WORDS: tortoanomaly, relapse of tooth turn, circumferential supracrestal fiberotomy, quality of life, orthodontic treatment

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INTRODUCTION

Consistency of results has always been a key principle in orthodontic treatment [1-15]. Without the stability of the treatment result, it will be impossible to achieve a combination of ideal aesthetics and the function of the masticatory apparatus.

Achieving the stability of the results of orthodontic treatment of the anterior group of teeth has always been very important, since in this area the tendency to recurrence of crowding is most often observed. Many factors influencing the instability of the incisor position have been described: the width of the intercanine distance [4, 8, 11], the position of the third molars [7, 11], the mesio-distal dimensions of the incisors [10], the type of bite [7, 8], interocclusal relationships [4, 7], the state of periodontal tissues [9, 15], the state of the apical basis [4, 7, 8, 11], the direction of mandibular growth [12, 13], and muscle tone [13].

Our study consists in determining the effectiveness of the use of methods that prevent the recurrence of tortoanomalies - circumferential supracrestal fiberotomy (CSF) in patients over the age of 16 years and the effect of CSF on the gingival junction in the treatment of tortoanomalies with fixed orthodontic multibonding equipment.

AIM

To evaluate the effectiveness of the use of circumferential supracrestal fiberotomy in the treatment of tortoanomalies to improve the effectiveness of treatment, prevent recurrence and increase the stability of the achieved result.

MATERIALS AND METHODS

To do this, we examined 23 patients aged 16 and older, who were treated with non-removable multibonding equipment. The mean age of patients at the start of treatment in the CSF group and the control group was

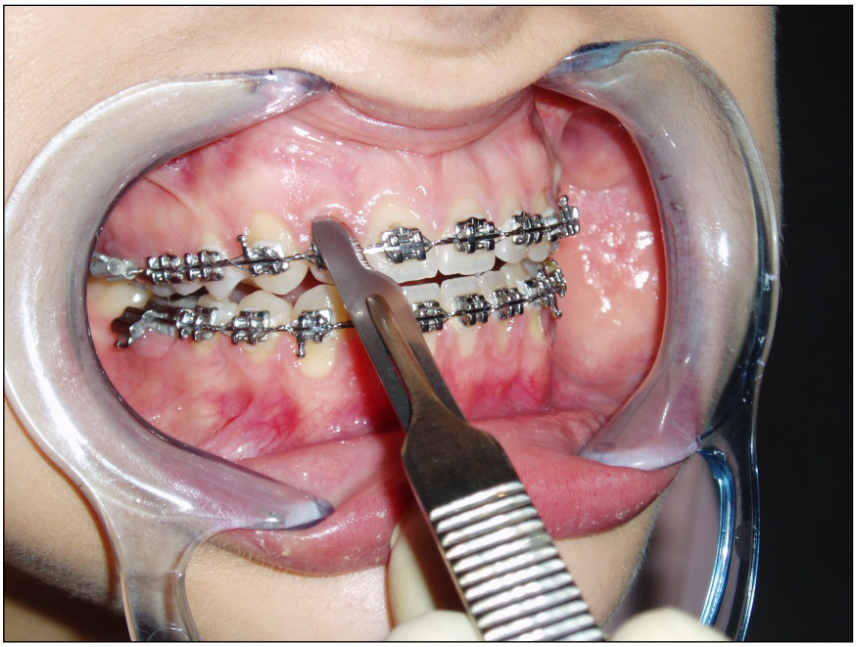

Fig. 1. Circumferential supracrestal fiberotomy of the 12th tooth.

16.0±1.5 and 15.8±1.3 years, respectively. The median treatment time was 21.5±4.4 months for the CSF group and 23.3±1.3 months for the control group.

The characteristics of the pathological occlusion were similar in both groups, namely: crowding of the teeth of the anterior part of the upper and lower jaws or the presence of vertical pathology with the preservation of the occlusion key.

At the beginning of orthodontic treatment, all patients had crowding of the incisors of the upper and lower jaw from 2.3 to 25.5 mm according to the Little index of deviations (irregularity). The Little Deviation Index makes it possible to measure the crowding of the mandibular incisors, as well as to measure the maxillary dental arch [16-18].

All 23 patients used fixed appliances until an optimal bite was formed. Of these, 11 patients underwent circumferential supracrestal fiberotomy (CSF) on the anterior area of the upper and lower jaw 5 weeks before the removal of fixed equipment, 12 patients made up the control group. 5 patients of the study group with CSF and 6 patients of the control group were treated with removal of premolars.

The CSF procedure was prescribed to each patient if there was a clear displacement of the supraalveolar fibers, in the presence of painful sensations when moving the teeth, in the presence of rotated, impaled, tilted teeth, and teeth that were moved vestibulo-orally. In the case of tooth extraction in the area of displacement, surgery with retention procedures had a positive effect on the stability of treatment outcomes.

Surgical interventions were performed by one dental surgeon on the basis of one clinic. All surgeries were performed according to the Edwards method [19-20]. During the operation, a scalpel No. 15 was inserted into the gingival groove and a circular incision was made lingually along the alveolar ridge, holding the blade parallel to the long axis of the tooth (Fig. 1). The surgery consisted of dissecting all fibrous tissues, including the supraalveolar fibers surrounding the tooth, to a depth of approximately 1 mm up to the alveolar ridge. The transseptal (interseptal) fibers were cut with a blade in the area of the periodontal ligament of the interdental septa.

The fiberotomy method involves dissecting vestibular and lingual transseptal fibers, semicircular fibers located between the cementum and the alveoli, and multidirectional fibers stretched between the cementum of one tooth and the free gingival edge of the adjacent tooth. Thus, intergingival, transgingival, transseptal, and semicircular fibers are susceptible to dissection during CSF.

The condition of periodontal tissues in all patients at the time of surgery was within the normal range, oral cavity sanitation and hygienic procedures were carried out before surgery. After the removal of the fixed equipment, all patients received removable lamellar retention devices with an acrylic-contoured vestibular arch, as well as recommendations for their use. The Little deviation index [16-18] and changes in the width of the intercanine and intermolar distance were measured in control models at the beginning of active treatment (P1), after the end of active treatment (P2), 6 months after active treatment (P3), and one year after active treatment (P4) using a compass with an accuracy of 0.1 mm.

Periodontal tissues were examined to determine the depth of the dentitional junction before and

Table 1. Recurrence of crowding of the anterior group of teeth of the mandible

Retention period	Control group	Group with CFS	Difference
After 6 months (P3)	(P3-P2)/P1= (1.97-0.17)/ /4.66=38.6%	(P3-P2)/P1= (0.94-0.88)/ /9.80=0.6%	38%
After 12 months (P4)	(P4-P2)/P1= (3.13-0.17)/ /4.66=63.6%	(P4-P2)/P1= (1.04-0.88)/ /9.80=1.5%	62,1%

Table 2. Recurrence of crowding of the anterior group of teeth of the Maxilla

Retention period	Control group	Group with CSF	Difference
After 6 months (P3)	(P3-P2)/P1= (1.74-0.33)/ /10=14.1%	(P3-P2)/P1= (0.84-0.72)/ /15.23=0.8%	13,3%
After 12 months (P4)	(P4-P2)/P1= (2.83-0.33)/ /10=26%	(P4-P2)/P1= (0.88-0.72)/ /15.23=1%	25%

Table 3. Study of control models of patient S-ko N. during follow-up periods P1, P2, P3, P4

Variable	Parameter	Absolute Number, mm
Deviation Index (Maxilla)	P1	18, 7
	P2	1,7
	P3	1,9
	P4	1,9
Deviation Index (Mandible)	P1	10,8
	P2	1,6
	P3	1,8
	P4	1,9
Width of Intercanine Distance (Maxilla)	P1	33,1
	P2	35,3
	P3	35,1
	P4	34,8
Width of Intercanine Distance (Mandible)	P1	26,3
	P2	29,8
	P3	27,4
	P4	27,1
Width of Intermolar Distance (Maxilla)	P1	38,5
	P2	44,3
	P3	42,8
	P4	42,2
Width of Intermolar Distance (Mandible)	P1	33,7
	P2	37,2
	P3	36,2
	P4	35,2

after the CSF procedure, as well as during the retention phase.

The results of anthropometric and clinical studies were subjected to statistical processing. To solve these problems, the methods of variational statistics and probability theory were used. Statistical analyses included: calculation of expected value (mean); variance as an indicator characterizing the degree of dispersion of individual values relative to the average and the degree of reliability of its use; confidence interval, within which values can vary at 95% degree of reliability; conditional probability of occurrence of an event (the occurrence of a certain type of deformation or anomaly) in the presence of a certain feature.

Fig. 2. Photograph of patient S-ko N. Fixed braces on the teeth of the maxilla.

Fig. 3. Photograph of patient S-ko N. Mouth slightly open.

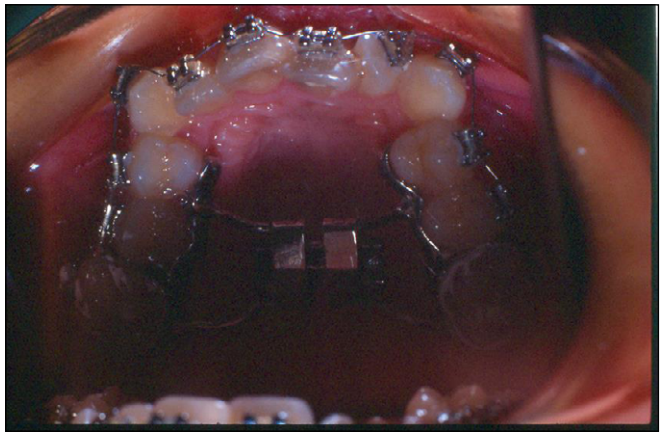

Fig. 4. Photograph of the patient S-ko N. Apparatus of rapid palatal dilation.

Fig. 5. Photograph of patient S-ko N. after 3 months of treatment. The braces on the mandible are fixed.

RESULTS

When comparing the changes that occurred in the groups, the increase in the deviation index for the maxillary dental arch in the control group was significant for the periods P2-P3 and P2-P4 ($R<0.01$ and $P<0.001$, respectively). In the mandibular dental arch, the increase in the deviation index was significant in comparison with group c CSF for periods P2-P3 and P2-P4 ($R<0.001$).

Tables 1 and 2 show the average overcrowding recurrence rate for both groups as a percentage. No significant changes in the level of epithelial attachment were found. The depth of the grooves measured by the periodontal probe did not change significantly from P1 to P2 and P3, as well as the depth of the gingival attachment zone after surgery (0.5 mm vestibular and 0.4 mm lingual).

To prevent the recurrence of tortoanom alies in case of crowding of the teeth of the anterior area, which determines the stability of long-term results, we used circumferential supracrestal fiberotomy.

The number of crowded teeth before treatment varied between the two groups in this study. In the control group, the Little deviation index averaged 10 mm in the mandibular arch and 4.6 mm in the upper jaw arch, while in the CSF group, the Little deviation index averaged 15 mm and 9.8 mm, respectively.

At the end of treatment, the deviation index of both groups was close to zero. In the group with CSF during the early retention periods at 6 and 12 months, no significant changes in the deviation index for the upper or lower jaw arches were noticed. The recurrence of the initial deviations of the anterior group of mandibular teeth was 0.6% at stage P3 and 1.5% at stage P4, and data for the anterior group of teeth of the maxilla were 0.8% at stage P3 and 1% at stage P4.

In the control group, an increase in deviations for the mandibular and maxillary dental arches was observed at 6 and 12 months of the retention period. In the mandibular arch of the control group, there was a greater recurrence after debonding of fixed appliances (38.6% at stage P3 and 63.6% at stage P4). The recurrence of crowding in the maxillary arch on average, based on the initial deviations, was 14.1% at stage P3 and 26% at stage P4.

Fig. 6. Photograph of patient S-ko N. after 8 months of treatment. Closed teeth.

Fig. 7. Photograph of patient S-ko N. 12 months after the removal of the braces. Mouth slightly open.

Fig. 8. Photograph of patient S-ko N. 12 months after the removal of the braces. View from the right.

Fig. 9. Photograph of patient S-ko N. 12 months after the removal of the braces. View from the left.

Preventing an early recurrence of crowding of the anterior group of teeth can help prevent a later recurrence. Late recurrence includes many factors, namely the growth of the jaws, third molars, changes in the width of the intercanine distance, vestibular inclination of the incisors. These factors are independent of the tendency to have an early recurrence of crowding, but this early recurrence may increase the likelihood of crowding later in the world if the above factors are present.

After treatment, changes in the inclination of the incisors of the lower and upper jaw were minimal. The same conclusion can be drawn about changes in the width of the intercanine distance.

Clinical results clearly indicate:

1) during the first year of active retention, a recurrence of anterior tooth protrusion and tooth rotation can be expected, even if the patient wears a retainer continuously;

2) CSF on the anterior group of teeth is effective in preventing recurrence of crowding for retention periods of 6 months and 1 year;

3) the stability of the CFS group was higher, despite the fact that the Little index of deviations of the upper and lower jaws before treatment was greater in the CSF group than in the control.

In the control group, the Little deviation index averaged 10 mm in the mandibular arch and 4.6 mm in the maxilla dental arch, while in the CSF group, the Little deviation index averaged 15 mm and 9.8 mm, respectively.

In the control group there was an increase in the index of deviations on average in the maxillary dental arch by 1.41 ± 1.46 mm in P2-P3 and 2.50 ± 1.68 in P2-P4. In the mandibular dental arch, the increase in the deviation index averaged 1.80 ± 0.92 mm during P2-P3 and 2.96 ± 1.43 mm during P2-P4. In the control group, at stages P3 and P4, there was a significant increase in the index of deviations for the anterior group of teeth of the upper and lower jaw ($P<0.05$, $P<0.01$).

In the CSF group, there were only minimal changes, ranging from 0.06 to 0.16 mm, numbers that were not statistically or clinically significant.

The conclusions of these studies indicate a slight recurrence of orthodontically rotated teeth with crowding of the anterior part of the upper and lower jaw after CSF.

In the clinic of the Department of Orthodontics and Propedeutics of Prosthetic Dentistry of the Bogomolets National Medical University, we observed a 16.5-year-old patient, Natasha S-ko, with a diagnosis: deep traumatic occlusion, narrowing of the dental arches of the upper and lower jaws, crowding of the frontal area of both jaws, supraocclusion of the lower frontal area, mesio-oral rotation of the 11th tooth by 30°, mesio-vestibular rotation of the 21st tooth by 30°, mesio-vestibular rotation of the 12th tooth by 60°, vestibular position of 13, 23, 33 and 43 teeth with space deficit, oral position of teeth 35 and 45 with space deficit in the dental arch. The patient has no history of injuries in the area of the front teeth and bad habits. The patient's malocclusion is genetically determined by the mother.

Estimation of the balance of space in the dental arch in control models using the Little method is described in Table 3.

In April 2019 brace-system is fixed on the teeth of the maxilla and a fast palatal expander of our modification (declarative patent for invention No. 2003043187 dated 15.01.2004). After fixing the brace, an initial orthodontic nitinol arch with a diameter of 0.14 was applied. After 4 weeks, it was replaced by an arc with a diameter of 0.16 (Fig. 2, 3, 4).

In July 2019 After leveling the upper dentition, the braces were fixed on the teeth of the lower dentition with a threadinol arch with a diameter of 0.14 (Fig. 5). Accordingly, the change of arcs.

Thus, the alignment of the rotated teeth in the horizontal and vertical planes, the correction of the Spee curve (normalization of the shape of the dentition) was carried out.

In March 2020, the signs of orthognathic occlusion and the "ideal" shape of the dental arches were determined, steel arches of 0.17x0.25 were fixed with a long metal ligature to achieve parallelism of the tooth roots (Fig. 6).

In February 2021, circumferential supracrestal fiberotomy of 11, 21, 12, 13, 23, 33, 43, 31, 41, 32, and 42 teeth was performed. In April 2021, the braces were removed and removable retention plate devices were put on the upper and lower jaw with an acrylic-contoured vestibular arch. The patient continues to be monitored. The fiberotomy procedure prevented the recurrence of tortoanomalies in the case of crowded teeth in this patient (Fig. 7, 8, 9).

DISCUSSION

At the same time, insufficient attention is paid to the problem of increasing the effectiveness of treatment of tortoanomalies in children and adults, taking into account the degree of space and the degree of formation of the tooth root. In order to achieve stable results in the treatment of cake anomalies, as a rule, treatment methods with hypercorrection are used. Nevertheless, according to the literature, treatment with hypercorrection is not always successful, and there are non-isolated cases of complications [1-4, 6, 7, 11-15]. This leads to the search for new means and the improvement of treatment methods aimed at optimizing the treatment of cake anomalies with the achievement of long-term stable results.

There is no irrefutable evidence that the recurrence of tortoanomalies occurs primarily due to the reorganization of connective tissue fibers [7, 21-23]. The displaced and stretched fibrous structures of the free gingival ligament are resistant to rotational forces; there are no displacements of fibrous structures in the marginal areas of the periodontium, where the supraalveolar fibers remain displaced and stretched even after a retention period of 33 weeks [12, 21-23].

The period after the removal of fixed equipment is the most critical, since relapse is most likely in the first 24 hours, and about 50% of relapse in general occurs during the first week after debonding [1-7].

Prevention of early recurrence of crowding of the frontal group of teeth contributes to the prevention of later recurrence. Late recurrence involves many factors, namely the growth of the jaws, third molars, changes in the width of the intercanine distance, vestibular inclination of the incisors, and interocclusal relationships [4, 6-8, 11]. These factors do not depend on the predisposition to early recurrence of crowding, but this early recurrence may increase the likelihood of early recurrence of teeth in the future if the above factors are present [16, 17, 19].

Thus, using circumferential supracrestal fiberotomy, we achieve high stability of the results of orthodontic treatment of crowding of the anterior group of teeth, which is confirmed by the low index of irregularity Little at the end of treatment in the CSF group and a statistically significant increase in the width of the intercanine distance in the maxillary dental arch and the intermolar distance in the maxillary and mandibular dental arches at the end of treatment.

We performed the circumferential supracrestal fiberotomy procedure in patients with vestibular and tortoanomaly teeth. Favorable results were obtained in groups with the study of long-term results of the retention period [6-17].

CONCLUSIONS

Clinical results indicate that CFS is effective in preventing the recurrence of tortoanomalies in the treatment of crowded teeth for retention periods of 6 months and 1 year. There is also a possibility that the recurrence may continue in later years, especially in the dental

arch in the lower jaw. Crowding of teeth may increase regardless of the method of treatment in all orthodontic patients due to the normal growth process. Prevention of early recurrence with CSF prevents late recurrence and leads to a more stable stable long-term result of treatment of tortoanomalies in crowded teeth.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Modern educational needs of specialists in the public health system

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ABSTRACT

Aim: Studying the opinion of public health system workers (emlpoyees) regarding existing educational problems and needs in the context of continuous professional development.

Materials and Methods: Bibliosemantic, medical-statistical, sociological methods are used in the study. The research program provided for conducting sociological surveys of public health specialists in different regions of the country regarding the establishment of priority training topics for public health specialists; preferred methods of learning; barriers to access to education, etc. The scientific base of the research the regional centers for disease control and prevention have become. Statistical processing and mathematical analysis of materials was carried out using methods of statistical analysis.

Results: The research has found that the priority topics of training for public health specialists are issues of epidemiology (which were indicated as very important by 67.7±3.7 and as important by 22.0±3.2 per 100 respondents); emergency and disaster management (67.7±3.7 and 31.1±3.6 per 100 respondents), quality and safety (53.0±3.9 and 38.4±3.8), practices based on on evidence (42.1±3.9 and 45.7±3.9) eHealth and digitalization (40.2±3.8 and 38.4±3.8), statistics (38.4±3.8 and 51 ,2±3.9), research methodology (32.9±3.7 and 51.2±3.9) and research ethics (12.8±2.6 and 67.7±3.7, respectively). Webinars (62.2±3.8 per 100 respondents) and online training (60.4±3.8), classroom (42.1±3.9) and hybrid (40.2±3.8) were identified as preferred forms. teaching. The obstacles to the continuous professional development of public health specialists are a lack of time and a lack of finances, a lack of information about desired training programs, their regulations, insufficient support from management, military aggression and the problems caused by it, etc.

Conclusions: The priority topics of training for public health specialists, preferred methods of training and barriers to access to training determined in the course of the study are the basis for improving the organization of continuous professional development of employees of public health centers.

KEY WORDS: public health system, public health professionals, educational aspects, continuous professional development, priority topics of study, forms of study, obstacles

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INTRODUCTION

There is a growing awareness of their unique role in solving many complex health care problems, with the development of public health systems in the world. The history of successes and achievements in the field of combating public health challenges is inextricably linked to the work of public health services. They ensure the performance of the main operational functions of public health and the provision of basic public health services, specifically: assessment and monitoring of population health; research, diagnosis and elimination of health hazards and root causes; effective communication for informing and training; strengthening, support and mobilization of communities and partnerships; creating, advocating and implementing policies, plans and laws; use of legal and regulatory measures; ensuring fair access; creating a diverse and qualified workforce; improvement and innovation through evaluation, research and quality improvement; creation and support of a powerful organizational infrastructure of public health [1].

Achieving the ambitious Sustainable Development Goals, which involve overcoming poverty; good health and well-being; provision of clean water and sewage; decent work and economic growth; reducing inequality; sustainable development of cities and communities; climate change mitigation, etc., requires strong communities, cross-industry, cross-sectoral linkages, strong health systems and strong public health services [2].

In a number of documents of the WHO it is, that the WHO Regional Committee for Europe, and other international institutions, the special importance of public health human resources in the directions of their development is emphasized. Thus, one of the priorities of the

"Health 2020" policy is the strengthening of health care systems oriented to the needs of people, the potential of public health care and preparedness for emergency situations [3]. The thirteenth general program of work 2019–2023 (GPW13) "Promoting health, maintaining security in the world, reaching vulnerable population groups with services" indicates the priority of the issue of human resources for health care, which includes public health personnel [4].

The policy document «Achieving progress in the field of public health in the WHO Regional Committee for Europe for sustainable development», which was approved by the 68th session of the WHO Regional Committee for Europe in 2018, indicated the need to allocate the necessary resources to strengthen the capacity of the structures involved in public health, within the health care system, and in other sectors involved; investing in training and continuous professional development of health care personnel to create a personnel base for health care systems and for other involved policy sectors [5].

The Thirteenth European Programme of Work «United Action for Better Health in Europe' for 2020-2025» envisages strengthening national, regional, and global capacity to ensure more effective protection of people from epidemics and other health emergencies and to ensure that populations affected by emergencies have rapid access to essential health services that save lives and provide health promotion and disease prevention [6].

The strategic goals of the World Federation of Public Health Associations (WFPHA) for 2023-2027 include the development of public health practice, education, training and research [7]. The European Public Health Association (EUPHA) is focused on preparing future generations of public health professionals for their leadership roles in public health [8].

WHO and other international organizations in health care emphasize the need to improve policies on the development of public health human resources and create conditions for the effective work of specialists who provide public health services.

The issue of improving the provision of public health services is extremely relevant for Ukraine in view of the epidemiological context, the significant need of the population for such services, existing problems and reorganizational changes in the health care system.

Considering the existing and potentially possible challenges and threats to public health, improving training and ensuring continuous professional development of public health personnel is an important task of the national health care system.

Determining directions and ways to improve the formation of public health personnel potential requires, among other things, studying the opinion of public health service providers regarding existing educational problems and ways to solve them. This necessitates the justification and development of appropriate tools and conducting sociological surveys among public health specialists.

AIM

To study the opinion of public health system workers regarding existing educational problems and needs in the context of continuous professional development.

MATERIALS AND METHODS

The research uses a systemic approach, bibliosemantic, medical-statistical, sociological methods.

The research program provided for the adaptation of the toolkit, which was developed as part of the EU Erasmus+ Program project, for its use in Ukraine and conducting sociological surveys of public health specialists in different regions of the country. The survey was anonymous. The specific objectives of the survey included establishing priority training topics for public health professionals and other health care professionals; preferred methods of learning; barriers to access to education, etc.

The scientific basis of the study was the disease control and prevention centers of Kyiv, Zhytomyr, Poltava, and Chernihiv regions. The sample size included 164 respondents. Statistical processing and mathematical analysis of anonymous sociological research materials was carried out using methods of statistical analysis.

RESULTS

According to the results of a sociological survey of specialists of disease control and prevention centers, it was found that the priority topics for training for public health specialists and other specialists in the field of health care are epidemiology, emergency and disaster management, quality and safety, evidence-based practice, eHealth and digitization (digitalization). Thus, 67.7±3.7 per 100 respondents indicated that training in epidemiology was determined to be very important; 22.0±3.2 per 100 people – important; and only 3.7±1.5 per 100 respondents – not important (Table 1). As a very important and important topic of training, the employees of public health centers identified the topic of emergency and disaster management with the corresponding indicators of 67.7±3 ,7 and 31.1±3.6 per 100 respondents.

Table 1. Priority topics of training for public health specialists and other specialists in the field of health care

Topics	Very important		Important		Not important	
	abs.	for 100 persons, 95% CI	abs.	for 100 persons, 95% CI	abs.	for 100 persons, 95% CI
Epidemiology	111	67,7±3,7 (60,3-75,1)	36	22,0±3,2 (15,6-28,4)	6	3,7±1,5 (0,7-4,5)
Emergency and disaster management	111	67,7±3,7 (60,3-75,1)	51	31,1±3,6 (23,9-38,3)	0	
Quality and safety	87	53,0±3,9 (45,2-60,8)	63	38,4±3,8 (27,2-30,8)	0	
Evidence-based practice	69	42,1±3,9 (34,3-49,9)	75	45,7±3,9 (37,9-53,5)	3	1,8±1,0 (-0,2-3,8)
eHealth and digitization (digitalization)	66	40,2±3,8 (32,6-47,8)	63	38,4±3,8 (27,2-30,8)	0	
Statistics	63	38,4±3,8 (27,2-30,8)	84	51,2±3,9 (43,4-59,0)	9	5,5±1,8 (1,9-9,1)
Research methods	54	32,9±3,7 (25,5-40,3)	84	51,2±3,9 (43,4-59,0)	9	5,5±1,8 (1,9-9,1)
Research ethics	21	12,8±2,6 (7,6-18,0)	111	67,7±3,7 (60,3-75,1)	18	11,0±2,4 (6,2-15,8)
Global health	15	9,1±2,2 (4,7-13,5)	48	29,3±3,6 (22,1-36,5)	8	4,9±1,7 (1,5-8,3)
Other	96	58,5±3,8 (50,9-55,1)	12	7,3±2,0 (3,3-11,3)	0	–

The demand for quality and safety topics, which were highly rated by 53.0±3.9 per 100 respondents and highly – 38.4±3.8 per 100 respondents, respectively, as well as the topic regarding evidence-based practice (42,1±3.9 and 45.7±3.9 per 100 respondents) and topics related to eHealth and digitization (digitalization), which was very highly rated by 40.2±3.8 and highly – 38.4±3.8 per 100 interviewed Above all, the topics of statistics and research methods, research ethics, and global health were prioritized as high (Fig. 1).

Among the topics that were less often identified as important were immunoprophylaxis (7.3±2.0 per 100 respondents), ethical norms in public health, communication, and occupational hygiene.

Only some respondents indicated the priority of the topic regarding the impact of environmental factors on health; informatization and modern technologies; intersectoral interaction in the implementation of programs; communications in the public health system; development of leadership competencies; ethical norms in public health; legal aspects in public health; ecology, state policy and legal foundations in public health; monitoring measures to strengthen the health of the population in the regions; prevention of non-infectious diseases; infection control, antibiotic resistance, medical waste management; sanitary protection of the territory; infectious diseases, public health management; health risk assessments; unified health, etc.

Among the various methods of training, public health specialists preferred webinars (62.2±3.8 per 100 respondents), online training (60.4±3.8 per 100 respondents), classroom (face-to-face) training (42.1± 3.9 per 100 respondents) or hybrid (full-time-correspondence) education (40.2±3.8 per 100 respondents) (Fig.2).

Other forms of training, such as trainings, academic mobility, practical online training, internships, self-education, independent work, video lectures, training in groups, master classes; round tables, scientific and practical conferences, exchange of experience between disease control and prevention centers, the Public Health Center of the Ministry of Health of Ukraine were identified as desirable by a total of 23.8±3.3 per 100 respondents.

The main barriers to access to education were identified by public health specialists as a lack of time (60.4±3.8 per 100 respondents), a lack of finances (56.7±3.8 per 100 respondents), a lack of an appropriate training program (42,1±3.9 per 100 respondents), a lack of training regulations (32.9±3.7 per 100 respondents), a lack of motivation (22.0±3.2 per 100 respondents), a lack of management support (14.6±2.8 per 100 respondents), a lack of an appropriate training program in the national language (5.5±1.8 per 100 respondents) (Fig. 3). A lack of specialists was indicated as significant barriers; ignorance of the legislative framework that regulates activity and the presence of an accredited

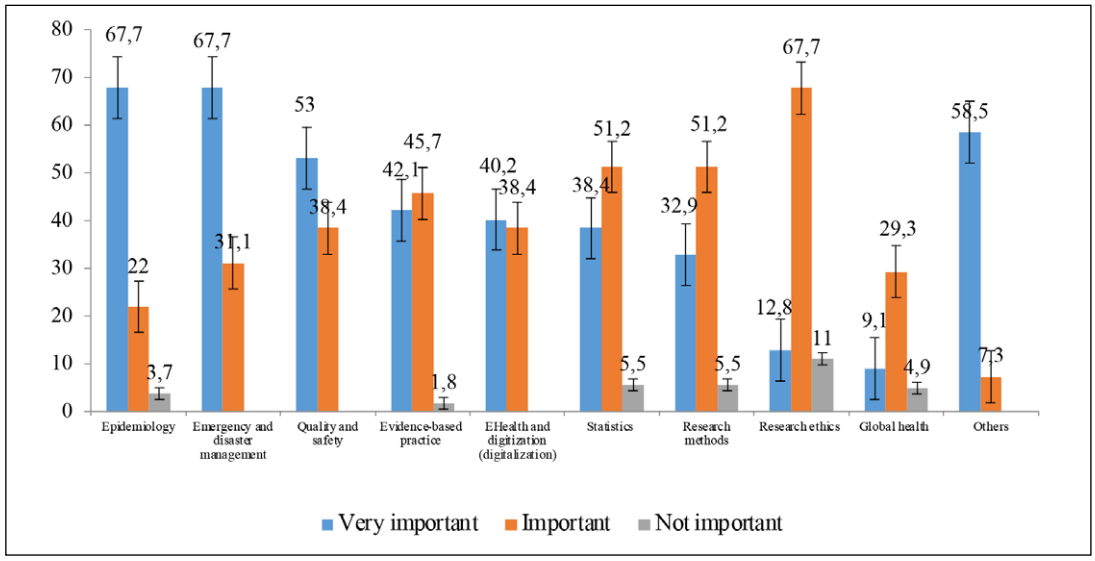

Fig. 1. Priority topics of training for public health specialists and other specialists in the field of health care (per 100 respondents).

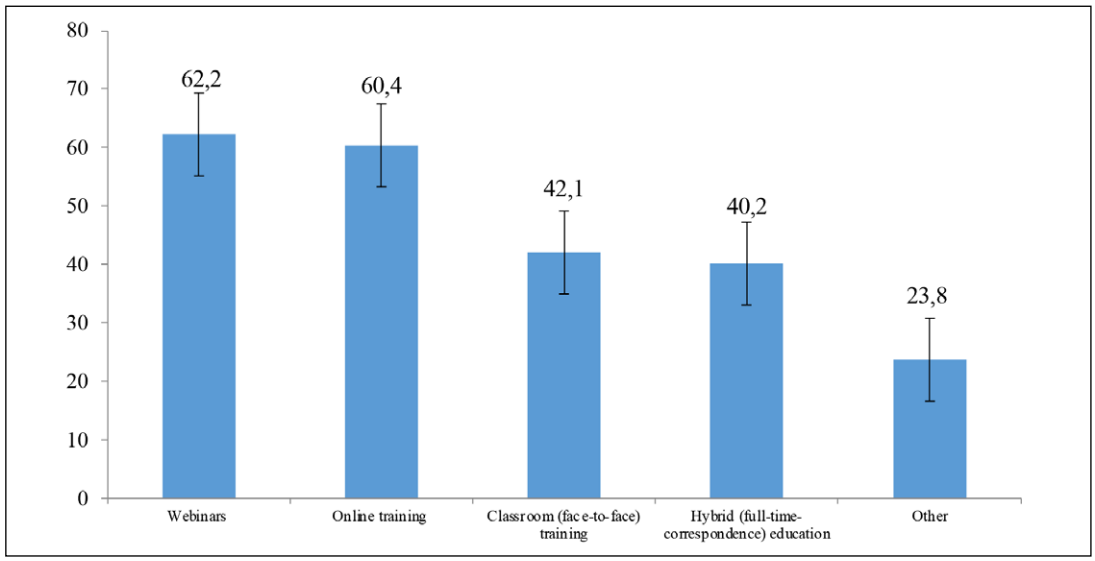

Fig. 2. Preferred methods of training for public health specialists and other specialists in the field of health care (per 100 respondents).

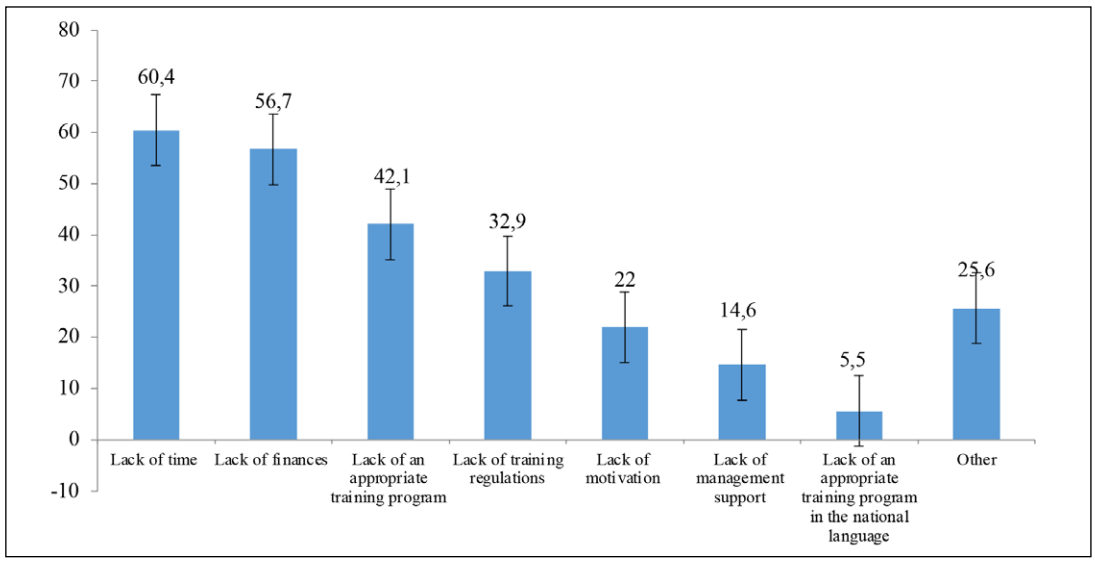

Fig.3. The barriers to access to training of public health specialists and other specialists in the field of health care (per 100 respondents).

educational and professional program in local institutions of higher education; military aggression and interruptions in the supply of electricity, the Internet, and communications caused by it; a lack of free access to modern scientific literature; psychological state, etc.

DISCUSSION

Considering the importance of providing the public health system with human resources of the appropriate number and quality, the conducted research on the opinion of public health system employees regarding the existing educational problems and needs in the context of continuous professional development is of significant scientific and practical importance. Its results make it possible to determine the priorities of the thematic improvement of the qualifications of public health service employees and to formulate measures for the implementation of the identified priorities.

This approach is fully consistent with the Resolution of the WHO „Human resources of health care. Global strategy for the development of human resources for health care 'Labor Resources-2030'" [9]. It emphasizes the importance of competence-oriented education. Expanding and strengthening this approach is one of the priority tasks in all the WHO regions. In order to facilitate the expansion of the scope of this activity and to determine the priority professional qualities, a global system of assessment of professional qualities and results was developed to ensure universal coverage of health care services, which will be used to develop training programs in the WHO member states [10].

The Bucharest Declaration on Health and Social Workforce indicated that national health systems face insufficient investment in skills development to meet the evolving need for health professionals and emphasized the need to strengthen continuous professional development by adapting relevant standards and methodologies, encouraging leadership development and providing lifelong learning opportunities [11].

The priority topics identified during the research, on which public health specialists want to improve their qualifications, are extremely relevant in view of the current context of problems in this field [12,13].

It is quite predictable that the priority in the topic is given to issues of epidemiology and statistics, which are the basis of the formation of many special competencies of public health specialists. The priority of issues of emergency and disaster management is determined by modern realities in the field of public health, the tendency to increase the frequency of emergency situations at the global and regional level, and the difficulty of eliminating their negative consequences for the health of the population. It is with this in mind that the WHO benchmarks for strengthening health capacity in emergencies through scaling up the Public Health and Social Measures (PHSM) have been updated. The document is aimed at supporting and implementing the International Health Regulations and the potential for preventing emergencies in the field of health care, preparedness, response, and resilience [14]. Issues of emergency and disaster management are extremely relevant for Ukraine, given the military aggression the country is experiencing and its medical and social consequences.

The topic of electronic health and digitalization of health care turned out to be in demand by public health specialists, given the widespread use of electronic and digital technologies in health care and public health in particular. This fully corresponds to the Global Strategy on Digital Health 2020-2025 [15] and is consistent with the provisions of the Bucharest Declaration on the health and care workforce [11], which emphasizes the need to expand the justified use of digital tools to provide more effective, efficient, and accessible services.

The priority of evidence-based practice issues in the educational needs of public health professionals is due to the demand for the best available evidence for safe and effective health care policies and programs [16].

The importance of studying issues related to research methods and research ethics is explained by the growing requirements for methodology and ethical aspects of conducting research in public health. The identification of global health issues as an important topic of study is due to the active processes of globalization in various spheres of economy and social life, which affect the health of the population and need to be taken into account when developing preventive measures and response measures.

As for another topic that the employees of the disease control and prevention centers rarely identified as a priority for training, in particular, the impact of environmental factors on health; intersectoral interaction in the implementation of programs; communications in the public health system; development of leadership competencies; legal aspects in public health; ecology, state policy and legal foundations in public health; monitoring measures to strengthen the health of the population in the regions; prevention of non-infectious diseases; infection control, antibiotic resistance, medical waste management; sanitary protection of the territory; infectious diseases, public health management; health risk assessments; unified health, etc., then this may be due to realized opportunities for professional development.

Giving absolute preference to webinars and online

training, which was expressed by more than half of the respondents, may be related to the desire to improve their qualifications without leaving the workplace. At the same time, there is a significant need for classroom (face-to-face) and hybrid (face-to-face) training, as confirmed by more than 40 out of 100 interviewed specialists. The lower demand for other forms of education, in particular trainings, internships, self-education, round tables, scientific and practical conferences, etc., can be explained by the unsuccessful previous experience of using such forms of continuous education, which indicates the need to improve their organization.

The important result of the study was the clarification of existing obstacles to the continuous professional development of public health specialists, which are, first of all, a lack of time and a lack of finances. This indicates the need to develop such forms of training that are the least time-consuming and financially inexpensive. A serious obstacle in obtaining the necessary training and improving qualifications is military aggression and interruptions in the supply of electricity, the Internet, and other types of communication caused by it.

The promising and long-term way to overcome existing obstacles in the way of continuous training of the staff of disease control and prevention centers is to provide broad information about existing training programs, training regulations, and to take measures to increase the motivation of specialists and support from the administration. The survey shows that there is a need to adapt foreign language programs of continuous professional development of public health specialists, to increase the availability of special educational literature, and to improve the conditions for lifelong learning.

CONCLUSIONS

The medical and social research has established priority topics of training for public health professionals, preferred methods of training and barriers to access to training. It was found that among the subjects of lifelong learning, employees of the Centers for Disease Control and Prevention consider issues of epidemiology, emergency and disaster management, quality and safety, evidence-based practice, eHealth and digitization (digitalization) to be priorities. According to respondents, issues of statistics, research methodology, research ethics, and global health are also important. The chosen topic of study is the basis for the formation and improvement of many competencies of public health specialists. At the same time, less interest in another topic may indicate confidence in one's own existing knowledge and skills, better access to their acquisition, etc.

Based on the results of the study, the desired forms of continuous professional development, primarily webinars and online training, were identified, which indicates the desire to learn without leaving work. A little less than half of the respondents confirmed the need for classroom and hybrid education.

The obstacles to the continuous professional development of public health specialists have been identified, which are, first of all, a lack of time and a lack of finances, a lack of information about the desired training programs, their regulations, insufficient management support, military aggression and the problems caused by it, etc.

The priority topics of training for public health specialists, preferred methods of training and barriers to access to training determined during the study are the basis for improving the organization of continuous professional development of public health centers employees.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Cost-effectiveness of dialysis and kidney transplantation to treat end-stage renal disease in Ukraine

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ABSTRACT

Aim: To determine the economic feasibility of using kidney transplantation compared to hemodialysis in end-stage renal disease in the long term in countries with a low and medium level of economic development using the example of Ukraine.

Materials and Methods: The cost effectiveness analysis method was used. Conducted Markov modeling and comparison of the consequences of kidney transplantation and hemodialysis in terms of treatment costs and the number of added years of life for a cohort of 1,675 patients were carried out. The incremental cost-effectiveness ratio is defined.

Results: Based on the results of modeling, it was determined that among 1,675 patients with end-stage kidney disease in Ukraine, 1,248 (74.5%) will remain alive after 10 years of treatment when kidney transplantation technology is used. The highest costs will be in the first year ($25,864), and in subsequent years - about $5,769. With the use of hemodialysis technology, only 728 patients (43.5%) will be alive after 10 years, the cost of treating one patient per year is $11,351. The use of kidney transplantation adds 3191 years of quality life for 1675 patients compared with hemodialysis (1.9 years per patient).

Conclusions: Kidney transplantation is an economically feasible technology for Ukraine, as the incremental cost-effectiveness ratio is $4694, which is 1.04 times higher than Ukraine's GDP per capita. The results of the study allow us to recommend that decision-makers in countries with a low and medium level of economic development give priority in financing to renal transplantation.

KEY WORDS: prevalence, kidney disease, Markov modeling, transplantation, hemodialysis, Ukraine

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INTRODUCTION

Significant attention and growing interest in most countries to the economic side of the health care system, characteristic of the last decades, is explained by the fact that health is becoming an increasingly valuable factor. The costs of maintaining the health care system are increasing. This trend persists in almost every country in the world and requires a thorough search for new solutions to curb the growth of costs. That is why it is urgent to implement an economic assessment of the feasibility of introducing new technologies in the medical field and the effectiveness of the existing approaches [1].

Treatment of end-stage renal disease is one of the areas that require such an assessment. Chronic kidney disease is a global socio-economic problem, as 5-10% of the world's population has signs of this disease [2, 3]. The number of terminally ill patients increases to 7% every year. They require treatment with renal replacement therapy (RRT). According to experts' forecasts, every 10 years the number of patients who will need treatment with RRT methods will double [4,5].

In 2020, there were 11,940 citizens with end-stage kidney disease in Ukraine (284.4 per 1 million population), of which 1,803 people were treated with renal replacement therapy for the first time. Hemodialysis technology was used for 1675 patients (93%), renal transplantation was performed in 128 patients (7%). 10,250 patients (244.1 per 1 million population) received various types of renal replacement therapy [6]. 8,791 patients were treated with various types of dialysis, which is 209.4 per 1 million population. In 2020, 1,675 people started dialysis treatment for the first time. The number of patients who underwent kidney transplantation is 1,459 (34.8 per 1 million population), of which 128 patients underwent transplantation in 2021 [7]. Among patients treated with hemodialysis, a high mortality rate is noted, because 11.1% of the total number of people treated by this method die annually, and in the case of transplantation, the mortality rate is 1.4% [7].

The main method of treatment for such patients is renal transplantation [8-11], while in Ukraine, hemodialysis is used for renal replacement therapy in more than 90% of cases [7, 12, 13]. That is why it is relevant for Ukraine to carry out a comparative economic evaluation of the treatment of end-stage renal disease by the method of hemodialysis and kidney transplantation.

AIM

The purpose of this study was to determine the economic feasibility of using renal transplantation technology compared to hemodialysis in end-stage renal disease in the long term in countries with a low and medium level of economic development, using Ukraine as an example.

MATERIALS AND METHODS

The cost effectiveness analysis (CEA) method was used to determine the economic feasibility of priority use of a certain technology. Markov modeling of the results of the use of two medical technologies for renal replacement therapy was carried out: hemodialysis (the first technology) and kidney transplantation (the second technology). This method is optimal for economic forecasting of the long-term impact of renal replacement therapy technologies on treatment outcomes, taking into account the quality and life expectancy of patients.

In the Markov model, a hypothetical cohort of patients who are in the initial state before the study and transition to different states during the cycle according to certain probabilities is studied [14, 15]. A patient can be in only one of the states, so the number of patients who are distributed by state is determined in each subsequent cycle. Costs for both options were estimated in monetary units.

Comparisons of the relative improvement in population health due to the use of new technology were assessed using the Quality Adjusted Life Years (QALY) indicator. The number of QALYs and treatment costs were calculated during each Markov cycle for the specified condition and the technologies studied.

A technology in which one unit of incremental health improvement (in our case - one QALY) can be achieved at an acceptable incremental cost of one technology to the comparison alternative (the second technology) is considered economically feasible (formula 1).

$$ICER = (C2-C1) / (QALY2-QALY1) \quad (1)$$

where: ICER – incremental cost-effectiveness ratio;

C1 – costs for the "first" technology in monetary units;

C2 – costs for the "second" technology in monetary units;

QALY1 - the number of years of quality life when using the "first" technology;

QALY2 - the number of years of quality life when using the "second" technology.

The research program included the following stages:

1. Development of the Markov model (definition of Markov states and variants of the transition between them).
2. Search for scientific and statistical data to calculate the matrix of transition probabilities between Markov states.
3. Calculation of the number of QALYs and the cost of renal replacement therapy by hemodialysis ("first" technology)
4. Calculation of the number of QALYs and the cost of renal replacement therapy by kidney transplantation ("second" technology).
5. Determining the ICER and deciding on the recommendations.

During the simulation of both technologies, we assumed that they are used for all patients with an established diagnosis of end-stage renal disease who require RRT for the first time in the current year.

When modeling the use of the "first" RRT technology (hemodialysis), the following Markov states were defined: 1. a patient who receives hemodialysis sessions and has no complications; 2. a patient who has complications due to hemodialysis that require treatment; 3. death.

Taking into account statistical data, we determined the probabilities of transitions between states (Table 1).

The indicators of the quality of life during the stay in different states of this model (taken into account when calculating the number of QALYs) were taken as follows: hemodialysis without complications – 0.61; hemodialysis with complications - 0.55; death is 0.

When creating the second model (kidney transplantation), we defined the following Markov states: 1. a patient with a transplanted kidney without complications (receives immunosuppressive therapy, supportive treatment, laboratory diagnostics, consultations); 2. a patient who underwent a kidney transplant and complications arose - rejection of the transplant (such patient is transferred to hemodialysis); 3. death.

Taking into account statistical data, we determined the probabilities of transitions between states (Table 2).

The indicators of the quality of life during the stay in various states were taken as follows: a patient with a transplanted kidney - 0.72, a patient with transplant rejection (on hemodialysis) - 0.59; death is 0.

The time horizon of the simulation was 10 years. The duration of the Markov cycle is 1 year. The discounting of life expectancy and the amount of expenses was taken into account in the amount of 3% per year.

Table 1. Probability matrix of transitions between Markov states during hemodialysis

From state/to state	1. hemodialysis without complications	2. hemodialysis with complications	3. Death
1. Hemodialysis without complications	0.81	0.11	0.08
2. Hemodialysis with complications	0.05	0.87	0.08
3. Death	0.00	0.00	1.00

Table 2. Probability matrix of transitions between Markov states during kidney transplantation

From state/to state	1. A patient with a kidney transplant	2. Transplant rejection	3. Death
1. Kidney transplant patient (first year after surgery)*	0.716	0.27	0.014
1. A patient with a kidney transplant (following years after surgery)	0.976	0.01	0.014
2. Transplant rejection	0	0.92	0.08
3. Death	0	0	1

*the first year after the operation, the graft rejection rate reaches 27%, in subsequent years - 1%.

Table 3. Aggregate costs of RRT by hemodialysis per year per patient

No. z/p	Name of expenses	Costs, USD
1	Hemodialysis procedure	8859
2	Laboratory tests	246
3	Medication correction of complications	769
4	Diagnosis and treatment of viral hepatitis	369
5	Indirect costs of the patient (transportation)	1108
	Together	11351

Table 4. Costs of RRT by kidney transplantation

Name	Costs, USD
Expenses during the first year	*28564*
Transplantation operation	21513
Immunosuppressive therapy	5128
Correction of complications	897
Laboratory diagnostics	385
Observations, consultations	641
Expenses during the second and subsequent years	*5769*
Immunosuppressive therapy	4359
Correction of complications	769
Laboratory diagnostics	385
Observations, consultations	256

RESULTS

Hemodialysis replacement therapy is life-long and is carried out in a medical facility three times a week (144-150 times a year). This technology requires additional costs (prevention and treatment of complications, transport) and significantly reduces the quality and length of life. The amount of expenses per patient during the year during hemodialysis treatment is 11,351 USD (Table 3).

The cost of a kidney transplant includes: expenses for management and examination of the donor and recipient; costs of the operation, including all con-

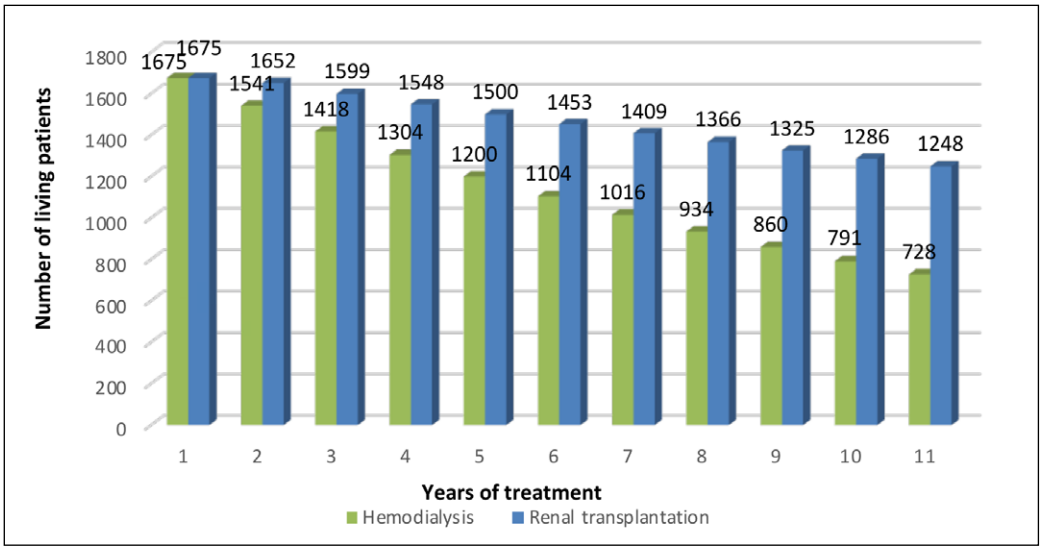

Fig. 1. Forecast of the dynamics of the number of patients who receive RRT by hemodialysis and kidney transplantation during 10 years of treatment.

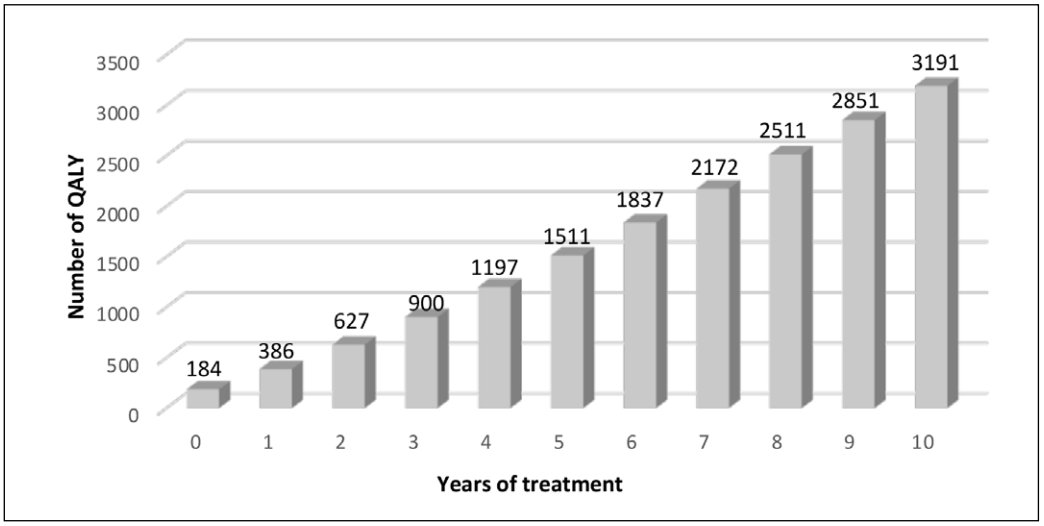

Fig. 2. The number of additional QALYs per 1,675 people obtained as a result of the use of RRT by the method of renal transplantation compared to hemodialysis, with discounting, years (forecast).

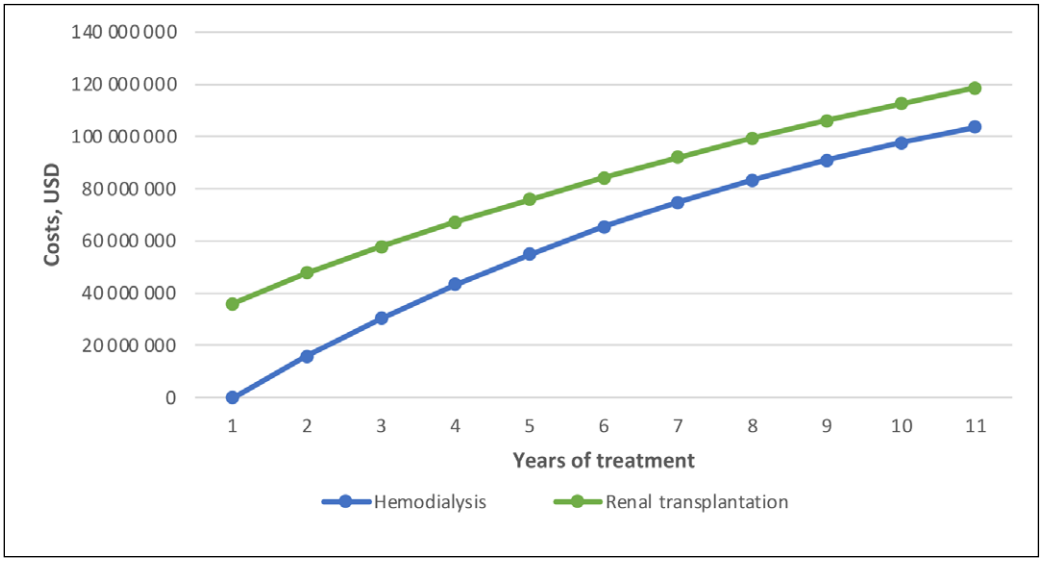

Fig. 3. Dynamics of cumulative costs for conducting RRT by methods of kidney transplantation and hemodialysis (with discounting, for 1675 people, forecast).

sumables; costs for preservation and transportation of the organ; costs for immunosuppressive therapy in the hospital are added; management of the patient in a medical institution after surgery, including costs for laboratory diagnostics, correction of complications, observation, consultations. We calculated the costs of transplantation, immunosuppressive therapy, treatment of complications, laboratory diagnostics, as well as the probability of transplant rejection in the period after discharge from the hospital (Table 4).

The highest costs when using a transplant will be in the first year ($25,864). In subsequent years, the annual cost will be about $5,769. Funds are spent mainly on life-long immunosuppressive therapy to prevent transplant rejection.

According to the results of Markov modeling in the case of renal replacement therapy by transplantation, it was determined that 1,248 (74.5%) of 1,675 patients will continue treatment at the end of the 10-year period. When using hemodialysis, due to the significant frequency of complications and the high mortality rate, only 728 patients (43.5% of the initial number) will continue treatment after 10 years (Fig. 1).

During 10 years of RRT by hemodialysis, the mortality rate per 1000 will be 565 people (56.5‰). In the case of transplantation, the mortality per 1000 people in 10 years is 255 people (25.5‰).

As for the calculation of the quality-adjusted life-year (QALY), it was found that using kidney transplantation, the number of QALYs for 1,675 patients during the 10-year treatment period would be 9,958 years (5,945 per 1,000 people). When performing RRT by the hemodialysis method, the number of QALYs will be 6,767 for 1,675 people or 4,040 per 1,000 people. The use of kidney transplantation adds 3,191 QALYs for 1,675 patients compared with hemodialysis (1.9 years per patient) (Fig. 2).

The total cumulative costs for conducting RRT by the method of renal transplantation, taking into account the cost of transplantation for 1675 people for 10 years, will be $118,738,529 ($70889 for one case). The amount of cumulative costs for hemodialysis for 10 years for the same number of patients, taking into account discounting, will amount to $103,758,684 ($61,945 per person) (Fig. 3).

We determine the cost of one QALY when using kidney transplantation compared to hemodialysis technology using the formula given earlier:

ICER = (118,738,529– 103,758,684) / (9958 - 6767) = 4694 USD

DISCUSSION

We conducted an analysis of a significant number of publications on the identification of priority technologies from the point of view of economic feasibility, which relate to strategies for the treatment of kidney diseases in different countries [2, 3, 10, 16, 17]. Under the optimistic scenario of an unlimited supply of kidneys and no waiting time for transplantation, renal transplantation for middle-aged and older adults provides a significant relative increase in life expectancy of at least 3.5 years compared to being on dialysis. Transplantation for young adults also achieves the greatest increase in life expectancy compared to those who remain on dialysis [18].

Studies have shown that kidney transplantation provides the greatest benefit and is the most effective method of renal replacement therapy compared to other methods [5, 9, 11, 19-21]. It is good value for money and sometimes provides cost savings. In contrast, dialysis is expensive, costing more than $20 billion annually in the United States, and demand for renal replacement therapy is increasing worldwide. Therefore, maximizing kidney transplantation is a priority in cost-effectiveness systems and clinical programs in most countries. Given current waiting times for transplants, the additional benefits of transplants over dialysis only become apparent after 4–5 years. Transplant increases life expectancy by 3–15 years compared to maintenance dialysis, with the increase depending on recipient and donor age[18].

Each state has special socio-economic conditions, so we determined the economic feasibility of renal transplantation compared to hemodialysis for Ukraine, which belongs to countries with a low and medium level of economic development. The size of the gross domestic product (GDP) in Ukraine in 2022 was 4,534 USD per capita [22]. According to the simulation results, the indicator of the cost of one QALY (ICER) is 1.04 times higher than GDP per capita. WHO recommends that the technology be considered economically feasible if the cost of one QALY is 1-3 GDP per capita [23]. Therefore, carrying out replacement therapy through renal transplantation in Ukraine is an economically feasible technology.

There are a number of limitations in the conducted research. Our estimates of increased survival do not take into account the possible presence of comorbidities. In the course of the simulation, we assume an ideal scenario regarding the availability of donor kidneys and the possibility of transplantation for all patients with end-stage renal disease. Treatment costs may differ from those calculated due to changes in the cost of drugs, examinations, and hospital expenses. But when conducting a sensitivity analysis, in the case of a doubling of transplant costs, the cost of one QALY will not exceed three GDP per capita in Ukraine. Therefore, transplantation will remain an economically feasible technology.

CONCLUSIONS

It was studied using Markov modeling that in Ukraine the use of kidney transplantation compared to hemodialysis gives the opportunity to save the life of 310 people out of 1000 who need RRT. Renal transplantation is an economically feasible technology for Ukraine, as the cost of one QALY of life is 4,694 USD, which is 1.04 times the size of Ukraine's GDP per capita. We hope that the results of our study will be useful to those who make decisions about the financing of medical technologies in countries with a low and medium level of economic development. Although transplantation is a valuable medical procedure and its cost exceeds the cost of hemodialysis, its use prolongs people's lives and makes them of higher quality. Therefore, it is advisable to give priority in financing to renal transplantation.

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ORIGINAL ARTICLE

CONTENTS

Morbidity and prevalence of diseases of the circulatory system in the adult population of the Kyiv region, including the working-age population

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ABSTRACT

Aim: To analyze the incidence and prevalence of diseases of the circulatory system in the adult population of the Kyiv oblast region, including the able-bodied population.

Material and Methods: Medical history records on cardiovascular diseases were the materials, and statistical methods of medical and social data procession were used in the study.

Results: The distribution of cardiovascular diseases in the adult population of the Kyiv oblast region was highlighted. The districts with the lowest and highest rates of myocardial infarction, strokes, ischemic disease and hypertension were found. The trends in relevant morbidity were described.

Conclusions: When analyzing data from statistical reporting, it was established that before the start of a full-scale invasion and partial quarantine restrictions due to the spread of SARS-CoV-2, the incidence of diseases in the circulatory system was characterized by significant unevenness across administrative units. However, a specific area with the highest morbidity was not singled out, only in respect of which it would be necessary to carry out measures to improve the provision of medical cardiology care. In general morbidity, areas with the highest levels of morbidity were established, which need to improve the provision of cardiac care, as this is a negative socio-economic factor with the need for intervention measures.

KEY WORDS: cardiovascular diseases, cardiology, social factors

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INTRODUCTION

Morbidity of the population, the level of disability and mortality are key negative indicators that characterize the interconnected vector of the influence of social, economic, and medical factors on a person. The higher the value of these indicators, the worse the state of health of the people of the studied population. According to WHO Mortality Database [1] according to ICD-10 and ICD-11 [2] in developed countries, the most frequent causes in terms of the absolute number of deaths and proportional mortality are cardiovascular diseases/ diseases of the circulatory system (Cardiovascular diseases (I00-199)/ 11. Diseases of the circulatory system) [3]. And although our country does not belong to developed countries according to OECD indicators, the incidence has a similar profile [4].

In the Global Reference List of 100 basic health indicators, conditions related to the circulatory system occupy one of the main places [5].

At the same time, one of the priority tasks of the relevant state bodies of the health care system (in Ukraine – the Ministry of Health) is the development, coordination and control over the implementation of state programs for the development of health care, in particular disease prevention, the provision of medical assistance, which is impossible without an analysis of morbidity on corresponding nosological forms

AIM

To analyze the morbidity and prevalence of cardiovascular diseases in adult people of the Kyiv oblast region, including the able-bodied population.

MATERIALS AND METHODS

Medical history records on cardiovascular diseases were the basic initial processed medical documentation. Range statistical method, demographic statistical method, general scientific methods of synthesis, generalization, scientific data interpreting, systemic approach method, medical statistical method, and analysis of the activity of state medical institutions dealing with cardiovascular pathology in Kyiv oblast region.

The performance analysis of state (public) medical institutions and the extent of certain cardiovascular diseases diagnosed in Kyiv oblast region of Ukraine. The analysis is based on epidemiological statistical frequency distribution, tabular summary, generalization, and comparison. The availability data of cardiological service were analyzed by the representative selective studies of medical facilities, distributed by the relevant districts of Kyiv oblast region.

RESULTS

According to the data in Table 1, which shows the incidence and prevalence of circulatory system diseases among the adult population of the Kyiv oblast region (by district), the lowest incidence rate was observed in the city of Slavutych. It did not exceed 1,407 per 10,000 of the corresponding population (2019), which was by 80.2% less compared to the general indicator for the region. At the same time, the highest incidence rate was observed in the Ivankiv district (2020), which was 84.1% higher than in the region. The difference between the highest and lowest incidence rates was 164.3%. The corresponding indicators were correlated with the levels of newly established diagnoses of relevant diseases per 10,000 population, where the lowest indicators were also in the city of Slavutych, and the highest in the Ivankiv district. According to open data, it was established that in 2021, there were only 5,649.8 diseases per 10,000 adult population (4,824.1 in 2022) and 3,031.5 per 10,000 working-age population (Fig. 1).

Indicators characterizing the working population are directly or indirectly indicators of the basis of the country's well-being, and not only economic. As a general characteristic, Table 2 presented information on the incidence and prevalence of diseases of the circulatory system in the able-bodied population of the Kyiv oblast region before the start of the COVID-19 pandemic, since the actual data changed their structure at the beginning of the pandemic and are not those that more clearly reflect the actual data. And after the beginning of a full-scale invasion - data with certain types of information were closed to public access.

The lowest value, as well as among the entire adult population, is the level of morbidity and prevalence of diseases of the circulatory system among the working population in the city of Slavutych - 83.4% lower than in the region. At the same time, the highest indicators among the able-bodied population were registered in the Pereyaslav-Khmelnytskyi district, which were 69.1% more than the indicators of the region.

According to individual nosological forms, among diseases of the circulatory system, the most common are hypertensive diseases (BA0X in accordance with ICD-11), coronary heart disease (BA4X), angina (BA40.Y) and myocardial infarction, acute and repeated (BA41 / BA42).

As in the case of general morbidity, the lowest indicators of the incidence of hypertension (80.3% lower compared to the indicator for the region) were in the city of Slavutych. In 2018, the highest indicators in the section of districts in the analysis per 10,000 of the relevant population were in Brovarsky district - 23.8%, and with a diagnosis established for the first time in life - in Skvyrsky district (by 110.1%); in 2019, the corresponding indicators were the highest in the Yagotyn district (by 35.9% per 10,000 of the corresponding population), with a diagnosis established for the first time in Ivankiv district (by 128.9%).

Regarding coronary disease, according to the lowest indicators, there is a similar situation in the city of Slavutych, where the incidence rate per 10,000 adults was 84.1%-81.2% (2018-2019), lower than in the region. However, it should be noted that in 2020, according to the indicator of the diagnosis established for the first time in life, the lowest level was in the city of Bucha. The highest levels were in Makarivskyi (by 65.7%, 2018), Yagotynskyi (by 59.2%, 2019) and Rokytnyanskyi (by 89.7%, 2020) districts. According to the diagnosis established for the first time in life, the highest incidence rate of coronary disease was in the Ivankiv district (by 140.5-222.6%, 2018-2020).

The highest incidence of angina pectoris (per 10,000 adults) was in Kagarlytskyi district (72.2% more than in the region, 2018; 101.6%, 2019); according to the diagnosis established for the first time in life, the highest level was in Ivankivskyi district (by 208.9%, 2018; 288.9, 2019) and Kagarlytskyi district (by 292.0%, 2019). The lowest indicators, according to the indicated levels, were in the city of Slavutych, where they corresponded to 90.2%-90.1% (2018-2019), lower than in the region (per 10 thousand adult population) and 1 case per diagnosis established for the first time in my life in 2018 and 2019. It should be noted that the city of Slavutych no longer had the lowest incidence of acute and repeated myocardial infarction; instead, the lowest rates were registered in 2018 in Zgurivskyi district (lower by 51.5% than in the region), in 2019 in Kyiv-Svyatoshinskyi district (by 68.9%) and in 2020 in Bilotserkivskyi district (by 61.5%). At the same time, the highest levels of morbidity were registered in Yagotyn district (2018, 50.7% higher than regional levels; 2019, 48.8%), Brovar district (2019, 55.0%) and Pereyaslav-Khmelnytskyi district (2020, by 108.7%). The relevant trends are shown in Fig. 2.

Table 1. Incidence and prevalence of diseases of the circulatory system in the adult population of the Kyiv oblast region (by district)

Names of districts	2018				2019				2020			
	All recorded diseases		Including the diagnosis established for the first time in his life		All recorded diseases		Including the diagnosis established for the first time in his life		All recorded diseases		Including the diagnosis established for the first time in his life	
	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population
Region	1120010.00	7929.70	73572.00	520.90	1008627.00	7114.80	63253.00	446.20	864642.00	6080.50	51382.00	361.30
Barishivskyi	23459.00	8170.20	1802.00	627.60	22701.00	7993.90	1846.00	650.00	18818.00	6708.30	1535.00	547.20
Bilotsepkivskyi	26629.00	6473.90	3095.00	752.40	26198.00	6410.70	2953.00	722.60	25705.00	6376.40	2699.00	669.50
Bohuslavskyi	20696.00	7277.30	1048.00	368.50	20798.00	7408.50	886.00	315.60	19096.00	6904.10	557.00	201.40
Borispilskyi	67753.00	7355.20	2102.00	228.20	41677.00	4521.00	1953.00	211.90	58028.00	6267.70	2124.00	229.40
Borodyanskyi	42521.00	9314.00	2920.00	639.60	39405.00	8687.90	2547.00	561.60	30905.00	6861.10	1597.00	354.50
Brovapskyi	139886.00	10200.00	8736.00	637.00	131188.00	9478.30	7435.00	537.20	109378.00	7852.80	4568.00	328.00
Vasylkivskyi	56457.00	7445.20	4374.00	576.80	48245.00	6407.00	3088.00	410.10	56617.00	7566.80	4885.00	652.90
Volodarskyi	10846.00	7734.40	1017.00	725.20	9041.00	6571.00	751.00	545.80	7731.00	5761.20	529.00	394.20
Vyshgorodskyi	43196.00	7279.70	3087.00	520.20	39423.00	6605.40	2505.00	419.70	29658.00	4922.00	2029.00	336.70
Zgurivskyi	12398.00	9277.90	659.00	493.20	12594.00	9585.90	677.00	515.30	12689.00	9931.10	644.00	504.00
Ivankivskyi	26611.00	10945.60	2673.00	1099.50	26674.00	11065.80	2661.00	1103.90	26801.00	11200.20	2702.00	1129.20
Kagarlitskyi	25713.00	9227.70	1876.00	673.20	25699.00	9327.80	1859.00	674.70	24913.00	9163.20	1789.00	658.00
K-Svyatoshynskyi	106032.00	7252.50	6329.00	432.90	92578.00	6031.40	4233.00	275.80	37827.00	2353.00	2665.00	165.80
Makarivskyi	30624.00	10407.50	1647.00	559.70	26421.00	9107.20	1180.00	406.70	22440.00	7770.10	1060.00	367.00
Myronivskyi	26089.00	9337.20	1459.00	522.20	25073.00	9060.80	770.00	278.30	23855.00	8742.90	881.00	332.90
Obukhivskyi	36428.00	6629.30	3130.00	569.60	35289.00	6452.30	2781.00	508.50	36136.00	6618.30	3178.00	582.10
P-Khmelnytskyi	35234.00	7823.00	2316.00	514.20	35134.00	7906.10	2287.00	514.60	33740.00	7706.70	2162.00	493.80
Polisky	3593.00	8138.20	209.00	473.40	3587.00	8089.80	209.00	471.40	3348.00	7744.60	167.00	386.30
Rokytnianskyi	20231.00	9572.30	1872.00	885.70	19809.00	9520.80	1458.00	700.80	19370.00	9463.60	1241.00	606.30
Squirsky	24104.00	7895.20	3097.00	1014.40	25209.00	8384.80	2923.00	972.20	22550.00	7637.30	2266.00	767.50
Stavishchenskyi	14394.00	8077.90	674.00	378.20	13801.00	7868.70	607.00	346.10	12123.00	7038.00	466.00	270.50
Tarashchanskyi	20137.00	8965.70	978.00	435.40	19715.00	8929.70	933.00	422.60	18868.00	8746.50	837.00	388.00
Tetiivskyi	26146.00	9915.80	1353.00	513.10	24695.00	9435.70	1218.00	465.40	24106.00	9323.90	932.00	360.30
Fastivskyi	45672.00	7470.60	4299.00	703.20	46054.00	7592.70	4335.00	714.70	45397.00	7590.80	4191.00	700.80
Yagotynskyi	26884.00	10162.90	1319.00	498.60	26627.00	10220.30	1073.00	411.90	25771.00	10078.60	703.00	274.90
the city of Bila Tserkva	124516.00	7326.80	4452.00	262.00	97422.00	5752.90	3609.00	213.10	70464.00	4166.80	2142.00	126.70
Irpin city	51992.00	7115.10	4698.00	642.90	41080.00	5387.90	4273.00	560.40	26096.00	3283.80	1471.00	185.10
Berezan city	9250.00	6787.50	464.00	340.50	9240.00	6832.80	450.00	332.80	10820.00	8036.80	542.00	402.60
the city of Rzhyshchiv	4002.00	6421.70	301.00	483.00	3728.00	6070.70	573.00	933.10	2574.00	4221.10	154.00	252.50
the city of Bucha	15641.00	5833.80	1297.00	483.80	16575.00	6022.70	888.00	322.70	6095.00	2172.30	422.00	150.40
m. Slavutych	2876.00	1373.90	289.00	138.10	2947.00	1407.00	292.00	139.40	2723.00	1308.00	244.00	117.20

DISCUSSION

Global patterns in the spread of cardiovascular disease are widely divergent across continents. An instant view on the epidemiology of cardiovascular diseases shows that there is no clear dependence between the country's general economic rates and the prevalence and incidence of circulatory system diseases. For example, China demonstrates that cardiovascular diseases (CVD) are the leading cause of death in the country. Among eight critical features of the epidemiology of CVD in China, some features indicate a transition in CVD epidemiology owing to interrelated changes in demography, environment, lifestyle, and health care, including the rising burden from atherosclerotic CVD (ischaemic heart disease and ischaemic stroke), declining mortality from haemorrhage stroke, varied regional epidemiological trends in the subtypes of CVD, increasing numbers of patients with moderate types of ischaemic heart disease and ischaemic stroke, and increasing ageing of patients with CVD. Other features highlight the problems that need particular attention, including the high proportion of out-of-hospital deaths of patients with ischaemic heart disease with insufficient prehospital care; the wide gaps between guideline-recommended goals and levels of lifestyle indicators; and the significant number of patients with undiagnosed, untreated, or uncontrolled hypertension, hypercholesterolaemia, or diabetes mellitus [6].

And these patterns are very close to Kyiv oblast region patterns revealed by us, besides the fact that China's economy is the second one around the globe. Meanwhile, Western patterns in developed countries

Table 2. Incidence and prevalence of diseases of the circulatory system among the able-bodied population of the Kyiv oblast region (by district)

Names of districts	2018				2019			
	All recorded diseases		Including the diagnosis established for the first time in his life		All recorded diseases		Including the diagnosis established for the first time in his life	
	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population	absolute data	per 10 thousand of the relevant population
Region	442727.0	4462.4	38426.0	387.3	383915.0	3869.9	30379.0	306.2
Barishivskyi	10844.0	5539.7	1012.0	517.0	10407.0	5402.9	1041.0	540.4
Bilotsepkivskyi	8863.0	3454.4	1760.0	686.0	8686.0	3429.9	1582.0	624.7
Bohuslavskyi	9661.0	5102.5	488.0	257.7	9923.0	5311.5	451.0	241.4
Borispilskyi	30648.0	4653.3	985.0	149.6	23443.0	3577.2	932.0	142.2
Borodyanskyi	16023.0	4981.7	1017.0	316.2	15244.0	4803.1	891.0	280.7
Brovapskyi	55531.0	5650.2	4137.0	420.9	50294.0	5092.8	2815.0	285.0
Vasylkivskyi	25046.0	4896.3	2733.0	534.3	20384.0	4034.0	1772.0	350.7
Volodarskyi	3308.0	3692.8	398.0	444.3	2620.0	3012.5	260.0	299.0
Vyshgorodskyi	14082.0	3346.3	1390.0	330.3	12219.0	2901.8	1186.0	281.7
Zgurivskyi	4629.0	5247.1	383.0	434.1	4911.0	5707.8	409.0	475.4
Ivankivskyi	9386.0	5635.5	1248.0	749.3	9389.0	5692.4	1219.0	739.1
Kagarlitskyi	7492.0	4073.3	909.0	494.2	7473.0	4132.4	891.0	492.7
K-Svyatoshynskyi	49122.0	4569.2	3655.0	340.0	42769.0	3778.4	2556.0	225.8
Makarivskyi	9180.0	4719.1	870.0	447.2	7486.0	3924.5	640.0	335.5
Myronivskyi	7758.0	4240.3	608.0	332.3	7001.0	3880.4	361.0	200.1
Obukhivskyi	21048.0	5477.5	2349.0	611.3	21215.0	5596.6	2147.0	566.4
P-Khmelnytskyi	19766.0	6440.3	1265.0	412.2	19702.0	6543.6	1276.0	423.8
Polisky	1803.0	5696.7	100.0	316.0	1798.0	5613.5	101.0	315.3
Rokytnianskyi	7287.0	5448.6	679.0	507.7	6759.0	5144.6	513.0	390.5
Squirsky	7718.0	3841.3	1657.0	824.7	6883.0	3489.8	978.0	495.9
Stavishchenskyi	5445.0	4696.8	409.0	352.8	5552.0	4883.0	349.0	306.9
Tarashchanskyi	6023.0	4064.4	490.0	330.7	5883.0	4063.1	431.0	297.7
Tetiivskyi	10602.0	5911.3	818.0	456.1	9280.0	5232.6	671.0	378.3
Fastivskyi	19742.0	4705.9	2160.0	514.9	19821.0	4792.5	2242.0	542.1
Yagotynskyi	9660.0	5640.5	520.0	303.6	9480.0	5668.8	409.0	244.6
the city of Bila Tserkva	43605.0	3508.0	2120.0	170.6	23292.0	1894.2	1298.0	105.6
Irpin city	18004.0	3253.5	2887.0	521.7	12321.0	2133.6	2122.0	367.5
Berezan city	2709.0	2719.9	279.0	280.1	2691.0	2751.5	251.0	256.6
the city of Rzhyshchiv	2367.0	5338.3	85.0	191.7	1272.0	2912.8	116.0	265.6
the city of Bucha	4151.0	2018.5	848.0	412.4	4374.0	2068.7	292.0	138.1
m. Slavutych	1224.0	739.1	167.0	100.8	1343.0	830.0	177.0	109.4

before SARS-CoV-2 demonstrated a severe drop in CVD morbidity and prevalence in the adult population and especially in the working-age population fraction [7].

The incidence rates of particular nosological forms of CVD reflect the population's age structure, non-compliance with a healthy lifestyle and its quality, the spread of social problems, life expectancy, etc. [8]. Knowing the structure and social and medical indices characterizing CVD epidemiology is the key to understanding and guiding the correct action plan to improve cardiovascular assistance in the mentioned population groups in particular areas. Our findings indicated the bilateral ways of CVD epidemiology in Kyiv oblast region.

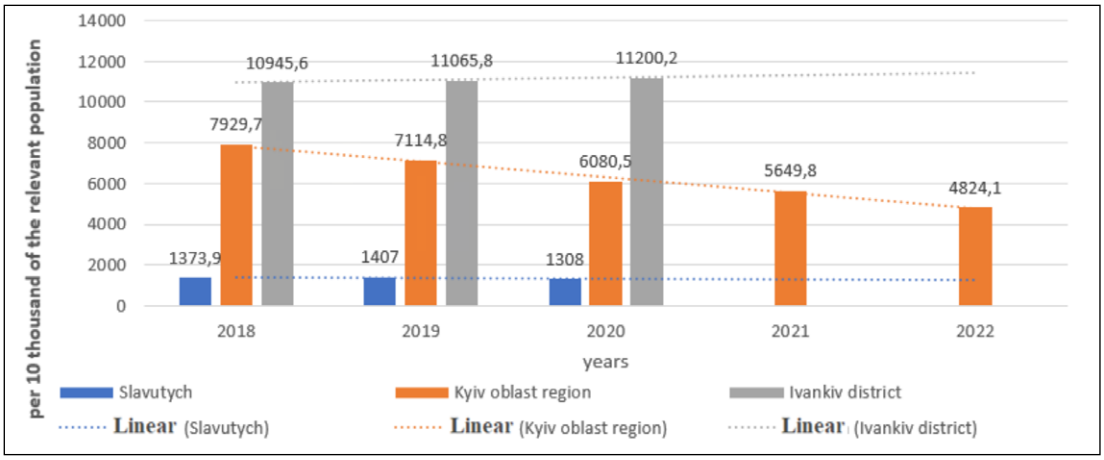

Fig. 1. Incidence rates of myocardial infarction in the adult population (by marginal rank distribution).

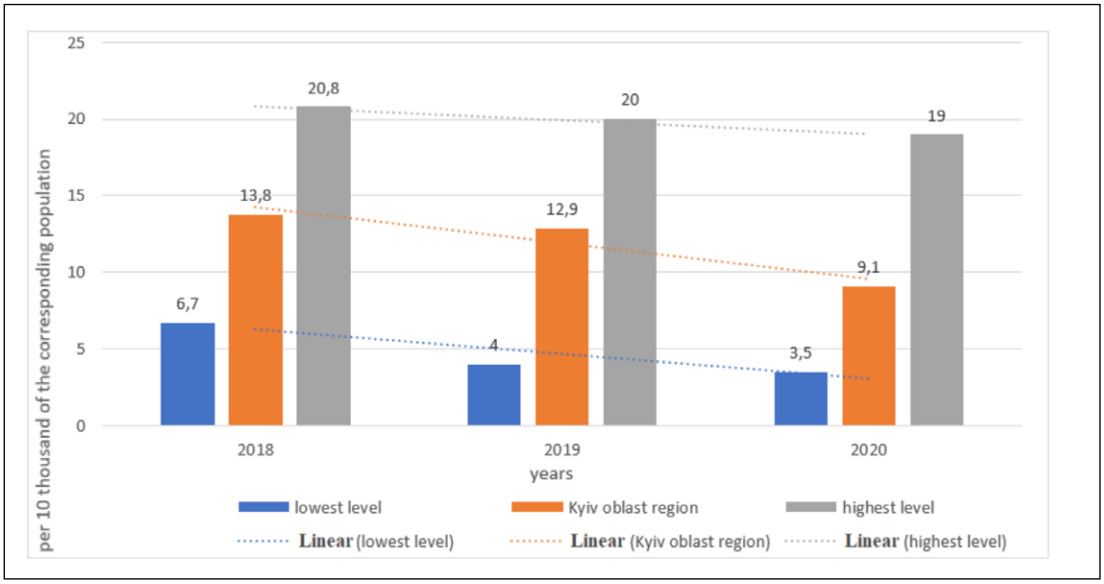

Fig. 2. Incidence rates of myocardial infarction in the adult population (by marginal rank distribution).

CONCLUSIONS

When analyzing data from statistical reporting, it was established that before the start of a full-scale invasion and partial quarantine restrictions due to the spread of SARS-CoV-2, the incidence of diseases in the circulatory system was characterized by significant unevenness across administrative units. Thus, in the city of Slavutych (an exclave of Kyiv oblast region on the territory of Chernihiv region), the lowest incidence rates of circulatory system diseases per 10,000 adult population as a whole, per 10,000 working-age population, the lowest incidence rates of hypertension, angina pectoris, and coronary heart disease were noted. However, a specific area with the highest morbidity was not singled out, only with respect to which it would be necessary to carry out measures to improve the provision of medical cardiology care. In general morbidity, it was established that the highest levels among the adult population with stable growth dynamics were registered in the Ivankivskyi district; however, in a detailed analysis by separate nosologies, such districts as Pereyaslav-Khmelnytskyi, Brovarskyi, Skvirskyi, Yagotynskyi, Makarivskyi, Rokytnyanskyi and Kagarlytskyi had the highest levels according to certain nosological forms and also need to improve the provision of cardiac care, as this is a negative socio-economic factor that requires intervention measures.

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CONFLICT OF INTEREST
The Author declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Patient-centered approach to the management of acute kidney injury in the Covid-19 outcomes

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ABSTRACT

Aim: To identify patients at risk of AKI with severe COVID-19 and to guide management strategies according to national and global scientific data for improving kidney-related outcomes.

Materials and Methods: We conducted retrospective study case-control analysing cases of hospitalisation patients with COVID-19 with or without AKI during hospital stay.

Results: In the study, we found that there was a positive correlation between AKI and respiratory insufficiency (0,513 – moderate, p<0,0001), moderate in the case of AKI grade 2 (0.301, <0,001) and mild in the case of AKI grade 1 and 3 correspondingly (0.252, p<0,01; 0.277, <0,001). Lethality (in-hospital death rate) correlated with respiratory insufficiency and AKI (0.733, 0,617; p<0,0001). We found that age had a reverse correlation with AKI and RI (younger patients were more likely to have a higher prevalence of AKI and RI, p<0,001). It was noticed that AKI correlated with the minimal albumin level (-0,35, p=0,016), minimal lymphocyte count (-0.377, p<0,0001), IL-6 (0.201, p=0,035), ferritin (0.34, p <0,0001), maximal CRP (0.439, p<0,0001). There was a mild correlation between Padua Score and AKI (0,232, p<0,01) and PLRI (0,172, p=0,05).

Conclusions: Early assessment of renal dysfunction could be used as a marker of severe outcomes of COVID-19, especially in the case of comorbidities such as metabolic disorders and cardiovascular events. We suggest using the Padua score, assessment of personal lethality risk index (PLRI), and rise of serum creatinine as additional tools for assessment criteria for hospitalisation.

KEY WORDS: COVID-19, prevention, acute kidney injury, public health, treatment

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INTRODUCTION

Community-acquired COVID-related acute kidney injury (AKI) is an important research direction. We tried to find approaches to optimise health care, focusing on diagnosing and managing AKI. The interrelationships between respiratory insufficiency, sepsis and AKI should still be discussed. According to the Kidney Disease Improving Global Outcomes (KDIGO) consensus, AKI is defined as a sudden loss of excretory kidney function [1], with the onset of development within seven days. AKI affects about half of patients admitted to the intensive care unit (ICU) and worsens their short- and long-term outcomes [2, 3]. AKI has a high prevalence in patients with COVID-19 hospitalised in the ICU [4]. Combining serum creatinine (SCr) and cystatin C provided good risk prediction in AKI [5, 6].

AIM

The study aims to identify patients at risk of AKI with severe COVID-19 and to guide management strategies according to national and global scientific data for improving kidney-related outcomes.

MATERIALS AND METHODS

The research methods included medical and statistical, content analysis, structural-logical analysis, clinical, laboratory, and instrumental techniques. We conducted retrospective study case-control analysing cases of hospitalisation patients with COVID-19 with or without AKI during hospital stay.

RESULTS

We conducted retrospective analysis of hospitalisation due to COVID-19 with or without AKI in the group of patients hospitalised to private hospital in Kyiv (n=129) (Table 1). The group was divided into 2 groups: those who had AKI and those who did not have significant changes in kidney function. We performed statistical analysis of data using

Table 1. Clinical and laboratory findings in hospitalised COVID- inpatients in the groups (with AKI and without AKI)

	AKI group (n=19) Males 10, females 9	**Non-AKI group (n=110) Males 46, females 64**	**p**
Males, %	52,6 (29,2-75,5)	41,8 (32,7-51,2)	p=0,536.
BMI, kg/m2	30.6±2.3	28.42±1.2	p=0,473.
Age, years (Me, IQR)	79 (64-80)	81 (78-84)	p<0,001
LYM*10^9/l (Me, IQR)	0,2 (0,1-0,39)	0,5 (0,34-0,76) (n=109)	p<0,001.
Maximum grade of respiratory insufficiency, (Me, IQR)	3 (3-3)	1 (1-2)	p<0,001
Duration of hospital stay (Me, IQR)	14 (9-22)	10 (7-13)	p=0,025
% CT (Me, IQR)	61 (40-75) N=14	30 (15-50) N=85	p=0,004.
CRP, mg/l (Me, IQR)	134,26 (93.54-185.06) N=19	44,765 (20.43-93.26) N=110	p<0,001.
HbA1c, % (Me, IQR)	5.5 (5.09-7.07) N=18	5.29 (4.79-5.95) N=106	p=0,111.
Ferritin, mcg/l (Me, IQR)	1094 (686-1176) N=17	375 (187-647.5) N=107	p<0,001.
IL-6 pg/mL, Me (Me, IQR)	48,55 (18-110,65) N=16	25,1 (10,2-46,2) N=97	p=0,029.
Baseline eGFR (on admission), ml/min*1,73 CKD,	60,41±5,61 N=19	60,06±1,96 N=106	p=0,944.
Minimal eGFR, ml/min*1,73 (Me, IQR)	18,4 (10,7-27,4) N=19	58,55 (42,1-74,9) N=94	p<0,001.
Min eGFR, ml/min*1,73 M±m	19,78±2,42 (p<0,001.)	-	p<0,001.
ALT, U/L, Me (QI-QIII)	29.1 (22,9-37,6) N=19	26.9 (16.9-41) N=108	p=0,339.
AST, U/L, Me (QI-QIII)	36.9 (26.8-67.9) N=19	35.4 (25.7-46.65) N=108	p=0,258.
AST/ ALT, Me (QI-QIII)	1,38 (1.11-1.47) N=19	1,31 (1-1.77) N=108	p=0,850.
Baseline Albumin (on admission), g/L, Me (QI-QIII)	32.07 (31.1-36.3)	33.68 (31.53-35.8)	p=0,588.
Albumin (on admission), g/L, M±m	33.37±1.1		
Minimal Albumin, g/L, M±m	27,64±0.9 (p<0,001.)	32.02 (26.37-35.91)	(p<0,001.)
Prevalence of Diabetes Mellitus, % (95% CI)	26,3 (8,6-49,4)	24 (16,1-32.9)	p=0,936.
Prevalence of cough, % (95% CI)	31.6 (12,1-55,2)	49.1 (39.7-58.5)	p=0,240.
Prevalence of Dyspnea, % (95% CI)	47.4 (24,5-70.8)	36.4 (27.6-45.6)	p=0,517.
Prevalence of fever, % (95% CI)	68,4 (44.8-87.9)	76.4 (67,9-83.9)	p=0,661.
Prevalence of frailty, % (95% CI)	94.7 (79.3-100)	96.4 (92-99.1)	p=0,742.
Prevalence of diarrhea, % (95% CI)	10.5 (0,8-29,2)	8,2 (3,8-14,1)	p =0,913.
Lethality (in both groups 31.8 (24-40.1)	100 (90.5-100)	20 (13-28)	p<0,001.
COMORBIDITY*[9]	2 (1-3)	2 (1-3)	p=0,547.
PLRI (personalized lethality risk index)[9]	5.1±0.4	4.3±0.2	p=0,048.
Padua Score	4 (3-4)	3 (3-3)	p=0,010.
Increase in SCr, times (95% CI)	2.25 (1.77-4.37)	1 (1-1.04)	p<0,001.
Prevalence of Grade 1 AKI, % (95% CI)	26,3 (8.6-49.4)		
Prevalence of Grade 2 AKI, % (95% CI)	36,8 (16-60,7)		
Prevalence of Grade 3 AKI, % (95% CI)	36,8 (16-60,7)		

Table 2. Rank correlation indexes between AKI and respiratory insufficiency (RI) -associated conditions

AKI & RI	0.513		AKI & RI		
			GRADE1	0.252	<0,01
			GRADE2	0.301	<0,001
			GRADE3	0.277	<0,001
RI & Lethality	0.733	<0,0001	AKI & Lethality	0.617	<0,0001
RI & AGE	-0.375	<0,0001	AKI & AGE	-0.304	<0,001
RI & ALB min	-0.532	<0.001	AKI & ALB min	-0.35	0,016
RI & PADUA	0.426	<0,0001	AKI & PADUA	0.232	<0,01
RI & IL-6	0.388	<0,0001	AKI & IL-6	0.201	0,035
RI & CRP max	0.467	<0,0001	AKI & CRP max	0.439	<0,0001
RI & FERR	0.451	<0,0001	AKI & FERR	0.34	<0,0001
RI & LYM	-0.611	<0,0001	AKI & LYM	-0.377	<0,0001
RI & Duration	0.376	<0,0001	AKI & Duration	0.206	0,02
RI & PLRI	0.406	<0,0001	AKI & I PLRI	0.172	0,05

Medstat. When performing the analysis for quantitative indicators, the mean value (M), standard error (±m) and 95% confidence interval (95% CI) were calculated for the normal distribution, and the median value (Me) and interquartile range (QI–QIII) were calculated for the non-normal distribution. For qualitative indicators, prevalence (%) and 95% confidence interval (95% CI) were calculated. The Mann-Whitney test was used to compare mean values in two groups for quantitative measures, and the chi-square test (with Yates' correction) was used to compare qualitative measures. All calculations were performed for a critical significance level of 0.05.

We used AKI criteria based on KDIGO (Kidney Disease Improving Global Outcomes) criteria in patients with elevated baseline serum creatinine (SCr); stage 1—increase in SCr by 0.3 mg/dl within 48 hours or a 1.5 to 1.9 times increase in SCr from baseline within seven days; stage 2—2.9 times increase in serum creatinine within seven days; stage 3—3 times or more increase in SCr within seven days or the initiation of RRT [1, 8].

In our previous study we proposed using personalized lethality risk index (PLRI) calculation as an indicator summarising the following criteria, such as presence of comorbidities (arithmetic sum of the number of organ systems affected by a chronic pathology according to ICD-10, or COMORB); 2) age over 70 years; 3) presence of obesity (BMI more than 30 kg/m2); 4) presence of cardiovascular disease; 5) neurological pathology (cerebrovascular events) in the past; 6) respiratory failure with decreased blood saturation (SpO2 < 92 %), requiring the oxygen therapy and glucocorticoid administration; 7) pulmonary parenchymal involvement over than 50 %.The presence of one of the above criteria resulted in a score of 1. The personalized lethality risk index was calculated as the sum of these scores [9].

We also calculated rank correlation indexes between AKI and respiratory insufficiency (RI) -associated conditions and presented them in the table 2.

In our study, we found that there was a positive correlation between AKI and respiratory insufficiency (0,513 – moderate, p<0,0001), moderate in the case of AKI grade 2 (0.301, <0,001) and mild in the case of AKI grade 1 and 3 correspondingly (0.252, p<0,01; 0.277, <0,001). Lethality (in-hospital death rate) correlated with respiratory insufficiency and AKI (0.733, 0,617; p<0,0001). We found that age had a reverse correlation with AKI and RI (younger patients were more likely to have a higher prevalence of AKI and RI, p<0,001). It was noticed that AKI correlated with the minimal albumin level (-0,35, p=0,016), minimal lymphocyte count (-0.377, p<0,0001), IL-6 (0.201, p=0,035), ferritin (0.34, p <0,0001), maximal CRP (0.439, p<0,0001). There was a mild correlation between Padua Score and AKI (0,232, p<0,01) and PLRI (0,172, p=0,05).

DISCUSSION

The pathophysiology of COVID-19-associated AKI could be due to multiple mechanisms such as direct viral kidney injury, immune-induces autoimmune reactions or hyperinflammation, sepsis, non-specific pre-renal mechanism, nephrotoxicity of some medications or mechanical ventilation, hypoxemia [3,7, 9, 10].

The pathophysiology of COVID-19-associated AKI could be related to non-specific mechanisms but also to COVID-induced mechanisms, such as direct injury resulting from viral entry through the receptor angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the kidney, an imbalanced renin-angiotensin-aldosterone system, pro-inflammatory cytokines

elicited by the viral infection and thrombotic events, as well it could be caused by non-specific mechanisms include hemodynamic alterations, right heart failure, high levels of PEEP in patients requiring mechanical ventilation, hypovolemia, administration of nephrotoxic drugs, and nosocomial sepsis [12]. Local inflammation and hyperinflammatory immune response could be considered a key role in AKI, as endothelial injury and microvascular clots are essential in the pathophysiology of AKI. However, the issue of renal tropism remains controversial [12].

AKI could be observed in the structure of multiple organ damage in severe and critically ill COVID-19 patients. As it illustrates the influence of cytokine storm on organ lesions, AKI is also caused by hypoxemia [13]. Hirsch J. S. et al., 2020 reported that among patients who required mechanical ventilation, 89.7% had AKI compared with 21.7% in nonventilated patients [14].

Ng J.H. et al., 2020, reported that among 9,657 patients admitted with COVID-19 to the 13 hospitals in New York in 2020, the AKI incidence rate was 38.4/1,000 patient-days and incidence rates of in-hospital death among patients without AKI, with AKI not requiring dialysis (AKI stages 1-3), and with AKI receiving dialysis (AKI 3D) were 10.8, 31.1, and 37.5/1,000 patient-days, respectively [11].

Menez S. et al., 2023 reported that an increase in soluble tumour necrosis factor receptor 1 (sTNFR1) and sTNFR2 was significantly associated with an increased risk of major adverse kidney events (MAKE) [15]. Noticeably, kidney dysfunction is considered to be quite frequent as mild proteinuria or any other urine abnormalities in urinalysis may be often observed in non-severe cases. Still, as well it could predict AKI that causes urgent dialysis necessity or other renal replacement therapy (RRT) [13]. The cost of hospital stay and duration of treatment increases while AKI happens [14, 16, 17]. Wainstein M. et al. (2023) suggest analysing AKI in the severity of the disease (on the individual level) and in the global context, comparing the international effectiveness of health systems while analysing results from countries with different income levels. The authors divided countries by income level and compared AKI incidence during hospital stays [16]. The critical question is whether prevention of AKI is possible and how it could be prevented. However, the answer could be challenging as the necessity of hospitalisation was considered differently in different countries and varied greatly, depending on the health system and medical facilities.

Understanding the mechanisms of kidney damage and AKI in the setting of critical illness and COVID-19 is important, and it can provide a possibility for improvement in health care [14, 17]. The main methods of RRT include dialysis and renal transplantation, but globally, it is thought to be challenging due to numerous economic, social, and other factors [18]. Hemodialysis and peritoneal dialysis are equally efficient, and it is essential to raise the awareness of patients and the level of medical staff education and provide equal access to all renal replacement therapy types worldwide [18]. During a pandemic or martial period in Ukraine, while the resources are limited and the massive hospitalization with the necessity of urgent RRT could be observed, acute kidney injury developing on the battlefield, in field hospitals or higher-level hospital settings is characterized by poor outcomes [19]. It was reported that patients with AKI and COVID-19 more often required RRT and less frewuently recovered kidney function [20].

Neirynck N. et al., 2015 concluded that both sTNFR1 and sTNFR2 could help predict the outcome of chronic kidney disease (CKD), including diabetic nephropathy, associated with increased all-cause mortality or an increased risk for cardiovascular events (CVE) in advanced CKD irrespective of the cause of kidney disease [21].

To prevent poor outcomes of COVID-19, we propose analysing clinical and laboratory findings. Suppose the person has chronic non-communicable diseases, such as CVD, arterial hypertension, diabetes, metabolic disorders, psychiatric or neurological pathology, especially with high initial ferritin, C-reactive protein, IL-6 levels or poor dynamics. In that case, it is advisable to hospitalise the person after assessing the individual risks. Further study is necessary to clarify the possibility of personal assessment and risk calculation tools based on evidence-based medicine. However, high mortality could be explained by late admission or rapid organ failure in the case of secondary hemophagocytic lymphohistiocytosis. It is necessary to use pandemic experience in the future. Early renal replacement therapy is essential for the effectiveness of AKI grade 3 management to prevent severe complications and in-hospital deaths.

CONCLUSIONS

It was noticed that AKI correlated with the minimal albumin level (-0,35, p=0,016), minimal lymphocyte count (-0.377, p<0,0001), IL-6 (0.201, p=0,035), ferritine (0.34, p<0,0001), maximal CRP (0.439, p<0,0001). There was a mild correlation between Padua Score and AKI (0,232, p<0,01) and PLRI (0,172, p=0,05). Early assessment of renal dysfunction could be used as a marker of severe outcomes of COVID-19, especially in the case of comorbidities such as metabolic disorders and cardiovascular events. We suggest using the Padua score, assessment of PLRI, and rise of serum creatinine as additional tools for assessment criteria for hospitalisation.

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ORIGINAL ARTICLE

CONTENTS

Values of academic integrity in higher medical education

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ABSTRACT

Aim: The aim is to identify features of theoretical and empirical research of academic integrity as characteristics of the educational environment of medical higher education institution (hereinafter – HEI).

Materials and Methods: A complex of general scientific methods: logical-analytical, dialectical, theoretical-logical, comparative analysis, formalization and generalization, as well as quantitative sociological methods for collecting, processing and analyzing information. The object of the pilot empirical study were domestic medical students of full-time education at the Bogomolets NMU (N=472) and scientific and pedagogical staff who provide teaching of fundamental, specialized and socio-humanitarian disciplines at the university (N=153).

Results: The values of academic integrity are the moral guideline that reveals the latest ethical demands of society and regulates the educational and scientific activities of all participants in the educational process. Opinions on the primary responsibility for compliance with the rules of academic integrity of a student differ between the surveyed scientific and pedagogical staff and students (p=0.000): the vast majority of the surveyed scientific and pedagogical staff tend to evenly divide the responsibility between a teacher and a student, and the majority of students-respondents noted that the student bears the primary responsibility.

Conclusions: Commitment to the principles of integrity motivates both students and teaching staff to act in an academic manner. Therefore, the creation of a methodology for studying the phenomenon of academic integrity in medical higher education institution through the study of attitude of the subjects of educational process to basic values is promising.

KEY WORDS: Academic integrity, values, higher medical education, social research

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INTRODUCTION

The current stage of development of Ukrainian society is characterized by existential changes and transformations in almost all spheres of its functioning. They did not bypass the system of higher medical education. On the one hand, this is due to bringing the legislative framework in line with European parameters, on the other – with the formation of a new educational worldview, a new conceptual model of the educational process. Therefore, the phenomenon of academic integrity is of particular importance, as a condition and determining factor not only for the provision of a wide range of quality educational services, but also for the development of scientific and research practices of our time.

Unfortunately, at the level of everyday consciousness, a narrow, simplified understanding of the meaning of the term "academic integrity" was formed. Usually it is associated with such phenomena as "the presence of plagiarism in scientific works", "data falsification", "usual cheating" or "passing off other people's thoughts as their own", etc. For the most part, it is not so much about academic integrity, but about identifying the facts of its non-compliance, dismissive attitude to clearly defined norms and requirements, academic dishonesty in general. Of course, the identification of the essential terminological features of this phenomenon and the representation of its basic principles is extremely important and relevant. This will avoid in the future emasculation of the very content of academic integrity, substitution of fundamental concepts, misunderstanding of its basic principles and principles of functioning in the domestic educational and scientific space.

At the legislative level, the essence and substantive characteristics of academic integrity are clearly outlined in Article 42 of the Law of Ukraine "On Education" as of July 02, 2023. Here, academic integrity is understood as "a set of ethical principles and rules defined by the law, which should guide the participants in the educational process during learning, teaching and conducting scientific (creative) activities in order to ensure confidence in the results of learning and/or scientific (creative)

achievements" [1]. At the same time, professional ethics and deontology treat this concept certainly in a positive perspective, focusing on the basic principles of academic integrity, which Western science is inclined to call values.

It should be emphasized that the very principles of academic integrity were outlined by the International Center for Academic Integrity (ICAI) in 1992. In particular, the international academic community implies a commitment to six fundamental values (principles): *honesty, trust, justice, respect, responsibility, courage* that regulate activities and behavior both within the community and outside it, in everyday life [2].

AIM

The aim is to identify the features of theoretical and empirical research of academic integrity as a characteristic of the educational environment of medical HEI.

MATERIALS AND METHODS

The choice and application of research methods are due to its interdisciplinary nature. The article implemented a systematic approach using a complex of general scientific methods: logical-analytical, dialectical, theoretical-logical, comparative analysis, formalization and generalization, as well as special sociological methods for collecting processing and analyzing information. The object of the pilot study were domestic medical students of full-time education at the Bogomolets NMU and scientific and pedagogical staff who provide teaching of fundamental, specialized and social and humanitarian disciplines at the University. As a result of applying on-line questionnaire in February 2023, 153 teaching staff and 472 students were surveyed. Information processing was carried out using the IBM SPSS Statistics software package.

RESULTS

Real human relationships have always been the subject of ethical science, they were formed on the basis of morality, existed on fundamental moral principles. In our opinion, the values of integrity are the moral guideline that reveals the latest ethical demands of society and regulates the educational and scientific activities of all participants in the educational process. The origins of the modern understanding of the principles of academic integrity reach philosophical and ethical thoughts of the ancient world, especially Plato and Aristotle. These thinkers paid considerable attention to the comprehension, theoretical content and practical implementation of ethical virtues that were considered the basis for the existence of not only an integral civil society, but also the basis for the functioning of educational institutions, the creation of a proper academic environment within them.

Plato connects the social good and personal happiness of man with the necessary presence of such moral virtues as prudence, restraint, courage, association and awareness of which leads in the hierarchy to the highest virtue – justice. As Pierre Hadot notes, "the highest form of mental activity is mastering oneself and fair actions implemented through the organization of the community or other institutions. Numerous historians saw in this mention of "institutions" a hint of Plato's founding the school" [3]. Plato's idea is to act; to act justly in public and personal life.

Instead, taking as a basis the Platonic list of virtues, Aristotle forms his own classification. He divides all virtues into ethical (virtues of will and character) and *dianoetic* (intellectual virtues). The first group includes: justice, dignity, sincerity, generosity, courage, moderation; the second – wisdom, knowledge, temperance. The thinker defines the essence of virtues through the concept of measure as a certain harmony between two opposites.

According to Aristotle, "reasonable life" is the greatest virtue of man, his happiness. Rational cognition, work on oneself, exercises in virtue and its practicing will help transforming the natural inclinations of man into conscious dianoetic virtues led by prudence. If a person is a slave to his own passions and does not have natural inclinations to virtues, in such a case, the educational work should be carried out by legislators and the community by adhering the requirements and laws. In Nicomachean Ethics, Aristotle calls for legalizing the various aspects of integrity for the education of moral virtues and the provision of opportunities for virtuous life to citizens of cities poleis. The philosopher is sure that virtues are actualized and truly manifest themselves not so much in the being of a particular person as in the life of society, because person is a "political being".

We can say that now more than ever the views of the ancient thinker acquire special significance. Aristotelian virtues ontologically find their manifestation in social associations of people, including the academic community, in particular, they form a framework and support the functioning of a virtuous academic environment. It is appropriate that in modern academic communities, group values and social virtues have been integrated into a single whole – into a system of principles of academic integrity. Representatives of a particular social institution or organization, for example, scientific and pedagogical staff of higher education institutions, taking into account personal beliefs and ideals, usually

are united by an idea, have a common goal, "strive for the realization of some good that is recognized by all participants of the plan" [4]. Knowledge and practical implementation of the principles of academic integrity contributes to the realization of their goals or benefits, while non-compliance with the principles is harmful for the academic community, as ties in the community are destroyed, seeds of distrust are sown among the participants of the educational process, it is impossible to achieve the common good or benefits.

A prominent place in the system of principles of academic integrity belongs to the principle of justice. The problem of the axiology of justice and its role among other moral values is conceptually significant for the formation of a holistic strategy for the embodiment of integrity in the educational and scientific practice of our time. Justice is terminologically defined and is a definition of the highest value, perfect goal, social virtue, moral quality inherent in a person or group of persons, etc. Today, the phrase "social justice" is no longer a metaphor, but is used quite habitually both in scientific discourse and in everyday speech. According to Bernhardt Sutor, justice as a virtue implies the existence of a valid and effective legal order. It needs not a nominal, but a valid law, which also depends on the willpower of people in their attitude to justice. Justice promotes the unification of people, mutual understanding between them; recognizes the Other as a personality with his rights and interests on the principles of equality and human dignity [5].

Often justice appeals to the inner feelings of a person, this is what it is similar to *honesty*. The latter is interested in justice and always reacts negatively to numerous distorted manifestations of justice. Honesty also requires legalization, recourse to some written or unwritten code. It contains the idea of integrity, purity, fairness (honest name) and requires compliance with certain rules. In this case, honesty is correlated with the decency and personal dignity of a person. The most important thing in honesty is the absence of deception, lies and fraud.

Trust is at the same time an internal value that strengthens the moral guidelines of a person and an instrumental principle that has social significance and can benefit a person, a collective, and society as a whole. It greatly increases our ability to cooperate with others and to benefit from that cooperation, although of course we only benefit if the people we trust also cooperate with us (Gambetta 1988b; Hardin 2002; Dimock 2020) [6]. Trust improves relations in the academic community, makes them "easier", strengthens cooperation, which is important for outlining further educational, scientific perspectives. Trust is a sign of *respect*, accordingly, distrust is a sign of disrespect. Both alternative judgments are meaningful as long as the trust is worthwhile and therefore justified. Otherwise, respect also becomes irrelevant, its internal potential is devalued. The importance of the principle of responsibility cannot be overestimated, it is considered a powerful motivator and driver of the actions of a person. Thanks to responsibility, a person outlines for himself the criteria by which he makes a moral choice: a clear understanding of good and evil; indifference in relation to others, to the fate of participants of the educational process, their professional successes, victories or failures. On the other hand, responsibility is able to act as a filter, through the prism of which one can observe the presence or absence of a stable system of moral beliefs in the performance of educational activities. Finally, the main beliefs of the representatives of the academic community are able to be broadcast and put into practice through courage. Being courageous means having the courage and inner need to act, in particular, under contradictory circumstances or adverse conditions, sometimes even contrary to authority. The main thing is the objectivity of beliefs, confidence in the correctness of one's own thoughts, ideas, initiatives, their bold advocacy.

When planning social research on academic integrity, a number of problems arise, some of which are related to the difficulty of defining the phenomenon of integrity in general and academic integrity in particular. In order to reveal the importance of higher education students' compliance with the basic values on which academic integrity is based, the respondents were asked to estimate how important it is for them personally to adhere to such values as respect, justice, responsibility, trust and honesty in the process of education (see Table 1). The question about the importance of compliance with such a value as courage was not asked of the students due to their disorientation regarding the meaning of this value, which was revealed during the approbation of a questionnaire.

It is worth noting that the declaration of the importance of compliance with certain values in the learning process does not mean their actual adherence, but rather provides information about the greater or lesser importance of certain values for the respondents – higher education students. Respondents noted the importance of personally comply with all basic values, but it is worth noting that personally adhere to such a value as respect in the learning process is important to the full extent for 82.0% of the interviewed students, and personally adhere to such a principle as honesty is fully important for 56.4%. However, the most common answer regarding the importance of compliance with all

Table 1. Answers to questions: "How important is it for you personally to comply with the following values in the educational process?", % (N=472)

Value	It is important to the full extent	It is rather important	In certain cases it is important, in certain cases it is not	It is rather not important	It is not important at all	Difficult to answer
Respect	82,0	12,3	4,0	0,4	0,6	0,6
Justice	79,2	15,7	3,6	0,0	1,1	0,4
Responsibility	77,5	17,2	3,8	0,4	0,8	0,2
Trust	60,6	26,1	8,5	2,1	1,3	1,5
Honesty	56,4	28,8	12,3	1,1	1,1	0,4

Table 2. Average evaluations of higher education students regarding the importance of compliance with the values of academic integrity at Bogomolets National Medical University

Value	Arithmetic mean	Mode	Median
Respect	4,75	5	5
Justice	4,72	5	5
Responsibility	4,70	5	5
Trust	4,44	5	5
Honesty	4,38	5	5

Table 3. Answers to questions: "Who, in your opinion, is primarily responsible for complying the rules of academic integrity of a higher education medical student?", %

	Scientific and pedagogical staff (N=153)	Students (N=472)
Primarily, the teacher	9,2	1,9
Primarily, the student	18,7	59,7
Teacher and student equally	71,9	35,8
Difficult to answer/refusal to answer	0,0	2,1
Another answer	0,7	0,4

values is the answer "it is important to the full extent". Average ratings of the importance of personally adhering to academic integrity in the learning process were calculated using the SPSS software under the condition that when responding to the importance of adhering to a certain value, 5 points were allocated for the answer "It is important to the full extent", 4 points – for "It is rather important", 3 points – for "In certain cases it is important, in certain cases it is not", 2 points – for "It is rather not important", 1 point – for "It is not important at all". The answer "Difficult to answer" was not taken into account when calculating average values (see Table 2).

A comparative analysis of ideas about the primary responsibility for complying with the rules of academic integrity of two groups of respondents – scientific and pedagogical staff and higher education students – proved to be quite fruitful (see Table 3).

Opinions regarding the primary responsibility for adhering the rules of academic integrity of a higher education students differ among the surveyed scientific and pedagogical staff and students (p=0,000). The vast majority of the surveyed scientific and pedagogical staff (71.9%) noted that a teacher and a student are equally responsible, while the majority of higher education students who took part in the study noted that a student is primarily responsible (59.7%).

DISCUSSION

It is worth noting that the empirical study of academic integrity through the attitude of subjects of the educational process to basic values and principles has a number of significant features.

Direct questions about the importance of certain values for the respondent personally can be classified as "sensitive" questions, to which the number of "expected" answers increases. In addition, it is worth taking into account the situation of a full-scale invasion, because "...external aggression activates the option of dual perception by people of events and processes: us – them, white – black, good – evil, true – wrong, objective – distorted, fair – lawless" [7].

Therefore, when studying the importance of compliance with certain values, it is appropriate to ask a

question that involves ranking the values of academic integrity by the respondents themselves in relation to the importance of their personal adherence in the learning process. A question that contains a proposal to assess how much the respondent's classmates adhere to basic values in the learning process can also be quite informative.

In addition, in our opinion, the results of questionnaires aimed at studying the issue of academic integrity in a specific higher education institution should be supplemented with results obtained using other methods. The results of focus group discussions on current issues of academic integrity in a particular higher education institution can be quite fruitful.

After the adoption of the new law of Ukraine on academic integrity, the draft of which has already been registered, it seems appropriate to create a methodology for a complex sociological study based on the provisions of the law. Important, in our opinion, when conducting the field stage of this kind of research, is the use of offline questionnaires to collect information, in order to increase respondents' confidence in confidentiality.

CONCLUSIONS

In fact, academic integrity is a multi-level system of academic culture, freedom and responsibility of participants in the educational process, the basis of which is moral rules, value orientations and defined norms of the law. Clearly prescribed ethical norms have a direct proportional effect on the efficiency and quality of the performance of professional duties. The performance of professional activities regulated by ethical standards contributes to the solidarity of members of the academic community, regardless of their social status or academic title.

On the basis of the interpretation of the results of the questionnaire of higher education students regarding the assessment of the importance of compliance with certain values in the learning process, it is possible to pay attention to the consideration of those issues related to values that turned out to be less important for the respondents in the framework of teaching the discipline "Anti-corruption and Integrity", which since 2023/2024 academic year is available for students of the Bogomolets National Medical University as a result of joining the pilot project "Transparent Universities" of the Integrity Office of National Agency on Corruption Prevention.

In the context of studying issues of academic integrity, it is worth paying attention to the readiness of higher education students to recognize the primary responsibility for complying with the rules of academic integrity of the student himself, revealed as a result of the pilot study. The democratization of the education system and the personal virtues of the modern generation of students contribute to the involvement of higher education students as full-fledged subjects of the formation of a virtuous academic environment.

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CONTENTS

Factors associated with female infertility in Ukraine: results a multicenter study

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ABSTRACT

Aim: To determine the current prevalence of female infertility and characterize and identify risk factors associated with infertility in Ukraine.

Materials and Methods: Multicenter prospective cohort study was conducted from January 2021 to December 2023 in twelve medical centers from nine regions of Ukraine. Definitions of infertility were adapted from the World Health Organization. According to the data collected from questionnaire, participants were divided into infertile and fertile groups and analyzed associated factors.

Results: Among all the 7,618 participants in this study, the prevalence of female infertility was 24.3%. The prevalence of primary infertility was 5.9%, and the prevalence of secondary infertility was 18.4%. In logistic multivariate regression analyses, female infertility was associated with age of women ($p<0.001$), age of first sexual intercourse ($p<0.001$), history of gynecological surgery ($p<0.001$), marital status ($p<0.001$), age of marriage ($p<0.001$), decreased ovarian reserve (DOR) ($p=0.006$), family history of infertility ($p<0.001$), history of cervicitis ($p=0.007$), history of surgical abortion ($p<0.001$), history of endometritis ($p=0.027$), bacterial vaginosis ($p=0.023$), and aerobic vaginitis (< 0.001).

Conclusions: Our data suggest a high prevalence of female infertility in Ukraine. The prevalence of secondary infertility was higher than primary infertility. Age of women, age of first sexual intercourse, history of gynecological surgery, marital status, age of marriage, DOR, family history of infertility, history of cervicitis, history of surgical abortion, history of endometritis, bacterial vaginosis, and aerobic vaginitis were associated with infertility.

KEY WORDS: Epidemiology, Infertility, Reproduction, Prevalence, Risk factors, Ukraine

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INTRODUCTION

The infertility of the population worldwide is an important public health issue. Every human and couples have the right to decide the number, timing and spacing of their children. Infertility can negate the realization of these essential human rights. Addressing infertility is therefore an important part of realizing the right of individuals and couples to found a family [1].

The World Health Organization (WHO) has identified infertility as a global public health problem. Infertility affects millions of people – and has an impact on their families and communities. 2022 global infertility prevalence estimates are: Estimates suggest that approximately one in every six people of reproductive age worldwide experience infertility in their lifetime. This is regardless of where they live and what resources they have. Estimates of infertility prevalence are similar across countries with different income levels. Lifetime infertility prevalence was 17.8% for high-income countries and 16.5% for low- and middle-income countries. Period infertility prevalence was 12.6% for high-income countries and 12.6% for low- and middle-income countries. The available data indicate that estimated lifetime prevalence of infertility is highest in the WHO Western Pacific Region (23.2%) and lowest in the WHO Eastern Mediterranean Region (10.7%). The prevalence of infer-

tility in WHO European Region were reported to 16.5% [2]. In Ukraine the prevalence of infertility was 25.4% [3].

Infertility may be caused by a number of different factors, in either the male or female reproductive systems. In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others [3-8]. The relative importance of these causes of female infertility may differ from country to country [9]. However, it is sometimes not possible to explain the causes of infertility. Understanding the magnitude of infertility is critical for developing appropriate interventions, for monitoring access to quality fertility care, and for mitigating risk factors for and consequences of infertility.

In Ukraine female infertility remains one of the mysteries in the reproductive health field, where the diagnostic evidence is still weak and the proposed treatments still work with unknown methods. However, several studies have proposed some possible causes and risk factors for female infertility [3, 5-8]. The high prevalence of infertility worldwide, especially in limited-resource countries like Ukraine, implies that the current assessment of the women reproductive system is far from perfect. Nevertheless, significant improvements in diagnostic tools and assisted reproductive technologies have led to the finding of many causes of infertility that in the past had only been suspected, but, up until now, some causes of female infertility are still unknown. Therefore, there is a need to search for more answers to the causes of female infertility to create better treatment options for patients. Currently, in Ukraine the risk factors of female infertility, have not been adequately studied.

AIM

The aim this study to determine the current prevalence of female infertility and characterize and identify risk factors associated with infertility in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTING AND POPULATION

We performed a multicentre, prospective cohort study. The study was carried out during the period from January 2021 to December 2023. Twelve medical centers (Maternity Hospital, Reproductive Clinic, and Fertility Center) from nine regions (Lviv, Vinnytsia, Cherkasy, Zhytomyr, Kyiv, Kharkiv, Kherson, Dnipropetrovsk, and Odessa) of Ukraine were all used to collect study samples. Those centers were purposefully selected because they are the largest centers providing assisted conception and modern antenatal care in Ukraine. In this study cities located respectively in the west and east, and north and south, as well as the in central region of Ukraine were used as objects of comparison, since they often resemble opposing views on social and demographic processes. The current study targeted 7,618 Ukrainian women between the ages of 19 and 50. The case group included 1,850 women with infertility. The women were chosen using a systematic random sampling technique from patients who had tried but were unable to conceive for at least a year (maintain regular unprotected vaginal sexual intercourse with their partner at least twice a week for a year) [10]. The control group consisted of 5,768 fertile, nonpregnant women who had at least one healthy 2-year-old child (end of lactation). In this study to exclusion criteria for participants were as follows: never had sexual intercourse; received continuous medical treatment that could affect fertility. In addition to that, women were also excluded if they were under the effect of anti-inflammatory medicines or if they were under the effect of hormonal contraception within the last 6 mo. Any women who refused to sign the informed consent form or withdrew during the study were excluded.

DEFINITION

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved [2]. Infertility among women was classified as primary and secondary. In our study primary infertility is defined as a woman who has never been diagnosed with a clinical pregnancy and meets the criteria of being classified as being infertile, while secondary infertility is defined as a woman unable to establish a clinical pregnancy who has previously been diagnosed with a clinical pregnancy [11]. Body Mass Index (BMI) is defined as an estimation of human body fat based on height and weight. BMI is expressed in kg/m^2, resulting from dividing body mass in kilograms by height in meters. Thin' means that BMI is less than 18.5 kg/m^2. 'Normal' means 18.5 kg/m^2≤ BMI < 24 kg/m^2. 'Overweight' means 24 kg/m^2≤ BMI < 28 kg/m^2. 'Obesity' means that BMI is more than 28 kg/m^2 [3]. The waist-to-hip ratio (WHR) was defined as an estimation of fat stored around the waist and hips. The waist-hip ratio was calculated by dividing the waist measurement by the hip measurement.

DATA COLLECTION

Our study includes interviews and questionnaires of women, also analyses medical records infertile women's. To assess female infertility risk factors, a structured pre-tested questionnaire containing information on socio-demographic variables, anthropometrics, clinical diagnosis of infertility, behavioral factors, physical activity assessment, dietary diversity, and consumption of different food groups by study participants was used. The questionnaire was prepared by reviewing several relevant published articles [3-8, 12-15] and adopting standardized data collection tools. After passing all quality check-ups, the questionnaire was filled out with the help of 9 research assistants who are experts in reproductive health (one in each previously mentioned healthcare facility). In this study the completeness of the data was checked each day at the end of data collection. Incomplete data was traced back and edited accordingly. The follow-up of study participants was done by tracking information (address, phone number of the participant as well as of relatives and close friends) and making periodic contact to minimize loss of follow-up, and the overall follow-up and data collection processes were coordinated and supervised by the research assistants' and principal investigators.

ETHICS

This study was carried out after obtaining the approval from the Ethics Committee of Shupyk National Healthcare University of Ukraine. Informed consent was obtained from all the study participants, and all necessary information regarding the study (objectives, requirements of the participants, and duration of the study) was given to the prospective study participants on an information sheet to ensure an informed decision to participate in the study.

STATISTICAL ANALYSIS

Data collected from this study were sorted and recorded in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) for analysis. To characterize the study population, descriptive statistics, frequencies, and percentages for categorical data and summary statistics (mean standard deviation (SD) with a 95% confidence interval (CI) for continuous data normally distributed and median and interquartile range for continuous data not normally distributed) were used. In addition, tables were used for data presentation. The association between the categorical variables in the study population was checked using the chi-square test at the statistically significant level of P = 0.05.

A binary logistic regression analysis (bi-variable and multivariable) was carried out to identify the independent predictors of unexplained infertility. All independent variables with a P value of less than 0.05 in the bivariable logistic regression model were considered candidate variables for the multivariable model. Finally, the relationship was presented using a crude odds ratio and an adjusted odds ratio (AOR) with their corresponding 95% confidence intervals, and a P value of 0.05 or less was considered to be statistically significant.

RESULTS

CHARACTERISTICS OF STUDY PARTICIPANTS

In during study period (2021-2023), we sampled 7,618 women who were 19–50 years old in nine hospitals of eight regions, Ukraine. Of all participants infertile was 1,850 and the fertile was 5,768. The mean ± SD age was 31.8±0.3 years for the fertile group and 33.7±0.4 years for the control (infertile) group. The difference in mean age between these two groups was statistically significant ($p<0.001$). Socio-demographic characteristics of study participants, and history and clinical characteristics of study participants are presented in Table 1 and Table 2, respectively.

As shown in Table 1 and Table 2, the difference in the region, residence, age, age of marriage, marital status, history of gynecological surgery, previous miscarriage or abortion, family history of infertility, ovarian dysfunction (Decreased Ovarian Reserve), history of cervicitis, aerobic vaginitis, bacterial vaginosis, and history of endometritis between the two groups were statistically significant ($p<0.05$).

PREVALENCE OF INFERTILITY

The prevalence of female infertility in this study cohort was 24.3% [95% confidence interval (CI) 23.8-24.8]. The prevalence of primary infertility and secondary infertility was about 5.9% (95% CI 5.6-6.2) and 18.4% (95% CI 18.0-18.8), respectively. Among the infertile women, the difference between primary and secondary infertility was statistically significant ($p < 0.05$) by factors associated with female infertility. Comparison of characteristics of primary and secondary infertile in study participants are presented in Table 3.

FACTORS ASSOCIATED WITH FEMALE INFERTILITY

To identify the infertility predictor factors among Ukrainian women, a logistic multivariate regression

Table 1. Characterization of selected anthropometry and socio-demographic variables of study participants

Characteristic	Infertile cases (n=1,850)		Control (fertile) (n=5,768)		p value
	n	%	n	%	
Region					
North	610	33.0	1,240	21.5	0.013
South	433	23.4	1,443	25.0	
East	454	24.5	1,608	27.9	
West	353	19.1	1,477	25.6	
Residence					
Rural	396	21.4	1,234	11.1	0.005
Urban	1,454	78.6	616	88.9	
Age (years)					
19-21	20	1.1	58	5.7	<0.001
22–26	217	11.7	675	27.4	
27–31	738	39.9	2,302	32.4	
32–36	531	28.7	1,655	16.5	
37–41	237	12.8	738	12.3	
46–50	107	5.9	340	5.7	
Education status					
Primary	242	13.0	750	17.6	0.396
Secondary	275	15.8	911	13.3	
Junior college degree	418	22.5	1,298	20.2	
Bachelor's degree and above	915	48.7	2,809	48.9	
Occupation					
Unemployed	296	16.0	921	12.8	0.541
Governmental	285	15.4	889	13.7	
Housewife	590	31.9	1,840	39.2	
Clerk	50	2.7	156	4.2	
Private business	256	13.8	796	13.7	
Agricultural and related worker	69	3.7	214	2.3	
Student	10	0.5	29	0.7	
Other	294	16.0	923	13.5	
Marital status					
Married	1,833	99.1	5,716	89.5	0.006
Divorced	17	0.9	52	6.8	
Widow	0	0	0	3.7	
BMI (kg/m^2)					
Underweight	158	8.5	493	6.8	0.486
Normal weight	1,082	58.5	3,377	64.6	
Overweight	472	25.5	1,470	21.7	
Obesity	138	7.4	428	6.9	
WHR					
Less than 0.75	407	22.0	1,271	28.0	0.08
075-0.84	467	25.2	1,454	18.4	
0.85-0.90	396	21.4	1,234	21.6	
Greater than 90	580	31.4	1,809	31.6	
Smoking					
No	20	1.1	81	1,4	0.592
No, secondhand smoke	383	20.7	1,390	24,1	
Yes	1,447	78.2	4,297	74,5	
Drinking					
No	148	8.0	162	12,8	0.072
Yes	1,702	92.0	5,606	97,2	

Table 2. History and clinical characteristics of study participants in Ukraine, 2021-2023

Characteristic	Infertile cases (n=1,850)		Control (fertile) (n=5,768)		p value
	n	%	n	%	
Irregular menstruation					
No	1,201	64.9	4,027	69.8	0.204
Yes	649	35.1	1,741	30.2	
Dysmenorrhea					
No	1,013	54.8	3,301	57.2	0.563
Yes	837	45.2	2,466	42.8	
Age of marriage (yrs.)					
≤24	768	41.5	3,031	52.5	0.042
25–29	964	52.1	2,549	44.2	
≥30	118	6.4	193	3.3	
Age of first sexual intercourse (yrs.)					
<20	177	9.6	776	13.5	0.197
20–25	1,209	65.4	3,821	66.2	
>25	463	25.0	1,173	20.3	
History of gynecological surgery					
No	1,467	79.3	5,373	93.2	<0.001
Yes	383	20.7	394	6.8	
Previous miscarriage or abortion					
No	1,745	94.3	5,007	86.8	0.021
Yes	106	5.7	764	13.2	
Family history of infertility					
No	1,330	71.9	5,402	93.7	0.001
Yes	520	28.1	366	6.3	
Decreased ovarian reserve					
No	1,614	87.2	5,604	97.2	<0.001
Yes	236	12.8	164	2.8	
History of colpitis					
No	1,368	73.9	4,039	70.0	0.304
Yes	482	26.1	1,733	30.0	
History of cervicitis					
No	1,761	95.2	5,647	97.9	0.048
Yes	88	4.8	88	2.1	
History of uterine fibroids					
No	1,761	95.2	1,761	97.7	0.071
Yes	88	4.8	134	2.3	
History of medical abortion					
No	1,584	85.6	4,688	81.3	0.172
Yes	266	14.4	1,076	18.7	
History of surgical abortion	0				
No	1,475	79.7	5,388	93.4	<0.001
Yes	375	20.3	381	6.6	
History of spontaneous abortion					
No	1,614	87.2	5,263	91.2	0.116
Yes	236	12.8	505	8.8	
History of endometritis					
No	1,451	78.4	5,379	93.3	<0.001
Yes	399	21.6	385	6.7	
Bacterial vaginosis					
No	1,611	87.1	5,601	97.1	<0.001
Yes	239	12.9	167	2.9	
Aerobic vaginitis					
No	1,744	94.2	5,004	86.5	0.032
Yes	107	5.8	767	13.5	

Table 3. Logistic multivariate regression analyses of the factors associated with female infertility in the study participants, Ukraine, 2021-2023

Characteristic	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)
Age (yrs.)				
	<0.001		<0.001	
19-21		Ref		Ref
22–26	0.276	2.297(0.515–10.249)	0.587	1.523 (0.334–6.942
27–31	0.011	6.618(1.549–28.274)	0.031	5.038 (1.163–21.830)
32–36	0.003	9.379 (2.165–40.622)	0.011	6.862 (1.557–30.248)
37–41	0.025	5.577 (1.244–25.007)	0.109	3.49 (0.758–16.070)
46–50	0.035	5.500 (1.131–26.756)	0.174	3.096 (0.607–15.798)
Age of first sexual intercourse (years)				
	< 0.001		0.003	
<20		Ref		Ref
20–25	0.867	1.098 (0.371–3.248)	0.648	1.302 (0.42–4.035)
>25	0.018	3.752 (1.257–11.201)	0.017	4.696 (1.326–16.635)
History of gynecological surgery				
No		Ref		Ref
Yes	< 0.001	3.611 (2.235–5.832)	< 0.001	3.063 (1.819–5.159)
Marital status				
	0.006		0.003	
Married		Ref		Ref
Divorced	0.003	0.563 (0.386–0.822)	0.002	0.517 (0.342–0.781)
Widow	0.017	0.557 (0.344–0.902)	0.008	0.494 (0.294–0.830)
Age of marriage (yrs.)				
	< 0.001		0.006	
≤24		Ref		Ref
25–29	0.024	2.102 (1.103–4.005)	0.373	1.434 (0.649–3.168)
≥30	< 0.001	7.117 (2.651–19.107)	0.002	6.258 (1.962–19.956)
Decreased ovarian reserve				
No		Ref		Ref
Yes	0.006	3.364 (1.407–8.045)	0.005	3.987 (1.52–10.456)
Family history of infertility				
No		Ref		Ref
Yes	< 0.001	2.937 (1.772–4.870)	< 0.001	2.695 (1.548–4.695)
History of cervicitis				
No		Ref		Ref
Yes	0.007	0.452 (0.253–0.806)	< 0.001	0.289 (0.152–0.547)
History of surgical abortion				
No		Ref		Ref
Yes	< 0.001	3.690 (1.913–7.114)	0.002	3.145 (1.532–6.455)
History of endometritis				
No		Ref		Ref
Yes	0.027	0.637(0.428–0.950)	0.002	3.145 (1.532–6.455)
Bacterial vaginosis				
No		Ref		Ref
Yes	0.023	0.637(0.428–0.950	0.043	0.650 (0.428–0.987)
Aerobic vaginitis				
No		Ref		Ref
Yes	< 0.001	3.613 (2.234–5.833)	< 0.001	3.064 (1.818–5.157)

Table 4. Comparison of characteristics of primary and secondary infertile in Ukrainian women, 2021-2023

Characteristics	Primary infertility (n=450)		Secondary infertility (n=1,400)		p-value
	n	%	n	%	
Age (years)					
19-21	18	4.0	0	0.0	<0.001
22–26	144	32.0	62	4.4	
27–31	189	42.0	548	39.1	
32–36	81	18.0	457	32.6	
37–41	18	4.0	222	15.9	
46–50	0	0.0	112	8.0	
Age of marriage (years)					
≤24	135	30.0	640	45.7	0.012
25–29	252	56.0	710	50.7	
≥30	63	14.0	51	3.6	
Age of first sexual intercourse (years)					
<20	36	8.0	141	10.1	<0.001
20–25	207	46.0	1,015	72.5	
>25	207	46.0	243	17.4	
History of gynecological surgery					
No	357	79.3	1,305	93.2	<0.001
Yes	93	20.7	95	6.8	
Previous miscarriage or abortion					
No	424	94.3	1,215	86.8	0.021
Yes	26	5.7	185	13.2	
Family history of infertility					
No	323	71.9	1,312	93.7	0.001
Yes	127	28.1	88	6.3	
Decreased ovarian reserve					
No	392	87.2	1,361	97.2	<0.001
Yes	58	12.8	39	2.8	
History of cervicitis					
No	423	94.0	263	18.8	0.028
Yes	27	6.0	1,137	81.2	
History of surgical abortion					
No	358	79.7	1,307	93.4	<0.001
Yes	92	20.3	93	6.6	
History of endometritis					
No	353	78.4	1,306	93.3	<0.001
Yes	97	21.6	94	6.7	
Bacterial vaginosis					
No	392	87.1	1,360	97.1	<0.001
Yes	58	12.9	40	2.9	
Aerobic vaginitis					
No	424	94.2	1,211	86.5	0.032
Yes	27	5.8	189	13.5	

analyses was used. Table 3 showed the odds ratio (OR) and 95% confidence interval (CI) for the factors associated with infertility in logistic multivariate regression analyses. The results found that the female infertility was associated with age of participants ($p<0.001$), age of first sexual intercourse ($p<0.001$), history of gynecological surgery ($p<0.001$), marital status ($p<0.001$), age of marriage ($p<0.001$), decreased ovarian reserve (DOR) ($p=0.006$), family history of infertility ($p<0.001$), history of cervicitis ($p=0.007$), history of surgical abortion ($p<0.001$), history of endometritis ($p=0.027$), bacterial vaginosis ($p=0.023$), and aerobic vaginitis (< 0.001) as shown in logistic regression analysis (Table 3).

Furter, our results found that there were differences among factors associated with female infertility, primary infertility and secondary infertility. Comparison of characteristics of factors associated with primary and secondary infertile in Ukrainian women showed in Table 4.

DISCUSSION

Reports about the prevalence of infertility are rare currently in Ukraine. This study is the first to investigate prevalence and characteristics of risk factors for infertility among 19–50 year old women in Ukraine. This study expands upon the previous reports focused to the prevalence and factors associated with female infertility in Ukraine [3].

High prevalence of female infertility remains one of the mysteries in the reproductive health field, where the diagnostic evidence is still weak and the proposed treatments still work with unknown methods. Infertility rates vary from country to country, and change all the times. According to the literature, infertility rates were highest in Africa and Central/Eastern Europe. Additionally, according to a variety of sources, rates of male infertility in North America, Australia, and Central and Eastern Europe varied from 4 5-6%, 9%, and 8-12%, respectively [16]. In the United States, the infertility prevalence rate of women in 2002 was 15.5% [17], in Canada ranged from 11.5% to 15.7% in 2009 [18], in Britain, during 2010–2012 was 12.5% [19], and 24.6% in 2019 in China 24,6% [20]. While in Turkey, the infertility rate decreased from 12.0% to 8.6% in 1993–2003 [21].

Ukraine is European country with large population. The infertility rates will be different in different regions of Ukraine. We performed a multicentre, prospective cohort study. In this study, nine family planning and reproductive health centers from different regions of Ukraine were all used to collect study samples. A self-reported questionnaire was used, which was been found to be a useful measure for quantifying fertility problems experienced in the community. In this study also investigated the clinical histories of the study participants. We designed a series of questions to determine infertility and specifically to minimize recall bias. The crude prevalence of infertility in this study cohort was 24.3%, which was close to the infertility rate of 25.4% among women attempting to become pregnant during 2019-2021 in Ukraine [3] and 24.6% among women in 2019 in China [20].

The occurrence of female infertility is related to various factors. In our study, multivariable logistic regression analyses showed that age of participants, age of first sexual intercourse, history of gynecological surgery, marital status, age of marriage, DOR, family history of infertility, history of cervicitis, history of surgical abortion, history of endometritis, bacterial vaginosis, and aerobic vaginitis were associated with infertility. In addition, our results showed that there are differences between factors associated with female infertility, primary infertility, and secondary infertility. It is universally acknowledged that fertility declines as age grows, and research reported that fertility starts declining approximately at age 32 years and rapidly declines after age 37 years. In this study, age has correlation with infertility obviously. One possible reason why the prevalence of infertility did not increase with age was that the desire of pregnancy decreased and the rate of protected sexual intercourse was high in women aged 40–49 years, so some potential infertile women aged 40–49 years were ignored according to our decision process. It could be explained that young infertile women were more likely to develop primary infertility than secondary infertility possibly. Further, age of marriage and age of first sexual intercourse might have a more important effect than age on primary infertility.

In our study the diagnosis of DOR was based on information from questionnaires filled out by participants of this study. Though recall bias did exist, DOR was still one of risk factors of infertility, primary infertility and secondary infertility according to our results. DOR means that response of child-bearing women to ovarian stimulation or fecundity is reduced when compared with women of same age [22].

History of gynecological surgery was another associated factor for female infertility, especially for secondary infertility. One research reported that surgery might reduce ovarian reserve [23]. Another research reported that myomectomy, as well as the coexistence of post-operation pelvic infection reduced the chance of conception among women [5, 8].

Our study found a significant association between the family history of infertility and unexplained infertility. Similar results to the findings of this study describing the association between family history of infertility and female infertility were reported in Netherlands [24]. This may indicate that there may be some genetic factors for unexplained female infertility, but due to the complexity of

the reproduction process in females, this possible gene(s) is still unknown. Nevertheless, many studies found that most infertility causes and conditions, such as poor egg quality or low egg reserves and blocked or damaged fallopian tubes, can't be inherited and can happen to anyone, regardless of family history [25, 26].

CONCLUSIONS

Our data suggest a high prevalence of female infertility in Ukraine. The prevalence of secondary infertility was higher than primary infertility. Age of women, age of first sexual intercourse, history of gynecological surgery, marital status, age of marriage, DOR, family history of infertility, history of cervicitis, history of surgical abortion, history of endometritis, bacterial vaginosis, and aerobic vaginitis were associated with infertility. Understanding the magnitude of infertility is critical for developing appropriate interventions, for monitoring access to quality female fertility care, and for mitigating risk factors for and consequences of female infertility.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Effect of ivabradine on structural and functional changes of myocardium and NT-proBNP levels in patients with stable coronary heart disease after coronary stenting

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ABSTRACT

Aim: To investigate the effect of ivabradine on the hemodynamics and contractility of the myocardium and the features of NT-pro-BNP production in patients with stable ischemic heart disease after endovascular revascularization of the myocardium depending on the number of affected coronary arteries during 12 months of therapy.

Materials and Methods: The object of the study was 120 patients with stable coronary artery disease: angina pectoris of functional class III with heart failure IIA FC III with preserved and moderately reduced ejection fraction of the left ventricle, who underwent coronary artery stenting. The examined patients were randomized according to the number of affected coronary vessels and the method of treatment.

Results: Ivabradine in patients with stable ischemic heart disease after 12 months of therapy had a significant beneficial effect on the structural and functional parameters of the myocardium (contributed to the reverse remodeling of the left ventricle), which did not depend on the number of stented coronary arteries ($p<0.05$). In patients with stented one coronary artery, all structural and functional indicators of the heart after 12 months of treatment reached the values of practically healthy individuals from the control group. The use of ivabradine in patients with stable ischemic heart disease with heart failure with preserved and intermediate ejection fraction of the left ventricle after coronary stenting made it possible to ensure the correction of a number of clinical and pathogenetic links of the disease, which generally contributed to the improvement of metric and volumetric parameters of the heart.

Conclusions: Ivabradine made it possible to significantly increase the effectiveness of standard therapy, which was manifested by a faster recovery of the geometry and contractility of the left ventricle. Therefore, the use of ivabradine along with standard therapy was appropriate for such a contingent of patients. The management of patients with stable coronary heart disease should combine adequate (surgical and pharmacological) treatment of the underlying disease, further individual medication correction of symptoms and circulatory disorders inherent in coronary heart disease and heart failure.

KEY WORDS: stable ischemic heart disease, coronary arteries, stenting, heart failure, ivabradine

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INTRODUCTION

Throughout the world, cardiovascular diseases (CVD) are the main cause of mortality and disability of the population. Among cardiac pathologies, ischemic heart disease (IHD) occupies a leading position [1]. IHD is projected to cause 23.4 million deaths by 2030, compared to 18 million in 2017 [2]. Ischemic heart disease is a disease caused by atherosclerosis of the coronary arteries (CA) with significant stenosis (≥ 50%). Coronary obstruction, ischemia, hypoxia, and necrosis of the myocardium, which profoundly affects both the structure and functions of the heart, thereby increasing the risk of acute myocardial infarction and heart failure (HF) are at the heart of the pathogenesis of IHD. [3, 4].

HF syndrome is a global problem of WHO, progressing in both developed and developing countries [5]. Heart failure is the most common cardiovascular cause of hospitalization, especially among patients over 60 years of age [6].

In the treatment of patients with coronary heart disease, it is important to improve the quality of life, which for the patient consists in the absence of angina attacks, improvement of tolerance to physical exertion, control of heart rhythm disorders. Today, the issue of controlling the symptoms of angina pectoris remains problematic, especially in conditions of chronic stress. Both 1st and 2nd line drugs are used to reduce the severity of the pain syndrome, in accordance with the recommendations of the European Society of Cardiology, [7].

An alternative method of treating such patients today is surgical revascularization of the myocardium, that is, the removal of stenoses of the coronary vessels in order to fully restore blood flow in the myocardium, which will eliminate polypharmacy, because old age and polyphar-

macy have been recognized as significant predictors of the problem of drug therapy [8]. Currently, there are three main options for coronary revascularization: coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), and stenting of coronary artery (CA). Patients with multiple coronary artery disease appear to have better outcomes with CABG. Minimally invasive bypass surgery is an evolving technique and its use is limited, and its advantages over traditional CABG have not yet been proven. Currently, CA stenting plays a significant role in percutaneous revascularization and is performed in more than two-thirds of all interventional procedures and improves long-term results in the treatment of CAD [9]. The choice of treatment depends on many factors, including the patient's age, comorbidities, the number and location of the affected CAs, and the severity of the cardiovascular pathology.

The ESC/EACTS Guidelines on myocardial revascularization (2018) state that only the infarct-related artery should be revascularized [10]. However, there are many randomized controlled trials that suggest a strategy of total revascularization, either during primary PTCA may be beneficial and safe in a selected population of patients with CHD. [11–14].

CHD treatment options and regimens have changed over the past few years and are likely to continue to evolve. Drug-eluting stents (DES) are an available treatment. They reduce the frequency of restenosis and, therefore, the frequency of repeated revascularizations. Solirimus-eluting stents are a real device with a very good safety profile and long-term clinical efficacy [15]. They may also be an important treatment option for people with diabetes and multivessel disease who have had the best results with CABG [9].

The recovery of symptoms of heart ischemia with the development and progression of chronic heart failure (CHF) in this category of patients is associated with a sufficiently large number of unfavorable prognostic factors, the most important of which are the severity of the patient's condition before percutaneous coronary intervention (PCI), the development of restenosis and stent thrombosis after stenting, heart rhythm disturbances and progression of dyslipoproteinemia as the main factor of coronary atherosclerosis [16].

Percutaneous coronary intervention is of crucial importance for the restoration of CA function [17]. Cardiac rehabilitation is a well-recommended and scientifically proven approach that includes patient education, behavior modification techniques, and exercise to significantly improve secondary prevention outcomes in patients diagnosed with CVD [18]. The safety of early complete recovery after PCI has been established [19-21]. So, from the above, it becomes quite clear the importance of one of the problems in modern cardiology - treatment and rehabilitation of patients who have undergone endovascular interventions for CA.

The importance of quantitative determination of the levels of natriuretic peptides (NUP) in plasma has attracted great attention of heart pathology researchers in recent years. These markers are believed to be released from the myocardium in response to wall stretch, and their levels correlate with the severity of heart failure. According to the NICE recommendations, even a slight increase in the number of NUP indicates the beginning of the development of HF [22]. Therefore, one of them - N-terminal pro-B-type NUP (NT-proBNP) is widely used in diagnosis and monitoring the effectiveness of HF treatment. Moreover, recent studies have shown the potential utility of NT-proBNP for the monitoring of CHF and selection of drug therapy [23].

It was established that NT-pro-BNP is secreted in normal amounts in healthy people mainly by the left ventricle. In patients with left ventricular (LV) dysfunction, the rate of NT-про-BNP secretion increases in proportion to the increase in LV pressure. In view of this relationship, Yasue et al. (1994) suggested the use of an increased level of NT-p-BNP in blood serum as a diagnostic and prognostic marker of cardiac dysfunction in patients with CHF on the background of IHD [24, 25].

Despite medically corrected angina, the myocardium of stented or shunted patients with chronic obstructive pulmonary disease is still remodeled in the course of life, which leads to the development or progression of HF. And that is why it is necessary to pay attention to the early markers of its development - the dynamics of NT-ppoBNP. So, from the above, it becomes quite clear the importance of one of the problems in modern cardiology - treatment and rehabilitation of patients who have undergone endovascular interventions for CA.

Pharmacotherapy of CHD with different drug classes - beta-blockers, calcium channel antagonists and nitrates - plays an important role in reducing heart rate (HR), thereby reducing the risk of tachycardia-related mortality. Although these drug classes have clinical applications in many cardiovascular diseases, they lack selectivity and specificity in reducing heart rate and are often associated with adverse effects [26]. For the treatment of patients with stable coronary heart disease (CHD), especially after undergoing PCI, the proposal to use a medicinal product with a fundamentally new mechanism of action, capable of reducing heart rate in order to increase blood supply to the heart muscle without negatively affecting other organs and systems of the patient, becomes attractive. Ivabradine is the first drug in a new therapeutic class with a long-lasting and persistent effect, which exhibits an antitachycardic

effect on the heart by selective and specific inhibition of If-sodium channels of pacemaker cells of the sinus node, which provides wide opportunities for its use in patients with CVD who need to reduce the heart rate (HR), which is confirmed by randomized controlled trials such as BEAUTIFUL, SHIFT and SIGNIFY [26, 27].

Despite the obtained positive effects of reconstructive and medical therapy of CAD, the effects of basic therapy using β-adrenoblockers (β-AB) and ivabradine on the clinical course of CAD, myocardial viability and coronary reserve for predicting outcomes after endovascular revascularization of the heart in patients remain unclear. who underwent coronary artery stenting, depending on the number of affected vessels in the remote period, which is the relevance of this study.

AIM

The purpose of the study was to investigate the effect of ivabradine on the hemodynamics and contractility of the myocardium and the features of NT-pro-BNP production in patients with stable ischemic heart disease after endovascular revascularization of the myocardium depending on the number of affected coronary arteries during 12 months of therapy.

MATERIALS AND METHODS

The study included 120 patients with coronary heart disease: angina pectoris, functional class (FC) III. Diffuse cardiosclerosis. HF IIA FC III with preserved and moderately reduced ejection fraction (EF) of the left ventricle (LV) and 15 practically healthy individuals, representative by age and sex. Among the examined, men predominated - 101 people (84.2%). The average age of the patients was 61.4±0.5 years. Our data agree with the data of other studies that male gender and age are important unmodified risk factors for the development of CHD [28]. The normal control group consisted of 15 practically healthy people (3 women and 12 men) with an average age of 60.0±0.8 years.

After analyzing the frequency of risk factors and accompanying pathology, it was established: arterial hypertension (AH) of the II-III stage of the 2nd degree in 51 (88.0%) and 55 (88.7%) patients of the main group (MG) and the group comparison (CG), respectively; compensated type 2 DM occurred exclusively in subgroups of patients with multiple vascular lesions in 10 (17.3%) and 9 (14.5%) of the studied MG and the CG, respectively; excess body weight was diagnosed in 35 (60.3%) and 33 (54.9%) patients of both groups; obesity of the 1st degree in 14 (17.2%) and 15 (19.4%) patients of MG and CG, respectively; dyslipidemia was established in 51 (87.9%) and 49 (79.0%) patients with MG and CG, respectively; commitment to smoking was noted in 43 (74.1%) and 49 (79.0%) patients of MG and CG. The data of other researchers are similar [29, 30, 31].

Diagnosis and treatment were carried out according to the Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care «Stable coronary heart disease» 2021 [32], recommendations of the Heart Failure Association (HFA) ESC 2023 [33].

Depending on the treatment, the patients were divided into 2 groups. The main group (MG) included 58 patients who, together with the basic treatment, took ivabradine at a dose of 12.55±1.94 mg/day. Among the drugs of basic therapy (BT), patients were recommended acetylsalicylic acid in a dose of 75 mg/day, clopidogrel — 75 mg/day, bisoprolol — 2.5 mg/day, ramipril — 8.61±2.85 mg/day or losartan — 84,62±24.02 mg/day, atorvastatin — 36.55±7.62 mg/day. Among MG patients, 15 individuals with single-vessel and 43 with multi-vessel lesions of CA were recorded. The comparison group (CG) included 62 patients who underwent percutaneous coronary intervention percutaneous coronary intervention (PCI) with coronary artery stenting and BT drugs were prescribed - acetylsalicylic acid at a dose of 75 mg/day, clopidogrel — 75 mg/day, bisoprolol — 7.56±2.53 mg/day, ramipril — 5.90±2 .58 mg/day or losartan — 63.33±22.89 mg/day, atorvastatin — 36.77±7.42 mg/day. In 16 patients with AH, a lesion of one CA was established, in 46 – a multivessel coronary lesion. All patients before PCI and 6 and 12 months after coronary stenting (CS) and the proposed medical treatment to assess the activity of the myocardium, intracardiac hemodynamics, and the typical and functional state of the myocardium had their NT-proBNP level determined and echocardiography (EchoCG) performed.

Coronary angiography (CAG) was performed with consent and in the absence of contraindications to all patients. The interventional angiographic system Infinix-sCore+INFX-8000V (InfinixVF-i/SP)/G3, Toshiba (Japan) was used for this study. Access to the spacecraft was carried out through a. radialis; Ultravist 370 mg/ml, Omnipaque 350 mg/ml or Visipaque 320 mg/ml were used to contrast vessels. The SYNTAX revascularization index was taken into account, which determines the severity and degree of initial coronary artery disease and its course after PCI and has prognostic value in further treatment [34, 35].

In order to optimally choose the method of myocardial revascularization, the Syntax Score 1 and Syntax Score 2 indices were calculated. According to the results of those indices, patients were included in the study, in whom, according to the value of these indices, it was necessary

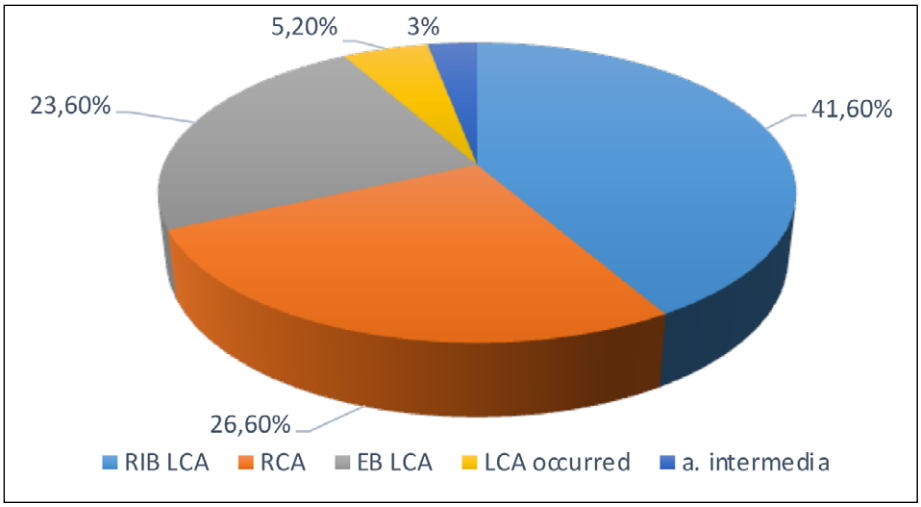

Fig. 1. The structure of coronary artery lesions in patients with coronary heart disease: angina pectoris FC III with HF IIA FC III with preserved LVEF.

to perform PCI by stenting coronary vessels - http://www.syntaxscore. com/calculator/start.htm [36]. Resolute Integrity (Medtronic, USA) zotarolimus-coated stents (DES-type stents) were used for CA dilation in all subjects.

Echocardiography was performed using a Philips device, HD11 XE (Germany), using a 2.5 MHz sensor and using M- and B-scanning modes. End-diastolic (EDD) and end-systolic (ESD) dimensions of the LV, end-diastolic (EDV) and end-systolic (ESV) volumes of the LV and LVEF were determined.

Determination of the level of NT-proBNP in the blood was carried out on the enzyme immunoassay «Stat-Fax 2100» of AWARENESS Technology, Inc. (USA) using «BIOMEDICA MEDIZINPRODUKTE» kits (GmbH&Co Austria), according to the manufacturer's method. Normal limits of NT-proBNP <350 fmol/ml (CH is absent), 250-350 fmol/ml is a gray zone (CH is possible), > 350 fmol/ml (CH is present).

The statistical processing of the obtained results was carried out with the help of the STATISTICA-8 computer program and the package of statistical functions of the program «Microsoft-Excel» on a personal computer, using the variational statistical method of analysis. At the same time, the arithmetic mean M, the mean square deviation δ, the mean error of the mean arithmetic m, the number of the variant (n), the probability of the difference between the two mean arithmetic «p» were calculated; values of $p<0.05$ were considered probable.

RESULTS

According to CAG data, the right type of myocardial blood supply was determined in 108 patients (90.0%), in 10 (8.3%) - left, and in 2 (1.7%) - undetermined. According to the results of the analysis of the Syntax Score I scale, it was established that in 31 patients with single-vessel atherosclerotic lesions of the CA, the number of points was 8.77±1.31, with lesions of two coronary arteries - 13.83±2.07 points, with stenosis of three coronary vessels - 17.92±3.01 points. Damage to the trunk of the left coronary artery (LCA) was not detected in any of the examined, and in 33 (27.5%) people, a stenotic narrowing of the proximal part of the anterior interventricular branch (AIB) of the LCA was established. The results of the analysis of the Syntax Score II scale in 87 (72.5%) cases made it possible to give preference to PCI, and in the rest - did not give preference to PCI over CABG. In this part of patients, the decision to choose a revascularization method was made according to the recommendations of the European Society of Cardiology (ESC), the European Association of Cardiothoracic Surgeons (EACTS) and with the participation of the European Association of Interventional Cardiologists in 2018 [37].

A single-vessel lesion of the CA, confirmed by the CAG method, was found in 31 (25.8%) patients, and a multi-vessel lesion of the CA was found in 89 (74.2%) patients, with two affected vessels in 65 (54.2%), and three affected vessels – in 24 (20.0%) patients.

In general, CA damage in quantitative terms: damage to RIB LCA usually prevailed - in 41.6% of patients, as well as right CA (RCA) - 26.6% and enveloping branch of LCA (EB LCA) - 23.6%, rarely lesions of the diagonal branch (DB) of the LCA occurred in 5.2% and a. intermedia - in 3% of patients (Fig. 1).

All 120 patients were divided depending on the number of affected coronary vessels after CAG. There were 15 (25.9%) cases of patients with a single-vessel lesion in the MG, and 16 (25.8%) cases in the CG. Multivessel lesions of CA were found in 43 (74.1%) cases of MG patients and in 46 (74.2%) patients with AH. Two-vessel lesion of CA was established in 31 (53.4%) patients with MG and in 34 (54.8%) patients with AH, and three-vessel lesion - in 12 (20.7%) and 12 (19.4%) in cases of MG and CG, respectively. The

Table 1. Dynamics of structural and functional changes of the myocardium under the influence of ivabradine in patients with CIHD after CA stenting

Indicator	Healthy (n = 15)	At the moment hospitalization		After treatment			
				Stented one CA		Stented several CA	
		Damage to one CA (n = 15)	Damage to several CAs (n = 43)	6 months (n = 15)	12 months (n = 15)	6 months (n = 43)	12 months (n = 43)
1	2	3	4	5	6	7	8
LA, sm p, Δ%;	3,59±0,02	3,99±0,04 p_{2-3}<0,05	4,31±0,08 p_{2-4}<0,05 p_{3-4}<0,05	3,75±0,06 p_{3-5}<0,05 6,0%	3,61±0,03 p_{3-6}<0,05 p_{5-6}<0,01 9,5%	4,06±0,06 p_{4-7}<0,05 5,8%	3,85±0,06 p_{4-8}<0,05 p_{7-8}<0,05 10,7%
EDD LV, sm p, Δ%;	5,21±0,03	5,79±0,08 p_{2-3}<0,05	6,19±0,09 p_{2-4}<0,05 p_{3-4}<0,05	5,57±0,05 p_{3-5}<0,05 3,9%	5,37±0,05 p_{3-6}<0,05 p_{5-6}<0,01 7,3%	5,97±0,06 p_{4-7}<0,05 3,7%	5,78±0,04 p_{4-8}<0,05 p_{7-8}<0,05 6,6%
ESD LV, sm p, Δ%;	3,80±0,03	4,36±0,06 p_{2-3}<0,05	4,67±0,06 p_{2-4}<0,05 p_{3-4}<0,05	4,11±0,05 p_{3-5}<0,05 5,7%	3,93±0,05 p_{3-6}<0,05 p_{5-6}<0,01 9,9%	4,48±0,06 p_{4-7}<0,05 4,1%	4,34±0,05 p_{4-8}<0,05 p_{7-8}<0,05 8,1%
EDV LV, sm p, Δ%;	130,13±3,85	166,27±5,22 p_{2-3}<0,001	193,02±6,40 p_{2-4}<0,001 p_{3-4}<0,05	151,67±3,42 p_{3-5}<0,05 8,8%	139,00±2,93 p_{3-6}<0,05 p_{5-6}<0,05 16,4%	177,63±4,10 p_{4-7}<0,05 8,0%	165,70±2,76 p_{4-8}<0,05 p_{7-8}<0,05 14,2%
ECV LV, sm p, Δ%;	62,07±2,15	85,93±3,01 p_{2-3}<0,05	100,82±3,30 p_{2-4}<0,05 p_{3-4}<0,05	74,67±2,97 p_{3-5}<0,05 13,1%	67,33±1,95 p_{3-6}<0,05 p_{5-6}<0,05 21,6%	91,23±2,40 p_{4-7}<0,05 9,5%	84,86±2,45 p_{4-8}<0,05 p_{7-8}<0,05 18,1%
PV, ml p, Δ%;	68,07±320	80,53±2,75 p_{2-3}<0,05	92,20±2,01 p_{2-4}<0,05 p_{3-4}<0,05	76,73±2,58 p_{3-5}<0,05 4,7%	71,27±1,49 p_{3-6}<0,05 p_{5-6}<0,05 11,5%	86,35±2,81 p_{4-7}<0,05 6,3%	80,79±2,14 p_{4-8}<0,05 p_{7-8}<0,05 12,4%
EF LV, % Δ%	55,94±0,68	51,07±1,22 p_{2-3}<0,05	48,37±0,69 p_{2-4}<0,05 p_{3-4}<0,05	54,07±0,59 p_{3-5}<0,05 5,5%	55,53±0,59 p_{3-6}<0,05 p_{5-6}<0,05 8,0%	50,97±0,41 p_{4-7}<0,05 5,1%	53,94±0,64 p_{4-8}<0,05 p_{7-8}<0,05 10,3%

Note: The indicators presented in % are in relation to the figures at the time of hospitalization.

clinical effectiveness of the treatment was evaluated and compared before CA stenting, 6 and 12 months after PCI.

The addition of BT ivabradine during 12 months of treatment changed the structural and functional state of the heart in patients with CHD (Table 1): the sizes of the left atrium (LA) and LV and its volumetric parameters - end systolic volume (SVV) - decreased statistically significantly, end diastolic volume (EDV) and PV ($p<0.05$). Ivabradine also optimized the contractile capacity of the LV - the increase in PV was reliably pronounced. It should be noted that during the entire period and at all stages of observation, a significant improvement in the structural and functional parameters of the heart was noted in MG patients, which was significantly different from the similar data of patients with AH (tables 1, 2). In MG patients with stented one coronary artery, all structural and functional indicators of the heart after 12 months of treatment reached the values of practically healthy individuals from the control group.

In MG patients with stented one coronary artery, 6 months after treatment, LVEF increased by 5.5%, and in similar patients, AH increased by 3.5% ($p<0.05$). LV ejection fraction increased by 5.1% in MG patients with stented multiple CAs, and by 2.6% in similar AH patients ($p<0.05$).

On the 12th month of treatment in MG patients who were stented with one and several CAs, the dynamics of LVEF had a positive increase and amounted to 55.53±0.52% and 53.94±0.64%, respectively, which is by 8.0 % and was 10.3% more than at the time of hospitalization ($p<0.05$). At the end of the study, the pumping function of the heart in AH patients with stented single and multiple CAs also tended to increase, but with less pronounced dynamics: LVEF (1 CA) increased by 4.3% and by 3.0% (2 and > CA).

Table 2. Structural and functional changes of the myocardium under the influence of BT drugs in patients with CIHD after stenting of one and several CAs

Indicator	Healthy (n = 15)	At the moment hospitalization		After treatment			
				Stented one CA		Stented several CA	
		Damage to one CA (n = 16)	Damage to several CAs (n = 46)	6 months (n = 16)	12 months (n = 16)	6 months (n = 46)	12 months (n = 46)
1	2	3	4	5	6	7	8
LA, sm p, Δ%;	3,59±0,02	3,91±0,01 p_{2-3}<0,05	4,24±0,05 p_{2-4}<0,05 p_{3-4}<0,05	3,85±0,05 p_{3-5}<0,05 1,5%	3,82±0,04 p_{3-6}<0,05 p_{5-6}>0,05 2,3%	4,15±0,11 p_{4-7}<0,05 2,1%	4,10±0,13 p_{4-8}<0,05 p_{7-8}>0,05 3,3%
EDD LV, sm p, Δ%;	5,21±0,03	5,74±0,08 p_{2-3}<0,05	6,12±0,08 p_{2-4}<0,05 p_{3-4}<0,05	5,65±0,05 p_{3-5}<0,05 1,6%	5,62±0,04 p_{3-6}<0,05 p_{5-6}>0,05 2,1%	6,06±0,08 p_{4-7}<0,05 1,0%	6,03±0,10 p_{4-8}<0,05 p_{7-8}>0,05 1,5%
ESD LV, sm p, Δ%;	3,80±0,03	4,33±0,07 p_{2-3}<0,05	4,62±0,08 p_{2-4}<0,05 p_{3-4}<0,05	4,28±0,04 p_{3-5}<0,05 1,2%	4,26±0,05 p_{3-6}<0,05 p_{5-6}>0,05 1,6%	4,56±0,05 p_{4-7}<0,05 1,3%	4,54±0,08 p_{4-8}<0,05 p_{7-8}>0,05 1,7%
EDV LV, sm p, Δ%;	130,13±3,85	163,38±2,70 p_{2-3}<0,001	187,21±5,53 p_{2-4}<0,001 p_{3-4}<0,05	157,00±3,10 p_{3-5}<0,05 3,9%	155,13±2,42 p_{3-6}<0,05 p_{5-6}>0,05 5,0%	184,26±5,81 p_{4-7}<0,05 1,6%	182,04±7,27 p_{4-8}<0,05 p_{7-8}>0,05 2,8%
ECV LV, sm p, Δ%;	62,07±2,15	84,43±2,89 p_{2-3}<0,05	95,63±2,94 p_{2-4}<0,05 p_{3-4}<0,05	81,50±2,00 p_{3-5}<0,05 3,5%	79,56±3,33 p_{3-6}<0,05 p_{5-6}>0,05 3,5%	95,04±2,47 p_{4-7}<0,05 0,6%	94,30±3,43 p_{4-8}<0,05 p_{7-8}>0,05 1,4%
PV, ml p, Δ%;	68,07±320	78,95±2,50 p_{2-3}<0,05	91,57±4,44 p_{2-4}<0,05 p_{3-4}<0,05	78,31±1,45 p_{3-5}<0,05 0,8%	76,69±3,03 p_{3-6}<0,05 p_{5-6}>0,05 2,9%	89,20±2,98 p_{4-7}<0,05 2,6%	87,74±7,78 p_{4-8}<0,05 p_{7-8}>0,05 4,2%
EF LV, % Δ%	55,94±0,68	51,22±0,74 p_{2-5}<0,05	48,91±0,54 p_{2-6}<0,05 p_{5-6}<0,05	53,06±0,68 p_{3-5}<0,05 3,5%	53,50±0,73 p_{3-6}<0,05 p_{5-6}>0,05 4,3%	50,23±0,28 p_{4-7}<0,05 2,6%	50,45±0,45 p_{4-8}<0,05 p_{7-8}>0,05 3,1%

Ivabradine contributed to the reduction of the volumetric parameters of the heart chambers, in particular the EDV, during the entire observation period, regardless of the number of stented coronary arteries. In patients with stented one coronary artery, after 12 months of follow-up, the value of EDV came as close as possible to the values of practically healthy individuals, that is, it decreased by 16.4%, and in similar patients with AH by 5.0% (p<0.05), with stented several coronary arteries - by 14.2%, in similar patients, BP decreased by only 2.8% (p<0,05).

The LV end-diastolic volume of patients of both groups after stenting of one CA at the 6th month of treatment decreased compared to admission, but with more pronounced changes in MG patients.

Already after 6 months of treatment, Ivabradine significantly improved the size of the LA and LV in patients with CIHD compared to BT. Thus, in patients with stented one coronary artery, after half a year of observation, the diameter of the left atrium decreased by 6.0% versus 1.5% in the LA (p<0.05), the LV EDD decreased by 3.9 versus 1.6% (p<0 .05), LV ESD - by 5.7% versus 1.2%, (p<0.05), LV ESV by 13.1% versus 3.5% (p<0.05), respectively. The decrease in PV by 4.7% versus 0.8% in MG and AH patients, respectively, indicated optimization of the LV contractile capacity by ivabradine and was confirmed by a sufficiently pronounced increase EF.

A similar trend was observed in patients with stented multiple CAs. After 6 months of treatment, the analysis of the structural and functional parameters of the myocardium according to the Echocardiogram data showed more pronounced positive dynamics in patients with the ivabradine-supplemented treatment complex. In a larger percentage value, the dimensions of the LV and LV and volume indicators - ESV and EDV of the left ventricle decreased.

After 12 months of treatment, in patients with OG and HP with multivessel lesions of the CA, the diameter of the LA decreased by 5.8% versus 2.1% ($p<0.05$), EDD LV by 3.7% versus 1.0% ($p<0.05$); LV ESD - by 4.1% versus 1.3%, ($p<0.05$); ESV LV by 9.5% versus 0.6% ($p<0.05$); PV by 6.3% versus 2.6% in MG and AH patients, respectively.

Optimizing the treatment of patients with intravascular coronary angioplasty with ivabradine after 6 months was confirmed by further observations regarding the intensity of changes in the size and volume of the heart according to Echocardiogram data.

After 12 months of treatment in MG patients, regardless of the number of stented coronary arteries, the studied hemodynamic parameters improved statistically and the pumping function of the myocardium increased ($p<0.05$). Greater dynamics were noted in patients with a stented single coronary artery, where the structural and functional parameters of the heart before the end of the study became identical to the same parameters of practically healthy individuals ($p<0,01$, $p<0,05$).

Comparing the trend of changes in the sizes of the LA and LV and their volumetric indicators between 6 and 12 months, it is clear that in patients who took BT drugs, the structural and functional parameters of the myocardium practically did not differ from the six-month indicators, and this did not depend on the number of stented coronary vessels. A statistically significant improvement in heart parameters was noted only in MG patients with stented CAs.

Thus, in patients after endovascular revascularization of the myocardium treated for 12 months with ivabradine and BT, there were significant changes in all parameters characterizing the size and function of the heart (both systolic and diastolic). In MG patients with stented one CA, compared to the moment of admission after 12 months of pharmacotherapy, the diameter of the LA decreased by 9.5% versus 2.3% in patients with AH, left ventricular EDD by 7.3% versus 2.1% in patients with AH; ESD of the left ventricle - by 5.7% against 1.6% in patients with AH; ESV of the left ventricle 21.6% against 3.5% in patients with AH; PV by 11.5% versus 2.9% in patients with AH, respectively (all $p<0.05$).

Analyzing the echocardiogram data in patients with stable angina pectoris with two or more stents installed, treated with ivabradine and BT drugs, after 12 months a decrease in the diameter of the left ventricle was established by 10.7% against 3.3% in CG, left ventricular EDD by 6.6% against 1.5% in CG, left ventricular ESD - by 8.1% against 1.7% in CG, left ventricular EDV 18.1% against 1.4% in CG, PV by 12.4% against 4.2% in CG, respectively ($p<0.05$).

After 12 months of therapy, ivabradine had a beneficial and reliable effect on the structural and functional parameters of the myocardium in patients with CIHD, which did not depend on the number of stented coronary arteries.

Natriuretic peptide is the main diagnostic biomarker of HF complicating IHD. The concentration of NT-proBNP after the use of pharmacotherapeutic complexes significantly decreased in all clinical groups of patients.

The content of NT-proBNP in healthy subjects was 178.7±17.62 fmol/ml. The amount of NT-proBNP in the serum of MG patients with single-vessel lesions of the CA before treatment was 690.67±15.80 fmol/ml, and 6 months after treatment - 398.00±9.60 fmol/ml, which is 42.4% less than before treatment ($p<0.05$). After 12 months, the amount of NT-proBNP was 281.33±8.55 fmol/ml, which was 59.3% less than before treatment ($p<0.05$). When two or more CAs were affected in MG patients, the content of NT-proBNP in blood serum 6 months after treatment significantly decreased by 40.2% (from 753.60±4.13 to 450.81±7.15 fmol/ml, $p<0.05$), and after 12 months the NT-proBNP indicator differed from the same level before treatment by 58.5% (up to 312.56±6.93 fmol/ml, $p<0.05$).

In CG patients with one CA affected before treatment, the level of NT-proBNP was 689.31±10.59 fmol/ml, after 6 months after treatment it significantly decreased by 41.2% and was 404.69±14.31 fmol/ml ($p<0.05$), after 12 months this indicator (395.31±11.61 fmol/ml) was not significantly different from the indicator after six months of treatment. In the same group of patients with lesions of two or more CA before treatment, the level of NT-proBNP was 752.72±15.76 fmol/ml, after 6 months it significantly decreased by 40.0% ($p<0.05$), and after 12 months of treatment was 454.89±13.48 fmol/ml, which did not significantly differ from the level of this prohormone in 6 months of treatment ($p>0.05$). When studying the relationship between cardiac volumetric parameters and NT-proBNP level depending on affected CA number (Fig.2, 3), there was observed a strong inverse correlation between LV EF and serum NT-proBNP level ($r=-0.77$, $p<0.05$ and $r=-0.86$, $p<0.05$).

Therefore, the use of ivabradine by patients with CIHD: angina pectoris III FC against the background of basic therapy within 12 months after the restoration of coronary circulation by stenting of coronary vessels optimizes the course of the disease, structural and functional indicators of the left ventricle and atrium, which generally stabilizes central and peripheral hemodynamics.

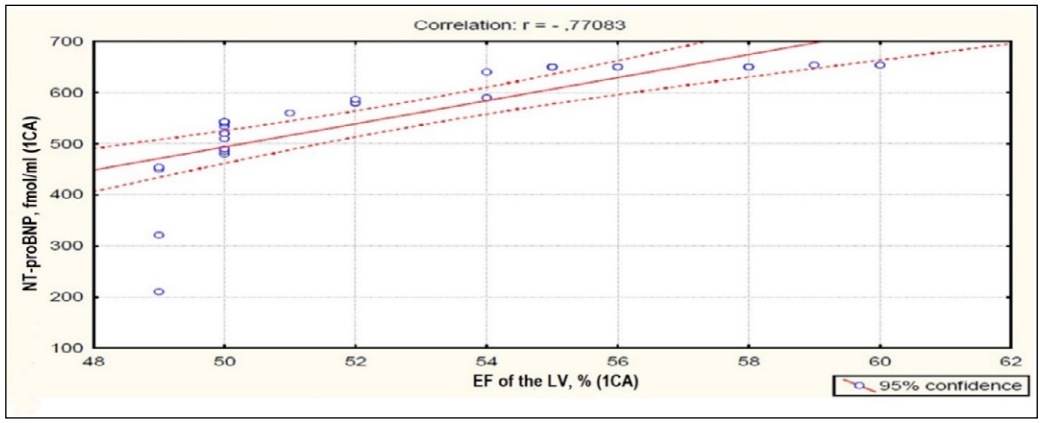

Fig.2. Correlation between EF LV and NT-proBNP in the patients with stable CIHD, namely FC III exertional angina, class IIA FC III HF with preserved and moderately reduced EF of the LV, single-vessel CAD.

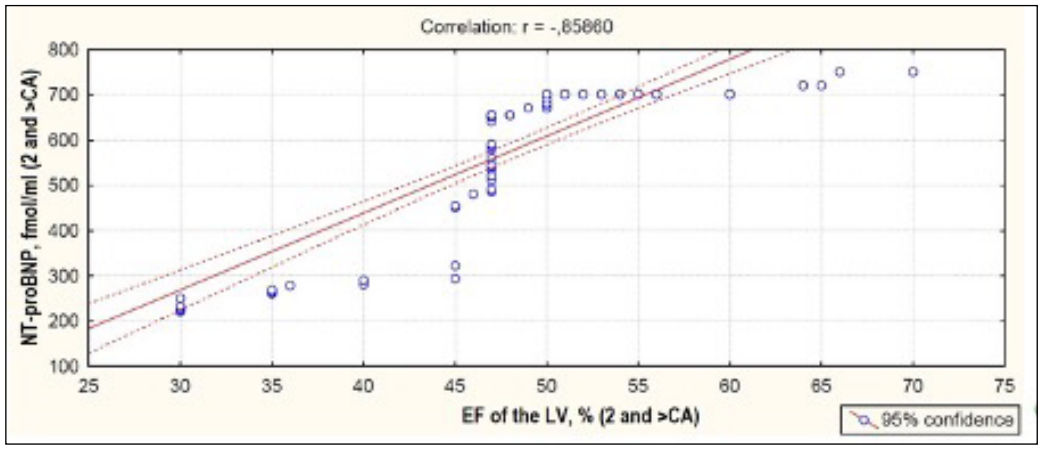

Fig.3. Correlation between EF LV and NT-proBNP in the patients with stable CIHD, namely FC III exertional angina, class IIA FC III HF with preserved and moderately reduced EF of the LV, multivessel CAD.

DISCUSSION

Our study describes the scheme of anti-ischemic therapy during 12 months of treatment for patients who underwent coronary artery stenting. The effectiveness of complete revascularization of the myocardium by implantation of DES-type stents has been demonstrated, regardless of the amount of atherosclerotic lesions of the coronary vessels. The results of our study are comparable to a meta-analysis [38], which included 7 studies and showed that DES implantation in the treatment of IHD, including lesions of the left main coronary artery, significantly reduces the risk of serious CV events and death from all causes and prevents the development and progression of HF. The TRYNON and DEFINITION trials demonstrated the high efficiency of coronary stenting using drug-eluting stents in patients with complex bifurcation lesions [39]. Thus, DES implantation is the optimal key to improving the results of treatment of patients with coronary artery disease, regardless of the number and location of coronary atherosclerosis lesions.

Undoubtedly, myocardial revascularization significantly improves the quality of life of patients with coronary heart disease, eliminating or significantly reducing the number of anginal attacks, but one should remember the pathogenetic mechanisms of the development of the pathology. Restorative treatment is a necessary part of the complex treatment of patients with coronary heart disease after endovascular revascularization of the myocardium.

Although multiple studies (SHIFT, CIBIS II, MERIT) have shown that reduction in heart rate is associated with improved clinical outcomes in patients with HF, it remains controversial whether the benefit of β-ABs is stronger by achieving target doses that help reduce heart rate [27]. Today, comorbidities of the pathology are of great importance, which is related to the optimal selection of pharmacotherapy of the disease. There are frequent clinical cases that make it impossible to use drugs from the β-AB group. These facts contribute to the intensive search for new drugs capable of regulating heart rhythm. According to the results of the HF-ACTION study, patients who received low-dose β-ABs for various reasons had worse outcomes for the endpoints of all-cause mortality and hospitalizations. There was a significant relationship between β-AB dose (the higher the better) and mortality from cardiac events [40].

Our results showed that ivabradine in combination with a minimum dose of β-AB maximally contributed to the remodeling of the myocardium, improved the prognosis regarding the development and progression of HF after coronary stenting. The hypothesis of the study was that ivabradine can significantly affect the reduction

of CV events in patients who underwent endovascular intervention on coronary vessels regardless of the number of stented CAs. The pharmacological effectiveness of ivabradine in these conditions is associated with its selective reduction of heart rate due to the effect on the If channels of the sinus node in the myocardium [26]. The effectiveness of ivabradine treatment in combination with BT drugs in patients with coronary artery disease and heart failure has been demonstrated in numerous studies (BEAUTIFUL, SHIFT, SIGNIFY), which prompted us to use this drug in the recovery period in patients after coronary stenting [27, 41].

For all patients with CIHS, regardless of the accompanying pathology and the number of affected CAs, complete myocardial revascularization with the installation of DES-type stents followed by pharmacotherapy with the inclusion of ivabradine in the treatment complex is an attractive treatment option, which is manifested by the stability of the course of the main pathology, prevents the development and progression of HF on long-term period.

CONCLUSIONS

1. Ivabradine in combination with BT drugs has a positive effect on central hemodynamic parameters: a decrease in LA and LV diameters in all patients, regardless of the number of affected CAs. During the 12 months of observation, a significant improvement in the structural and functional parameters of the heart was noted.
2. In patients with stented one CA, the structural and functional parameters of the heart after 12 months of treatment with ivabradine reached the values of practically healthy individuals from the control group. Regardless of the number of CAs affected by atherosclerosis, ivabradine promotes reverse remodeling of the left ventricle, regression of heart failure, which in turn will affect the minimization of the number of cardiac events.
3. When prescribing ivabradine, a decrease in the level of brain natriuretic peptide in blood serum was recorded 12 months after the start of endovascular and drug treatment by 59.3%, in contrast to the comparison group, where there is stability only up to 6 months of pharmacotherapy.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Professional self-determination of future doctors: priorities in conditions of the war in Ukraine

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ABSTRACT

Aim: Our goal was to find out the dynamics of the levels of professional self-determination of the higher medical education applicants who acquire information technology competence within the learning of 'Medical Informatics' and 'Modern Information Technologies in Medicine' during the war in Ukraine and investigate how the professional self-determination of future doctors develops.

Materials and Methods: The questionnaire for the survey consisted of 15 questions. 382 future specialists covered the questionnaire survey. All respondents studied majoring in 222 'Medicine' at the medical faculty of the Ivano-Frankivsk National Medical University. The results of this research we evaluated according to the defined algorithm.

Results: We established that under the condition of the formation of information technology competence, during the war there is a positive dynamic of the professional self-determination levels and their quality as the cognitive-reflexive component of future doctors' readiness to use digital technologies in their professional activity and there is also a change in the priorities of professional self-determination.

Conclusions: In extreme conditions, during the war in Ukraine, the future doctors as subjects of professional activity who use digital technologies within the information technology competence which formed during the learning of 'Medical Informatics' and 'Modern Information Technologies in Medicine' changed the priorities of professional self-determination, the quality of the levels of which has improved.

KEY WORDS: digital technologies, cognitive-reflexive component of readiness, information technology competence, professional self-determination

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INTRODUCTION

The large-scale war in Ukraine, which began on February 24, 2022, changed our country's economic structure and led to many new challenges in Ukrainian civil society. The massive migration of labour resources abroad, connected with the war, causes Ukraine to continue to lose a competitive population. Under such conditions, it's especially relevant for future specialists to obtain higher education not only in the territory of Ukraine but also to realize it in institutions of higher medical education in the direction of professional self-determination of the educational process participants.

In the conditions of the war in Ukraine, the accent is on aspects of the functioning not only of healthcare institutions but also institutions of higher medical education, some of which have changed dramatically. Therefore, during higher medical education, future healthcare professionals' professional self-determination should focus on choosing:

– Of direction and the content of the personal development;
– Of spheres of individual qualities and abilities, as well as means for their implementation;
– Of a social environment for the embodiment of moral values and life goals [1].

By researching, we believed that professional self-determination during higher medical education was a holistic and integrative process, the course of which depends on the activity of its participants and their responsibility for our own development. Socioeconomic conditions, interpersonal relationships, and situational factors impact this process [2]. Professional self-determination is also directed at the self-realization of each individual in the future professional activity of a doctor in the presence of constant reflection, the rethinking of professional choice and of one's being, professional self-affirmation, etc.

In our opinion, one of the ways to optimize future doctors' professional self-determination during higher medical education is to direct its applicants to the independent, conscious acquisition of readiness to use digital technologies in professional activity. This pro-

cess occurs during the learning of '*Medical Informatics*' ('*MI*') and '*Modern Information Technologies in Medicine*' ('*MITM*'), which ensures the development of the *information technology competence* (*IT* competence) of the higher medical education applicants [1, 3]. It's also is conditioned by the future doctors' internal resources, including their life goals, supported by needs, abilities, motives, etc., that does not contradict the requirements and possibilities of the future profession.

By researching, we thought that the future specialist's professional self-determination is the complex process of personality developmen t that involves the self-assessment of personal educational and professional potential, as well as the selection of criteria and standards for self-evaluation during the activity [2].

The phenomenon of self-determination is multifaceted and complex. Therefore, there is no unambiguous interpretation of the concept of 'professional self-determination' on the results of scientific research [4-16].

The future doctors' professional self-determination can be characterized as a person's attitude to his profession and toward himself as the professional activity subject that determines the entire path of becoming a professional.

By researching, we thought that:

– Professional self-determination is the permanent process at all stages of the higher medical education applicants' preparation for the use of digital technologies in professional activity;
– The periods of professional self-determination while studying the '*MI*' and '*MITM*' in time coincide with stages of professional becoming future doctors;
– The development of professional self-determination by studying the '*MI*' and '*MITM*' reflects the development of the cognitive-reflexive component of future specialists' readiness to use digital technologies in professional activity [2].

The purpose of scientific research was as follows:

– To find out the dynamics of the levels of the future specialists' professional self-determination by considering the peculiarities of the educational process in general and also the learning process of the '*MI*' and '*MITM*' in peacetime (the ascertaining stage of the research) and during the large-scale war (the formative stage) in Ukraine;
– To investigate in the process of learning the '*MI*' and '*MITM*' in extreme conditions during the war in Ukraine how the professional self-determination (reflects the cognitive-reflexive component readiness of future specialists to use digital technologies in professional activity) develops, i.e. find out whether his priorities are changing provided that *IT* competence of the higher medical education applicants formed.

AIM

The research focuses on the professional self-determination of future doctors in the context of their training in institutions of higher medical education in the modern extreme conditions of Ukrainian society. Our goal was to find out the dynamics of the levels of professional self-determination of the higher medical education applicants who acquire information technology competence within the learning of '*Medical Informatics*' and '*Modern Information Technologies in Medicine*' during the war in Ukraine and investigate how the professional self-determination of future doctors develops.

METHODS AND MATERIALS

The research took place at the Department of Medical Informatics, Medical, and Biological Physics of the Ivano-Frankivsk National Medical University within the teaching and studying of the '*MI*' and '*MITM*' in the 2017-2018, 2021-2022 academic years.

382 respondents (the higher medical education applicants) participated in the research:

– Two *control groups* (*CG*): 150 (*CG 1*) the second year of studying respondents and 52 (*CG 2*) the second year of studying after college graduation respondents (The educational process participants studied in January-June of the 2017-2018 academic year.);
– Two *experimental groups* (*EG*): 133 (*EG 1*) the second year of studying respondents and 47 (*EG 2*) the second year of studying after college graduation respondents (The educational process participants studied in January-June of the 2021-2022 academic year.) [1, 3].

The respondents studied at the Ivano-Frankivsk National Medical University, majoring in 222 'Medicine' at the Faculty of Medicine.

The creation of the questionnaire consisting of 15 questions preceded the research [2]. We formulated the questionnaire questions bearing in mind that the future specialists' professional self-determination under the condition of the *IT* competence development when studying the '*MI*' and '*MITM*' provides as follows:

– Delineation of the higher medical education applicants' professional interests;
– Identification of preferences for the self-assessment by the future specialists of their professional suitability;
– Finding the meaning of future professional activity considering the needs of society in doctors, capable of implementing professional activity according to standards.

We evaluated the answers to the questions from zero to two points (0, 1, or 2).

The levels (*high*, *medium*, *satisfactory*, *low*) of future

Table 1. The correlation analysis results (by the number of respondents' answers to the questionnaire questions)

The criteria and conclusions		The second year of studying		The second year of studying after college graduation	
		***CG 1*, n = 150 (2018)**	***EG 1*, n = 133 (2022)**	***CG 2*, n = 52 (2018)**	***EG 2*, n = 47 (2022)**
Pearson's r	r	– 0.84	– 0.91	– 0.94	– 0.75
	r*	0.51			
The conclusion		$\lvert r \rvert \geq r^*$, there is statistically significant correlation			
Student's t-test t*	t	– 5.65	– 7.72	– 9.87	– 4.04
		2.16			
The conclusion		$\lvert t \rvert > t^*$, there is linear correlation			

doctors' professional self-determination, which we have characterized in advance, were evaluated by such an indicator as *the sum of points* (*SP*) according to the described algorithm [2, 17].

This research used methods such as analysis, synthesis, comparison, concretization, systematization, and generalization, as well as methods of mathematical statistics for the evaluation of data, namely correlation analysis, Kolmogorov-Smirnov test, Cronbach's alpha, Fisher's test (F-test of equality of variances), Student's t-test and ranking [17, 18].

The questionnaire survey data have been processed using Microsoft Excel (Microsoft Office 365) according to the described algorithm [2, 17].

This research was carried out under the Ethical Guidelines for Educational Research of the British Educational Research Association (fourth edition, 2018) and of the Code of Ethics of the American Educational Research Association (approved by the AERA Council, 2011).

RESULTS

We claim that:

– The research participants answered the formulated questions thoughtfully and motivated because there is a statistically significant negative linear correlation ($\lvert r \rvert \geq r^*$, $r < 0$, $\lvert t \rvert > t^*$ in Table 1) between the numbers of positive (The answers have been evaluated by two points.) and negative (zero points) answers of the educational process subjects (the probability $p \geq 0.95$ ($p = 1 - \alpha$, the type I error probability $\alpha = 0.05$), Table 2);

– The internal consistency of the questionnaire survey results conducted among the respondents of *CG 1* and *CG 2* in 2018 was acceptable ($0.7 \leq \alpha < 0.8$), and among the respondents of *EG 1* and *EG 2* in 2022 was good ($0.8 \leq \alpha < 0.9$) (Table 3);

– The questionnaire survey results *SP* are subject to the normal distribution (the probability $p \geq 0.99$ ($p = 1 - \alpha$, the type I error probability $\alpha = 0.01$), Table 4).

We wanted to make sure that the learning of the '*MI*' and '*MITM*' (implementation of organizational and methodical measures, peculiarities of the course of the educational process at IFNMU in general (organisation of the educational process in the mixed form, namely, *e-learning using MS Teams + studying in university classrooms at a safe time with access to information and educational resources*) and at the Department of Medical Informatics, Medical, and Biological Physics in the conditions of the war in Ukraine) and of the *IT* competence formation of future doctors influenced the development of their professional self-determination. Therefore, we statistically tested the truth of the hypothesis about the equality of the distribution centres of two normal populations (*CG 1* and *EG 1*, *CG 2* and *EG 2*) at the ascertaining and formative stages of research. The criterion for testing the hypothesis was chosen, given that the variances of the studied populations are the same or not the same (Table 5).

By analysing the obtained results, we can claim that the organizational and methodical measures to ensure the educational process in IFNMU as a whole, as well as when studying the '*MI*' and '*MITM*' at the Department of Medical Informatics, Medical, and Biological Physics and features of their implementation in the conditions of the war in Ukraine in 2022 for the higher medical education applicants, didn't differ in terms of the opportunities regarding of the professional self-determination development in 2018 ($\lvert t \rvert < t^*$ – the distribution centres of the two populations are equal (the probability $p \geq 0.95$, $p = 1 - \alpha$, the type I error probability $\alpha = 0.05$ in Table 5) which fully provided the development of the cognitive-reflexive component readiness of the future specialists to use digital technologies in professional activity.

Table 2. The number of positive answers given by future doctors during the questionnaire survey, %

The questionnaire question	The second year of studying						The second year of studying after college graduation					
	CG 1, n = 150 (2018)			*EG 1*, n = 133 (2022)			*CG 2*, n = 52 (2018)			*EG 2*, n = 47 (2022)		
	The points used to evaluate the respondents' answers											
	2	0	1	2	0	1	2	0	1	2	0	1
The question 1: Do you understand the purpose of using *IT* competence in the future professional activity of doctors?	70.0	2.0	28.0	73.7	2.3	24.0	67.3	3.8	28.9	59.6	6.4	34.0
The question 2: Do you know when studying the '*MI*' and '*MITM*' about the basic requirements regarding the formation of *IT* competence of future doctors?	58.0	7.3	34.7	54.9	9.0	36.1	53.9	9.6	36.5	42.6	14.8	42.6
The question 3: Do you know what knowledge, skills and abilities a future dentist must have to carry out the professional activity within the confines of the formed *IT* competence?	53.3	8.0	38.7	66.9	5.3	27.8	57.7	9.6	32.7	51.1	17.0	31.9
The question 4: Are you familiar with the primary responsibilities that future doctors must perform within the confines of *IT* competence formed while studying the '*MI*' and '*MITM*'?	57.3	8.7	34.0	54.9	5.3	39.8	50.0	13.5	36.5	57.4	14.9	27.7
The question 5: Do you agree that the formed *IT* competence is significant during the future professional activity of a dentist?	60.0	6.7	33.3	78.9	3.0	18.1	57.7	9.6	32.7	85.1	2.1	12.8
The question 6: Do you think it's necessary to independently form *IT* competence for professional development while studying the '*MI*' and '*MITM*'?	57.3	5.3	37.4	69.9	7.5	22.6	53.9	11.5	34.6	70.2	6.4	23.4
The question 7: Do you think it's necessary to form professionally oriented *IT* competence outside of studying the '*MI*' and '*MITM*'?	60.7	8.6	30.7	58.6	8.3	33.1	59.6	9.6	30.8	55.3	8.5	36.2
The question 8: Are you interested in forming professionally oriented *IT* competence while studying the '*MI*' and '*MITM*'?	56.7	6.0	37.3	55.6	9.0	35.4	51.9	5.8	42.3	53.2	8.5	38.3
The question 9: Are you trying to find new ways of performing professionally oriented tasks by forming *IT* competence while studying the '*MI*' and '*MITM*'?	50.0	9.3	40.7	49.6	12.0	38.4	48.0	13.5	38.5	57.5	10.6	31.9
The question 10: Are you interested in non-standard ways of forming *IT* competence under the condition of its use during future professional activity?	54.0	6.7	39.3	53.4	10.5	36.1	46.2	11.5	42.3	42.6	10.6	46.8
The question 11: Do you like to learn new facts about future professional activity by forming *IT* competence while studying the '*MI*' and '*MITM*'?	61.3	4.7	34.0	68.4	8.3	23.3	61.5	9.6	28.9	63.8	4.3	31.9
The question 12: Do you rely on the experience gained during the formation of *IT* competence by performing professionally oriented tasks?	59.3	6.7	34.0	70.7	7.5	21.8	46.1	15.4	38.5	70.2	10.6	19.2
The question 13: Do you think that the knowledge, skills and abilities acquired within the confines of the formation of *IT* competence while studying the '*MI*' and '*MITM*' will allow you to become a highly qualified specialist?	66.7	6.0	27.3	65.4	8.3	26.3	44.2	19.2	36.6	57.5	10.6	31.9
The question 14: Do you ask for help if problems arise at runtime of professionally oriented tasks if you form *IT* competence by studying the '*MI*' and '*MITM*'?	33.3	14.7	52.0	15.0	45.1	39.9	15.4	42.3	42.3	38.3	19.1	42.6
The question 15: Do you learn new terminology by forming *IT* competence and studying the '*MI*' and '*MITM*' that will use in future professional activity?	59.3	2.7	38.0	61.6	9.8	28.6	50.0	11.5	38.5	55.3	8.5	36.2

Table 3. Assessment the internal consistency of the questionnaire survey results (analysis of the respondents' answers to the questionnaire questions)

The criterion and conclusion		The second year of studying		The second year of studying after college graduation	
		***CG 1*, n = 150 (2018)**	***EG 1*, n = 133 (2022)**	***CG 2*, n = 52 (2018)**	***EG 2*, n = 47 (2022)**
Cronbach's alpha	α	0.76	0.81	0.79	0.84
The conclusion		The internal consistency			
		is acceptable	is good	is acceptable	is good

Table 4. The Kolmogorov–Smirnov test results (according to the questionnaire survey results SP)

The criterion and conclusion		The second year of studying		The second year of studying after college graduation	
		***CG 1*, n = 150 (2018)**	***EG 1*, n = 133 (2022)**	***CG 2*, n = 52 (2018)**	***EG 2*, n = 47 (2022)**
Kolmogorov–Smirnov test	d	0.09	0.12	0.08	0.11
	d*	0.13	0.14	0.23	0.24
The conclusion		d < d*, there is a normal distribution			

Table 5. The results of statistical testing of the hypotheses (according to the questionnaire survey results SP)

The criteria and conclusions		The second year of studying *CG 1* (n = 150) and *EG 1* (n = 133)	The second year of studying after college graduation *CG 2* (n = 52) and *EG 2* (n = 47)
F-test of equality of variances	f	1.58	1.34
	f*	1.32	1.61
The conclusion		f > f*, the variances are not the same	f < f*, the variances are the same
Student's t-test	t	– 0.14	1.38
	t*	1.97	1.99
The conclusion		|t| < t*, the distribution centres of the two populations are equal	

We established that because of the *IT* competence acquisition when studying the '*MI*' and '*MITM*' in 2022, the levels of the research participants' professional self-determination and their quality had positive dynamics in comparison with 2018 [19], namely [1]:

– *In the second year of studying*: the low level decreased by 1.2%, the satisfactory – by 10.8%, the medium level increased by 8.2%, the high – by 3.8%, and the quality of the levels – by 12.0% (Table 6);
– *In the second year of studying after college graduation*: the low level decreased by 4.3%, the satisfactory – by 13.2%, the medium level increased by 11.8%, the high – by 5.7%, and the quality of the levels – by 17.5% (Table 6).

We found out that because of the *IT* competence formation, the quality of the levels of professional self-determination of research participants who studied in the second year, both in 2018 (52.7%) and in 2022 (64.7%), was higher (Table 6) than in the research participants of the second year studying after college graduation (In 2018, the quality of the levels was 44.3%, and in 2022 – 61.7% (Table 7).) [1].

In our opinion, for the research participants in the second year of studying, the *IT* competence formation was ensured by:

– The constant use of the developed manuals when studying the '*MI*' and '*MITM*' in 2018 and 2022 [20, 21];
– The responsible attitude to obtaining higher medical education in 2022, in the conditions of the large-scale war in Ukraine (Table 6).

We believed that in 2022, the positive dynamics of the professional self-determination levels and their quality (Table 6) of the research participants in the second year of studying after college graduation is because some of them using college education diplomas began the professional activity (evening and night shifts, working on weekends) outside of studies at IFNMU with the beginning of the large-scale war on February 24, 2022. During this activity, future doctors successfully used digital technologies to give medical care to various categories of patients in medical and preventive

Table 6. The levels of the future doctors' professional self-determination and the dynamics of their quality (The quality of the levels characterise the medium and high levels in total.), %

The levels of the professional self-determination	The second year of studying			The second year of studying after college graduation		
	CG 1, n = 150 (2018)	*EG 1*, n = 133 (2022)	The dynamics	*CG 2*, n = 52 (2018)	*EG 2*, n = 47 (2022)	The dynamics
low	14.0	12.8	– 1.2	19.2	14.9	– 4.3
satisfactory	33.3	22.5	– 10.8	36.5	23.4	– 13.2
medium	40.7	48.9	+ 8.2	30.8	42.6	+ 11.8
high	12.0	15.8	+ 3.8	13.5	19.1	+ 5.7
The quality of the levels	52.7	64.7	+ 12.0	44.3	61.7	+ 17.5

Table 7. The questions' ranks by the number of positive answers (%) to them (The positive answers were evaluated with 2 points.)

The questionnaire question	The second year of studying		The second year of studying after college graduation		The final ranks	
	CG 1, n = 150 (2018)	*EG 1*, n = 133 (2022)	*CG 2*, n = 52 (2018)	*EG 2*, n = 47 (2022)	2018 (n = 202)	2022 (n = 180)
The question 1	1	2	1	5	1	4
The question 2	8	11	6	13	5	13
The question 3	13	6	4	12	9	9
The question 4	9	11	9	6	10	7
The question 5	5	1	4	1	4	1
The question 6	9	4	6	2	6	3
The question 7	4	9	3	9	3	9
The question 8	11	10	8	11	12	12
The question 9	14	14	11	6	14	11
The question 10	12	13	12	13	13	14
The question 11	3	5	2	4	2	5
The question 12	6	3	12	2	10	2
The question 13	2	7	14	6	8	6
The question 14	15	15	15	15	15	15
The question 15	6	8	9	9	6	7

institutions (hospitals, polyclinics, emergency rooms) and also to refugees from occupied territories and active participants in the volunteer movement in Ukraine.

It was this activity that contributed to the understanding (because of the acquired practical experience) of the advisability of forming *IT* competence when studying the '*MI*' and '*MITM*' that ensured the development of the cognitive-reflexive component readiness of future doctors to use digital technologies in professional activity. That is why we believe that professional experience gained by the second year of studying after college graduation respondents in the first month and subsequent months of the large-scale war in Ukraine became the catalyst of *IT* competence development when learning the '*MI*' and '*MITM*.'

In our opinion, the basis for the development of the professional self-determination of future doctors, and also increasing the quality of its levels, in the process of research, was understood that *IT* competence is a transversal competence because, without it, they will not be able to realize most of the professional competencies, even at a professionally sufficient level especially in times of war [2].

DISCUSSION

To date, there is no scientific research by other scientists in the context of the purpose of this research. Therefore, the scope of the scientific discussion is limited only by our reflections.

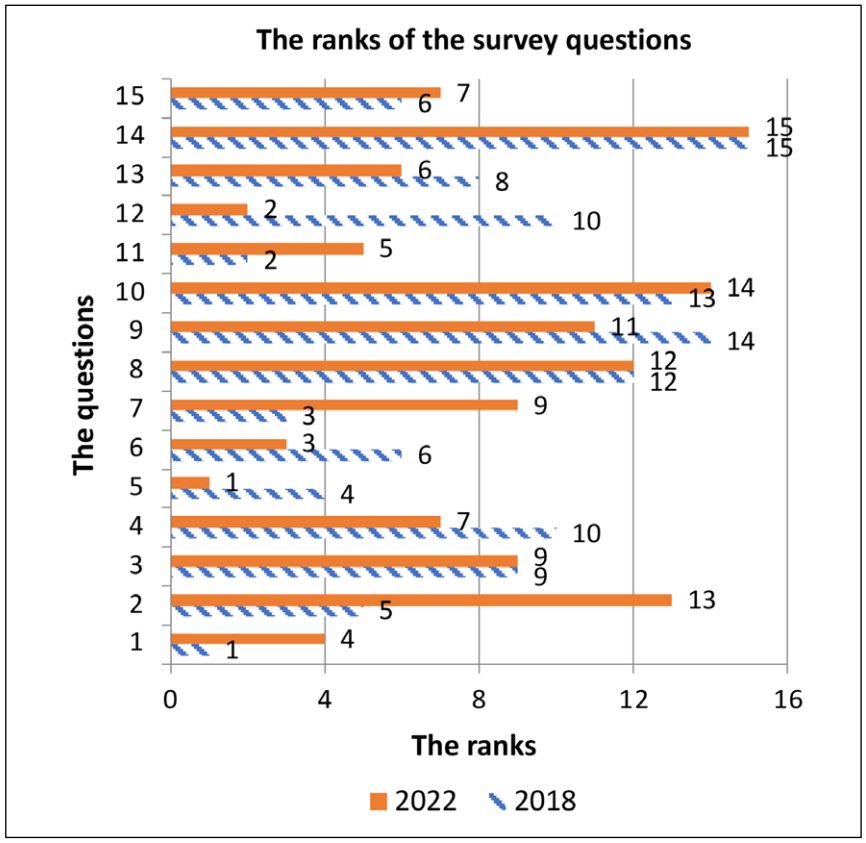

Fig. 1. The ranks of the survey questions by the number of positive answers (%) to them.

By analysing the questionnaire survey results (Table 2) according to the ranks (Table 7 and Fig. 1.) assigned to the questions, we concluded that in 2022, compared to 2018, the future specialists have changed priorities during the development of the cognitive-reflexive component of their readiness to use digital technologies in the professional activity.

In 2018, for future doctors who studied the '*MI*' and '*MITM*' and acquired *IT* competence (Table 7 and Fig. 1.), it was primarily important to gain general ideas about the application of this competence, which provides for the use of digital technologies in future the professional activity, as well as find out interesting facts about her, forming professionally oriented *IT* competence outside the studying of the '*MI*' and '*MITM*.' In 2022, the educational process subjects, who were professionally self-determined by the results of studying the '*MI*' and '*MITM*', primarily were convinced that the *IT* competence formation was significant for the future professional activity of a doctor who uses digital technologies. By performing professionally oriented tasks, future doctors used the experience acquired earlier during the *IT* competence formation within the performance of other problems. Therefore, they considered it necessary to independently form *IT* competence for professional development by studying the '*MI*' and '*MITM*.'

In 2018, 60.0% of the second year of studying respondents (*CG 1*) emphasized the importance of forming *IT* competence for the use of digital technologies in the doctors' future professional activity, compared to 57.7% of the second year of studying after college graduation respondents (*CG 2*). In 2022, the ratio of percentages changed to 78.9% (1.32 times more) of the second year of studying respondents (*EG 1*) against 85.1% (1.47 times more) of the second year of studying after college graduation respondents (*EG 2*) (Table 2) [3].

In 2018, by performing professionally oriented tasks, 59.3% of the second year of studying respondents (*CG 1*) relied on the experience gained during the formation of *IT* competence, compared to 46.1% of the second year of studying after college graduation respondents (*CG 2*). In 2022, the ratio of percentages was 70.7% (1.19 times more) of the second year of studying respondents (*EG 1*) against 70.2% (1.52 times more) of the second year of studying after college graduation respondents (*EG 2*) (Table 2) [3].

In 2018, 57.3% of the second year of studying respondents (*CG 1*) who studied the '*MI*' and '*MITM*' wanted to independently form the *IT* competence for professional development compared to 53.9% of the second year of studying after college graduation respondents (*CG 2*). In 2022, 69.9% (1.22 times more) of the second year of studying respondents (*EG 1*) and 70.2% (1.30 times more) of the second year of studying after college graduation respondents (*EG 2*) intended by themselves to form *IT* competence (Table 2) [3].

We believe that the change in the priorities of future doctors, who were professionally self-determined within the formation of *IT* competence when studying the '*MI*' and '*MITM*' in 2022, is due to their motivated understanding of the significance of using digital technologies in the future professional activity, in particular, due to of the social upheavals of Ukrainian society, that caused by the large-scale war in Ukraine.

In our opinion, by changing the priorities of professional self-determination while forming *IT* competence when studying the '*MI*' and '*MITM*' in the extreme conditions of today's Ukrainian state, higher medical education applicants find the personal meaning of future professional activity and also are acquiring the readiness to use digital technologies within its cognitive-reflexive component thanks to the development of the 'Self-concept' of a professional [22, 23].

We can say that the professional self-determination of future specialists who acquire *IT* competence during higher medical education is a continuous dynamic process that, in the conditions of the war in Ukraine, is significantly intensified and determines the professional development of each applicant of such education, considering:

– Understanding the significance of *IT* competence for the realization of future professional activity by a doctor who uses digital technologies;
– Increasing the specific weight of future specialists' self-education during the formation of qualities, gaining the experience necessary for them as future doctors;
– Acquisition of professional independence and readiness for future professional activity.

CONCLUSIONS

1. The change in the professional self-determination priorities of future doctors, provided that they acquire *IT* competence during the war, reflects the development of the cognitive-reflexive component of the future specialists' readiness to use digital technologies in their professional activities, particularly in the special conditions of life and activity in Ukraine.
2. The acquisition by future doctors of readiness to use digital technologies in professional activities within the cognitive-reflexive component by improving its levels and their quality, which, as part of the research in 2022, increased by 12.0% (for future specialists in the second year of studying) and 17.5% (for future specialists in the second year of studying after college graduation) compared to 2018, was ensured by development the *IT* competence while learning at the higher medical education institution of Ukraine, whose education process now is often limited by war.
3. Understanding in the realities of wartime the importance of the development of the future specialists' readiness (within the cognitive-reflexive component) to use digital technologies in their professional activities and acquire *IT* competence for doctors' professional activity in the special conditions of the modern Ukrainian state is a guarantee of professionalism in providing quality medical care to all categories of patients in the most diverse situations in the country that seeks peace and fights for it.

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ORIGINAL ARTICLE

CONTENTS

Asthma in patients with the syndrome of undifferentiated dysplasia of connective tissue: peculiarities of the course or mutually aggravating mechanisms?

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ABSTRACT

Aim: To analyse laboratory and biochemical features of the severe persistent course of asthma in patients with undifferentiated connective tissue dysplasia (UCTD) syndrome, and their phenotypic and visceral stigmas of dysembryogenesis.

Materials and Methods: We enrolled 60 male patients with asthma, aged from 23 to 62 years (mean age (46.83 ± 0.85) years): 30 patients with the background of UCTD, and 30 - without UCTD. We analysed clinical, somatometric, surveying (original questionnaire based on the phenotypic map of Glesby), instrumental (spirography, echocardiography, endoscopy, esophagofibrogastroduodenoscopy) and laboratory (including eosinophilic granulocytes and aldosterone levels) data.

Results: Correlations were found in men with UCTD between the number of UCTD markers and rate of earlobe diagonal fold ($r=+0.75$; $p<0.05$), asthenic constitution ($r=+0.72$; $p<0.05$), easy bruising ($r=+0.7$; $p<0.05$) and straight abdominal line hernia ($r=+0.52$; $p<0.05$). Average aldosterone serum level in patients with UCTD (176,10 ± 11,22) was significantly higher than in those without UCTD (142,77 ± 9,43), ($p<0.05$), as well as average eosinophils levels (1.3 ± 0.25 vs. 0.57 ± 0.12, $p<0.05$). In the absolute majority of patients with UCTD (93.3%) asthma onset was confirmed after pneumonia, and their age of asthma manifestation was significantly higher (37.2 ± 1.21) than in patients without UCTD (21.4 ± 1.13). Also, in patients with UCTD there was a high number of severe exacerbations during the last year (2.7 ± 0.12 per year) on the background of high doses of combined inhaled glucocorticosteroids use.

Conclusions: Identified "phenotypic profile", clinical and biochemical features of patients with asthma on the background of UCTD syndrome, which determine the severe course and early formation of asthma complications, will further accelerate the diagnosis of this asthma phenotype and improve approaches to the selection of treatment regimens for these patients.

KEY WORDS: asthma, undifferentiated connective tissue dysplasia, eosinophils, aldosterone

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INTRODUCTION

Asthma is one of the most important medical and social problems. The disease affects all age categories of the population and, with ineffective control, leads to a significant impairment of the quality of life, and in some cases, to the death of patients. Today, the heterogeneous nature of asthma is described in many scientific publications [1-4], its diversity is reflected in the GINA guidelines in the new definition of the disease [5], and the concept of asthma phenotype is increasingly being introduced into clinical practice, which should be taken into account when choosing a treatment regimen [6, 7].

The doctor's daily practice shows that clinical response to the proposed therapy of patients with the same disease severity may be different.

Polyvalent sensitization is recognized as one of the prerequisites for the severe course and development of fatal asthma complications [8, 9]. Today, molecular and statistical methods are used to determine clinical phenotypes. Continuous research, that would allow finding a connection between the phenotype, genotype, mechanism of disease development and the body's response to disease therapy, is being conducted, and thus improving the choice of drugs, taking into account the specifics of the course of asthma [9-11].

In pulmonology practice, asthma is defined as the result of complex interaction of environmental factors and genetic predisposition [12-14]. Pathomorphological changes in this disease are characterized by the accumulation of inflammatory effector cells in the submucosal layer of the bronchial tree, hyperplasia of mucous glands, accumulation of deposits in the submucosal matrix, degranulation of mast cells, hypertrophy and hyperplasia of bronchial smooth muscle and thick-

ening of the subepithelial collagen layer [4, 9, 15-17]. The involvement of collagen in the pathomorphological changes in asthma can become an interesting common pathogenetic link in the general picture of the course of this disease in people with undifferentiated connective tissue dysplasia syndrome (UCTD) - a hereditary connective tissue (CT) disorder of the same heterogeneous nature as asthma and a fairly high prevalence in the population [8, 9, 18,19-21].

AIM

The aim of our study was to analyse laboratory and biochemical features of the severe persistent course of asthma in patients with UCTD syndrome, and their phenotypic and visceral stigmas of dysembryogenesis.

MATERIALS AND METHODS

Clinical characteristics of the examined patients. For the period from 2018 to 2023, 103 male patients with a verified diagnosis of asthma, who were undergoing inpatient treatment in the National Pirogov Memorial Medical University clinic therapeutic department, were examined.

To achieve the goal, among them we selected 60 patients with a diagnosis of: "asthma, non-allergic, severe persistent course, uncontrolled", aged from 23 to 62 years (mean age (46.83 ± 0.85) years).

The diagnosis of asthma was established in accordance with medical care protocol for patients with bronchial asthma [22], WHO classification, and taking into account the recommendations of the Global Initiative for Asthma - GINA, 2022 [5].

Patients were divided into two groups. The main group (group I) included 30 men with asthma on the background of UCTD, aged from 36 to 62 years, average age (50.11 ± 1.28) years. The comparison group (group II) consisted of 30 men with asthma without UCTD (number of phenotypic and visceral stigmas of UCTD 5 or less), aged from 23 to 54 years, average age (43.53 ± 1.29) years.

Analysis of anamnestic data of both groups of patients revealed certain features, in particular: the onset of the disease in patients of group I was significantly later: (37.2 ± 1.21) years, against (21.4 ± 1.13) years in group II. The first episode of asthma in the absolute majority of patients with UCTD (93.3%) was established after pneumonia. No such anamnestic feature was found in group II.

In addition, among patients with asthma on the background of UCTD, there is a significantly higher number of severe exacerbations during the last year against the background of the use of high doses of combined inhaled glucocorticosteroids (GCS) - (2.7 ± 0.12 per year) versus (1.9 ± 0.1) in patients without UCTD ($p<0.05$).

Exclusion criteria were concomitant nosologies associated with hypereosinophilia: systemic diseases of CT, helminthiasis, skin diseases, allergic diseases, malignant neoplasms, pulmonary eosinophilia.

Clinical and instrumental studies were performed on all patients, followed by statistical processing of the data obtained. In particular, the following was carried out:

Somatometric examination (analysis of the following anthropometric features by the method of Bunak modified by Shaparenko [23] such as body weight, body length, torso length, neck length, chest length, lower limbs length, head circumference, chest circumference) [24].

Survey of patients. All subjects were surveyed using a specially designed original questionnaire based on the phenotypic map of Glesby in the modification of Martinov and co-authors [23]. The questionnaire included 54 positions of microanomalies. Based on examination, the number of UCTD stigmas was counted. The diagnosis of UCTD was established by detecting 6 or more positions of microanomalies [24].

Instrumental methods. Determination of the external breathing function (EBF) was carried out on a BTL 08 SpiroPRO computer spirograph (Great Britain). The reversibility of bronchial obstruction was studied in the inhalation test with a short-acting β2-agonist (salbutamol at a dose of 400 μg).

Structural and hemodynamic characteristics of the heart muscle were determined using echocardiography. Echocardiography and Doppler cardiography were performed in standard positions on a General Electric Vivid 7 Dimension ultrasound system (USA). Visceral stigmas were determined using the data of ultrasound examination of the internal organs of the abdominal cavity using the General Electric "Logic- 7" (Vivid – 3) (USA).

Laboratory methods. All patients underwent general clinical and biochemical tests in the accredited clinical and biochemical laboratory of Synevo Ukraine LLC (accreditation cert. No. 30016, valid until March 15, 2025). In particular, a general blood test was performed with the calculation of the absolute level of eosinophils (in g/l) and serum aldosterone (pg/ml). Prior to the study, alcohol intake, smoking, food intake, physical activity was limited, and medications intake was excluded.

The normative absolute value of the eosinophilic granulocytes level in the blood is 0.12-0.5 g/l. Eosinophilia is defined as this level is greater than 0,5 g/l. Hypereosinophilia is defined as moderate to severe eosinophilia (≥1,5 g/l). Monitoring of the eosinophils

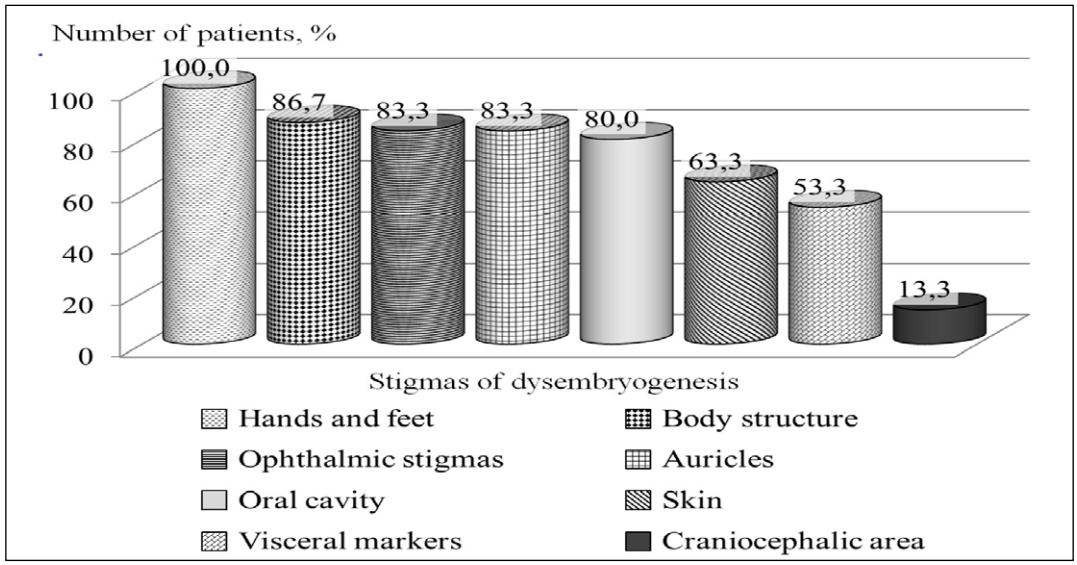

Fig. 1. Qualitative analysis of stigmas of dysembryogenesis in patients with asthma and UCTD.

level was carried out regularly (at least once a week), during each exacerbation of asthma during the year of observation.

Determination of the aldosterone level was carried out by the method of solid-phase enzyme-linked immunosorbent assay (ELISA) using the DRG analyser and test system (Germany). The design of our study provided that in patients with uncontrolled asthma, the level of aldosterone was determined no earlier than six months after the last exacerbation of the disease or hospitalization with the use of systemic GCS. Normative indicators of aldosterone in serum: in the supine position - (10.0 - 160.0) pg/ml.

Data analysis was performed in SPSS Statistics v.23. Summary statistics of mean, standard deviation and percentiles were used for quantitative measurements. The association between measures was assessed using the correlation test and t-test. The probability value was estimated at 0.05 confidence level (P=0.05).

RESULTS

The analysis of UCTD markers in both groups revealed that the average number of stigmas in patients of group I was 10.41 ± 0.35, and in patients of the group II - 4.48 ± 0.16. The majority (73.3%) of people of group I (with UCTD) showed a high level of stigmatization (13 or more stigmas).

Qualitative analysis of stigmas of dysembryogenesis by lesion location in group I revealed the features shown on Fig. 1. In particular, among patients' phenotypic stigmas, we most often noted: lateral clinodactyly – in 93,3% patients, 4th finger is longer than 2nd – in 73,3%, asthenic constitution – in 80%, scoliosis – in 56.7%, radial-lacunar iris and diagonal fold of the earlobe – in 60%. diastema – in 43,3% of patients. Frequency of visceral stigmas were somewhat inferior: easy bruising – in 30%, varicose veins of the lower extremities – in 26,7%, hernia of the abdomen straight line – in 16,7% of patients.

Direct strong correlations were found in men with UCTD between the number of UCTD markers and the frequency of detection of the diagonal fold of the earlobe ($r=+0.75$; $p<0.05$), asthenic constitution ($r=+0.72$; $p< 0.05$), easy bruising ($r=+0.7$; $p<0.05$); direct correlations of medium strength - for the radial-lacunar type of the iris ($r=+0.64$; $p<0.05$) and hernia of the straight abdominal line ($r=+0.52$; $p<0.05$).

The data we obtained are to some extent consistent with the data of other authors and our own studies conducted on another cohort of patients [24, 25].

The study of the levels of eosinophils and aldosterone in patients revealed the following features (Table 1).

The average level of aldosterone in serum of patients in group I was above the norm, and in group II it did not go beyond the normative indicators. In addition, a statistically significant difference ($p<0.05$) was established in the average aldosterone levels between patients with asthma on the background of UCTD and those with asthma without UCTD.

Therefore, almost a quarter of patients in group I (23.3%) had a significantly elevated aldosterone level, compared to only 6.7% of patients in group II.

Analysis of average values of blood plasma eosinophils levels in patients with asthma confirmed that number of eosinophils in patients of group I was much higher than normal level, and significantly higher than in patients of group II. (1.3 ± 0.25 vs. 0.57 ± 0.12, $p<0.05$). Eosinophilia is a typical laboratory finding, typical for

Table 1. Distribution of eosinophils and aldosterone levels in patients with asthma (n=60)

Indicators	Patients with UCTD (n=30)		Patients without UCTD (n=30)	
	Levels	Number of patients, %	Levels	Number of patients, %
Total average level of eosinophils, g/l	1,3 ± 0,25*	100	0,57 ± 0,12	100
Normal level of eosinophils, g/l	0,42 ± 0,10	20	0,43 ± 0,11	33,3
High level of eosinophils, g/l	1,42 ± 0,28	80	0,81 ± 0,19	66,7
Total average aldosterone level, pg/ml	176,10 ± 11,22*	100	142,77 ± 9,43	100
Total average level of eosinophils, g/l	1,3 ± 0,25*	100	0,57 ± 0,12	100
Normal aldosterone level, pg/ml	145,74 ± 16,41	76,7	132,85 ± 11,16	93,3
High aldosterone level, pg/ml	280,56 ± 24,04	23,3	178,34 ± 26,89	6,7

$p<0.05$, * - the difference is significant between the main and the comparison group.

most patients with severe asthma [9, 18]. In a large part of our patients, we found eosinophilia in both groups of the study. However, in such patients with asthma on the background of UCTD, the average number of eosinophils reached a higher level (1.42 ± 0.28).

It should be noted that just among patients with a large number of stigmas (12 or more) and increased aldosterone level and hypereosinophilia (≥1.5 g/l), the largest number of patients (5 men) had combination of dysembryogenesis stigmas as following: asthenic constitution, hernia of the abdomen straight line and easy bruising.

DISCUSSION

The obtained data suggest the search for the role of elevated aldosterone level and moderate eosinophilia in the pathogenesis of asthma in UCTD.

The accumulation of inflammatory effector cells in the submucosal layer of the bronchial tree plays a significant role in the formation of the components of bronchial obstruction in asthma. Besides, eosinophilic inflammation is dominant in asthma. Eosinophilia as a phenomenon is the result of myelopoiesis on the one hand, and the destruction and fixation of eosinophils in the tissues on the other. What exactly affects the increase in eosinophils in the blood of patients with asthma against the background of UCTD syndrome? Attention is drawn to the fact that in the anamnesis of patients with asthma on the background of UCTD, there is a high number of severe exacerbations during the last year (2.7 ± 0.12 per year) on the background of the use of high doses of combined inhaled GCS and the late onset of asthma at a fairly mature age. The combination of an elevated level of eosinophils in the blood and this clinical symptomatology is typical for severe eosinophilic asthma, where the leading pathogenetic link of immune damage is an increase in the level of interleukin-5 (IL-5). Hyperproduction of IL-5 is accompanied by absolute eosinophilia, since this cytokine specifically regulates the maturation of eosinophils, enhancing the differentiation of progenitor cells and the proliferation of eosinophils in the bone marrow, activates the interaction between eosinophils and endotheliocytes, which leads to increased adhesion and migration of eosinophils, strengthening of chemokine connections with eosinophils, activation and destruction of mature eosinophils [14, 17, 18].

Another interesting biochemical feature of the group of patients with asthma on the background of UCTD is the increased level of aldosterone. It is known that the synthesis and secretion of cortisol and aldosterone are regulated according to the law of feedback by the hypothalamic-pituitary-corticosuprarenal apparatus [13, 24, 25]. The level of eosinophils in peripheral blood depends on the level of adrenocorticotropic hormone and adrenal cortex hormones [9]. Therefore, a decrease in adrenocorticoid activity accelerates the release of eosinophils from the bone marrow. In patients with asthma on the background of UCTD, this mechanism also has the right to exist and can determine both the features and the severity of the course of the disease.

Eosinophil is primarily a tissue cell. The end point of eosinophil migration is the skin and mucous membranes of organs that have direct contact with the environment, in particular, the lungs. Migration of eosinophils to tissues is controlled by chemotactic factors, including complement components, histamine, leukotrienes, lymphokines, tumor-associated factors, and IL-5 [18]. At the same time, activated by the chronic inflammatory process, these factors together with eosinophils stimulate the accumulation of fibrin in the lumen of the alveoli and small bronchi, which ultimately leads to an increase in collagen formation in the lungs. If this process is accompanied by inefficient resorption of CT, as well as excessive regeneration and repair, the normal architecture of the lung tissue is distorted and eventually pneumofibrosis develops.

Fibrosis is traditionally viewed as a progressive pathological process that involves numerous cellular and molecular mechanisms that lead to the accumulation of excess carbohydrate-protein matrix components in the extracellular space. Sweating of fibrinogen in the composition of various plasma proteins in the lumen of the respiratory tract is one of the manifestations of inflammation of the respiratory tract. It is known that fibrin, which is formed from fibrinogen, inactivates the surfactant in the alveoli, thereby contributing to the collapse of the alveoli and the deepening of diffusion-perfusion disorders [17].

Hypersecretion of transforming growth factor beta and type I collagen DNA should be highlighted among the known mechanisms of aldosterone's fibrotic action. Aldosterone induces local inflammatory processes in the endothelium of medium and small vessels, increases the level of plasminogen activator inhibitor. It is a proven fact that with a long-term (more than 3 weeks) persistent increase of aldosterone, there is a significant acceleration of the proliferation of fibroblasts with excessive accumulation of collagen I and III ("wrong") types and with a pronounced stimulation of the processes of perivascular fibrosis, the formation of interstitial fibrosis and the so-called "expansion" of interstitial tissue. The morphological substrate of this action of aldosterone is the presence of receptors on endothelial cells and fibroblasts [24, 25]. Back in 1997, W. Timens and co-authors put forward a hypothesis about the role of fibroblast dysfunction in the development of emphysema. Fibroblasts synthesize components of the extracellular matrix: collagen, elastin, proteoglycans, and also interact with immune and inflammatory cells with the help of cytokines. The first and third types of collagen perform the function of interstitial tissue stabilizer. Failure of fibroblasts to ensure adequate tissue homeostasis can lead to abnormal repair with the formation of emphysema. It is obvious that the development of pulmonary fibrosis occurs not so much as a result of enhanced collagen synthesis, but as a result of a violation of its metabolism. Also, when the level of aldosterone increases, the physiological regulation of mineralocorticoid receptors in macrophages with the initiation of pro-inflammatory cytokines that support the process of chronic inflammation is disturbed [25].

The multifunctional nature of CT determines its distribution in all organs and systems of the human body [24]. The significant content of abnormal collagen types I and III in patients with UCTD, in particular, in the lung tissue, suggests that atypical protein-polysaccharide complexes fixed in such defective CT, and other antigens of local and tissue origin may serve as a target for immunopathological processes [7, 11].

Such mutually aggravating mechanisms of increased levels of eosinophils and aldosterone, which are observed in patients with asthma on the background of UCTD, lead to the maintenance of a chronic inflammatory process in the lungs and accelerated fibrosis in the lungs. Chronic inflammation in the bronchopulmonary system stimulates the processes of increasing collagen formation in the lungs, mediated by various factors, which can further lead to the development of fibrous changes in the bronchi walls and pneumofibrosis with the formation of emphysema and respiratory failure [5].

CONCLUSIONS

1. Features of the course of asthma in patients with UCTD syndrome include late onset of asthma, debut after pneumonia, severe course of the disease (frequent exacerbations on the background of using high doses of inhaled GCS), elevated levels of eosinophils and aldosterone in serum, presence of such phenotypic stigmas: asthenic constitution, hernia of the abdomen straight line and easy bruising.
2. The revealed increased levels of eosinophils and aldosterone in serum in patients with asthma on the background of UCTD are mutually aggravating in terms of maintaining the processes of chronic inflammation and accelerated fibrosis in the lungs, which can be prognostically unfavorable in the formation of early pneumofibrosis, emphysema of the lungs, and respiratory failure.

The identified "phenotypic profile", clinical and biochemical features of patients with asthma on the background of UCTD syndrome, which determine the severe course and early formation of asthma complications, will further accelerate the diagnosis of this phenotype of asthma and improve approaches to the selection of treatment regimens for such patients.

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ORIGINAL ARTICLE

CONTENTS

Effect of Enoxaparin on D-dimer levels in hospitalized Corona Virus patients with a comparison of its level in patients with comorbid conditions

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ABSTRACT

Aim: The main goal is to assess the levels of comorbid diseases and examine the changes in D-dimer in hospitalized patients before and following SC enoxaparin medication.

Material and Methods: At the Al-Yarmouk Teaching Hospital in Baghdad, Iraq, from October 2022 to May 2023, 86 patients who were hospitalized and had severe to critical COVID-19 infections provided data for a retrospective analysis.

Results: The medical records of all COVID-19 patients who were hospitalized and whose D-dimer level was greater than 0.5 mg/l and who were given enoxaparin (40 mg subcutaneously) were reviewed with the requisite authorization from the relevant authorities. The D-dimer level was assessed following therapy on the day of admission and day five after commencing enoxaparin. An examination of 86 case records revealed that persons with COVID-19 had significantly decreased D-dimer levels after taking subcutaneous enoxaparin (p-value<0.0001). The comorbidities (diabetes mellitus, hypertension) of patients who received the drug were compared.

Conclusions: Enoxaparin and other anticoagulants were utilized to treat the coagulopathy brought on by COVID-19. Low molecular weight heparin enoxaparin has demonstrated positive outcomes in the management of VTE. A decrease in D-dimer level is anticipated when COVID-19 patients are treated with subcutaneous enoxaparin, partly because decreased coagulation results in lower fibrin formation.

KEY WORDS: COVID-19, enoxaparin, D-dimer, venous thromboembolism, diabetes mellitus, hypertension

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INTRODUCTION

COVID-19, which was identified as a pandemic by WHO in March 2020, presents a serious threat to global health. Several coagulation problems, including venous thromboembolism (VTE), is thought to be linked to COVID-19, according to a recent literature review [1, 2]. Leukopenia, lymphopenia, elevated levels of lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, and aminotransferase are among the laboratory results [3]. It also causes difficulties with the heart, hematology, kidneys, and other systems. Patients with COVID-19 experience thromboembolic events, with critically sick patients at the highest risk, where Between 25 and 53 percent of COVID-19 hospitalized patients experience thrombosis [4]. A rise in the Padua prediction score of >4 associated with infection with COVID-19 has been observed 40 percent of patients. A score >4 indicates a higher risk of venous thromboembolism (VTE), and the Padua score was developed to predict VTE risk in hospitalized medical patients. Endothelial dysfunction, hypercoagulable state, and stasis-the three components of Virchow's triad-are all made worse by COVID-19 infection. It makes thrombosis and endothelial dysfunction more likely, which is brought on by ACE2 and leads to an increase in D-dimer, fibrin, and fibrinogen. Prothrombin time, activated partial thromboplastin time, and thrombin time are also impacted and appear to be longer [5, 6]. In these patients, elevated D-dimer readings have been associated with poor prognosis and increased mortality [7]. People with numerous co-morbid conditions, such as diabetes, hypertension, and hypothyroidism, frequently have elevated D-dimers and higher death rates [8]. Low molecular weight heparin enoxaparin has demonstrated positive outcomes in the treatment and prevention of VTE, lowering the risk of mortality. It activates ant thrombin to produce

an anticoagulant action. A decrease in D-dimer level is anticipated when COVID-19 patients are treated with subcutaneous enoxaparin, partly because decreased coagulation results in lower fibrin formation. In light of the foregoing, research is being planned to determine how enoxaparin affects D-dimer levels [9]. Model WHO Lists of Essential Drugs includes enoxaparin, which has the benefit of a daily dose and a recommended standard thrombi prophylaxis duration until hospital release. Clinicians must to be knowledgeable about the elevated risk of bleeding if the therapeutic dose is administered. This risk includes substantial hemorrhage requiring transfusion (gastrointestinal, for example) as well as clinically significant bleeding even in the absence of transfusion (intracranial, for example). Patients should obtain baseline values for Prothrombin time or the international normalized ratio, partial thromboplastin time, platelet count and creatinine before starting therapeutic or intermediate-intensity anticoagulation [10].

AIM

The main goal is to assess the levels of comorbid diseases and examine the changes in D-dimer in hospitalized patients before and following SC enoxaparin medication.

MATERIAL AND METHODS

PATIENTS AND STUDY DESIGN

Data for this observational retrospective study were taken from the case notes of patients hospitalized in a hospital with a focus on COVID-19.

INCLUSION CRITERIA

With at least two measurements for the D-dimer (the first one before receiving the treatments and the second one on the last day of receiving the treatments), hospitalized patients with COVID-19 infection and D-Dimer level >0.5 mg/l, age of at least 18 years, being free of pregnancy, and having taken an injectable anticoagulant for at least three days. Patients who did not meet these requirements were not included in the trial. The study was carried out between October 2022 and May 2023. 86 patients made up the sample.

EXCLUSION STANDARDS

- Disorder of Bleeding (cirrhosis, hemorrhagic stroke within a year, malignancy and so on)
- Thrombocytopenia (100 109/L)
- Severe Anemia (Hemoglobin less than 8 g/dl)
- Abnormalities in coagulation
- DVT or pulmonary embolism; previous heparin-induced thrombocytopenia; antiplatelet therapy

DATA COLLECTION

With proper authorization from the appropriate authorities, characteristics of the patient, including age, sex, and the presence of another disease (such as HT, and DM), were retrieved from the medical records department. Hospitalized COVID-19 patients' D-dimer levels were documented within 24 hours of their hospitalization, and alters were assessed 120 hours after therapy with SC enoxaparin.

STUDY SETTING AND ETHICAL APPROVAL

The study was carried out at Al-Yarmouk Teaching Hospital in Baghdad, Iraq, from October 2022 to May 2023 with the Department of Pharmacy at Al-Maarif University College's clearance.

STATISTICAL ANALYSIS

The statistical analysis for this study was completed using a Microsoft Excel spreadsheet was used to gather, compile, and evaluate all of the data. Conduct extra statistical analysis to assess the outcomes of treatments. The Statistical Package for the Social Sciences (SPSS), version 24, was used. P values less than 0.05 are considered significant. Numerical data were described using the mean, and standard deviation. An independent student T-test was used to compare the effects of the therapies on the indicator as an average change in the number per patient per day. The null hypothesis was tested, and the p-values were used to assess the significance of the testing. A p-value of less than 0.05 was used to determine if a result was significant.

RESULTS

To determine if gender and age had an impact on the D-dimer, the typical baseline D-dimer value was determined in consideration of the demographic variances. Males had greater D-dimer baseline averages than females before to treatment, yet the distinction was not statistically meaningful P-value > 0.05. Individuals under 60 years old had greater D-dimer baseline averages than individuals over 60. The average age difference was a sizable disparity (Table 1).

Table 1. Baseline D-dimer average by age, gender (male, female)

Demography	D-dimer mg/L	SDV mg/L	Number of patients	P-value
Gender				
Male	2559.87	±3275.719	56	0.6
Female	2463.11	±2204.845	30	
Age				
≥60 years	3267.32	±3604.521	53	0.03
<60 years	1864.05	±1778.583	33	

Table 2. D-dimer baseline average for COVID-19-infected hospitalized patients before and after enoxaparin treatment

General	D-dimer prior to therapy Mg /l	D-dimer after therapy Mg/l	P - value
patient	6.79±7.22	3.84±5.05	<0.0001

Table 3. Effect of enoxaparin use on D-DIMER before and after in general people with COVID-19 who have diabetes

Diabetes	D-dimer prior to therapy Mg /l	D-dimer after therapy Mg/l	P-value
Positive	7.3654±7.65	4.401±4.8	0.056
Negative	6.7538±6.84	3.60±5.08	<0.0001

D-dimer prior to therapy Mg /l:
Positive- mean ± SD of D-dimer level in diabetic patient before enoxaparin treatment
Negative- mean ± SD of D-dimer level in Non- diabetic patient before enoxaparin treatment
D-dimer after therapy Mg/l:
Positive- mean ± SD of D-dimer level in diabetic patient after enoxaparin treatment
Negative- mean ± SD of D-dimer level in Non- diabetic patient after enoxaparin treatment

Table 4. Effect on D-DIMER before and after enoxaparin usage among general COVID-19 patients having hypertension

Hypertension	D-dimer before treatment mg/L	D-dimer after treatment mg/L	P-value
Positive	4.8716±6.06795	2.61±4.054	0.18
Negative	7.3154±7.17541	3.87±5.261	<0.0001

D-dimer before treatment Mg /L:
Positive- mean ± SD of D-dimer level in hypertension patient before enoxaparin therapy
Negative- mean ± SD of D-dimer leDvel in hypertension patient before enoxaparin therapy
D-dimer after treatment Mg/L:
Positive- mean ± SD of D-dimer level in hypertension patient after enoxaparin therapy
Negative- mean ± SD of D-dimer level in hypertension patient after enoxaparin therapy

Anticoagulants like enoxaparin were evaluated for effectiveness using the D-dimer value. Those infected with coronavirus had their D-dimer baseline average determined both before and after using enoxaparin. Look at (Table 2).

Patients who got low molecular weight heparin (Enoxaparin) had their comorbidities (diabetes mellitus, hypertension) compared. Both Tables 3 and 4 present the analysis.

DISCUSSION

According to the results of the current investigation, patients with coronavirus disease had D-dimer levels that were above average. Numerous factors could be at play in this increase in D-dimer readings in coronavirus patients, including:

I) A disease, which may result in the release of cytokines that are pro-inflammatory and a storm of inflammation
II) Some COVID-19 patients have varying degrees of inflammation and hypoxia, which might result in thrombosis or higher oxygen requirements
III) Blood coagulation may also be impacted by severe infection or acute inflammation brought on by sepsis. D-dimer tests are therefore very helpful for identifying thrombotic conditions, which is why individuals with coronavirus were noted to be in hypercoagulable condition [11].

In the collection of information generally gathered at admission, age, and sex were very significant indicators of disease severity. With age, sexual differences become less pronounced. If disease severity was

measured using clinical markers rather than radiologic markers, age discrepancies were more significant. This study is consistent with another one where Jecko Thachil et al., 2020 demonstrated that Enoxaparin anticoagulation therapy appeared for a more favorable prognosis about mortality when coagulopathy brought on by sepsis scores were applied to clients with high levels of D-dimer of greater than six times what is considered to be normal [12]. Even though D-dimer decreases in diabetic patients after using enoxaparin (p-value=0.056), it is not statistically significant. The D-dimer concentration following and before enoxaparin revealed a considerable decrease in non-diabetic subjects (p-value 0.0001), which is extremely important. According to recent research, diabetic patients have a much higher chance of dying in hospitals from COVID-19 than individuals without impaired glucose tolerance (HR=2.36) [13]. According to Gregory et al., people with type 2 (DM2) and type 1 (DM1) diabetes are more likely than healthy people to experience a serious disease brought on by COVID-19. In this study, individuals with DM1 and DM2 had similar adjusted odds ratios (OR) for hospitalization rates (3.90 for DM1 *vs.* 3.36 for DM2) and disease severity (3.35 *vs.* 3.42) [14]. Patients with coronavirus may have increased D-dimer levels on account of thrombin production-inducing inflammation brought on by viral infections and dysfunctional endothelium cells. Higher levels of D-dimer can also occur in these people if they have a physiological state, such as pregnancy, and a concurrent ailment, such as diabetes, cancer, or a stroke [15]. D-dimer readings among hypertensive decreased after taking enoxaparin, although they did not change significantly (p-value=0.18). The D-dimer value was lower in non-hypertensive, and the significance of this group difference was determined by a p-value of 0.0001. In their study, Diana Delali, Juraj Jug, and Ingrid Prkain demonstrated that post-COVID arterial hypertension, which affects 1 in every 6 patients and is most common in women, is a true and dangerous side effect of a COVID-19 infection. The time frames given in this research are meant to help provide a framework for reasonable and sufficient follow-up patient evaluations following acute COVID-19, particularly for the time from the positive PCR test to the onset of post-COVID symptoms. This will make it possible to identify any post-COVID sequelae in a timely manner and begin treating them before they get worse [16]. Additionally, COVID-19 individuals with underlying comorbidities, such as hypertension, are linked to reduced SARS-CoV-2 viral clearance [17]. Trump et al., [18] noted that due to hypertension's aberrant immune response and airway inflammation, SARS-CoV-2 clearance is delayed and lung inflammation in COVID-19 patients is exacerbated. As a result, hypertension may worsen COVID-19 and its associated consequences by delaying SARS-CoV-2 clearance. Lippi and others [19] noted that there is the link between hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19). Dyspnea, hypertension, coronary heart disease, diabetes, male gender, advanced age and cerebrovascular illness are all linked to critical D-dimer concentrations [20]. According to the findings, patients over 60 years of age had aberrant D-dimer readings, with a P-value of 0.001 showing no effect of gender on D-dimer levels. Higher D-dimer levels have been linked to both the male and female genders in other studies [20], with women having a greater chance of contracting thrombotic disorders in the coronavirus study. In general, it appears that age and D-dimer levels are related [21]. Additionally, several research suggested that the use of enoxaparin in COVID-19 may have both anti-inflammatory and anticoagulant effects. The danger of thrombosis in important organs will therefore be reduced by beginning Enoxaparin treatment sooner [22].

CONCLUSIONS

This observational study demonstrates that individuals admitted to the hospital for COVID-19 experienced a drop in D-Dimer levels while receiving treatment with enoxaparin. Enoxaparin and other anticoagulants were utilized to treat the coagulopathy brought on by COVID-19. Low molecular weight heparin enoxaparin has demonstrated positive outcomes in the management of VTE. A decrease in D-dimer level is anticipated when COVID-19 patients are treated with subcutaneous enoxaparin, partly because decreased coagulation results in lower fibrin formation.

Since the usefulness of enoxaparin in improving clinical outcome in corona virus 2019 patients seem consistent and its use is routine in many COVID hospitals and important to evaluate its clinical efficacy in corona virus 2019 patients.

RECOMMENDATION

There is an urgent need for multi-centric trials to assess enoxaparin's clinical efficacy in COVID-19 patients because its value-enhancing clinical outcomes in patients with COVID-19 appears reliable and its usage is commonplace in numerous coronavirus institutions.

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CONFLICT OF INTEREST

The Author declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Health-saving technologies as a need and lifestyle of Ukrainians

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ABSTRACT

Aim: The article analyzes the health-saving technologies of Ukrainians in Eastern Galicia (the end of the XIX century – 1939).

Materials and Methods: In the investigation a number of scientific methods are used: chronological, historical, specific-search, content analysis, providing selection, analysis of the source base, allowing to identify general trends, directions of development, achievements and gaps in the movement for the health of children and adults in Galicia; sources of Ukrainian and Polish authors of different generations in the field of health protection and preservation, physical education and sports, education and upbringing were used, their views and research results were presented.

Conclusions: A component of the health-saving philosophy of Ukrainians (children, youth and adults) of Eastern Galicia in the late XIX – 30s of the XX century was the idea of physical education. Through traveling and camping, playing sports, improving children, youth and adults in places of active recreation («dwellings,» «half-dwellings,» «cuttings,» etc.), the philosophy of health conservation took a leading position in the interwar period of the XX century. The physical education movement had particular successes when a wide circle of Ukrainian youth joined it. There was an original Plast method of physical education of a Ukrainian – physically, spiritually, morally, mentally healthy person, for whom health preservation is a way and philosophy of life, a vital need. All this actualizes the problem of health-oriented public initiatives, which should be creatively used in the current challenges in Ukraine.

KEY WORDS: health-saving technologies, pupils, adults, national education, physical development, public association, plast methods, physical education, Galicia, the end of the XIX century – 1939, medical students

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INTRODUCTION

The health of any nation is a significant indicator not only of the state social and economic development, but also of its medicine development level, cultural and educational level of its citizens, the attitude to their own health-saving. The problem of children, youth and adults health in Ukraine under the conditions of the russian-Ukrainian war has become so urgent that today we are talking about it as a global threat to the entire Ukrainian nation, the loss of its gene pool, when its best sons and daughters die in the war, hundreds of children die from russian terror, millions of Ukrainian citizens became internally displaced persons or were forced to emigrate. In addition, the problem of health-saving is actualized by such phenomena as the strengthening of the socio-economic crisis, the death of civilians as a result of terrorist actions of russia, the spread of infectious and chronic diseases, unfavorable demographic trends (negative natural population growth, demographic aging, increased drug dependence and abuse of alcohol, tobacco smoking, etc.), sedentary lifestyle of children and youth, etc. All this slows down the realization of the state-building potential of Ukraine, increases the risks of losing the gene pool of the Ukrainian nation. One way out of this situation is to assert the idea of health care (physical education). Therefore, under modern conditions, the historical experience of the activities of Ukrainian cultural, educational, youth, sports, philanthropic, and other public organizations of Eastern Galicia in the late XIX – 30s of the XX century, who developed effective forms, original mechanisms, means of mass enlightenment aimed at the formation of children, youth and adults health skills. Ukrainians used world experience, in particular European and Pol-

ish. Therefore, the accumulation of significant world and national experience in the functioning of the children and adults' health-saving system and its insufficient study and application in modern conditions, in particular in the formation among citizens, especially youth, ideas, knowledge, beliefs about the need to adhere to a healthy lifestyle, the importance of physical education (physical education and sports. – authors), active lifestyle, motor activity, the need to establish mass education and promotion of health-saving knowledge among children and adults and ineffective activities in this direction of state authorities, teachers, medical and social workers, especially in rural areas – all this actualizes the problem of health-saving technologies and public initiatives, which should be creatively used in the conditions of modern challenges in Ukraine.

AIM

The article analyzes the health-saving technologies of Ukrainians in Eastern Galicia (the end of the XIX century – 1939).

MATERIALS AND METHODS

In the investigation a number of scientific methods are used: chronological, historical, specific-search, content analysis, providing selection, analysis of the source base, allowing to identify general trends, directions of development, achievements and gaps in the movement for the health of children and adults in Galicia; sources of Ukrainian and Polish authors of different generations in the field of health protection and preservation, physical education and sports, education and upbringing were used, their views and research results were presented.

REVIEW AND DISCUSSION

In the path of development of the movement for health care, the ideas of physical education were Ukrainian public children's and youth societies, sports organizations, religious institutions, and others. Plast has played an extremely important role in shaping a healthy lifestyle for children and youth. This was due to his cornerstones, which aimed to eradicate the defects of the Ukrainian national character and the formation of values of health as a prerequisite for a full life, productive work, and performance of «public duties». According to O. Tysovsky, health promotion should have become «the basis of activity in Plast» as only a healthy person always has «a lot of energy for life, passion and desire to work» [1].

According to O. Tysovsky, health promotion should have become «the basis of activity in Plast», as only a healthy person always has «a lot of energy for life, passion and desire to work» [1].

In the phenomenon of the Plast way of life, physical and spiritual existence were inextricably linked, merged, the ideologists of the Plast idea always emphasized this: Plast education for Ukrainians, A. Richynsky noted, «triple important" because it "not only hardens young people physically and spiritually, not only provides ... cadres of trained wrestlers, but also serves as a good tool for directing the negative aspects of our national character» [2]. Paragraph 12 of the Plast Law obliged to take care of one's own physical health, in particular through abstinence from alcohol and tobacco, as «a Scout respects and nurtures health as a value of the public and as a prerequisite for his ability to work; he does not use any poisons – does not drink alcohol and does not smoke tobacco; in general, it does not do anything that could undermine its young forces or stop their development» [1]. There have been discussions about alcohol consumption in Plast for some time. Due to the «folk character», some figures advocated the possibility of its «moderate» use by young people [3]. However, the position of «complete abstinence» won. These principles were substantiated by a special normative act called «Alcohol Abstinence» adopted in 1925 by the Military-Industrial Complex. It argued that Scouts do not drink alcohol because it is harmful to health, «to exercise willpower», to cultivate the qualities of leaders, to promote thrift in the Ukrainian environment, and is necessary to «stand out in a group of others». Scouts undertook to abstain themselves, «spread it among others» and refrain from participating in parties where they drank alcohol or tobacco; it was the «complete abstinence» from alcohol and smoking that was supposed to give Scouts special «value and significance» in the eyes of the public. It was a kind of social marker [3, p. 160].

The actualization of these tasks was facilitated by the aggravation of social problems associated with high mortality, injuries, and the need to maintain health, in particular, due to unsatisfactory sanitary and hygienic conditions of Ukrainian children, excessive alcohol consumption, which threatened the preservation of the national gene pool. This was constantly emphasized by Ukrainian doctors and public figures, organizing educational events with the participation of youth and adults, as well as speaking to a large readership from the pages of periodicals [4].

According to sources [3, 4], the leading forms and means of anti-alcohol education in Plast were the conversations of educators and «read», which Scoutss prepared and delivered at the «meeting». On the pages of Plast publications («Young Life», «Ukrainian Plast»,

«Yunak-Scout»), foreign experience and examples were popularized when a person achieved great success by refusing to drink. Anti-alcohol centers conducted active public educational work among the local population: they organized «reads», «questionnaires», chambers, courses, explaining the harm of using «strong drinks», etc. Particular attention was paid to the personal example of the educator [3]. Anti-alcohol and «anti-nicotine education» were closely combined with social and patriotic, physical, moral and ethical, economic. There is reason to believe that the creation of appropriate pedagogical conditions for the successful development of the movement for the health of the growing individual, organically fits into the cornerstones of the ideology: self-improvement and the desire for maximum self-realization of personal potential throughout life. Scouts of Plast (such as the Plast kurin` (a group created by 3-7 smaller groups named hurtok) contributed significantly to the spread of the idea of abstinence among Ukrainian students, students, and the activities of the anti-alcohol society «Renaissance».

The second component of the formation of a healthy lifestyle in Plast was the inculcation of knowledge in health and hygiene. Work in this direction has already begun at the level of innovation. In particular, the textbooks by L. Bachynskyi and O. Vakhnianyn obliged to give «wolf cubs» and «foxes» an idea of proper breathing, treatment of burns, bandaging, stopping nosebleeds, preventing sunstroke, etc., as well as to develop appropriate skills [5]. Knowledge of a healthy lifestyle was associated with the formation of appropriate norms of behavior and habits: children who want to «live in Plast way» must get used to cleanliness, avoid harsh words, do not envy anyone, enjoy life, be polite and cheerful. Continuity, purposefulness, systematic education of a healthy lifestyle in Plast testifies to its continuation in the power of young people who committed to have a high level of knowledge in the field of health and promote them in their social environment. It is about gaining knowledge about the structure of the human body, the basics of occupational hygiene and clothing, the symptoms, ways of spreading infectious diseases and means of preventing them, etc. [3]. Plast «skills» in the field of health included the acquisition of knowledge and skills of youth in hygiene, animal husbandry, dairy, veterinary medicine (see «Friends of the Beasts»), etc.

Special literature for educators directed to the realization of these tasks, in particular popular science editions of A. Korchak-Chepurovsky «Life and health of human», I. Kurovets «Health of the house, bowery, village», A. Gonchariva-Goncharenko «General hygiene» and others. Having mastered the knowledge of the «dangers of unruly, unhealthy living» and the dangers of alcohol and nicotine, young members of Plast undertook to hold ten-minute «talks» on «nurturing health and strength»: about habits that impair vision and the rules of its preservation; the benefits of solar, air and water treatments, hardening, their possible negative consequences, etc. [3]. Requirements for knowledge of a healthy lifestyle, the basics of hygiene, and first aid were put forward and constantly deepened. At the same time, they were based on the advice outlined in O. Tysovsky's textbook «Life in the Plast» [1]. They were formulated in the form of questions and answers, which determined the actions to assist in various «emergencies» (when receiving sunstroke in the field, at the first signs of frostbite during a winter walk, fainting at worship, scalding with boiling water, dislocations, sprains, nosebleeds, etc). Using the tools at hand, the Scout had not only quick and skillful actions to alleviate the disaster, but also morally and psychologically support the victim [1].

Travel and camping – «alpha and omega» of scouting, its «beginning» and «final stage», it is the direction and form and method of formation education, they have become separate educational «subsystems» with their methods and means of forming physical, spiritual, moral qualities of the individual that correspond to the idea of «Plast Ideal» [1, 6]. The success of the camp was ensured by the theoretical knowledge of children and youth acquired during the formation of «tests» and exams of «skills», in particular, the ability to build a «tents», to equip them; cooking, lighting, cartography, orienteering, signaling, «pionirka» (training which is connected to the knitting of knots), knitting, «rescuing» (first aid, hygiene), etc.

Some of the material in the periodical «Ukrainian Youth» – Catholic Association of Ukrainian Youth «Eagles» – was devoted to the problems of travel and camping, it contained practical recommendations for those who set out on a journey, advised on how to pack a shoulder bag to take with you. the way how to «camp», how «cheap» for young people to relax in the mountains, combining recreation with educational work, arranging «lectures», concerts for the peasantry, etc. [5, 7, 8]. It is worth noting the «Nine Commandments of Traveling Scouts» – a unique monument of Ukrainian pedagogical thought, which emphasized: that travel is not for racing, but for «learning about God's nature» [9]. Therefore, their participants must «consider [study] the customs and characteristics of the population, which preserves the millennial traditions». The «commandments», in particular, required: «Do not despise nature. Do not pluck flowers without hosen ... Do not scatter around any paper, any waste from vegetables. The resting place of the platoon should look the same when leaving, as well as at its entrance» [9].

The educational process in the camps was based on certain organizational and pedagogical principles: taking into account the principles of pedagogical science (age and gender differentiation of requirements, comprehensive approach, accessibility, systematic and consistent implementation of tasks, connection with practice, taking into account individual characteristics, etc.). Separate girls' and boys' camps contributed to the formation of their participants' skills and abilities inherent in different sexes: boys learned to cook, wash, etc.; the girls «harvested the forest», pitched tents, guarded the camp, and so on. [5].

Thus, the pedagogical phenomenon of travel in Plast and camping is that it became a practical school for the formation of competencies in the field of health, from all spheres of formation, the educational system that ensures harmonious comprehensive development of personality: not only physical education but also the community-patriotic education, moral and religious, aesthetic, environmental, labor education. Travel and camping have become a real philosophy of the Ukrainian health care and physical education system, as evidenced, among other things, by the titles of articles published in the periodical «Ukrainian Youth»: Rodan «Camp life – a seasoning for tough competition», «Camp – a forge of health and physical fitness», V. Malanchuk «Camp - a fairy tale of our days», and others [1, 7-9].

After the banning of Plast in 1930, the Catholic Association of Ukrainian Youth «Eagles» took over the baton of physical education and Plast's method of health care. Based on the study of the journal, it can be stated: most of the publications were devoted to health issues; Top topics – travel and camping, promotion of healthy lifestyles, the idea of physical education, physical development, and sports (much attention is paid to the promotion of vulture as a promising area of physical development in mountain conditions), medical education in the context of physical education, literary creativity, promoting social medical care, activities of summer traveling student schools as a form of public education on relevant topics, anti-alcohol advocacy, practical medical guidelines and daily advice on health, promotion of success in sports and physical education, spiritual development, and more. So, even though the children's association of the Catholic Association of Ukrainian Youth «Eagles» had a «religious-Catholic» orientation, however (this is evident from the topics of publications in the periodical «Ukrainian Youth» (1933–1939)) it is quite correct can be called the «Catholic Plast». The first hurtky were established in 1933, but only on March 20, 1937, it was officially registered in the Lviv Voivodship as the companionship «Eagles – Catholic Association of Ukrainian Youth», on April 24 A. Melnyk was elected as the Main Council [10-12].

Health issues were the focus of the Mariiske companionship. They promoted the ideas of «healthy education», the cult of spiritual, mental, moral, and physical health, conducted anti-alcohol propaganda. School companionships operated not only in educational institutions established at monasteries by the Ukrainian Greek Catholic Church [10, 12] but also in the Ukrainian Hungarian People's People's Party «Ridna shkola». Mariiskyi movement was gaining popularity in Galicia, for example, in 1939 in the Galician metropolitanate Ukrainian Greek Catholic Church actively worked almost 250 branches of mariiske companionship (20,000 people), which were divided into: Mariiski society for youth secondary and higher education; Mariiski hurtky for children; Mariiski unions of helpers». So, according to statistics – Mariiske youth society as for 1936 had 314 centers, numbering about 22 thousand people, in 1939 in 189 hurtkakh of the Catholic Association of Ukrainian Youth «Eagles», of which 25 were women, there were 4979 persons [12], as well as the fact that the Catholic Association of Ukrainian Youth «Eagles» and mariiski society united different age groups of children and youth, adults, we can say that in this social structure, as in Plast, there was a formation of a healthy lifestyle throughout life.

A special place in the activities of «kaumivtsiv» is occupied by travel and camping thanks to the two labor camps in the vicinity of Princely Halych, which had a public and educational purpose, which was a combination of leisure and work, where physical labor was considered an important factor in personal education. philosophy of camping Catholic Association of Ukrainian Youth «Eagles».

In addition to travel and camping, the means and form of health care in Galicia was the rehabilitation of children and adults in «homes», «semi-villages», «zhyvtsiakh» and other public institutions that performed health and medical functions [13-16]. Ukrainian public (usually caste) societies have made a significant contribution to the organization of recreation for their members, as well as ensuring health (usually for urban children) in mountainous areas. The construction of the «houses» took place under difficult financial difficulties and required, among other things, efforts aimed at overcoming numerous obstacles, including the legal order. Noteworthy is the «feat in the eyes of citizenship» carried out by the Mutual Aid of Ukrainian Teachers: the construction of a house in Vorokhta in 1914-1928 and in Cherche in 1929-1935, which marked a bright page in the history of public health guardianship of Ukrainians in the region. «Organized teaching» (self-reliant) managed to collect for the «construction» of two «due to» great sacrifice» housing over 200 000 zł. [11, 17].

Although the «homes» did not offer special medical treatment, they helped «persons» in the early stages of the disease, physically exhausted, wanting to strengthen the body and relax, as well as healthy people looking for comfort in the mountains, hygienic breaks, and in the society. These health-improving and medical institutions also became important centers of Ukrainian culture: in the summer they organized self-education courses for teachers and numerous various «lectures» and friendly meetings [17, 18].

According to researchers, similar projects to build their own homes have long been nurtured by the Teachers' Community, but the small number of society and the dispersion of its local organizations have hindered this (in Rozhanka (Carpathians)). The Society of Writers and Journalists for 10 years through the press actively called on the public to help build a sanatorium in Yamnytsya, but it was not successful: fundraising could not be completed [3, 17].

In the article «Zhyvets Cherche» [19], published in the diary «Dilo» (July 5, 1930), I. Kurovets describes his journey on June 29, 1930, to «Ukrainian Zhyvets Cherche», «to see him clearly and to know his value». Here are some «assessments» of a well-known doctor and public figure to find out the direction of «zhyvtsia»; we can quote: «A useful assessment of the personal value of Cherchansk waters and hogs was given by Dr. Panchyshyn, Associate Professor Dr. Sabatovsky, balneologist and others»; «Patients who have been there praising the waters of Cherche in various ailments»; «At the entrance from the hills to Cherche, it gives a nice impression of a clean small town, which shows beautiful private institutions, pavilions, and then a brick church, a large storey Narodny dim, which houses local cultural and economic societies»; «I am very impressed by the private pavilions and all the font houses that are clean and beautiful»; «In front of the main building is a large square, sidewalks and flower beds, kept in order. There is a lack of greenery, and even cramps and trees ... «; «Noise, laughter, and merriment can be heard everywhere». The author of the publication notes that famous Galicians are recovering here, including priests, Teofil Okunevsky and others, who «seek health and praise the waters of Cherchany», and emphasizes the great professionalism of «solid» «institution doctor Dr. Chaplinsky» who «takes good care of the health of patients» [20].

As a scientist, I. Kurovets, who personally became convinced of the «healing power» of the «cuttings» in Cherche («tasted water from all sources, drank about 8-10 glasses»), warns against «wild treatment», emphasizes that it is necessary to consume medicinal water «only according to the doctor's instructions» and gives recommendations for the implementation of sanatorium and medical care [20]. Recommendations of I. Kurovets about the perspective development of the «cuttings» proved the almost 80-year existence of the sanatorium, which is actively developing today, and the recommendations of I. Kurovets about the construction of a «pavilion» for sick (wealthy) Jews, which will entail additional investments [20], and his other «assessments» should also be «taken into account» by today's organizers of sanatorium and recreation in the Carpathians.

A separate page in the history of the formation and development of health protection was inscribed by Ukrainian institutions, the Greek Catholic clergy, especially metropolitan A. Sheptytsky, is primarily about creating a system of medical care and rehabilitation of children by organizing summer holidays, in particular in summer «half-dwellings» in Korshev, Milovanny (Stanislavivshchyna), where they organised summer rehabilitation of preschoolers and pupils [21]. According to sources [6, 10-12, 20-24], for 34 years (since the creation of these institutions), about 100-140 children each summer gained strength, health and learned the peculiarities of rural life and work in Mylovannya and Korshev. Educational, pedagogical and recreational purpose of children staying in summer «dwellings», camps, wandering ideologists of Catholic Association of Ukrainian Youth «Orly», «Plast», TVO, Ukrainian National Society for Child Protection and Youth Care, Ukrainian Pedagogical Association «Ridna Shkola», sports societies, other public organisations considered not only in «ruddy faces of children and increased body weight», but also in «national upbringing» of urban children, the development of their motor activity and health care in general. [6, 10-12, 20-24].

A completely new direction in the movement for a healthy lifestyle was the system of public health education for children, youth and adults, medical examination, the development of physical culture and sports (physical education), etc. So, in May 1931 (according to some reports, 1930 [25]) a special "sports and medical council" (consultation) was created in Lviv, which worked 3–4 times a week. Thanks to the ascetic work of doctors (I. Mryts, S. Kotsyuba, S. Korenets, B. Makarushka) for the first time in the history of the development of the physical education workouts and public medical care, a professional preventive examination of sports and other public societies members was carried out («Sokil-Batko», Ukrainian Sich Rifleman, Catholic Association of Ukrainian Youth «Orly» etc.), moreover, systematically and constantly at the direction of school doctors or teachers of the workouts (physical culture), doctors provided various kinds of professional assistance [25]. Doctors «consultants» participated in sports competitions [25]. This reflects the only exploration we found «Doctors in the Ukrainian physical education movement»

by R. Kopach, a public figure in Galicia, an activist of the Plast movement, an organizer of Plast huts [25]. The author notes that the leaders of the Ukrainian movement for health protection, in particular prof. I. Bobersky, drew attention to the achievements of other European peoples in the field of physical education and indicated the way of development of «our physical education movement» [25].

We believe that the merit of doctors and students of medicine is to promote the idea of health protection, by their own example. They and the leaders or activists of the Ukrainian physical education movement led to the upbringing of a healthy lifestyle, the involvement of not only youth, but also adolescents, and especially girls, in physical education [2].

CONCLUSIONS

The component of the philosophy of health-saving of Ukrainians was the idea of physical education. Through traveling and camping, sports, recreation for children, youth and adults in places of active recreation («dwellings,» «half-dwellings,» «cuttings,» etc.) it took a leading position especially in the interwar period of the XX century. The physical education movement had special successes in the 1930s, when an ever wider circle of Ukrainian youth joined it, and the adult population showed no longer a biased attitude to it, but a sincere and conscious interest and admiration. «Plastuny», «sokoly», athletes, medical students, «kaumivtsi» served as an example to follow and convinced the nationals of the need to lead a healthy lifestyle («a healthy unit is a healthy nation», in a healthy body is a healthy mind, where strength, there will flies "). Ukrainian youth led the movement for a healthy lifestyle. «Plast» played an extremely important role: in the Ukrainian scouting, there was an original Plast method of physical education of an Ukrainian - physically, spiritually, morally, mentally healthy person, for whom health-saving is a way and philosophy of life, vital needs, which were aimed at eradicating the blemishes of the Ukrainian national character and the formation of value ideas about health as a prerequisite necessary for a full life, productive work and the performance of public duties. At Catholic Association of Ukrainian Youth «Orly» and «Plast» there was a formation of a healthy lifestyle throughout the life of the individual. Health problems were the focus of Mari societies, which had a distinct religious orientation. Effective means and form of health-saving in Galicia was the rehabilitation of children and adults in «dwellings», «half-dwellings», «cuttings» and other public institutions that performed health and medical functions. Ukrainian public (usually professional) societies significantly contributed to the organization of recreation for their members, as well as the provision of recreation (usually urban children) in the highlands. Ukrainian social activists became a kind of public enlighteners, conducting «national awareness» among the urban and rural population, joined the youth of the city and village to work in the field of health protection, creating real oases of physical education, where mass and professional sports were harmoniously combined, great attention was paid not only to physical, but also to the general and cultural-aesthetic, spiritual development of the individual, anti-alcohol and anti-nicotine propaganda, active motor activity, etc.

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CONFLICT OF INTEREST
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REVIEW ARTICLE

CONTENTS

Influence of respiratory infections pandemics on the mortality of the population of Ukraine

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ABSTRACT

Aim: To analyze the dynamics and structure of the excess mortality of the population of Ukraine for 76 years (1945-2021).

Materials and Methods: An observational population study was conducted. Epidemiological methods were used, in particular, the method of graphical construction of time series, intensive, extensive indicators and indicators of excess mortality were calculated.

Conclusions: The coronavirus disease pandemic in Ukraine became the largest documented respiratory infection pandemic after 76 years, but did not outweigh the dramatic increase in mortality in the 1990s–2000s, in including death in 1995.

KEY WORDS: excess mortality, COVID-19, pneumonia, influenza, pandemics

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INTRODUCTION

The COVID-19 pandemic has become a significant, complex, cross-sectoral problem worldwide. As stated in the Report on the COVID-19 Pandemic: Lessons and Recommendations for the Future (2023), "COVID-19 has cost millions of lives and has had a horizontal impact on all levels and aspects of society, causing enormous damage both in Europe and throughout the world; (…) The EU, like the rest of the world, was not sufficiently prepared to deal with a crisis of this magnitude or its waves, which affected societies and economies around the world, including the provision of continuing education services in the case of confinement; (…) the impact of the COVID-19 pandemic has caused the most complex socio-economic crisis that Europe has had to face since the Second World War" [1].

On a global scale, the coronavirus disease pandemic caused significant excess mortality in 2020-2021 - about 14.83 million deaths. Of them, the excess in 2020 and 2021 was 4.47 and 10.36 million, respectively [2]. The indicator of "excess mortality" has been widely used to assess the consequences of past pandemics and crises in the field of health care, in particular, to assess the impact of the 1918-1920 influenza pandemic, known as the "Spanish flu" [3]. Taking into account the introduction by the WHO of the concept of "disease X" as a framework concept for theoretically possible pathogens capable of epidemic or even pandemic spread and requiring the adaptation of health care systems for a timely response to emergency large-scale challenges, this indicator can be considered as one of the indicators of the effectiveness of the response to such challenges [4].

A model of monthly excess mortality in Ukraine in 2020 using mortality trends for 2016-2020 showed 38,095 excess deaths. The excess mortality in Ukraine was average compared to 30 other European countries [5].

According to an estimate that used data for 2016-2020 in Ukraine in 2021, the excess of deaths related to the COVID-19 pandemic amounted to 150,049 (21.01% of all registered deaths) [6].

Excess all-cause and cause-specific mortality in 34 categories across models using data from January 2015 to December 2021 were also noted. Excess deaths were caused by pneumonia, circulatory system diseases, these categories accounted for the majority of all cases at the peak of expected all-cause mortality and laboratory-confirmed mortality from COVID-19 [7].

AIM

To analyze the dynamics and structure of the excess mortality of the population of Ukraine for 76 years (1945-2021).

MATERIALS AND METHODS

An observational population study was conducted. The object of the study is the epidemic processes of respira-

tory infections that cause pandemics, in particular, the new coronavirus infection caused by the SARS-CoV-2 virus. Epidemiological and statistical methods were used in the work, in particular, the method of graphical construction of time series, intensive, extensive indicators and indicators of excess mortality were calculated.

The main data on the annual number of deaths in Ukraine until 2000 were obtained from the reference edition [8]. Statistical data on the annual number of deaths for the period 2001-2015 were obtained from the directories of the Ukrainian Center for Disease Control and Monitoring of the Ministry of Health of Ukraine (form C-8 "Distribution of the deceased by sex, age groups and causes of death"). Mortality data for 2016-2021 were taken from the website of the State Statistics Service of Ukraine [9]. Data on population mortality for 2022-2023 are not available due to the introduction of martial law in Ukraine.

REVIEW AND DISCUSSION

Almost immediately after the Second World War in 1947, in the dynamics of the mortality of the population of Ukraine, a peak of deaths was observed, which was related to the famine, which arose due to the drought and the inept or deliberate actions of the Soviet government, which did not avert mass starvation (Fig. 1).

Since 1948, mortality rates have stabilized. From 1950 to 1958, excess mortality was negative (Fig. 2).

The first documented pandemic of a respiratory infection in the second half of the 20th century was the "Asian Flu" a global pandemic of influenza A virus subtype H2N2 of 1957–1958, which probably manifested itself in Ukraine in 1959 with a total excess mortality of the population to the level of 17,009 deaths per 100,000 population. In the following 1960, the total excess mortality, as in the previous years before this pandemic (1950–1956), again became negative (Fig. 2). Another and more powerful influenza pandemic occurred already one decade later in 1968-1970 ("Hong Kong flu" caused by an H3N2 strain of the influenza A virus). The total excess mortality from H3N2 influenza in Ukraine at the peak of the pandemic in 1969 reached the level of 54,967 deaths per 100,000 population, and the number of people who died from pneumonia in 1968, 1969, and 1970 was 9,317, 10,254, and 11,359, respectively (Fig. 1). During the Hong Kong flu pandemic in 1970, excess mortality from respiratory diseases (+23.55 per 100,000 population) and circulatory system diseases (+47.34 per 100,000 population) was recorded in Ukraine, but excess mortality from some infectious and parasitic diseases (Class 1) was negative (Fig. 3, Fig. 4, Fig. 5).

The next pandemic (the "Russian flu" caused by strain Influenza A (H1N1) in 1978–1979 showed total excess mortality in Ukraine, which did not differ from the excess mortality of the Hong Kong flu. The number of people who died of pneumonia in 1978 and 1979 was 9,254 and 8,768, respectively (Fig. 1). All of the above-mentioned manifestations of excess mortality, in particular, pandemics of respiratory infections, occurred during the period when Ukraine was part of the Soviet Union, and the next dramatic increase in overall excess mortality was registered in independent Ukraine in the 1990s.

In 1995, the total number of registered deaths was 792,587, the highest annual death rate since World War II, but this rate was not associated with pandemics of respiratory infections, except for the tuberculosis pandemic (Fig.1). The probable reason for the growth in Ukraine of both overall mortality and mortality from individual nosological groups (diseases of the circulatory system, respiratory diseases, some infectious and parasitic diseases) was the socio-economic crisis that occurred in Ukraine after the collapse of the Soviet Union. This crisis lasted from the mid-1990s to the end of the 2000s. During these years, the death rate remained at a high level. At that time, there were severe re-emergent epidemics of diphtheria, tuberculosis and the pandemic of HIV in Ukraine. Also, there was a high overall excess mortality and a high excess mortality from diseases of the circulatory system during this period (Fig. 4), but starting from 2009 to 2019, the economic condition of the country improved somewhat and mortality rates had a pronounced tendency to decrease (Fig. 1). From 2009 to 2019, total excess mortality and infectious excess mortality were negative (Fig.2). The impact of the H1N1 swine flu pandemic was not significantly felt in Ukraine in 2009-2010.

The COVID-19 pandemic began in Ukraine in 2020 and lasted until 2023. The first two years of the pandemic showed a rapid consecutive increase in total excess mortality +32,569 deaths in 2020 and +125,589 deaths in 2021. There were 20,709 deaths from COVID-19 in 2020 or 50.6% of excess mortality and in 2021 there were 87,567 deaths or 64.02% of excess mortality (Fig. 1). COVID-19 (Class 22) was responsible for 3.36% of total deaths in 2020 and for 12.26% of total deaths in 2021. Non-COVID-19 pneumonia, influenza and other acute respiratory infections (Class 10) almost doubled (in 2020) and almost tripled (in 2021) compared to the previous five years (2015–2019). Other infectious mortality (some infectious and parasitic diseases – class 1) showed a drop in mortality in 2020 and 2021 (Fig. 5).

While understanding the direct and indirect effects of a pandemic is important for preparing for and responding to future emergencies, it is also important to

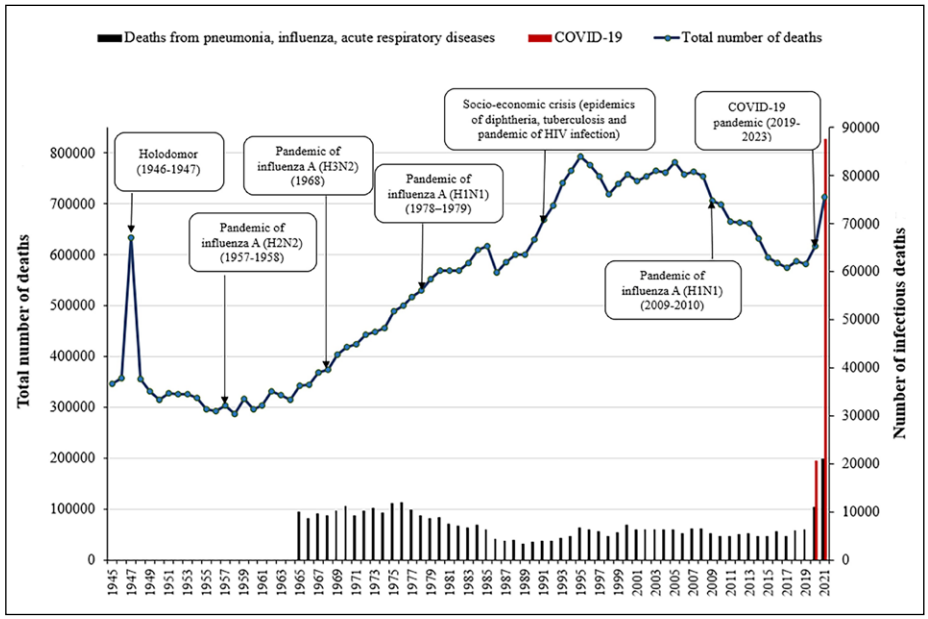

Fig. 1. Total mortality, mortality from pneumonia, influenza, acute respiratory infections and COVID-19, Ukraine, 1945–2021.

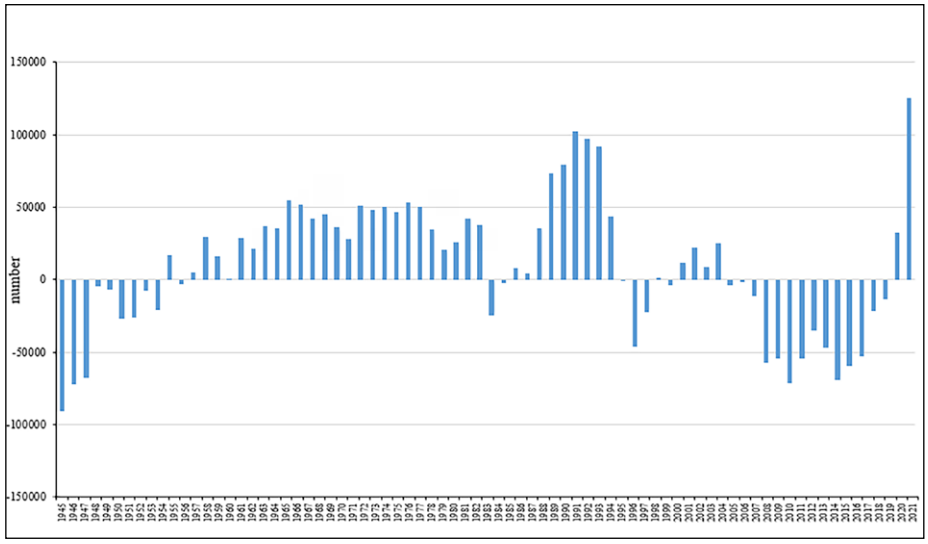

Fig. 2. Total excess mortality, Ukraine, 1950–2021.

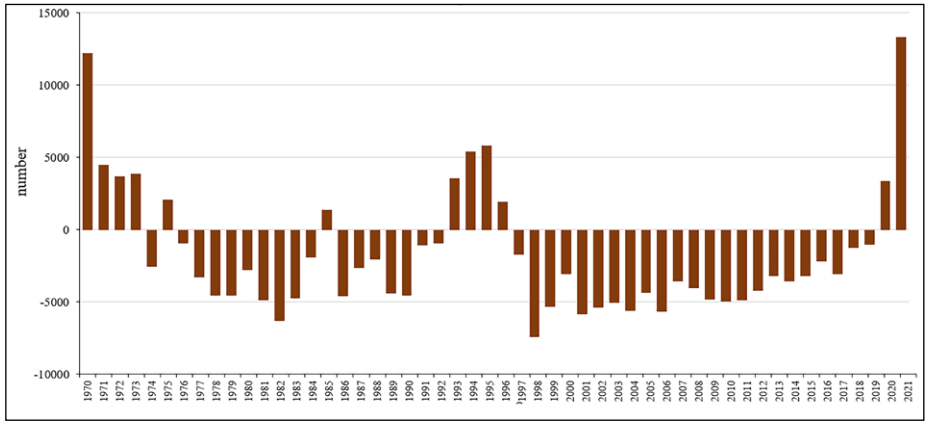

Fig. 3. Excess mortality from respiratory diseases, Ukraine, 1970–2021.

compare mortality during a pandemic with non-pandemic times. According to the CDC/National Center for Health Statistics, deaths in New York state caused by non-communicable diseases lead during non-pandemic periods, with cardiovascular disease and cancer being the leading causes of death, accounting for more than 44,000 and 34,000 per year respectively [10, 11].

A study of excess mortality from epidemic influenza, 1957–1966, showed that more than half of the excess deaths were attributable to diseases of the heart, circulatory, or nervous systems, and that severe influenza epidemics resulted in a small but signifi-

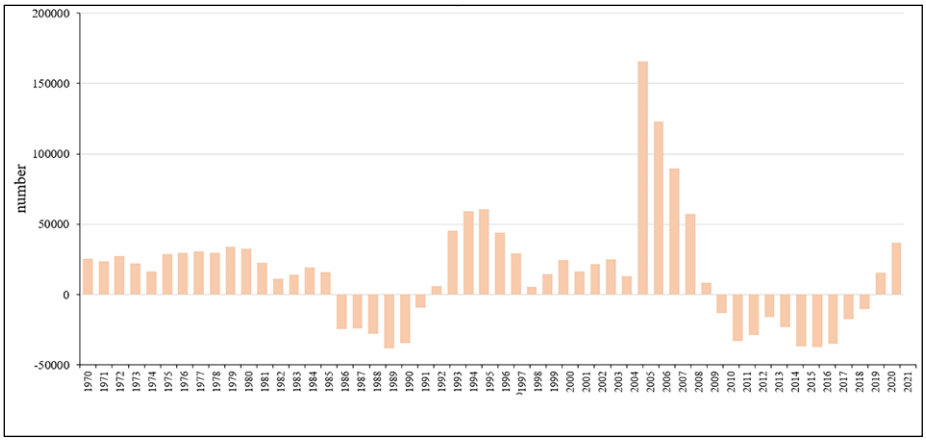

Fig. 4. Excess mortality from diseases of the circulatory system, Ukraine, 1970–2021.

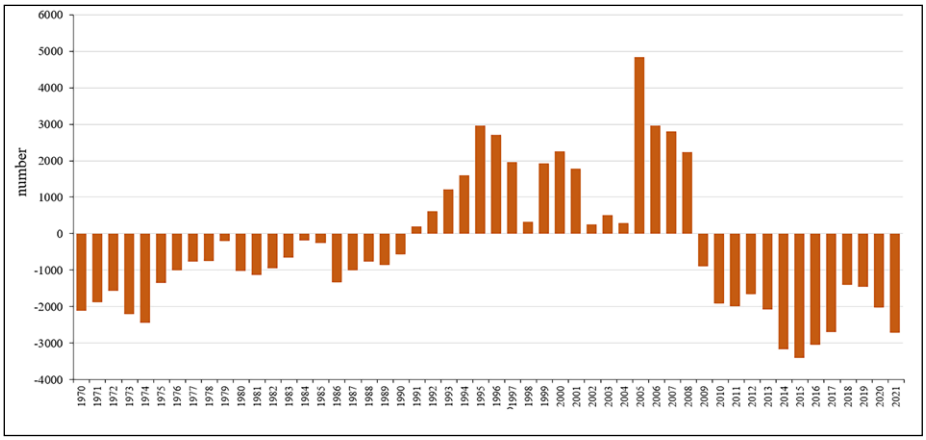

Fig. 5. Excess mortality from some infectious and parasitic diseases, Ukraine, 1970–2021.

cant excess mortality attributable to tuberculosis, asthma, chronic rheumatic heart disease, diabetes and neoplasms [12].

The total number of deaths in Ukraine shows significant fluctuations over the past 76 years. In 1947, one can see a jump not related to pandemics and epidemics of respiratory infections. Subsequent influenza A pandemics, particularly in 1957–1958 and 2009–2010, did not cause significant overall excess mortality. The influenza pandemics of 1968–1970 and 1978–1979 resulted in modest increases in total excess mortality, but total mortality between these two pandemics (throughout the 1970s) remained at the same level. Moderate excess mortality from diseases of the circulatory system was also present in the 1970s, but it was not only during the influenza pandemics of 1968–1970 and 1978–1979. During this period, the largest number of deaths from pneumonia, influenza, and acute respiratory infections were recorded both in pandemic years: 1969 – 10,254 deaths and 1970 – 11,359 deaths, and in non-pandemic years: 1975 – 11,935 deaths and 1976 – 12,091. Such data may indicate that that only part of the excess mortality is of pandemic origin. Perhaps this is also evidenced by the dramatic increase in all types of excess mortality (the highest in Ukraine over the past 76 years) in the 1990s and 2000s. Pandemics of respiratory infections were absent in Ukraine during this period.

The COVID-19 pandemic has had a global impact on all areas of human life, has slowed advances in healthcare and highlighted deficiencies in healthcare infrastructure worldwide, as healthcare systems were unprepared and ill-equipped to deal with the pandemic and simultaneously provide general and specialized medical care [13, 14]. The diversion of health care system resources to respond to the coronavirus disease pandemic has led to a prolonged disruption in the provision of basic medical services. New challenges impeding demand for health care services, such as limited mobility, fear of infection, and shortages of infection prevention and testing facilities create additional, unprecedented challenges [14].

Previous studies examining changes in non-COVID-19 hospitalizations and all-cause mortality during the pandemic show that the decline in other-cause hospitalizations was likely due to hospital overcrowding during peak periods of coronavirus disease, and also with a drop in demand for help from citizens who were afraid of contracting COVID-19 [15].

Our results also confirm previous data, as in the 5 years (2015–2019) preceding the COVID-19 pandemic, an

average of 584,266 deaths per year were registered in Ukraine, and during the COVID-19 pandemic in 2021, a peak of 714,263 deaths was registered, of which 125,589 (or 64 .02%) of deaths were excess. Of these excess deaths, 87,567 were attributable to COVID-19 (more than 95% of these deaths were laboratory confirmed). The occurrence of 35.08% of non-COVID-19 deaths probably contributed to the overload of the health care system in the conditions of anti-epidemic restrictive measures (lockdowns).

Thus, both the total excess mortality and its components in different periods of time cannot always be caused only by pandemics of respiratory infections. In some periods, excess mortality may be higher when there are no pandemics.

CONCLUSIONS

If during influenza A pandemics, a significant part of non-infectious excess mortality can be explained by the lack of laboratory diagnostics, then during the COVID-19 pandemic, non-infectious excess mortality can be explained, among other things, by the overloading of the health care system in the context of anti-epidemic restrictive measures (lockdowns).

Despite the fact that the COVID-19 pandemic has become in Ukraine over the past 76 years the largest documented pandemic of a respiratory infection with the largest number of annual laboratory-confirmed excess deaths, it did not exceed the dramatic increase in mortality in the 1990s-2000s, in particular, the indicator of 1995 year.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Current challenges in accessibility to ophthalmological care in Ukraine

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ABSTRACT

Aim: The purpose of the study is to identify challenges in the organization and access to ophthalmic services through the analysis of expert opinion of practitioners and government officials.

Materials and Methods: Materials developed during expert interviews with practitioners and government officials were used in the study. We also used materials worked out within the project ID 22120107 supported by Visegrád Fund.

Conclusions: Despite all the challenges in access to high-quality ophthalmology services, practitioners and government officials have common opinions on how to improve the organization of eye services, how to make care more inclusive and effective, so that the development of blindness and visual impairment does not cause a burden on the state and society.

KEY WORDS: organization of ophthalmological care, management of healthcare, ophthalmology, cataract, glaucoma, expert interviews

Wiad Lek. 2024;77(4):847-852. doi: 10.36740/WLek202404134 DOI

INTRODUCTION

Ophthalmological care in Ukraine has been developing dynamically in recent years, it includes more classical traditional practices in medical care, as well as modern innovative methods of treatment and support of patients. The main components of ophthalmic care in Ukraine still remain diagnosis, treatment and prevention of disorders related to the eyes and visual system. The ophthalmic care network may also vary, depending on the availability of personnel, resources, medical products, medicines and facilities, as well as on the location of the provision of care to the population [1]. For example, coverage of quality ophthalmology services is currently may be limited in rural areas or in regions of de-occupation or close to the demarcation line.

Although Ukraine boasts a greater wealth of medical and quality expertise, the public ophthalmology may still face various challenges, including resource constraints, infrastructure limitations, and possible inequities in access to quality ophthalmology services and care [2]. The national Ukrainian healthcare system has undergone transformations in recent years, creating both obstacles and opportunities for both ophthalmologists and patients [3].

Despite these challenges, Ukrainian ophthalmology is characterized by stability and development. Clinicians across the country are constantly striving to improve diagnostic techniques, surgical procedures, and patient care protocols. In addition, the joint efforts of medical professionals, researchers and policymakers contribute to the development of ophthalmic services and the dissemination of best practices.

This article examines the organization of the national ophthalmology system in Ukraine via delving into expert review, current challenges, and possible new perspectives for improvement in the field. By examining the healthcare system and specific support and services, we aim to provide insight into the current status of eye care in Ukraine and emphasized the efforts of practitioners and state to improve public ophthalmological care system in Ukraine.

AIM

The aim of this study is to analyze the existing healthcare system of providing services in ophthalmology in Ukraine to identify gaps in the national system and propose preliminary solutions for their elimination or improvement in further research, in particular in the provision of medical services for cataract and glaucoma.

MATERIALS AND METHODS

The study included conducting expert interviews with ophthalmologists from the public and private sectors,

managers of public health care facilities and the management of the National Health Service of Ukraine (NHSU) regarding their experience in medical practice and their expert opinion on the organization of ophthalmology care and challenges in the healthcare system. Expert interviews were conducted in accordance with the requirements of qualitative research methods, including interview recording, transcription, protection of the rights of respondents during the interview and were approved by the Scientific Research Ethics Committee of the National University of Kyiv-Mohyla Academy, Resolution No. 3 of from July 7th, 2022. All respondents gave informed consent to process and use the responses for scientific purposes and publications.

This study presented materials that were partially developed within the framework of the project ID 22120107, supported by the Visegrád Fund, and were used in part of the study on Ukraine in agreement with partners.

REVIEW AND DISCUSSION

Expert interviews are an invaluable tool in the field of ophthalmology research, providing researchers with the first-hand information, perspectives and experiences of thought leaders and practitioners in the field. In the pursuit of deepening knowledge, understanding new trends and solving complex problems, expert interviews offer a unique opportunity to take advantage of the wealth of experience and knowledge possessed by experienced professionals and influential stakeholders.

As quality ophthalmological care in Ukraine still continues to develop, particularly under the influence of technological progress, demographic changes and changing healthcare paradigm and reforming, the need for informed decision-making and evidence-based practical solutions is becoming increasingly important in today's realities. Also, expert interviews serve as a conduit for synthesizing multiple perspectives, fostering interdisciplinary collaboration, and elucidating the nuances of issues that may not be apparent through quantitative research methods.

This article presents the main results and theses of expert interviews with ophthalmologists from the public and private sectors, managers of public healthcare facilities and the management of the National Health Service of Ukraine, analysing the issues of organization of ophthalmological care in Ukraine, coverage of services in Program of Medical Guarantees (PMG) packages [3], early diagnosis and challenges facing practitioners. By providing practical recommendations and examples from experts' experiences, we aim to enable the full potential of expert interviews as a means of generating comprehensive, contextually informed insights and driving significant progress in the field.

During the conducted interviews, a number of important directions in the organization and support of ophthalmic care were revealed, which currently appear to be important for the provision of quality services and their availability.

FINANCIAL COVERAGE OF OPHTHALMOLOGICAL SERVICES FROM THE STATE BUDGETS

A big discussion with experts considers if the public healthcare system of ophthalmological care fully covers all the costs of patients for treatment, (micro)surgery for eye diseases and the purchase of lenses for cataracts and other diseases [3]. All experts emphasized that PMG covers all costs of primary medical care, most examinations and even surgical intervention in packages. However, if the treatment involves more specific medical devices, medicines or additional supporting or more advanced care and rehabilitation, then these additional costs may be payable by the patient [4]. It was also pointed out that expensive lenses are not covered by government programs, instead mid-range decent quality lenses are. The expert 1 practicing surgery doctor noted in the interview: «Not all services are fully covered by the Programme of Medical Guarantees. Now, some of cataract patients are covered by local budget programmes. The Programme of Medical Guarantees covers examinations, consultations, that is, more at the level of primary medical care. There is a local program «Health of Kyivans» in Kyiv city, which has been operating for several years, and it operates more or less stably. To date, it fully cover all consumables: lenses, knives, and solutions.»

At the same time, the management of NHSU understands the need to expand the capacity of PMG packages to cover the necessary services, in particular ophthalmology. In this way, expert 2 from the management of NHSU noted about the plan of the state institution for the coming years: «Right now, we are preparing a more detailed list, which will, as it were, break down the general services in order to understand that we cannot fully cover by PMG now. And these services will be included in a separate Resolution, supplemented with paid services, where it will be clearly understood what services and medical care we pay for and what we absolutely do not cover.»

THE USE OF INNOVATIVE TECHNOLOGIES AND PRACTICES IN OPHTHALMOLOGY

Despite the fact that some services are not covered by PMG packages [3], ophthalmic care is still provided in

Ukraine according to modern standards, especially in private facilities that lead in the country in providing ophthalmological services. In one of the interviews of expert 3 practitioner and WHO expert on the fight against blindness in Ukraine, noticed the following: «Our service quality in ophthalmology is already at a high level, both in private and in public clinics, but private ones have slightly more opportunities. If the National Health Service has more funds, they also can cover intraocular lenses, but full or partial reimbursement will not change or encourage the use of the latest technologies. There is a standard - doctors follow it.» In addition, expert 1, a practicing ophthalmic surgeon, said that «Within local public programs, intraocular lenses of average statistical characteristics are purchased. Premium lenses or stigmatic lenses are not covered by government programs or the government budget. This will not increase the use of modern technologies, because we already use the latest practices in Ukraine.»

AVAILABILITY OF ADVANCED OPHTHALMIC MEDICINES (ESPECIALLY FOR THE TREATMENT OF GLAUCOMA)

The Affordable Medicines in Ukraine program is an important initiative aimed at expanding the population's access to vital medicines. By reimbursing the cost of essential medications, the program aims to ease the financial burden on patients, promote equitable care delivery, and improve overall health outcomes [5]. Also, the Affordable Medicines program plays a key role in overcoming systemic barriers to access of vulnerable patients to medicines in Ukraine, contributing to the realization of universal coverage of medical services and promoting social integration and inclusion. The Affordable Medicines Program is already well established, but the list of medicines that are reimbursed is limited, especially for original ophthalmic medicines. All interviewed experts agreed that the program should be expanded to ensure equality and access to effective treatment, especially for glaucoma. «Glaucoma patients should be transferred to government programs so that all necessary eye drops are covered by these programs. It is definitely necessary to expand Affordable Medicines Program and National List, because it is very profitable for the state. The drops are very expensive and elderly people and pensioners cannot afford such treatment. Glaucoma leads to blindness and then to the disability, what is a burden on the state. Patients must be provided with all necessary medications without additional payments. Our market of anti-glaucoma medications is very wide, but all effective ones should definitely be added to the National List, because there are generics and there are original ones, and their effectiveness can be different», - expert 4 sharing thoughts regarding the state Program. Another expert 1 also emphasized that some clinics may allow separate direct purchases of expensive medications that are not included in the Affordable Medicines Program or are unaffordable for vulnerable patients: «In general, few medicines are included in this program for macular dystrophy, including VEGF for retinopathy, because these medicines are expensive. We very occasionally have purchases. For example, last year the "Eye Microsurgery Center" bought about 8,000 VEGF vials and they are secured by the free program for vulnerable patients.»

Addressing the challenges of access to medicines requires a multifaceted approach that includes policy reforms, stakeholder collaboration, and continued investment in health infrastructure and human resources. By overcoming these obstacles, the Affordable Medicines Program can realize its potential to provide equitable access to essential щphthalmological medicines, promote equity in health care and improve the well-being of Ukrainian population.

DISEASE PREVENTION, EARLY DIAGNOSIS AND OPHTHALMIC SCREENING PROGRAMS

Early detection and screening play a key role in health care, especially in the context of disease prevention and treatment. Early detection through screening allows practitioners quickly intervene early to prevent disease development or complications, improve treatment outcomes, and reduce morbidity and mortality. Early detection and screening are cost-effective for the state, as they can lead to significant cost savings for healthcare system by avoiding the need for more extensive and expensive treatments associated with advanced stages of eye disease [2-3]. Preventing disease progression through early intervention reduces healthcare costs associated with hospitalizations, surgeries, long-term care and rehabilitation. Furthermore, screening programs that identify high-risk individuals for preventive intervention are often more cost-effective than treating late-stage eye diseases, in particular, cataract and glaucoma. Some of the ophthalmological screening measures are included in PMG. Thus, the management of NHSU notes: "It is also included in the scope of PMG. We provide this as part of the outpatient package. Another issue if it is currently covered and reimbursed at a needed rate and volume. State medical institutions want to be motivated by providing early detection measures, that is why the rate should be adjusted. Moreover, the scope of providing this detection in the form of screening is already precisely included in specialized medical care

package, it is precisely included in ambulatory medical care package, as part of the PMG specifications."

Also, practicing experts are fully united in the idea of paying more attention to the development of issues of early diagnosis in ophthalmology and better advocacy, as noted by expert 1: «Screening programs are needed, because cataract and glaucoma are the diseases that, in suppressed stages, can carry a social burden for the state and increase disability due to blindness. We have international standards of treatment, including following the rules of primary diagnosis, but perhaps the government and the Ministry of Health should pay more attention to screenings and diagnostics.» The same theses were emphasized by the WHO expert «Early prevention is usually more expensive than treatment. It is very expensive for us [Ukraine], we will not fully cover it [expensive treatment] from the state budget, but screening programs are possible.»

Summing up the experts' reflections on ophthalmic care in Ukraine, they emphasize the resilience of medical workers and the main stakeholders to challenges and the potential for transformational changes through the implementation of modern solutions and the development of a network of professional cooperation between practitioners and state. Addressing systemic barriers, key change reformers can achieve universal access to high-quality ophthalmological care and improve the quality of vision for the population, reducing the social and medical burden.

Ophthalmological care in Ukraine covers a number of key topics, starting from the general organizationn of the healthcare system in Ukraine, the systematic review and implementation of improvements at different levels of medical care, the development of healthcare infrastructure and access to advanced technologies and methods of treatment. Understanding the nuances of these components provides valuable insight into the challenges facing medical practitioners, patients, researchers, and governmental authorities, as well as opportunities for advancement.

Ukraine's health care system has undergone significant reforms in recent years aimed at modernizing infrastructure and improving access to basic ophthalmological services. However, challenges remain, particularly in rural areas where access to ophthalmology care can be limited. For now, the main effort should be to ensure the inclusion of patients by applying the principles of Do No Harm and leaving no one behind. The spread of mobile clinics or mobile health units, the introduction of telemedicine, and partnerships with national non-governmental organizations can serve as such solutions to reach populations that are underserved in hard-to-reach or liberated regions [6]. In addition, there is a need for continued investment in healthcare facilities, equipment and development of qualified human resources to ensure the availability of comprehensive quality ophthalmic services at a broad national level [2].

As expert discussions with practicing ophthalmologists revealed, they face a variety of eye diseases and conditions, including cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration. These conditions not only affect the quality of life of individual patients, but also create significant problems for public health system. Also, the blindness in recent years shows an increase in prevalence in the younger age group, in particular, cataract and glaucoma [4,7], which may increase the social burden among the working population and for the state. Early detection strategies, screening programs, and patient education in the primary medical care level are essential to mitigate the burden of these diseases and prevent irreversible vision loss. There is also a shortage of qualified ophthalmologists who meet the needs of the population, which may indicate an increase in the incidence of ophthalmosurgical diseases and a decrease in the number of primary diagnoses of the population in various types of ophthalmic medical care [8].

Despite limited and sometimes poor resources, Ukrainian ophthalmologists are able to implement technological advances to improve the accuracy of ophthalmological diagnosis and treatment results. Innovations such as optical coherence tomography (OCT), laser-assisted cataract surgery, and minimally invasive glaucoma surgery have improved and innovated the practice of ophthalmology, enabling more accurate diagnosis and personalized treatment plans that are more patient centralized and focused on the individual patient's health improvement. However, the implementation of these innovative approaches and technologies, their quality of implementation and access to them may differ in different regions of Ukraine, which emphasizes the need for a fair distribution of resources in healthcare facilities and continues professional learning of personnel and patients in order to ensure uniform standards of ophthalmological care [2].

It should also be mentioned that joint efforts between scientific and research institutions, healthcare facilities, private business and industry partners are crucial for the implementation of innovations and quality services in ophthalmology in Ukraine. Research covers a wide range of topics, including new early diagnostic and therapeutic approaches, genetic susceptibility to eye diseases, personalized treatment and health financing, providing recommendations for improving the organization of ophthalmological care in the country.

By promoting interdisciplinary cooperation and knowledge exchange, Ukrainian researchers contribute to the global array of ophthalmological knowledge, meeting the specific needs of domestic population.

While Ukraine overcomes (geo)political and military difficulties and economic uncertainty, the future of ophthalmology depends on sustainable growth and development strategies. Investments in education, training and professional development are critical to building a skilled workforce capable of meeting evolving healthcare needs. In addition, initiatives to strengthen primary ophthalmological care, integrate ophthalmic services into the primary medical care network, and mainstream preventive interventions that are important to promote lifelong and stable eye health.

CONCLUSIONS

To sum, the field of ophthalmology is poised for transformative advancements and meaningful impact on vision health. Moreover, the field of ophthalmology in Ukraine is characterized by collaboration and use of modern practice, as clinicians, researchers, and industry partners work together to push the boundaries of knowledge and technology. The future holds immense promise for advancements that will revolutionize the practice of ophthalmology and improve patient care.

Despite challenges, ophthalmological care in Ukraine is characterized by resistance to challenges and efforts to implement innovative solutions. Clinicians and practitioners seek to improve diagnostic methods, surgical procedures and patient care protocols, and monitoring measures to monitor services and support provided to patients. In addition, the joint efforts of medical professionals, researchers and politicians can contribute to the development and availability of quality ophthalmic services and the dissemination of best practices.

However, amidst the optimism and progress, challenges remain. Access disparities, resource constraints, and the burden of eye diseases continue to pose significant obstacles to achieving universal ophthalmic care coverage and ensuring equitable access to services. Addressing these challenges requires collective governmental and public action, innovative solutions and a commitment to prioritizing eye health on the national agenda.

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REVIEW ARTICLE

CONTENTS

Environmental competencies for healthcare management at a 2nd education level as a component of strategic management

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ABSTRACT

Aim: To present the results of the analysis of educational standards and curricula of the second educational level of training of specialists, who may be managers of healthcare, on the content of the environmental component as an element of strategic management.

Materials and Methods: Content analysis 24 educational standards of the Ministry of Education and Science of Ukraine of Ukraine for 6 fields of knowledge and 200 master's curricula from 87 institutions of higher education of Ukraine.

Conclusions: There is a distribution of basic leadership and management competencies both by types of these competencies and between specialties. The requirements for the inclusion of the environmental component in the framework documents are poorly expressed. The content of environmental issues in the curricula is insufficient.

KEY WORDS: Education Medical, Social Responsibility, Health Personnel, Environmental Health, Leadership

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INTRODUCTION

The integrity of the natural and anthropogenic environment, defined in the OneHealth concept (human-animal-environment), is no longer controversial. Scientists agree that further interdisciplinary interaction will minimize the imbalance of effort that may arise due to the inequality of socio-economic aspects between countries. Without wider involvement of environmental specialists, especially from low-income countries, key areas of attention will be missed [1-3].

Improving the quality of healthcare is a constant challenge, and improving it with the principles of One-Health is a strategic objective. The multidisciplinary approach in healthcare management enables to take into account a greater number of aspects while increasing the coverage of quality medical services [4]. One of the responses to the challenges of environmental change and improving populational health is the education of healthcare professionals [5]. Understanding contexts, system thinking, interdisciplinary cooperation, and rational use of resources are essential for sustainable development [6]. Healthcare workers must not only assist patients and the community but also take into account the environmental determinants of which they are producers [7]. Some organizations note that the health sector is responsible for 4.4% of CO2 emissions, more than half of which comes from the United States, China, and the European Union [8].

The other component of climate change is the waste management. It is established that the healthcare sector contributes 1-2% of all waste. The main producers are hospitals, medical centers, laboratories, etc. [9]. High-income countries predominate in the amount of production of medical waste from beds, over low- and middle-income countries [10]. The last ones prevail in cheaper ways of waste disposal, such as capture, incineration, or storage. The storage takes place in open landfills along with municipal waste, influencing the environment and human and animal health [11, 12].

The same applies to the sustainable use of water resources. Unsustainable water consumption, high concentrations of chemicals, antibiotics, etc. in sewage, and the filtration network inadequacy in combination with the management imperfection of the hospitals lead to the deterioration of human and animal health [13-15].

The need to involve healthcare professionals in the problems of climate change, including the environmental component in healthcare curricula, was highlighted in official statements by the Canadian Medical Association, the American Medical Association, and

the Association of Medical Education in Europe [16-18]. Healthcare leaders should be responsible and have the opportunity to start a movement towards reducing emissions, and improving healthcare delivery while creating economic and environmental benefits.

AIM

To present the results of the analysis of educational standards (ES) and curricula of the second educational level of training of specialists, who may be managers of healthcare, on the content of the environmental component as an element of strategic management.

MATERIALS AND METHODS

The content analysis of ES identified the strategic management competencies, as well as the signs of environmental competencies. The content analysis of curricula shows subjects that can contain environmental knowledge.

Analyzed 24 ES for 6 fields of knowledge of the Ministry of Education and Science of Ukraine and 200 Master's curricula (accreditated by the National Agency for Higher Education Quality Assurance of Ukraine) from 87 institutions of higher education in Ukraine for Specialties that can occupy the position of Head of healthcare facilities of Ukraine according to the Order of the Ministry of Health of Ukraine of 29.03.2002 No. 117.

22 «Health»: 221 Dentistry, 222 Medicine, 223 Nursing, 224 Medical Diagnostics and Treatment Technologies, 225 Medical Psychology, 226 Pharmacy, Industrial Pharmacies, 227 Physical Therapy, Ergotherapy, 229 Public Health; 07 «Management and Administration»: 071 Accounting and Taxation, 072 Finance, Banking and Insurance, 073 Management, 075 Marketing, 076 Entrepreneurship, Trade and Exchange Activities; 28 «Public Administration»: 281 «Public Administration «; 08 «Law»: 081 «Law»; 05 «Social and Behavioral Sciences»: 051 Economics, 052 Political Science, 053 Psychology, 054 Sociology; 03 «Humanitarian Sciences»: 031 Religious Sciences, 032 History and Archaeology, 033 Philosophy, 034 Culturology, 035 Philology.

The ES for the specialty 1501 «State Administration» was excluded from the analysis as at the end of 2023 is missing from State Standards.

REVIEW AND DISCUSSION

The ES analysis was carried out based on the manager competencies, which were divided into «strongly expressed» and «mediated». The content analysis of the master's degree ES showed the most direct competencies in the aspects of systemic thinking, strategic planning, and ability to see the prospect, in the standards of specialties: 031, 034, 035, 051, 052, 053, 071, 072, 073, 081, 221, 223, 281. Strong competencies in this unit were chosen: abstract thinking, analysis and synthesis, and the ability to generate new ideas (creativity). Mediated competencies are for example: "to identify and solve problems", "to adapt and act in a new situation", "to apply a creative approach to work in the profession", "to solve the problems of forecasting development processes", etc.

As for the competencies that involve the ability to form a goal, communicate it to the team, and bring people together, they are not identified in 052, 075, 223, 224, 225. The strong competencies in this area are found in 051, 073, 076: "to motivate people and move towards a common goal". Mediated competencies are formulated in the following form: "to communicate with representatives of other professional groups of different levels", "to organize professional development of specialists", "appreciation and respect for diversity and multiculturalism", "awareness of equal opportunities and gender problems", etc. The combination of strong and mediated competencies is most strongly expressed in 053, 071, 229.

To implement effective management, the manager needs to be able to work in a team, develop and manage projects, based on informed decisions. The content of project management competencies and the ability to work in a team in the ES of a Master's degree is strongly expressed in 075, 225, 227, 229: "to develop projects, manage them, show initiative and entrepreneurship", "to manage work or processes", "to make informed decisions", "to work in a team", mediated expressed in the formulations: "insistence on the tasks and responsibilities taken", "to adapt and act in a new situation", " to evaluate and ensure the quality of the work performed", etc.

Concerning the last block: the ability to self-development and work autonomously ("working independently" "capability for self-development, lifelong learning, and effective self-management"), as an element of self-discipline, such skills were identified only in 7 Specialties: 031, 032, 035, 054, 224, 227, and skills to self-development will receive Masters in 073.

In the context of this article, it is important to include the environmental component in the process of training specialists. Such aspects have been identified in 7 specialties, in professional competencies, one specialty in general competencies, as well as in the normative content of the program:

- 054 normative content: "develop and implement social and interdisciplinary projects taking into account... environmental and other aspects of life".

- 221
- general: «to preserve the environment»;
- professional: «to assess the impact of the disease on the health of the population…»;
- normative content: «to evaluate the impact of the environment on the public health…».
- 222
- professional: «to assess the impact of the environment… determinants on the individual, family, public health «;
- normative content: «to assess the influence of environment on human health to evaluate the morbidity», «to organize the necessary level of individual safety … in typical hazardous situations …».
- 224
- professional: to evaluate the safety and compliance with the requirements of the sanitary legislation of Ukraine, according to the results of health and hygiene studies of environmental … factors";
- normative content: «to assess the impact of the environment determinants on the public health».
- 226 normative content: «to predict and determine the impact of environmental factors on the quality and consumer characteristics of medicines …"
- 229
- professional: «to assess risks and justify appropriate actions in response to emergencies in the field of public health»;
- normative content: «to formulate conclusions, develop forecasts and conduct an analysis of the impact of determinants on public health (… environmental); "to determine the needs of different groups of the population concerning health, based on information obtained from the systems of epidemiological surveillance», etc.
- 281 professional: "the ability to identify sustainable development indicators at the higher, central, regional, local and organizational levels".

As for the availability of elements of environmental education, approximately 200 master's curricula have been analyzed.

38 master's curricula were presented in the field 28, specialty 281. In 12 curricula, there were 16 subjects (7 were elective) that can be attributed to the environmental education component of future healthcare managers.

Of the 168 curricula of field 07, 25 master's programs of Specialty 071 were presented. In 6 programs were 9 subjects, which can be attributed to the component of environmental education of future managers (4 selective).

In specialty 072 features of environmental competencies are noted in 6 of 32 master's curricula (1 of 9 subjects - selective).

The largest number of accredited master's programs was in specialty 073. 21 of 59 curricula enclosed 28 subjects covering the component of environmental education (15 selective).

In specialty 075 (21 curricula in total) and 076 (25 programs), the component of environmental education was identified in 11 curricula (1 of 11 subjects - elective) and 14 programs (8 of 18 subjects - elective).

The directions of the subjects were: sustainable development, environmental security, social responsibility, emergency management, civil protection, and labor protection in interpretations that are close to one or another specialty. For example, some specific formulations: European integration and sustainability, State management of environmental use, Sustainable development and national security in the context of Euro-Atlantic integration, State policy in the area of ecological security, Emergency Management, Ecological safety, Environmental accounting and auditing, etc.

The University's autonomy and the absence of a strong requirement for manager competencies lead to a different list of management skills among specialists with different basic education, which is shown in this study. Therefore, the acquisition of additional qualifications, and the need to modernize the training of managers, encourages them to engage in additional continuous education at the postgraduate level, which should contain elements of environmental education.

The development of leadership and management competencies in the general healthcare workers' training should focus on the specific competencies of the manager. For example, the National Health Service of Great Britain has developed a Healthcare Leadership Model, which consists of nine basic parameters that can be compared with the basic parameters of our study. Another model presented by the researchers determines the competencies for the senior and middle management staff of hospitals [19, 20].

The results of the study indicate the heterogeneity of the inclusion of management competencies In the ES, especially in the unit of autonomous work, self-development, and self-discipline. Most ES mostly focus on project management and teamwork skills, as well as motivation and communication skills. However, even they are not expressed in all standards equally or equally strongly. The competencies of strategic management and system thinking are considered to be expressed on average.

The inequality of the inclusion of different leadership and management competencies in the training programs are noted by other researchers, in particular at the undergraduate level and higher educational levels

[21, 22]. Interesting is the fact that medical specialists in low- and middle-income countries are more likely to take executive training courses than doctors in high-incoming countries [23].

In addition to management qualities, we are interested in environmental education. This component is poorly presented in ES and therefore can be poorly expressed in the training programs. Only in 7 of the 24 ES were identified signs of environmental training [24].

In addition to the ES as framework documents, we also analyzed the curricula. Not everyone had topics that related to environmental education. The main areas of the subjects were: sustainable development, environmental security, social responsibility, emergency management, civil protection, and labor protection in interpretations that are close to one or another specialty. While sustainable development, environmental safety, and even social responsibility consider themes that broadly highlight the environmental direction, civil protection and occupational safety usually express the ecological component weaker. Most of these subjects are mandatory professional or general. Only in specialty 073 the majority of ecological subjects are selective.

Despite the challenges of climate change, anthropogenic pollution, and increasing environmental health needs, researchers note insufficient coverage of this topic in the training of future health workers [17]. Others note the insufficient awareness of educators on climate change, One Health and environmental sciences, and talk about the need to develop such skills in the scientific and pedagogical staff, because there is a positive correlation between the inclusion of environmental components in education and the change of behavioral factors, the ability of communities to solve environmental problems, inclusion in environmental actions and actions [25, 26]. As for environmental education for healthcare workers, there are approaches and researchers note the need to include this component in the educational process, especially the leaders of the medical industry [27, 5, 6].

Since medical specialties need to pass the Specialization «Organization and management of healthcare», to take the position of Head of healthcare facilities in Ukraine, analysis of the presence of an environmental component in these programs is the object of further study.

CONCLUSIONS

The analysis showed the uneven distribution of basic leadership and management competencies both by types of these competencies and between specialties. The requirements for the inclusion of the environmental component expressed weak, in most ES they are not contained at all, in some indirectly and in a small amount. The trend of inclusion of environmental subjects in the Master's programs is not widespread. Main topics: sustainable development, environmental security, social responsibility, emergency management. Most of these subjects are assigned to compulsory professional or general disciplines.

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REVIEW ARTICLE

CONTENTS

Current challenges in the healthcare sector and respective response measures

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ABSTRACT

Aim: To improve the classification of current challenges in the healthcare sector and specify the areas of appropriate response measures.

Materials and Methods: The work uses a systematic approach that enables the analysis of the study of individual challenges in the field of healthcare. The following scientific methods were used: analysis; dialectic; specification.

Conclusions: The classification of current challenges and mechanisms for responding to them in the field of healthcare has been improved according. Each of these areas of response to healthcare challenges is to some extent interrelated and therefore has a synergistic effect.

KEY WORDS: public health, social development, COVID-19, healthcare reform, areas of response

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INTRODUCTION

The scale of everyday priorities of the majority of the population is traditionally dominated by preserving life, ensuring safety, creating comfortable living conditions, caring for loved ones, as well as personal and professional development. For all this to become a reality, not only funds are needed, but also health – "which should be understood as reasoned judgments about the parameters of physical, mental, and social aspects of the state of a living organism, which largely determine its capabilities and place in the hierarchy among its peers" . Since health (like other values) needs to be "protected," states form and develop national healthcare systems. Despite their specificity, each system faces certain challenges that require an appropriate response. The key to this is the scientific substantiation of existing challenges in this area. The above-mentioned determines the relevance of this research.

AIM

The aim is to improve the classification of current challenges in the healthcare sector and specify the respective response measures.

MATERIALS AND METHODS

The paper uses a systematic approach that enables the analysis of the work of leading scholars who have studied current individual challenges in the healthcare sector. The empirical study was conducted in compliance with the principles of comprehensiveness, validity, and impartiality. The following scientific methods were used: *analysis* – to study the healthcare sector as a whole and its individual components; *dialectic* – to explain the relationship between social processes and challenges in the healthcare sector; *specification* – to study trends of major changes in this sector under the influence of current challenges.

REVIEW AND DISCUSSION

The generalisation of publications on this issue [1-20] and the results of the authors' own research helped to improve the classification of current healthcare challenges and respective response measures with a focus on the following criteria:

– *type* (problems, opportunities; medical, economic, social, psychological...);
– *level* (global, national, regional, local, individual);
– *origin* (internal, external; inherited, acquired);
– *field of manifestation* (healthcare, politics, economy, demography...);
– *form of manifestation* (aging of the nation, emergencies (COVID-19 pandemic), martial law, healthcare reform...);
– *consequences* (positive, negative; short-, medium- and long-term; medical, economic, social, political...);
– *response entities* (authorised public administration bodies, staff of healthcare facilities (HCF), representatives of related businesses, and the public);

– *response objectives* (prevention of threats, localisation of problems, elimination of their consequences, restoration of normal operation; utilisation and/or creation of opportunities, taking advantage of them);
– *response mechanisms* (administrative, economic, organisational, legal, psychological).

It is worth noting that most of today's challenges in the field of healthcare are interrelated, as they can:
– *condition each other: insufficient resource provision of HCF* – limited ability to generate income *(*both from the provision of paid medical services and from interaction with the National Healthcare Service of Ukraine as part of guaranteed medical care packages) – lack of funds for updating the material base of HCF and incentivise their staff;
– *overlap*: the continuous healthcare reform in Ukraine first in the context of the COVID-19 pandemic and later despite the full-scale military aggression of the Russian Federation;
– *replace one another*: interaction with the authorised public administration bodies on budget financing of healthcare facilities – autonomisation and commercialisation of their activities.

At the same time, these challenges are perceived differently by different actors. For example, the COVID-19 pandemic is mostly a significant problem for HCF, as it has led to higher costs and more complicated procedures for providing medical care (primarily due to epidemiological restrictions); however, COVID-19 is an opportunity for manufacturers of medical products (in particular, personal protective equipment, disinfectants, etc.), which have seen their revenues increase sharply due to extremely favourable market conditions. The same applies to the situation when, due to the optimisation of the healthcare network (including the closure of individual departments or HCF as a whole), patients (especially in rural areas) are forced to travel longer distances to receive medical care, while HCF in adjacent areas receive additional income. At the same time, there are many who do not recognise the lost "opportunity" as a "problem."

To minimise the negative and maximise the positive consequences, it is necessary to ensure that these challenges are appropriately addressed. In particular, when it comes to an individual, self-management is primarily used; when it comes to specific enterprises, administrative management is used; and when it comes to a particular industry/sector of the national economy, public management is used. The specifics of addressing the challenges in the healthcare sector are determined by their level: at the individual level, it all boils down to the degree of concern of the population (primarily of a particular person and his/her family) for their own health; at the local level, it is the redistribution of healthcare resources, depending on changes in the epidemiological situation and/or the market conditions for healthcare services; at the local (regional, national, global) level – targeted actions of authorised public administration bodies that respond to public demands related to existing and potential problems with public health and/or healthcare development within their competence.

The scientific community is characterised by the prioritisation of current healthcare challenges, primarily depending on their social significance. Most likely for this reason, the majority of recent publications have been devoted to the COVID-19 pandemic, which has generated four interrelated crises in this system that reveal and complicate its underlying problems and, coincidentally, point the way to reforms that could improve the ability not only to cope with possible future epidemics but also to meet the basic health needs of the population [4]. At the same time, the scientific debate has largely centred on the choice of priority areas and mechanisms for responding to the challenge posed by the COVID-19 pandemic.

The first such area was, in fact, national healthcare systems, as they were unable to cope with the abnormally large flow of "complex" patients who required immediate (and oftentimes complex) treatment. Thus governments were forced to ensure the sustainability of the healthcare system by establishing interaction in time and space between its micro-, meso- and macro-levels [3]. At the same time, governments' responses have largely focused on coordination through local health systems that rapidly adapt services and rely on expanding the roles of frontline workers [18], and have focused on recovery and reliability, but have paid less attention to sustainable adaptation, smooth scalability, monitoring, forecasting, and learning [3]. The ministries of health, together with the authorised local public authorities and representatives of HCF, were forced to take the following measures: develop, approve, and follow protocols for the treatment of patients with COVID-19; "forced to reorganise HCF" [13], which included a significant expansion of infectious disease beds, as well as the allocation of "red" (for infected patients and personnel who provided them with medical care) and "white" zones (for departments that continued to operate in compliance with the relevant requirements); approval of patient routes; provision of doctors, medical staff, and patients with everything they need (personal protective gear, medicines and equipment (in particular, the number of "oxygen points" has been significantly increased)); changes to the working conditions of doctors and medical personnel in the "red zones" (including a significant increase in their remuneration); mass vaccination of the population; introduction of restrictions on the provision of "planned" medical services by HCF; "development of Internet hospitals" [14], "further digitalisation of the healthcare sector, expansion of telemedicine and remote patient monitoring systems" [7], as well as "artificial intelligence" [14, 16] and "machine learning" [16]; organisation of training of healthcare personnel and exchange of experience... However, the effectiveness of the measures taken to combat COVID-19 was below the desired

level due to the following: insufficient resource provision of healthcare facilities; "burnout, physical and psychological disorders of doctors and medical staff" [18] due to their unpreparedness for such challenges; unwillingness of the population to comply with epidemiological restrictions; existing disproportions in the population's access to specialised medical care depending on the territory of residence, due to the lack of "insurance policies, racial and ethnic differences" [4], "belonging to marginalised, minoritized and low-income groups" [12], etc. In addition, the introduction of innovations, healthcare delivery, and other responses has been hampered by information asymmetries in crises and severe constraints on public services [15], as well as by the lack of a comprehensive, interdisciplinary understanding of how healthcare systems successfully respond to infectious agents [2].

The second area of response to the challenges posed by COVID-19 was society and the economy: allocating additional funding for the purchase of medical supplies, vaccines, etc.; providing benefits to manufacturers and/or suppliers of such goods, as well as to those businesses that have directly lost revenue due to mass diseases and restrictions; conducting public awareness campaigns on the need for vaccination; ensuring compliance with epidemiological requirements at enterprises and public places; imposing restrictions on the movement of the population and medical goods between territories...

The third area of influence is responding to "combined" challenges: "the dual epidemic of COVID-19 and Ebola in the Democratic Republic of the Congo" [14], i.e. situations where it is necessary to respond to challenges that are superimposed on each other; "the needs of modern elderly people" [20], which is consistent with the global trend of "ageing of nations"; health needs of civilians (women, children and adolescents) during the military conflict in Syria [2], which implies the need to address numerous medical, social, humanitarian and other problems (in particular, the destruction of HCF, reduction of its staff...).

It should be agreed that "the COVID-19 pandemic should push governments and scientists to reform national health systems" [4], ensuring their "resilience to such and similar challenges" [19], which involves anticipating threats and securing resources, responding appropriately to uncertainty and anticipating side effects, monitoring critical indicators to assess progress, and learning from practice [10]. This demands adherence to the following principles: "capture, analyze, and act on information in real-time; innovate, try new methods, and learn quickly from mistakes; incorporate anticipatory and proactive measures; possess a flexible organizational structure; maintain open lines of communication within and across functional units; respect personnel at all levels; maintain sufficient personnel, supplies, and resources to effectively respond to the crisis" [5]. Ultimately, all this will provide the population with access to quality healthcare, and the staff of HCF with appropriate (in particular, safe) working conditions and a fair level of pay.

CONCLUSIONS

The classification of current challenges and mechanisms for responding to them in the field of healthcare has been improved according to the following criteria: type, level, origin, area of manifestation, form of manifestation, consequences, responders, response objectives, and response mechanisms. Each of these areas of response to healthcare challenges is to some extent interrelated and therefore has a synergistic effect. The continuation of scientific research on this issue will contribute to the further development of the national healthcare sector, e.g., by improving the public management of this component of the national economy under martial law.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ABSTRACT BOOK

CONTENTS

SCIENTIFIC AND PRACTICAL CONFERENCE WITH INTERNATIONAL PARTICIPATION DEDICATED TO THE WORLD HEALTH DAY 2024 «MY HEALTH, MY RIGHT»

APRIL 5, 2024, BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

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Analysis of the dynamics of the medical consequences of the accident at the chernobyl nuclear power plant

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ABSTRACT

Introduction: This year, 38 years have passed since the accident at the Chornobyl nuclear power plant (ChNPP), the largest man-made disaster in the history of mankind. Monitoring of medical consequences, along with ecological and socio-economic consequences of the accident, continues. The situation that developed after the accident at the ChNPP is unique, as there is an opportunity to observe the impact of small doses of radiation on the health of a large contingent of the population living in a large area and for a long time. Immediately after the accident, a medical register of victims was formed, consisting of four groups: 1 - liquidators, II - evacuees, III - living in the territories of radio-ecological contamination, and IV - persons born to parents of groups 1-3. Subsequently, individuals of the IV group themselves became parents. Therefore, a new V group was formed - children born to parents of the IV group, in fact, the third generation of victims.

Aim: is to study the dynamics of the state of health of the Ukrainian population affected by an accident at the Chornobyl nuclear power plant during 2014-2022.

Materials and Methods: The research materials were official statistical data of the Center for Medical Statistics of the Ministry of Health of Ukraine. Medical statistical and analytical methods were used in the research.

Results: In 2022, the number of the affected contingent, which consists of 66.8% of the population living in the territories of radio-ecological pollution, was 2,011,779 and decreased by 31.4% during the studied period. The contingent of victims is present in each of the regions of Ukraine due to migration, but 75% live in the four regions of Ukraine that suffered the most - Kyiv, Zhytomyr, Rivne, and Volyn. Victims of the accident at the ChNPP are subject to annual medical examinations, according to the results of which the percentage of those recognized as sick is 88.57%; in particular, among the children of the V group, they are 71.17%, and then all 100% of liquidators are recognized as sick. The analysis of the prevalence and incidence indicators of the adult affected contingent revealed their positive dynamics in the period 2014-2022. These indicators decreased by 9.8% and 19.7%, and amounted to 2289.9‰ and 493.5‰, respectively. The rate of primary disability also decreased to 14.83 cases per 10,000 of the relevant population (by 37.9%). However, the death rate of victims among the adult population increased by 14.1% and amounted to 23.3‰. For example, by 2022, were 137,095 liquidators left; their number decreased by 23% in almost 10 years, and therefore every fourth liquidator died during this period. Analysis of the health indicators of children, whose specific weight among the contingent of victims is 18.7%, has an even more pronounced positive dynamic. Thus, the prevalence of diseases decreased by 18.0%, incidence - by 19.0%, primary disability - by 16.7%, and the mortality rate of affected children decreased by half. On the one hand, this trend can be explained by the natural decrease in the level of radiation exposure in the environment over time. On the other hand, there is obviously an incomplete record of cases of diseases that are registered upon appeal, and people are unwilling to register their disability, possibly for financial reasons. A more detailed comparative analysis is needed for the health status of certain groups of the affected population, certain classes of diseases, and certain regions, with a mandatory comparison of the obtained indicators with the general ones for adults and children.

Conclusions: The positive dynamics of the health of the population affected by accident at the ChNPP cannot but please, but the dissonance between the decrease in the levels of the vast majority of indicators and the increase in the share of patients among those examined, especially in relation to the adult population, is alarming.

KEY WORDS: population health, morbidity, disability, mortality, radiation exposure

Analysis of valuations of the accessibility and quality of mental health care in the conditions of the coronavirus disease pandemic and during state of war

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ABSTRACT

Introduction: Mental health care is an important component of the health care system. The quality and accessibility of appropriate care are important indicators of the system's activity under the influence of extreme risks. Therefore, within the framework of sociological surveys within the framework of the PsyCare-Kyiv Region project of the Ukrainian Association of Doctors-Psychologists regarding the state of the mental health system of Kyiv city and the Kyiv region, respondents' valuations of the accessibility and quality of mental health care for patients in the conditions of the COVID-19 pandemic and during state of war were studied.

Aim: To carry out a comparative analysis of the impact of extreme risks in the conditions of the COVID-19 pandemic and during state of war on the accessibility and quality of mental health care on the example of the Kyiv city and the Kyiv region.

Materials and Methods: Epidemiological, sociological, medical-statistical methods, including correlation analysis by calculating Spearman's rank correlation coefficient (Rho), Kendall's rank correlation coefficient (Tau), rank Gamma correlation coefficient. Statistical processing of research materials was carried out using methods of biostatistical analysis implemented in Microsoft Excel 2016 and Biostat, AnalystSoft Inc. Version 7.3, software packages.

Results: In the Kyiv region, 315 respondents were interviewed, of which 69.8% were educators, 16.5% were representatives of the social sphere, 13% were specialists in health care institutions, and 0.6% were representatives of the non-governmental sector.

Evaluating on a scale from 1 to 7 points whether the quality of mental health care for patients has undergone changes in the conditions of the COVID-19 pandemic, the respondents gave an estimate of 4.0 ± 1.2 points, accessibility in the same conditions - at 4, 2±1.2 points. Similar valuations in the conditions of state of war were 4.6 ± 1.4 points for the quality of assistance, accessibility - 4.9 ± 1.4 points.

In the Kyiv city, 206 respondents were interviewed, of which 52.4% were educators, 29.6% were health care professionals, 17.5% were representatives of the social sphere, and 0.5% were representatives of the non-governmental sector.

Evaluating on a scale from 1 to 7 points, whether the quality of mental health care for patients has undergone changes in the conditions of the COVID-19 pandemic, the respondents gave an estimate of 4.2±1.3 points, accessibility in the same conditions – at 4.2±1.3 points. Analogous evaluation in conditions of state of war was drafted of quality granting assistance 4.8±1.5 points, accessibility - 4.8±1.4 points.

Correlation analysis proved the presence of a strong direct correlation between the valuations of changes in the quality of mental health care provided to patients in the conditions of the COVID-19 pandemic and during state of war (Kyiv region: Rho =0.611, Tau =0.558, Gamma=0.669, p< 0.05; Kyiv city: Rho =0.584, Tau =0.522, Gamma=0.644, p<0.05) and between the valuations of changes in the accessibility of mental health care to patients in the conditions of the COVID-19 pandemic and during state of war (Kyiv region: Rho =0.596, Tau =0.564, Gamma=0.670, p<0.05; Kyiv city: Rho =0.602, Tau = 0.539, Gamma=0.657, p<0.05).

Conclusions: The problems of the organization of mental health care, manifested during the fight against the COVID-19 pandemic, have deepened in the conditions of martial law and the emergence of challenges related to full-scale war, and require a systemic organizational solution.

KEY WORDS: Mental health, health services and mental health administration, health care quality assessment, accessibility of health services, COVID-19

Artificial intelligence potential in the acceleration of healthcare system digital transformation according to the patient-centric model

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ABSTRACT

Introduction: Artificial intelligence (AI) is revolutionizing healthcare, and its impact on digital health and eHealth programs is becoming increasingly significant due to the acceleration of digital transformation according to the patient-centric model. In many countries, Digital Health and eHealth are the primary tools for managing healthcare costs and accumulating patient health information. AI can potentially transform digital health services by making them more efficient, accessible, and personalized.

Aim: To analyze the current trends of AI in optimizing the processes of working with Digital Health and eHealth data to achieve better healthcare outcomes and facilitate digital transformation according to the patient-centric model.

Material and Methods: Scientific publications on using AI in Digital Health and eHealth were analyzed in PubMed, ScienceDirect, Springer, and Google Scholar. From 2019 to February 2024, a bibliographic analysis of indexed publications in PubMed was performed using the VOS viewer service. WHO normative documents on AI in health care were analyzed.

Results: Based on the bibliographic analysis, visualization maps were built, reflecting the interdependence of keywords in 471 publications indexed in PubMed by the query "artificial intelligence AND electronic health". 10 main clusters between the most used keywords from the selected research topic were identified. The main clusters that reflect the integration of AI, Digital Health and eHealth systems include: AI; machine learning; deep learning; electronic health records, ehealth; digital health; telemedicine; mHealth; telehealth; big data; precision medicine.

AI technologies include machine and deep learning, computer vision, and natural language processing. These technologies allow automated processing of various data, interpreting voice commands, analyzing processes, and generating effective solutions when working with data. Integrating AI in Digital Health and eHealth provides automated support and control of the physician's work when entering electronic health records and making decisions about the patient's treatment plan based on the best evidence. This increases the accuracy of diagnostic and treatment appointments, reduces medical errors, and improves the doctor's workflow. A fairly common practice in this direction is using chatbots with AI support as personalized assistants for doctors when working in the Digital Health or eHealth environment. Such chatbots are successfully used to perform various routine tasks of a doctor and are also helpful in monitoring health and mentoring patients.

Developing a patient-centered Digital Health and eHealth model creates prospects for expanded and continuous monitoring of patient health indicators. This can be ensured through mHealth, telemedicine, telehealth, the Internet of medical things, digital twins, etc., and convergent technologies in the healthcare system. Such technological innovations allow, if necessary, to constantly collect and process data on the health of patients using medical wearable devices as personal sensors for monitoring physiological indicators. The successful integration of many biomedical data sources into the AI model is essential in this regard. In addition to data generated from wearable patient devices, multimodal AI solutions can also include individual profile metrics based on genome sequencing, different levels of omics, continuous monitoring of blood biomarkers, metabolites, and more. Applying AI to analyze this multimodal biomedical data is a valuable resource for better diagnostic performance, comprehensive and improved patient care. This creates favorable conditions for applying personalized decision support systems and promotes the implementation of personalized medicine.

Another trend is using one type of generative AI, large multi-modal models (LMMs). Recently, the WHO published guidance on LMMs in health care (2024). LMMs have potential applications in diagnosis and clinical care, patient-centered applications, clerical and administrative tasks, medical and nursing education, scientific research, and drug development.

Conclusions: The considered AI trends contribute to optimizing the processes of working with Digital Health and eHealth data. The use of AI opens up new opportunities for the introduction of precision health and personalized medicine. It contributes to developing a patient-centric health care model and implementing valuable services for patients, such as hospital at home and virtual health coaches, etc., for continuous health care.

KEY WORDS: artificial intelligence, eHealth, electronic health records

The relevance of creating a methodical base of the environmental monitoring national system based on international approaches as a basis for preserving public health

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ABSTRACT

Introduction: Environmental monitoring of pesticides is a crucial component of efficient agricultural practices and environmental protection. Pesticide formulations are designed to control a specific pest, but unintended consequences for beneficial insects, birds, aquatic organisms (non-target species) can be significant. Ecological and biological monitoring aims to understand these ecological interactions and mitigate potential threats to biodiversity. Different countries and regions, including the European Union (EU), use different monitoring strategies. Monitoring of pesticides non-target effects is a critically important aspect of environmental management and public health in Ukraine and the world.

Aim: Assessment of the relevance of creating a methodical base of the environmental monitoring national system based on international approaches as a basis for preserving public health.

Materials and Methods: The following information sources were for analysis: domestic and European regulatory documents and methodological recommendations. We used the methods of empirical and theoretical research of scientific information, namely analysis, synthesis, induction, deduction and systematization.

Results: Currently, Ukraine is at the initial stage of integration of the state system of environmental assessment and monitoring of non-target effects of pesticides with European approaches. State toxicological and hygienic examination of pesticides is carried out by accredited research institutions. The State Food Safety and Consumer Protection Service of Ukraine plays a key role in overseeing pesticide monitoring activities. There is a large scientific and regulatory base for conducting toxicological and hygienic examination and control of pesticides, a system of organizations for study, pre-registration tests and post-registration monitoring is functioning.

For ecological and hygienic monitoring, everything is limited to a pre-registration assessment. Ukrainian research institutions, such as the Plant Protection Institute of the National Academy of Agrarian Sciences and other accredited scientific institutions, conduct research on the environmental impact of pesticides on non-target organisms, providing valuable data for regulatory decisions. However, post-registration assessment, control and monitoring are actually not provided for. Only in cases of emergency, such as bee poisoning, etc., research is conducted. But they are, of course, one-time and do not give an idea about the circulation of a certain pesticide in the environment or the long-term, cumulative effect on non-target species.

In the EU, USA and other countries, there are approaches to post-registration studies: studying the dynamics of the pesticides active ingredients concentrations in water, soil, air, plants; study of residues in insects, soil organisms; observation of the behavior and state of health of birds, fish, aquatic invertebrates, non-target insects, etc., which live in areas of active agricultural production using chemical plant protection technologies.

These approaches, with appropriate modification to domestic conditions, must be integrated into the Ukrainian system of ecological and hygienic assessment and monitoring.

Conclusions: It is important to implement in Ukraine world-class approaches to post-registration ecological and hygienic monitoring and control, to prevent the accumulation of pesticides, the remote consequences of their impact on the ecosystem, and subsequently on human health, the possibility of timely response to changes in the state of animal, bird, and insect populations, the state of the water, soil and air environment.

KEY WORDS: Ecological monitoring, pesticides, population health

Epidemiological characteristics of scarlet fever in Ukraine

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ABSTRACT

Introduction: Scarlet fever is an infectious disease caused by the bacterium Streptococcus pyogenes, also known as group A streptococcus. Recovered scarlet fever can lead to dangerous complications such as sinusitis, otitis, myocarditis, nephritis, and others. Scarlet fever is primarily transmitted through airborne droplets. According to literature data, the basic reproductive number for scarlet fever is 5-8 (Yiman Geng, Leiliang Zhang, 2022). This means that each person with scarlet fever can potentially infect 5 to 8 other individuals in the susceptible population. Infectious diseases with such values of the basic reproductive number spread quite easily and can lead to outbreaks or epidemics if not controlled. Knowledge of the epidemiological situation regarding scarlet fever in Ukraine is crucial for the prevention and control of this disease.

Aim: To clarify the epidemiological characteristics of scarlet fever in Ukraine for the years 2018-2023.

Materials and Methods: A retrospective epidemiological analysis was used to describe and assess the spread of scarlet fever for the years 2018-2023 in Ukraine using Form No. 2 (annual reporting) "Report on certain infectious and parasitic diseases."

Results: The average incidence rate of scarlet fever during 2018-2023 was 14.0 per 100,000 population. During the period from 2020 to 2022, the average incidence rate of scarlet fever was 6.6 per 100,000 population. It is necessary to note that restrictive preventive measures were introduced due to the COVID-19 pandemic from March 2020 to 2022. After the lifting of quarantine measures regarding COVID-19 worldwide, including Ukraine, there was a resurgence in the level of infectious diseases. Regarding scarlet fever: during periods when quarantine restrictions were not yet implemented and when they were already lifted, the average incidence rate of scarlet fever was 28.14 per 100,000 population. In 2023, the incidence of scarlet fever is 25.5 per 100,000 population, which corresponds to the overall trend of scarlet fever incidence and does not exceed the average multi-year indicator. In the age structure of the incidence of scarlet fever, children account for 98% of cases. The highest incidence is observed in children aged 5-9 years and 1-4 years, reaching 172.6 and 138.9 per 100,000 population, respectively, which is more than 10 times higher than the incidence in other age groups. Thus, children aged 1 to 9 years are at risk group for scarlet fever. The highest number of scarlet fever cases in 2023 in Ukraine was registered in the cities of Kyiv, Ivano-Frankivsk, Zhytomyr, Rivne, and Lviv regions. Over the period from 2018 to 2022, the "leading" regions in terms of scarlet fever incidence were Rivne, Volyn, and Zaporizhzhia regions. The incidence of scarlet fever in cities is 2.25 times higher than in rural areas, which almost reflects the predominance of scarlet fever incidence among the child population in cities compared to the incidence among children in rural areas - 2.6 times higher. In 2023, scarlet fever incidence is observed throughout the year, but an increase in cases is recorded in the autumn-winter period.

Conclusions: Scarlet fever is not subject to controlled immunoprophylaxis measures for infectious diseases; it remains a childhood infection. This infectious disease can be prevented by adhering to preventive measures and timely implementation of anti-epidemic measures. The age distribution shows that the highest incidence is registered among children aged up to 9 years attending preschool and general educational institutions. Scarlet fever can spread in childcare or educational institutions through close contact among children. It is necessary to encourage children and adults to cover their mouth and nose with a tissue when coughing or sneezing, as well as to wash hands after coughing, sneezing, or using tissues, that is, to observe cough etiquette, personal hygiene practices, and regularly ventilate premises. The predominance of morbidity in urban areas compared to rural areas is likely associated with a higher frequency of seeking medical care specifically in cities. It remains necessary to monitor the incidence of scarlet fever by regions of Ukraine.

KEY WORDS: scarlet fever, incidence, age distribution, urban-rural differences

Trends in acute myocardial infarction incidence under the influence of emergency situations

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ABSTRACT

Introduction: Despite advances in the diagnosis and treatment of acute myocardial infarction (MI), it continues to be a pathology associated with mortality and disability among patients with cardiovascular diseases. In recent years, under the influence of emergency situations, the incidence of MI may have increased.

Aim: To assess the trends in the incidence of MI during the years 2019-2023 at both national and regional levels in Ukraine.

Materials and Methods: The study utilized data from the Public Health Center of the Ministry of Health of Ukraine regarding the level of hospitalized patients due to AMI and mortality rates in Ukraine and Ternopil region for the period 2019-2023. The research employed a systemic analysis method and statistical research methods.

Results: During the period 2019-2023, the population of Ukraine was significantly affected by adverse factors of emergency situations. These factors play a significant role in the risk of developing MI, particularly the impact of coronavirus infection on blood coagulation system disorders, psychosocial stress, and worsening ecological conditions.

Taking into account these peculiarities, we conducted an analysis of hospitalization rates for MI during the period 2019-2023 at both national and regional levels. Hospitalization rates in Ukraine decreased from 137.6 in 2019 to 122.4 in 2022 per 100,000 population. The mortality rate ranged from 13.8% to 15.9%, with the highest level observed in 2021. There is an increasing proportion of patients with ST segment elevation myocardial infarction (STEMI) among all patients from 67.3% to 70.6% over the study period. Hospitalization rates for STEMI in Ukraine decreased from 92.6 in 2019 to 86.4 in 2022 per 100,000 population. Mortality from this form of MI ranged from 15.4% to 17.9%, with the highest level also in 2021.

In Ternopil region, hospitalization rates for MI increased from 92.8 in 2019 to 116.5 in 2022 per 100,000 population. The mortality rate ranged from 12.5% to 14.5%. The proportion of patients with STEMI among all patients ranged from 56.4% to 70.2%. Mortality for this form of MI ranged from 11.4% to 15.9%, with the highest level also in 2021.

Conclusions: The analysis conducted revealed a decrease in hospitalization rates for MI during the period 2019-2022 at the national level in Ukraine. However, in 2021, there was an increase in mortality from MI overall and in particular STEMI, indicating an increased susceptibility to thromboembolic complications in the cardiovascular system against the backdrop of a high incidence of coronavirus infection. This suggests a possible influence of COVID-19 on the occurrence and more severe course of MI.

KEY WORDS: myocardial infarction, COVID-19 pandemic, incidence

Peculiarities of formulations approved in ukraine to use against «gray rot» in comparison with european formulations

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ABSTRACT

Introduction: Since 2009, new regulations have been introduced in Europe that tighten the requirements for chemical compounds used as pesticides. Considering Ukraine's active course towards joining the European Union, signing agreements on the harmonization of standards and obtaining the status of a candidate for EU membership, all the above-described approaches will gradually be integrated into domestic legislation and agricultural practice. As a result, the range of chemical plant protection products will be significantly reduced. Which, in turn, carries the risk of reduced harvests and a worsening of the world's hunger situation, given the volume of imports from Ukraine and its crop losses during a full-scale invasion. An alternative to chemical plant protection products today are biopesticides, the use of which for plant protection can lead to many positive results, such as reducing pesticide residues in food, thereby reducing the risk to the consumer.

Aim: Assessment of peculiarities of formulations approved in Ukraine to use against "gray rot" and their comparison with European formulations.

Materials and Methods: The following data were used to analyze and compare formulations: List of pesticides and agrochemicals approved for use in Ukraine 2022; EU Pesticides Database; information from the websites of manufacturers and official regulation documents.

Results: Already today, throughout the world, the use of chemicals is the main method of combating plant diseases both before and after harvest. Fungicides used exclusively to control *B. cinerea* account for 10% of the global fungicide market. Several families of synthetic botrycides are used to control plant diseases caused by it. However, resistant strains of *B. cinerea* may exist, as this fungus can generate and accumulate mutations in its genome. In addition, consumers prefer organic products, the production of which does not use pesticides. The use of biopesticide formulations, in particular based on *Bacillus amyloliquefaciens*, is gaining more and more popularity in Europe and the world.

Today, in Ukraine, there are fungicides to combat gray rot. But, to date, there are certain problems with every fungicide against "gray rot" in Ukraine: a long period before harvesting, which significantly exceeds the duration of the therapeutic and protective effect, primarily berries; impossibility of processing before storage; absence of the possibility of processing ripe berries, since they are used raw, without any processing that could reduce pesticide residues; the ban of active substances in the EU, which will potentially lead to their ban in Ukraine in the near future; maximum residue limits (MRLs) values significantly exceed the EU MRLs, which contradicts the requirements of the harmonization of the regulatory framework.

The solution to these problems can be the use of biopesticides. Today in Ukraine there are several drugs recommended for combating gray rot based on *Bacillus amyloliquefaciens*. However, only two of these preparations contain exclusively *Bacillus amyloliquefaciens*, are used on special crops (berries) and are declared by their manufacturers as biofungicides.

Conclusions: It has been established that the only full-fledged alternative to chemical means of plant protection today are biopesticides, the use of which in plant protection systems will reduce pesticide residues in food products, and therefore the risk for the consumer. It is shown that considering the current processes of European integration of Ukraine, which include the harmonization of medical and sanitary standards and the review of the entire base of plant protection products, the development, study and introduction of new biological preparations is an extremely urgent and promising task.

KEY WORDS: Biofungicide, regulations harmonization, "gray rot"

The role of biostatistics in the professional training of future masters of medicine and pharmacy

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ABSTRACT

Introduction: Education has always been at the base of human development and our progress as a society, since it's role is not only limited to ensuring the individual development, but also creating the intellectual and spiritual potential of the country in general. Today, the need to preserve the public health encourages institutions of higher medical education to train personnel, ready to solve various complex tasks of modern medicine. Saying that, the teaching of the course "Biostatistics" is becoming vital and should be a necessary component of curricula, implemented in medical schools.

Aim: Studying of the importance of teaching "Biostatistics" for the formation of professional competencies of future health care professionals in Ukraine.

Materials and Methods: The authors used information-analytical, bibliosemantic and comparative methods during the research.

Results: The first year curriculum of masters's degree in medicine at the Bogomolets National Medical University includes the elective course "Biostatistics", the assessment of which will help the future doctor to master the general basics of statistical science, methodology and practical skills of statistical analysis, actual methods for calculating performance indicators of healthcare institutions, methods for processing social and medical information arrays. There is a wide range of statistical methods, which are used in clinical and preventive medicine by standardising various factors of the working environment, carrying out experimental, clinical and laboratory studies, calculating drug doses, assessing the treatment and prevention effectiveness, etc.

We also studied the perspectives of studying biostatistics by future pharmacists. In some universities, for the specialty 226 "Pharmacy, industrial pharmacy" the future masters of pharmacy may choose elective courses, the purpose of which is to form theoretical knowledge, master practical skills in the use of modern pharmaceutical information systems and the latest applied statistical programs in the field of pharmacy. For example, at the National University of Pharmacy during the first or the second year of study, students have the opportunity to study the course "Statistical Methods in Pharmacy." The elective course "Pharmaceutical Informatics and Statistics" is taught at the Odesa National Medical University. Mastering statistical knowledge will provide students-pharmacists with the necessary professional competencies that might help them use international clinical guidelines and recommendations for evidence-based medicine, independently collect, develop, systematize data from pharmaceutical studies, carry out their statistical analysis, formulate conclusions about the results of the study. At the Bogomolets National Medical University first-year pharmacy students are studying normative course "Higher Mathematics and Statistics," as well as "Information Technologies in Pharmacy," which cover some problems of statistical analysis and data processing.

Conclusions: Having analysed the importance of studying biostatistics for the future healthcare professionals, we sorely advise to introduce the variable discipline "Biostatistics," into the curriculum of master's degree in pharmacy at Bogomolets National Medical University, as it would contribute to the formation of holistic ideas about the realm and introduce the basic concepts for further studying of specialized theoretical and professional disciplines by the students.

KEY WORDS: biostatistics training, preparation of masters in medicine and pharmacy, educational plan, curriculum, competencies formation

The process of differentiation of teaching hygiene disciplines in the first half of the XX century

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ABSTRACT

Introduction: preventive care is an important part of the activities of the national health care system. Its importance has grown over the past two centuries. And this was clearly visible in connection with the pandemic of a new coronavirus disease. In this regard, studying the experience of teaching Hygienic disciplines in higher medical schools is of great interest.

Aim: explore how the differentiation of teaching Hygienic disciplines occurred in the first half of the 20th century using the example of the Odessa Scientific and Medical Center.

Materials and Methods: Materials are published historical sources; method is historical.

Results: The Faculty of Medicine at Odessa University appeared in 1900, and in 1920 the Faculty of Medicine was separated from the university into a separate higher academic institution. In accordance with the general university charter of 1884, there were to be 23 Departments (Professors) at the medical faculty of universities. One of them was "Hygiene and its use: Epidemiology and Medical Police, Medical Statistics, the doctrine of Epizootic Diseases and Veterinary Police." It is necessary to clarify the term "Medical Police" (MP), which has fallen into disuse. MP is an empirical science and subject of teaching about the forms of government activity in the field of health care. For the sake of brevity, we will further refer to this department as the Department of Hygiene. In 1903, the Department of Hygiene at the Faculty of Medicine was organized by Professor G.V. Khlopin (1863-1929); in 1905-1914 this Department was headed by Professor I.I. Kiyanitsin (1855-?), and in 1914-1941, 1944-1952 Professor N.N. Kostyamin (1869-1958). In 1920, Soviet power was established in Odessa. The transformation of the Odessa Scientific and Medical Center began. In 1923, an academic discipline was separated from the Department of Hygiene into a separate Department, which in the charter of 1884 was called "Medical Police", and now, in accordance with German tradition, it began to be called "Social Hygiene". In 1923-1928 the head of this Department was Professor L.V. Gromashevsky (1887-1980), and in 1928-1941, 1944-1963 by Professor I.L. Dailis (1889-1981). (Since 1941, this Department was called the Department of Health Organization). In 1924, the Department of Professional Hygiene (Occupational Hygiene) was separated from the Department of Hygiene, which was jointly headed by Professor N.N. Kostyamin. In 1926-1930 it was headed by Professor M.L. Lewontin (1876-1945); then M.B. Zlatopolsky (1886-?), and in 1937-1941, 1945-1960 by Professor Ya.B. Reznik (1902-1979). The next stage of differentiation in the teaching of Hygienic disciplines began in 1932 in connection with the creation of the Sanitary-hygienic Faculty at the Odessa Medical Institute. In 1932-1941, 1944-1957 the head of the Department of Municipal Hygiene was Professor S.S. Aglitsky (1885-1957). In 1945-1953 the head of the Department of School Hygiene (Hygiene of Children and Adolescents) was Professor L.E. Berestechko (1888-1957). In 1933-1941 and 1944-1962 Professor A.I. Burshtein (1890-1965) was the head of the Department of Food Hygiene.

Conclusions: A periodization of differentiation in the teaching of Hygienic disciplines in the first half of the 20th century is proposed. Three periods have been identified. 1) at the beginning of the century there was one Department of Hygiene; 2) in the first half of the 1920s (since 1923), two Departments were separated from the Department of Hygiene: Social Hygiene and Occupational Hygiene; 3) since 1932, three academic disciplines were separated from the Department of Hygiene, which made up three Departments: Municipal Hygiene, School Hygiene (Hygiene of Children and Adolescents) and Food Hygiene.

KEY WORDS: Hygiene, Social Hygiene (Public Health), Ukraine, 20th century

The influence of structural elements of the daily routine on school-age children's mental health in Ukraine

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ABSTRACT

Introduction: The mental health of school-aged children has been greatly affected by both the COVID-19 pandemic and the ongoing war in Ukraine. Therefore, it is crucial to develop programs that aim to reduce the negative impact of war on children and adolescents, while improving their well-being. To promote the mental well-being of school-age children, it is important to maintain a balance between different activities during the day and getting enough sleep. Therefore, the study of this issue is an urgent problem that needs to be solved.

Aim: This study aimed to assess the impact of 24-hour behavior patterns on the mental health of Ukrainian children and adolescents during wartime.

Materials and Methods: A cross-sectional online survey was conducted in 2022 among parents of Ukrainian children aged 7-18 (n=1243, 51% boys) using the Q-RAPH and RCADS-P-25 questionnaires. The data was analyzed using Compositional Data Analysis (CoDA). The models were adjusted for gender, age, body mass index, and war factors (moving from a permanent place of residence, occupation, unsatisfied basic needs, separation from relatives, shelling and bombing, loss of housing and work, death of relatives or parents).

Results: CoDA analysis revealed significant links between better mental health and higher levels of moderate-to-vigorous physical activity (β=-0.09, $p<0.01$) as well as longer sleep duration (β=-0.15, $p<0.01$). Sedentary behavior was associated with higher depression and anxiety t-scores (β=0.19, $p<0.001$). The war has worsened the negative impact on mental health, with a significant interaction effect ($\beta = 0.23$, $p < 0.001$).

Conclusions: We have found that promoting a balanced daily routine is crucial to maintaining the mental health of children and adolescents, particularly during times of war. Public health policies and school-based programs should include strategies that help improve activity behaviors and mental well-being in this vulnerable population.

KEY WORDS: school-age children, physical activity, sedentary behaviour, sleep, war