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Long-term risk predictors of adverse events in patients with chronic heart failure

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Abstract

Aim – to identify predictors of the risk of adverse events over a three-year period in patients with chronic heart failure (CHF).

Material and methods. A retrospective study was conducted on 278 people diagnosed with CHF in patients with coronary heart disease (CHD). A sample of data was made, survival assessment, Charson comorbidity index was calculated. Statistical data processing was carried out using Excel and XLSTAT programs with linear regression calculations.

Results. A statistically significant direct relationship between three-year survival was identified with the following indicators: age over 66 years, stage IIB-III CHF, Echo-CG data (low LVEF, left ventricular diameter, systolic pressure in the pulmonary artery (SPAP), the presence of hypertension (HBP) and atrial fibrillation (AF), Charlson comorbidity index of more than 5 points, glomerular filtration rate (GFR) less than 60 ml/min, complete blood count (CBC) data - a decrease in hemoglobin level below 131 g/l and an increase in ESR level above 14 mm/h. Surgical interventions such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) were associated with better patient survival.

Conclusion. In order to ensure qualified monitoring of patients with CHF and ensure continuity of management of these patients, it seems relevant to create a specialized office for the management of patients with CHF.

Keywords: chronic heart failure, survival, anemia, low ejection fraction, comorbid pathology, ESR, age, atrial fibrillation, hypertension, CKD.

Conflict of Interest: nothing to disclose.

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Предикторы риска неблагоприятных событий в отдаленном периоде у пациентов с хронической сердечной недостаточностью

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Аннотация

Цель – выявить предикторы риска неблагоприятных событий в трехлетнем периоде у пациентов с хронической сердечной недостаточностью (ХСН).

Материал и методы. Проведено ретроспективное исследование 278 человек с диагнозом ХСН у больных с ишемической болезнью сердца. Произведены выборка данных, оценка выживаемости, рассчитан индекс коморбидности Чарлсона. Проведена статистическая обработка данных с помощью программ Excel и XLSTAT с расчетом линейной регрессии.

Результаты. Статистически значимая прямая связь трехлетней выживаемости выявлена со следующими показателями: возраст старше 66 лет, ХСН IIБ-III стадии, данные ЭхоКГ (низкая фракция выброса левого желудочка, диаметр левого желудочка, систолическое давление в легочной артерии); наличие гипертонической болезни и фибрилляции предсердий; индекс коморбидности Чарлсона более 5 баллов; скорость клубочковой фильтрации менее 60 мл/мин; данные общего анализа крови – снижение уровня гемоглобина ниже 131 г/л и повышение уровня СОЭ выше 14 мм/ч. Ассоциировалось с лучшей выживаемостью пациентов выполнение оперативных вмешательств – аортокоронарного шунтирования и чрескожных коронарных вмешательств.

Заключение. Для обеспечения квалифицированного наблюдения пациентов с ХСН и обеспечения преемственности их ведения этих больных представляется актуальным создание специализированного кабинета.

Ключевые слова: хроническая сердечная недостаточность, выживаемость, анемия, низкая фракция выброса, коморбидная патология, СОЭ, возраст, фибрилляция предсердий, гипертоническая болезнь, ХБП.

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Список сокращений
ИБС – ишемическая болезнь сердца; НЖО – нарушение жирового обмена; ПИКС – постинфарктный кардиосклероз; СД2 – сахарный диабет 2 типа; СН – сердечная недостаточность; СОЭ – скорость оседания эритроцитов; ФВ ЛЖ – фракция выброса левого желудочка; ХСН – хроническая сердечная недостаточность; ЖКТ – желудочно-кишечный тракт, ХБП – хроническая болезнь почек, ЦВЗ – цереброваскулярные заболевания, ХОБЛ – хроническая обструктивная болезнь легких, БА – бронхиальная астма, ЗНО – злокачественные новообразования; БАБ – бета-адреноблокаторы; иАПФ – ингибиторы ангиотензинпревращающего фермента; БРА – блокаторы рецепторов ангиотензина II; БКК – блокаторы кальциевых каналов; АКШ – аортокоронарное шунтирование; ЧКВ – чрескожное коронарное вмешательство.

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INTRODUCTION

About 60 million patient are currently living with the diagnosis of chronic heart failure (CHF) [1]. Following the data of the EPOKHA epidemiological study, in the period from 1998 to 2014, the number of cases of heart failure (HF) doubled [2]. By the year 2030, the prevalence of CHF is expected to reach 46%, and the number of patients will increase by more than 6 million people, especially in the less developed countries [3].

Over the past decades, there has been an increase in the incidence of hospitalization for heart failure worldwide [4–6]. The hospitalization rate grows both within the year after the diagnosis and subsequently, reaching, on average, 64 events per 100 patient years [4]. Approximately 20% of the patients are re-admitted within the first month after the discharge resulting in the total cost of treatment worth 30.7 billion USD per year [7]. Heart failure affects the patients' quality of life, leading to incapability of self-care, disruption of regular lifestyle, deterioration of mental health and psychosocial well-being [8, 9]. Earlier research showed that patients with HF had more restrictions than patients with diabetes mellitus, oncological conditions, or Alzheimer's disease [9]. Mortality resulting from CHF remains high despite the advent of new pharmaceutical products and instrumental methods of CHF treatment [10]. Studies looking for predictors of poor outcome in patients with CHF do not always provide clear answers. Thus, the PARADIGM-HF study identified the following predictors: New York Heart Association class, age, sex, history of prior admissions with HF, diabetes mellitus, extracardiac vascular diseases, systolic blood pressure, left ventricle ejection fraction, N-terminal pro-B-type natriuretic peptide and glomerular filtration rate [11], whereas another study identified as predictors such indicators as number of admissions, age, glomerular filtration rate, natriuretic peptide, NYHA heart function class, absolute value of lymphocytes, serum albumin, hemoglobin, total cholesterol, and pulmonary artery systolic pressure [12]. However, these studies did not take into account the presence of many concomitant diseases in patients with CHF, which significantly worsen the prognosis. To take into account the disease burden in polymorbid patients, the Charlson Comorbidity Index has been developed, in which concomitant diseases are assigned from 1 to 3 points depending on the severity of the disease, and an additional 1 point is added for every 10 years of life after 40 years. The Charlson Index considers the burden from concominant diseases such as myocardial infarction, CHF, peripheral arterial disease, cerebrovascular disease, dementia, chronic lung disease, connective tissue disease, peptic ulcer, liver damage, diabetes mellitus; hemiplegia, chronic kidney disease, malignant tumor, leukemia, lymphomas, and AIDS [13].

AIM

Retrospectively identify predictors of the risk of adverse events over a three-year period in patients with chronic heart failure.

MATERIAL AND METHODS

A retrospective study of 278 cases of hospital treatment of patients with chronic heart failure in 2019 at the Komi Republic Cardiologic Dispensary.

Inclusion criteria: dispensary patients with coronary heart disease (CHD), male and female, whose diagnosis indicated NYHA Class II-IV CHF. Optimal visualization of the heart under echocardiography was performed with evaluation of the ejection fraction of the left ventricle (LVEF), ventricular diameter, and calculation of systolic pulmonary artery pressure (SPAP).

Exclusion criteria: indication in the main diagnosis of the hypertrophic cardiomyopathy, dilated cardiomyopathy, hemodynamically relevant cardiac defects, septic endocarditis, arterial hypertension.

The data sampled included sex, age, principal diagnosis, comorbidity, previous surgeries, EchoCG data, body mass index, hemoglobin and leukocyte level, and erythrocyte sedimentation rate (ESR) in the full blood exam.

The EchoCG data included the LVEF, SPAP, ventricular diameter. The LVEF is measured in percent and shows the volume of blood ejected from the left ventricle into the aorta with each cardiac contraction. Currently, it is customary to classify the CHD using the LVEF: CHD with preserved EF (≥ 50%), CHD with midrange EF (40–49%), and CHF with reduced EF (<40%).

The Charlson Comorbidity Index was then calculated, and the three-year survival and number of subsequent hospitalizations were evaluated using the Regional Medical Information System (RMIS). The data was added to an Excel 2019 spreadsheet, and the statistical processing of data was performed with Excel and XLSTAT with calculation of linear regression.

RESULTS

The clinical and demographic characteristics of patients are given in **Table 1**.

Among them, there were more men, 65% (n=181), than women, and the average age at the moment of treatment was 65.2±12.4 years (25–94 years).

Within the studied group, the leading condition in the structure of the CHD is the acute myocardial infarction, diagnosed in 38% (n=105), 18% cases of stable angina (n=51), 16% of unstable angina (n=44), and post-infarction cardiosclerosis and recurrent myocardial infarction are diagnosed in 15 % (n=43) and 13% (n=35), respectively.

185 patients had undergone surgical treatment. The majority of surgical interventions was PCI, 176 surgeries, including stenting of coronary arteries, balloon surgeries, thromboaspirations, and 51 cases of coronary artery bypass grafting.

25% of patients were identified with (n=70) Class IIB-III heart failure, which corresponds severe cardiac damage with marked changes in the hemodynamics in both circulation circuits. Arterial hypertension was diagnosed in 83% of cases (n=231). As far as the rhythm disorders are concerned, the most frequent was the atrial fibrillation found in 15.5% of cases (n=43).

Among concomitant pathologies, the diseases of the gastrointestinal tract are most frequent: 49.6% (n=138). The most common of these was the chronic gastritis diagnosed in 19% (n=53), gastric ulcer, 11.1% (n=31), gastroesophageal hernia, 7.9% (n=22), cholelithiatis, 5.7% (n=16), and other gastrointestinal pathologies, 5.7% (n=16).

Endocrine disorders were diagnosed in 36% of patients (n=101): type II diabetes mellitus in 25.9% (n=72), glucose intolerance, 4.7% (n=13), including thyroid disorders: diffuse nodular goiter in 2.1% (n=6), hypothyroidism in 3.6% (n=10). Obesity was found in 26.6% (n=74), including first-degree obesity in 15.8% (n=44), second-degree obesity in 7.5% (n=21), and third-degree obesity in 3.2% (n=9).

Chronic kidney disease (CKD) was identified in 22% of patients (n=62).

Cerebrovascular diseases were diagnosed in 18.3% of cases (n=51): atherosclerosis of the brachiocephalic arteries in 13.6% (n=38), peripheral arterial disease in 3.6% (n=10), and atherosclerosis with other localization in 1% of cases (n=3).

In 11% of cases (n=31), pulmonary damage was identified, chronic obstructive pulmonary disease (COPD) being most prevalent in 9% of cases (n=26) and bronchial asthma in 1.8% of cases (n=5).

Characteristics	Average	Diseased	Survived
Male sex, %	65,1	60,4	67,4
Age, years	65,2	71,3	61,8
Weight, kg	80	78	80
Height, cm	167	166	167
BMI, kg/m2	28	28,6	28,1
CABG and PCI, %	64,7	51,6	73,2
FC 2B-3 CHF, %	25,1	45,1	15,5
History of MI, %	41,4	43,9	40,6
Arterial hypertension, %	83,2	91,2	80,2
Diabetes mellitus, %	29,5	35,1	28,3
Atrial fibrillation, %	15,5	24,2	11,8
Oncological diseases, %	0,15	0,2	0,04
HR, bpm	82,3	93,4	76,9
CKD, %	79,8	77,4	82,8
LV size, cm	5,6	5,75	5,53
LV EF, %	38,9	35	40,8
SPAP, mmHg	45	53	42
Erythrocytes, 10*12/l	4,97	5,9	4,5
Thrombocytes, 10*9/l	201,2	69,7	210
Band neutrophils, %	2,11	2,08	2,12
Segmented neutrophils, %	67,6	69,6	66,7
Lymphocytes, %	23,2	21,8	24,04
Monocytes, %	5,47	5,15	5,62
Leukocytes, 10*9/l	9,12	9,15	9,105
GFR, ml/min	63	52,9	67,6
Glucose, mmol/l	6,7	6,8	6,6
Total cholesterol, mmol/l	4,1	4,05	4,07
LDLP, mmol/l	2,5	2,4	2,58
HDLP, mmol/l	0,95	0,9	0,98
Triglycerides, mmol/l	1,5	1,4	1,5

Table 1. *Clinical and demographic characteristics of patients*
Таблица 1. *Клинико-демографическая характеристика пациентов*

The least frequent conditions were pathologies of the joints, in 5% of cases (n=14), and histories of malignant tumors, 4.3% (n=12).

The percentages of concomitant conditions in patients are shown in **Fig. 1**.

Charlson's Comorbidity Index was calculated (**Fig 2**).

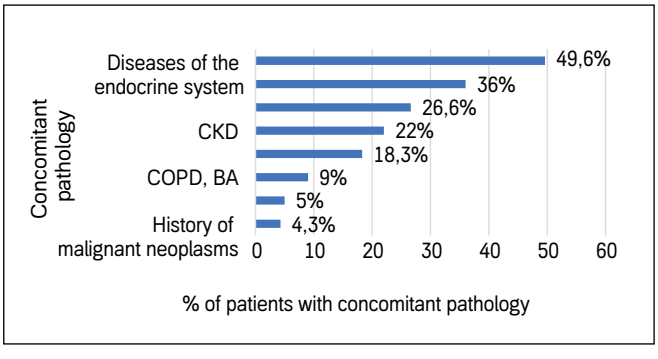

Figure 1. *Concomitant diseases.*
Рисунок 1. *Сопутствующие заболевания.*

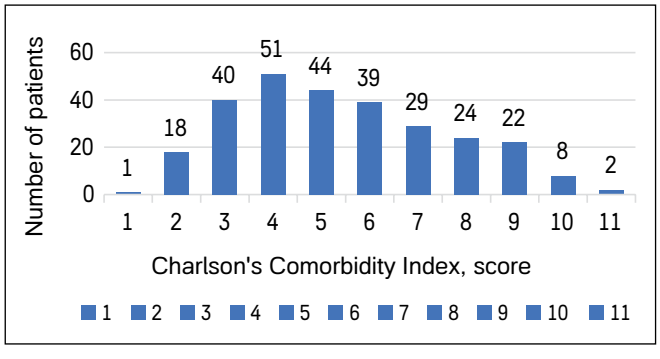

Figure 2. *Charlson's comorbidity index in patients with CHF.*
Рисунок 2. *Индекс коморбидности Чарлсона у пациентов с ХСН.*

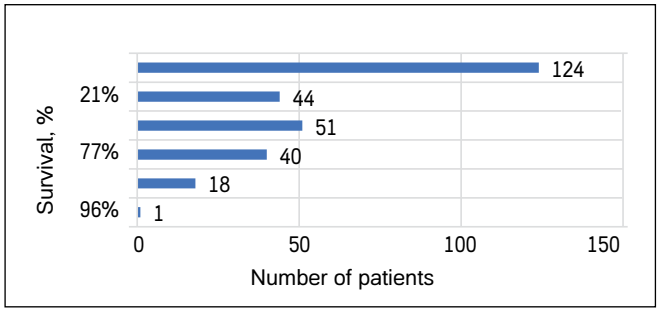

Figure 3. *Ten-year survival according to the Charlson comorbidity index.*

Рисунок 3. *Десятилетняя выживаемость в соответствии с индексом коморбидности Чарлсона.*

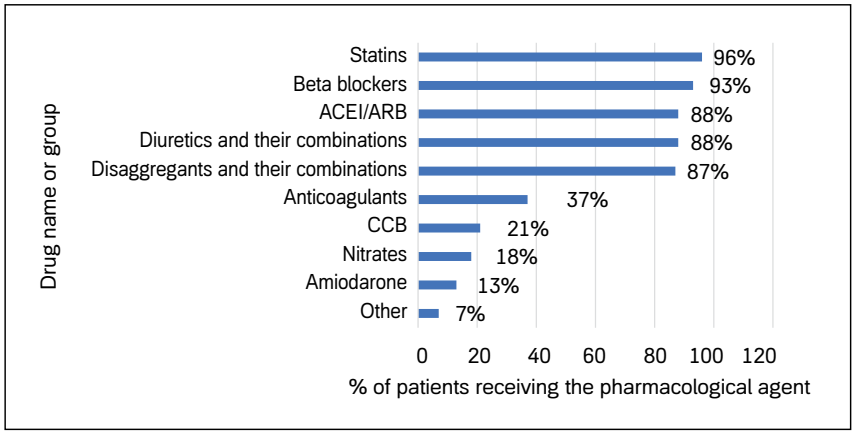

Figure 4. *Drug therapy.*

Рисунок 4. *Медикаментозная терапия.*

As per the Charlson Comorbidity Index, 43% (n=121) of the subjects have the index of 6 and above, which fits the possible 10 years' survival under 21%. Only 0.3% (n=1) have the 10 years' survival at 96% (**Fig. 3**).

The following EchoCG data are very important: left ventricle ejection fraction (LV EF), systolic pulmonary artery pressure (SPAP), left ventricular diameter. In the studied group of patients, the average EF was 39±9.7%, among them 53% (n=149) with midrange EF, 42% (n=117) with reduced EF, and 4.3% (n=12) with preserved EF. As per the EchoCG data, the ventricular diameter was 5.6 cm on average, and SPAP 46 mmHg.

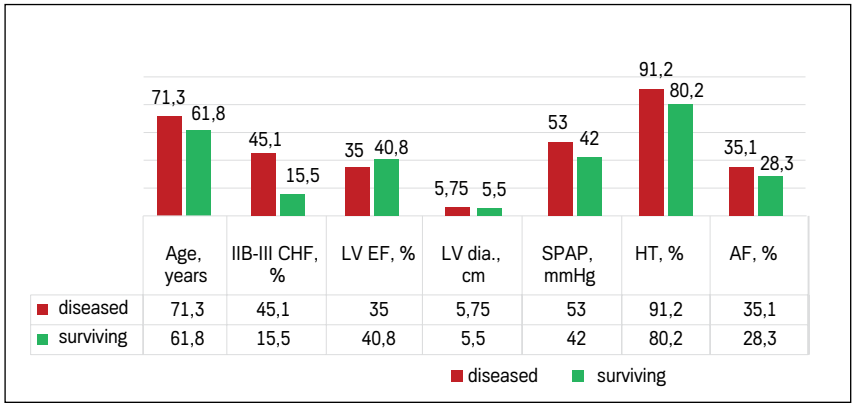

Figure 5. *Factors associated with a decrease in the long-term survival of patients with CHF in the three-year follow-up period.*

Рисунок 5. *Факторы, ассоциирующиеся со снижением отдаленной выживаемости пациентов с ХСН в трехлетнем периоде наблюдения.*

The full blood exam data was as follows: hemoglobin level 131±20.4 g/l, leukocytes, 9±3.44 109/l, ESR 18.6±14.4 mm/hour. According to the biochemical blood analysis, the average glomerular filtration rate (GFR) was 63±21 ml/min.

Pharmacological treatment of patients in the study group was performed: 93% (n=258) received beta-blockers, most often, bisoprolol was prescribed. Angiotensin converting enzyme (ACE) blockers and angiotensin-II receptor blockers (ARB) were mentioned in the therapy as well as diuretics with their possible combinations in 88% of cases (n=245). 87% of patients (n=242) received disaggregants: their combinations were prescribed to patients after acute myocardial infarction and PCI. Among statins, atorvastatin was prescribed most often; statins were received by 96% of patients (n=267). Anticoagulants, calcium-channel blockers and nitrates were indicated in 37% (n=102), 21% (n=58) and 18% (n=50) of cases, respectively. Amiodarone was prescribed in 13% (n=36). Least frequently, in 7% of cases (n=19), digoxin, moxonidine, empagliflozin, ivabradine, and sacubitril/valsartan were prescribed.

The pharmacological treatment and the share of patients receiving the treatment is shown in **Figure 4**.

When analyzing data from patients with CHF, three-year survival was 67.3% (n=187) of patients in the study group, 32.7% (n=91) of patients died.

A statistically significant direct relationship was found between three-year survival and the following indicators: senior and old age (p <0.0001), stage IIB-III CHF (p <0.0001), reduced ejection fraction of the left ventricle (p <0.0001), ventricular diameter (p <0.01), SPAP ((p <0.0001) following the EchoCG data, presence of arterial hypertension (p <0.02) and atrial fibrillation (p <0.01), high Charlson comorbidity index (p <0.0001), GFR below 60 ml/min (p <0.0001), increase of ESR (p <0.0001), low hemoglobin (p <0.001). In the group of surviving patients (73.2%), surgical treatment was performed, 21.6% higher than in the group of diseased patients (51.6%), which has a protective significance (p <0.0001). The average values of the above parameters in surviving and diseased patients are shown in **Figure 5**.

DISCUSSION

In order to identify factors aimed at preventing the development of decompensation of the clinical condition, reducing the frequency of hospitalizations, improving the quality and prognosis of life of patients, the study of the clinical features of the course of CHF is currently coming to the forefront.

C. Xu et al. (2023) used the machine-learning model to identify the correlation of the mortality of patients with CHF and age, GFR and presence of natriuretic peptide, and number of hospitalizations. According to the authors, a greater number of timely

hospitalizations improves survival, since patients have better compliance and will receive effective interventions. The authors calculated the average survival rate for all patients - 0.53. The authors also selected two patients who best matched the visibility of the sample. The first patient (value: 0.55, above baseline level, poor prognosis) had the following factors with a positive view on the prognosis: age of 53 years, DBP of 85 mmHg, GFR of 56.72 ml/min, and a negative factor of 4 recurrent hospitalizations. The second patient (value: 0.33, below baseline level), aged 89, had positive factors: GFR of 43.14 ml/min, UAlevel of 314.3 mmol/l, and negative factors of the age of 89, 3 recurrent hospitalizations, BNP level of 3.190. Despite the initially poor prognosis, the patient aged 53, survived [12].

N.R. Jones et al. (2019) performed a meta-analysis of 60 studies on survival data of patients with CHF that included a total of 1.5 million people. It identified cumulative survival rates after 1 month, 1 year, and within three, five, and ten years, that were 95.7%, 86.5%, 72.6%, 56.7, and 34.9% respectively. After analyzing the data obtained, the authors noted that mortality increases with age. The overall survival rate after 1 year at the age of over 75 years was 83.3% compared to the age of under 65 years – 91.5%. Five-year survival rate was 49.5% and 78.8% respectively [14]. According to the data obtained, reduced LVEF increases mortality in patients with CHF, which is consistent with the data of studies in which mortality in patients with HFrEF is significantly higher than in patients with HFpEF [14].

Our study showed that comorbidity significantly worsens the prognosis and is associated with increased mortality in patients with CHF. The following comorbidities are reliably associated with a high risk of death: COPD, anemia, CKD, diabetes, which is associated with an increased level of inflammation in the body, reduced ability to exercise, and polypharmacy [15]. In patients with a Charlson Comorbidity Index of 6 or more points, belonging to the high comorbidity group, the relative risk of death within 12 months is 1.68 times higher than the risk of death in patients with low comorbidity [16]. Atrial fibrillation makes a significant contribution to the risk of developing cardiovascular complications and death. It is also becoming a significant problem for the health care system due to its active spread, which may be due to an increase in the average age of the population and an increase in etiopathogenetic links in its development and the development of other cardiovascular diseases [18, 19].

M.A. Druzhilov et al. (2023) discuss, in their retrospective study, that the patient with AF and HF have a higher comorbidity and frequency of onset of cardiovascular exacerbations that patients with AF without HF [20]. Our study confirms that patients with CHF and AF have an unfavorable prognosis and the presence of AF worsens the course of HF.

According to our data, a separate factor influencing the prognosis of patients with CHF is the level of SPAP, which is assessed using transthoracic Doppler echocardiography. Right heart catheterization is performed as the "gold standard" for diagnosing pulmonary hypertension (PH) [21], which can be used to assess parameters such as medium pulmonary arterial pressure, pulmonary vascular resistance and pulmonary artery wedge pressure [22]. Right heart catheterization also allows assessment of right atrial pressure, cardiac index, and mixed venous oxygen saturation. These parameters have important prognostic value in patients with PH. [23]. Despite its high information content, right heart catheterization is a difficult-to-access research method that requires large financial costs, specialized equipment, and specially trained medical personnel. Therefore, transthoracic echocardiography is currently an accessible, less expensive method that allows assessing pulmonary hemodynamic parameters, which can be successfully used instead of right heart catheterization [24].

Pulmonary hypertension is a common cardiovascular disease affecting about 1% of the population. The generally accepted classification of PH forms distinguishes five groups of causes that lead to this pathophysiological condition [23]. A group of diseases associated with left heart pathology is the most common cause of pulmonary hypertension and is detected in 75% of cases of the disease. It is also known that 60% of patients with CHF due to systolic dysfunction of the left ventricle show signs of pulmonary hypertension [25]. The incidence of PH increases to 70% in isolated left ventricular diastolic dysfunction [26].

For a long time, efforts were focused on finding informative prognostic markers of the structural and functional state of the heart in patients with CHF. In relation to patients with CHF and PH, such an indicator is LVEF. As shown by the study of elderly patients, patients with established PH have lower EF than patients without PH (43.9% vs. 50%). It should also be noted that the prognosis in patients in the group where PH and CHF were combined was less favorable [27]. Severe pulmonary hypertension was detected in patients with terminal CKD complicated by HFrEF [28].

The prognosis of patients with CHF can be improved by optimizing the treatment of patients taking into account the characteristics of elderly patients, improving the qualifications of doctors, training and involving patients, ensuring continuity of medical care, preferential drug provision for these patients, creating a heart failure registry [29, 30], and creating CHF rooms at large specialized cardiology hospitals [31].

CONCLUSION

The study revealed a significant relationship between CHF and age, CHF stage, presence of hypertension and AF, hemoglobin and ESR levels, ejection fraction, pulmonary artery disease and LV size, comorbid pathology affecting mortality. To increase the duration and improve the quality of life of patients with CHF, it is necessary to prescribe optimal drug therapy for the treatment of CHF, use a multidisciplinary approach and monitor concomitant pathology, increase patient adherence to therapy, which will contribute to improving the quality of life, reducing the frequency of hospitalizations and increasing the life expectancy of patients.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
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Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Sazhina A.N., Korotkov D.A. – material analysis, writing of manuscript. Kurochkina O.N., Baranov A.V. – development of study concept and design, editing of the article. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Сажина А.Н., Коротков Д.А. – анализ материала, написание текста. Курочкина О.Н., Баранов А.В. – разработка концепции и дизайна исследования, редактирование статьи. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
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