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Reaction of coagulopathy markers in patients with long bone fractures in the setting of COVID–19

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Abstracts

Objective. To study the dynamics of the level of the diagnostic marker D–dimer to characterize the course of COVID–19 and early diagnosis of thromboembolic complications in patients with long bone fractures.

Materials and methods. To fulfill the objectives of the study, a retrospective array of 289 patients with skeletal fractures treated at the Kyiv City Clinical Emergency Hospital from March 2020 to February 2021 was formed. The main group included 157 patients with skeletal fractures in the setting of COVID–19, and the control group included 132 patients with skeletal fractures without COVID–19.

Results. On the 1st day of treatment, 45.9% of patients in the main group had high levels of D–dimer, while among patients in the control group such results were recorded more than 4 times less often. Extremely high levels of D–dimer were observed in 26.0% of patients in the main group, and no such patients were found in the control group. On the 3rd day of treatment, 53.5% of patients in the main group had high levels of D–dimer, which was 5.5 times more frequent than in the control group. Extremely high levels of D–dimer were observed in 26.7% of patients in the main group and were not observed in the control group. On the 10th day of treatment, normal and subnormal levels of D–dimer were detected in 44.0% of patients in the main group, but this is more than twice as rare as in the control group. High levels of D–dimer were found in 49.0% of patients in the main group and only 3.0% of patients in the control group.

Conclusions. Initial levels of D–dimer have a prognostic value for detecting thromboembolic complications at the earliest possible time.

Peak D–dimer values are determined on day 3 of treatment and tend to decrease on day 10. High levels of D–dimer in patients with long bone fractures in the setting of COVID–19 have the value of an unfavorable prognostic factor, but this thesis requires additional research.

Key words: venous thromboembolism; complications; diagnosis; polytrauma; COVID–19; fractures; treatment.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS–CoV–2) caused the 2019 Coronavirus Disease (COVID–19), an epidemic outbreak in Wuhan, China, that quickly escalated into a pandemic, with millions of people infected with the virus and billions of people forced to observe social distancing measures. To date, numerous clinical and epidemiological data on COVID–19 have been published, and risk factors for adverse treatment outcomes and prognosis of the disease have been assessed [1].One of the serious complications in patients with COVID–19 is the development of venous and arterial thromboembolism. Venous thromboembolism was first reported in 30% of patients with COVID–19 hospitalized in intensive care units in China and the Netherlands [2]. Intravenous catheter thrombosis and arterial occlusive events, including acute myocardial infarction, acute lower extremity ischemia, and stroke, have been reported in severe COVID–19 patients in the United States, Italy, and France [3]. Kollias and colleagues [4] found that the incidence of deep vein thrombosis and pulmonary embolism in patients with COVID–19 in intensive care units ranged from 0 to 54%.

D–dimer is a product of fibrin breakdown, it contains two combined D–fragments of the fibrinogen protein (hence the name "dimer"), which are present in the blood after the destruction of a blood clot (fibrinolysis), and is widely used to diagnose (exclude) venous thrombosis. In addition, D–dimer is known to have prognostic value in various pathologies, including cancer and cardiovascular disease. When the COVID–19 epidemic caused by SARS CoV–2 began, it became clear that there was a high correlation between the incidence of this infection and the prevalence of thromboembolic complications. Some authors have pointed out the need for timely diagnosis of thromboembolic complications in COVID–19, especially in patients with long bone fractures. However, the diagnosis of complications in COVID–19 can be difficult due to the prolonged course of the disease, during which medical procedures, such as oxygen supply and intubation, mask the signs and symptoms of coagulopathy. The onset and development of complications in patients infected with COVID–19, especially those with limb fractures and impaired motor activity, is an objective process.

The aim of the study is to determine the dynamics of the level of the diagnostic marker D–dimer to characterize the course of COVID–19 and early diagnosis of thromboembolic complications in patients with long bone fractures.

Materials and methods

This retrospective study involved 289 patients with skeletal fractures treated at the Kyiv City Clinical Emergency Hospital from March 2020 to February 2021, who were divided into two groups: the main group and the control group. The main group included 157 (54.3%) patients with skeletal fractures in the setting of COVID, and the control group included 132 (45.7%) patients with skeletal fractures without COVID–19.

In the main group, there were 88 men (56.1%) and 69 women (43.9%). The average age of the patients in the main group was (52.1 ± 8.8) years. In the control group, there were 82 (62.1%) men and 50 (37.9%) women.

For the qualitative diagnosis of the D–dimer reaction in patients with long bone fractures in the setting of COVID–19, its levels were investigated on the 1st, 3rd and 10th day of treatment.

Statistical processing of the data was performed using nonparametric methods. Taking into account the number of features that were analyzed and the need to ensure the uniformity of the performance indicators, the method of calculating the coefficient of polychoric correlation proposed by K. Pearson was chosen for a correct comparison. The protocol and materials of the study were reviewed and approved by the local bioethics committee at the Ukrainian Scientific and Practical Center for Emergency Medical Care and Disaster Medicine of the Ministry of Health of Ukraine (minutes of the meeting № 4 of 16.10.2023). The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patients.

Results

The most common patients in the main group were those with a D–dimer level of 1001 – 1500 ng/ml, accounting for 30.6%, and they occupied the first rank in the distribution (*Table 1)*. In the control group, a similar level of D–dimer was observed in 10.6% of patients, which is almost three times less frequent than in the main group, and they were in the third rank. In 17.8% of patients in the main group, subnormal D–dimer levels of 501–1000 ng/ml were determined, and they were ranked second. In the control group, the number of such patients was almost twice as high – 34.1%, and they also took the second rank.

In 15.3% of patients in the main group, D–dimer levels increased to 1501 – 2000 ng/ml. Patients with such an increase in D–dimer levels in the main group took the third place in the rank distribution. In the control group, patients with a similar level of D–dimer were very rare, accounting for only 0.7%, and they occupied the fourth rank. The fourth rank in the main group was occupied by patients with D–dimer levels of 2001 – 2500 ng/ml. Such levels of D–dimer were observed in 14.0% of patients. In the control group, no such increase in D–dimer levels was detected.

Normal levels of D–dimer were found in 9.5% of patients in the main group, and they were ranked fifth. In the control group, 54.5% of patients had normal D–dimer levels, which was more than 5 times higher than in the main group and ranked them first. The sixth rank in the main group was occupied by patients with a D–dimer level of 2501 – 3000 ng/ml, they accounted for 6.4%. In the control group, no patients with a similar level of D–dimer were found. A high increase in D–dimer levels was observed in 4.4% of patients in the main group. According to the rank distribution, they took the seventh rank. No patients with such a level of D–dimer were found in the control group. In the main group, a critical increase in the level of D–dimer was observed: from 3501 to 4000 ng/ml in 1 (0.6%) and more than 4000 ng/ml in 1 (0.6%) patient. These D–dimer levels placed these pa-

Table 1. **Levels of D-dimer in the blood of patients of the study groups on the 1st day of treatment**

D-dimer level, ng/ml	Patient group					
	basic		rank	control		rank
	abs.	%		abs.	%	
0 - 500	15	9,5	5	72	54,5	1
501 - 1000	28	17,8	2	45	34,1	2
1001 - 1500	47	30,6	1	14	10,6	3
1501 - 2000	26	15,3	3	1	0,7	4
2001 - 2500	22	14,0	4	-	-	-
2501 - 3000	10	6,4	6	-	-	-
3001 - 3500	7	4,4	7	-	-	-
3501 - 4000	1	0,6	8	-	-	-
> 4000	1	0,6	8	-	-	-
In total ...	157	100,0	-	132	100,0	-

Table 2. **Levels of D-dimer in the blood of patients of the study groups on the 3rd day of treatment**

D-dimer level, ng/ml	Patient group					
	basic		rank	control		rank
	abs.	%		abs.	%	
0 - 500	19	12,2	4	87	65,9	1
501 - 1000	12	7,6	5	32	24,2	2
1001 - 1500	55	35,0	1	13	9,8	3
1501 - 2000	29	18,5	2	-	-	-
2001 - 2500	24	15,3	3	-	-	-
2501 - 3000	17	10,8	6	-	-	-
3001 - 3500	1	0,6	7	-	-	-
3501 - 4000	-	-	-	-	-	-
> 4000	-	-	-	-	-	-
In total ...	157	100,0	-	132	100,0	-

Table 3. **Levels of D-dimer in the blood of patients in the study groups on day 10 of treatment**

D-dimer level, ng/ml	Patient group					
	basic		rank	control		rank
	abs.	%		abs.	%	
0 - 500	32	20,4	3	114	86,4	1
501 - 1000	37	23,6	2	14	10,6	2
1001 - 1500	53	33,7	1	4	3,0	3
1501 - 2000	24	15,3	4	-	-	-
2001 - 2500	7	4,5	5	-	-	-
2501 - 3000	5	3,2	6	-	-	-
3001 - 3500	-	-	-	-	-	-
3501 - 4000	-	-	-	-	-	-
> 4000	-	-	-	-	-	-
In total ...	157	100,0	-	132	100,0	-

tients in the last eighth rank. In the control group, no patients with a critical increase in D–dimer levels were found.

Statistical analysis of the data showed that there is a positive, moderate relationship between the studied attributes, and the indicated positions are within the field of probability: χ^2 17.34 ≥ χ^2st 15.5 (p≤ 0.05).

On the 3rd day of treatment, D–dimer levels of 1001 – 1500 ng/ml were most often detected in patients of the main group (*Table 2)*. D–dimer levels within these limits were recorded in 35.0% of patients in the main group. These patients occupied the first rank in the main group. In the control group, patients with D–dimer levels of 1001 – 1500 ng/ml were only 9.8%, which is 3.5 times less than in the main group. In the rank distribution in the control group, these patients occupied the third rank. In 18.5% of patients in the main group, the level of D–dimer was increased to 2000 ng/ml, they occupied the second rank. In the control group, no patients with a similar level of D–dimer were found.

The third rank was occupied by patients with D–dimer levels in the range of 2001 – 2500 ng/ml. Such a D–dimer level was detected in 15.3% of patients in the main group. No such patients were found in the control group. Normal D–dimer levels were observed in 12.2% of patients in the main group. In the rank distribution, these patients occupied the fourth rank. In the control group, normal D–dimer levels were observed in 65.9% of patients, which was more than 5 times more frequent than in the main group and determined the first place in the rank distribution for these patients. Subnormal D–dimer levels were observed in 7.6% of patients in the main group. These patients occupied the fifth rank in the main group. Such a level of D–dimer was found in 24.2% of patients in the control group, which was more than three times more frequent than in the main group. Patients with subnormal levels of D–dimer in the control group were ranked second. Patients

with high levels of D–dimer – up to 3000 ng/ml – took the sixth place in the main group. This level of D–dimer was observed in 10.8% of patients in the main group. In the control group, no patients with such a level of D–dimer were found. In 1 (0.6%) patient of the main group, an extremely high level of D–dimer was detected – up to 3500 ng/ml. This patient was in the last seventh rank position.

According to the statistical analysis of the data, there is a positive, weak relationship between these features, and the indicated positions are within the field of probability: χ^2 15.1 ≥ χ^2st 12.4 (p≤ 0.05).

The analysis of D–dimer values on day 10 of treatment (*Tabl. 3*) showed the following features of patient distribution. In the main group, there were the most patients with D–dimer levels of 1001 – 1500 ng/ml. Such an elevated level of D–dimer was detected in 33.7% of patients in this group. According to the rank distribution in the main group, they were assigned the first place. In the control group, patients with a similar level of D–dimer were also detected, but only 3.0% of them were detected, which is 11 times less than in the main group. In the control group, patients with elevated levels of D–dimer occupied the last third rank.

Subnormal levels of D–dimer were observed in 23.6% of patients in the main group on day 10 of treatment, and they were ranked second. In the control group, 10.6% of patients also had subnormal levels of D–dimer, but this was more than three times less frequent compared to the main group. Despite this, in the rank distribution in the control group, such patients also took the second place.

The third rank in the main group on the 10th day of treatment was occupied by patients with a normal level of D–dimer, 20.4%. At the same time, the control group was dominated by patients with normal D–dimer levels – 86.4%. That is, the proportion of such patients in the control group was more than 4 times higher than the corresponding proportion of patients in the main group, which indicates the existing diagnostic value of this coagulopathy marker. In the rank distribution in the control group, these patients occupied the first rank. The fourth rank in the main group was occupied by patients with a high level of D–dimer – 1501 – 2000 ng/ml. Such a level of D–dimer was found in 15.3% of patients in the main group. There were no patients with high D–dimer levels in the control group.

The fifth rank in the main group was occupied by patients whose D–dimer level reached 2500 ng/ml. There were 4.5% of such patients in the main group. No such patients were found in the control group. Patients with extremely high levels of D–dimer were the least common in the main group, their proportion was 3.2%. Patients with such a level of D–dimer on the 10th day of treatment occupied the last sixth rank in the main group. In the control group, no patients with a similar level of D–dimer were found.

The statistical analysis of the data showed that there is a positive, weak relationship between the studied traits, and the indicated positions are within the field of probability: χ^2 23.12 ≥ χ^2st 11.1 (p≤ 0.05).

Discussion

In patients with bone fractures and COVID–19 infection, the vascular endothelium is damaged, which has a dual nature: both the development of thrombocytopenia with a decrease in anticoagulant levels and activation of hemostasis with the development of thrombotic disseminated intravascular coagulation syndrome (DIC). Due to the fact that D–dimer is a fibrin breakdown product, its amount increases in thrombotic complications, which in turn indicates increased fibrinolysis [5]. Our study showed that on the 1st day of follow–up, normal and subnormal levels of D–dimer were detected in 27.3% of patients in the main group, which is more than three times less frequent than in the control group. D–dimer levels were high in 45.9% of patients in the main group, while among patients in the control group this result was recorded more than 4 times less often. Extremely high levels of D–dimer were observed in 26.0% of patients in the main group, and no such patients were found in the control group. The same data have been published by other authors [6]. According to the results of the study, S. R. Mucha and co–authors [7] determined the threshold value of D–dimer for high–risk patients on the 1st day of treatment as six times its upper limit, i.e. 3000 ng/ml. M. Panigada and colleagues [8] considered a sharp increase in D–dimer levels in the first days after the onset of COVID–19 to be a marker of poor prognosis, which led to patient death.

On day 3, normal and subnormal levels of D–dimer in the main group were detected in 19.8% of patients, which is 4.5 times less frequent than in the control group. In , 53.5% of patients in the main group had high levels of D–dimer, which is 5.5 times more frequent than in the control group. Extremely high levels of D–dimer were observed in 26.7% of patients in the main group and were not observed in the control group. A study by M. Artifoni and colleagues [3], which included 71 patients with COVID–19 associated with thromboembolic complications, showed a positive predictive value of 44 and 67% for D–dimer levels of≥ 1000 and≥ 3000 ng/ml, respectively. S. Cui and colleagues [9] found that such high levels of D–dimer in patients with bone fractures in the setting of COVID–19 are due to activation of the coagulation cascade, which occurs as a secondary effect to the systemic inflammatory response syndrome.

F. A. Klok and colleagues [10] demonstrated the association between high levels of D–dimer and disease severity in 129 patients with COVID–19 who were hospitalized at the Shanghai Public Health Clinical Center. According to the results, the increase in D–dimer levels in mild and se-

vere forms of infection was less than 2000 ng/ml and more than 5000 ng/ml, respectively. P. Demelo–Rodriguez and colleagues [1] also noted the association between the level of D–dimer and the risk of thromboembolic complications in orthopedic patients who did not receive treatment in the intensive care unit. After analyzing data from 156 patients with COVID–19, they found that the level of D–dimer in thromboembolic complications was 4527 ng/ml, and without thromboembolic complications – 2050 ng/ml. The association between D–dimer levels and the risk of pulmonary embolism was confirmed by the studies of I. Leonard–Lorant and co–workers [6]: a D–dimer concentration of more than 2660 μg/L as a marker had a sensitivity of 100% and a specificity of 67%.

Thus, high levels of D–dimer in long bone fractures in the setting of COVID–19 may be associated with persistent coagulation disorders, microthrombotic formations, and pulmonary embolism. Patients who stay in the hospital for a long time may develop refractory hypoxemia, respiratory failure, DIC, or death, which indicates the need for daily assessment of D–dimer levels in severe disease, and anticoagulant therapy should be initiated as soon as possible when D–dimer levels tend to increase.

Prospects for further research include the study of serum markers of inflammation in patients with long bone fractures in the setting of COVID–19.

Conclusions

1. Initial levels of D–dimer have a prognostic value for detecting thromboembolic complications at the earliest possible time.

2. The peak values of D–dimer were detected on the 3rd day of treatment, they tended to decrease on the 10th day of treatment.

3. High levels of D–dimer in patients with bone fractures in the setting of COVID–19 are an unfavorable prognostic factor, but this thesis requires further research.

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Conflict of interest. None.

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