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ОСОБЕННОСТИ ПРОГНОЗИРОВАНИЯ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ПЕРИФЕРИЧЕСКИМ АТЕРОСКЛЕРОЗОМ В ОТДАЛЕННОМ ПЕРИОДЕ

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Features of Prediction of Heart Failure in Patients with Peripheral Atherosclerosis in the Long Period

Резюме

Цель: оценить вероятность развития сердечной недостаточности в течение трехлетнего проспективного наблюдения и разработать способ ее комплексной оценки у лиц с атеросклеротическим поражением различных сосудистых бассейнов. **Материалы и методы:** В исследование включено 519 пациентов (средний возраст 60,0±8,7лет) с атеросклеротическим поражением различных сосудистых бассейнов, из них — 360 (69,4 %) мужчин, 159 (30,6 %) — женщин. Всем пациентам выполнялись стандартные биохимические исследования с определением показателей липидного профиля. Комплекс инструментальных исследований включал выполнение эхокардиографии, ультразвукового исследования почек, брахиоцефальных артерий, при наличии клинических проявлений, вызывающих подозрение на атеросклеротическое поражение сосудистых бассейнов, были проведены коронароангиография, ангиография почечных сосудов, брахиоцефальных артерий и артерий нижних конечностей. Срок наблюдения составил — 36 месяцев, первичная конечная точка — новые случаи развития сердечной недостаточности. **Результаты:** Анализ вероятности развития сердечной недостаточности продемонстрировал, что такие факторы, как величина фракции выброса, % (p=0,04), значение основания аорты, мм (p=0,049), степень атеросклеротического поражения ствола левой коронарной артерии, % (p=0,013) и степень тяжести стеноза задней боковой ветви коронарной артерии, % (p=0,048) оказывали влияние на риск развития сердечной недостаточности в отдаленном периоде у пациентов с периферическим атеросклерозом. **Заключение:** Проведена оценка вероятности развития сосудистых событий и неблагоприятных исходов в течение трехлетнего проспективного наблюдения. Установлено, что госпитализация по поводу сердечной недостаточности в течение трехлетнего периода имела место у 3,4 % пациентов с атеросклеротическим поражением различных сосудистых бассейнов и их комбинаций. Отмечено, что такие группы факторов, как «величина фракции выброса % + значение основания аорты, мм» (p=0,025), «степень атеросклеротического поражения задней боковой ветви, % + величина фракции выброса, %» (p=0,046), оказывали влияние на риск развития сердечной недостаточности в отдаленном периоде у лиц группы обследования. С использованием уравнений логистической регрессии разработаны оригинальные таблицы прогноза, позволяющие получить информацию

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в отношении вероятности развития сердечной недостаточности, которые могут быть использованы в реальной клинической практике у пациентов с периферическим атеросклерозом.

Ключевые слова: *сердечная недостаточность, периферический атеросклероз, атеросклероз почечных артерий, атеросклероз сонных артерий*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Aim: To assess the likelihood of developing heart failure during a three-year prospective follow-up and develop a method for its comprehensive assessment in individuals with atherosclerotic lesions of various vascular beds. **Materials and methods:** The study included 519 patients with atherosclerotic lesions of various vascular regions, of which 360 (69.4 %) were men, 159 (30.6 %) were women (mean age 60.0±8.7 years). **Results:** Analysis of the likelihood of developing heart failure clearly demonstrated that factors such as the value of the ejection fraction, % (p = 0.040), the value of the base of the aorta, mm. (p = 0.049), the degree of atherosclerotic lesions of the left coronary artery trunk,% (p = 0.013) and the severity of posterior lateral branch stenosis,% (p = 0.048) influenced the risk of developing the discussed endpoint in the long-term period in patients with peripheral atherosclerosis. **Conclusions:** The probability of developing vascular events and adverse outcomes during a three-year prospective follow-up was assessed. It was found that hospitalization for heart failure over a three-year period occurred in 3.4 % of patients with atherosclerotic lesions of various vascular beds and their combinations. It is noted that such groups of factors as "the value of the ejection fraction% + the value of the base of the aorta, mm." (p=0.025), "the degree of atherosclerotic lesions of the posterior lateral branch, % + the value of the ejection fraction, %" (p=0.046), influenced the risk of developing heart failure in the long-term period in the subjects of the survey group. Using logistic regression equations, original prognosis tables have been developed that provide information on the likelihood of developing heart failure, which can be used in real clinical practice in patients with peripheral atherosclerosis.

Key words: *heart failure, peripheral atherosclerosis, renal atherosclerosis, carotid atherosclerosis*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, BCA — brachiocephalic arteries, CHF — chronic heart failure, CKD — chronic kidney disease, ECG — electrocardiography, EF — ejection fraction, FC — functional class, GFR — glomerular filtration rate, HF — heart failure, LCA — left coronary artery, LLA — lower limb arteries, LV — left ventricle, MI — myocardial infarction, PLB — posterolateral branch, TIA — transient ischemic attack

Introduction

Despite the continuous improvement of diagnostic methods, optimal drug treatment in accordance with accepted standards and implementation of new preventive programs, patients with cardiovascular pathologies still demonstrate a high incidence of adverse long-term events and outcomes [1].

Atherosclerotic lesions of peripheral vessels are, no doubt, associated with high risk of heart failure development. In general, this association is characterized by increased left ventricular (LV) afterload due to the increased stiffness of aortic walls and, as a result, deterioration of coronary blood flow that results in hypertension, LV hypertrophy, diastolic dysfunction, and the development of heart failure [2,3].

High mortality due to heart failure is undoubtedly caused by cardiac issues and rapid progression of the underlying disease. According to OPTIMIZE-HF register data, about 30 % of individuals with reduced LV ejection fraction (EF) and 29.2 % with EF >40 % are rehospitalized within 90 days after discharge from the hospital [4].

A long-term task related to cardiovascular diseases is the development of a personalized approach to patients with atherosclerosis of any vascular territory.

Despite the fact that the prevalence of peripheral atherosclerosis is high, and the patients with this pathology

belong to one of the most difficult to cure groups, today we have no reliable scores for qualitative assessment of long-term prognosis [5].

The issue of treating patients with atherosclerotic pathology of peripheral arteries requires multidisciplinary solutions due to the high risk of adverse vascular events.

Study objective

To assess the probability of heart failure development during a three-year prospective follow-up and to develop a method for its comprehensive assessment in individuals with atherosclerotic lesions of various vascular territories.

Materials and methods

This prospective study included 519 patients (average age 60.0 ± 8.7 years) with atherosclerotic lesions of different vascular territories and their combinations (380 men and 139 women) who received treatment in specialized departments of State Budgetary Institution of Rostov Region Rostov Regional Clinical Hospital (GBU RO ROKB). The study protocol was approved by the local independent Ethics Committee of Federal State Budgetary Institution of Higher Education Rostov State Medical University of the Ministry of Health of the Russian Federation.

Inclusion criteria were as follows: peripheral arterial diseases in patients that meet the criteria of the recommendations of European Society of Cardiology (ESC) and the European Society of Vascular Surgeons (EOVS) for the diagnosis and management of peripheral arterial diseases (2017) [6]; informed consent form signed by the patient. Exclusion criteria were as follows: comorbidity with severe dysfunction of organs and systems; oncological and mental diseases; acute infectious processes.

Arterial hypertension (AH) was diagnosed according to the Guidelines for the Management of Arterial Hypertension developed by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (2013). [7]. Chronic heart failure was diagnosed according to the Guidelines "Chronic Heart Failure (CHF)" developed by the Society of Heart Failure Specialists of the Russian Cardiological Society (2016) [8].

Standard laboratory test with lipid panel was performed for all patients. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (2011). The set of instrumental studies included electrocardiography (ECG), echocardiographic examination, ultrasound examination of kidneys, brachiocephalic arteries (BCA); if there were clinical signs with suspected atherosclerotic lesions of vascular territories, coronary angiography, angiography of renal vessels, BCA and lower limb arteries (LLA) were performed.

Design of this clinical study is provided in Figure 1.

AH was observed in 500 (96.3 %) patients. Hereditary diseases were registered in 239 (46.0 %) patients, smoking — in 209 (40.2 %) patients (Table 1).

Based on the results of angiographic examination, the patients were divided into groups depending on the number and combinations of the affected vessels.

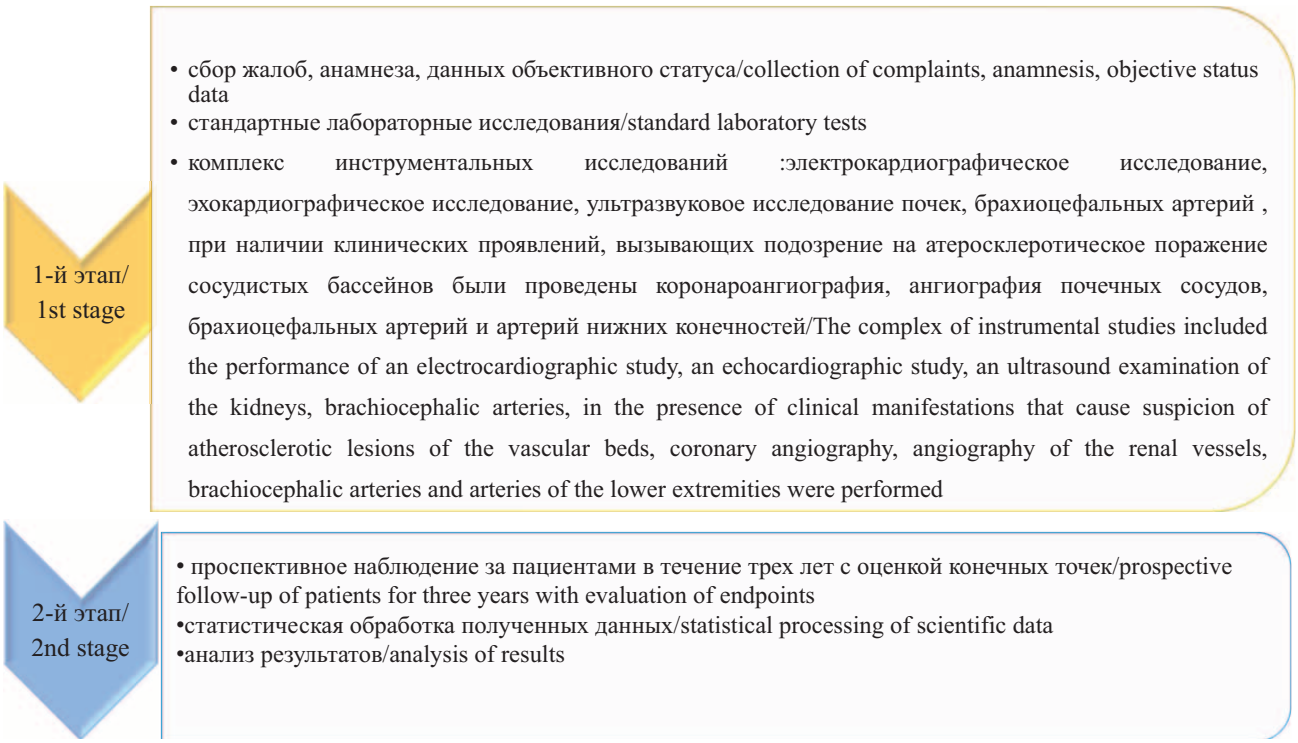


Figure 1. *Study Design*

Atherosclerotic lesion of one vascular territory was confirmed in 258 (49.7 %) patients, of two territories — in 171 (2.9 %) patients; of three territories — in 84 (16.2 %); of four vascular territories — in 6 (1.2 %) patients.

BCA lesion was diagnosed in 199 (38.3 %) patients, while BCA mono-lesion was confirmed in 4.6 % of cases. Atherosclerotic lesions of renal arteries were observed in 103 (19.8 %) patients, of LLA — in 105 (20.2 %) examined individuals (Table 2).

The second stage of this study included a prospective three-year follow-up. The patients or their relatives were contacted by telephone survey.

Table 1. *Clinical characteristics patients*

Parameter	n (%)
men/women (n, %)	380/139 (73,2/26,8)
smoking (n, %)	209 (40,2)
burdened heredity (n, %)	239 (46,0)
presence of hypertension (n, %)	500 (96,3)
acute cerebrovascular accident in history (n, %)	98 (18,8)
myocardial infarction in history (n, %)	205 (39,4)
history of lower limb amputation (n, %)	3 (0,57)
chronic cerebrovascular insufficiency (n, %)	173 (33,3)
the presence of chronic ischemia of the lower extremities (n, %)	90 (17,3)
history of angina pectoris (n, %)	362 (69,7)
chronic heart failure (n, %)	333 (64,2)
functional class of chronic heart failure 1 FC	135 (40,5)
2 FC	166 (49,8)
3 FC	32 (9,7)
CHF with low EF (less than 40 %) (n, %)	15 (4,5)
CHF with intermediate EF (from 40 % to 49 %) (n, %)	113 (33,9)
CHF with preserved EF (50 % or more) (n, %)	205 (61,6)
glomerular filtration rate less than 60ml/min/1.73m^2	130 (25,1)
presence of diabetes (n, %)	112 (21,5)

Note: FC/functional class of chronic heart failure / CHF/chronic heart failure / EF/ejection fraction

Table 2. *Features of atherosclerotic lesions of various vascular beds in patients*

Parameter	n (%)
damage to one vascular bed	258 (49,7)
damage to two vascular beds	171 (32,9)
damage to three vascular beds	84 (16,2)
damage to four vascular beds	6 (1,2)
monolesion (coronary arteries)	225 (43,4)
monolesion (brachiocephalic arteries)	24 (4,6)
monolesion (renal arteries)	3 (0,6)
monolesion (arteries of the lower extremities)	4 (0,8)
coronary arteries + renal arteries	83 (15,9)
coronary arteries + brachiocephalic arteries	70 (13,4)
coronary arteries + arteries of the lower extremities	5 (0,9)
lower extremity arteries + brachiocephalic arteries	12 (2,3)
brachiocephalic arteries + renal arteries	2 (0,4)
coronary arteries + brachiocephalic arteries + lower extremity arteries	76 (14,8)
brachiocephalic arteries + lower extremity arteries + renal arteries	2 (0,4)
coronary arteries + brachiocephalic arteries + renal arteries	7 (1,3)
coronary arteries + brachiocephalic arteries + lower extremity arteries + renal arteries	6 (1,2)

During the period specified, the following events and outcomes were analyzed: development of transient ischemic attack, stroke (nonfatal/ fatal stroke), myocardial infarction (MI) (nonfatal/fatal MI), development of heart failure (HF) (nonfatal/fatal HF), chronic kidney disease (CKD) (nonfatal/fatal CKD) , hospitalization for cardiovascular reasons, amputation of lower limb.

Statistical data analysis was performed using a set of applied statistical programs Microsoft Office Excel 2010 (Microsoft Corp., USA) and STATISTICA 10.0 (StatSoft Inc., USA). Kolmogorov–Smirnov test was used to assess the type of data distribution; for $p > 0.05$, distribution was considered to be normal. The data were presented as M±SD (M — arithmetic mean, SD — standard deviation) for normal distribution, and as Me [Q1; Q3] (Me — median, Q1 and Q3 — first and third quartiles) for abnormal distribution. Student's test was used for a normal distribution of sample, and Mann-Whitney test and $\chi 2$ test or Leuven test with F — for those different from the normal distribution. Besides, the authors used logistic regression analysis with the calculation of relative risks (RR) and the determination of χ^2; the relationship was considered statistically significant at $p < 0.05$.

Results

The development of vascular events and adverse outcomes was registered in 126 (24.2 %) patients, while hospitalization for new cases of heart failure was confirmed in 14 (3.4 %) patients.

During the analysis of the heart failure development probability, such factors as EF, % ($p = 0.04$), aortic base, mm ($p = 0.049$), degree of atherosclerotic lesion of left coronary artery (LCA), % ($p = 0.013$), and the severity of posterior lateral branch (PLB) stenosis, % ($p = 0.048$), affected the risk of developing the discussed endpoint in patients with peripheral atherosclerosis (Table 3).

Based on the data obtained, a nomogram was constructed to assess the possibility of heart failure development depending on risk factors. Thus, at EF 40 %, the risk of heart failure development during three year follow-up was 10 %, at EF 50 % — 7 %. In cases of LCA trunk stenosis 40 %, the risk of heart failure development during three years was 10 %; if the diagnosis of LCA stenosis 60 % was confirmed, the risk was 40 % (Table 4).

Two-factor logistic regression analysis allowed defining a combination of features that had a pathological

Table 3. *Probability of developing heart failure*

*Parameter	B0	Estimate	OR (ratio)	χ^2	p
ejection fraction, %	0,21	-0,006	0,03	4,21	0,040
base of the aorta, mm	-8,35	0,13	593	3,97	0,049
lesion of the trunk of the left coronary artery, %	0,63	-0,19	0,0001	6,17	0,013
damage to the posterior lateral branch, %	-13,2	0,11	1163	3,88	0,048

* p <0,05

Table 4. *Nomogram for assessing the risk of developing heart failure within three years, depending on risk factors*

ejection fraction, %	20	30	40	50	60	70
risk of developing heart failure, %	24	17	10	7	3	1
base of the aorta, mm	25	30	35	40	50	55
risk of developing heart failure, %	1	3	5	7	17	26
lesion of the trunk of the left coronary artery, %	10	20	30	40	50	60
risk of developing heart failure, %	1	4	8	10	25	40
damage to the posterior lateral branch, %	50	60	70	80	90	100
risk of developing heart failure, %	1	2	3	4	9	20

Table 5. *The likelihood of developing heart failure, depending on a combination of factors*

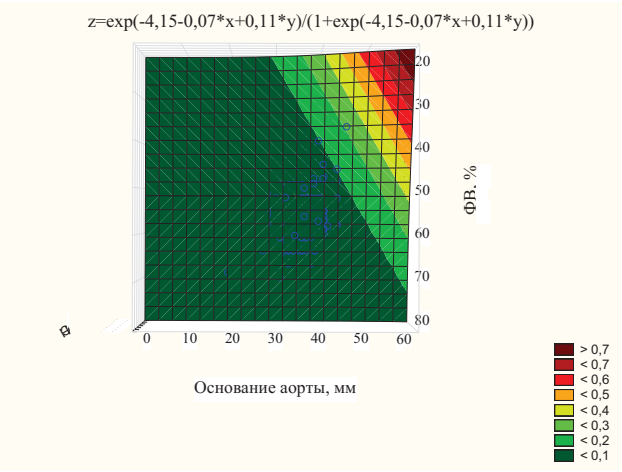
*Parameter	B0	Estimate	OR (ratio)	χ^2	p
ejection fraction, % + aortic base, mm	-4,15	-0,07 /0,11	0,04 /234	7,4	0,025
damage to the posterior lateral branch, % + ejection fraction, %	-9,24	-0,09 /0,12	0,05 /1732	4,9	0,046

* p <0,05

effect on long-term prognosis, namely, “EF, % + aortic base, mm” (p = 0.025), “PLV, % + EF, %” (p = 0.046) (Table 5, Figure 2).

Nomograms based on logistic regression equations demonstrated that, if a patient has an aortic base equal to, for example, 30 mm and EF 60 %, the risk of heart failure during three years will be 13 %; in the case of EF v40 % with the same value of aortic base, the risk is 28 % (Table 6).

Confirmed EF 50 % and an atherosclerotic plaque 60 % in PLB area lead to the risk of developing heart failure during three years of 24 %, while vessel occlusion lead to 41 %. PLB stenosis 50 % and EF 40 % lead to the possibility of heart failure development 20 % (Table 7).



(a) / (a)

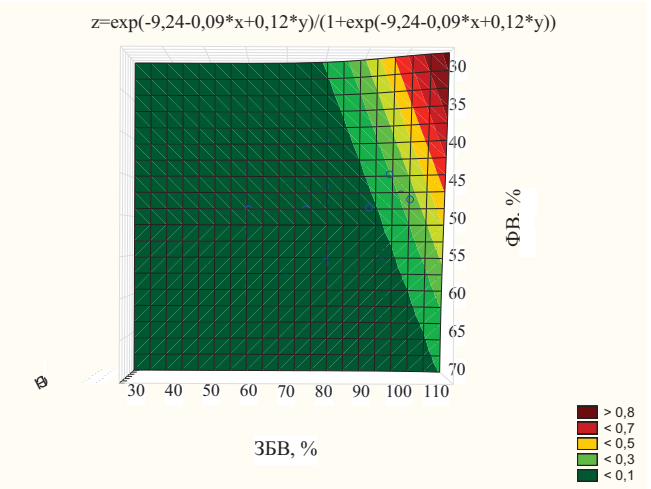


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Figure 2. *Assessment of the risk of developing heart failure depending on the size of the ejection fraction and the base of the aorta (a), the magnitude of the ejection fraction and the severity of the lesion of the posterior juic branch (b)*
Note: PBV — posterior lateral branch, EF — ejection fraction

Table 6. *Nomogram for assessing the risk of developing heart failure depending on the size of the ejection fraction and the base of the aorta*

		Ejection Fraction, %					
		20	30	40	50	60	70
aortic base, mm	5	9	8	7	5	4	3
	10	20	10	8	6	5	4
	20	45	29	16	10	8	6
	30	56	40	28	17	13	7
	40	68	52	39	24	17	8
	50	82	76	54	32	20	9

Table 7. *Nomogram for assessing the risk of developing heart failure depending on the value of the ejection fraction and the severity of the lesion of the posterior lateral branch of the*

		Ejection Fraction, %					
		20	30	40	50	60	70
damage to the posterior lateral branch, %	30	8	7	6	5	4	2
	40	25	20	17	14	10	8
	50	44	33	20	18	16	13
	60	57	48	29	24	20	17
	80	69	51	34	28	24	20
	100	85	68	50	41	33	22

Discussion

In atherosclerotic lesions of a certain vascular territory, not only this area of blood supply is at risk. Atherosclerosis quite often becomes generalized, and if a patient has a monofocal lesion, the risk of adverse cardiovascular events nevertheless remains high.

According to a review of 17 studies involving more than 10,000 patients with asymptomatic carotid stenosis (>50 %), about 60 % of deaths were directly related to the existing cardiac pathology [9]. The following cardiovascular events were registered in patients with peripheral arterial disease during the first year of follow-up: 1.8 % — death due to cardiovascular causes, 1.4 % — noncardiovascular death, 1.9 % — acute myocardial infarction, 1 % — hospitalization for unstable angina, 0.9 % — ischemic stroke, 1.3 % — acute limb ischemia, 1.2 % — amputation [10].

Results of many studies clearly demonstrated that patients with peripheral atherosclerosis, even with adjusted risk factors, remain at high risk of fatal and non-fatal vascular events (myocardial infarction, stroke, HF) [11].

Analysis of literature sources demonstrated that existing models for predicting heart failure have been actively created and modified over the past decades, while most of them have been created and validated for patients with low EF and are used to assess one-year survival. The most common models are SHFMHFSS, MAGGIC, MECKI, 3C-HF, MUSIC. Thus, SHFM (Seattle Heart Failure Model) is the most common for assessing the life expectancy of patients with CHF at the outpatient stage. It was developed on the basis of the PRAISE1 trial and tested in USA and Italy. [12].

MAGGIC risk score can be applied to patients with reduced or preserved ejection fraction. The only biomarker considered by this score is serum creatinine; thus, on the one hand, it is easily available for common use, however, on the other hand, its informative value is reduced. [13].

At the same time, none of the presented models is aimed at assessing the risk of heart failure development in patients with peripheral atherosclerosis during three-year period.

It is known that the survival rate of patients with the new onset of heart failure that requires hospitalization is about 40 % during the first year [14]. According to a meta-analysis of 60 trials in the period from 1950 to 2016 that included 1.5 million patients with heart failure with reduced EF in the "stable" phase of the disease, the total one-year survival rate is 86.5 % [15].

Certain established risk factors that determine the prognosis of patients with regard to the nature and severity of heart failure include LV EF, functional class of CHF (NYHA), and appropriate treatment strategy [16]. In addition, one of the main indicators of the severity of pathological process in patients with heart failure is LV EF. Meanwhile, heart failure can also develop along with preserved LV EF [17].

Analysis of literature sources revealed that more than half of the total number of patients with CHF have preserved LV EF, and their number continues growing rapidly [18]. Results of the Rochester Epidemiological Project clearly demonstrated that more than 40 % of patients with heart failure are diagnosed with LV EF >50 % [19]. According to the EPOCH-CHF study, preserved or intermediate LV EF in the range of 40–60 % was diagnosed in more than 50 % of patients [20]. The analysis of a Canadian study results revealed that above 40 % of the examined patients had preserved EF [21]. The complex of such endpoints as total mortality + rehospitalizations in the groups with reduced and preserved EF had no statistical differences, while the mortality rate during the first year in patients with preserved EF was 29 %. [22]. It was found that patients with reduced EF and ejection fraction >35–40 % had a more favorable prognosis [23].

Based on the results of our study, EF <40 % was registered in 4.5 % of patients, intermediate EF was observed in 33.9 %, and preserved EF was observed in 61.6 % of patients. It should be mentioned that EF value had an effect on the long-term prognosis of patients what is consistent with the literature data. At the same time, in the course of our study, combinations of factors were presented that have an effect on the long-term prognosis of the presented group of patients.

Conclusion

Thus, in the course of a prospective study, it was found that hospitalization for heart failure occurred in 14 (3.4 %) patients with atherosclerotic lesions of various vascular territories and their combinations.

It was mentioned that such factors as EF, aortic base, size of atherosclerotic lesions of LCA trunk, and severity of PLB stenosis had an effect on the risk of long-term heart failure development in patients with peripheral atherosclerosis.

It was revealed that the risk of heart failure was influenced by such groups of factors as EF + aortic base, severity of PLB atherosclerotic lesions + EF.

Based on logistic regression equations prognosis, original tables were developed allowing to obtain information on the possibility of heart failure development that can be used in real clinical practice in individuals with peripheral atherosclerosis.

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Author Contribution

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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