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Characteristics of heart failure and the predictors of adverse outcomes in patients with cardiovascular pathology, type 2 diabetes mellitus and chronic kidney disease

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The aim of the study was to evaluate clinical and functional parameters, markers of myocardial and renal dysfunction, and the potential of multimarker models for predicting adverse outcomes in patients with chronic heart failure with preserved left ventricular ejection fraction (HFpEF) with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).

Methods. The study included 246 patients with HFpEF and T2DM, including 122 males and 124 females. The study participants were divided into two groups. The first group included 168 patients with HFpEF with T2DM and CKD, and the second group included 78 patients with HFpEF with T2DM without CKD. Follow-up period was 18 months. The combined endpoint of the study was patients' death from cardiovascular causes, hospitalization due to decompensation of chronic heart failure, or outpatient visits due to worsening heart failure symptoms. Clinical and functional parameters, quality of life, echocardiographic parameters, renal function, NT-proBNP, sST2, galectin-3, cystatin C concentrations were evaluated in all patients.

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Statistical data processing was performed using the Python programming language (version 3.10, sklearn, scipy, statmodels libraries) and R (version 4.2.2).

Results. Patients in group 1 had a longer course of DM (p<0.001) and chronic heart failure (CHF) (p=0.01), higher body mass index, waist circumference (p<0.001), lower indices of exercise tolerance (p<0.001) and quality of life (p<0.001) compared to patients in group 2. Patients with CKD had multivessel coronary artery disease (p<0.001) more frequently and a more severe course of DM. More patients in this group had a history of myocardial infarction (p<0.001), stroke (p<0.001) and aortocoronary bypass surgery (p=0.04). More severe haemodynamic disturbances, severity of left ventricle remodeling in patients with renal impairment corresponded to higher levels of the biomarkers studied. Different correlations between the parameters of renal dysfunction and indicators of the structural and functional state of the heart, cardiac biomarkers, were found. A higher degree of correlation from moderate to high was found with the calculated glomerular filtration rate than with the degree of albuminuria. The predictive models for the decompensation of heart failure using the markers of cardiac and renal dysfunction obtained by multivariate analysis were of high quality. The area under the curve (AUC) in the ROC analysis in model 1 with NT-proBNP concentration was 0.822 (95% CI: 0.677-0.967; p<0.001). In model 2 with NT-proBNP and sST2 — AUC = 0.942 (95% CI: 0. 876-1.0; p<0.001); in model 3 with NT-proBNP and galectin-3 — AUC = 0.869 (95% CI: 0.738-0.982; p<0.001); in model 4 with NT-proBNP and cystatin C — AUC=0.862 (95% CI: 0.736-0.992; p<0.001);

Conclusion. Patients with HFpEF, T2DM and CKD have more severe clinical and functional disorders of the cardiovascular system and carbohydrate metabolism than HFpEF patients without CKD. Evaluation of NT-proBNP, sST2, galectin-3, cystatin C levels allows the differentiation of stable patients with HFpEF with T2DM and CKD and those with the high risk of heart failure decompensation. The model including NT-proBNP and sST2 levels had the best prognostic value.

Keywords: chronic heart failure with preserved ejection fraction, diabetes mellitus, chronic kidney disease, NT-proBNP, sST2, galectin-3, cystatin C.

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Introduction

Chronic kidney disease (CKD) often occurs in patients with chronic heart failure with preserved ejection fraction (HFpEF) in combination with type 2 diabetes mellitus (DM) and has an unfavourable impact on prognosis. To date, biomarkers have played an important role in the diagnosis, severity assessment and prognosis of chronic heart failure (CHF). However, there is variability in the levels of some markers in CHF patients with comorbidities, which may affect their diagnostic significance [1]. Therefore, it is necessary to further investigate the influence of renal dysfunction on the course of CHF and to evaluate the role of biomarkers in predicting adverse outcomes in patients with type 2 DM and CHF in order to select their optimal combination.

The prevalence of NYHA functional class (FC) I–IV CHF in the European part of the Russian Federation (RF) is approximately 7.0%. Approximately half of all patients with CHF have preserved left ventricular ejection fraction (LVEF) [2]. Arterial hypertension (AH) and coronary heart disease (CHD) remain the main causes of the development of heart failure (HF). However, the role of DM in the development of HF has increased from 10.6% in 1998 to 16.6% in 2017 [3]. This is associated, among other things, with a steady increase in new cases of DM both in our country and worldwide. Despite significant progress in risk factor modification, diagnosis and treatment of carbohydrate metabolism disorders, the number of people with diabetes aged 20–79 years will exceed 537 million by the end of 2021 and, according to the International Diabetes Federation, will increase to 643 million by 2030 and to 783 million by 2045. In the Russian Federation, 4.9 million people (3.34% of the population) are registered as having diabetes, of whom 91.8% (4.5 million) are type 2 DM patients. The actual number of patients is almost twice as high as

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the official statistics, which is confirmed by the results of the NATION study [4].

DM may be the underlying cause of myocardial damage and the subsequent development of HF. According to the Framingham study, the risk of developing HF in patients with type 2 DM aged 45–74 years is more than twice as high in men and five times as high in women as in patients without DM. It not only increases the likelihood of HF, but also worsens its course, with an almost twofold increase in the number of hospitalizations associated with CHF decompensation compared with patients without DM, regardless of LVEF [5].

The development of HFpEF is closely associated not only with type 2 DM, AH, but also with CKD. Persistent renal dysfunction may occur in patients with CHF secondary to the progression of HF and/or long-term diabetes or as a result of common cardiometabolic risk factors [6]. Renal pathology, regardless of its cause and mechanism of development, is common in patients with HF [7]. Increased attention to the diagnosis and treatment of CKD is due to the unfavourable impact of renal dysfunction on prognosis. A large-scale systematic review showed a 33.7% increase in deaths over a ten-year period (2007–2017) associated with CKD, and these rates were higher than those for cancer (+25.4%), cardiovascular disease (CVD) (+21.1%) and comparable to those for DM (+34.7%) [8]. Renal dysfunction leads to increased mortality in all CHF subtypes, but more so in HFpEF patients [9]. The severity of myocardial dysfunction and mortality rates increase in parallel with the stage of CKD [10].

The pathogenetic model for the development and progression of HFpEF in patients with cardiovascular disease, type 2 DM and CKD includes systemic inflammatory and metabolic disorders with the development of endothelial dysfunction, left ventricular (LV) hypertrophy, oxidative stress and myocardial fibrosis, leading to diastolic and systolic cardiac dysfunction [11]. Symptoms of diastolic dysfunction in patients with DM and CKD are often non-specific, making early detection of CHF difficult and the diagnosis of HFpEF challenging [12]. The lack of accurate indicators to detect HFpEF in groups of patients with different phenotypes requires further investigation of the influence of renal dysfunction on the course of CHF to improve diagnosis and therapeutic efficacy.

Clinical guidelines include B-type natriuretic peptide (BNP) and N-terminal BNP peptide (NT-proBNP) as "reference" diagnostic biomarkers for CHF. However, NT-proBNP may not reflect all pathogenetic aspects of the course of CHF. In addition, the results of studies show variability in the levels of this biomarker in patients with DM, CKD and obesity [1]. More informative in this regard is the cardiac marker soluble ST2 (sST2) — a member of the interleukin-1 receptor family, which shows the least intra- and inter-individual variability and reflects the degree of severity of fibrotic processes and pathological remodelling of the heart. The level of sST2 provides independent prognostic information in addition to clinical data and other biomarkers such as high-sensitivity troponin (hsTn), cystatin C and NT-proBNP in patients with CHF and renal failure [13].

In recent years, much attention has been paid to the study of galectin-3 in patients with cardiovascular pathology. This biomarker is of particular interest for HF diagnosis and outcome prediction because its level is stable during rapid haemodynamic changes. Galectin-3 stimulates fibroblast activation and may be involved in the development of cardiac fibrosis, processes of pathological ventricular remodelling and renal dysfunction, which is very important in patients with CHF, type 2 diabetes and CKD [13].

Despite the established association of galectin-3 with CKD, cystatin C is considered to be a more accurate indicator of renal dysfunction [15]. It is not only a sensitive indicator of glomerular filtration rate (GFR), capable of diagnosing early stages of renal disorders, but also a highly effective prognostic marker of cardiovascular complications (CVC), clinically the most significant for coronary risk stratification when used in combination with other biomarkers. Since the diagnostic and prognostic value of a single biomarker at a given time point in a comorbid patient is limited, they should be combined and monitored for optimal diagnostic and clinical effect [16].

Thus, the wide prevalence of CKD, type 2 DM and their unfavourable impact on the prognosis of HFpEF patients necessitate further study of the pathogenetic features of the course of HF in the population of comorbid patients using polymarker evaluation and determination of the optimal marker for predicting HF decompensation for timely correction of therapy.

The aim of the study

To evaluate clinical and functional parameters, markers of myocardial and renal dysfunction, and the po-

tential of multimarker models for predicting adverse outcomes in patients with HFpEF, type 2 DM and CKD.

Methods

The study was approved by the Inter-University Ethical Committee. The study included 246 stable patients with type 2 DM, including 122 men (49.6%) and 124 women (50.4%). The median (Me) age of the participants was 70 years and the interquartile range (Q1; Q3) was (62; 73). All patients were diagnosed with HFpEF with clinical manifestations of CHF I–III FC according to NYHA criteria. HFpEF was diagnosed according to the clinical recommendations on chronic heart failure of the Ministry of Health of the Russian Federation from 2018 [2]. The study participants were divided into two groups. Group 1 included 168 HFpEF patients with type 2 DM and CKD, group 2 included 78 HFpEF patients with type 2 DM without CKD. All patients suffered from AH of stage 1–2. CHD was confirmed in 180 patients (73.17%). 71 patients had a history of atrial fibrillation (AF): 28 had paroxysmal form and 43 had persistent form. The majority of participants were in NYHA class II FC. The median LVEF was 55.5% (52; 58). Patients with acute myocardial infarction, stroke or transient ischemic attack within 6 months prior to inclusion in the study, patients with CHF IV FC, haemodynamically significant heart defects (above moderate) were excluded. Patients with grade 3 AH, with marked impairment of renal function and a calculated GFR (cGFR) < 25 ml/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) 2012, glycated haemoglobin (HbA1c) level above 12%, and no informed consent to participate in the study were also excluded. The follow-up period was 18 months. The combined endpoint (CEP) in the study included patients dying of cardiovascular cause, hospitalization due to CHF decompensation or outpatient visit to a health care facility due to worsening of CHF symptoms. All patients underwent clinical and laboratory examination with assessment of NYHA CHF FC, Clinical Status Scale (CSS), Charlson and Kaplan-Feinstein comorbidity indices [17], distance in the six-minute walk test (6MWT) [2], quality of life using the Kansas Cardiomyopathy Questionnaire (KCQ) [18] and Minnesota Heart Failure Quality of Life Questionnaire (MLHFQ) [2]. Echocardiography (ECHO-CG) data [1], HbA1c levels, renal impairment (cGFR using the CKD-EPI creatinine-cystatin C formula (2012) and urinary albumin-to-creatinine ratio (ACR) [19], biomarkers of cardiac and renal dysfunction: NT-proBNP, sST2, galectin-3, cystatin C were also assessed.

Transthoracic ECHO-CG was performed on a Samsung HS70A device using tissue myocardial dopplerography. LV systolic function was measured using the disc method (Simpson method). LV diastolic function was assessed in case of sinus rhythm by the indices of transmitral blood flow in pulse-wave mode: peak velocity of early diastolic filling (E) and peak velocity of late diastolic filling of the left ventricle (A), their ratio (E/A). In tissue doppler mode — velocity of early diastolic motion of septal and lateral parts of the mitral valve fibrous ring with calculation of average velocity (e`) and ratio (E/e`) were assessed.

Biomarker concentrations were quantified by enzyme-linked immunosorbent assay (sandwich) using the following kits: "Biomedica NT-proBNP" (Austria), "Presage® ST2 Assay Critical Diagnostics" (USA), "human Galectin-3 ELISA", Bender MedSystems (Austria), Cystatin C — "Human Cystatin C ELISA", BioVendor (Czech Republic).

Statistical analysis

Statistical data processing was performed using Python (version 3.10, sklearn, scipy, statmodels libraries) and R (version 4.2.2) programming languages. Main group indicators were described using fractions for categorical traits and mean with standard deviation (M±SD) for normal distribution or medians (Me) with interquartile range (25^{th} and 75^{th} percentiles) for continuous variables for other distribution. Normality of distribution was confirmed using the Kolmogorov-Smirnov method. Differences between proportions of a trait in different groups were assessed using the two-proportion Z-test, between medians — using the Kraskell-Wallace test. Spearman correlation was used to assess the closeness of the relationship between continuous variables, Fisher's exact test was used between categorical variables. The relationship between dichotomous and continuous variables was investigated using point-biserial correlation. Risk was assessed by calculating the odds ratio and relative risk. Differences between groups were considered statistically significant at $p<0.05$. Multivariate analysis by binary logistic regression with stepwise exclusion of features depending on their contribution to the model was performed to create a model of CEP prediction. In the multivariate analysis, continuous

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indicators were standardised (reduced to the 0–1 interval). The quality of prognostic models was determined using ROC analysis.

The results

The main clinical and demographic characteristics of the participants are shown in Table 1. As shown in the

Table 1. **Demographic and clinical characteristics of the patients**

Parameter	1 group HFpEF, Type 2 DM with CKD, n=168	2 group HFpEF, Type 2 DM without CKD, n=78	p
Age, years	70 (61; 74)	67 (64; 72)	0.78
Females, n (%)	85 (50.59)	39 (50.0)	0.86
Duration of CHF, years	5.0 (3; 8)	3.5 (2; 7)	0.01
Duration of DM, years	12 (9; 17)	5 (5; 8)	<0.001
BMI, kg/m^2	31.64 (29.72; 34.89)	29.29 (25.83; 31.63)	<0.001
Waist circumference, cm	107.0 (98.5; 117.0)	98.5 (91.0; 105.0)	<0.001
CHF FC according to NYHA, n(%) I II III	 4 (2.38) 118 (70.24) 46 (27.38)	 16 (20.51) 62 (79.49) 0 (0)	 <0.001 0.13 <0.001
CSS, average score	5.0 (4; 6)	4.0 (3; 6)	<0.001
6MWT, minutes	365.0 (290; 403)	402.5 (380; 420)	<0.001
KCCQ, score	57.29 (48.59; 63.96)	66.95 (64.58; 70.94)	<0.001
MLHFQ, score	41.0 (35; 51)	25.0 (22; 29)	<0.001
HbA1c,%	7.9 (7.1; 9.1)	7.1 (6.7; 7.1)	<0.001
Creatinine, μmol/l	102.0 (85.0; 118.4)	80.15 (73.1; 89.0)	<0.001
Cystatin C, mg/l	1.46 (1.17; 1.95)	1.09 (0.87; 1.12)	<0.001
cGFR with creatinine and cystatin, ml/min/1.73 m^2	46.98 (35.58;67.35)	73.81 (66.07; 84.55)	<0.001
NT-proBNP, pg/ml	589.0 (423; 890)	335.0 (251; 462)	<0.001
sST2, ng/ml	33.92 (30.8; 37.45)	29.1 (26.7; 30.84)	<0.001
Galectin-3, ng/ml	10.8 (8.9; 13.8)	7.15 (5.9; 8.2)	<0.001
Comorbidities, n (%) CHD History of MI PCI CABG History of stroke AF COPD BA	 125 (74.4) 46 (27.38) 57 (33.93) 9 (5.36) 29 (17.26) 55 (32.74) 10 (6.02) 7 (4.22)	 55 (70.51) 8 (10.26) 24 (30.77) 0 (0.0) 0 (0.0) 16 (20.51) 8 (10.26) 8 (10.26)	 0.52 <0.001 0.62 0.04 <0.001 0.05 0.23 0.06
CA atherosclerosis, n (%) 1 CA 2 CA 3 or more	 9 (5.42) 30 (17.85) 27 (16.27)	 16 (20.51) 8 (10.26) 0 (0.0)	 <0.001 0.12 <0.001
Charlson index	6 (5; 7)	4 (3; 5)	<0.001
Kaplan-Feinstein index	15.0 (12; 16)	10.0 (8; 13)	<0.001
Hospitalization due to CHF in the previous 12 months, n (%)	73 (43.45)	8 (10.26)	<0.001
Treatment, n (%) ACEi (ARB) Diuretics Beta-blockers MRA CCB Antiplateletes Anticoagulants Statins	 168 (100) 164 (97.62) 153 (91.07) 89 (52.97) 98 (58.33) 119 (70.83) 51 (30.36) 164 (97.61)	 63 (80.77) 61 (78.21) 47 (60.26) 8 (10.26) 55 (70.51) 46 (58.97) 16 (20.51) 78 (100.0)	 <0.001 <0.001 <0.001 <0.001 0.07 0.07 0.11 0.17
DM treatment, n (%) Peroral drugs Peroral drugs+insulins	 168 (100.0) 84 (50.0)	 78 (100.0) 7 (8.97)	 n/a <0.001
Distal neuropathy, n (%) Sensory Motor Sensorimotor	 93 (55.36) 1 (0.59) 58 (34.52)	 39 (50.0) 0 (0.0) 0 (0.0)	 0.43 0.49 <0.001
Retinopathy, n (%) Non-proliferative, n (%) Pre-proliferative, n (%) Proliferative, n (%)	 105 (62.5) 53 (31.93) 10 (5.95)	 70 (89.74) 8 (10.26) 0 (0.0)	 <0.001 <0.001 0.03

table, patients in the observation groups were comparable in age and sex (p=0.78; p=0.86). However, patients with CKD were older: the median age was 70 years (61; 74) vs 67 years (64; 72) in the comparison group. Patients in group 1 had higher body mass index (BMI) and waist circumference (p<0.001), higher comorbidity indices (Kaplan-Feinstein, Charlson index) (p<0.001), more severe stages of diabetic neuropathy (p<0.001) and retinopathy (p=0.03), and were more likely to require combined glucose-lowering therapy (p<0.001). They also had a longer duration of DM (p<0.001) and CHF (p=0.01). Multivessel coronary disease was more common in patients with CKD (p<0.001). More patients in this group had a history of myocardial infarction (p<0.001), stroke (p<0.001) and aortocoronary bypass surgery (p=0.04). The majority of patients (73.17%) in the observation groups were in FC 2. At the same time, the group with CKD had higher CSS scores (p<0.001), about 27% of patients had III FC and patients with I FC were less frequent (p<0.001). The lower functional status of patients with CKD was objectively confirmed by the shorter distance travelled in 6MWT (p<0.001). Quality of life assessment showed a significant decrease in patients with renal dysfunction compared to patients without CKD both by the KSSQ and MLHFQ scores (p<0.001). Patients with CKD had more severe impairment of carbon metabolism (p<0.001). Thus, HFpEF, type 2 DM patients with CKD compared to patients without CKD had longer duration of DM and CHF, more severe clinical condition, unfavourable course of CHD and DM, low indices of exercise tolerance and quality of life.

Patients with renal impairment had, as expected, higher systolic and diastolic blood pressure (BP) values (p<0.001) and a greater degree of cardiac damage (Table 2). According to the algorithm for the instrumental diagnosis of HFpEF, functional and structural indices were assessed by ECHO-CG in all participants: left atrial volume (LAV), E/è, left ventricular wall thickness, left ventricular myocardial mass (LVMM), LVMM index (LVMMI), left atrial volume index (LAVI) and relative left ventricular wall thickness index (RLWTI) were calculated. Most patients had increased E and decreased A, with a median E/A ratio of 1.3 (0.78; 1.5). More severe diastolic dysfunction up to the development of the "restrictive" type was more common in patients with CKD. Increases in LAV size, LVMM, and in their indices were observed in patients of both observation groups, but were more significant in patients with CKD. The change in LV geometry was characterised by an increase in RLWTI with a median of 0.51 (0.48; 0.54). The RLWTI was significantly higher in the first group, indicating more severe concentric LV remodelling in patients with renal impairment (see Table 2).

Data analysis showed increased concentrations of markers of cardiac dysfunction in the observation groups, but the medians of the parameters studied prevailed in patients with CKD (p<0.001) and corresponded to the severity of remodelling and the degree of LV diastolic dysfunction. In patients with CKD, the median levels of creatinine, cystatin C and cGFR were significantly different from those in the control group. At the same time, the levels of NT-proBNP, sST2,

Table 2. **Hemodynamic and structural-functional parameters of the left heart chambers**

Parameter	1 group HFpEF, Type 2 DM с CKD, n=168	2 group HFpEF, Type 2 DM без CKD, n=78	p
HR, b/min	74,5 (68; 79)	65,0 (63; 70)	<0,001
SBP, mmHg	144,0 (138,0; 150,0)	130,0 (130,0; 140,0)	<0,001
DBP, mmHg	90,0 (82; 90)	82,5 (80; 85)	<0,001
LV EDVI, ml/m^2	60,48 (54,55; 68,67)	58,13 (53,39; 60,93)	<0,001
LV EDVI, ml/m^2	21,31 (17,45;25,89)	19,2 (18,24; 21,25)	<0,001
LV EF, %	55,0 (52; 58)	56 (55; 57)	<0,001
LAVI, ml/m^2	35,07 (34,35; 36,91)	34,35 (34,11; 34,6)	<0,001
LV EDD, cm	5,1 (4,8; 5,2)	4,8 (4,8; 5,0)	<0,001
LV ESD, cm	3,3 (3,0; 3,5)	3,1 (3,1; 3,2)	<0,001
RLWTI	0,52 (0,48; 0,55)	0,51 (0,48; 0,52)	0,01
LVMM, g	276,44 (239,86; 306,81)	233,75 (204,99; 255,46)	<0,001
LVMMI, g/m^2	137,41 (116,96; 155,81)	113,81 (104,87; 129,65)	<0,001
E/A	1,4 (1,1;1,6)	1,19 (0,75;1,38)	<0,001
E/è	15,1 (11,38;16,57)	11,77 (9,24;13,22)	<0,001

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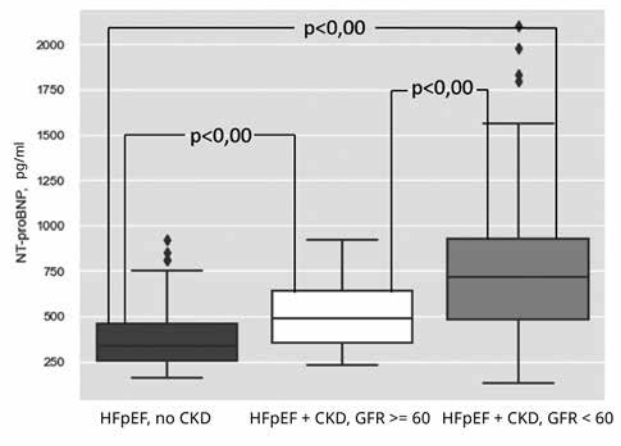

Fig. 1. NT-proBNP values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1,73 м^2 and GFR < 60 ml/min/1.73 м^2 groups

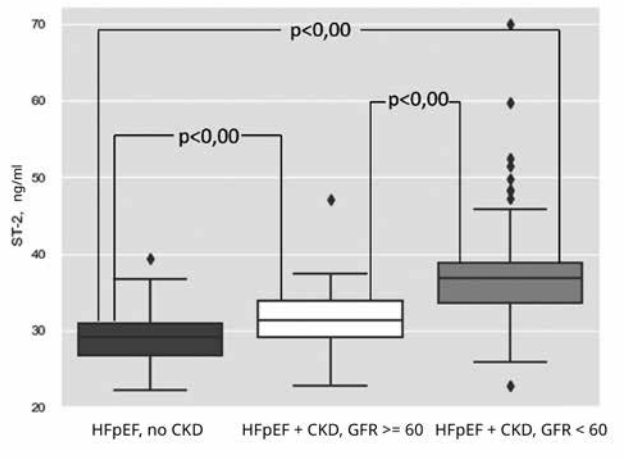

Fig. 2. sST2 values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1,73 м^2 and GFR < 60 ml/min/1.73 м^2 groups

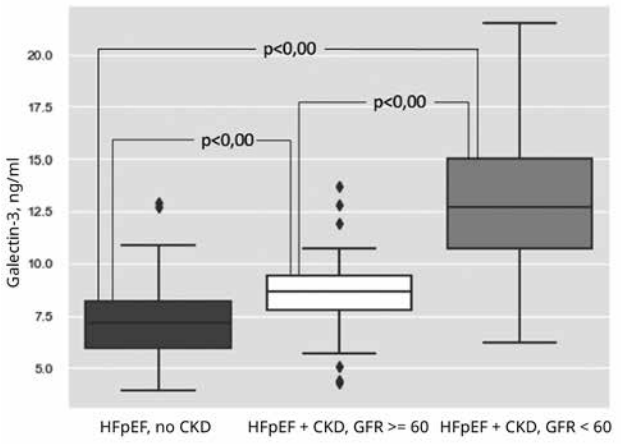

Fig. 3. Galectin-3 values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1.73 м^2 and GFR < 60 ml/min/1,73 м^2 groups

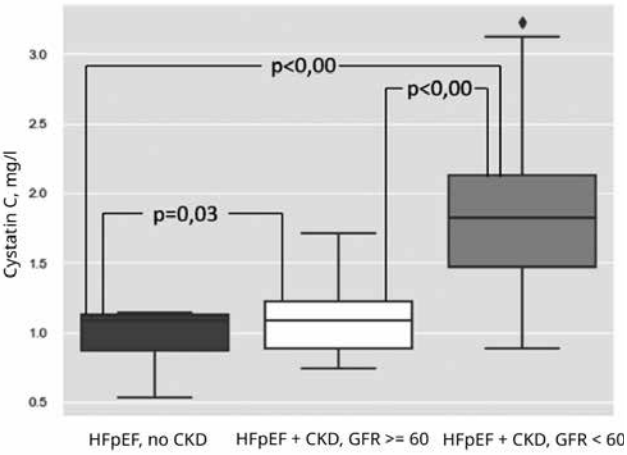

Fig. 4. Cystatin C values in patients with HFpEF, Type 2 DM without CKD and with CKD in GFR ⩾ 60 ml/min/1.73 м^2 and GFR < 60 ml/min/1,73 м^2 groups

galectin-3 and cystatin C increased in proportion to the degree of renal impairment, indicating the interdependence of heart and renal failures (Figures 1–4).

Correlation analysis confirmed close causal relationships between diastolic dysfunction, cardiac remodelling parameters and renal function in patients with HFpEF, type 2 DM combined with CKD. The main criteria of renal dysfunction (cGFR, ACR) showed varying degrees of correlation with parameters of cardiac structural and functional status and cardiac biomarkers. An inverse moderate to high degree of correlation was found between cGFR and LAVI (r=–0.338, p<0.001), E/è (r=–0.481, p<0.001), LVMMI (r=–0. 511, p<0.001), NT-proBNP levels (r=–0.5, p<0.001), sST-2 (r=–0.556, p<0.001), galectin-3 (r=–0.731, p<0.001) and cystatin C (r=–0.931, p<0.001). At the same time, moderate and low direct correlations were observed between ACR levels and the following parameters studied: E/è (r=0.341, p<0.001), LAVI (r=0.254, p=0.001), LVMMI (r=0.250, p=0.001), NT-proBNP levels (r=0.294, p<0.001), sST-2 (r=0.334, p<0.001), galectin-3 (r=0.317, p<0.001), cystatin C (r=0.225, p=0.003). There were also moderate inverse correlations between cGFR levels and the type of diastolic function (r=–0.416, p=0.001), presence of AF (r=–0.327, p<0.001), CHD (r=–0.404, p<0.001) and hospitalization due to CHF in the 12 months prior to enrolment (r=–0.324, p<0.001). The levels of the biomarkers studied had a direct significant association with hospitalization for CHF in the 12 months prior to the study: NT-proBNP (r=0.496, p<0.001), sST2 (r=0.507, p<0.001), cystatin C (r=0.347, p<0.001), galectin-3 (r=0.312, p<0.001).

When analysing the incidence of HF worsening and cardiovascular death (CVD), CEP had been reached in the initially more severely affected patients (Table 3).

Table 3. **Parameters of HFpEF, Type 2 DM and CKD patients according to the development of the combined endpoint of the study**

Parameter	Did not reach CEP, n=111	Reached CEP, n=57	p
Age, years	70 (61; 73)	71 (65; 75)	0.13
Females, n (%)	59 (53.15)	26 (45.61)	0.27
Duration of CH, years	4 (2; 6)	7.0 (5; 11)	<0.001
Duration of DM, years	10.5 (9; 17)	14 (11; 19)	0.003
Duration of CKD, years	2 (1; 3)	3 (2; 4)	<0.001
BMI, kg/m^2	31.62 (29.94; 34.68)	31.64 (29.4; 35.2)	0.82
FC according to NYHA, n (%) I II III	 4 (3.6) 91 (81.98) 16 (14.41)	 0 (0) 27 (47.37) 30 (52.63)	 0.15 <0.001 <0.001
CSS, average score	5.0 (4; 6)	7.0 (5; 8)	<0.001
6MWT, m	385 (336; 410)	290 (270; 365)	<0.001
KCCQ, score	61.3 (53.33; 65.26)	49.53 (45.36; 55.94)	<0.001
MLHFQ, score	37.0 (33; 46)	51.0 (43; 65)	<0.001
HbA1c,%	7.8 (7.1; 8.9)	8.3 (7.1; 9.3)	0.59
Creatinine, μmol/l	95.85 (82.3; 114.8)	109.0 (98.0; 125.0)	<0.001
Cystatin C, mg/l	1.31 (1.09; 1.68)	2.02 (1.6; 2.41)	<0.001
cGFR with creatinine and cystatin, ml/min/1.73 m^2	60.22 (42.15; 69.12)	39.61 (30.99;45.4)	<0.001
NT-proBNP, pg/ml	498 (409; 689)	893 (690; 1112)	<0.001
sST2, ng/ml	32.45 (29.7; 34.1)	38.4 (37.2; 42.39)	<0.001
Galectin-3, ng/ml	9.85 (8.3; 11.9)	14.8 (11.3; 16.9)	<0.001
ACR, mg/g	84 (63; 228)	231 (68; 472)	0.003
Comorbidities, n (%) CHD History of MI PCI CABG History of stroke AF COPD BA	 74 (66.66) 20 (18.02) 31 (27.93) 4 (3.6) 19 (17.12) 25 (22.52) 5 (4.5) 7 (5.65)	 51 (89.47) 26 (45.61) 26 (45.61) 5 (8.77) 10 (17.54) 30 (52.63) 5 (8.77) 0 (0)	 <0.001 <0.001 0.02 0.16 0.94 <0.001 0.27 0.06
CA atherosclerosis, n (%) 1 CA 2 CA 3 or more	 8 (7.2) 16 (14.4) 12 (10.81)	 1 (1.75) 14 (24.56) 15 (26.32)	 0.14 0.1 0.01
Hospitalization due to CHF in the previous 12 months, n (%)	30 (27.03)	43 (75.44)	<0.001
Charlson index	5.5 (5; 7)	7 (6; 8)	<0.001
Kaplan-Feinstein index	13.0 (11; 15)	16.0 (15; 18)	<0.001
Treatment, n (%) ACEi (ARB) Diuretics Beta-blockers MRA AC Antiplateletes Anticoagulants Statins	 111 (100) 107 (94.39) 99 (89.19) 47 (42.34) 67 (60.36) 92 (82.88) 19 (17.12) 110 (99.1)	 57 (100) 57 (100) 54 (94.74) 42 (73.68) 31 (54.39) 27 (47.37) 32 (56.14) 54 (94.74)	 n/a 0.15 0.23 <0.001 0.46 <0.001 <0.001 0.08
DM treatment, n (%) Peroral drugs Peroral drugs+insulins	 111 (100) 48 (43.24)	 57 (100) 36 (63.16)	 n/a 0.01
Distal neuropathy, n (%) Sensory Motor Sensorimotor	 67 (60.36) 0 (0.0) 31 (27.93)	 26 (45.61) 1 (1.75) 27 (47.37)	 0.07 0.16 0.01
Retinopathy, n (%) Non-proliferative Pre-proliferative Proliferative	 74 (66.67) 34 (30.63) 4 (3.6)	 31 (54.39) 19 (33.33) 6 (10.52)	 0.12 0.72 0.07
HR, b/min	74.5 (68;78)	74 (68;81)	0.85
SBP, mmHg	143.5 (137;150)	144 (138;150)	0.90
DBP, mmHg	90 (83;90)	85 (80;90)	0.06
LV EDVI, ml/m^2	58.48 (53.6;64.79)	66.24 (59.3;76.56)	<0.001

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Table continuation 3

Parameter	Did not reach CEP, n=111	Reached CEP, n=57	p
LV EDVI, ml/m²	20.58 (16.85;24.45)	24.43 (18.91;30.32)	<0.001
LV EF, %	55 (53; 58)	53 (51;55)	0.001
LV EDD, cm	4.9 (4.8;5.2)	5.3 (5.0;5.6)	<0.001
LV ESD, cm	3.2 (2.9;3.4)	3.4 (3.2;3.8)	<0.001
RLWTI	0.52 (0.49;0.55)	0.53 (0.46;0.55)	0.09
LAVI, ml/m²	34.65 (34.14; 35.44)	36.59 (35.09; 44.86)	<0.001
LVMM, g	255.46 (234.61; 293.82)	297.0 (267.94; 335.47)	<0.001
LVMMI, g/m²	131.62 (115.03; 148.29)	149.8 (129.9; 164.19)	<0.001
E/A	1.2 (0.74; 1.5)	1.5 (1.3; 1.6)	<0.001
E/è	13.23 (10.21; 15.6)	16.38 (13.26; 17.61)	<0.001

During the follow-up period in the group of patients with HFpEF, type 2 DM and CKD, there were 3 cases of death from cardiovascular causes; 23 cases of hospitalization due to HF decompensation; 31 patients sought outpatient care due to worsening HF symptoms. Logistic regression analysis was used to construct baseline statistical models to predict the likelihood of CVD and HF decompensation in patients with HFpEF, type 2 DM and CKD. Baseline model 1 included CSS, hospitalization due to HF in the previous 12 months, BMI, E/è, distance in the 6MWT and NT-proBNP concentration (Table 4). In the ROC analysis of this model, the AUC was 0.822 (95% confidence interval (CI) 0.677–0.967; p<0.001), indicating good predictive quality of the model (Figure 5). The sensitivity, specificity and accuracy of the model 1 were 61.5%, 80.9% and 77.7%, respectively.To determine the significance of the biomarkers in predicting CEP, we added the concentrations of the studied markers to the baseline model and evaluated their quality. The inclusion of sST2 in the baseline model improved the predictive ability of model 2 (AUC = 0.942; 95% CI: 0.876–1.0; p<0.001), increasing its sensitivity to 92.3%, specificity to 81.8% and accuracy to 87.0% (Table 4, Figure 6). Models 3 and 4, obtained by adding galectin-3 and cystatin C concentrations respectively to the basic components, had almost the same effect on prognostic value with a slight advan-

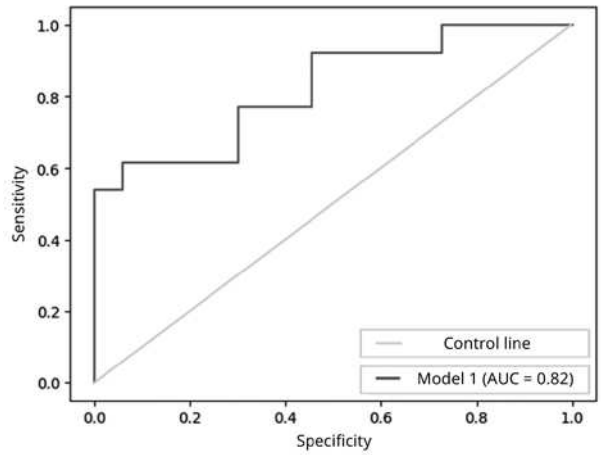

Fig. 5. ROC curve for the baseline model 1 with included NT-proBNP

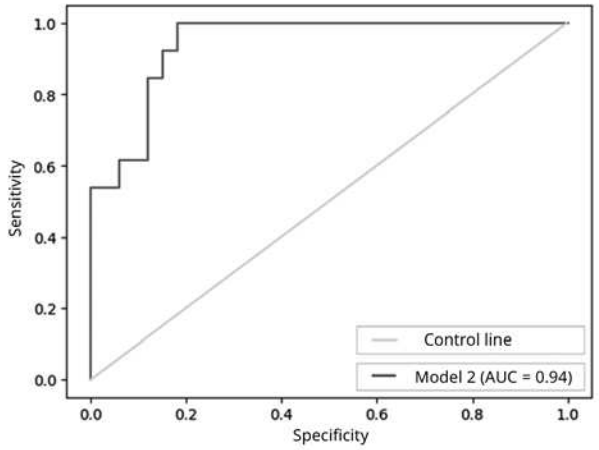

Fig. 6. ROC curve for model 2 with included NT-proBNP and sST2

Table 4. **Risk factors for an unfavourable course of heart failure in multivariate regression analysis (models 1, 2)**

Parameter	Model 1 (AUC 0.822)			Model 2 (AUC 0.942)		
	β	OR (CI 95%)	p	β	OR (CI 95%)	p
NT-proBNP	0.0024	1.01 (1.00–1.02)	0.026	0.0011	1.01 (0.99–1.02)	0.342
BMI	0.1070	1.11 (0.98–1.25)	0.086	0.0112	1.01 (0.89–1.14)	0.86
CSS	0.1958	1.21 (0.59–1.43)	0.238	0.4374	0.64 (0.42–0.97)	0.04
6MWT	–0.0157	0.98 (0.97–0.99)	0.642	–0.0232	0.97 (0.96–0.98)	<0.001
Hospitalization due to CHF in the previous 12 months	1.4077	4.08 (1.38–12.08)	0.011	0.5361	1.71 (0.55–5.23)	0.349
E/è	0.0091	1.01 (1.00–1.02)	0.918	0.0597	1.06 (0.90–1.22)	0.523
sST2	–	–	–	0.2547	1.29 (1.11–1.51)	<0.001

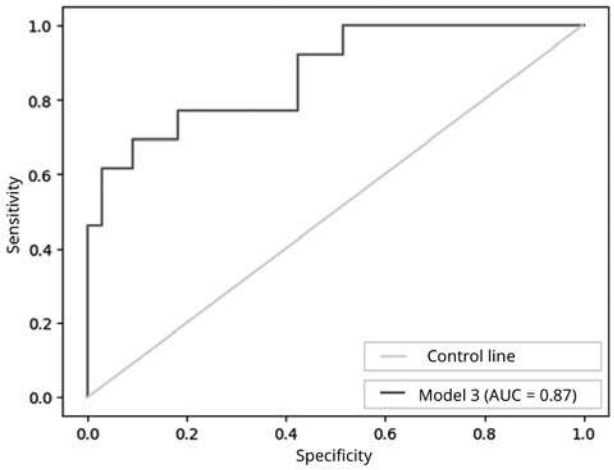

Fig. 7. ROC curve for model 3 with included NT-proBNP and galectin-3

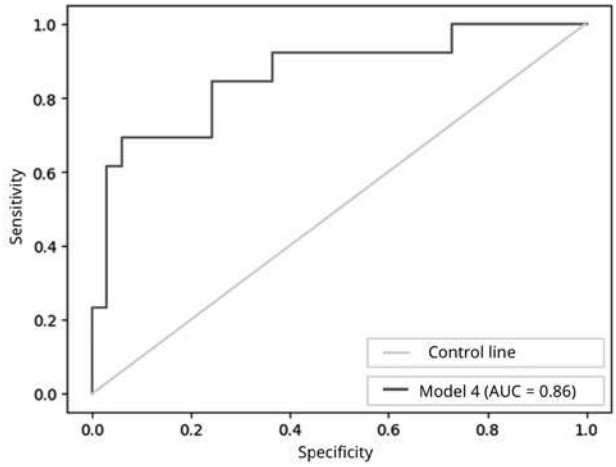

Fig. 8. ROC curve for model 4 with included NT-proBNP and cystatin C

tage of galectin-3 (Table 5). The ROC curves of model 3 (AUC=0.869; 95% CI: 0.738–0.982; p<0.001) and model 4 (AUC=0.862; 95% CI: 0.736–0.992; p<0.001) are shown in Figures 7, 8. The sensitivity, specificity and accuracy of model 3 were 65.0%, 80%, 79% and 63.4%, 79.2%, 78.7% in model 4.

Thus, the best model for predicting CHF and CVD decompensation in HFpEF, Type 2 DM and CKD patients was model 2, including CSS, HF hospitalization in the previous 12 months, BMI, E/è, 6MWT distance, NT-proBNP and sST2 concentrations. Cut-off values for biomarker concentrations and relative risk (RR) of CEP in the next 18 months were determined using single-factor ROC analysis: For NT-proBNP ≥865.88 pg/ml (RR=4.096 with 95% CI: 2.7–6.2; p<0.001), for sST2 ≥37.43 ng/ml (RR=7.1 with 95% CI: 4.4–11.4; p<0.001), for galectin-3 ≥12.83 ng/ml (RR=4.241 with 95% CI: 2.7–6.7; p<0.001), for Cystatin C ≥1.69 mg/l (RR=3.436 with 95% CI: 2.1–5.5; p<0.001).

Discussion

CHF in patients with DM and CKD is a complex pathogenetic model involving multiple links. DM and CKD may be causative and/or aggravating factors in the onset, development and progression of CHD and AH, the main etiological causes of CHF. In our study, all HFpEF and Type 2 DM patients had AH and more than 70% suffered from CHD. However, patients with CKD differed in the longer duration of DM and CHF. Duration of exposure to metabolic and haemodynamic factors is important in the development and progression of cardiovascular diseases, renal dysfunction, complications of DM and increases the risk of cardiovascular events [20,21]. Therefore, patients with a history of myocardial infarction, stroke, and more severe stages of diabetic neuropathy and retinopathy were significantly more common in the cohort of patients with CKD. Patients in the CKD group also had a significantly higher BMI. The polysystemic effects of obesity contribute to the progression of HF, type 2 DM and renal dysfunction [22]. This was also reflected in our study. BMI was included in the baseline prediction model of HF and CVD decompensation in the studied patient population.

Patients with CKD had significantly higher values of SBP and DBP, which may be due to volume overload

Table 5. **Risk factors for an unfavourable course of heart failure in multivariate regression analysis (models 3, 4)**

Parameter	Model 3 (AUC 0.869)			Model 4 (AUC 0.862)		
	β	OR (CI 95%)	p	β	OR (CI 95%)	p
NT-proBNP	0.003	1.01 (1.00–1.02)	0.026	0.0023	1.01 (1.00–1.02)	0.04
BMI	0.0415	1.04 (0.91–1.19)	0.547	0.0532	1.05 (0.93–1.18)	0.383
CSS	0.1960	1.21 (0.96–1.49)	0.304	0.1598	1.17 (0.93–1.53)	0.362
6MWT	–0.0163	0.98 (0.97–0.99)	0.002	–0.0145	0.98 (0.97–0.99)	0.002
Hospitalization due to CHF in the previous 12 months	0.4025	1.49 (0.47–4.73)	0.494	0.6966	2.0 (0.68–5.91)	0.207
E/è	0.0834	1.08 (0.94–1.26)	0.356	0.0231	1.02 (0.86–1.21)	0.798
Galectin-3	0.2817	1.32 (1.10-1.59)	0.003	–	–	–
Cystatin C	–	–	–	1.0259	2.78 (1.00–7.71)	0.048

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from increased renal sodium reabsorption, systemic proinflammatory state aggravating microvascular dysfunction [6]. Significant structural and functional changes of the heart detected in all study participants are associated with the features of CHF formation in the disorders of carbohydrate metabolism and renal function impairment. Thus, in Type 2 DM myocardial damage occurs in conditions of insulin resistance (IR), hyperinsulinemia with inadequate activation of renin-angiotensin-aldosterone system (RAAS), leading to LV myocardial rigidity, pathological remodelling processes, and LAV increase. In this case, IR alters energy metabolism, impairs mitochondrial function and reduces cardiomyocyte contractility. In the context of inadequate glucose delivery to the cell, metabolism shifts towards fatty acid oxidation. The end products of non-enzymatic glycosylation of lipids, lipoproteins and amino acids affect the processes of collagen formation, lead to increased expression of transforming growth factor ß, impair the degradation of the extracellular matrix by decreasing the expression of matrix metalloproteinase-2, increase fibrosis and diastolic dysfunction of the heart [23]. The product of glucose metabolism β-N-acetylglucosamine has a similar negative effect on myocardium through modification of Ca2þ/calmodulin-dependent protein kinase II, phospholamban and myofilaments. β-N-acetylglucosamine, by binding to mitochondrial proteins, impairs mitochondrial function and increases the production of reactive oxygen species. Multifactorial negative effects lead to the progression of fibrosis and inflammation in the myocardium with subsequent activation of cardiomyocyte apoptosis [24]. In renal dysfunction additional unfavourable pathogenetic mechanisms are involved. More pronounced diastolic dysfunction and higher values of indexed LAV, LVMM, RLWTI in the group of patients with CKD can be associated with both impaired water-electrolyte metabolism and the systemic negative effect of uremia.

In addition to direct damaging effect on cardiomyocytes, uremic toxins lead to an increase in the level of proinflammatory cytokines, which inhibit proliferation and increase apoptosis of endothelial cells, reduce nitric oxide (NO) bioavailability by inhibiting endothelial nitric oxide synthase (eNOS), and increase the expression of adhesion molecules. There is leukocyte activation with differentiation of fibroblasts into myofibroblasts, increased collagen production in the extracellular matrix, migration and proliferation of vascular smooth muscle cells. In addition, the level of circulating and cellular advanced glycation end products (AGEs) increases in patients with DM and CKD due to their increased production and decreased clearance. It was found that prolonged circulation of AGEs worsens the course of CHF and positively correlates with diastolic dysfunction [24, 25].

All these processes contribute to the development and progression of microvascular dysfunction and pathological remodelling of the heart and vessels. Although we have demonstrated a relationship between CKD, remodelling processes and LV diastolic function, the direction of this relationship cannot be precisely established. CKD may be an aggravating factor that leads to impaired cardiac functioning. At the same time, changes in cardiac structure and/or function, reduced cardiac output in HFpEF may increase renal venous congestion and worsen renal function. Thus, in patients with HFpEF, Type 2 DM and CKD a vicious circle of bilateral relationships is formed, the rupture of which may positively influence the rate of progression of cardiorenal insufficiency and reduce the risks of complications.

Our study revealed a strong relationship between cardiac structural changes, myocardial remodelling, LV diastolic function, cGFR, and biomarkers of cardiorenal dysfunction. We observed an increase in biomarker concentrations corresponding to the degree of cGFR decline, indicating the interdependence of cardiac and renal dysfunction. In the study, we also evaluated the impact of NT-proBNP and a number of markers actively studied in cardiorenal pathology on prognosis in patients with HFpEF, type 2 DM and CKD. To date, the assessment of NT-proBNP levels is an integral part and "gold standard" of CHF diagnosis. According to the results of numerous studies, an NT-proBNP concentration <125 pg/ml is highly predictive of HF absence [1, 2]. The dependence of NT-proBNP concentration on CHF phenotype has been established. In one study, despite higher NT-proBNP levels in CHF patients with reduced ejection fraction (HFrEF) than in HFpEF individuals (median 2723 vs. 5644 ng/l, p<0.001), the relationship between elevated levels of this marker and prognosis did not differ between these groups (p=0.956 for death from any cause; p=0.351 for the CEP including all-cause death or hospitalization for HF) [26]. The results of another study in outpatients showed that NT-proBNP levels

above the median of 1428 pg/ml in HFpEF patients were associated with an increased risk of death and hospitalization for HF [27].

In our study, a cut-off value of NT-proBNP ≥865.88 pg/ml significantly predicted the development of CHF decompensation and CVD. This finding may be due to the characteristics of the patient population studied. An inverse correlation was found between NT-proBNP levels, hyperinsulinemia and degree of obesity. Therefore, in CHF patients with type 2 DM, whose median BMI was 31.14 kg/m^2 (28.09; 33.73), additional markers were used to assess the severity of CHF progression. One of these is sST2, whose gene is also expressed in cardiomyocytes and fibroblasts in CHF and reflects the development of pathological remodelling and fibrosis [16]. Two isoforms of ST2 are important in cardiovascular pathology: sST2 and transmembrane ligand (ST2L). Under conditions of cardiomyocytes stress, ST2L becomes susceptible to interleukin-33 (IL-33), the synthesis of which is increased. The interaction of IL-33 with ST2L exerts a cardioprotective antifibrotic effect, whereas sST2 blocks the beneficial effect of IL-33. When the ST2/IL-33 system is disturbed, sST2 hyperproduction with the development of inflammatory and neurohormonal activation leads to the formation and progression of HF. In addition, sST2 is involved in the development of vascular remodelling [28,29].

Numerous studies have shown an association between sST2 and myocardial stretch, fibrosis, pathological cardiac remodelling, inflammation, haemodynamic impairment and vascular disease. The high independent prognostic significance of this marker in CHF patients has been demonstrated in many studies. Several studies in CHF patients with different phenotypes have performed a multimarker analysis to predict adverse events. In a study by Dupuy A.M. et al, 2016, sST2 predicted both all-cause mortality (RR=2.75) and CVD risk (RR=3.78) well compared to other classical markers: NT-proBNP, hsTn alone or in combination. The results of studies show different sST2 thresholds in patients depending on cardiovascular pathology. An sST2 level >24.6 ng/ml was an independent predictor of death in stable CHD, and in the HF-ACTION study in CHF patients, a threshold sST2 level of 35 ng/ml was used to assess prognosis [30]. In another study, the optimal level of sST2 for predicting all-cause death, CVD and hospitalization due to HF was 28 ng/ml [31]. In the study by Grakova E.V. et al, sST2 levels ≥34.18 ng/ml were associated with the development of cardiovascular events within 12 months in patients with stable CHD and CHF after revascularisation [32]. In our study, the addition of sST2 to the baseline model including NT-proBNP increased the prognostic value to a greater extent than the addition of the other markers studied. The threshold of sST2 ≥37.43 ng/ml obtained by ROC analysis (RR=7.1 with 95% CI: 4.4–11.4; p<0.0001) significantly stratified the risk of negative course of CHF. The value of the marker was higher than that reported in several other studies. In our opinion, this is due to the severity of health condition in comorbid CHF patients studied.

To improve the prognostic value in CHF with different phenotypes, many studies have investigated the influence of several markers simultaneously. For example, in CHF patients with moderately reduced EF, the prognostic value of NT-proBNP, hsTn, sST2, galectin-3, high-sensitivity C-reactive protein, cystatin C, neprilysin and soluble transferrin receptor biomarkers was similar to CHF patients with HFrEF, except for lower NT-proBNP levels. In HFpEF, neprilysin and galectin-3 showed greater importance in risk stratification [13]. We also evaluated the significance of galectin-3 in the studied cohort of patients with HFpEF. Interest in this biomarker is related to its pathophysiological features. Galectin-3 is secreted by activated macrophages and is involved in the processes of inflammation and fibrosis. The biomarker may reflect the processes of fibrosis in the heart and ventricular remodelling, impaired renal function, which is very important in patients with CHF and CKD [14, 33]. A recent meta-analysis using data from 27 studies showed that high levels of galectin-3 are associated with the risk of HFpEF developing, with a high risk of death and CEP (all-cause death, CVD, hospitalization for HF), as well with parameters reflecting diastolic function (E/è r=0.425, 95% CI: 0.184-0.617; p<0.001). In addition, galectin-3 levels are stable during rapid haemodynamic changes. Therefore, the determination of galectin-3 levels may help in the diagnosis of HFpEF, the assessment of the risk of unfavourable outcomes and the efficacy of therapy [34]. Galectin-3 levels were significantly elevated in patients with both acute and chronic HF and predicted the risk of new-onset HF and the likelihood of adverse outcomes in patients with CHF [35-37]. The results of experimental and clinical studies have demonstrated the possibility of using galectin-3 as a

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prognostic factor not only in HFpEF but also in CKD. In our study of patients with HFpEF, type 2 DM and CKD, we confirmed the association of elevated galectin-3 levels with parameters of cardiac and renal dysfunction. There were moderate direct correlations between galectin-3 concentration and diastolic function markers, such as LV remodelling: E/è (r=0.452, p<0.001), LAVI (r=0.350, p<0.001); LVMMI (r=0.436, p<0.001); high direct correlation with cystatin C level (r=0.803, p<0.001) and high inverse correlation with cGFR (r=–0.731, p<0.001). ROC curve analysis showed that galectin-3 levels ⩾12.83 ng/ml increased the risk of CVD and HF decompensation in HFpEF, type 2 DM and CKD patients in the next 18 months (RR=4.241 with 95% CI: 2.7–6.7; p<0.0001). The increased concentration of this marker in patients with CKD may be due to a decrease in its clearance, which may reduce its prognostic value in CHF patients with CKD. On the other hand, the decreased excretion of galectin-3 in CHF patients not only explains the association between renal dysfunction and galectin-3, but is also one of the reasons for the unfavourable impact of renal dysfunction on the long-term prognosis of CHF patients. The high concentration of galectin-3 may also be related to its increased production in organs other than the heart and kidneys with ongoing systemic inflammation in conditions of cardiorenal dysfunction [38].

In our study, we evaluated the level of the reference marker for renal dysfunction, cystatin C, and its role in predicting CEP. Significant differences in creatinine, cystatin and cGFR levels were observed between the study groups. In all patients, GFR using serum creatinine concentration was overestimated compared to GFR using cystatin C. In the HFpEF, type 2 DM and CKD group, the median cGFR using creatinine was 58.07 ml/min/1.73 m^2 (42.28; 73.1) and was significantly different from the cGFR using cystatin C of 42.53 ml/min/1.73 m^2 (29.42; 60.37), p<0.001. In view of this, the use of cystatin C will be most useful in the early stages of CKD to take timely action to prevent CKD progression. Correlation analysis confirmed strong cardiorenal correlations. Moderate to high correlations were found between cystatin C and NT-proBNP (r=0.564; p<0.001), sST2 (r=0.602; p<0.001), galectin-3 (r=0. 803; p<0.001), LVEF (r=–0.410; p<0.001), LAVI (r=0.350; p<0.001), LVMMI (r=0.480; p<0.001), E/è (r=0.448; p<0.001). Numerous studies have demonstrated not only the diagnostic value of cystatin C in evaluating GFR, but also its high prognostic value in determining the risk of new cases of HF, CHF decompensation and death [29]. In our study, the addition of cystatin C concentration to the baseline model for estimating the probability of CEP improved the prognostic quality of the model. The obtained cut-off value for cystatin C ⩾1.69 mg/l allows a reliable classification of CHF patients with CKD into high and low risk categories for the development of CEP (RR=3.436 with 95% CI: 2.1–5.5; p<0.001).

Conclusion

Patients with CHFpEF, type 2 DM and CKD have more severe clinical and functional cardiovascular and carbohydrate metabolic disorders than patients with CHFpEF without CKD. In the course of the study, a significant inverse relationship was found between the degree of renal function decline (cGFR) and structural and functional cardiac parameters, LV diastolic function, concentration of markers of myocardial dysfunction. The analysis of the obtained results showed that the use of multimarker models improves the quality of prediction of unfavourable course of HF in patients with CHFpEF, type 2 DM and CKD. At the same time, the determination of myocardial and renal dysfunction markers in clinical practice will allow the selection of patients at high risk for HF decompensation and cardiac death in the population of comorbid patients and the timely implementation of therapeutic measures.

Conflict of interest: none declared.

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