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Comorbidity of chronic heart failure of ischemic etiology and chronic obstructive pulmonary disease: 5-year follow-up

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ABSTRACT

BACKGROUND: The combination of chronic heart failure and chronic obstructive pulmonary disease contributes to the formation of the phenotype and survival of patients.

AIM: To study the 5-year prognosis and develop a prognostic model of adverse events in patients with chronic heart failure of ischemic origin in comorbidity with chronic obstructive pulmonary disease.

MATERIAL AND METHODS: Clinical signs of patients with chronic heart failure of ischemic origin (n=517), including those in combination with chronic obstructive pulmonary disease (n=118), and outcomes over 5 years according to end points: death from all causes, cardiovascular death, composite endpoint — all fatal and non-fatal cardiovascular events, were studied. Quantitative variables were presented as mean and standard deviation or median and interquartile range; categorical — in the form of absolute value and percentage. Quantitative intergroup differences were assessed using the Mann–Whitney test, and categorical differences were assessed using the Pearson χ^2 test. Time to event was analyzed using the Kaplan–Meier method; hazard ratio — by Cox regression. Models were developed using binary logistic regression. Statistical processing was carried out in the Jamovi, R 4.3.1 programs.

RESULTS: The clinical portrait of a patient with chronic heart failure of ischemic origin in the presence of chronic obstructive pulmonary disease was characterized by a predominance of men in older age groups, a high frequency of smoking, a worse quality of life, determined by the Minnesota Questionnaire, and a high level of high-sensitivity C-reactive protein, α_1- and α_2-globulins. Patients with heart failure in the presence of chronic obstructive pulmonary disease had higher overall and cardiovascular mortality (p=0.029 and p=0.02), the frequency of hospitalizations not related to cardiovascular disease (p=0.02), less non-fatal cardiovascular events (p=0.04).

CONCLUSION: In patients with heart failure, the presence of chronic obstructive pulmonary disease increased the risk of death from all causes by 2.07 times, cardiovascular mortality by 2.24 times, and achieving the combined endpoint by 1.68 times. Regression models were developed to determine the probability of risk of death from all causes and cardiovascular death.

Keywords: chronic heart failure; chronic obstructive pulmonary disease; prognosis.

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Коморбидность хронической сердечной недостаточности ишемической этиологии и хронической обструктивной болезни лёгких: 5-летнее наблюдение

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АННОТАЦИЯ

Актуальность. Сочетание хронической сердечной недостаточности и хронической обструктивной болезни лёгких вносит вклад в формирование фенотипа и выживаемость пациентов.

Цель. Исследовать 5-летний прогноз и разработать прогностическую модель неблагоприятных событий у пациентов с хронической сердечной недостаточностью ишемического генеза в коморбидности с хронической обструктивной болезнью лёгких.

Материал и методы. Изучены клинические признаки пациентов с хронической сердечной недостаточностью ишемического генеза (n=517), в том числе в сочетании с хронической обструктивной болезнью лёгких (n=118), и исходы в течение 5 лет по конечным точкам: смерть от всех причин, сердечно-сосудистая смерть, комбинированная конечная точка — все смертельные и несмертельные сердечно-сосудистые события. Количественные переменные представлены в виде среднего значения и стандартного отклонения либо медианы и межквартильного диапазона; категориальные — в виде абсолютного значения и процента. Количественные межгрупповые различия оценивали тестом Манна–Уитни, категориальные — критерием χ^2 Пирсона. Время до наступления события анализировали методом Каплана–Мейера; отношение рисков — регрессией Кокса. Разработаны модели методом бинарной логистической регрессии. Статистическая обработка проведена в программах Jamovi, R 4.3.1.

Результаты. Клинический портрет пациента с хронической сердечной недостаточностью ишемического генеза при наличии хронической обструктивной болезни лёгких характеризовался преобладанием мужчин старших возрастных групп, высокой частотой курения, худшим качеством жизни, определяемым по Миннесотскому опроснику, большим уровнем высокочувствительного С-реактивного белка, α_1- и α_2-глобулинов. У пациентов с сердечной недостаточностью при наличии хронической обструктивной болезни лёгких были выше общая и сердечно-сосудистая смертность (p=0,029 и p=0,02), частота госпитализаций, не связанных с сердечно-сосудистым заболеванием (p=0,02), реже несмертельные сердечно-сосудистые события (p=0,04).

Вывод. У пациентов с сердечной недостаточностью наличие хронической обструктивной болезни лёгких повышало риск смерти от всех причин в 2,07 раза, сердечно-сосудистой смертности — в 2,24 раза, достижения комбинированной конечной точки — в 1,68 раза; разработаны регрессионные модели для определения вероятности риска смерти от всех причин и сердечно-сосудистой смерти.

Ключевые слова: хроническая сердечная недостаточность; хроническая обструктивная болезнь лёгких; прогноз.

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Abbreviations

CI, confidence interval; LV, left ventricle; HR, hazard ratio; FEV_1, forced expiratory volume in the first second; OR, odds ratio; EF, ejection fraction; FVC, forced vital capacity; FC, functional class; COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure.

BACKGROUND

The improvement of prognosis and quality of life of patients with chronic heart failure (CHF) is a primary concern of modern cardiology [1]. Scientists have focused on the clinical features that determine the abnormalities of the course of CHF and on concomitant chronic noninfectious diseases that significantly affect the course and treatment and outcome of CHF. Chronic obstructive pulmonary disease (COPD) represents a significant proportion of comorbidities in CHF, being diagnosed in 7%–13% of CHF outpatients [2] and 9%–51% of hospitalized CHF patients [3].

In a study by deMiguel-Díez et al., the incidence of COPD in heart failure was 20%–32% [4]. Moreover, COPD was found to occur predominantly in CHF patients with preserved left ventricular (LV) ejection fraction (LVEF). Iversen et al. diagnosed COPD in 35% of CHF patients with functional class (FC) III–IV (n = 532) and more frequently in patients with LVEF >45% than in those with LVEF <40% (41% vs. 31%, $p = 0.03$) [5].

The relationship between the mechanisms of development and progression of COPD and cardiovascular disease is poorly understood. However, it may be based on the commonality of various pathogenetic links, including systemic inflammation, oxidative stress, endothelial dysfunction, and renin–angiotensin–aldosterone system hyperactivation [6]. Among the modifiable risk factors, smoking, hypodynamia, and irrational diet, in addition to systemic inflammation, are considered to play the most critical roles. Additionally, genetic predisposition and aging are crucial [7].

Data from epidemiological studies indicate a higher prevalence of CHF in patients with COPD than in the general population. In older patients, it reaches 62%, with a 15-year survival rate <25% [8]. Interestingly, COPD causes heart failure in 13% of Russian patients [9]. Cardiovascular diseases (e.g., coronary heart disease and heart failure) are the leading cause of death in patients with mild and moderate COPD [10].

Sin et al. investigated the prognostic aspects of COPD in patients with cardiovascular disease and found a 3.26-fold increased risk of cardiovascular mortality in the presence of COPD [11]. Furthermore, Polikutina et al. revealed that in patients with ST-elevation myocardial infarction, the presence of COPD increased the risk of nonfatal myocardial infarction and stroke by 1.9 times (95% confidence interval [CI]: 1.1–3.6; $p = 0.043$) and decompensation of heart failure by 2.6 times (95% CI: 1.3–5.4; $p = 0.006$) [12].

Gazizyanova et al. reported a worse 1-year prognosis in CHF with COPD than in CHF without COPD. The incidence of cardiovascular events was 29.7% and 15.4%, respectively. The authors found a higher proportion of hospitalizations because of acute decompensation of CHF (32.7% and 15.4%) in CHF patients with COPD and in those who reached the combined endpoint (all outcomes + hospitalizations) within 12 months (29.7% and 15.4%, respectively; odds ratio [OR]; 2.32; 95% CI: 1.05–5.16).

A higher risk of cardiovascular events was observed in patients with grade III–IV CHF compared to those with grade I–II CHF with COPD (OR: 3.28; 95% CI: 1.19–9.01; $p < 0.05$); no significant difference was observed in CHF patients without COPD. The analysis of endpoints within 1 year, considering the severity of COPD, showed a higher incidence of stroke (14.8% vs. 2.1%; $p < 0.05$) and CHF decompensation (42.6% vs. 21.3%; OR: 2.75; 95% CI: 1.14–6.64, $p < 0.05$) in patients with severe COPD than in those with moderate COPD [13].

Similar data were reported by Macchia et al. who found that the 1-year mortality was 42% higher ($p = 0.01$) and the number of hospitalizations because of decompensation of CHF was 35% higher ($p = 0.05$) in CHF patients with COPD than in those without COPD [14].

In the REPOSI registry (n = 2343), hospitalized elderly patients (median age: 81 years) diagnosed with COPD (49%), CHF (35%), and CHF + COPD (16%) had significantly higher 12-month all-cause mortality when COPD and CHF were combined (hazard ratio [HR]: 1.74; 95% CI: 1.16–2.61; $p = 0.008$) [15]. Data from the VALIANT study show that CHF patients with COPD had an increase in all-cause mortality of up to 30% compared to those without COPD [16].

Thus, the combination of COPD and CHF implies a patient-oriented approach for determining the structural and functional status of the cardiac and pulmonary systems, choice of the priority strategy of drug therapy, and prevention of complications.

The present study aimed to evaluate the 5-year prognosis of and develop a prognostic model for adverse events in patients with CHF of ischemic genesis co-occurring with COPD.

MATERIALS AND METHODS

The study enrolled 517 patients of both sexes aged 66.4 (10.4) years with stable CHF caused by ischemic heart disease, including 118 patients with concomitant COPD. The median duration of CHF and COPD was 8 (5; 10) and 5 (5; 10) years, respectively.

The study protocol and informed consent were approved by the local ethics committee of the Kazan State Medical University of the Russian Ministry of Health (protocol no. 5, dated May 23, 2023).

CHF was diagnosed according to the Russian recommendations [1]. The study group was formed in the therapeutic and cardiology departments of the City Clinical Hospital No. 7 in Kazan (2014–2016).

Inclusion criteria: ischemic heart disease with diagnosed stable CHF and age ⩾18 years.

Non-inclusion criteria:

– Previous myocardial infarction, coronary intervention, and cerebral stroke within 3 months before inclusion in the study

– Decompensation of heart failure

– Hemodynamically significant congenital or acquired heart defects

– Presence of a disease with life expectancy <1 year

– Pregnancy and lactation

– Bronchial asthma

– Alcohol or drug dependence

– Severe cognitive impairment

The examination of patients was complex and included an assessment of their clinical condition and a 6-minute walk test, electrocardiography, and echocardioscopy, which involved calculating the LV myocardial mass according to the Devereux formula. CHF FC was based on the results of the scale for evaluation of severity of clinical condition of a patient with heart failure and 6-minute walk test. The resulting categories were FC I (2.6%), FC II (34.3%), FC III (43.5%), and FC IV (19.6%).

The patients' quality of life was evaluated using the Minnesota Living with Heart Failure Questionnaire (Rector & Cohn, 1987). As indicated by transthoracic echocardiography, CHF was diagnosed with preserved LVEF at ⩾50%, moderately reduced LVEF at 40%–49%, and low LVEF at <40% [1].

COPD and the degree of bronchial obstruction were confirmed by spirometry based on the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (2014), with a forced expiratory volume in the first second (FEV_1) <80% and the ratio of FEV_1 to forced vital capacity (FVC) <70% in accordance with the Federal Clinical Guidelines [17]. Based on the degree of pulmonary obstruction, patients were classified as having mild (33.8%), moderate (36.4%), or severe (29.9%) CHF.

Information on the achievement of 5-year endpoints was collected by telephone interview of study CHF patients or their relatives. The endpoints included all-cause death, cardiovascular death, and nonfatal events. All cardiovascular events (fatal and nonfatal) were combined into a single endpoint. In the absence of events at 5 years, event-free survival was considered.

Statistical analysis and data visualization were performed using Jamovi (version 2.3.16; Computer Software), R 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean and standard deviation (M [SD]) or median and interquartile range (Me [25%; 75%]) and categorical variables as absolute values and percentages. Intergroup differences in categorical variables were tested using Pearson's χ^2 test, and quantitative variables were tested using the Student's t-test or Mann–Whitney U test.

Comparative analysis of time to event was performed using the Kaplan–Meier method, log-rank test, and Cox proportional hazards models to estimate risk ratios and corresponding 95% CIs. The prognostic model for calculating the probability of outcome was developed using logistic regression, and its diagnostic significance was determined with ROC analysis. The cutoff value of the quantitative trait was determined with the highest value of the Youden index. Differences at $p < 0.05$ were considered significant.

RESULTS AND DISCUSSION

Ischemic heart disease was the leading cause of CHF in the sample, including 82.3% of patients in combination with arterial hypertension. Myocardial infarction prior to the study was found in 45.1% of patients and cerebral stroke in 8.1% of patients, indicating a high risk of cardiovascular complications in the cohort of patients analyzed.

Anamnesis revealed inherited cardiovascular diseases in 37.3% of patients, smoking in 16.6%, and coronary intervention performed in 13.5%. The high comorbidity of CHF with chronic kidney disease (40% of patients) attracts attention. The mean glomerular filtration rate at baseline was 65.6 (19.2) mL/min/1.73 m^2.

Rhythm disturbances (any form of atrial fibrillation) were found in 26.7% of patients and diabetes mellitus in 21.8%. Analysis of myocardial contractility showed a prevalence of CHF patients with preserved LVEF (67%), and 19% had moderate reduction in LVEF and 14% had LVEF <40%.

The patients' medical history indicated that 19.1% of patients did not receive regular therapy. Angiotensin-converting enzyme inhibitors were administered in 49.6% of CHF patients, angiotensin II receptor blockers in 17.4%, beta-adrenergic blockers in 48.7%, and mineralocorticoid receptor antagonists in 13.9%. Disaggregants (35%), diuretics (34.6%), calcium antagonists (22.7%), nitrates (15.7%), and cardiac glycosides (8.9%) were less frequently present in the drug regimen. Lipid-lowering therapy with statins was used in 28.8% of patients for at least 1 year.

The phenotype of CHF patients with COPD in remission (n = 118) compared to those without COPD (n = 399) was characterized by a higher proportion of men (68.6 vs. 47.5%, $p < 0.001$) and older age (68.6 [8.96] vs. 65.8 [10.7] years, $p = 0.011$).

In the study patients, the etiology of CHF was coronary artery disease, including in combination with arterial hypertension in 91.5% of CHF patients with COPD and in 91% of CHF patients without COPD. CHF patients with and without COPD did not differ in the duration of CHF, which was exacerbated by cardiovascular disease heredity.

CHF patients with COPD were characterized by a higher frequency of smoking (38.1% vs. 10.3%; $\chi^2 = 51.2$; $p < 0.001$), worse quality of life (44.8 [18.4] vs. 39.9 [18.3]; $p = 0.043$), lower diabetes mellitus prevalence (14. 4% vs. 24%; $\chi^2 = 4.27$; $p = 0.027$), less frequent previous myocardial infarction (33.9% vs. 48.4%; $\chi^2 = 7.7$; $p = 0.006$), and lower systolic (139 [19.8] vs. 147 [25.4] mmHg; $p = 0.002$) and diastolic (83.7 [11.7] vs. 86.9 [13.6] mmHg; $p = 0.002$]) blood pressure.

Table 1. Parameters of external respiration function in patients with chronic heart failure

Parameters	Due values	CHF + COPD, n=69	CHF without COPD, n=47	p
FEV_1, % d.v., M (SD)	>80%	42,3 (13,3)	73,3 (23,0)	**<0,001**
FVC, % d.v., M (SD)	>80%	67 (19,3)	76,2 (20,2)	**0,048**
FEV_1/FVC, %, M (SD)	>70%	62,9 (5,37)	95,4 (13,0)	**<0,001**
VC, % d.v., M (SD)	>80%	61,1 (13,5)	73,0 (19)	**0,019**
MEF_{25}, % d.v., Me [25; 75%]	>60%	19 [15,7; 28]	58 [40,5; 81,3]	**<0,001**
MEF_{50}, % d.v., Me [25; 75%]	>60%	17 [14,5; 22,5]	50 [33; 86,0]	**<0,001**
MEF_{75}, % d.v., Me [25; 75%]	>60%	22 [40,5; 27]	49,5[32,5; 79]	**<0,001**

Note: Bold text indicates significant differences between groups; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; d.v., due value; FVC, forced vital capacity; FEV_1/FVC, modified Tiffeneau index; VC, vital capacity; MEF25, maximal expiratory flow at 25% of FVC; MEF50, maximal expiratory flow at 50% of FVC; MEF75, maximal expiratory flow at 75% of FVC.

Similar data were reported by Gazizyanova [18]. When comparing symptoms and signs of CHF according to severity of clinical condition of a patient with heart failure, rales in the lungs were detected more often in CHF patients with COPD (26.4% vs. 15%; $p = 0.004$), whereas body weight changed less often in the last week (8.8% vs. 18.3%; $p = 0.014$), which is consistent with the data of the study by Karoli [19].

The distribution by FC of patients with and without COPD was as follows: FC I, 0.8% vs. 3.5%; FC II, 37.3% vs. 37.3%; FC III, 51.7% vs. 43.1%; and FC IV, 10.2% vs. 16%. Patients with congestive heart failure (CHF) with COPD exhibited a shorter distance walked in the 6-minute walk test (236 [94.7] m vs. 266 [113] m; $p = 0.009$). The structure of the group with CHF with bronchoobstruction and without concomitant COPD did not differ regarding LVEF ranges. The LVEF was 69.2% in the group with preserved LVEF, 17.9% in the group with moderately reduced LVEF, and 12.8% in the group with low LVEF.

Comparison of most blood parameters, including electrolytes and lipid spectrum, showed no differences in CHF with COPD and without pulmonary pathology. The levels of high-sensitivity C-reactive protein (4.61 [1.99; 8.5] and 2.66 [1.38; 5.72] mg/L; $p = 0.012$), α1-globulin (3.4 [0.732] and 3.17 [0.635] g/L; $p = 0.01$), and α2-globulin (7.94 [1.33] and 7.34 [1.23] g/L; $p = 0.001$) in CHF patients with COPD exceeded those in CHF patients without COPD. Furthermore, a study revealed increased high-sensitivity C-reactive protein level in CHF patients with COPD compared to that in CHF patients without COPD [19].

The study of external respiratory function confirmed normal ventilatory capacity of the lungs in 32.5% of CHF patients. Dyspnea of restrictive type was found in 46.5% of patients, mixed type in 16%, and obstructive type in 5%. Pulmonary function was within the normal range in all CHF patients with FC I, in 47.8% of those with FC II, and in 22% of those with FC III. Restrictive disorders were observed in 32.1% of patients with FC II, 45.3% of those with FC III, and 22.6% of those with FC IV. Obstructive and mixed lung function abnormalities were more common in patients with FC III (66.7% vs. 61.1%).

With normal lung function, CHF with preserved LVEF characterized 82.8% of patients. Moderately reduced LVEF and low LVEF were equally common (8.6% each). In mixed and obstructive lung function disorders, 83.3% of patients had CHF with preserved LVEF, whereas 16.7% had CHF with moderately reduced LVEF. In the cohort with a restrictive type of respiratory impairment in CHF, LVEF was predominantly preserved (58.5%), and moderate reduction of LVEF was observed in 28.3% and LVEF <40% in 13.2% of patients.

All parameters of external respiratory function were significantly lower in CHF patients with COPD than in CHF patients without lung pathology (Table 1). FVC 25%, 50%, and 70% were lower than normal in CHF patients with COPD and those without lung disease. FEV_1/FVC was within normal limits in CHF patients without COPD (95.4; 13.0%), whereas it was decreased in those with COPD (62.9; 5.37%).

LV end-systolic, LV end-diastolic, and left atrial dimensions were lower in CHF patients with COPD than in those without COPD (Table 2). The mean values of LVEF in CHF patients with COPD and those without bronchial obstruction were not different. LV hypertrophy was more common in CHF patients without COPD than in those with COPD (60.6% vs. 40.8%; $\chi^2 = 8.43$; $p = 0.004$). The LV myocardial mass and its index of men with CHF without COPD were higher than those of men with CHF with COPD ($p < 0.001$).

Analysis of the patterns of structural and geometric LV remodeling revealed a higher frequency of concentric remodeling in CHF patients with COPD than in those without COPD (23.4% vs. 14.9%; $\chi^2 = 4.36$; $p = 0.036$) and a lower frequency of eccentric hypertrophy (15.3% vs. 25.5%; $\chi^2 = 5.01$; $p = 0.025$).

Akramova reported the development of concentric remodeling and hypertrophy in 67.9% of patients with COPD with arterial hypertension [20]. This trend persisted in CHF FC III–IV patients with COPD compared to those without COPD: concentric remodeling (24.3% and 8.6%; $\chi^2 = 12.07$; $p < 0.001$) and eccentric hypertrophy (17.1% and 30.7%; $\chi^2 = 4.95$; $p = 0.03$). No significant differences were noted in myocardial remodeling variants in CHF patients according to COPD severity.

Data on the achievement of 5-year endpoints were obtained in 313 patients (252 CHF patients without COPD and 61 CHF patients with COPD). The all-cause mortality in the studied cohort of CHF patients was 28.1%, and the cardiovascular

Table 2. Echocardioscopy parameters of patients with chronic heart failure (CHF) depending on the presence of chronic obstructive pulmonary disease (COPD)

Parameters	Reference values	CHF + COPD, n = 118	CHF, n = 399	p
LVESD, cm, M (SD)	2.3–3.6	3,63 (0,68)	3,81 (0,88)	**0,048**
LVEDD, cm, M (SD)	3.7–5.6	4,94 (0,695)	5,24 (0,8)	**<0,001**
LAD, cm, M (SD)	2.3–3.7	3,84 (0,61)	4,0 (0,65)	0,018
LVEF, %, M (SD)	50.0–70.0	52,8 (8,01)	52,2 (10,6)	0,845
RVD, cm, M (SD)	2.5–3.0	2,77 (0,386)	2,79 (0,478)	0,663
LVM, g, M (SD)	men 88–224 women 67–162	210 (69,9) 205 (48,9)	258 (84,6) 221 (73,0)	**<0,001** 0,212
LVMI, g/m^2, M (SD)	men <115 women <95	105 (40,1) 112 (34,7)	128 (41,7) 117 (47,4)	**<0,001** 0,422
LVH, n (%)	men >115 women >95	30 (38,5%) 25 (67,6%)	111 (59%) 135 (69,6%)	**0,002** 0,807

Note: Bold text indicates significant differences between groups; LVESD, left ventricular (LV) end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LAD, left atrial dimension; RVD, right ventricular dimension; LVM, left ventricular mass; LVMI, left ventricular mass index; LVH, LV hypertrophy.

mortality was 24.6%. CHF patients with COPD had a higher risk of all-cause mortality and death due to a cardiovascular event (39.3% vs. 25.4%; OR: 1.9; 95% CI: 1.06–3.42; $p = 0.029$ and 36% vs. 21.8%; OR: 2.02; 95% CI: 1.11–3.69; $p = 0.02$, respectively) and risk of non-cardiovascular-related hospitalization (8.2% vs. 1.2%; OR: 7.41; 95% CI: 1.72–31.92; $p = 0.02$). Nonfatal cardiovascular events were reported more frequently in CHF patients without pulmonary dysfunction than in those with COPD (25.4% vs. 13.1%; OR: 2.25; 95% CI: 1.018–4.99; $p = 0.04$).

The prognostic significance of COPD was reported in the Echocardiography and Heart Outcome Study, wherein at a follow-up of 2.93–5.49 years in patients with CHF FC III–IV (n = 532), the risk of all-cause mortality was higher in the presence of COPD according to spirometry (OR: 1.47; 95% CI: 1.13–1.9; $p = 0.004$), with a 10% decrease in FEV_1 (OR: 0.84; 95% CI: 0.79–0.9; $p < 0.001$).

COPD severity was found to have a significant prognostic significance with respect to 5-year mortality (log-rank test, $p = 0.004$). The hazard ratio for 5-year mortality in the presence of COPD was determined for moderate severity (OR: 1.26; 95% CI: 0.90–1.77) and for severe/very severe (OR: 1.68; 95% CI: 1.23–2.30) [21].

Rusinaru et al. compared the 5-year survival of CHF patients with COPD to that of CHF patients without concomitant COPD (31% vs. 42%; $p = 0.03$). Compared to the expected survival of the general population of the same age and sex, the 5-year survival rate in patients with COPD was significantly lower (31% vs. 71%). On multivariate analysis, COPD was a strong predictor of worse outcome (OR: 1.53; 95% CI: 1.21–1.94; $p < 0.001$). The risk of death in the presence of COPD was differentiated for CHF patients with preserved LVEF (OR: 1.74; 95% CI: 1.22–2.49; $p = 0.002$) and low LVEF (OR = 1.48; 95% CI: 1.03–2.14; $p = 0.035$) [22].

In the current study, Cox regression analysis showed that the presence of COPD was associated with a 2.07-fold (95% CI: 1.25–3.41; $p = 0.004$; Fig. 1) increased risk of 5-year all-cause mortality, a 2.24-fold (95% CI: 1.32–3.82; $p = 0.002$) increased risk of cardiovascular mortality, and the achievement of the combined endpoint (OR: 1.68; 95% CI: 1.09–2.58; $p = 0.018$).

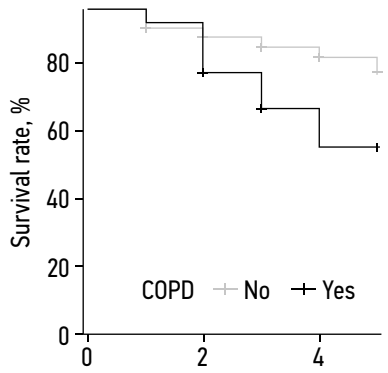

Fig. 1. Overall 5-year survival depending on the presence of chronic obstructive pulmonary disease (COPD)

Survival of CHF patients with concomitant COPD did not depend on duration of CHF, presence of diabetes mellitus, atrial fibrillation, previous myocardial infarction and cerebral stroke, heredity aggravated by cardiovascular diseases, smoking, and CHF class.

All-cause and cardiovascular deaths were more common in CHF patients with COPD (83.3% vs. 16.7%; $p = 0.037$; OR: 3.64; 95% CI: 1.04–12.72 and 86.4% vs. 13.6%; $p = 0.02$). Male CHF patients were 4.41 times more likely to reach the combined endpoint if COPD was present compared to female CHF patients (95% CI: 1.35–14.43; $p = 0.011$), and cardiovascular death was 4.68 times more possible (95% CI: 1.19–18.41).

Previous coronary intervention reduced the risk of all-cause mortality by 9.37-fold (OR: 0.107; 95% CI: 0.013–0.89; $p = 0.02$) and cardiovascular death by 7.97-fold (OR: 0.126; 95% CI: 0.015–1.049) in CHF patients with COPD.

LVEF was lower in patients who died from all causes compared to those without a fatal event (50.7% [7.78%] and

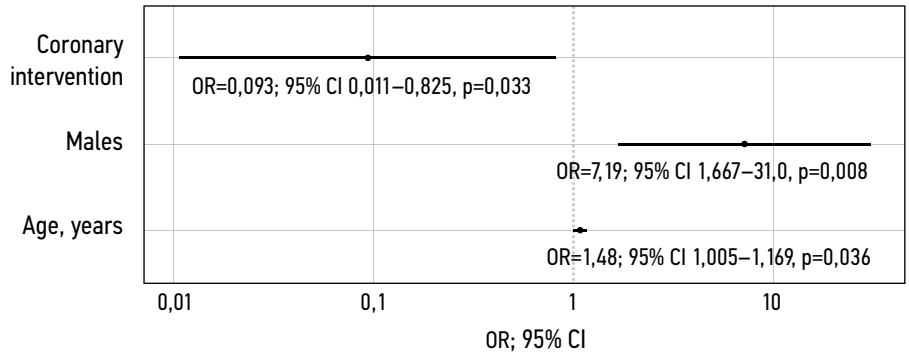

Fig. 2. Odds ratio (OR) with 95% confidence interval (CI) of predictors of death from all causes

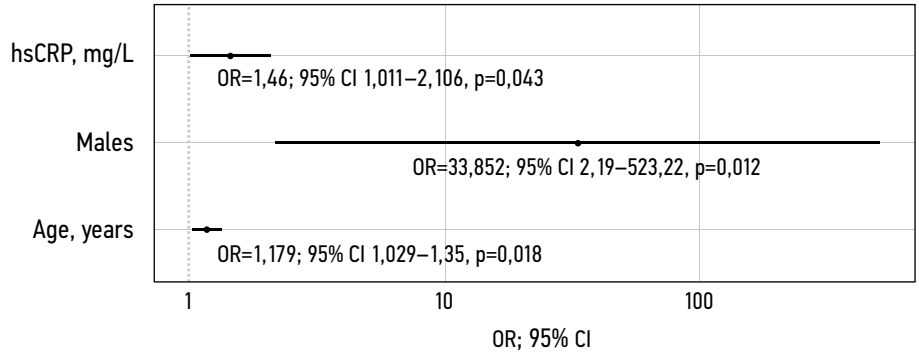

Fig. 3. Odds ratio (OR) with 95% confidence interval (CI) of predictors of cardiovascular death; hsCRP — high-sensitivity C-reactive protein

54.7% [8.16]; $p = 0.025$]), as well as in patients who reached the combined endpoint compared to those who did not (51.5% [7.65%] and 54.8% [8.48%]; $p = 0.044$]. The exercise function parameters did not differ significantly between groups in CHF patients with COPD with different 5-year prognoses.

A statistically significant ($p < 0.001$) prognostic model was developed to determine the probability of all-cause mortality, described by the following equation:

$$P = 1/(1 + e^{-z}) \times 100\%,$$
$$z = -7.067 - 2.374 \times CI + 1.973 \times (sex) + 0.08 \times (age)$$

where P is the probability of death; z, the function in the logistic regression equation; CI, coronary intervention (0, no intervention; 1, intervention); and sex (1, male; 0, female).

Male sex increased the risk of all-cause mortality by 7.19 times. Previous coronary intervention reduced the risk of all-cause mortality by a factor of 10.74. A 1-year increase in age increased the odds of death by a factor of 1.08 (Fig. 2).

The area under the ROC curve visualizing the dependence of the probability of all-cause death on the value of the logistic function P was 0.797 ± 0.063 (95% CI: 0.674–0.919; $p < 0.001$). The threshold value of P at the cutoff point was 0.295, which, when reached and exceeded, predicted all-cause death. The sensitivity and specificity of the model were 91.3% and 63.2%, respectively.

A significant regression model ($p = 0.003$) was developed to determine the probability of cardiovascular death, described by the following equation:

$$P = 1/(1 + e^{-z}) \times 100\%,$$
$$z = -16.303 + 3.522 \times sex + 0.164 \times age + 0.378 \times hsCRP$$

where P is the probability of cardiovascular mortality; z, the function in the logistic regression equation; sex (1, male; 0, female); and hsCRP, the level of high-sensitivity C-reactive protein.

The probability of cardiovascular death in men was 33.85 times higher than that in women (Fig. 3). The annual increase in age was associated with a 1.18-fold increase in the risk of death from a cardiovascular event. A 1 mg/L increase in high-sensitivity C-reactive protein level was associated with a 1.46-fold increase in the risk of death due to a cardiovascular event.

The relationship between cardiovascular death probability and the logistic function P value was evaluated using ROC analysis, which yielded an area under the curve of 0.853 ± 0.073 (95% CI: 0.710–0.995; $p < 0.001$). The logistic function P value at the cutoff point corresponding to the highest value of the Youden index was 0.451; this value was defined as the threshold. Thus, when this value was reached or exceeded, cardiovascular death was predicted. The sensitivity and specificity of the developed model were 84.6% and 87.5%, respectively.

In the developed models, age was a significant prognostic factor, consistent with the findings of Iversen et al. who observed 532 patients with a median age of 4.46 (2.93–5.49) years and identified age (OR: 1.05; 95% CI: 1.04–1.07;

$p < 0.001$) as a crucial marker of unfavorable outcomes in CHF patients with COPD [21].

None of the CHF patients with COPD who died from any cause were taking statins, and no deaths were reported in patients on statin therapy. Statin use was associated with a 57.4-fold reduction in the risk of all-cause mortality (OR: 0.017; 95% CI: 0.001–0.308; $p < 0.001$), 47.31-fold reduction in the risk of cardiovascular mortality (OR: 0.021; 95% CI: 0.001–0.373; $p < 0.001$), and 10.93-fold reduction in the risk of the combined endpoint (OR: 0.092; 95% CI: 0.023–0.366; $p < 0.001$).

All CHF patients with COPD taking cardiac glycosides met the combined endpoint ($p = 0.049$). It was achieved by 90% of patients not taking statins and 10% of patients on statin therapy ($p < 0.001$). The use of acetylsalicylic acid (aspirin) had a protective effect on the risk of all-cause mortality by a factor of 8.9 (OR: 0.112; 95% CI: 0.023–0.547; $p = 0.002$) and cardiovascular mortality by a factor of 7.391 (OR: 0.135; 95% CI: 0.028–0.659; $p = 0.006$).

CONCLUSIONS

1. In CHF patients, the presence of COPD is associated with a 2.07-fold increase in the 5-year risk of death from any cause, 2.24-fold increase in the risk of a cardiovascular event, 1.68-fold increase in the risk of a composite endpoint, and 7.41-fold increase in the risk of a non-cardiovascular hospitalization.

2. In CHF patients with COPD who have undergone coronary intervention, the risk of all-cause mortality is reduced by 9.37-fold and cardiovascular death by 7.97-fold. When statins are used, all-cause mortality is reduced by 57.4-fold and mortality from cardiovascular events by 47.31-fold.

3. The risk of reaching the combined endpoint is 4.41-fold higher in men with CHF with COPD than in women with CHF with COPD and 10.93-fold lower with statin use.

4. The odds of all-cause mortality increased 7.19-fold in men, increased 1.08-fold per year with increasing age, and decreased 10.74-fold with a history of coronary intervention.

5. The probability of cardiovascular death is 33.85 times higher in men than in women. With increasing age, the risk increases by 1.18-fold annually. Furthermore, increased high-sensitivity C-reactive protein per 1 mg/L is associated with a 1.46-fold increase in risk.

ADDITIONAL INFORMATION

Authors' contribution. E.V.Kh. — investigation, writing — original draft, visualization, project administration, writing — review & editing; O.V.B. — conceptualization, supervision; V.M.Ia. — investigation, resources, writing — original draft; M.I.M. — investigation, resources, writing — original draft.

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Вклад авторов. Е.В.Х. — исследование, создание черновика, визуализация, администрирование проекта, редактирование рукописи; О.В.Б. — концептуализация, общее руководство; В.М.Я. — исследование, ресурсы, создание черновика; М.И.М. — исследование, ресурсы, создание черновика.

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