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CLINICAL PORTRAIT OF PATIENTS WITH STAGE II HYPERTENSION AT DIFFERENT LEVELS OF TRANSFORMING GROWTH FACTOR β1 IN BLOOD PLASMA

Abstract. The aim of the study was to determine the clinical portrait of patients with stage II hypertension at different levels of transforming growth factor β1 (TGF-β1) in blood plasma. Echocardiography, Holter electrocardiographic monitoring, stress tests and/or coronary ventriculography were performed in 120 patients (mean age 57.3±0.9 years) to verify the diagnosis of stage II hypertension and concomitant chronic coronary heart disease (CCHD) and frequent ventricular extrasystole (VE). We allocated 4 groups of patients (30 persons in each): Group 1 – stage II hypertension without concomitant CCHD and frequent VE; Group 2 – stage II hypertension with concomitant frequent VE; Group 3 – stage II hypertension with concomitant CCHD; Group 4 – stage II hypertension with concomitant CCHD and frequent VE. Using an enzyme-linked immunosorbent assay with the "Human TGF-β1 (Transforming Growth Factor Beta 1) ELISA Kit" (Elabscience Biotechnology Inc., USA), the concentration of TGF-β1 in blood serum was determined according to the manufacturer's instructions. Microsoft Excel (2019) and Statistica 12.0 (Statsoft, USA) were then used for statistical processing of the obtained results. By the method of variation statistics, the mean plasma concentration of TGF-β1 in the examined patients (n=120) was 9238.3±97.2 pg/mL. The median value was 222.0 pg/mL, and the interquartile range (25th and 75th percentiles) was 165.5 and 303.0 pg/mL, respectively. Taking the median into account, we distinguished groups of patients with a relatively low level (≤222 pg/mL) and a relatively high level (>222 pg/mL) of TGF-β1. It was determined that in 50% of the examined patients the plasma TGF-β1 concentration was 165.5–303.0 pg/mL, in 25% it was below 165.5 pg/mL, and in the remaining 25% it was above 303.0 pg/mL. Moreover, an increase in its concentration was observed from Group 1 to Group 4. Clinical portraits of patients with stage II hypertension and different plasma TGF-β1 levels were determined using discriminant analysis ("Discriminant analysis"). The baseline parameter for the analysis was the mediator level expressed in points,

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where 1 point indicated a relatively low level and 2 points indicated a relatively high level of the hormone for the studied population of patients with stage II hypertension. Before performing discriminant analysis, a preliminary “filtering” of clinical and instrumental indicators (n=76) was carried out using Spearman rank correlation to determine their associations with the plasma hormone level. Indicators that showed a statistically significant ($p<0.05$) rank correlation with the plasma hormone concentration were included in the subsequent discriminant analysis. It was found that in patients with stage II hypertension and plasma TGF-β1 ≥222 pg/mL the following clinical portraits should be expected: 1) the presence of concomitant obesity; 2) the presence of concomitant obesity and angina pectoris without/with frequent VE. In this case, for functional class II angina the minimum number of VE episodes per day is 5000, whereas for functional class III it is 2500 VE episodes per day; 3) the presence of concomitant frequent VE >10,000 VE episodes per day.

Keywords: transforming growth factor-β1, hypertension, chronic coronary disease, ventricular premature beats, discriminant analysis

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КЛІНІЧНИЙ ПОРТРЕТ ПАЦІЄНТІВ ІЗ ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ІІ СТАДІЇ ПРИ РІЗНИХ РІВНЯХ ТРАНСФОРМУЮЧОГО ФАКТОРУ РОСТУ-В1 В ПЛАЗМІ КРОВІ

Анотація. Метою роботи було визначити клінічний портрет пацієнтів із гіпертонічною хворобою ІІ стадії при різних рівнях трансформуючого фактору росту-β1 в плазмі крові. 120 пацієнтам (середній вік - 57,3±0,9 років) проведено ехокардіографію, холтерівського моніторування електрокардіограми, стрес-тести і/або коронаровентрикулографію з метою верифікації діагнозу гіпертонічної хвороби ІІ стадії та супутніх хронічної коронарної хвороби (ХКХ) та частої шлуночкової екстрасистолії (ШЕ). Ми виділили 4 групи пацієнтів по 30 чоловік у кожній: 1 група – із ГХ ІІ стадії без супутніх ХКХ та частої ШЕ; 2 група – пацієнти із ГХ ІІ стадії та супутньою частою ШЕ; 3 група – пацієнти із ГХ ІІ стадії та супутньою ХКХ; 4 група – пацієнти із ГХ ІІ стадії та супутніми ХКХ та частою ШЕ. За допомогою імуноферментного методу із використанням набору «Human TGF-β1 (Transforming Growth Factor Beta 1) ELISA Kit» («Elabscience Biotechnology Inc.», США) визначали концентрацію TGF-β1 в сироватці крові за інструкцією фірми-виробника. Потім використовували програми Microsoft Excel

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(2019) і Statistica 12.0 (Statsoft, USA) для статистичної обробки результатів, які отримали. З використанням методу варіаційної статистики визначено середню концентрацію ТФР-β1 (9238,3±97,2 пг/мл) у плазмі крові в обстежених пацієнтів (n=120). Медіана показника становила 222,0 пг/мл, інтерквартильний розмах (25-й і 75-й персантиль) - 165,5 і 303,0 пг/мл відповідно. Враховуючи показник медіани, нами виділено групи пацієнтів із відносно низьким рівнем (≤222 пг/мл) та відносно високим рівнем (> 222 пг/мл) ТФР-β1. Визначено, що у 50 % обстежених концентрація ТФР-β1 у плазмі крові становила 165,5-303,0 пг/мл, у 25 % пацієнтів - нижче 165,5 пг/мл, а в інших 25 % - вище за 303,0 пг/мл. При чому, збільшення його концентрації спостерігалося від 1-ої до 4-ої групи. Клінічні портрети пацієнтів з ГХ ІІ стадії і різним рівнем ТФР-β1 у плазмі визначали за допомогою дискримінантного аналізу (“Discriminant analysis”). У якості вихідного параметру аналізу був взятий рівень медіатору в балах, де 1 бал – відносно низький рівень і 2 бали – відносно високий рівень гормону для вивченої популяції хворих з ГХ ІІ стадії. До проведення дискримінантного аналізу методом рангової кореляції Спірмена була здійснена попередня “фільтрація” клінічних та інструментальних показників (n=76) з метою визначення їх асоціацій з рівнем гормону в плазмі. Показники, які визначали статистичну значиму ($p<0,05$) рангову кореляцію з концентрацією гормону в плазмі були включені в подальший дискримінантний аналіз. З’ясовано, що у пацієнтів із ГХ ІІ стадії і рівнем ТФР-β1 ≥ 222 пг/мл у плазмі крові слід очікувати наступні клінічні портрети: 1) наявність супутнього ожиріння; 2) наявність супутніх ожиріння і стенокардії без/та із частою ШЕ. При цьому, в разі ІІ функціонального класу стенокардії мінімальна кількість ШЕ за добу складає 5000, в той час як при ІІІ функціонального класу – 2500 епізодів ШЕ за добу; 3) наявність супутньої частої ШЕ > 10000 епізодів ШЕ за добу.

Ключові слова: трансформуючий фактор росту-β1, гіпертонічна хвороба, хронічна коронарна хвороба, шлуночкова екстрасистолія, дискримінантний аналіз

Statement of the problem. Myocardial fibrosis leads to left ventricular remodeling, which is associated with chronic pressure or volume overload. Myocardial fibrosis contributes to an increase in cardiovascular events, including ventricular arrhythmias [1].

Transforming growth factor-β1 (TGF-β1) triggers myocardial fibrosis by stimulating fibroblasts to release many factors, including angiotensin II [2], which is involved in the regulation of blood pressure (BP). It has been established that the concentration of TGF-β1 positively correlates with BP in children with primary arterial hypertension and with hypertensive heart damage [3].

In addition, in patients with coronary artery disease (CAD), an association is observed between TGF-β1 concentration and left ventricular diastolic dysfunction and the occurrence of arrhythmias [4].

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Our study aims to assess the relationship of serum TGF-β1 in patients with stage II hypertension and various clinical indicators.

The aim of the study was to determine the clinical portrait of patients with stage II hypertension at different levels of transforming growth factor-β1 in blood plasma.

Resear chobjects and methods. Echocardiography, Holter electrocardiographic monitoring, stress tests and/or coronary ventriculography were performed in 120 patients (mean age 57.3±0.9 years) to verify the diagnosis of stage II hypertension (HTN) and concomitant chronic coronary heart disease (CCHD) and frequent ventricular extrasystole (VE).

We identified 4 groups of patients, 30 persons in each: Group 1 – stage II HTN without concomitant CCHD and frequent VE; Group 2 – stage II HTN with concomitant frequent VE; Group 3 – stage II HTN with concomitant CCHD; Group 4 – stage II HTN with concomitant CCHD and frequent VE [5, 6].

Using an enzyme-linked immunosorbent assay with the "Human TGF-β1 (Transforming Growth Factor Beta 1) ELISA Kit" (Elabscience Biotechnology Inc., USA), the concentration of TGF-β1 in blood serum was determined according to the manufacturer's instructions. Microsoft Excel (2019) and Statistica 12.0 (Statsoft, USA) were then used for statistical processing of the obtained results.

Clinical portraits of patients with stage II HTN and different plasma TGF-β1 levels were determined using discriminant analysis ("Discriminant analysis"). The baseline parameter for the analysis was the mediator level expressed in points, where 1 point indicated a relatively low level (RLL) and 2 points indicated a relatively high level (RHL) of the hormone for the studied population of patients with stage II HTN.

Before performing discriminant analysis, a preliminary "filtering" of clinical and instrumental indicators (n=76) was carried out using Spearman rank correlation to determine their associations with the plasma hormone level. Indicators that showed a statistically significant ($p<0.05$) rank correlation with the plasma hormone concentration were included in the subsequent discriminant analysis.

The main stages of discriminant analysis were:

1. determination of a linear discriminant model (equation of the linear discriminant function) and the independent variables of the model. In doing so, only the most informative variables and those least dependent on each other were included in the model using the direct forward stepwise method (forward stepwise);
2. coefficients of the linear discriminant functions for each value of the dependent factor (in our case, the plasma hormone level);
3. a classification matrix as the main result of the discriminant analysis, which made it possible to assess the informativeness of this model.

Presentation of the main material.

Research results and their discussion.

Using the method of variation statistics, the mean plasma concentration of TGF-β1 in the examined patients (n=120) was 9238.3±97.2 pg/mL. The median value was 222.0 pg/mL, and the interquartile range (25th and 75th percentiles) was 165.5 and

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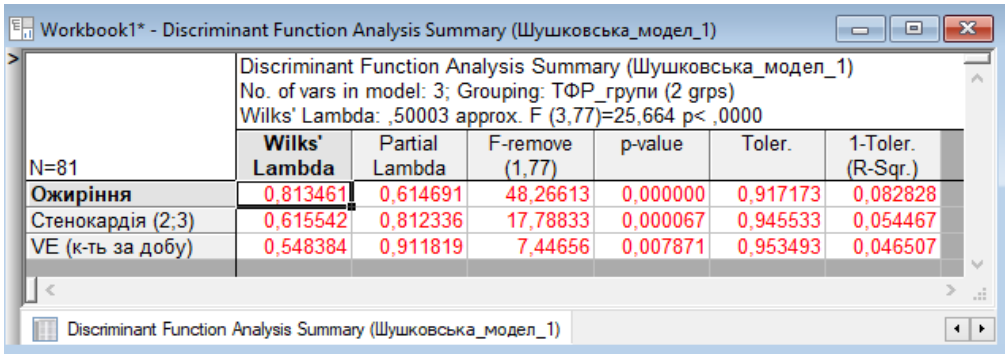
303.0 pg/mL, respectively. Taking the median into account, we distinguished groups of patients with RLL (≤222 pg/mL) and RHL (>222 pg/mL) of TGF-β1.

It was determined that in 50% of the examined patients the plasma TGF-β1 concentration was 165.5–303.0 pg/mL, in 25% it was below 165.5 pg/mL, and in the remaining 25% it was above 303.0 pg/mL. Moreover, an increase in its concentration was observed from Group 1 to Group 4 [7].

Figures 1–3 demonstrate the results of the main stages of the discriminant analysis performed for plasma TGF-β1 level expressed in points (1 point – ≤222 pg/mL and 2 points – >222 pg/mL, respectively).

Stage 1 of the analysis involved identifying statistically significant associations between various clinical and instrumental indicators and the plasma TGF-β1 level (pg/mL) (Spearman rank correlation results).

Using forward stepwise selection, a discriminant model was formed that consisted of the most informative variables (Fig. 1).


Workbook1* - Discriminant Function Analysis Summary (Шушковська_модел_1)

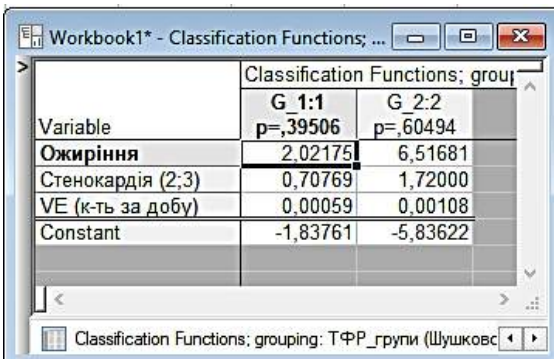
Discriminant Function Analysis Summary (Шушковська_модел_1)
No. of vars in model: 3; Grouping: ТФР_групи (2 grps)
Wilks' Lambda: ,50003 approx. F (3,77)=25,664 p< ,0000

N=81	Wilks' Lambda	Partial Lambda	F-remove (1,77)	p-value	Toler.	1-Toler. (R-Sqr.)
Ожиріння	0,813461	0,614691	48,26613	0,000000	0,917173	0,082828
Стенокардія (2;3)	0,615542	0,812336	17,78833	0,000067	0,945533	0,054467
VE (к-ть за добу)	0,548384	0,911819	7,44656	0,007871	0,953493	0,046507

Discriminant Function Analysis Summary (Шушковська_модел_1)

Fig. 1. Independent variables of the discriminant model of the clinical portrait for different levels of TGF-β1 in plasma (output of STATISTICA v.12)

Figure 2 shows the results of the second stage of the discriminant analysis with calculation of the coefficients of the independent variables for the discriminant equations corresponding to different plasma TGF-β1 levels—the first for a relatively low level (RLL, ≤222 pg/mL) and the second for a relatively high level (RHL, >222 pg/mL), respectively.


Workbook1* - Classification Functions; ...

Classification Functions; grou

Variable	G_1:1 p=,39506	G_2:2 p=,60494
Ожиріння	2,02175	6,51681
Стенокардія (2;3)	0,70769	1,72000
VE (к-ть за добу)	0,00059	0,00108
Constant	-1,83761	-5,83622

Classification Functions; grouping: ТФР_групи (Шушковс

Fig. 2. Coefficients of the linear discriminant functions for the equations of relatively low and high plasma TGF-β1 levels (output of STATISTICA v.12)

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The last and most important stage of the discriminant analysis was to determine the informativeness of the obtained model by evaluating the classification matrix (Fig. 3).

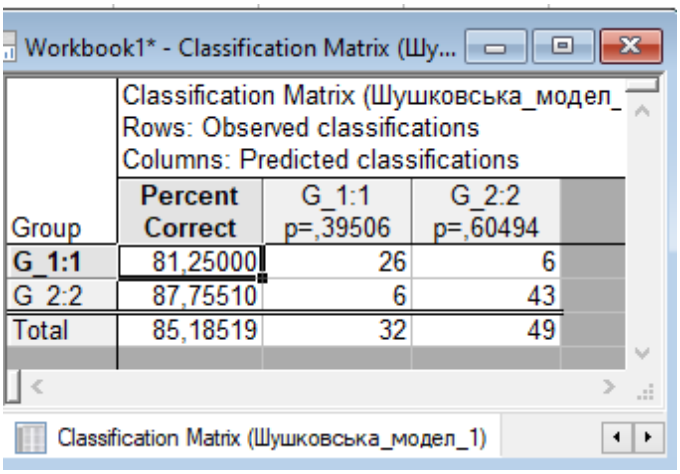

Fig. 3. Classification matrix for assessing the informativeness of the discriminant model (output of STATISTICA v.12)

It was observed that the most informative factors characterizing plasma TGF-β1 levels were: the presence of alimentary-constitutional obesity scored in points (0 or 1) (Wilks' Lambda = 0.81; F=48.26; p<0.00001) and the functional class (FC) of angina scored in points (2 or 3) (Wilks' Lambda = 0.62; F=17.79; p=0.00007). In addition, an independent variable included in the obtained model was the daily number of ventricular extrasystoles (VE) determined by Holter electrocardiographic monitoring (Wilks' Lambda = 0.55; F=7.45; p=0.008). The latter variable clearly demonstrated that the plasma TGF-β1 level in patients with stage II hypertension, to a certain extent, determines the arrhythmogenic activity of the ventricles.

Thus, it was impossible to deny the fact that the clinical portrait of a relatively high plasma TGF-β1 level in patients with stage II hypertension is determined, to a greater extent, by the presence of obesity and the FC of concomitant angina and, to a lesser extent, by the arrhythmogenic activity of the left ventricular myocardium, characterized by frequent VE on ECG.

The results of the second stage of discriminant analysis with calculation of the coefficients of the independent variables for the discriminant equations corresponding to different plasma TGF-β1 levels (for RLL ≤222 and RHL >222 pg/mL, respectively) indicated that for the RLL level (in the figure G_1:1) the following equation should be used:

RLL TGF-β1 = −1.84 + 2.02 * obesity (0 or 1) + 0.71 * angina FC (2 or 3) + 0.0006 * VE/day,

and for the RHL level:

RHL TGF-β1 = −5.83 + 6.52 * obesity (0 or 1) + 1.72 * angina FC (2 or 3) + 0.001 * VE/day, respectively.

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Assessment of the informativeness of the obtained discriminant model using the classification matrix demonstrated that the correct prediction for patients with RLL TGF-β1 was 81.3%, whereas for patients with RHL it was slightly higher—87.8%. The average informativeness of correct prediction for any TGF-β1 level was 85.2%.

Table 1 presents the possible clinical portraits of patients with stage II hypertension and a relatively high plasma TGF-β1 level (>222 pg/mL) (this level was of the greatest clinical interest), taking into account all variables of the obtained discriminant model. The results of the corresponding table were obtained by sequential substitution of data into the discriminant equations under the condition that the RHL value was greater than the RLL value.

Table 1

Clinical portraits of patients with stage II hypertension and plasma TGF-β1 level >222 pg/mL

Obesity (BMI >30 kg/m²)	Angina FC	Minimum number of VE per day
Yes	**-**	**-**
-	*II* FC	-
-	*III* FC	-
-	-	**10 000**
Yes	**II FC**	**-**
Yes	**III FC**	**-**
-	**II FC**	**5000**
-	**III FC**	**2500**

Note. BMI – body mass index; FC – functional class; VE – ventricular extrasystole.

According to the obtained data, in all patients with stage II hypertension and concomitant obesity, even in the absence of CCHD and frequent VE, a relatively high plasma TGF-β1 level is expected. In contrast, the combination of stage II hypertension and CCHD (angina II–III FC) cannot be used as a portrait of a relatively high hormone level. The use of angina FC guarantees a relatively high plasma TGF-β1 level only when combined with other model variables—obesity and frequent VE. In this case, in the presence of angina II FC the minimum number of VE per day is 5,000, whereas in angina III FC it is 2,500 VE episodes per day. Notably, the presence of concomitant frequent VE as an independent factor of the portrait of a relatively high plasma TGF-β1 level is possible only when it exceeds 10,000 VE episodes per day.

Conclusions. It was found that in patients with stage II hypertension and plasma TGF-β1 ≥222 pg/mL the following clinical portraits should be expected: 1) the presence of concomitant obesity; 2) the presence of concomitant obesity and angina pectoris without/with frequent VE. In this case, for angina II FC the minimum number of VE episodes per day is 5,000, whereas for angina III FC it is 2,500 VE episodes per day; 3) the presence of concomitant frequent VE >10,000 VE episodes per day.

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