

## Matrix Predictor of the Recurrence of Atrial Fibrillation.

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**Background**—Tissue inhibitor of metalloproteinases-1 (TIMP-1) is involved in extracellular matrix remodeling which is considered to be a marker of regulation of matrix metalloproteinase activity.

**Methods**—An enzyme-linked immunosorbent assay prior to a radiofrequency catheter ablation (RFA) procedure was used for measuring the serum level of TIMP-1 in 210 patients: 80 patients without history of atrial fibrillation (AF) and 80 patients with idiopathic AF (paroxysmal AF – 30, persistent AF – 32, long-standing AF – 35 and permanent AF – 33). Their relationship with intraoperative efficacy and recurrence of AF was evaluated throughout the observation period.

**Results:** The observation period was  $22.2 \pm 7.9$  months. TIMP-1 level was higher in the groups of patients with AF than in the control group:  $131.51 \pm 36.40$ ,  $149.5 \pm 42.7$ ,  $151.5 \pm 42.7$  and  $155.9 \pm 44.7$  ng/ml for paroxysmal, persistent, long-standing and permanent forms of AF. In the control group, TIMP-1 level was  $103.6 \pm 14.7$  ng/ml. TIMP-1 level increased with the progression of AF ( $p < 0.05$ ). A multifactor analysis showed that TIMP-1 level, history of atrial fibrillation and left atrial volume were independent predictors of sinus rhythm recovery and recurrence of AF.

**Conclusion**—An increase in TIMP-1 level in patients with AF has been shown. An increase in TIMP-1 levels was observed as AF progressed. TIMP-1 is prognostic criteria of arrhythmia recurrence after RFA.

**Key words:** TIMP-1, fibrillation, ablation, matrix.

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### Abbreviations and Acronyms

AF	=	atrial fibrillation
AFL	=	atrial flutter
AT	=	atrial tachycardia
ESC	=	European society of cardiology
LA	=	left atrium
MMPs	=	matrix metalloproteinases
RFA	=	radiofrequency catheter ablation
TIMPs	=	tissue inhibitors of metalloproteinases

### I. Introduction

Atrial fibrillation is the most common sustained arrhythmia in clinical practice. Recent prevalence estimates suggest that at least 33.5 million persons are affected by atrial fibrillation (AF) (1). Its prevalence increases with age, from 0.1% in people younger than 55 years to more than 9% by 80 years of age (2).

Catheter ablation is the most promising treatment for AF. The multiple procedure success rate of pulmonary vein isolation for paroxysmal AF is approximately 70% - 80% after long-term follow-up (3,4). However, the success rates of pulmonary vein isolation for non-paroxysmal forms are ranging from 55%-70% for persistent and 50-60% for long standing AF. Recurrences are common after an initial procedure for non-paroxysmal forms of AF ablation and repeat ablation is often required to maintain freedom from AF (5). Thus, new non-invasive preoperative predictors for assessment atrial structure remodeling are necessary to select the optimal ablation strategy for patients with AF.

Experimental and clinical researches have shown that, whatever the initial cause or trigger, there is a relationship between AF and alterations in atrial electrical properties (6). The longer the duration of AF, the more persistent it becomes because of atrial remodeling. Remodeling of cellular ultra-structures, such as myolysis occurring in the atrial myocardium, is known to develop progressively during AF (14). An increase in the expression of the gap junctions (connexin 40) has been reported to induce changes in the biophysical properties of the atrial tissue during AF (15,16). Enhanced disintegrin and metalloproteinase activity was also reported to be an important mechanism of AF (10,11) that could lead to atrium diameter expansion, atrial wall thinning and, thus, atrium structure reconstruction. (12)

Endogenous proteolytic enzymes involved in extracellular matrix remodeling include the matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs), consequently, the serum level of MMP-9, TIMP-1 and their relationship are considered to be a marker of extracellular collagen degradation (13). In particular, many reports have demonstrated that TIMP-1 may be implicated in the development of myocardial fibrosis. For example, the TIMP-1 level is an important index for myocardial fibrosis, (14,15) and also has a close relationship with other cardiovascular diseases (16,17).

The purpose of this study was to investigate the relationship between the serum TIMP-1 level and arrhythmia recurrence after catheter ablation in patients with AF at different stages of disease progression.

## II. Methods

Using a case-control study design, TIMP-1 in a group of patients with atrial fibrillation was compared with TIMP-1 in a control group of patients in sinus rhythm who were undergoing routine physical examination. Atrial fibrillation were categorized into paroxysmal, persistent, long-standing and permanent according to a manual (ESC Clinical Practice Guidelines 2016). Exclusion criteria were structural heart diseases; hematologic, renal, or hepatic disorders; inflammations; neoplastic diseases; recent (<3 months) myocardial infarction or stroke; thyrotoxicosis-associated AF; or any acute infections. The study was approved by the Ethical Committee of the Odessa Regional Clinical Hospital, Odessa National Medical University. All patients signed an informed consent.

### Study groups

This study included 208 consecutive patients with various forms of AF. The main group consisted of 128 patients with AF resistant to drug therapy. The control group consisted of 80 patients without heart rhythm disorders and practically healthy patients (Table 1). The mean age of patients in the main group was  $53.5 \pm 7.6$  years, of them: 54 (41%) women and 77 (59%) men. The mean age of patients in the control group was  $52.7 \pm 5.6$  years, of them: 31 (38.8%) women and 49 (61.3%) men. Both groups are comparable in age (U-test,  $p = 0.17$ ) and gender (Fisher test,  $p = 0.55$ ).

### Data Collection

The day before the RFA, the serum TIMP-1 level was determined, and a transesophageal echocardiography was performed. The method for determining the serum TIMP-1 level is described in the literature (11). In brief, blood samples were obtained by puncture of the peripheral vein and centrifuged at 3200xg for 10 minutes at a temperature of 4°C within one hour after collection. The serum was separated and stored at a temperature of -80 °C until the patient-blinded personnel performed the analysis. The serum TIMP-1 level was determined using a standard commercial enzyme-linked immunosorbent assay *in vivo* according to the manufacturer's guidelines (Ray Biotech INC, Atlanta, Georgia, USA). The coefficient of variation within and between assays was <10 and <12%, respectively.

The anatomical study of the left atrium (LA) and pulmonary veins was carried out on a spiral computed tomography (computed tomography) scanner "HiSpeed computed tomography/i" manufactured by "General Electric" (USA), with a gantry rotation speed at spiral scanning of 1 rotation per second. The study was conducted against the background of the administration of non-ionic contrast agents using an automatic injector "SimtRac DH" manufactured by Siemens (Germany). The procedure was performed on an empty stomach, under conventional therapy. As a rule, the left cubital vein was punctured to perform a computed tomography scan with angiography of the LA and LV. A 20G venous catheter was inserted into the vein and an automatic injector was connected. The volume of the contrast agent and the rate of its injection were set up in the injector. The volume of the contrast agent depended on the patient's weight and height (usually 70-100 ml). Contrast agents "Iohexol (GE Healthcare AC, Ireland/Norway)" and "Iopromid (Bayer Pharma AG, Germany)" were used.

Data post-processing included the reconstruction of axial slices, the construction of two- and three-dimensional images. A soft-tissue filter was always used to reduce noise and increase contrast resolution.

The results of the study were evaluated first by axial slices. Subsequently, reconstructed axial slices were used for a multiplanar reconstruction (multiplanar reconstruction). The construction of two- and three-dimensional reconstructions was performed on the GE workstation "Advantage Windows 2.0". The dimensions of the mouth of the pulmonary veins were measured in the axial plane and in the oblique plane of the multiplanar reconstruction. The three-dimensional reconstruction was performed in SSD mode, the anatomical structure of the left atrium and pulmonary veins was assessed (the number of veins flowing into the LA by their own mouth, the convergence of the pulmonary veins mouths, the common pulmonary veins collector).

### **Catheter ablation**

All patients had a catheter AF ablation under general anesthesia. Patients were heparinized to maintain an activated clotting time for more than 300 s. A three-dimensional electroanatomical model was constructed using a NavXelectroanatomical mapping system (St. Jude Medical, St. Paul, MN). The ablation procedure included following steps: 1) isolation of pulmonary veins, 2) linear ablation of the mitral isthmus, in the absence of an effect – ablation of the left atrial roof. In the absence of efficiency of the stages 1 and 2, linear ablations were additionally performed, which included a line along the posterior wall of the LV, a line along the cavotricuspid isthmus and isolation of the superior vena cava. The endpoint of the procedure was considered the termination of AF. In the absence of an effect, the sinus rhythm (sinus rhythm) was restored using electrical cardioversion.

According to the 2015 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF, any atrial tachycardia (AT), atrial flutter (AFL) or an episode of AF lasting more than 30 seconds three months after ablation should be defined as a recurrence.

### **Observation period**

All patients were monitored every month at the Polyclinic Department of the Odessa Regional Clinical Hospital. If patients complained of heart palpitations, fatigue, or other symptoms related to arrhythmias, the patients underwent 24-hour ECG monitoring. Patients were also advised to visit the attending doctor at any time when they develop symptoms for a 12-lead ECG or 24-hour ECG monitoring. Asymptomatic patients underwent 24-hour or situational ECG monitoring every 3 months after the procedure. The endpoint of the observation period was recording of an AT/AFL/AF recurrence with a duration of more than 30 s.

### **Statistical analysis methods**

Statistical data processing was carried out with the aid of the statistical package Statistica 6.1. Testing of the parameters for normality was carried out using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive data for quantitative features with normal distribution were presented as mean and standard deviation ( $M \pm \sigma$ ), those with non-normal distribution were presented in the form of median and interquartile interval (Me). Correlation analysis was performed using the Spearman's R-test for quantitative values. The relationship between values was evaluated as significant at  $R > |0.7|$ , moderate at  $R$  from  $|0.3|$  to  $|0.7|$ , weak at  $R < |0.3|$

## **III. Results**

In the postoperative period ( $12.3 \pm 6.4$  months), 35 (27.3%) patients developed recurrent AT/AFL/AF. The baseline characteristics of the patients in both groups are shown in Table 1. The data in the table showed no significant differences in age, gender, body mass index (body mass index), hypertension, left ventricle ejection fraction, or medication between the two groups. However, the group of patients with recurrent arrhythmias had a longer history of arrhythmias, greater LA diameter and a higher TIMP-1 level compared to the group without recurrence (Table 2).

### **Ablation procedure and electric cardioversion**

We retrospectively analyzed data from patients in both groups. The level of the recovery of sinus rhythm at stages 1, 2 and 3 in the two groups did not differ significantly. The only difference between the two groups was the linear ablation of the LA roof. At this stage, rhythm recovery was observed in 9 patients in group 1 and 7 patients in group 2 (9.7% and 20%, respectively,  $p = 0.04$ ) (Table 2).

### **Correlation analysis**

Calculations according to formula:

$$|r| = \frac{\exp[2t/(n-1,5)^{0,5} - 1]}{\exp[2t/(n-1,5)^{0,5} + 1]}$$

give following threshold values of correlation coefficient modules for a sample of  $n=130$  persons. (Table 3, 4, 5).

Graphic image of correlation between TIMP-1 and LAV is shown on Figure 1.

If the effectiveness in the absence of recurrence after 2 years is estimated according to the Harrington scale using integers, we obtain a non-linear relationship graph.

If non-integers are used to quantify the severity of arrhythmias, we obtain a practically straight-line dependence of the effect of the operation on the severity of arrhythmia (Figure 2).

### **Cluster analysis**

Using Cluster analysis, the preoperative level of TIMP-1 was determined in patients with various effects of the operation (Table 6). In the group of patients without relapse, TIMP-1 level was higher in the groups of patients with relapses of AF than in the group without relapses:  $195.5 \pm 9.0$ ,  $201,0 \pm 5,4$  and  $129,2 \pm 3,4$  ng/ml for the

groups with relapse through 2 years and 7 days and in a group without relapse, respectively. In the group without effect, the TIMP-1 level was  $187.9 \pm 8.9$  ng/ml, which indicates the completion of structural myocardial remodeling. In the control group, TIMP-1 level was  $170.0 \pm 2.0$  ng/ml. TIMP-1 level increases with the progression of AF until complete structural myocardial remodeling (Figure 3).

It should be noted that the clinical features of the patients played an important role on the consequences of the operation (Table 7). The main contribution to the recurrence of atrial fibrillation made hypertonic disease and heaviness of the arrhythmia (Figure 4).

#### **IV. Discussion**

In the present study, we have prospectively studied the TIMP-1 level as predictors of the recurrence of arrhythmia after a procedure of RFA of AF. We found that TIMP-1 levels in patients with AF were significantly higher than those in the healthy control population, indicating that TIMP-1 may play a role in the occurrence and maintenance of AF. The mechanism behind AF is complicated and AF is often caused by several factors (18). Including myocytes of the atrium and fibrous changes in the connective extracellular matrix (EM), which contribute to the development of AF. In turn, fibrosis is caused by an imbalance between degradation and deposition of cardiac EM, which is a nonspecific response to cardiomyocyte necrosis or apoptosis.

TIMP-1 is a member of the TIMP family which represent a group of peptidases involved in degradation of the extracellular matrix. In addition to its inhibitory role against most of the known MMPs, the encoded protein is able to promote cell proliferation in a wide range of cell types, and may also have an anti-apoptotic function and can play a determining role in the structural remodeling of atriums involved in the development and maintenance of AF (19). Previous experimental studies showed that TIMP-1 plays a key role in heart remodeling and promotes chamber dilatation and excessive collagen accumulation in both senile hearts and in post-infarction hearts (20,21). It has recently been established that TIMP-1 levels are closely related to the initiation and maintenance of AF. According to various researchers, elevated TIMP-1 levels were shown to be independently associated with an increased risk of AF development (22). It is noteworthy that the TIMP-1 level correlated with AF development. With progression of idiopathic AF, the TIMP-1 level gradually increased from paroxysmal to persistent and constant form of AF (23). In addition, previous studies also showed that the TIMP-1 level was associated with atrial remodeling in patients with AF. For the first time, a close relationship between TIMP-1 and AF (24) was demonstrated. It has been shown that increased expression of TIMP-1 may contribute to the structural remodeling of atriums and to atrial dilatation during AF. TIMP-1 also participates in atrial remodeling after catheter ablation. In addition, a significant increase in TIMP-1 regulation is associated with a large decrease in the size of the left atrium (25). Patients who developed recurrence had a higher serum TIMP-1 level, indicating a more serious atrial remodeling and form of AF. These assumptions were confirmed by a long history of AF and large sizes of the LA in this group. To date, the efficacy of RFA in patients with persistent, long-standing and permanent forms of AF remains unsatisfactory. Despite the adoption of new techniques, recent studies have shown that up to 40% of patients had a recurrence of tachycardia after the primary procedure (26). What patient characteristics can be used to evaluate their prognosis remains unclear. Various candidates were reported to predict the recurrence of AF after catheter ablation, including age, gender, body mass index, ECG, echocardiographic data, observations made using cardiovascular magnetic resonance imaging (magnetic resonance imaging) and some serum or plasma factors (27). Some of these studies contradict one another, while the most accurate predictors of recurrences after ablation of AF remain uncertain. AF progresses with worsening fibrosis and inflammation. Various inflammatory factors cause focal myocardial necrosis, modulate the functionality of the ion channel, and then initiate structural and electrical atrial remodeling. TIMP-1 is one of the markers of fibrosis and inflammation, which is associated with atrial remodeling in patients with AF. Elevated levels of TIMP-1 are associated with the occurrence and maintenance of AF (28). In this article, we investigated the factors that may have prognostic significance for the results of catheter ablation of AF in the early and late postoperative period. We observed that traditionally reported factors, such as a history of AF and left atrium diameter, were also significantly associated with AF recurrence. In addition, the serum TIMP-1 level was found to be an independent predictor of recurrence. Thus, to eliminate this bias, the presence of AF without structural heart disease was confirmed in all patients registered in our study. Our data showed that serum TIMP-1 level was effective in predicting the recurrence of AF in this cohort. There are many members in the superfamily of TIMPs. In addition to TIMP-1, some other members (TIMP-2, TIMP-3) and MMPs, such as MMP-2, MMP-3 and MMP-7, also have a strong association with the frequency of AF (29). In this study, we focused on TIMP-1, so other TIMP and MMP are candidates for further studies. Whether any of these MMPs/TIMPs (or their combinations) are also indicators of the risk of AF recurrence after catheter ablation remains a mystery. Our results can be useful for selecting the optimal candidate for catheter ablation of AF. Since the TIMP-1 level correlates with atrial fibrosis and predicts AF recurrence, it can also be a therapeutic target. MMP inhibition and regulation of the extracellular collagen matrix can be therapeutically useful in patients with AF. Gene removal or pharmacological inhibition of MMP activity weakens atrial

remodeling and reduces vulnerability to AF (30). In the TIPTOP study, the MMP tissue inhibitor doxycycline was used briefly in patients with acute myocardial infarction and left ventricular dysfunction. The results of the study showed that doxycycline therapy inversely correlated with the size and severity of infarction during six months and left ventricle dilatation (31). No clinical trials have been reported on the use of MMP platelet inhibitors for the treatment of AF. A prospective randomized study to determine the TIMP-1 level in predicting AF recurrence and to evaluate the effect of a tissue MMP inhibitor on AF may be justified.

### **Limitations**

Limitation of the present study is its sample size a larger sample is needed for further research. Given that AF is a multifactorial disease with unclear etiology, that in the TIMPs superfamily many members and MMPs also have a strong connection with the progression of AF (29) further research should also be directed to study them. Whether any of these MMPs/TIMPs (or their combinations) are also indicators of the risk of AF recurrence after catheter ablation remains a mystery. In conclusion, our study found that TIMP-1 levels are higher in patients with AF than in healthy controls, and that TIMP-1 may therefore be associated with the development of AF. In addition, our findings provide indications of a relationship between the increase in the TIMP-1 level and the progression of AF. Our results can be useful for choosing the optimal tactics of catheter and drug treatment. This study evaluated only patients with idiopathic AF without apparent structural concomitant pathology which could limit its generalizability. Further research is necessary.

### **V. Summary**

The patients included in this study were a special group of AF. The TIMP-1 level correlates with the intraoperative efficacy of rhythm recovery and relapse in the early and late postoperative period and increases as AF progresses. Patients with constant AF had more extensive fibrosis than patients with persistent AF (32). Constant AF usually coexists with structural heart disease, which can aggravate fibrosis and inflammation. In recent recommendations, catheter ablation is not recommended for patients with constant AF. This study evaluated only patients with idiopathic AF without apparent structural concomitant pathology which could limit its generalizability. Serum TIMP-1 levels were higher in patients with recurrence and were identified as an independent predictor of arrhythmia recurrence after catheter ablation. In conclusion, we explained that the expression of TIMP-1 increases with the progression of AF and may contribute to structural atrial remodeling and increase the risk of relapse in the postoperative period. This requires the use of more complex integrated approach for the treatment.

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**Table 1. Baseline characteristics of the patients.**

	Paroxysmal AF (n = 30)	Persistent AF (n = 32)	Long-standing AF (n = 35)	Permanent AF (n = 33)	Control (n=80)	p
	30	32	35	33		
Age (years)	52.6±6.8	53.4±7.2	54.1±8.1	53.9±8.2	51.8±7.9	0.41
Gender (male), n (%)	19 (63.3)	18 (56.3)	21 (60)	20 (60.6)	39 (48.8)	0.3
Gender (female), n (%)	11 (36.7)	14 (43.8)	14 (40)	13 (39.4)	41 (51.3)	0.28
Body mass index (kg/m <sup>2</sup> )	25.9±4.9	26.4±5.3	27.1±4.4	26.6±4.8	26.7±4.5	0.34
AF history (years)	5.3±0.7	6.1±0.6	5.7±1.1	6.4±1.3	-	0.31
AH, n (%)	19 (63.3)	20 (62.5)	23 (65.7)	21 (63.6)	11 (13.8)	0.2
IHD, n (%)	4 (13.3)	4 (12.5)	5 (14.3)	4 (12.1)	-	0.24
AH+IHD, n (%)	2 (6.7)	2 (6.3)	3 (8.6)	4 (12.1)	-	0.29
Idiopathic AF, n (%)	5 (16.7)	6 (18.8)	4 (11.4)	4 (12.1)	-	0.28
EHRA I, n (%)	5 (16.7)	5 (15.6)	10 (28.6)	15 (45.5)	-	NS
EHRA II, n (%)	19 (63.3)	18 (56.3)	4 (11.4)	10 (30.3)	-	NS
EHRA III, n (%)	6 (20)	9 (28.1)	21 (60)	8 (24.2)	-	NS
Ventricular arrhythmias, n(%)	11 (36.7)	11 (34.4)	12 (34.3)	11 (33.3)	-	*0.38
Supraventricular arrhythmias, n(%)	13 (43.3)	12 (37.5)	14 (40)	14 (42.4)	32 (40)	*0.06
NYHA I class, n (%)	18 (60)	6 (18.8)	6 (17.1)	6 (18.2)	27 (33.8)	NS
NYHA II class, n (%)	12 (40)	25 (78.1)	28 (80)	26 (78.8)	-	NS
absent	0 (0)	1 (3.1)	1 (2.9)	1 (3.0)	53 (66.3)	0.45
TIMP-1,(ng/ml)	131.51±36.40	149.5±42.7	151.5±42.7	155.9±44.7	103.6±14.7	0.05
LA diameter, mm	35.7±2.1	41.4±3.2	44.3±3.4	47.5±4.4	34.3±2.0	0.05
Right lower pulmonary vein, mm	15.6±0.7	15.1±0.5	15.1±0.8	15.7±0.9	14.8±0.7	0.05
Right upper pulmonary vein, mm	15.6±1.1	15.9±0.9	15.7±1.2	16.0±1.3	15.1±1.1	0.05
Left lower pulmonary vein, mm	14.5±1.2	14.4±1.1	14.1±1.3	14.7±1.4	14.3±1.2	0.05
Left upper pulmonary vein, mm	16.0±1.1	16.1±0.8	15.8±1.2	16.2±1.3	15.3±1.1	0.05

p = Mann-Whitney test, p\* = Fisher criterion, AF = atrial fibrillation, AH = artery hypertension, IHD = Ischemic heart disease, EHRA = European heart rate association, NYHA = New York Heart Association, CHF = chronic heart failure, TIMP-1 = tissue inhibitor of metalloproteinase-1.

**Table 2.** Patients characteristics depending on the effectiveness of the ablation

	Without recurrence (n = 93)	With recurrence (n = 35)	p
Age (years)	51.3±7.6	54.6±7.9	0.057
Gender (male), n (%)	50 (53.8)	18 (51.4)	0.83
Body mass index (kg/m <sup>2</sup> )	26.1±4.9	27.4±6.1	0.33
AF history (months)	43.2±15.9	52.7±17.7	0.03
Hypertension n, (%)	12 (12.9)	4 (11.4)	0.82
Left atrial diameter (mm)	39.4±7.6	44.8±9.2	0.01
Left ventricle diameter (mm)	51.3±8.1	53.4±7.3	0.49
LVEF (%)	56.8±7.3	57.5±9.2	0.74
ACE inhibitor n, (%)	19 (20.4)	4 (11.4)	0.36
Amiodarone n, (%)	47 (50.5)	20 (57.1)	0.74
B-blockers n, (%)	87 (93.5)	33 (94.3)	0.99
TIMP-1 (ng/ml)	140,6±40,3	152,7±44,9	0.05
<b>Catheter ablation results</b>			
Step 1: Pulmonary vein isolation n, (%)	19 (20.4)	4 (11.4)	0.33
Step 2: linear ablation of left atrium n, (%)	40 (43)	20 (57.1)	0.29
Mitral Isthmus ablation n, (%)	31 (33.3)	13 (37.1)	0.55
Left atrial roofn, (%)	9 (9.7)	7 (20)	0.04
Step 1 + 2n, (%)	59 (63.4)	24 (68.6)	0.61
Step 3: additional linesn, (%)	34 (36.6)	11 (31.4)	0.33
Step 1 + 2 + 3n, (%)	76 (81.7)	26 (74.3)	0.08
Electrical cardioversionn, (%)	15 (16.1)	9 (25)	0.15

p = Mann-Whitney test, AF = atrial fibrillation, LVEF = left ventricle ejection fraction, ACE = angiotensin-converting-enzyme, TIMP-1 = tissue inhibitor of metalloproteinase-1.

**Table 3.** Matrix of correlation relationships between enzymes/cytokines and clinical indices

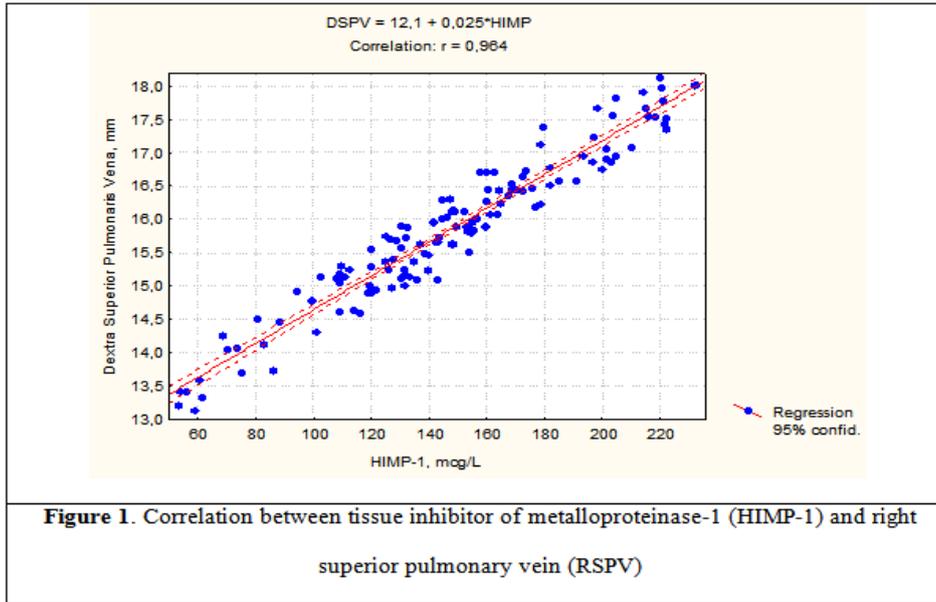
	HD	IHD	Arhythm-1	EHRA	NYHA	Sex	Age
TIMP-1	0.50	0.41	<b>0.73</b>	<b>0.70</b>	0.12	-0.01	0.13

TIMP-1 = tissue inhibitor of metalloproteinase-1., HD = Hypertension disease, IHD = ischemic heart disease, EHRA = European heart rate association, NYHA = New York Heart Association, Arhythm-1 = supraventricular arrhythmia.

**Table 4.** Matrix of correlation relationships between enzymes/cytokines and left atrium volume/pulmonary vein diameter

	LAVZ	LAV	RIPV	RSPV	LIPV	LSPV
TIMP-1	0.59	<b>0.76</b>	0.83	<b>0.96</b>	0.93	0.93

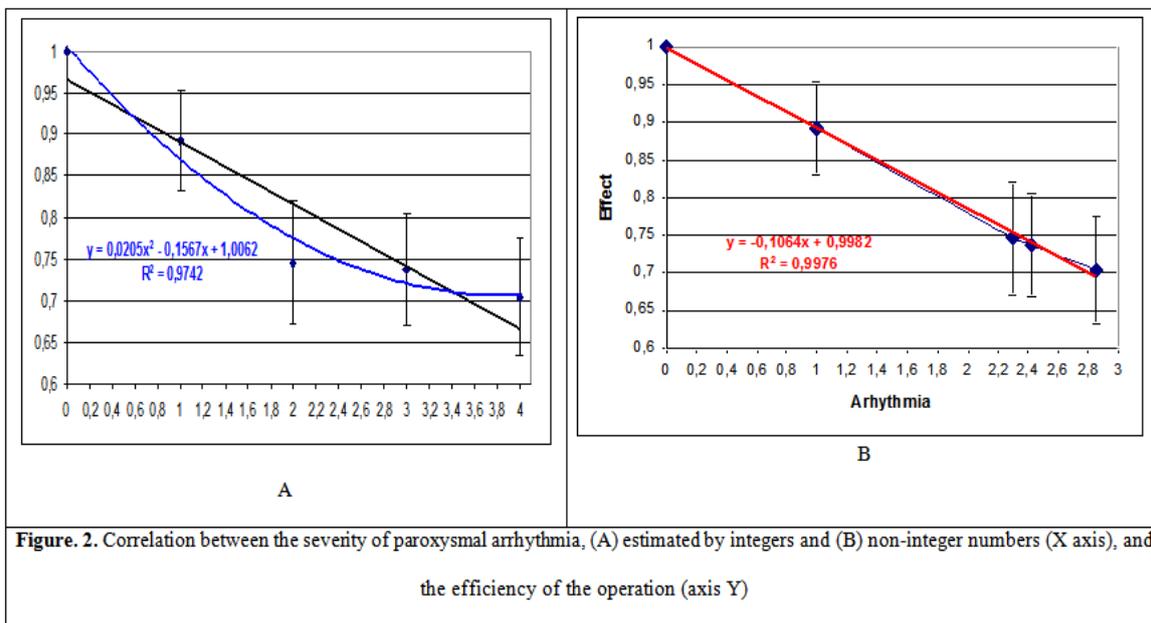
LAV = left atrial volume, RIPV = right inferior pulmonary vein, RSPV = right superior pulmonary vein, LIPV = left inferior pulmonary vein, LSPV = left superior pulmonary vein, TIMP-1 = tissue inhibitor of metalloproteinase-1.



**Table 5.** Four-fold matrix of the relationship between the form of atrial fibrillation and operation efficacy

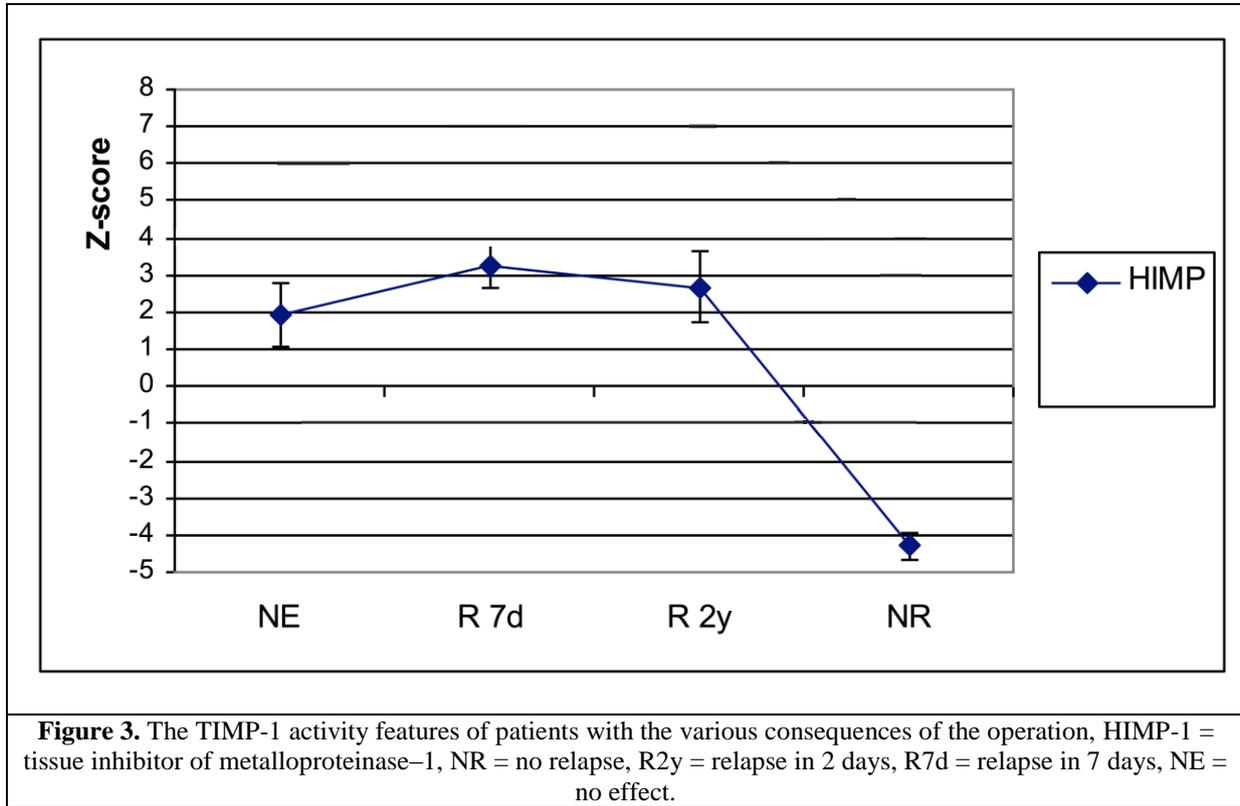
		Effect after procedure			Total	$(\sum n^2/Nx)/N$
		Without recurrence	Recurrence after 2 years	Recurrence after 7 days		
Paroxysmal AF	n	23	0	2	26	0.790
	$n^2/Nx$	20.346	0	0.154	20.538	
Persistent AF	n	22	2	3	31	0.534
	$n^2/Nx$	15.613	0.516	0.290	16.548	
Long-standing AF	n	25	4	4	36	0.514
	$n^2/Nx$	17.361	0.444	0.444	18.499	
Permanent AF	n	23	4	5	35	0.473
	$n^2/Nx$	15.114	0.457	0.714	16.543	
Total	$Ny$	93	10	14	128	2.311

AF – atrial fibrillation,  
 $\xi^2 = [(\sum n^2/Nx)/N] - 1 = 1.311$   
 $\varphi^2 = \xi^2 - (x-1)(y-1)/N = 1.311 - (4-1)(4-1)/128 = 1.241$   
 $R = \{\varphi^2 / (1 + \varphi^2) [xy / (x-1)(y-1)]^{0.5}\}^{0.5} = [1,241 / 2,241 \cdot (16/9)^{0.5}]^{0.5} = 0.860$   
 $\mu_R = (1 - R^2) / (N - 2)^{0.5} = 0.023$   
 $R = 0.860 \pm 0.023$ .



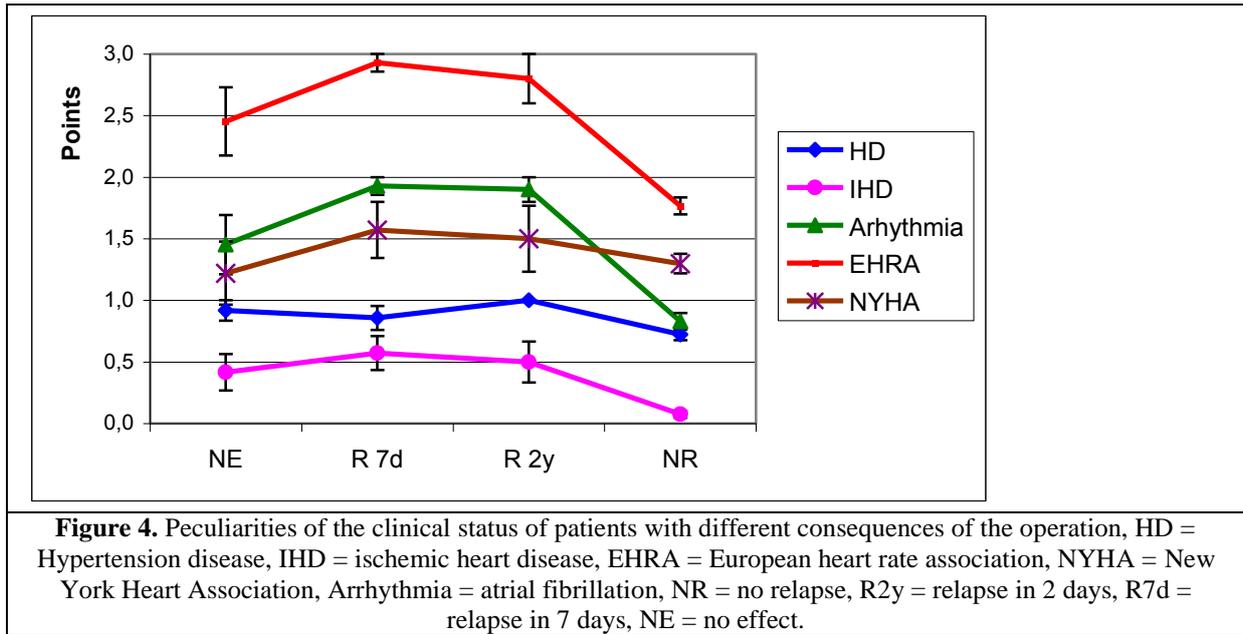
	NR	R2y	R7d	NE	Norm
TIMP-1, µg/L	129.2±3.4	195.5±9,0	201.0±5.4	188.4±8.3	170.0±2.0

TIMP-1 = tissue inhibitor of metalloproteinase-1, NR = no relapse, R2y = relapse in 2 days, R7d = relapse in 7 days, NE = no effect.



Clusters of Consequences (n)	Hypertonic Disease (No=0; Yes=1)	Ischemic Heart Disease (No=0; Yes=1)	NYHA (0; 1; 2)	EHRA (1; 2; 3)	Arhythmia-1 (No=0; Supraventricular=1; Ventricular=2)	Arhythmia-2 Fibrillation Heaviness, points
No Relapse (93)	0.72±0.05	0.08±0.03	1.31±0.08	1.76±0.07	0.83±0.07	2.15±0.07
Relapse after 2years (10)	1.00±0.00	0.50±0.17	1.50±0.27	2.80±0.20	1.90±0.10	2.57±0.08
Relapse after 7days (14)	0.86±0.10	0.57±0.14	1.57±0.23	2.93±0.07	1.93±0.07	2.35±0.16
No Effect (11)	0.91±0.09	0.36±0.15	1.16±0.29	2.41±0.32	1.41±0.28	2.37±0.15

EHRA = European heart rate association, NYHA = New York Heart Association



Oleksiy V. Goriachyi. "Matrix Predictor of the Recurrence of Atrial Fibrillation.." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 4, 2019, pp 25-34.