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The role of 3D speckle-tracking echocardiography in predicting long-term outcomes after a first myocardial infarction

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ABSTRACT

Aim. To determine the role of 3D echocardiography parameters in the prognosis of long-term cardiovascular complications in patients with a first acute myocardial infarction (AMI).

Materials and methods. A prospective, single-center, observational study included 46 patients with a first AMI and successful PCI without a history of heart failure (HF) and shortness of breath upon admission. The examination of patients was performed in accordance with the Russian standards of medical care provision. Additionally, 3D echocardiography was performed, and N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined. The main outcomes assessed were hospitalization with HF, sudden cardiac death, and combined endpoint. Median follow-up was 554 days (IQR 550–785).

Results. During the follow-up period, 9 hospitalizations with HF, 3 sudden cardiac deaths, and 12 combined endpoints were registered. The effect of 3D echocardiography parameters on the development of sudden cardiac death and combined endpoint has not been revealed. The effect of the studied parameters on the development of HF during the follow-up period that required hospitalization was evaluated. A statistically significant increase in the LV sphericity index was revealed in the group of patients with the registered outcome. We found significant direct correlations of left ventricular volume indices with prescription of diuretics in the post-discharge period; hospitalization with HF in the post-infarction period with the level of NT-pro-BNP, left atrial volume with the duration of index hospitalization, duration of eventless survival with ST elevation. We found a negative correlation of radial strain with prescription of diuretics in the post-discharge period. Predictors of hospitalization with HF in the post-infarction period were identified – parameters of radial strain, area strain, and circumferential strain, which were included in the model for calculating the risk of the outcome under study.

Conclusion. In patients with the first AMI in the absence of clinical signs of HF, to calculate the risk of hospitalization with HF within 550 days after MI, it is advisable to take into account the level of radial strain and use a prognostic model (1), including parameters of circumferential and area strain (according to 3D echocardiography data).

Keywords: three-dimensional echocardiography, myocardial infarction, heart failure

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Conformity with the principles of ethics. All individuals signed an informed consent to participate in the study. The study was approved by the Ethics Committee at RUDN University.

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Роль спекл-трекинг эхокардиографии в трехмерном режиме для прогнозирования отдаленных исходов после первого инфаркта миокарда

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РЕЗЮМЕ

Цель: определение роли параметров эхокардиографии в 3D-режиме (3D-ЭхоКГ) в прогнозе развития сердечно-сосудистых осложнений в отдаленном периоде у пациентов с первым острым инфарктом миокарда (ОИМ).

Материалы и методы. В проспективное одноцентровое наблюдательное исследование включены 46 пациентов с первым ОИМ, успешным чрескожным коронарным вмешательством без анамнеза сердечной недостаточности (СН), одышки при поступлении. Обследование пациентов выполняли в соответствии с российскими стандартами оказания медицинской помощи, дополнительно выполняли трехмерную эхокардиографию и определяли мозговой натрийуретический гормон (NT-proBNP). Основными оцениваемыми исходами были госпитализация с СН, сердечно-сосудистая смерть и комбинированная конечная точка. Медиана периода наблюдения — 554 сут, IQR 550—785.

Результаты. За период наблюдения зарегистрировано девять госпитализаций с СН, три сердечно-сосудистые смерти, 12 комбинированных точек. Влияния параметров 3D-ЭхоКГ на развитие сердечно-сосудистой смерти и комбинированной конечной точки не получено. Оценивали влияние изучаемых параметров на развитие СН в течение периода наблюдения, потребовавшей госпитализации. Выявлено статистически значимое повышение индекса сферичности левого желудочка в группе пациентов с зарегистрированным исходом. Выявлены значимые прямые корреляционные связи объемных показателей левого желудочка с назначением диуретиков в постгоспитальном периоде; госпитализации с СН в постинфарктном периоде с уровнем NT-рго-BNP, объемом левого предсердия и продолжительностью индексной госпитализации, срока бессобытийной выживаемости с элевацией ST; отрицательная корреляционная связь радикальной деформации с назначением диуретиков в постгоспитальном периоде. Выявлены предикторы госпитализации с СН в постинфарктном периоде — показатели радиальной деформации, а также деформации площади и циркулярной деформации, которые вошли в модель расчета риска наступления изучаемого исхода.

Заключение. У пациентов с первым ОИМ при отсутствии клинических признаков СН для расчета риска госпитализации с СН в течение 550 сут после ИМ целесообразно учитывать уровень радиальной деформации и использовать прогностическую модель (1), включающую показатели циркулярной деформации и деформации площади (по данным 3D-ЭхоКГ).

Ключевые слова: трехмерная эхокардиография, инфаркт миокарда, сердечная недостаточность

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено комитетом по этике Медицинского института РУДН.

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INTRODUCTION

Acute myocardial infarction (AMI) is associated with a high risk of adverse outcomes: more than half of surviving patients require readmission within the same year [1]. One of the key factors in the unfavorable prognosis is reduction of left ventricular (LV) function [2], traditionally assessed by LV ejection fraction (EF) [3]. However, this generally accepted parameter has a number of significant limitations, including significant inter- and intraoperator variability and underestimation of subclinical LV dysfunction. At an early stage, weakening of some muscle layers in the heart is compensated by others, which contributes to relative preservation of LVEF. In recent decades, to more accurately assess the systolic function of the heart, three-dimensional echocardiography (3D Echo) with a speckle tracking assessment of longitudinal, circumferential, and radial strain and LV rotation parameters has been used. In addition, determination of LV volume and sphericity index with 3D Echo provides more correct data indicating early post-infarction remodeling [4–8].

Therefore, the aim of the study was to determine the role of 3D Echo parameters in the prognosis of long-term cardiovascular complications in patients with a first AMI.

MATERIALS AND METHODS

A prospective, single-center, observational study included 46 patients hospitalized in the ICU of Vinogradov City Clinical Hospital. Inclusion criteria: first AMI diagnosed according to the fourth universal definition of MI [3]; successful primary PCI in patients with ST-segment elevation MI (STEMI), early (within 24 hours) PCI in patients with non-ST-segment elevation MI (NSTEMI), i.e. achieving TIMI 3 flow in the affected vessel; no history of heart failure (HF), shortness of breath on admission, Killip 1.

Exclusion criteria: use of diuretics and vasopressors, pulmonary pathology, development of complications of AMI (rupture of the interventricular septum, separation of the papillary muscle), severe disturbances of cardiac rhythm and conduction at the time of inclusion, including atrial fibrillation / flutter.

The study complied with ethical standards set out in the WMA Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" and the "Rules of Good Clinical Practice in the Russian Federation." All individuals participating in the study signed an informed consent to participate in

the study. The study was approved by the Ethics Committee at RUDN University.

Upon admission, all patients included in the study underwent history taking, a standard physical examination, electrocardiography, chest X-ray, Echo, coronary angiography, and angioplasty with stent placement. Laboratory tests were performed in accordance with the Russian standards of medical care provision: complete blood count and blood biochemistry, including determination of the troponin I level upon admission and 6–12 hours after hospitalization, and additional determination of N-terminal pro-brain natriuretic peptide (NT-proBNP).

Echo was performed on the best-in-class Vivid E90 device (GE Healthcare, USA) upon discharge, followed by post-processing on the EchoPAC™ station (GE Healthcare, USA) with semi-automated assessment of LVEF. LV diastolic function was assessed in accordance with current recommendations [9].

All patients during the in-hospital period and for a year after discharge received standard dual antiplatelet therapy before and after the intervention.

The primary outcomes assessed were hospitalization for HF, sudden cardiac death, and a composite endpoint. Data were obtained from a unified medical information and analytical system, as well as from telephone contacts during the follow-up (fixed follow-up 550 days; median follow-up (random censoring) 554 days (IQR 550–785)).

Statistical data analysis was performed using the SPSS software (version 23.0). Quantitative variables were described as the arithmetic mean and the standard deviation $(M \pm SD)$ (for normal distribution) or as the median and the interquartile range (Me [IQR]) (for non-normally distributed variables). The significance of differences between the two groups in quantitative variables was assessed using the Man - Whitney Utest (for normal distribution) or the Student's t-test (for non-normally distributed variables). For qualitative variables, the significance of differences between the groups was assessed by the Pearson's chi-square $(\chi 2)$ Fisher exact test depending on the minimum expected number. The differences were considered statistically significant at p < 0.05. The direction and strength of a correlation between parameters were assessed using the Spearman's rank correlation coefficient. The dependence of binary parameters on quantitative and categorical ones was identified by the binary logistic regression (univariate and multivariate) analysis with determination of the odds ratio (OR). The ROC analysis was used to evaluate the prognostic value by

determining the area under the curve (AUC). The influence of the studied parameters on the risk of developing endpoints was assessed using the univariate and multivariate Cox regression analysis with determination of the hazard ratio (HR). Quantitative variables with negative values were analyzed by taking the modulo.

RESULTS

Clinical, demographic, laboratory, and Echo characteristics of patients are presented in Table 1.

Table 1

Characteristics of patients, $n = 46$		
Parameter	Value	
Age, years, $M \pm SD$	61.13 ± 8.84	
Men, <i>n</i> (%)	32 (69.6)	
Body mass index, kg / m^2 , $M \pm SD$	28.26 ± 3.99	
Smoking, n (%)	18 (39.1)	
SBP / DBP, mm Hg, $M \pm SD$	$141.10 \pm 23.86 / 81.84 \pm 12.76$	
History of atrial fibrillation, n (%)	3(6.5%)	
STEMI, <i>n</i> (%)	12 (26.1)	
Anterior MI, n (%)	22 (47.8)	
Single-vessel disease, n (%)	14 (30.4)	
Type 2 diabetes mellitus, n (%)	10 (21.7)	
Dyslipidemia, n (%)	20 (43.5)	
Glucose, mmol / l, Me [IQR]	6.89 [5.59; 8.70]	
NT-proBNP, pg / ml, Me [IQR]	580.0 [264.60; 989.00]	
Troponin I, ng / ml, Me [IQR]	0.26 [0.03; 4.65]	
Troponin II, ng / ml, Me [IQR]	7.79 [1.54; 30.61]	

Note. SBP – systolic blood pressure; DBP – diastolic blood pressure; Troponin I – the level upon admission to the intensive care unit; Troponin II – the level 6–12 hours after hospitalization.

To identify predictors of adverse outcomes, the patients were divided into groups with and without recorded outcomes. During the follow-up, 9 hospitalizations with HF, 3 sudden cardiac deaths, and 12 composite endpoints were registered. The influence of 3D Echo parameters on the development of sudden cardiac death and the composite endpoint was not identified. The influence of the studied parameters on the development of HF during the follow-up period requiring hospitalization was assessed. A statistically significant increase in the LV sphericity index was revealed in the group of patients with a registered outcome (Table 2).

The obtained associations of clinical data with 3D Echo parameters in the study group following the correlation analysis are presented in Table 3.

To identify predictors of the development of the studied endpoint using the binary logistic regression analysis, a prognostic model was developed using 3D Echo parameters (the analysis also included significant risk factors for HF, ST-segment elevation, MI localization, number of affected coronary arteries, levels of NT-proBNP, troponin, EFLV, LV diastolic function parameters, 2D-GLS, all 3D Echo parameters). The identified dependence is described by equation (1):

$$P\frac{1}{1 + e - z} \times 100\%$$

$$z = 2.615 - 0.102 \times CS - 0.286 \times AS$$

where P is the probability of developing HF requiring hospitalization (%), CS is the index of circumferential strain, %, and AS is area strain, %.

Table 2

Comparative characteristics of patients with and without hospitalization with HF in the long-term period after MI, $n = 46$			
Parameter	Hospitalization with HF, $n = 9$	No outcome, $n = 37$	p
Age, years, $M \pm SD$	63.0 [61.0; 73.0]	61.0 [57.0; 66.0]	0.146
Men, <i>n</i> (%)	6 (66.7)	26 (70.3)	0.975
Body mass index, kg / m^2 , $M \pm SD$	27.60 ± 3.27	28.48 ± 4.60	0.613
Smoking, n (%)	3 (33.3)	18 (48.6)	0.539
Hypertension, n (%)	9 (100.0)	27 (73.0)	0.172
Dyslipidemia, n (%)	7 (77.8)	13 (35.1)	0.290
Single-vessel disease, n (%)	3 (33.3)	11 (29.7)	0.833
Multivessel disease, n (%)	6 (66.7)	26 (70.3)	0.833
STEMI, <i>n</i> (%)	3 (33.3)	9 (24.3)	0.581
LVEF upon admission, %, Me [IQR]	47.0 [45.0; 54.0]	50.0 [45.0; 52.0]	0.845
LVEF at discharge, %, Me [IQR]	52.0 [45.0; 54.0]	54.0 [51.0; 58.0]	0.265
LAVI, ml / m², Me [IQR]	27.0 [22.0; 40.0]	28.0 [21.0; 31.0]	0.454
E/e', Me [IQR]	6.6 [5.6; 7.2]	6.5 [5.7; 7.9]	0.825
PASP, mm HG, Me [IQR]	28.0 [25.0; 36.0]	21.0 [14.0; 27.0]	0.108
3D LVEF, %, Me [IQR]	51.0 [47.0; 54.0]	51.0 [48.0; 55.0]	0.617
$3D \text{ SpI}, M \pm SD$	0.38 ± 0.04	0.33 ± 0.07	0.025*

Table 2 (continued)

Parameter	Hospitalization with HF, $n = 9$	No outcome, $n = 37$	p
3D LVEDV, ml, Me [IQR]	106.0 [99.0; 152.0]	113.0 [98.0; 140.0]	0.901
3D LVESV, ml, Me [IQR]	52.00 [46.0; 78.0]	57.0 [48.0; 66.0]	0.945
3D MBV/CO, 1 / min, Me [IQR]	4.5 [3.8; 4.6]	4.1 [3.6; 4.7]	0.438
2D-GLS, %, <i>Me</i> [<i>IQR</i>]	-14.0 [-14.0; -12.0]	-14.6 [-17.0; -11.0]	0.290
3D-GLS, %, <i>Me</i> [<i>IQR</i>]	-11.0 [-13.0; -7.0]	-9.0 [-13.0; -7.0]	0.738
3D circumferential strain, %, Me [IQR]	-11.0 [-13.0; -6.0]	-12.0 [-15.0; -10.0]	0.309
3D area strain, %, Me [IQR]	-18.84 ± 7.21	-18.8 ± 4.97	0.987
3D radial strain, %, Me [IQR]	28.00 ± 12.87	27.86 ± 9.26	0.971
3D torsion, °, Me [IQR]	3.56[1.3; 7.3]	4.30 [1.8; 8.1]	0.504
3D twist, °/cm, Me [IQR]	0.90 [0.30; 1.15]	1.10 [0.6; 1.4]	0.319

Note. BMI – body mass index; LAVI – left atrial volume index; E/e' – the ratio of peak early mitral inflow velocity (E) to the early diastolic mitral annular velocity; PASP – systolic pressure in the pulmonary artery; SPI – left ventricular sphericity index; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; MBV / CO – minute blood volume/cardiac output; GLS – global longitudinal strain * differences in the parameters were statistically significant

Table 3

Associations of 3D echocardiography parameters			
3D parameter	Parameter	R	<i>p</i> *
3D LVEDV	BMI	0.324	0.028
3D LVEDV	Mineralocorticoid antagonists in the post-hospital period	0.303	0.041
2D-GLS		-0.520	< 0.001
3D LVESV	Diuretics in the post-hospital period	0.370	0.011
3D SpI	History of hypertension	0.455	0.001
Radial strain	BMI	-0.303	0.040
Kadiai Strain	Diuretics in the post-hospital period	-0.469	0.001
	NT-pro-BNP level	0.399	0.026
Hospitalization with HF	$LAVI > 34 ml / m^2$	0.422	0.003
	Duration of index hospitalization	0.338	0.022
HF-free period	ST-segment elevation upon admission	-0.805	0.050

^{*} correlation is statistically significant

The resulting regression model is statistically significant (p = 0.004). Based on the Nigelkirk's coefficient of determination, the model (1) determines 35.4% of the variance in the probability of hospitalization with HF.

According to the values of the regression coefficients, the parameters of circumferential strain and area strain have an inverse relationship with the probability of hospitalization with HF. Characteristics of the factors are presented in Table 4.

Thus, with an increase in the circumferential strain by 1%, the odds for hospitalization with HF within 1.5 years after the first AMI decrease by 2.49 times; with an increase in the area strain index by 1%, the odds for hospitalization with HF decrease by 1.67 times.

Table 4

Characteristics of the relationship between model predictors (1) and the probability of hospitalization with HF in the long-term follow-up period in patients after a first AMI

Predictors	OR; 95% CI	p
Circumferential strain, %	0.40; 0.20-0.80	0.010*
Area strain,%	0.60; 0.41–0.89	0.012*

Note. OR – odds ratio, CI – confidence interval.

Figure 1 compares the values of the adjusted hazard ratio with 95% CI for the studied factors included in model (1).

The cut-off value of the logistic probability function P(1) was determined using the ROC analysis. The resulting curve is shown in Figure 2.

^{*} the influence of the predictor is statistically significant

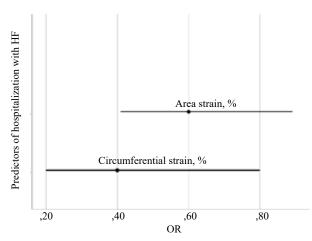
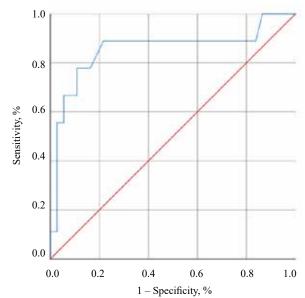


Fig. 1. Hazard ratio estimates with 95% CI for the studied predictors of the model (1) for hospitalization with HF



 $P_2 > 26.6\%$; Sensitivity 77.8%, Specificity 89.2%, p = 0.026, AUC = 0.85

Fig. 2. The ROC curve characterizing the dependence of the probability of hospitalization with HF on the values of the prognostic function (1)

AUC was 0.85 ± 0.09 (95% CI: 0.68-1.00). The value of the logistic function (1) at the cut-off point was 26.6%. P(1) values greater than or equal to 26.6% were associated with a high risk of hospitalization with HF, and lower P(1) values were associated with a low risk. The sensitivity and specificity of the model (1) at the cut-off were 77.8 and 89.2%, respectively.

Table 5 shows an example of using the prognostic model (1) in two patients with a first AMI. We calculated logistic regression values P(1) taking into account the values of the predictors and inferred high and low risk. Patient 2, who was at high risk based on

the model, was hospitalized with HF on day 291 of the follow-up.

Table 5

Example of using the prognostic model (1)			
Patient	Patient 1 Woman, 64 years old, history of hypertension, STEMI, single-vessel disease	Patient 2 Woman, 58 years old, history of hypertension, STEMI, single-vessel disease	
NTproBNP, pg / ml	556	630	
Troponin I, II, ng / ml	0.98–1.46	0.76–1.72	
Echocardiography	LAVI 29 ml / m ² (< 34 ml / m ²) Baseline LVEF 44% 2D GLS 16% CS 12.2% AS 18.8%	LAVI 32 ml / m ² (< 34 ml / m ²) Baseline LVEF 40% 2D GLS 10% CS 6% AS 9.8%	
Index P	$z = 2.615-0.102 \times 12.2-0.286 \times 18.8$ = -4 e ⁻⁽⁻⁴⁾ = e ⁴ = 54.9 P = 1/55.9 = 1.8% (<23.8%) Low risk	$z = 2.615 - 0.102 \times 6 - 0.286 \times 9.8 = -0.8$ $e^{(-0.8)} = e^{0.8} = 2.23$ $P = 1/3.23 = 31.0\%$ (>23.8%) High risk	
Hospitalization with HF	Not registered	Registered after 291 days	

In the univariate analysis of the dependence of changes in the risk of hospitalization with HF on 3D Echo parameters using the Cox regression method, statistically significant predictors of the development of this endpoint were identified (Table 6).

Table 6

$Characteristics \ of \ predictors \ of \ hospitalization \ with \ HF$ in the long-term follow-up period in patients after the first AMI			
Predictors	HR; 95% CI	p	
Circumferential strain, %	0.76; 0.597-0.968	0.026*	
Radial strain, %	0.91; 0.831–0.995	0.039*	

Note. HR – hazard ratio. * the influence of the predictor is statistically significant.

According to the data obtained, with an increase in circumferential strain by 1%, the risks of developing the starting point are reduced by 1.32 times, for radial strain – by 1.1 times.

DISCUSSION

In our study, in patients with first AMI with and without ST-segment elevation in the history of HF, non-invasive parameters of volumes, geometry and strain of the LV myocardium were studied according to 3D Echo data. Their prognostic value was established

in relation to the development of cardiovascular complications within 1.5 years.

In patients hospitalized with HF within 1.5 years after AMI, a significant increase in the LV sphericity index according to 3D Echo data was shown. This result is consistent with a study by H.F. Mannaerts et al., which included 33 patients with AMI. The follow-up lasted 12 months, and the sphericity index was shown to be the strongest echocardiography predictor of adverse post-infarction LV remodeling [6].

In a study by R.K. Ola et al., the information value of 3D parameters, such as LVEDV and sphericity index, as predictors of myocardial remodeling was also shown. These parameters were examined by the authors at 7 days and at 6 months after acute STEMI. The presence of adverse remodeling was defined as an increase in LVEDV, measured using 3D Echo, by 15% or more after 6 months. It was found, in particular, that the sphericity index in the group with adverse postinfarction remodeling was significantly higher than in the group with preserved LVEF (0.41 \pm 0.05 and 31 ± 0.05 , respectively; p < 0.001), but decreased in both groups after 6 months of follow-up (0.35 \pm 0.05 and 28 ± 0.05 , respectively; p < 0.001). Thus, the authors concluded that determination of the sphericity index allows for early identification of patients at high risk of developing adverse myocardial remodeling after AMI [7]. Similar results were obtained in a study by M.L.Vieira et al. [10].

Predictors of the development of HF requiring hospitalization within 1.5 years of the post-infarction period, according to the multivariate binary regression analysis in our study, were parameters of circumferential strain and area strain. With an increase in circumferential strain by 1%, the chance of hospitalization with HF within 1.5 years after the first AMI decreases by 2.49 times; with an increase in the area strain by 1% – by 1.67 times; in radial strain – by 1.1 times. These factors were included in the prognostic model we developed (p = 0.004). According to the results of the univariate Cox regression analysis, with an increase in circumferential strain by 1%, the risks of developing the endpoint are reduced by 1.32 times (p = 0.026), in radial strain – by 1.1 times (p = 0.039).

A number of studies have also been published describing the use of strain indices measured by 3D Echo in post-AMI patients. The study by L. Xu et al. included 110 STEMI patients who underwent primary PCI. All patients underwent 3D Echo with the determination of longitudinal, radial, and circumferential strain in the three-dimensional

mode, as well as longitudinal strain and routine Echo parameters in the two-dimensional mode. Similar to our results, it was found that 3D and 2D longitudinal strain, as well as 3D radial strain, are independent predictors of LV remodeling [11]. In a study by A. Sugano et al., it was confirmed that changes in circumferential strain were a predictor of adverse LV remodeling and showed that its decrease was associated with the presence of microvascular obstruction according to MRI in patients with STEMI who underwent primary PCI. This observation is of great importance, since it is known that the presence of microvascular obstruction is also an independent predictor of adverse LV remodeling [12].

In a study by N. Iwahashi et al. [13], as in our study, the prognosis for the development of cardiac death and hospitalization with HF in patients with STEMI and PCI was studied according to 3D Echo. It was found that 3D examination parameters were stronger predictors of outcomes compared to two-dimensional ones. Specifically, 3D longitudinal strain was the strongest predictor, followed by circumferential strain. 3D-GLS > -11.0% was an independent predictor of the studied outcomes ($\chi 2 = 132.2$, p < 0.001). When combined with circumferential strain > -18.3%, patients were found to have an extremely high risk of adverse outcomes. Another study by this group of authors [14] examined the clinical and prognostic significance of 3D Echo parameters obtained over time in 272 patients with a first STEMI and PCI. Patients were followed-up for an average of 108 months. The primary endpoint was the occurrence of major cardiovascular events: sudden cardiac death and HF requiring hospitalization. It was shown that deterioration of 2D-GLS and 3D-GLS over 1 year was a significant prognostic factor ($\chi 2=36.7$, p < 0.001).

CONCLUSION

In patients with a first AMI, regardless of LVEF upon admission in the absence of clinical signs of HF, to calculate the risk of hospitalization with HF within 550 days after MI, it is advisable to take into account the level of radial strain and use the prognostic model (1), including parameters of circumferential and area strain (by data from 3D Echo). P(1) values > 26.6% indicate a high risk of hospitalization with HF (sensitivity and specificity of 77.8 and 89.2%, respectively).

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