Varionchik N. V.[1], Blagova O. V. [1], Pavlenko E. V. [1], Nedostup A. V. [1], Sedov V. P. [1], Gagarina N. V. [1], Mershina E. A.[2], Sinitsyn V. E.[2], Polyak M. E.[3], Zaklyazminskaya E. V.[3]

[1] Sechenov First Moscow State Medical University, Moscow, Russia

[2] Medical Research and Educational Center, Lomonosov Moscow State University, Moscow, Russia

[3] State Medical Center of the Russian Federation, Petrovsky National Scientific Center of Surgery, Moscow, Russia

Adverse Events in Patients With Left Ventricular Noncompaction: Risk Stratification and Treatment Options

Aim	To study the clinical manifestations, incidence of life-threatening complications, and their possible mechanisms and outcomes of left ventricular non-compaction (LVNC) in adults.
Material and methods	This study included 125 adult patients with LVNC, 74 men (59.2%) and 51 women (40.8%) aged 46.4±15.1 years. Echocardiography (EchoCG) (n=125), Holter monitoring (n=125), cardiac magnetic resonance imaging (MRI) (n=60), and contrast-enhanced multislice computed tomography (MSCT) of the heart (n=90), and, if indicated, coronary angiography (CAG) (n=33) and myocardial scintigraphy (n=27) were performed. The diagnosis of LVNC was confirmed in 74 cases using two methods, and in 21 cases, using three imaging methods. DNA diagnostics was performed in most patients. For most patients, the level of anticardiac antibodies and the genome of cardiotropic viruses were determined in the blood. Mean left ventricular (LV) ejection fraction (EF) was 38.6±14.0%; LV end-diastolic volume (EDV) was 158.1±67.8 ml; LV end-diastolic dimension (EDD) was 6.1±0.9 cm; and left atrial (LA) volume was 97.1±38.1 ml. The mean follow-up period was 14 months [4.0; 41.0]; from 1 month to 10 years.
Results	Death rate was 14.4%; heart transplantation was performed in 5.6% of cases. Nonsustained ventricular tachycardia (VT) was detected in 45.6% of cases and sustained VT in 13.6%. The presence of VT was associated with poor R-wave progression in the precordial ECG leads, low QRS voltage, QRS duration >105 ms, NYHA chronic heart failure functional class (CHF FC) ≥2-3, LV EF <40%; LV EDD >6.1 cm, the presence of myocarditis, and higher death rate. Cardioverter defibrillators, including cardiac resynchronization therapy defibrillators (CRTD), were implanted in 38 patients. Appropriate defibrillator shocks were associated with frequent premature ventricular contractions (PVCs). The incidence of thrombosis and embolism was 22.4%. Their predictors included CHF FC ≥2-3, RV anteroposterior dimension >3.1 cm, LA volume >98 ml, E/A >1.65, LV EDD >6.3 cm, LV EDV >153 ml, LV EF <35%, and myocardial necrosis of unknown origin (in patients without coronary atherosclerosis). The incidence of myocardial necrosis in LVNC was 16.0%. The mechanisms identified, in addition to coronary atherosclerosis, were embolism in unchanged coronary arteries, secondary myocarditis, and the presence of genetically determined thrombophilia.
Conclusion	LVNC is associated with a high risk of life-threatening conditions, such as ventricular arrhythmias, thrombosis and embolism, and myocardial necrosis, that are typical complications of LVNC in adults. Reassessing the predictors for the risk of thromboembolic and arrhythmic events, specifying the indications for implantable cardioverter defibrillator and anticoagulants, and actively identifying and treating concomitant myocarditis are essential.

Keywords	Noncompaction of the myocardium; thrombosis; embolism; ventricular arrhythmias; myocardial necrosis; mortality
For citations	Varionchik N. V., Blagova O. V., Pavlenko E. V., Nedostup A. V., Sedov V. P., Gagarina N. V. et al. Adverse Events in Patients With Left Ventricular Noncompaction: Risk Stratification and Treatment Options. Kardiologiia. 2024;64(6):3–11. [Russian: Вариончик Н. В., Благова О. В., Павленко Е. В., Недоступ А. В., Седов В. П., Гагарина Н. В. и др. Угрожающие жизни осложнения некомпактного миокарда левого желудочка у взрослых: стратификация риска и подходы к лечению. Кардиология. 2024;64(6):3–11].

Corresponding author	Pavlenko E. V. E-mail: evd88@mail.ru

Introduction

Left ventricular non-compaction (LVNC) is a cardiomyopathy characterized by an excessive trabecular layer, deep intertrabecular lacunae communicating with the LV cavity, and a thinned compact layer. The diagnosis of LVNC is based on the imaging findings of echocardiography using the proposed criteria [1–4] and magnetic resonance imaging (MRI) [5, 6].

LVNC may be asymptomatic or have an advanced clinical picture associated with high mortality, development of

Central illustration. Adverse Events in Patients With Left Ventricular Noncompaction: Risk Stratification and Treatment Options

OBJECTIVE: Evaluate the clinical manifestations, incidence of life-threatening complications, possible mechanisms, and outcomes of left ventricular non-compaction in adults.

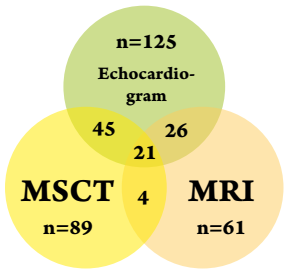
MATERIAL AND METHODS

Total n=125 patients

Mean age 46.4 ± 15.1 years

A total of 125 patients underwent echocardiography, 89 underwent MSCT, and 61 underwent MRI

The diagnosis of LVNC was confirmed by all three modalities in 21 cases



Echocardiographic parameters	Mean
LVEF	38.6 ± 14.0 %
LVEDD	6.1 ± 0.9 cm
LVEDV	158.1 ± 67.8 mL
LVESV	92.5 [61.5; 130.0] mL
dp/dt	764.8 ± 257.1 mm Hg/s
VTI	11.8 ± 3.7 cm
IVS thickness	10.0 [8.0; 11.0] mm
LA volume	97.1 ± 38.1
RA volume	63.0 [47.0; 88.3] mL
LV dimension	3.0 ± 0.7 cm
PASP	36.1 ± 16.9 mm Hg

RESULTS

	Ventricular tachycardia (stable + unstable)		p
	Event «+» (n=65)	Event «–» (n=60)	
Mortality	20.6%	6.5%	0.019
CHF NYHA class	2,.25 [1.9; 3.0]	2 [0.75; 3.0]	0.01
LVEF, %	34.8% ± 13.6%	42.4% ± 13.4%	0.002
LVEDD, cm	6.2 ± 0.78	5.9 ± 0.89	0.039
PASP	40.7 ± 16.4	31.8 ± 16.3	0.013
Low voltages on ECG	22.8%	5.4%	0.007
Duration of QRS	119 [100; 140]	100 [90; 114]	0.001
Poor R wave progression	49.1%	23.6%	0.005
Myocarditis	69.4%	38.7%	0.001

	Thrombosis + embolism		p
	«+» (n=28)	«–» (n=97)	
LVEF, %	31.3 ± 11.7%	40.8 ± 13.9%	0.001
LVEDV	184.2 ± 60.8	149.6 ± 66.5	0.005
LVEDD, cm	6.5 ± 0.9	5.9 ± 0.8	0.006
LA volume, mL	109.3 ± 31.8	93.2 ± 39.2	0.014
E/A	2.1 ± 0.8	1.5 ± 0.9	0.01
VTI	10.0 ± 3.5	12.7 ± 3.5	0.016
CHF class	3 [2.0; 3.0]	2 [1.0; 3.0]	0.006
AF	39.3%	27.8%	-

	Myocardial necrosis		p
	«+» (n=20)	«–» (n=105)	
Significant coronary atherosclerosis	41.2%	4.8%	<0.001
Thrombosis, embolism	52.6%	17.1%	0.003
LVEF, %	33.5 [24.0; 42.0]	40.0 [29.0; 50.75]	0.039
Angina pectoris	36.8%	20.0%	0.016

The authors have no conflicts of interest to declare.

LVNC, left ventricular non-compaction; MSCT, multislice computed tomography; MRI, magnetic resonance imaging; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; VTI, velocity time integral; IVS, interventricular septum; LA, left atrium; RA, right atrium; RV, right ventricle; P, statistical significance; CHF NYHA class, functional class of chronic heart failure according to the New York Heart Association classification; ECG, electrocardiogram; AF, atrial fibrillation.

heart failure (HF), ventricular arrhythmias, and systemic thromboembolism [1, 6–8]. We have previously described the classification and clinical forms of non-compaction cardiomyopathy (NCC) [9, 10].

Despite the increasing interest in LVNC [11, 12], the predictors of life-threatening complications are still poorly understood. Possible predictors include the degree of LV systolic dysfunction (left ventricular ejection fraction (LVEF)) and functional class (FC) of CHF [13–16], the presence and character of late gadolinium enhancement (LGE) on MRI [17], the level of brain natriuretic peptide (NT-proBNP) [14, 18], QT interval prolongation [19], and positive T waves in the aVR lead [20]. Some authors also discuss the role of identified genetic mutations [21]. In patients with NCC, the indications for anticoagulant therapy and implantable cardioverter defibrillator (ICD) implantation remain undefined.

Objective

The objective of this study was to evaluate the clinical manifestations, incidence of life-threatening complications, possible mechanisms, and outcomes of LVNC in adults.

Material and Methods

A total of 125 adult patients with confirmed LVNC were included in the study; 74 (59.2%) were male and 51 (40.8%) were female. The study is a prospective registry. The mean age was 46.4±15.1 years (from 18 to 78 years). Inclusion criteria: age older than 18 years; presence of NCC signs confirmed

ISSN 0022-9040. Kardiologiia. 2024;64(6). DOI: 10.18087/cardio.2024.6.n2502

by imaging techniques (echocardiography, MRI, MSCT). Exclusion criteria: childhood; refusal to participate.

In addition to standard cardiac evaluation, 60 patients underwent cardiac MRI, and 90 patients underwent contrast-enhanced cardiac MSCT. Two imaging modalities were used in 74 cases and three imaging modalities were used in 21 cases to confirm the diagnosis of NCC. Coronary arteriogram (CAG) (n=33) and myocardial scintigraphy (n=27) were performed when indicated. Anti-cardiac antibodies were detected in the blood of 93.6% of patients. A morphological study of the myocardium was performed in 26 cases. The majority of patients (63.2%) have undergone or are undergoing DNA testing. The mean follow-up period was 14 [4.0; 41.0] months.

Table 1. Basic characteristics of patients LVNC

Parameters	Value
CHF class 3–4	36.8 % (n = 46)
Myocarditis	54.0 % (n = 67)
Hypertensive heart disease	41.8 % (n = 51)
Angina pectoris	20.0 % (n = 25)
Myocardial infarction (necrosis)	15.0 % (n = 18)
Thrombosis + embolism	23.2 % (n = 29)
Sick sinus syndrome	10.5 % (n = 13)
Atrioventricular block I–III	14.5 % (n = 18)
Bundle branch block	42.3 % (n = 52)
Atrial fibrillation, atrial flutter	30.4 % (n = 38)
Ventricular extrasystoles more than 500 beats/day	47.2 % (n = 59)
Ventricular tachycardia	50.4 % (n = 63)
Implanted devices (pacemaker + ICD + CRTD)	34.4 % (n = 43)
LVEF, %	38.6 ± 14.0
LVEDD, cm	6.1 ± 0.9 (3.8–8.2)
LVEDV, mL	158.1 ± 67.8 (29.0–501.0)
LVESV, mL	92.5 [61.5; 130.0]
dP/dt, mm Hg/sec	764.8 ± 257.1
VTI, cm	11.8 ± 3.7
IVS thickness, mm	10.0 [8.0; 11.0]
LA volume, mL	97.1 ± 38.1 (30.0–190.0)
RA volume, mL	63.0 [47.0; 88.3]
RV dimension, cm	3.0 ± 0.7
PASP, mm Hg	36.1 ± 16.9

Data are presented as number of patients (n (%)), median and interquartile range (Me [Q1; Q3]), mean ± standard deviation (M ± SD); CHF, chronic heart failure; ICD, implantable cardioverter defibrillator; CRTD, cardiac resynchronization therapy defibrillator; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; VTI, velocity time integral; IVS, interventricular septum; LA, left atrium; RA, right atrium; RV - right ventricle; PASP, pulmonary artery systolic pressure.

All-cause, cardiovascular, and arrhythmic mortality, heart transplantation rate, mortality+transplantation rate, incidence of intracardiac thrombosis, emboli, myocardial infarction (necrosis), ventricular tachycardia (VT), and appropriate ICD discharges were evaluated.

The study was approved by the local ethics committee of the Sechenov First Moscow State Medical University. All patients signed a voluntary informed consent to be included in the study.

Statistical analysis was performed using SPSS Statistics v.21. The Kolmogorov–Smirnov test was used to determine the normality of the distribution. Normally distributed quantitative indicators were described as mean and standard deviation, otherwise as median and interquartile range. Student's t-test, Mann–Whitney U test, chi-squared test, and Fisher's exact test were used to assess the statistical significance of differences. Differences were considered statistically significant with $p<0.05$. When calculating frequencies in the absence of a complete data set, a valid percentage was reported.

Results

Clinical characteristics of patients

37% of patients had severe CHF class 3–4. The frequency of the combination of LVNC and myocarditis was 54.0% (67 cases). Genetic diagnosis revealed pathogenic mutations in MyBPC3, MYH7, TTN, DSP, DES, LAMP2 genes in 12 (9.6%) patients, and variants of unknown clinical significance (VUCS) in 7 patients. The main clinical and echocardiographic data are presented in Table 1.

Thrombosis and embolism in patients with LVNC

Intracardiac thrombosis was observed in 19.2% of cases (24 patients), including 8 patients with a history of thrombosis. Thrombi were detected in the left atrium (LA) (n=7), LV (n=13), both ventricles (n=2), isolated in the right ventricle (RV) in one patient with biventricular NCC (n=1), and simultaneously in LA and LV (n=1).

Embolism occurred in 10 (8.0%) patients: 7 patients had a cerebrovascular accident (CVA), one patient had renal artery thromboembolism, and one patient had small ophthalmic artery embolism. In a single case, an embolic myocardial infarction (AMI) was confirmed at autopsy in a female patient without coronary atherosclerosis. In another 8 (6.4%) cases, myocardial necrosis was observed in patients with intact coronary arteries in the presence of proven intracardiac thrombosis, which seems to be the most likely embolic mechanism of AMI.

Cumulatively, intracardiac thrombosis and embolism were observed in 22.4% of cases (n=28). In 19 cases, anticoagulants were not being administered at the time of the event, and in another 7 cases, thrombosis or embolism developed with irregular use or self-discontinuation of medication.

The development of thrombosis and embolism was statistically significantly associated with an increase in the size of LV, RV, and LA, a decline in LV systolic and diastolic functions, and an advancement in the functional classification of CHF (Table 2). No differences were found in the incidence of atrial fibrillation (AF) in patients with and without thrombosis/embolism.

ROC analysis was performed to determine the threshold values of the indicators, and the parameters obtained were used in the regression analysis, Table 3. The mathematical model including E/A, EF<35%, LVEDV > 153 mL and LV anteroposterior dimension >3.1 cm was statistically significant (p=0.03). In the ROC analysis, the area under the curve was AUC=0.749 with p=0.004 (Figure 1).

Arrhythmic events in patients with LVNC

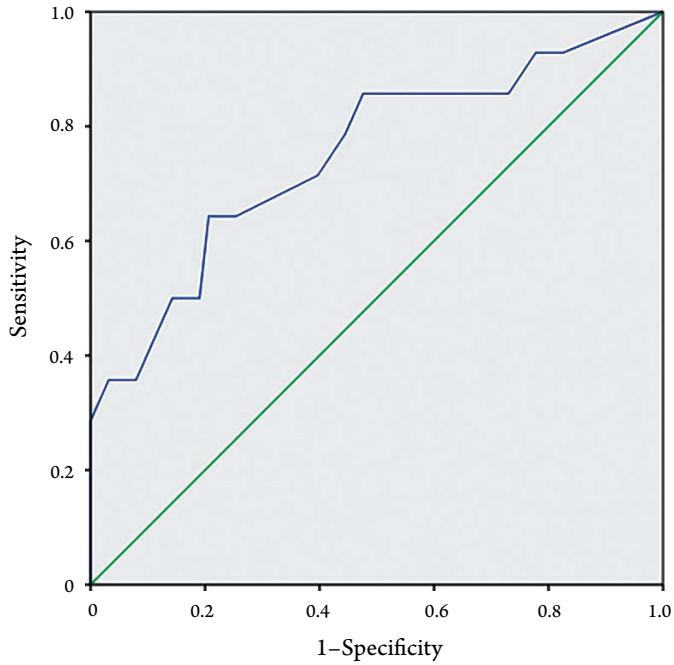
Unstable VT was detected in 45.6%, stable VT in 13.6%, and ventricular extrasystoles (VEs) in 47.2% of patients. Unstable VT and stable VT were associated with sever CHF, reduced LVEF, and the presence of myocarditis (Table 4). In addition, in patients with unstable VT and stable VT, the ECG more often showed poor R wave progression in the thoracic leads; low voltages of the QRS complexes (amplitude of the QRS complexes less than 0.5 mV in the limb leads), their long duration. Mortality was statistically significantly higher in patients with VT. ROC analysis was used to determine the threshold values of the indicators, which were subsequently employed in the regression analysis (Table 5). The combined

Table 2. . Factors associated with the development of thrombosis and embolism in patients with LVNC

Associated factors	Patients with thrombosis, embolism, n=28	Patients without thrombosis, embolism, n=97	p
CHF NYHA class	3 [2.0; 3.0]	2 [1.0; 3.0]	0.006
LVEF, %	31.3 ± 11.7	40.8 ± 13.9	0.001
LVEDD, cm	6.5 ± 0.9	5.9 ± 0.8	0.006
LVEDV, mL	184.2 ± 60.8	149.6 ± 66.5	0.005
LVESV, mL	114.0 [80.8; 156.3]	87.5 [57.3; 122.5]	0.01
LA volume, mL	109.3 ± 31.8	93.2 ± 39.2	0.014
RV anteroposterior dimension, cm	3.4 ± 0.8	2.9 ± 0.6	0.002
E/A	2.1 ± 0.8	1.5 ± 0.9	0.01
VTI	10.0 ± 3.5	12.7 ± 3.5	0.016
Atrial fibrillation, %	39.3	27.8	ns
Duration of disease, months	22.5 [4.8; 51.0]	53.0 [13.0; 120.0]	0.02

LVEF, ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LV, left atrium; RV, right ventricle; VTI, velocity time integral; p, significance.

Figure 1. ROC curve for determining the risk of thrombosis and embolism in patients with LVNC. Area under the curve AUC = 0.749, p = 0.004



results yielded a statistically significant mathematical model (p=0.001), with ROC analysis providing an area under the curve AUC=0.837; p<0.001 (Figure 2).

Seven patients received implantable pacemakers. A total of 38 patients with NCC received an implanted defibrillator, comprising 28 patients with an ICD and 10 patients with a CRT-D. Over the course of the mean follow-up period of 14 months, appropriate discharges were observed in 34.2% of cases. They were found to be associated not only with stable VT, but also with the frequency of VEs (Table 6). In single-factor regression analysis, the rate of frequent VEs remained statistically significant as a factor associated with appropriate discharges: p=0.008, B=2.3, Exp (B) =10.0.

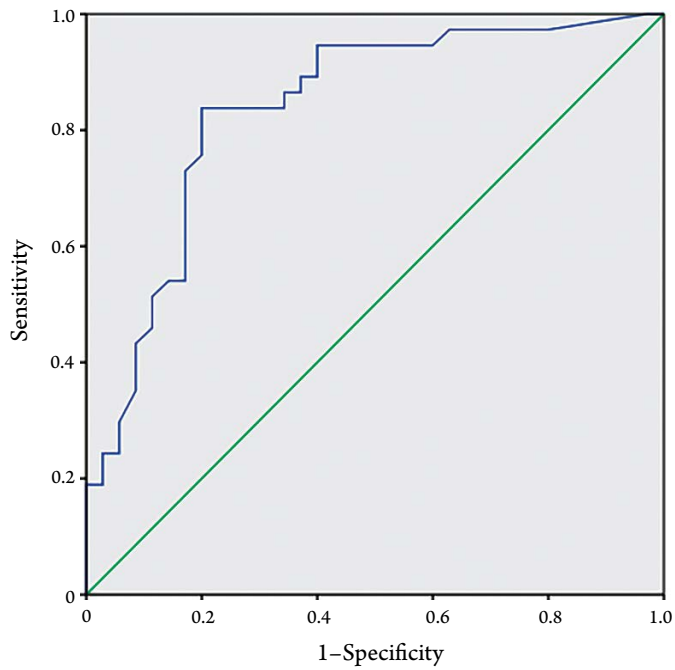
Ischemic events in patients with LVNC

The incidence of all ischemic events (myocardial necrosis, clinical picture of angina pectoris) in NCC was 35.2% (n=44), of which myocardial necrosis was 16.0% (n=20).

CAG (17.8%) and coronary MSCT combined with CAG (73.3%) were performed in patients with ischemic manifestations. Four patients (8.9%) were not evaluated for various reasons. Stenosis greater than 50% was found in 24.4% of cases. Coronary arteries were intact in 68.9% of cases with clinical manifestations of ischemia. In light of the fact that coronary atherosclerosis was ruled out in the majority of patients presenting with ischemia we hypothesize that alternative mechanisms may be responsible for the development of ischemia in NCC. In light of the aforementioned, we believe that «myocardial necrosis» is a more appropriate term than AMI. In patients with myocardial necrosis, not only

ISSN 0022-9040. Kardiologiia. 2024;64(6). DOI: 10.18087/cardio.2024.6.n2502

Figure 2. ROC curve for determining the risk of VT in patients with LVNC. Area under the curve AUC = 0.837, p < 0.001



was coronary atherosclerosis statistically significantly more frequently detected, but also thromboembolism was registered (Table 7). These two mechanisms appear to be the primary mechanisms in patients with NCC.

The development of myocardial necrosis due to myocarditis (in some cases verified by biopsy) was observed in individual patients. In two instances, myocardial necrosis was attributed to coronary thrombosis associated with genetically predisposed thrombophilia.

The results of regression analysis are provided in Table 8. The mathematical model that accounted for all indicators was found to be statistically significant (p<0.001). In the ROC analysis of the model, the area under the curve was AUC=0.826 with p=0.001 (Figure 3).

Outcomes

The mortality rate among patients with NCC was 14.4% (18 patients), and the rate of the «death + transplantation» indicator was 19.2% (24 patients).

Six patients experienced sudden cardiac death (SCD), while the remaining five cases demonstrated a high probability of SCD, including patients who had declined ICD implantation. In the remaining cases, the cause of death was determined to be terminal CHF, thromboembolism, and complications following heart transplantation.

The fatality was associated with more severe LV dysfunction (LVEF 23.0 [19.0; 32.5] vs. 40.0 [31.75; 50.25], p<0.001; E/A ratio 2.47±0.99 vs. 1.5±0.75, p<0.001, and VTI 8.6±2.1 vs. 12.7±3.6, p<0.001), more severe CHF (class 3 [2.0; 3.25] vs. class 2 [1.0; 3.0], p=0.001), higher incidence of VT (77.8%

Table 3. Risk factors for thrombosis and embolism in patients with LVNC (logistic regression)

Indicator (variable)	Univariate analysis			Multivariate analysis		
	B	Exp (B)	p	B	Exp (B)	P
LVEF < 35 %	1.1	3.0	0.014	0.7	1.9	0.33
LVEDV > 153 mL	0.9	2.5	0.046	0.7	2.0	0.3
LVEDD > 6.3 cm	1.2	3.3	0.008	–	–	–
LA volume > 98 mL	0.9	2.5	0.043	–	–	–
RV anteroposterior dimension > 3.1 cm	1.1	3.1	0.013	0.8	2.1	0.24
E/A > 1.65	1.1	3.1	0.047	1.6	4.8	0.02
CHF NYHA class ≥ 3	1.1	3.0	0.013	–	–	–

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVEDD, left ventricular end-diastolic dimension; LV, left atrium; RV, right ventricle; CHF, chronic heart failure; B, regression coefficient; Exp (B), predicted change of the risk when the value of the independent variable changes by one unit; p, significance.

Table 4. Factors associated with the development of stable VT and unstable VT in patients with LVNC

Associated factors	VT (unstable + stable), n = 65	Patients without VT n = 60	p
Mortality	20.6 %	6.5 %	0.019
CHF FC (NYHA)	2.25 [2.0; 3.0]	2 [0.25; 3.0]	0.01
Concomitant myocarditis, %	69.4	38.7	0.001
LVEF, %	34.8 ± 13.6	42.4 ± 13.4	0.002
LVEDD, cm	6.2 ± 0.78	5.9 ± 0.89	0.039
PASP, mm Hg	36.0 [28.5; 50.0]	25.0 [20.0; 40.0]	0.002
LA volume, mL	103.8 ± 38.5	90.5 ± 36.8	0.06
Low voltages on ECG, %	22.8	5.4	0.007
QRS duration, ms	119 [100; 140]	100 [90; 114]	0.001
Poor R wave progression, %	49.1	23.6	0.005
Bundle branch block, %	56.5	27.9	0.001
Duration of disease, months	60 [16.0; 133.5]	24.5 [24.5; 70.8]	0.026

VT, ventricular tachycardia; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; PASP, pulmonary artery systolic pressure; LA, left atrium; p, significance.

Figure 3. ROC curve of the prognostic significance of the model for determining the risk of myocardial necrosis in patients with LVNC. Area under the curve AUC = 0.826, p < 0.001

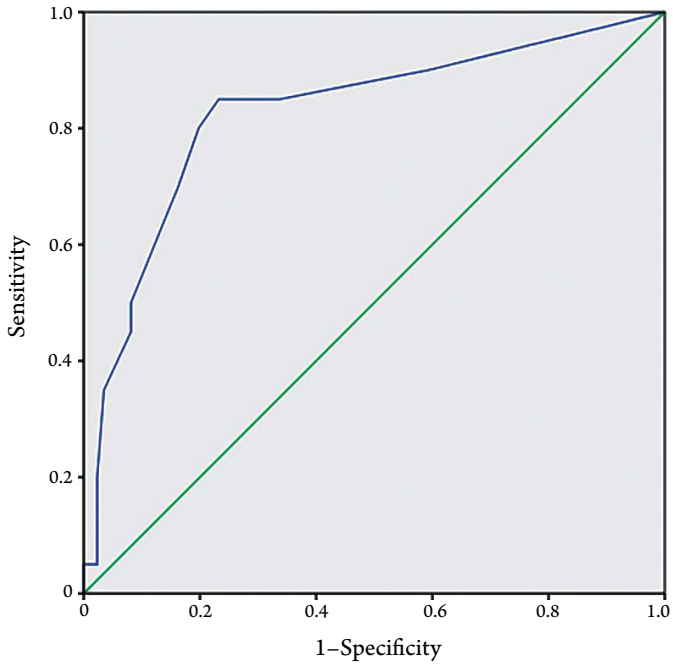


Figure 4. ROC curve of the model of fatal outcomes in patients with LVNC. Area under the curve AUC = 0.874, p < 0.001

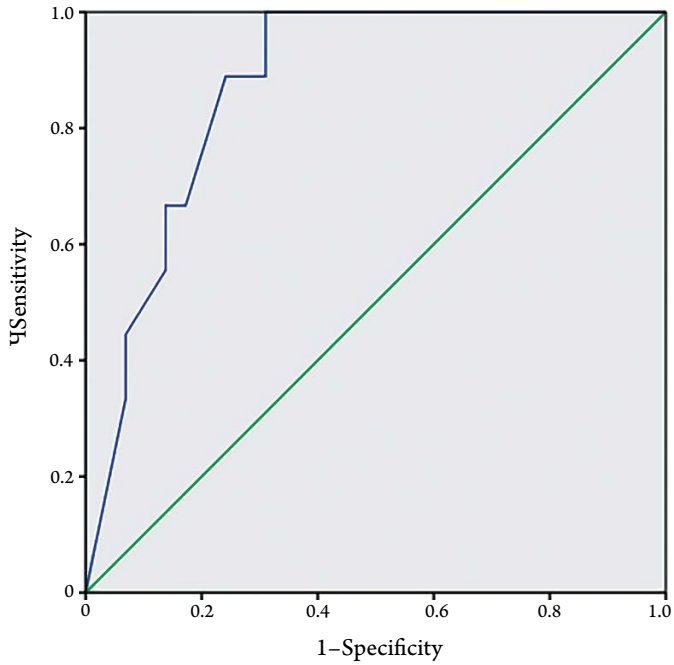


Table 5. Risk factors for stable VT and unstable VT in patients with LVNC (logistic regression)

Indicator (variable)	Univariate analysis			Multivariate analysis		
	B	Exp (B)	p	B	Exp (B)	p
CHF NYHA class ≥ 3	0.9	2.4	0.03	0.4	1.4	0.6
Concomitant myocarditis	1.4	4.1	< 0.001	1.1	3.0	0.09
LVEF < 40 %	0.8	2.2	0.04	0.8	2.3	0.3
LVEDD > 6.1 cm	0.7	2.1	0.048	-0.4	0.7	0.68
PASP > 32 mm Hg	1.2	3.4	0.006	0.8	2.2	0.25
RA volume > 94 mL	0.9	2.5	0.02	1.2	3.2	0.09
Low voltages on ECG	1.6	4.8	0.02	2.0	7.2	0.07
QRS duration > 105 ms	1.0	2.7	0.01	0.1	1.1	0.8
Poor R wave progression	1.2	3.3	0.005	0.5	1.6	0.5

CHF, chronic heart failure; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; PASP, pulmonary artery systolic pressure; LA, left atrium; B, regression coefficient; Exp (B), predicted change in the risk when the value of the independent variable changes by one unit; p, significance.

Table 6. Factors associated with appropriate discharges in patients with LVNC

Associated factors	Appropriate discharges		p
	Event +, n = 14	Event -, n = 24	
Myocarditis	84.6 %	56 %	0.078
Mortality	15.4 %	16 %	0.672
VEs more than 500 beats per day	92.3 %	36 %	0.001
Stable VT	100 %	0 %	< 0.001
LVEF, %	35.5 [31.0; 46.5]	30.5 [21.0; 40.0]	0.06

VE, ventricular extrasystole; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; p, significance.

Table 7. Factors associated with myocardial necrosis in patients with LVNC

Associated factors	Patients with myocardial necrosis, n=20	Patients without myocardial necrosis, n=105	p
Significant coronary atherosclerosis	41.2 %	4.8 %	< 0.001
Thrombosis, embolism	52.6 %	17.1 %	0.003
LVEF, %	33.5 [24.0; 42.0]	40.0 [29.0; 50.75]	0.039
Angina pectoris	36.8 %	20 %	0.016

LVEF, left ventricular ejection fraction.

ISSN 0022-9040. Kardiologiia. 2024;64(6). DOI: 10.18087/cardio.2024.6.n2502

vs. 48.6%, p=0.011), including unstable VT (72.2% vs. 45.8%, p=0.014), and the presence of concomitant myocarditis (83.3% vs. 41.1%, p=0.006).

The results of regression analysis are provided in Table 9. When all parameters except unstable VT were included in the regression equation, a statistically significant mathematical model was obtained (p=0.036). The results of the ROC analysis indicated an area under the curve (AUC) of 0.874 at p<0.001 (Figure 4).

Discussion

The most common complications associated with LVNC are intracardiac thrombosis, systemic embolism, ventricular arrhythmias, and myocardial necrosis. The formation of an intracardiac thrombus is facilitated by the presence of a loose noncompact layer with deep lacunae, particularly in instances where there is a reduction in LVEF.

No complete correspondence was observed between the detection of thrombosis and the subsequent development of embolism. It was not always the case that massive thrombosis was complicated by embolism, and not every embolism was able to confirm the presence of thrombi in the heart cavities. In such instances, thrombi are likely to be situated within the intertrabecular lacunae, which can render their diagnosis challenging.

The analysis revealed no statistically significant differences in the incidence of AF between patients with and without thrombosis/embolism, which is associated with the high frequency and timeliness of anticoagulant prescription in patients with thrombosis/embolism. The development of thrombosis and embolism was associated with an increase in the size of the heart chambers, a decline in LV systolic and diastolic functions, and an advancement in the functional classification of CHF.

Previously, Stöllberger [22] attempted to elucidate the indications for anticoagulant therapy through a retrospective evaluation of the CHADS2 and CHADS2VASc scales in 169 patients with NCC, including those without AF. The authors conclude that these scales can be utilized to assess the risk of thromboembolism in patients with NCC irrespective of the presence of AF. Nevertheless, this approach has not been widely adopted in clinical practice. At present, the primary indications for anticoagulant prescription in patients with LVNC are believed to be a reduction in LVEF, the presence of concomitant AF/AFL, and the identification of intracardiac thrombosis [23, 24].

Our data indicate that, when prescribing anticoagulants to patients with NCC, it is advisable to consider the NYHA classification of CHF, echocardiographic indicators of cardiac chamber dilatation, and a decline in systolic and diastolic function. An increase in the E/A ratio was the most significant predictor of thrombosis and embolism development in our study.

Table 8. Risk factors for myocardial necrosis in patients with LVNC (logistic regression)

Indicator (variable)	Univariate analysis			Multivariate analysis		
	B	Exp (B)	p	B	Exp (B)	p
Significant coronary atherosclerosis	2.7	15.1	< 0.001	2.8	16.3	< 0.001
Thrombosis, embolism	1.6	4.8	0.002	1.5	4.5	0.01
LVEF < 35 %	0.8	2.2	0.1	0.6	1.7	0.4
Angina pectoris	1.3	3.7	0.014	0.8	2.3	0.2

LVEF, left ventricular ejection fraction; B, regression coefficient; Exp (B), predicted change in the risk when the value of the independent variable changes by one unit; p, significance.

Table 9. Predictors of fatal outcomes in patients with LVNC (logistic regression)

Indicator (variable)	Univariate analysis			Multivariate analysis		
	B	Exp (B)	P	B	Exp (B)	P
CHF NYHA class ≥ 3	1.5	4.3	0.007	1.2	3.5	0.4
LVEF < 35 %	2.2	8.6	0.001	-0.4	0.7	0.8
E/A > 1.9	2.4	10.8	0.001	1.1	2.9	0.4
VTI < 11	2.0	7.2	0.02	1.6	5.2	0.2
Stable VT + unstable VT	1.3	3.8	0.025	1.1	3.0	0.3
Unstable VT	1.3	3.6	0.023	–	–	–
Myocarditis	1.6	5.2	0.013	1.6	5.0	0.2

CHF, chronic heart failure; LVEF, left ventricular ejection fraction; VTI, velocity time integral; VT, ventricular tachycardia; B, regression coefficient; Exp (B), predicted change in the risk when the value of the independent variable changes by one unit; p, significance.

Among the arrhythmic events, the most frequently documented were stable VT, unstable VT, and frequent VEs. VT is associated with a reduction in LVEF, an increase in the severity of CHF (as indicated by an elevation in NYHA class and a worsening of echocardiographic parameters), the presence of concomitant myocarditis, which appears to be associated with an intensification of the degree of systolic dysfunction and a more rapid development of decompensation, as well as with an elevated electrical instability of the myocardium and fibrosis in patients with myocarditis.

In patients with VT, ECG frequently revealed poor R wave progression in the thoracic leads, an extended duration of the QRS complexes, and low voltages. These findings are indicative of diffuse myocardial damage and have been proposed by some researchers as predictors of unfavorable outcomes in other forms of cardiomyopathies [25]. It is noteworthy that the occurrence of appropriate discharges in patients with ICDs was found to be statistically significantly associated with the presence of frequent VEs. It seems reasonable to suggest that frequent VEs should be considered as one of the additional selection criteria for ICD implantation. In a previous study, we demonstrated the impact of myocarditis and low voltages of QRS complexes on the generation of appropriate ICD discharges in patients with NCC [26].

Myocardial necrosis is less frequently described as a complication of LVNC [27], yet in our study, it was observed with a relatively high frequency (16.0%). However, a mere one-third of patients exhibiting myocardial necrosis were found to have coronary atherosclerosis. In more than half of the cases presenting with AMI, the coronary arteries were observed to be intact. This suggests other mechanisms of ischemia in patients with NCC, including embolism to normal coronary arteries in patients with intracardiac thrombosis (in one case such a mechanism was confirmed at autopsy, while in several others, it can be postulated). In addition to the aforementioned mechanisms of necrosis in NCC, it is necessary to consider myocarditis [28], inadequate blood supply beneath the noncompact layer, and the possibility of coagulation system pathology resulting in thrombosis within coronary arteries.

Our findings support the hypothesis that myocardial systolic dysfunction is a mechanism underlying the development of life-threatening complications in LVNC. A reduction in LVEF was associated with an increased risk of thromboembolism, VT, myocardial necrosis, and all-cause mortality. These observations are consistent with those reported in previous studies [17, 29–32].

Conclusion

LVNC is associated with a high risk of threatening complications. At a mean follow-up of 14 months, the mortality rate was 14.4%, and transplantation was performed in 5.6% of cases.

VEs occurred in 47.2% of cases, with stable VT/unstable VT being observed in 45.6%/13.6%. The presence of VT was associated with an increased mortality rate, poor R wave progression in the thoracic ECG leads, low voltages of QRS complexes, a duration of QRS greater than 105 ms, CHF class 3 or greater, LVEF<40%, LVEDD > 6.1 cm, and the presence of concomitant myocarditis.

Appropriate discharges were documented in 34.2% (n=13) of cases, with the presence of frequent VEs identified as a significant predictor, which should be considered when determining the necessity for ICD implantation.

The incidence of thrombosis and embolism was observed in 22.4% of cases. Thromboembolism was associated with AF and a variety of conditions, including CHF class 3 or greater, RV anteroposterior dimension > 3.1 cm, LV volume > 98 mL, E/A > 1.65, LVEDD > 6.3 cm, LVEDV > 153 mL, and LVEF<35%, which should be considered when prescribing anticoagulants, and myocardial necrosis of unspecified origin with intact coronary arteries.

Myocardial necrosis occurred in 16.0% of cases, with etiological mechanisms including not only coronary atherosclerosis but also emboli in normal coronary arteries, concomitant myocarditis, and concomitant genetic thrombophilia.

In order to reduce the incidence of life-threatening complications in patients with NCC, it is necessary to reevaluate the risk predictors, clarify the indications for ICD implantation and anticoagulant therapy, and implement active detection and treatment of concomitant myocarditis.

Funding

The study was performed at the Vinogradov Departmental Therapeutic Clinic, Sechenov First Moscow State Medical University of the Ministry of Health of Russia.

No conflict of interest is reported.

The article was received on 08/05/2023

REFERENCES

1. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation. 1990;82(2):507–13. DOI: 10.1161/01.CIR.82.2.507
2. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart. 2001;86(6):666–71. PMID: 11711464
3. Stöllberger C, Finsterer J. Left ventricular hypertrabeculation/noncompaction. Journal of the American Society of Echocardiography. 2004;17(1):91–100. DOI: 10.1016/S0894-7317(03)00514-5
4. Stöllberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. The American Journal of Cardiology. 2002;90(8):899–902. DOI: 10.1016/S0002-9149(02)02723-6
5. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. Journal of the American College of Cardiology. 2005;46(1):101–5. DOI: 10.1016/j.jacc.2005.03.045
6. Jacquier A, Thuny F, Jop B, Giorgi R, Cohen F, Gaubert JY et al. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. European Heart Journal. 2010;31(9):1098–104. DOI: 10.1093/eurheartj/ehp595

ISSN 0022-9040. Kardiologiia. 2024;64(6). DOI: 10.18087/cardio.2024.6.n2502

7. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. Journal of the American College of Cardiology. 2000;36(2):493–500. PMID: 10933363
8. Lofiego C, Biagini E, Pasquale F, Ferlito M, Rocchi G, Perugini E et al. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. Heart. 2007;93(1):65–71. DOI: 10.1136/hrt.2006.088229
9. Blagova O.V., Nedostup A.V., Sedov V.P., Gagarina N.V., Kogan E.A., Sulimov V.A. et al. Noncompaction myocardium as a primary phenomenon or consequence of myocardial dysfunction: clinical masks of the syndrome. Kardiologiia. 2012;52(11):17–26. [Russian: Благова О.В., Недоступ А.В., Седов В.П., Гагарина Н.В., Коган Е.А., Сулимов В.А. и др. Некомпактный миокард как первичный феномен или следствие дисфункции миокарда: клинические маски синдрома. Кардиология. 2012;52(11):17–26]
10. Pavlenko E.V., Blagova O.V., Varionchik N.V., Nedostup A.V., Sedov V.P., Polyak M.E. et al. Register of adult patients with noncompact left ventricular myocardium: classification of clinical forms and a prospective assessment of progression. Russian Journal of Cardiology. 2019;24(2):12–25. [Russian: Павленко Е.В., Благова О.В., Вариончик Н.В., Недоступ А.В., Седов В.П., Поляк М.Е. и др. Регистр взрослых больных с некомпактным миокардом левого желудочка: классификация клинических форм и проспективная оценка их прогрессирования. Российский Кардиологический Журнал. 2019;24(2):12–25]. DOI: 10.15829/1560-4071-2019-2-12-25
11. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D et al. Contemporary Definitions and Classification of the Cardiomyopathies: An American Heart Association Scientific Statement From the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807–16. DOI: 10.1161/CIRCULATIONAHA.106.174287
12. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P et al. Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases. European Heart Journal. 2007;29(2):270–6. DOI: 10.1093/eurheartj/ehm342
13. van Waning JI, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM et al. Genetics, Clinical Features, and Long-Term Outcome of Noncompaction Cardiomyopathy. Journal of the American College of Cardiology. 2018;71(7):711–22. DOI: 10.1016/j.jacc.2017.12.019
14. Stämpfli SF, Erhart L, Hagenbuch N, Stähli BE, Gruner C, Greutmann M et al. Prognostic power of NT-proBNP in left ventricular non-compaction cardiomyopathy. International Journal of Cardiology. 2017;236:321–7. DOI: 10.1016/j.ijcard.2017.02.064
15. Arenas IA, Mihos CG, DeFaria Yeh D, Yucel E, Elmahdy HM, Santana O. Echocardiographic and clinical markers of left ventricular ejection fraction and moderate or greater systolic dysfunction in left ventricular noncompaction cardiomyopathy. Echocardiography. 2018;35(7):941–8. DOI: 10.1111/echo.13873
16. Oechslin E, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? European Heart Journal. 2011;32(12):1446–56. DOI: 10.1093/eurheartj/ehq508
17. Casas G, Limeres J, Oristrell G, Gutierrez-Garcia L, Andreini D, Borregan M et al. Clinical Risk Prediction in Patients With Left Ventricular Myocardial Noncompaction. Journal of the American College of Cardiology. 2021;78(7):643–62. DOI: 10.1016/j.jacc.2021.06.016
18. Ramchand J, Podugu P, Obuchowski N, Harb SC, Chetrit M, Milinovich A et al. Novel Approach to Risk Stratification in Left Ventricular Non-Compaction Using A Combined Cardiac Imaging and Plasma Biomarker Approach. Journal of the American Heart Association. 2021;10(8):e019209. DOI: 10.1161/JAHA.120.019209
19. Zhou H, Lin X, Fang L, Zhu W, Zhao X, Ding H et al. Prolonged QTc indicates the clinical severity and poor prognosis in patients with isolated left ventricular non-compaction. The International Journal of Cardiovascular Imaging. 2017;33(12):2013–20. DOI: 10.1007/s10554-017-1209-9
20. Ekizler FA, Cay S, Ulvan N, Tekin Tak B, Cetin EHO, Kafes H et al. Importance of lead aVR on predicting adverse cardiac events in patients with noncompaction cardiomyopathy. Annals of Noninvasive Electrocardiology. 2020;25(3):e12719. DOI: 10.1111/anec.12719
21. Ichida F. Left ventricular noncompaction – Risk stratification and genetic consideration. Journal of Cardiology. 2020;75(1):1–9. DOI: 10.1016/j.jjcc.2019.09.011
22. Stöllberger C, Wegner C, Finsterer J. CHADS2- and CHA2DS-2VASc Scores and Embolic Risk in Left Ventricular Hypertrabeculation/Noncompaction. Journal of Stroke and Cerebrovascular Diseases. 2013;22(6):709–12. DOI: 10.1016/j.jstrokecerebrovasdis.2011.10.014
23. Kido K, Guglin M. Anticoagulation Therapy in Specific Cardiomyopathies: Isolated Left Ventricular Noncompaction and Peripartum Cardiomyopathy. Journal of Cardiovascular Pharmacology and Therapeutics. 2019;24(1):31–6. DOI: 10.1177/1074248418783745
24. Chimenti C, Lavalle C, Magnocavallo M, Alfarano M, Mariani MV, Bernardini F et al. A proposed strategy for anticoagulation therapy in noncompaction cardiomyopathy. ESC Heart Failure. 2022;9(1):241–50. DOI: 10.1002/ehf2.13694
25. Saguner AM, Ganahl S, Baldinger SH, Kraus A, Medeiros-Domingo A, Nordbeck S et al. Usefulness of Electrocardiographic Parameters for Risk Prediction in Arrhythmogenic Right Ventricular Dysplasia. The American Journal of Cardiology. 2014;113(10):1728–34. DOI: 10.1016/j.amjcard.2014.02.031
26. Blagova O.V., Lutokhina Yu.A., Varionchik N.V., Solovyeva E.A., Bukaeva A.A., Shestak A.G. et al. Risk stratification of sudden death and selection criteria for the implantation of defibrillators in patients with cardiomyopathies (dilated, arrhythmogenic right ventricular, noncompact myocardium). Clinical and Experimental Surgery. Petrovsky journal. 2018;6(3):34–49. [Russian: Благова О.В., Лутохина Ю.А., Вариончик Н.В., Соловьева Е.А., Букаева А.А., Шестак А.Г. и др. Стратификация риска внезапной смерти и критерии отбора на имплантацию дефибрилляторов у больных с кардиомиопатиями (дилатационной, аритмогенной правожелудочковой, некомпактным миокардом). Клиническая и экспериментальная хирургия. Журнал имени академика Б.В. Петровского. 2018;6(3):34–49]. DOI: 10.24411/2308-1198-2018-13004
27. Sigvardsen PE, Fuchs A, Kühl JT, Afzal S, Køber L, Nordestgaard BG et al. Left ventricular trabeculation and major adverse cardiovascular events: the Copenhagen General Population Study. European Heart Journal - Cardiovascular Imaging. 2021;22(1):67–74. DOI: 10.1093/ehjci/jeaa110
28. Blagova O.V., Pavlenko E.V., Varionchik N.V., Nedostup A.V., Sedov V.P., Kogan E.A. et al. Myocarditis as a legitimate phenomenon in non-compaction myocardium: diagnostics, management and influence on outcomes. Russian Journal of Cardiology. 2018;23(2):44–52. [Russian: Благова О.В., Павленко Е.В., Вариончик Н.В., Недоступ А.В., Седов В.П., Коган Е.А. и др. Миокардит как закономерный феномен у больных с первичным некомпактным миокардом: диагностика, лечение и влияние на исходы. Российский кардиологический журнал. 2018;23(2):44-52]. DOI: 10.15829/1560-4071-2018-2-44-52
29. Jefferies JL. Left Ventricular Noncompaction Cardiomyopathy: New Clues in a Not So New Disease? Journal of the American Heart Association. 2021;10(2):e018815. DOI: 10.1161/JAHA.120.018815
30. Vaidya VR, Lyle M, Miranda WR, Farwati M, Isath A, Patlolla SH et al. Long-Term Survival of Patients With Left Ventricular Noncompaction. Journal of the American Heart Association. 2021;10(2):e015563. DOI: 10.1161/JAHA.119.015563
31. Feng Y, Ning L, Zhang J, Wang H, Zhang H, Zhang R et al. Prognosis and subtype analysis of left ventricular noncompaction in adults: A retrospective multicenter study. Clinical Cardiology. 2023;46(4):390–6. DOI: 10.1002/clc.23991
32. Cuevas J, Ptaszynski R, Cigarrán H, Calvo J, Martín M. Left ventricular noncompaction cardiomyopathy: Recent advances. Kardiologia Polska. 2022;80(5):529–39. DOI: 10.33963/KP.a2022.0089