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ADD-ON GRADE-RANKING SCALE FOR ASSESSING THROMBOTIC RISK IN PATIENTS WITH ISCHEMIC HEART DISEASE AND PERCUTANEOUS CORONARY ANGIOPLASTY

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ABSTRACT

Introduction: The anticipation of the development of thrombotic complications in coronary angioplasty patients helps to prevent this dangerous complication. Development of the available informative scales on the basis of mathematical methods taking into account the main clinical and biochemical parameters significantly simplifies the classification of patients in terms of thrombotic risk.

The aim of the paper is to concentrate information on the state of hemostasis in the studied category of patients using the method of the main components and to obtain a matrix with minimal loss of information, which is convenient for analysis and the creation of a grade-ranking scale.

Materials and methods: Data of 70 patients with coronary heart disease and percutaneous coronary angioplasty were analyzed. The level of soluble fibrin, fibrinogen, D-dimer, protein C, and ratios rf/dd×100 were determined, and also the presence of diabetes mellitus and restenosis in the history was considered.

Results: As a result of a stepwise study using the method of the main components, in the first stage two most singular matrices were obtained that describe 70% of the entire data variance (one of them is the component rf+dd, and the second one is fg+pc), which led to the first indicator of the level of thrombotic risk. At the second stage, the level of thrombotic risk was clarified, taking into consideration the presence of diabetes and history of restenosis, and it is recommended to use a second indicator for its determination (rf/dd×100).

Conclusions: The presented grade-ranking scale scale allows the anticipation of the development of thrombotic complications in the studied category of patients with high probability.

KEY WORDS: hemostasis, thrombotic risk, coronary angioplasty, method of main components

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INTRODUCTION

For clinical and biochemical studies of hemostasis, a significant array of investigated parameters and indicators is characteristic, which is caused by the desire to improve the information component in relation to external and internal factors that affect the condition of the coagulating blood system. In the meantime, large masses of initial clinical data cause considerable difficulty in their processing and interpretation, since, on the one hand, they are directed to the completeness and depth of the research, and, on the other hand, erode the existing interrelationships between the results of the study. The mentioned problem is solved by methods of compaction of information using the method of the main components, as one of the methods of factor analysis, which allows obtaining a convenient matrix analysis with a minimum loss of information [1].

THE AIM

To obtain the integral biochemical and clinical parameters characterizing the state of hemostasis in patients with ischemic heart disease (IHD) and performed percutaneous coronary angioplasty for the development of an add-on grade-ranking scale for assessing the thrombotic risk, i.e. finding algorithms for the classification of patients depending on the assessment of the formidability and risk of thrombotic complications (average, high, very high).

MATERIALS AND METHODS

The data of 70 patients, determined by random sampling, who underwent necessary biochemical and clinical examination underwent surgery and percutaneous coronary angioplasty, are included in the matrix. To biochemical laboratory parameters belong the data of soluble fibrin (rf) (mkg/ml) as a measure of «pre-thrombosis»; fibrinogen (fg) (mg/ml) as the main protein of the coagulation system; protein C (pc) (in % relative to normal index) as a natural anticoagulant; D-dimer (dd) (ng/ml) as a «post-thrombosis» indicator, which characterizes the presence of thrombus and fibrinolytic activity; to the clinical data – the presence of type II diabetes mellitus (DM)

and restenosis (R) in the medical history [2, 3, 4, 5]. The latter was taken into account in connection with a number of scientific studies that indicate that the presence of these clinical factors may significantly affect the development of thrombogenesis [6, 7].

Methodologically, the research was carried out in three stages.

In the first stage, using the method of the main components to the initial biochemical data, the percentage of the total dispersion described by each component was analyzed. After the analysis it was decided to leave only the first two main components. Subsequently, by expert evaluation, groups of patients with the average, high and very high risk of stent thrombosis were pre-allocated and the values of the first and second main components for each of the selected groups of patients were determined.

The measure of thrombotic risk was determined by the remoteness of the biochemical parameters from the normal values. To determine the measure of this distance in the space determined by the first two main components, the Minkowski metric with weighted coefficients [8][1] was used.

After performing the inverse transformation by the ratios for calculating the values of the main components, the formulas for assessing the degree of thrombotic risk in terms of absolute values of the four indices: rf, fg, dd i pc were established. Also, the value of the grade index B_1 (which is equal to «1» for an average risk level, «2» – for high, «3» – for very high) was determined.

In the second and third stages, the grade scale was specified by an additional indicator, namely: the presence of diabetes mellitus and/or restenosis. For these patients, the values of score points B_2 and B_3 were obtained.

Eventually, the final indicator was determined by the formula:

$P = \max\{B_1, \alpha B_2, \beta \cdot B_3\}$

where α = 1, if the patient is diagnosed with diabetes mellitus (0 – otherwise), β = 1, if the patient is diagnosed with restenosis (0 – otherwise), with:

P = 1 – average thrombotic risk;

P = 2 – high thrombotic risk;

P = 3 – very high thrombotic risk.

RESULTS AND DISCUSSION

Table I presents the correlation data of selected indicators. Before applying the method of the main components, we perform data transformation, centering them relatively to «0» and making the standard deviation equal to «1». The latter is carried out according to the formula:

$$z = \frac{x - \mu}{\sigma}$$

where μ is the mean value of the parameter x,

σ is its standard deviation.

As an example, we will take the indictors of two random patients after the conversion (Table II).

Let X be a matrix with 70 lines and 4 columns with the obtained data. To determine the main components, we diagonize the matrix of covariates $X^T X$ (Table III). We obtain the two largest singular values of the matrix X, which describe 70% of the entire data variance: $\sigma_1 = 11{,}24$, $\sigma_2 = 8{,}34$. The proper vectors corresponding to these singular values are as follows:

$\boldsymbol{\nu}_1 = (0{,}61; 0{,}39; 0{,}63; -0{,}27)$

$\boldsymbol{\nu}_2 = (0{,}11; 0{,}51; -0{,}07; 0{,}84)$

The value of the i-th main component is calculated by the formula:

$$C_i = \frac{rf - \mu_1}{\sigma_1} x_{1(i)} + \frac{fg - \mu_2}{\sigma_2} x_{2(i)} + \frac{dd - \mu_3}{\sigma_3} x_{3(i)} + \frac{pc - \mu_4}{\sigma_4} x_{4(i)},$$

where rf, fg, dd, pc – are respectively the values of soluble fibrin, fibrinogen, D-dimer and protein C;

$\mu_1, \mu_2, \mu_3, \mu_4$ – mean values according to these indicators;

$\sigma_1, \sigma_2, \sigma_3, \sigma_4$ – their root mean square deviations;

$x_{1(i)}, x_{2(i)}, x_{3(i)}, x_{4(i)}$ – coordinates of the *i*-th of the proper vector ν_i.

The projection of data on a plane, which is determined by the proper vectors of two components with the boundary of the area of the middle level of thrombotic risk, is presented in Fig. 1.

Let us analyze the obtained results. All the indicators significantly affect the value of the first main component, but above all – it is equally soluble fibrin and D-dimer. The incremental value of this component indicates that the values of soluble fibrin and D-dimer significantly differ from the norm, and the compensatory mechanism as an anticoagulant of protein C is insufficient, and patients with this value of the first main component should be classified as having high or very high thrombotic risk.

The value of the second main component depends significantly on the protein C and fibrinogen, while the levels of soluble fibrin and D-dimer do not actually affect their values. The high value of this indicator with a low first major component in a number of patients may indicate an elevated protein C level, which is positive, taking into account the prediction of possible thrombotic complications. Instead, the low value of this component (less than -1) indicates low protein C content, and patients with this value can not be classified as an intermediate level of thrombotic risk.

Let us add the extent of distance from this area, on which we will evaluate the level of thrombotic risk. For convenience, we use the Minkowski distance with weighted coefficients. We calculate the distance to the centre of the median risk area, which we defined as (-1; 0,5), and weighted the coefficients are to be assigned 2 and 1, based on the expert estimates (the area highlighted in Figure 1 is twice elongated along the second component than the first one).

Thus, for each point (*x; y*) we attribute the number of its distance from the centre of the region with an average thrombotic risk, which is calculated by the formula:

$R = 2|x + 1| + |y - 0{,}5|$

[1] – the mathematical part of the work was performed with the help of consulting company «Nestlogic Inc» (www.nestlogic.com).

Table I. Correlation matrix of the studied indicators.

№	Indicator	Soluble fibrin (rf)	Fibrinogen (fg)	D-dimer (dd)	Protein C (pc)
1	rf		0,26	0,57	-0,11
2	fg	0,26	1	0,24	-0,02
3	dd	0,57	0,24	1	-0,22
4	pc	-0,11	-0,02	-0,22	1

Table II. The value of standard indicators of the studied patients (№№ 8, 28) after the conversion.

№	№ of the patient	Biochemical indicators				Value of biochemical indicators after data centering			
		rf	fg	dd	pc	rf	fg	dd	pc
1	8	14,5	5,6	151	97	2,75	0,87	3,33	0,18
2	28	3,1	3,6	20	86	-047	-0,50	-0,62	-0,47

Table III. Coordinate indices of the vectors of the main components.

№	№ of the component	% described dispersion	Singular value	Proper vectors
1	1st	45,1	11,24	(0,61; 0,39; 0,63; -0,27)
2	2nd	24,9	8,34	(0,11; 0,51; -0,07; 0,85)
3	3rd	19,7	7,43	(-0,39; 0,76; -0,28;-0,43)
4	4th	10,3	5,38	(0,68; -0,01; -0,72; -0,15)

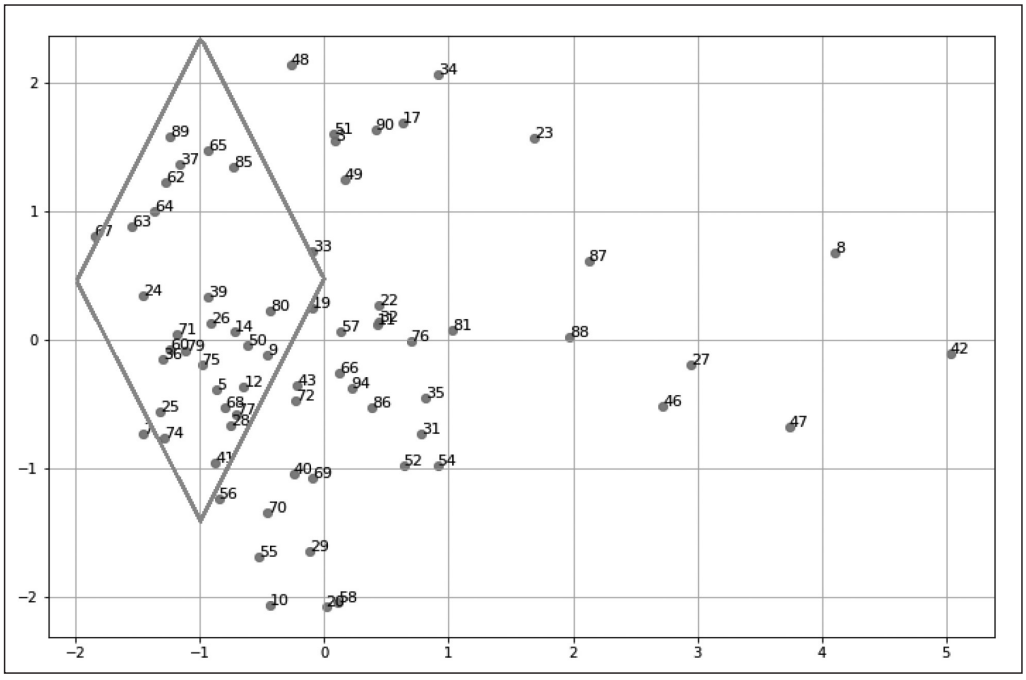

Fig. 1. Projection of data on the plane by the first two main components with the boundary of the site which corresponds to the average thrombotic risk.

The resulting number below will be called the first indicator of thrombotic risk.

For instance, the value of the first two components for patient №3 is 0,09 and 1,55, respectively. Therefore, the value of the first indicator of thrombotic risk for this patient will be equal to:

$R = 2|0{,}09 + 1| + |1{,}55 - 0{,}5| = 3{,}23$

At the same time, for example, for patient №25 the value of the first two main components is equal to -1,32 and -0,56, so the value of the first index of thrombotic risk is equal to:

$R = 2| -1{,}32 + 1| + | -0{,}56 - 0{,}5| = 1{,}7$

The classification of patients in accordance with the level of thrombotic risk according to the value of the first indicator R will be carried out according to the following scheme:

- if $0 \le R < 2{,}5$ – average thrombotic risk;
- if $2.5 \le R < 4{,}5$ – high thrombotic risk;
- if $R \ge 4{,}5$ – very high thrombotic risk.

We perform a reverse transformation, which allows us to determine the level of thrombotic risk without calculating the values of the main components. To do

this, we use the mean values of each of the indicators, the standard deviation, and the coordinates of the main component vectors, which are presented in Table III. We substitute these values for the formula for calculating the first main component and, after simplifications, we obtain:

$C_1 \approx 0{,}17 \cdot rf + 0{,}27 \cdot fg + 0{,}019 \cdot dd - 0{,}015 \cdot pc - 1{,}259$

Hereupon, we calculate the value of the first summand in the formula for deriving the first indicator of the level of thrombotic risk:

$2|C_1 + 1| = |0{,}34 \cdot rf + 0{,}54 \cdot fg + 0{,}04 \cdot dd - 0{,}0318 \cdot pc - 0{,}518|$

If this value appears to be higher than 4,5, then the value of the second component can not be calculated, since unequivocally the patient must be classified into a category with a very high thrombotic risk.

By analogy we calculate the value of the second main component:

$C_2 \approx 0{,}031 \cdot rf + 0{,}352 \cdot fg - 0{,}0021 \cdot dd + 0{,}05 \cdot pc - 6{,}3$

$|C_2 - 0{,}5| = |0{,}031 \cdot rf + 0{,}352 \cdot fg - 0{,}0021 \cdot dd + 0{,}05 \cdot pc - 6{,}8|$

Thus, the value of the first indicator of thrombotic risk can be calculated by the formula:

$R = 2|C_1 + 1| + |C_2 - 0{,}5| = |0{,}34 \cdot rf + 0{,}54 \cdot fg + 0{,}04 \cdot dd - 0{,}0318 \cdot pc - 0{,}518| + |0{,}031 \cdot rf + 0{,}352 \cdot fg - 0{,}0021 \cdot dd + 0{,}05 \cdot pc - 6{,}8|$

We define a relatively convenient scale for assessing thrombotic risk based on the performed research. For this purpose, we will carry out the normalization of the first indicator of thrombotic risk, dividing the two parts of the last equality with a factor of 0,0318 (with the change in pc in the first clause will be = 1) and we will make certain roundings. We get the following modified indicator:

$R' = |10 \cdot rf + 20 \cdot fg + 1{,}25 \cdot dd - pc - 20| + |10 \cdot fg + 1{,}5 \cdot pc - 215|$ (1)

After calculations we get a modified scale in which:

- if $0 \le R' < 80$ – the average thrombotic risk ($B_1 = 1$);
- if $80 \le R' < 140$ – high thrombotic risk ($B_1 = 2$);
- if $R' \ge 140$ is a very high thrombotic risk ($B_1 = 3$).

When comparing the values of the first indicator of thrombotic risk and its modification, the compliance is 92,9%, that is, the prognostic value is practically unchanged.

Thus, the first stage is reduced to calculating the value of R' by the formula (1) and finding the obtained value of the ball B_1.

At the second stage, the level of thrombotic risk was determined, taking into account the presence of diabetes mellitus (DM) and diagnosed restenosis. Let us analyze more detailed indicators of patients with diabetes and restenosis. Of the 70 patients who reached the final sample, 18 had diabetes mellitus and 23 patients were with history of restenosis, herewith eight patients were diagnosed with DM and restenosis.

Since the rank correlation coefficient, determined by us earlier in the general group among other indicators, is significantly higher than with rf and is positive (r = 0,28), and in the group with diabetes – with dd, which has a negative value (r = -0,51), then with the aim of identifying stronger correlation bonds it is possible to add another integral index, namely: ratio rf/dd×100. Given that rf is an indicator of «prethrombosis» and dd is «postthrombosis», the indicated ratio of these indices may demonstrate the state of the coagulating and antigreshing hemostasis units.

The obtained data testify that in the group of patients with diabetes mellitus, a rather high direct correlation between the ratio rf/dd and the diagnosed restenosis (r = 0,67) compared with the general group (r = 0,35) was distinguished. Consequently, the ratio of rf/dd can be taken as an additional integral indicator that would characterize the degree of thrombotic risk for patients with diabetes mellitus.

Analyzing the results, obtained in the patients in this sample, who were diagnosed with restenosis (n = 23) and those without restenosis (n = 47) for 18 months, it was found that for patients with restenosis, the mean ratio of rf/dd×100 is 21,5 with a standard deviation of 11,5, and for patients without restenosis the mean value is 14,3 with a standard deviation of 12,6.

Thus, when the actual standard deviation is virtually unchanged, there is a significant difference between the mean values of rf/dd×100 in these groups.

Summarizing the aforementioned, it is possible to conclude that when a patient is diagnosed with diabetes, the second indicator of thrombotic risk should be recommended, namely: rf/dd×100. At the same time, according to our estimates:

- if the indicator R" > 8, , then the patient should be classified into a group with an average thrombotic risk (then $B_2 = 1$);
- If R' is in the range of 8 to 16, then the patient should be classified into a group with a high thrombotic risk ($B_2 = 2$);
- if R" <16, , then the patient should be classified into a group with a very high thrombotic risk ($B_2 = 3$).

If the patient is diagnosed with restenosis, then, again, it is recommended to determine the second indicator of thrombotic risk and obtain the value of B_2 on the same scale.

As noted, the final indicator is determined by the formula:

$P = \max(B1, \alpha \times B2, \beta \times B3)$

where $\alpha = 1$, if the patient is diagnosed with diabetes mellitus (0 – otherwise), $\beta = 1$, if the patient is diagnosed with restenosis (0 – otherwise).

Table IV gives examples of the final grade scale for the assessment of thrombotic risk.

The verification of the developed grade-ranking scale of the results of the 18-month inspection showed that in 73,9% of cases it corresponds to very high risk (patients with restenosis) and in 26,1% of cases it corresponds to high thrombotic risk, in patients who also had restenosis. According to the results of the grade-ranking scale, none of the 23 patients with restenosis fell into the average-level category.

Hence, the presented grade-ranking scale scale allows a high probability to predict the development of thrombotic complications in patients with percutaneous coronary angioplasty.

Table IV. Results of evaluation of thrombotic risk level on the example of patients №8 and №28

№	№ of the patient	rf mkg/ml	fg mg/ml	dd ng/ml	pc %	DM	R	Risk assessment			G/r scale
								1 stage	2 stage	3 stage	
1	8	14,5	5,6	151	97	-	+	3	3	2	3
2	28	3,1	3,6	20	86	-	-	1	0	0	1

Note: DM – diabetes; R – restenosis; G/r scale – grade-ranking scale.

CONCLUSIONS

1. The application of the method of the main components allows obtaining the value of individual and accumulated contributions of the studied hemostasis to total dispersion, giving rank evaluation of the influence of the initial parameters on the formation of the main components and the percentage explained by the latest information.
2. Consideration of the four indicators that characterize hemostasis in patients with coronary angioplasty (rf, fg, dd, pc), rf/dd×100 and binary index (DM, history of restenosis) makes it possible to classify patients with the help of developed grade-ranking scale of thrombotic risk.

Prospects for further research. Further introduction of informative biochemical markers for thrombogenesis and the use of available mathematical methods of compaction of information will further improve the process of predicting the level of thrombotic risk.

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