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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Clinical, laboratory and echocardiographic left atrial appendage thrombus predictors in patients with atrial fibrillation

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Abstract. Relevance. The most common and persistent arrhythmia today is atrial fibrillation (AF). Decrease in blood flow velocity in the left atrium appendage (LAA), endothelial dysfunction and hemostatic system changes can cause the development of left atrium appendage thrombosis (LAAT), which is the main source of thromboembolism in patients with AF. Numerous studies have explored various clinical, echocardiographic, and laboratory parameters as potential predictors, however, the predictive power of these parameters is still insufficient for real clinical practice. *Aim of the study* was to evaluate predictive ability of clinical, laboratory and echocardiographic markers in diagnosis of LAAT in patients with non-valvular AF. *Materials and methods.* The study included 100 patients with persistent non-valvular AF who were admitted for direct electrical cardioversion. All patients underwent clinical, laboratory, and instrumental studies, including transthoracic and transesophageal echocardiography (TEE). According to TEE results, patients were divided into 2 groups: patients with LAA thrombus «LAAT» (n = 30) and without LAA thrombus «Non LAAT» (n = 70). Statistical analysis was performed using the STATISTICA 10.0 software. *Results and Discussion.* Patients in both groups were comparable in age, gender, prevalence of hypertension, coronary artery disease, obesity, prior stroke, and diabetes mellitus ($p > 0.05$). Patients with LAAT had a significantly longer duration period of persistent AF (7 [4; 9] months vs 4 [3; 6] months, $p = 0.004$) in comparison with patients without LAAT. Laboratory markers of patients in both groups had no significant differences except for eGFR ($p = 0.047$) and NT-proBNP level ($p = 0.011$). According to the results of echocardiography, patients didn't have differences in left atrial (LA) diameter and volume ($p > 0.05$). However, LA volume index was higher in patients with LAAT ($p = 0.007$). When conducting a one-way ROC analysis, the NT-proBNP level of ≥ 1689 pg/ml showed the largest area under the ROC-curve (0.747) as well as the highest specificity (92.6%). Duration of persistent AF ≥ 4.5 months showed the highest sensitivity (90%). *Conclusion.* Patients with LAAT had longer duration of persistent AF, higher values of LA volume index, as well as higher NT-proBNP levels. Further use of these parameters could help predict LAAT development in patients with AF.

Keywords: atrial fibrillation; left atrial appendage thrombus; echocardiography; left atrial volume index; NT-proBNP

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Introduction

The most common and persistent cardiac arrhythmia today is atrial fibrillation (AF). According to European and North American registries, AF occurs in 3% of cases among adults aged 20 years and older [1]. According to Russian statistics, the incidence of AF among people from 35 to 70 years old is 0.75%, and significantly increases with age [2].

The clinical and social significance of AF is determined by the severity of its complications and increased mortality [3]. In patients suffering from AF, mortality is twice as high, and the likelihood of acute cerebrovascular accident increases six times compared to patients without AF [3]. Therefore, in modern recommendations for the management of these patients, anticoagulant therapy takes first place.

However, decrease in blood flow velocity in the left atrium appendage (LAA), endothelial dysfunction and hemostatic system changes can cause the development of left atrium appendage thrombosis (LAAT) [4], which is the main source of thromboembolism in patients with AF. A. Cresti et al. showed that only 0.07% of atrial thrombi in

non-valvular AF form outside the LAA [5]. Among patients with ischemic stroke caused by AF, LAAT can be detected in 75% [4].

According to several studies LAAT is present in up to 2.7% of patients with AF despite guideline-directed anticoagulation and 23% of patients with inadequate anticoagulation [6, 7].

Identifying predictors of LAAT formation is imperative for risk stratification, guiding therapeutic decisions, and ultimately improving the outcomes [4–7]. Numerous studies have explored various clinical, echocardiographic, and laboratory parameters as potential predictors [6–12].

Among the clinical risk factors, the authors determine coronary artery disease, heart failure, diabetes [8], as well as high risk according to the CHADS2 and CHA2DS2-VASc scores [9].

Some publications have information about a potentially significant role of increase in the NTproBNP level >75 pg/ml [10], as well as a decrease in eGFR less than 56 ml/min/1.73 m² in LAAT formation [8].

Echocardiography remains a cornerstone in the assessment of LAA function and thrombus formation. Many studies have focused on the search for

echocardiographic parameters that predict the risk of LAAT, revealing that left atrium (LA) diameter, area and LA index volume (LAVI) increase are associated with thrombus formation [11, 12].

However, the predictive power of these parameters alone is still insufficient for real clinical practice. The development of complex models based on clinical indicators, laboratory and instrumental markers is currently of particular interest. The simplicity and ease of use of these scales determine the possibility of their use both on an outpatient basis and in a hospital setting at any level in order to clarify the indications for additional methods of research and treatment, the use of which will optimize diagnostics, forecasting capabilities and the choice of treatment strategy for patients with AF.

The aim of our study was to identify clinical, laboratory and echocardiographic markers associated with LAAT in patients with non-valvular AF.

Materials and methods

The study included 100 patients with persistent non-valvular AF who were admitted to the Grodno State Cardiological Center for direct electrical cardioversion.

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Exclusion criteria from the study were: chronic rheumatic heart disease, valvular pathology of the heart requiring surgical correction, prosthetic heart valves, recent acute myocardial infarction, coronary artery bypass grafting, or coronary angioplasty (less than 3 months before enrollment in the study); left ventricular hypertrophy (Sokolov-Lyon index > 35mm); oncological diseases and severe concomitant extracardiac pathology.

All patients underwent clinical, laboratory, and instrumental studies, including transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE).

TTE was performed on Phillips iE33 device with a multi-frequency sensor (frequency 2.5–5.0 MHz). The examination was performed with the patient lying on his left side with his back to the researcher or on his back. The study protocol included the following indicators: diameter (mm) of the aorta, LA and right atrium (RA) in 2-chamber and 4-chamber mode, LA and RA area (mm²), volume (ml) and volume index (ml/m²), end-systolic diameter and end-diastolic diameter (mm) of the left ventricle (LV), left ventricular mass index (LVMI) (g/m²), LVEF; assessment of the state of the valvular apparatus of the heart, degree of regurgitation on the valves.

TEE was performed using Phillips iE33 device by an experienced echo cardiologist to assess for the presence of LAAT. The LAA was imaged in multiple views to identify thrombus.

According to TEE results, patients were divided into 2 groups: patients with LAA thrombus «LAAT» (n = 30) and without LAA thrombus «Non LAAT» (n = 70). The CHADS₂ VASc and HAS-BLED scores were calculated for each patient according to standard definitions.

Statistical analysis was performed using the STATISTICA 12.0 software package with a preliminary check for normal distribution using a distribution histogram. Quantitative data, the distribution of which was not normal, were given as a median, 25% and 75% quartiles. Since most of the quantitative characteristics did not obey the normal distribution law, non-parametric methods were used for comparison. The Mann-Whitney test was used to assess differences in quantitative traits between two independent groups. At a significance level of p less than 0.05, it was believed that the studied indicator in the compared groups had statistically significant differences. To compare the diagnostic value of indicators that showed statistically significant differences between groups, ROC curves of sensitivity and specificity were constructed.

Results and discussion

Clinical characteristics of the patients are presented in Table 1.

Table 1
Clinical characteristics of patients

Parameters	LAAT (n = 30)	Non LAAT (n = 70)	p
Male gender, n (%)	20 (66.7%)	42 (60%)	0.591
Age, years (M±SD)	63.6 [58; 69]	61.3 [54; 68]	0.166
Body mass index, kg/m ²	32.0 [27.9; 35.6]	31.3 [28.0; 34.0]	0.599
Obesity, n (%)	16 (53.3%)	38 (54.3%)	0.901
Hypertension, n (%)	28 (93.3%)	62 (88.5%)	0.665
Coronary artery disease, n (%)	27 (90%)	65 (92.8%)	0.870
Prior stroke, n (%)	1 (3.3%)	2 (2.8%)	0.788
Myocardial infarction history, n (%)	3 (10%)	2 (2.8%)	0.010
Diabetes mellitus, n (%)	3 (10%)	10 (14.2%)	0.455
Heart failure with reduced LVEF, n (%)	12 (40%)	5 (7.2%)	<0.001

Note: LVEF – left ventricular ejection fraction.

Patients in both groups were comparable in age (63.6 [58; 69] vs 61.3 [54; 68], $p = 0.166$) and gender (male sex 66.7% vs 60%, $p = 0.591$). There were no significant intergroup differences in the prevalence of hypertension, coronary artery disease, obesity, prior stroke, and diabetes mellitus ($p > 0.05$). However, patients with LAAT had a higher prevalence of prior myocardial infarction (10% vs 2.8%, $p = 0.01$) and heart failure with reduced EF (40% vs 7.2%, $p < 0.001$).

Patients with LAAT also had higher CHADS₂VASc scores (4 [3; 5] vs 3 [2; 4], $p = 0.031$), but their HAS-BLED scores were comparable (1.1 [1; 2] vs 1.18 [1; 1.4], $p = 0.720$) (Fig. 1.).

Also, it is important to add that patients with LAAT had a significantly longer duration period of persistent AF (7 [4; 9] months vs 4 [3; 6] months, $p = 0.004$) in comparison with patients without LAAT. All patients included in the study had a sufficient period (more than 3 weeks) of direct oral anticoagulation prior to hospital admission.

Laboratory parameters of the patients are presented in Table 2.

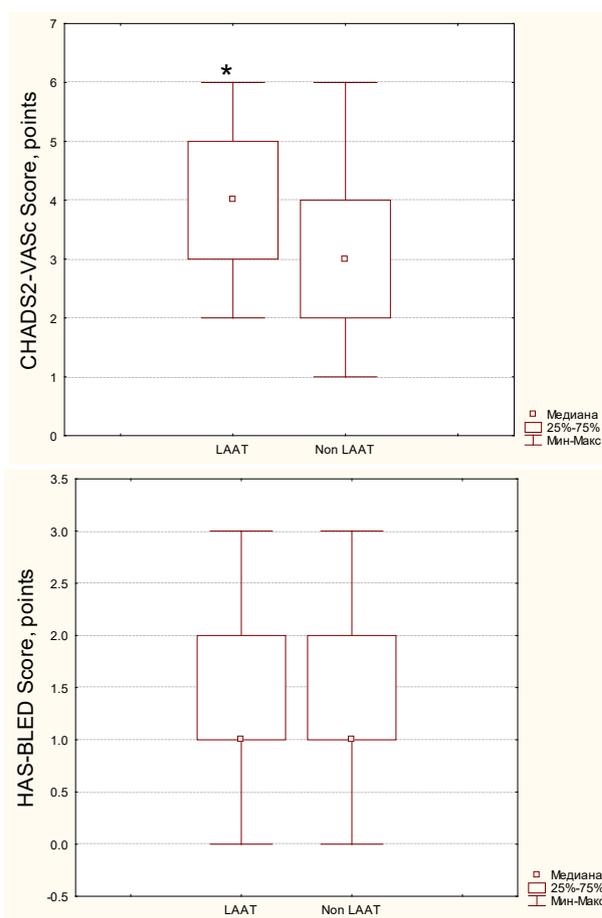


Fig. 1. CHADS₂VASc and HAS-BLED scores of patients

Table 2
Laboratory parameters of patients (Me [25%;75%])

Parameters	LAAT (n = 30)	Non LAAT (n = 70)	p
Urea, mmol/L	7.5 [5.9; 8.1]	6.4 [5.1; 7.4]	0.068
Creatinine, μmol/L	101.4 [78.7; 119.7]	91.7 [80.2; 101.3]	0.173
eGFR, ml/min/1.73m ²	71.2 [54; 84]	90.0 [64; 103]	0.043
Cholesterol, mmol/L	4.1 [3.2; 4.8]	4.5 [3.5; 5.3]	0.162
Glucose, mmol/L	6.3 [5.9; 6.8]	6.9 [5.5; 7.3]	0.891
Sodium, mEq/L	140 [137; 143]	139 [137; 142]	0.625
Potassium, mEq/L	4.5 [4.3; 4.9]	4.5 [4.2; 4.8]	0.915
APTT, seconds	33.3 [28.4; 36.4]	34.7 [27.9; 36.6]	0.702
Fibrinogen, g/L	3.15 [2.58; 3.71]	3.41 [2.4; 4.0]	0.929
D-dimer, ng/mL	301 [190; 405]	303 [190; 321]	0.602

End of the table 2

Parameters	LAAT (n = 30)	Non LAAT (n = 70)	p
INR (for patients taking rivaroxaban)	1.16 [1.02; 1.19]	1.12 [1.03; 1.14]	0.876
INR (for patients taking warfarin)	2.9 [2.6; 3.5]	3.2 [2.7; 3.7]	0.440
NT-proBNP, pg/mL	2076 [930; 2568]	1249 [602; 1595]	0.011

Note: eGFR – estimated glomerular filtration rate; APPT – activated partial thromboplastin time; N-terminal pro-B-type natriuretic peptide.

Laboratory markers of patients in both groups had no significant differences except for eGFR ($p = 0.047$) and NT-proBNP level ($p = 0.011$). Hemostatic screening tests such as prothrombin time, activated partial thromboplastin time, and fibrinogen levels did not show statistically significant intergroup differences.

Patients with LAAT more often used warfarin for anticoagulation (26.6% vs 4.3%, $p = 0.003$). However, there were no significant intergroup differences in INR values in these groups of patients ($p = 0.44$). The target level of INR (2.0–3.0) was reached in 75% of patients with LAAT and in 100% of patients without LAAT.

The values of echocardiographic parameters recorded in patients of both groups are presented in Table 3.

According to the results of TTE, patients didn't have significant differences in left atrial diameter ($p = 0.060$) and left atrial volume ($p = 0.056$). However, LAVI was higher in patients with LAAT ($p = 0.007$) as well as LA area ($p = 0.004$). Moreover, patients with LAAT

had lower left ventricular ejection fraction (LVEF) ($p = 0.019$) and higher RA diameter ($p = 0.019$) and area ($p = 0.007$).

Table 3
Echocardiographic parameters of patients (Me [25%;75%])

Parameter	LAAT (n = 30)	Non LAAT (n = 70)	p
LA diameter, mm	46.8 [43; 50]	44.2 [41; 46]	0.060
LA area, mm ²	30.1 [27; 33]	27.2 [24; 30]	0.004
LA volume, ml	74.6 [61; 85]	63.8 [52; 72]	0.066
LAVI, ml/m ²	37.6 [31; 42]	30 [24; 36]	0.007
RA diameter, mm	43.1 [41; 45]	41.1 [39; 44]	0.019
RA area, mm ²	26.7 [23; 30]	23.8 [21; 27]	0.007
LV ESD, mm	41.6 [33; 45]	36.1 [32; 40]	0.030
LV EDD, mm	54.8 [51; 58]	52 [48; 56]	0.220
LVEF, %	49.2 [44; 60]	57.4 [55; 62]	0.019
LVMI, g/m ²	147.4 [119; 164]	121.3 [99; 136]	0.003

Note: LA – left atrium; LAVI – left atrial volume index; RA – right atrium; LV – left ventricle; ESD – end-systolic diameter; EDD – end-diastolic diameter; LVEF – left ventricular ejection fraction; LVMI – left ventricular mass index.

It is interesting to say that patients didn't have differences in values of end-diastolic diameter of the left ventricle ($p = 0.22$), but patients in the LAAT group had significantly higher end-systolic diameter of the left ventricle ($p = 0.03$) and LVMI ($p = 0.003$).

When conducting a one-way ROC analysis, threshold values of clinical, laboratory and echocardiographic parameters associated with the development of LAAT were identified (Table 4).

Table 4**Results of one-way ROC analysis**

Parameter	Thresholdvalue	AUC	CI 95%	Se,%	Sp,%	p
Duration of persistent AF, months	4,5	0.682	0.563–0.802	90.0	38.6	0.019
NT-proBNP, pg/ml	1689	0.747	0.568–0.926	63.6	92.6	0.032
LA area, mm ²	27.9	0.682	0.563–0.802	73.3	62.8	0.019
LAVI, ml/m ²	30.0	0.680	0.561–0.800	76.7	52.8	0.020
RA diameter, mm	41	0.649	0.526–0.771	83.3	41.2	0.047
RA area, mm ²	29.9	0.670	0.552–0.792	36.7	91.4	0.025
LVEF, %	51	0.701	0.584–0.819	53.3	85.7	0.011
LVMI, g/m ²	135.8	0.687	0.568–0.806	56.7	74.3	0.016

Note: AUC – area under the curve; CI – confidence interval; Se – sensitivity; Sp – specificity.

The NT-proBNP level of more than 1689 pg/ml showed the largest area under the ROC-curve (0.747) as well as the highest specificity (92.6%). Duration of persistent AF ≥ 4.5 months showed the highest sensitivity (90%), however, the lowest specificity. Among the echocardiographic parameters LVEF $\leq 51\%$ demonstrated the largest area under the ROC-curve (0.701), as well as pretty high specificity (85.7%).

In patients with persistent AF both systolic and diastolic LV functions are impaired significantly [11, 12]. NT-proBNP is an endogenous biomarker, which is secreted primarily by ventricular as well as atrial myocardial cells in response to the overload of volume and pressure in the heart chamber and can be produced by atria and ventricles during AF. G. Yu et al. reported that elevated plasma NT-proBNP levels and LV filling pressure can be associated with high thromboembolic risk in patients with AF [13]. In that study plasma NT-proBNP levels were significantly correlated with LAA emptying flow velocity ($r = -0.492$, $p < 0.001$) and LAVI ($r = 0.405$, $p < 0.001$) [13]. D.V. Chien et al. have found that in patients with LVEF $> 50\%$, the cutoff value of NT-proBNP to predict LAAT was 1325 pg/mL (AUC — 0.57; Se — 57%, Sp — 78%) [14]. Multiple logistic regression analysis in that study showed that prior stroke, E/e' index, and NT-proBNP correlated with LAAT ($r = 0.887$; $p < 0.001$; $r = -0.092$, $p = 0.035$ and 0.022 ; $p = 0.004$, respectively) [14]. The above-mentioned results are in accordance with our findings, but the cut-off value of NT-proBNP in Belarusian population was higher (1689 pg/ml than in Vietnamese).

H. Okuyama et al. identified fibrin monomer as an independent predictor of LAAT (OR 2.9; 95% CI 1.1–4.8; $p = 0.02$) [15]. H. Wan et al. performed a meta-analysis of 21 studies assessing the relationship between D-dimer levels and LAA thrombosis. The analysis showed moderate sensitivity (0.75 [95% CI: 0.65–0.83]) and specificity (0.81 [95% CI: 0.59–0.93]) of D dimer level for diagnosing LAA thrombosis [16]. However, in our study there were no significant associations between D-dimer level and LAAT formation.

Several studies have investigated echocardiographic parameters as predictors of LAAT formation [11,

12, 17–19]. For instance, a study by D. Fatkin et al. revealed that spontaneous echo contrast was identified as the cardiac factor most significantly linked with formation of thrombus and embolism in the LAA [17]. Similarly, Y. Agmon et al. highlight the significance of utilizing echocardiography in identifying patients at increased risk of LAAT formation [18]. Their study demonstrates how TEE assists in the comprehensive assessment of the appendage's structure and function, utilizing imaging in two dimensions and Doppler assessment of appendage flow. Furthermore, as cited by Y. Liu et al., an enlarged LA (anteroposterior diameter ≥ 49.5 mm) and non-paroxysmal AF are identified as an independent risk factor for LAAT formation in individuals diagnosed with non-valvular AF [19]. In our study LVEF $\leq 51\%$ demonstrated the largest area under the ROC-curve and specificity among all the studied parameters, but there were significant intergroup differences in LAVI and LA area, which is also in accordance with above mentioned studies.

With the advent of new modern ultrasound diagnostic methods, new predictors of LAAT are emerging. Thus, K. Kupczynska et al. studied the relationship between LAAT and echocardiographic parameters: a retrospective study included 87 patients with AF, and a multivariable model showed that LVEF (OR 0.94; 95% CI 0.91–0.98), longitudinal systolic LA strain (OR 0.89; 95% CI 0.82–0.98), early diastolic (OR 5.3; 95% CI 1.5–18.3) and systolic LA strain rates (OR 0.14; 95% CI 0.02–0.96) were independently associated with the presence of LAAT [12].

The role of LV remodeling in thrombus formation in non-valvular AF has been less studied. H. Kishima et al. studied 230 patients with AF taking warfarin and found that LV hypertrophy (OR 5.59; 95% CI 1.6–19.3; $p = 0.006$) was independently associated with LAA thrombosis [20]. Also A.C. Boyd et al. found out that LVMI is able to predict the presence of LAAT in patients with persistent AF. In multiple logistic regression analysis, the only independent predictor of thrombus was LVMI ($p < 0.001$) [21]. In our study LMVI also demonstrated pretty high specificity (74.3%) for identifying patients with LAAT.

Conclusion

Patients with LAAT had higher values of left atrial and right atrial diameters and indices, as well as lower LVEF and higher NT-proBNP levels. The NT-proBNP level of more than 1689 pg/ml showed the largest area under the ROC-curve (0.747) as well as the highest specificity (92.6%). Further use of these parameters could help predict LAAT development in patients with persistent non-valvular AF and will optimize the algorithm for selecting and preparing patients with AF for planned cardioversion and reduce the risk of thromboembolic complications, especially when TEE is not available.

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Клинико-лабораторные и эхокардиографические предикторы тромбоза ушка левого предсердия у пациентов с фибрилляцией предсердий

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Аннотация. *Актуальность.* Наиболее распространенной аритмией на сегодняшний день является фибрилляция предсердий (ФП). Снижение скорости кровотока в ушке левого предсердия (ЛП), эндотелиальная дисфункция и изменения в системе гемостаза могут стать причиной развития тромбоза ушка ЛП, который является основным источником тромбоэмболии у пациентов с ФП. В многочисленных исследованиях различные клинические, эхокардиографические и лабораторные параметры рассматривались как потенциальные предикторы, однако прогностическая сила этих параметров все еще недостаточна для реальной клинической практики. Цель исследования — оценить прогностическую способность клинических, лабораторных и эхокардиографических маркеров в диагностике тромбоза ушка ЛП у пациентов с неклапанной ФП. *Материалы и методы.* В исследование включены 100 пациентов с персистирующей неклапанной ФП, госпитализированных для проведения электрической кардиоверсии. Всем пациентам проводились клинико-лабораторные и инструментальные исследования, включая трансторакальную и чреспищеводную эхокардиографию (ЧП-ЭхоКГ). По результатам ЧП-ЭхоКГ пациенты были разделены на 2 группы: пациенты с тромбом ушка ЛП ($n = 30$) и без тромба ушка ЛП ($n = 70$). Статистический анализ проводили с использованием программы STATISTICA 10.0. *Результаты и обсуждение.* Пациенты обеих групп были сопоставимы по возрасту, полу, распространенности артериальной гипертензии, ишемической болезни сердца, ожирения, перенесенного инсульта и сахарного диабета ($p > 0,05$). У пациентов с тромбозом ушка ЛП выявлена большая длительность эпизода персистирующей ФП (7 [4; 9] мес против 4 [3; 6] мес, $p = 0,004$) по сравнению с пациентами без тромбоза ушка ЛП. Лабораторные маркеры пациентов обеих групп не имели достоверных различий, за исключением СКФ ($p = 0,047$) и уровня NT-proBNP ($p = 0,011$). По результатам эхокардиографии у пациентов не было различий в диаметре и объеме ЛП ($p > 0,05$), однако индекс объема ЛП был выше у пациентов с тромбом ушка ЛП ($p = 0,007$). При проведении ROC-анализа уровень NT-proBNP ≥ 1689 пг/мл показал наибольшую площадь под ROC-кривой (0,747), а также самую высокую специфичность (92,6%). Длительность персистирующей ФП $\geq 4,5$ мес показала наибольшую чувствительность (90%). *Выводы.* Пациенты с тромбом ушка ЛП имели большую длительность персистирующей ФП, более высокие значения индекса объема ЛП, а также более высокие уровни NT-proBNP. Дальнейшее использование этих параметров может помочь прогнозировать развитие тромбоза ушка ЛП у пациентов с ФП.

Ключевые слова: фибрилляция предсердий, тромб ушка левого предсердия, эхокардиография, индекс объема левого предсердия, NT-proBNP

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Вклад авторов. Л.В. Колоцей — концепция и дизайн исследования, А. Ибрахим, Ч.Э.С. Фернандо — сбор и обработка материала, Л.В. Колоцей — статистическая обработка, Л.В. Колоцей, А. Ибрахим, Ч.Э.С. Фернандо — написание текста, Л.В. Колоцей — редактирование. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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