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Mathematical Models for the Prediction of Coagulation Activity in Patients with Paroxysmal Atrial Fibrillation

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Abstract*: Our previous studies showed activation of coagulation in the early hours of the clinical manifestation of paroxysmal atrial fibrillation (PAF). Plasma coagulation activity of factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, factor XII, vWF, tissue factor levels, FVIII, vWF, prothrombin fragment 1+2(F1 + 2) and fibrinopeptide A (FPA) were significantly increased as early as the first twenty-four hours of the disease. The results suggest that there is a correlation between the studied parameters and development of the disease. Aim: To search for a statistical model that predicts coagulation activity in PAF patients. Materials and methods: Coagulation parameters were examined in 51 PAF patients (26 males, 25 females; mean age 59.84 ±1.60 years, onset of PAF episode < 24h prior to hospitalization). Controls included 52 individuals (26 males, 26 females; mean age 59.50 ± 1.46 years) with no prior anamnestic or ECG AF data, corresponding to patients in sex, age, BMI and comorbidities. A linear regression model was used to predict coagulation activity in PAF. Regression models showed good correlation between the duration of arrhythmia and six of the fourteen coagulation parameters studied: F1+2 ($r = 0.83$, $p < 0.001$), FPA ($r = 0.84$, $p < 0.001$), FVIII levels ($r = 0.85$, $p < 0.001$) as well as activity of FII ($r = 0.83$, $p < 0.001$), FVIII ($r = 0.83$, $p < 0.001$) and FXII ($r = 0.78$, $p < 0.001$). Changes in F1+2 plasma levels were most sensitive to PAF duration, where the contribution of duration to the values of the indicator is the greatest ($b = 15.31$). Conclusion: Linear regression analysis allowed us to create models with a high correlation coefficient for predicting the values of F1+2, FPA, FVIII levels, as well as activity of FII, FVIII and FXII in PAF patients. These models could allow for quantification of the procoagulatory process and thrombotic potential of the disease.

Keywords: coagulation, atrial fibrillation, predictive models.

I. INTRODUCTION

Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia and it affects up to 3% of the total population [1, 2]. By the end of 2060, it is expected to affect around 18 million people in Europe and more than 12 million by 2050 in the USA [3]. AF is being increasingly referred to as the "current epidemic" of modern medicine [4]. One of the major clinical and socio-economic problems that AF causes are thromboembolic events. As early as the beginning of the last century, Harvey and Levine found thrombosis in the left atrial appendage in the presence of atrial fibrillation, and in the 1970s, the Framingham study presented the first epidemiological data for an increased risk of stroke in patients with the disease [5, 6]. Today, the connection between them is undeniably accepted. It is estimated that about 30% of all strokes are associated with manifestation of AF, with longer hospital stays, higher disability and mortality in these cases [7]. Paroxysmal atrial fibrillation (PAF) accounts for about 30% of all AF cases, with some authors believing the percentage to be much higher and reaching up to 60% due to frequent asymptomatic course of the disease [8]. Only 1 in 12 paroxysms of AF are actually symptomatic in PAF patients [9]. Studies in populations with implanted pacemakers confirm the frequent asymptomatic course of the disease [10, 11]. Despite its short duration and usually mild clinical course, PAF is associated with high incidence of embolic events [12, 13]. High morbidity and embolic risk arouse the interest in the coagulation changes occurring in PAF. The creation of mathematical models to determine coagulation activity in PAF patients would be a significant clinical contribution. This will allow for quantification of the coagulation process and thrombotic potential of the disease. At the same time, this could complement and expand the established embolic risk assessment scale for AF – the CHA2DS2-VASc score. Our previous studies showed that the clinical manifestation of PAF is associated with very early activation of the coagulation process [14-17]. We found that as early as the first twenty-four hours of the disease there was a significant increase in plasma coagulation activity of factor II (FII, $p < 0.001$), factor V (FV, $p < 0.001$), factor VII (FVII, $p < 0.001$), factor FVIII (FVIII, $p < 0.001$), factor IX (FIX, $p < 0.001$), factor X (FX, $p < 0.001$), factor XI (FXI, $p < 0.001$), factor XII (FXII, $p < 0.001$), vWF activity ($p < 0.001$), as well as plasma levels of tissue factor (TF, $p < 0.001$), FVIII ($p < 0.05$), vWF ($p < 0.001$), prothrombin fragment 1+2 (F1 + 2, $p < 0.001$) and fibrinopeptide A (FPA, $p < 0.001$) in the studied patient population, compared to controls without prior arrhythmic data. This led us to assume that there is a relationship between the studied indicators and the development of the disease itself, and gave us the reason to conduct this study. All mentioned above formed our aim to analyze the established deviations in the fourteen coagulation indicators (presented above) in PAF patients in order to seek a statistical model for predicting procoagulant activity in the disease.

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Table 1. Plasma levels and activity of the coagulation factors in patients with PAF and controls

	Patients with PAF	Controls	P value
FII activity (%)	167.81±9.12	100.43±5.77	*P<0.001*
FV activity (%)	198.47±10.88	121.53±4.79	*P<0.001*
FVII activity (%)	170.82±8.32	95.17±5.26	*P<0.001*
FVIII activity (%)	200.03±11.11	109.73±4.90	*P<0.001*
vWF activity (%)	200.92±12.45	110.80±5.14	*P<0.001*
FIX activity (%)	170.43±6.62	117.72±5.95	*P<0.001*
FX activity (%)	193.20±11.85	116.20±5.86	*P<0.001*
FXI activity (%)	178.41±7.99	111.75±5.50	*P<0.001*
FXII activity (%)	218.31±11.77	148.41±7.48	*P<0.001*
TF levels pg/mL	268.63±12.69	170.21±9.18	*P<0.001*
FVIII levels (%)	107.52±4.36	93.85±2.93	*P<0.05*
vWF levels (%)	178.40±12.95	119.53±6.12	*P<0.001*
F1+2 plasma levels (pmol/L)	292.61±14.03	183.40±8.38	*P<0.001*
FPA plasma levels (ng/mL)	4.47±025	3.09±0.15	*P<0.001*

II. MATERIALS AND METHODS

Study population and design

Coagulation indicators were examined in a population of 51 patients (26 males, 25 females; mean age 59.84±1.60 years) with PAF onset <24 hours before hospitalization. Based on the inclusion and exclusion criteria (see below), they were sequentially selected from 338 patients admitted to the ward for the study period. 52 people (26 males, 26 females; mean age 59.50 ± 1.46 years) without anamnestic or ECG AF data were included as controls. We screened 169 volunteers for the selection and used the same exclusion criteria we applied to patients (see below).

Inclusion criteria (for the patient group):

1. Ability to clearly define the onset of arrhythmia, continuing at the time of hospitalization;
2. Lack of exclusion criteria.

Exclusion criteria:

1. cardiovascular diseases: ischemic heart disease, heart failure, high-grade and / or uncontrolled hypertension, moderate or severe acquired valve defects, cardiomyopathy, implanted device for the treatment of rhythm-conduction disorders, inflammatory heart disease, congenital heart diseases;
2. other diseases - kidney or liver failure, inflammatory and/or infectious diseases, neoplastic and autoimmune diseases, chronic pulmonary insufficiency, endocrine disorders (except for non-insulin dependent, well-controlled DM type 2); previous thromboembolic incidents, bleeding diathesis, miscarriages (for women);
3. intake of hormone replacement therapy, contraceptives, oral anticoagulants or antiplatelet drugs, pregnancy, systemic intake of analgesics (incl. NSAIDs), obesity with BMI >35;
4. unsuccessful restoration of sinus rhythm with drugs (propafenone) (for the patient group)

The parameters were examined once in plasma, obtained after centrifugation of peripheral venous blood. In patients, the blood sample was taken immediately after diagnosis in still persistent disease, and in controls during a conducted outpatient examination. The preparation, storage and examination of samples is duly described elsewhere [14-17].

The study was conducted in the Intensive Cardiology Unit of the First Cardiology Clinic at the University Hospital St. Marina – Varna for the period October 2010 – May 2012. It was initiated after written approval of the local Ethics Committee (No.9/14.10.2010) and was fully compliant with the requirements of the WMA Declaration of Helsinki, 2008 [18].

Statistical analysis

In the present study we applied simple linear regression to represent the observed coagulation changes in PAF as a function of time. We used the simple linear regression equation with one predictor (univariate regression analysis):

$Yi=a+bXj$, $i=1,2$ and $j=1,2,3$,

where Yi are the values of the dependent variable (in this case the coagulation indicator), Xj is the predictor (in this case the duration of atrial fibrillation), a is a constant or intercept of the regression line (i.e., the average of Y, when X is 0), b – regression coefficient (slope), showing the average increase of the dependent variable when the factor variable is changed by one measure unit.

Based on the predicted and observed values of the indicators, we evaluated the adequacy of the models using the obtained correlation coefficient R and the adjusted correlation coefficient R2 of the model. The correlation coefficient R indicates a presence of a linear relationship between the dependent and the independent variable. The adjusted R2 coefficient of the corresponding indicator represents the proportion of the Y variance, which is related to or can be explained by the X variance, i.e. shows how much of the change in the values of this indicator can be explained by the change in the values of the predictor. It is one of the criteria for assessment of the adequacy of the regression model.

Continuous variables were expressed as mean ± standard error of the mean (SE) and categorical variables were expressed as percentage of the total group. Normality of distribution was assessed by the Kolmogorov-Smirnoff test. Two-tailed Student's t-test for independent samples was used to compare quantitative variables. Fisher's exact test was used to compare categorical variables. Values $p<0.05$ were adopted for statistically significant.

STATISTICA 13.3.0, StatSoft Inc, USA software package was used for all statistical analysis.

III. RESULTS

The obtained values for the coefficients a and b of the simple linear regression equation for each coagulation activity indicator are presented in Table 2.

Based on these, regression models were created to predict the values of the indicators depending on the duration of the rhythm disturbance (Table 3).

F1 + 2 plasma levels ($r = 0.83$, $p <0.001$; Fig. 1), FPA ($r = 0.84$, $p <0.001$; Fig. 2), FVIII ($r = 0.85$, $p <0.001$; Fig. 3) have a good correlation with arrhythmia duration, as well as FII coagulation activity ($r = 0.83$, $p <0.001$; Fig. 4), FVIII ($r = 0.83$, $p <0.001$; Fig. 5) and FXII ($r = 0.78$, $p <0.001$; Fig. 6) (Table 2). The positive value of coefficient ***b*** determines the direct proportionality between the values of these parameters and duration of arrhythmia (Table 2), i.e. an increase in PAF duration, increases indicator values increase. FXI activity has low correlation with disease duration ($r = 0.39$, $p <0.001$) (Table 2). The adjusted correlation coefficient R^2 for the corresponding indicator indicates how much the change in the values of this indicator can be explained by the change in the arrhythmia duration.

For example, for the F1+2 values, this coefficient is 0.67, i.e. 67% of the change in F1+2 values are due to the change in arrhythmia duration. Accordingly, for FPA levels this percentage is 70%, for FVIII - 72%, for FVIII activity - 69%, for FII activity - 67% and 61% for FXII activity. A very weak correlation was found between PAF duration and vWF levels (r = 0.15, p> 0.05), vWF activity (r = 0.13, p> 0.05), FV activity (r = -0.11, p> 0.05; Fig. 7), FVII activity (r = 0.20, p> 0.05; Fig. 8), FX activity (r = 0.11, p> 0.05) and FXI (r = 0.20, p> 0.05). R^2 was not applicable for these indicators.

Table2. Values of the estimated parameters of univariate regression models and the obtained correlation and adjusted determination coefficients.

Coagulation marker	a p-value	b p-value	R	Adjusted R^2
F1+2 plasma levels	167.68 <0.001	15.31 <0.001	0.83	0.67
FPA plasma levels	2.22 <0.001	0.28 <0.001	0.84	0.70
FVIII levels	67.46 <0.001	4.91 <0.001	0.85	0.72
FVIII activity	100.30 <0.001	12.23 <0.001	0.83	0.69
vWF levels	198.97 0.05	-2.53 0.30	0.15	n.a.
vWF activity	217.79 <0.001	-2.07 0.38	0.13	n.a.
FII activity	86.62 <0.001	9.95 <0.001	0.83	0.67
FIX activity	150.48 <0.001	2.45 0.04	0.39	0.13
FV activity	211.23 <0.001	-1.57 0.44	0.11	n.a.
FX activity	207.26 <0.001	-1.73 0.44	-0.11	n.a.
TF levels	245.53 <0.001	2.83 0.24	0.17	0.01
FVII activity	189.01 <0.001	2.23 0.15	-0.20	0.02
FXII activity	118.84 <0.001	12.20 <0.001	0.78	0.61
FXI activity	195.63 <0.001	-2.11 0.15	0.20	0.02

(n.a. – not available)

Table 3. Regression models for the values of the corresponding coagulation indicators as a function of the arrhythmia duration.

F1+2 plasma levels=167.68 + 15.31X
FPA plasma levels=2.22 + 0.28X
FII activity=86.63 + 9.95X
FV activity=211.23– 1.57X
FVII activity=189.01+ 2.23X
FVIII levels=67.46 + 4.91X
FVIII activity=100.30 + 12.23X
vWF levels=198.97– 2.53X
vWF activity=217.79 – 2.07X
FIX activity=150.48 + 2.45X
FX activity=207.26– 1.73X
FXII activity=118.84 + 12.20X
FXI activity =195.63– 2.11X
TF levels=245.53 + 2.83X

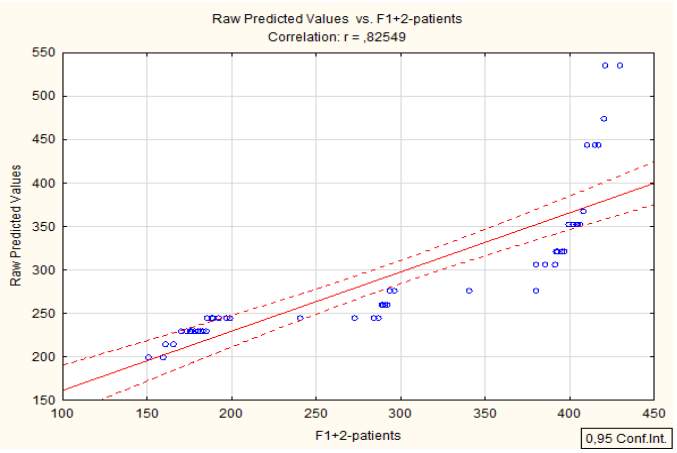

Figure 1. Scatter plot of measured versus predicted F1 + 2 plasma levels in PAF patients.

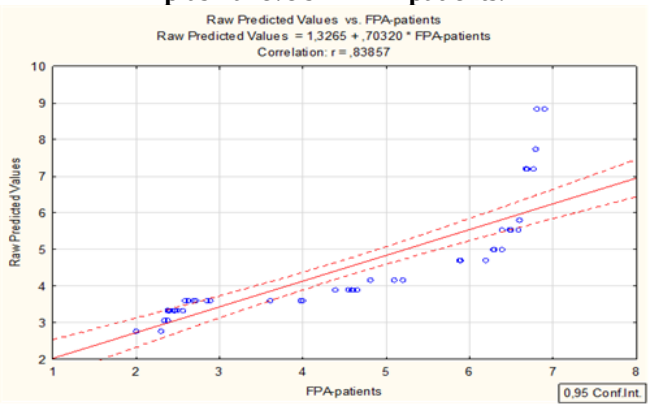

Figure 2. Scatter plot of measured versus predicted FPA plasma levels in PAF patients.

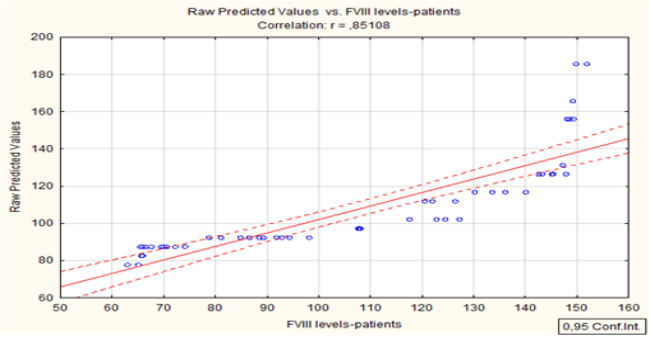

Figure 3. Scatter plot of measured versus predicted FVIII plasma levels in PAF patients.

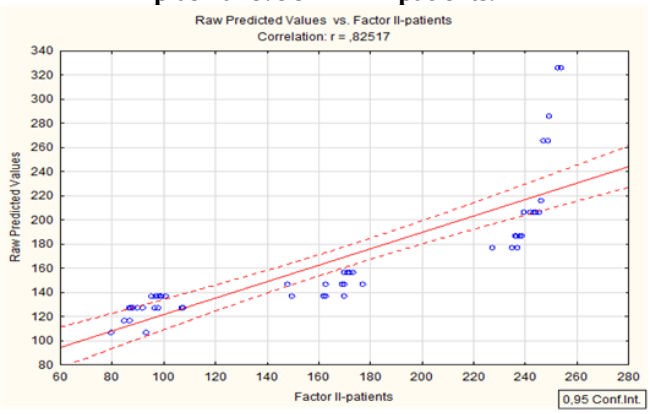

FIGURE 4. Scatter plot of measured versus predicted FII plasma levels in PAF patients.

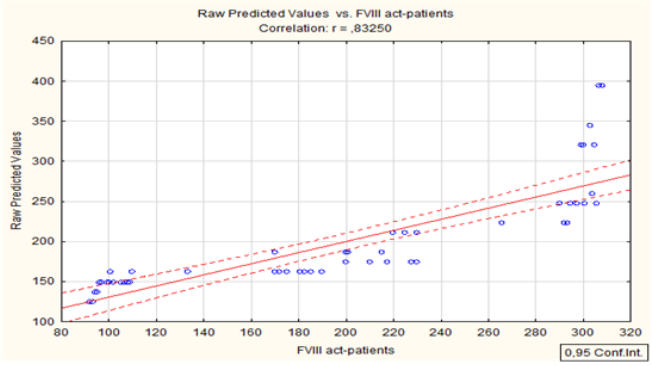

Figure 5. Scatter plot of measured versus predicted FVIII activity in PAF patients.

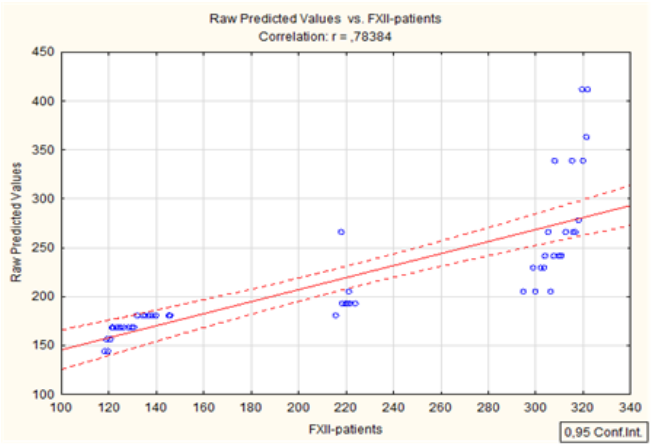

Figure 6. Scatter plot of measured versus predicted FXII activity in PAF patients.

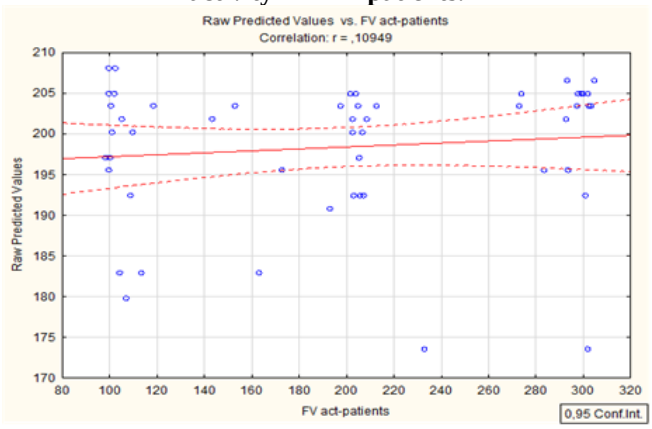

Figure 7. Scatter plot of measured versus predicted FXII activity in PAF patients.

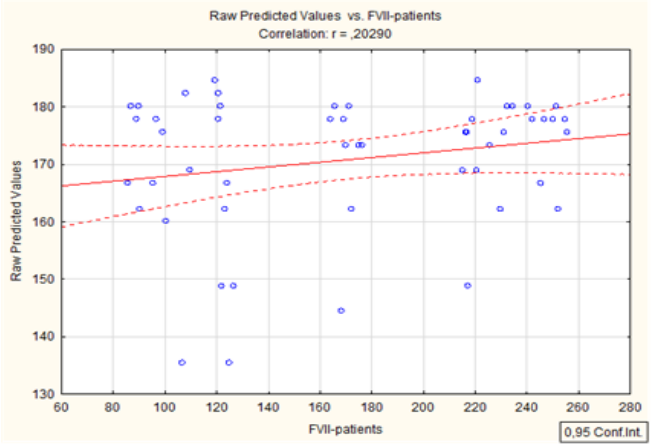

Figure 8. Scatter plot of measured versus predicted FVII activity in PAF patients.

IV. DISCUSSION

Atrial fibrillation is associated with high risks of stroke or other thromboembolic events [7]. The pathophysiological mechanism associated with thrombus formation process is multifactorial [19]. Stasis in a poorly contracting left atrium has its own contribution, but in recent years there has been increasing evidence of hypercoagulation in AF [20-22]. Other studies have denied this [23, 24]. Of particular interest is the coagulation balance in PAF. Studies here are also controversial [25-27]. Our results showed significant activation of coagulation [14-17]. The statistical analysis showed no significant difference between the patient and the control group in terms of age and sex demographics, as well as in accompanying diseases and treatment, deleterious habits and BMI (p> 0.05) (Table 4).

Table 4. Clinical characteristics of the participants.

	Patients with PAF	**Controls**	**P values**
Number of participants	51	52	p=0.89
Mean age (years)	59.84±1.60	59.50±1.46	p=0.87
Men/Women	26/25	26/26	p=1/ p=0.93
Accompanying diseases			
Hypertension	37 (72.54%)	34 (65.38%)	p=0.44
Diabetes mellitus type 2	3 (5.88%)	2 (3.84%)	p=0.62
Dyslipidemia	4 (7.84%)	3 (5.77%)	p=0.69
Medicaments for Hypertension and Dyslipidemia			
Beta blockers	19 (37.25%)	17 (32.69%)	p=0.62
ACE inhibitors	15 (29.41%)	14 (26.92%)	p=0.78
Sartans	11 (21.57%)	9 (17.31%)	p=0.58
Statins	4 (7.84%)	3 (5.77%)	p=0.69
Deleterious habits			
Smoking	8(15.69%)	7(13.46%)	p=0.75
Alcohol intake	7(13.72%)	6(11.53%)	p=0.74
BMI (kg/m^2)	23.85±0.46	24.95±0.45	p=0.09
CHA_2DS_2–VASc score*		No score	
Patients with score < 2	25		
Patients with score ≥ 2	26		

The equalization of the two groups makes the comparison between them in terms of coagulation indicators as objective as possible. It also makes it possible to take into account the effect of PAF itself on the studied indicators.

Regression analysis is a method of examining the functional dependency between variables, presented as an equation (model) linking the response or the dependent variable with one or more explanatory or predictor variables [28]. These characteristics of the regression analysis led us to seek models through which we could reliably predict the values of coagulation parameters depending on the arrhythmia duration in PAF patients. Correlation coefficient R and adjusted coefficient R^2 are the main indicators of the adequacy of the created model. They show, respectively, the correlation strength and the proportion of changes in a given indicator that depend on the duration of the disease. Of the fourteen regression models presented above (Table 3), eight have a very weak correlation coefficient (<0.2) and a statistically insignificant ***b*** coefficient (p> 0.05). Only six of them are associated with a good correlation coefficient (R> 0.6), showing high correlation between the values of the corresponding coagulation indicator and PAF duration.

These are the models representing F1 + 2 plasma levels, FPA plasma levels, FVIII levels, FVIII activity, FII activity and FXII activity (Table 5). It is from these models that we expect good prediction of the time-varying coagulation indicators in PAF patients.

Table 5. Regression models of coagulation indicators in PAF with high correlation

F1+2 plasma levels=167.69 + 15.31X
FPA plasma levels=2.22 + 0.28X
FVIII levels=67.46 + 4.91X
FVIII activity=100.29 + 12.23X
FII activity=86.63 + 9.95X
FXII activity=118.84 + 12.20X

These models also showed a high, approximately the same, adjusted coefficient of determination R^2, which is also indicative of the models' reliability (Table 2). Looking at the F1+2 model, $R^2 = 0.67$ indicates that 67% of the total F1+2 plasma levels dispersion can be explained by the factor time dispersion (PAF duration). The remaining 33% are due to factors not included in the model. Similarly with the models presented for FPA plasma levels, FVIII levels, FVIII activity, FII activity and FXII activity, we could explain 70%, 72%, 69% and 61% of the variance of the indicator as a result of time variance (Table 2).

In formulating conclusions about the quality of the linear model for predicting the values of Y (dependent variable), its coefficient ***b*** **(**determines the contribution of X in forming the values of Y) is of major importance. The greater the value of ***b***, the greater the change in the dependent variable by changing the factor variable X with one measure unit. In this sense, of the six models with good correlation, the model for the plasma levels of F1+2, where ***b*** = 15.31, is the most impressive. It turns out that with a single unit change in the time of arrhythmia, the largest changes are expected in the values of this indicator. Changes in F1+2 plasma levels are most sensitive to PAF duration.

V. CONCLUSION

Linear regression analysis allowed us to create models with a high correlation coefficient for predicting the values of F1+2, FPA, FVIII levels, as well as the activity of FII, FVIII and FXII in PAF patients. These models could allow for quantification of the procoagulatory process and the thrombotic potential of the disease.

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Conflicts of interest

No conflicts of interest to declare.

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