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Prognostic value of selected biomarkers in comorbid patients with chronic heart failure after COVID-19

Kovalenko E.V., Belaya O.L., Markova L.I., Evdokimov V.V.

Federal Scientific State Budgetary Institution "N.A. Semashko National Research Institute of Public Health", Moscow, Russia.

AUTHORS

Elena V. Kovalenko*, MD, PhD, Professor of the Department of Hospital Therapy № 2, Federal Scientific State Budgetary Institution "N.A. Semashko National Research Institute of Public Health", Moscow, Russia. ORCID: 0000–0001-9202-3522

Olga L. Belaya, MD, PhD, Professor of the Department of Hospital Therapy № 2, Federal Scientific State Budgetary Institution "N.A. Semashko National Research Institute of Public Health", Moscow, Russia. ORCID: 0000–0002-5256-3580

Lyudmila I. Markova, MD, PhD, Professor of the Department of Hospital Therapy № 2, Federal Scientific State Budgetary Institution "N.A. Semashko National Research Institute of Public Health", Moscow, Russia. ORCID: 0000–0002-3396-9235

Vladimir V. Evdokimov, MD, PhD, Professor, Head of the Department of Hospital Therapy № 2, Federal Scientific State Budgetary Institution "N.A. Semashko National Research Institute of Public Health", Moscow, Russia. ORCID: 0000–0003-3910-2488

The aim of the study was to evaluate the role of such biomarkers as N-terminal prohormone of brain natriuretic peptide (NT-proBNP), cystatin C, and galectin-3 for prediction of poor outcomes of chronic heart failure with preserved ejection fraction (HFpEF) of the left ventricle (LV) in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) with a history of COVID-19.

Methods. This study included 135 patients with HfpEF and cardiovascular disorders, T2DM, CKD, and a history of COVID-19 from more than 3 months prior to enrollment. Patients were assessed clinically, instrumentally and using laboratory methods, including NT-proBNP, cystatin C, and galectin-3 assays and echocardiography. The occurrence of heart failure (HF) decompensation and cardiovascular death (CVD) was recorded over 18 months.

Results. A multivariate regression analysis was used to build a basic model for estimation of probability of HF decompensation and CVD in patients with a history of COVID-19, HFpEF, T2DM, and CKD and included risk factors, such as rating scale of clinical state (ShOKS), stroke volume, left ventricular mass index, E/e' ratio, and NT-proBNP, which showed a high prognostic potential

* Corresponding author. Tel. +7 (915) 262-89-82. E-mail: elkovalenko76@mail.ru

(AUC=0.856; 95% CI: 0.717–0.994; p<0.001, sensitivity 85.6%, specificity 79.2%). Adding cystatin C and galectin-3 improved prognostic properties of the resulting models (AUC=0.867; 95% CI: 0.808–0.923, p<0.001, sensitivity 86.3%, specificity 75% and AUC=0.866; 95% CI: 0.809–0.923, p<0.001, sensitivity 84.9%, specificity 83.3%, respectively). The best model was developed using levels of assessed biomarkers (AUC=0.879; 95% CI: 0.845–0.913, p<0.001, sensitivity 87.5%, specificity 88.8%).

Conclusion. Including NT-proBNP, cystatin C, and galectin-3 into a multifactorial model can improve the prediction of HF worsening and CVD in patients with a history of COVID-19, HFpEF, T2DM, and CKD.

Keywords: chronic heart failure, NT-proBNP, galectin-3, cystatin C, COVID-19, prognosis.

Conflict of interest: none declared.

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Introduction

Many chronic heart failure (CHF) patients have a preserved ejection fraction (EF) of the left ventricle (LV). These patients often have arterial hypertension (AH), type 2 diabetes mellitus (T2DM), obesity, coronary heart disease (CHD), chronic kidney disease (CKD), and are elderly [1]. These comorbidities mutually exacerbate each other, regardless of their order of appearance [2].

Long-lasting impact of established risk factors (RF) in comorbid patients lead to systemic inflammation, atherosclerosis, and ischemia. Against the background of metabolic and hemodynamic disorders, associated with insulin resistance, renin angiotensin aldosterone system (RAAS) activation, elevated levels of glycation end products and adipokines, patients experience oxidative injury of cardiomyocytes, glomerular filter structures, tubular epitheliocytes, mesangial cells, accompanied by increased active transforming growth factor ß production, stimulation of collagen formation and fibrosis. Structural changes in heart and kidneys result in pathologic remodeling and dysfunction. In turn, cardiorenal dysfunction leads to compensatory activation of RAAS and establishes a vicious circle [3]. Thereby, inflammation and fibrosis compose the basis of cardiorenal dysfunction formation and progression pathogenesis in patients with CHF, T2DM, and CKD. Therefore, biomarkers reflecting these processes hold promise for prognostic assessment and represent a sought-after area of research/medicine.

Cystatin C is one of well-studied markers in cardiovascular and renal disorder, which is a member of cysteine proteinase inhibitors family. Serum cystatin C levels are known to represent glomerular filtration rate (GFR) more accurately, than serum creatinine. In addition to renal dysfunction, high cystatin C concentration might be associated with inflammatory and atherogenic processes [4]. Levels of this marker were studied during the coronavirus infection pandemic (COVID-19). The meta-analysis revealed an association between high serum concentrations of this biomarker and both COVID-19 infection severity and mortality in hospitalized patients [5]. Nevertheless, the significance of cystatin C in patients after the COVID-19 infection is yet to be defined.

In the past few years, the possibility of the use of galectin-3 in patients with cardiovascular disorder, including CHF. Controversial study results preclude its recommendation as a reliable indicator of heart failure (HF). However, the use of galectin-3 in combination with gold-standard HF biomarkers (B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) might improve the prognostic assessment of adverse events [6]. The significance of galectin-3 in the pathogenesis of cardiovascular remodeling, inflammatory and autoimmune processes, and neoplasia [7]. Moreover, the increase in galectin-3-positive macrophages in renal glomeruli in T2DM is associated with level of albuminuria, progression of kidney dysfunction, and a poor prognosis [8]. For the time

being, galectin-3 is considered one of the markers of fibrosis and inflammation [9].

Most studies on multiple-marker prognostic assessment were conducted before the COVID-19 pandemic, and its delayed consequences are still to be researched. It has been established that patients with CHD, AH, T2DM, CKD, and CHF fall into the category of poor COVID-19 outcomes and very high risk of cardiovascular complications [10, 11]. Despite the significant evidence base of clinical application of various biomarkers, the question of the gold-standard indicator for long-term CHF poor prognosis in patients with cardiorenal dysfunction after COVID-19 remains open [12].

Aim of the study

The aim of the study is to estimate the role of biomarkers, such as NT-proBNP, cystatin C, and galectin-3 for prognostic assessment of poor outcomes in patients with HFpEF, T2DM, CKD, and COVID-19 in medical history.

Methods

The study included 135 stable patients with HFpEF, T2DM, CKD, and a confirmed COVID-19 from 3 or more months prior to the hospitalization. All participants signed an informed consent form. The median age was 70 [62, 74]. The study included patients with CHF of I–III NYHA functional class with medical history of grade 1–2 of AH, and 85 (76.58 %) participants had CHD. The exclusion criteria were acute myocardial infarction, stroke or a transient ischemic attack for 6 months prior to the enrollment, IV NYHA functional class of CHF, hemodynamically significant cardiac abnormalities, grade 3 AH, severe renal dysfunction with estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) 2012, level of glycated hemoglobin (HbA1c) > 12 %. The period of observation was 18 months. NYHA functional class of CHF, clinical severity assessed by the Rating Scale of Clinical State, Kaplan-Feinstein comorbidity index, 6-minute walk test distance (6MWT), echocardiographic data (EchoCG), eGFR by the CKD-EPI 2012, urine albumin-to-creatinine ratio (uACR), serum levels of NT-proBNP, galectin-3, and cystatin C assessment. Transthoracic EchoCG with myocardial tissue Doppler imaging was carried out. Left ventricular ejection fraction was estimated with Simpson's method of disks. Diastolic function of the left ventricle was estimated using transmitral flow in pulsed-wave and tissue Doppler modes. Biomarker levels were quantitatively assessed with Enzyme-Linked Immunosorbent Assay (ELISA) with the following kits: "Biomedica NT-proBNP" (Austria), "human Galectin-3 ELISA", Bender MedSystems (Austria), "Human Cystatin C ELISA", BioVendor (Czech Republic). Additionally, a group of 21 participants (12 women and 9 men) with no signs of disease and no medical history of COVID-19 for to establish control biomarker levels. This group had a median age of 54 [49, 58] and median levels of NT-proBNP 77 [49, 91] pg/mL, galectin-3 – 2.7 [1.8, 3.6] ng/mL, cystatin C 0.781 [0.694, 0.820] mg/L.

The Inter-University Committee on ethics from 20.01.2022 (protocol № 01–22) approved the study.

Statistical analysis

Statistical data were processed using Python programming language (3.10 version, scipy, statmodels, pandas, math libraries) and MedCalc software. Descriptive statistics for group parameters included frequencies and percentages for categorical variables, and medians with interquartile ranges (Q25, Q75) for continuous variables, accounting for the distribution type. The Kolmogorov-Smirnov method was used for normality tests. Differences in proportions of a trait between groups were assessed using the proportion Z-test. Differences in medians were evaluated with the Kruskal-Wallis test. The strength of association between continuous variables was measured using Spearman's correlation, while differences between categorical variables was assessed with Fisher's exact test. The association between dichotomous and continuous variables was examined using point-biserial correlation. Risk was estimated by calculating the odds ratio and relative risk. Differences in indicators between groups were considered statistically significant at $p<0.05$. Cut-off values for the concentrations of the investigated markers, along with their sensitivity and specificity, were derived from ROC analysis. A predictive model for adverse events of the composite endpoint (CEP), including cases of cardiovascular death (CVD) and HF decompensation, was created using multivariate binary logistic regression analysis. The sensitivity and specificity of the predictive model were determined via ROC analysis.

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Results

According to medical history, the median duration of CHF, AH, T2DM, and CKD was 5.0 [3.0, 8.0] years, 19 [17, 21] years, 12 [9, 17] years, and 2 [2, 3] years, respectively. Among the 85 (76.58 %) patients with CHD, 49 (36.3 %) had two or more affected coronary arteries, 34 (30.63 %) had a history of myocardial infarction, 38 (34.23 %) had undergone percutaneous coronary intervention, and 7 (6.31 %) had undergone coronary artery bypass grafting. Preproliferative and proliferative stages of diabetic retinopathy were identified in 42 (31.11 %) and 10 (7.41 %) patients, respectively. Distal diabetic neuropathy was diagnosed in 126 (93.33 %) patients, of whom 54 (40.0 %) had sensorimotor neuropathy. The median Kaplan-Feinstein comorbidity index score was 15 [12, 16] points. The majority of included patients, 87 (66.44 %), had NYHA FC II of CHF, 46 (34.07 %) patients had NYHA FC III of CHF, and 2 (1.48 %) had NYHA FC I of CHF. Key clinical, functional, and laboratory parameters are presented in Table 1.

Table 1. **Clinical, functional, and laboratory parameters, median [Q25, Q75]**

Parameter	Value
BMI, kg/m^2	31.51 [29.7, 34.41]
Waist circumference, cm	105.0 [98.5, 115.0]
ShOKS (Rating Scale of Clinical State, Russian), points	5.0 [4.0, 7.0]
6MWT (6-Minute Walk Test), m	348.0 [285.0, 395.0]
HbA1c,%	7.8 [7.1, 9.1]
Cholesterol, mmol/L	4.45 [3.78, 4.99]
Sodium, mmol/L	140.2 [139.3, 141.6]
Potassium, mmol/L	4.53 [3.91, 5.04]
Urea, mmol/L	7.17 [6.1, 9.45]
Creatinine, μmol/L	105.0 [92.0, 123.9]
Creatinine eGFR, mL/min/1,73 m^2	51.89 [39.67, 69.39]
Cystatin C, mg/L	1.54 [1.26, 2.08]
Cystatin eGFR, mL/min/1,73 m^2	39.0 [27.49, 53.03]
uACR, mg/g	150.0 [66.0, 297.0]
NT-proBNP, pg/mL	679.0 [452.0, 911.0]
Galectin-3, ng/mL	11.52 [9.4, 14.58]

All patients had concentrations of NT-proBNP, galectin-3, and cystatin C above control values. An analysis of the levels of the studied biomarkers was performed across different ranges of creatinine-based eGFR, corresponding to CKD stages 1 through 4 (Figures 1–3).

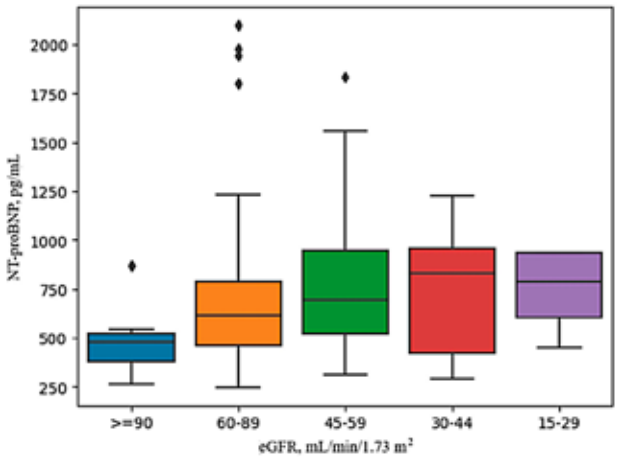


Fig. 1. NT-proBNP levels depending on eGFR, p=0.123

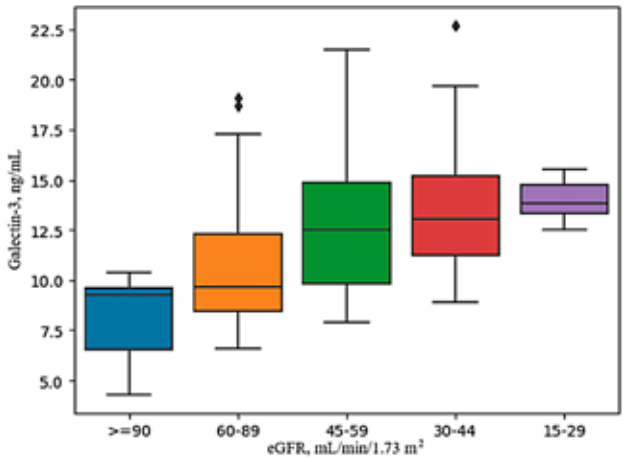
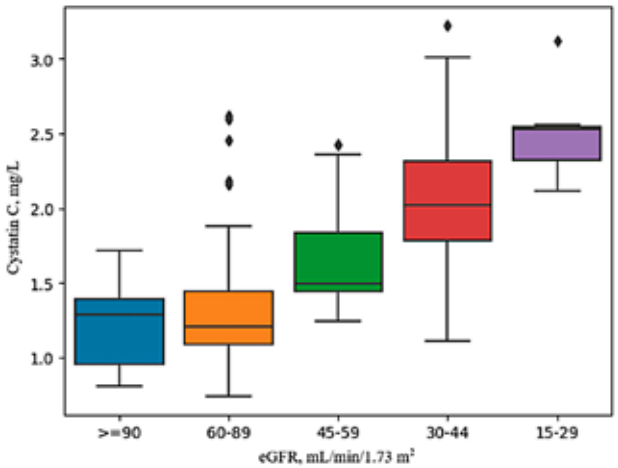


Fig. 2. Galectin-3 levels depending on eGFR, p<0.001



Unlike NT-proBNP concentration, showing no significant difference across the subgroups (p=0.123), galectin-3 and cystatin C levels increased significantly with worsening renal dysfunction (p<0.001).

Correlation analysis revealed moderate positive correlations between cystatin C level and CHF duration (r=0.325, p=0.0001), Kaplan-Feinstein comorbidity index (r=0.449, p<0.0001), Left ventricular myocardial mass index (LVMMI) (r=0.442, p<0.0001), NT-proBNP concentration (r=0.498, p<0.0001). Strong positive correlations were found between cystatin C and Creatinine levels (r=0.717, p<0.0001), Galectin-3 levels (r=0.777, p<0.0001). Significant negative correlations existed between cystatin C and 6MWT distance (r=–0.456, p<0.0001) and LVEF (r=–0.430, p<0.0001).

Galectin-3 concentration correlated with T2DM duration (r=0.371, p<0.0001), HF duration (r=0.323, p=0.00013), Kaplan-Feinstein comorbidity index (r=0.429, p<0.0001), 6MWT distance (r=-0.417, p<0.0001), uACR level (r=0.345, p<0.0001), Creatinine level (r=0.603, p<0.0001), eGFR (r=-0.490, p<0.0001), LVEF (r=-0.363, p<0.0001), LVMMI (r=0.361, p<0.0001), E/e' ratio (r=0.519, p<0.0001), NT-proBNP level (r=0.533, p<0.0001). As the analysis reveals, markers reflecting diverse processes within the complex pathogenesis of CHF in comorbid patients, and parameters of functional status, target organ damage severity, and duration of risk factor exposure, are closely associated.

Using point-biserial correlation, a significant association was established between the severity of prior COVID-19 and levels of the studied biomarkers: NT-proBNP (r=0.238, p=0.005), galectin-3 (r=0.371, p<0.0001), and cystatin C (r=0.279, p=0.001). The stronger correlation of prior COVID-19 severity with galectin-3 concentration may be attributed to patients' initially more severe clinical status or consequences of the infectious process.

During the period of observation, CEP events occurred in 54 patients (40%): 3 (2.2%) patients died from cardiovascular causes, 23 (17.03%) patients were hospitalized due to CHF decompensation, 28 (20.74%) patients required outpatient medication adjustment for worsening HF symptoms. Assessment of CEP cases revealed that adverse outcomes occured more frequently in patients with higher baseline functional impairment, higher Kaplan-Feinstein comorbidity index (16.0 points [15.0, 18.0] compared to 14.0 points [11.0, 15.0] in patients without CEP, p<0.001; Table 2), more pronounced cardiorenal dysfunction. Moreover, 41 patients (75.93%) who experienced CEP had a CHF hospitalization within the 12 months prior to the study, compared to 28 patients (34.57%) in the non-CEP subgroup, p<0.001.

Table 2. **Baseline characteristics of patients stratified by composite endpoint occurrence**

Parameter	No CEP (n=81)	CEP (n=54)	p-value
Age, years	70 (61; 73)	71 (65; 75)	0.16
Male, n (%)	33 (40.74)	31 (57.41)	0.04
CHF duration, years	4 (2; 6)	7 (5; 12)	<0.001
T2DM duration, years	10 (9; 17)	14 (11; 19)	0.002
CKD duration, years	2 (1; 3)	3 (2; 4)	<0.001
BMI, kg/m^2	31.38 (29.94; 34.09)	31.51 (29.07; 35.02)	0.59
ShOKS, points	5 (4; 6)	7 (6; 8)	<0.001
6MWT, m	380 (325; 405)	290 (269; 365)	<0.001
Creatinine, μmol	98.0 (82.5; 122.0)	108.7 (96.0; 134.0)	0.003
uACR, mg/g	122.3 (66.0; 263.0)	263.0 (75.0; 526.0)	0.007
NT-proBNP, pg/mL	512 (410; 746)	897 (690; 1112.0)	<0.001
galectin-3, ng/mL	10.5 (8.74; 12.3)	14.94 (11.4; 17.01)	<0.001
Cystatin C, mg/L	1.4 (1.16; 1.79)	2.02 (1.53; 2.41)	<0.001
Comorbidities, n (%)			
CHD	57 (70.37)		
Myocardial infarction in medical history	16 (19.75)	46 (85.19)	0.04
Atrial fibrillation	21 (25.93)	25 (46.3)	0.001
		29 (53.7)	0.001
Obstructive sleep apnea	3 (3.7)	7 (12.96)	0.04
LVEF, %	54 (52; 57)	53 (51; 56)	0.03
Left atrial volume index, mL/m^2	34.67 (34.17; 35.6)	36.96 (35.1; 45.26)	<0.001
LVMMI, g/m^2	139.25 (116.96; 153.45)	151.03 (132.53; 164.19)	0.001
E/e`	14.18 (10.6; 15.6)	16.48 (15.26; 17.79)	<0.001

When assessing the prognostic significance of NT-proBNP, cystatin C, and galectin-3, the markers were tested in ROC analysis. The area under the

Table 3. **Prognostic characteristics of investigated markers in univariate analysis**

Parameter	AUC	95%CI	Threshold	Sensitivity, %	Specificity, %	p
NT-proBNP, pg/mL	0.787	0.633–0.942	897.0	82.5	73	<0.001
Cystatin C, mg/L	0.788	0.634–0.945	1.683	83.3	73.6	<0.001
galectin-3, ng/mL	0.791	0.637–0.949	13.08	84.1	72.7	<0.001

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curve (AUC) was 0.787, 0.788, and 0.791, respectively. Marker levels above established cut-off values – NT-proBNP: 897 pg/mL (relative risk (RR) = 4.523, 95 % confidence interval (CI): 3.277–5.77; p<0.001), cystatin C: 1.683 mg/L (RR=6.428, 95 % CI: 5.735–7.122; p<0.001), galectin-3: 13.08 ng/mL (RR=3.214, 95 % CI: 2.103–4.325; p<0.001) identified patients as having an elevated CEP risk (Table 3).

Using multivariate logistic regression analysis, baseline mathematical Model 1 was constructed to predict the probability of HF decompensation and CVD, incorporating the ShOKS score, stroke volume (SV), LVMMI, E/e' ratio, and NT-proBNP concentration (Table 4). The resulting model demonstrated high prognostic value (AUC = 0.856; 95 % CI: 0.717–0.994; p<0.001; sensitivity 85.6 %, specificity 79.2 %) (Fig. 4).

Table 4. **Risk factors for HF decompensation in multivariate regression models (Models 1, 2)**

Parameter	Model 1 (AUC=0.856; p<0.001)		Model 2 (AUC=0.867; p<0.001)	
	OR (95 %CI)	p-value	OR (95 %CI)	p-value
NT-proBNP	1.01 (1.00–1.02)	0.001	1.01 (1.00–1.02)	<0.001
ShOKS	1.06 (0.77–1.46)	0.335	1.01 (0.72–1.41)	0.933
SV (Stroke volume)	0.98 (0.94–1.02)	0.929	0.99 (0.95–1.03)	0.73
LVMMI	0.96 (0.94–0.99)	0.045	0.96 (0.93–0.99)	0.01
E/e`	1.14 (0.97–1.34)	0.194	1.09 (0.91–1.29)	0.311
Cystatin C	No data	No data	2.52 (0.78–8.09)	0.199

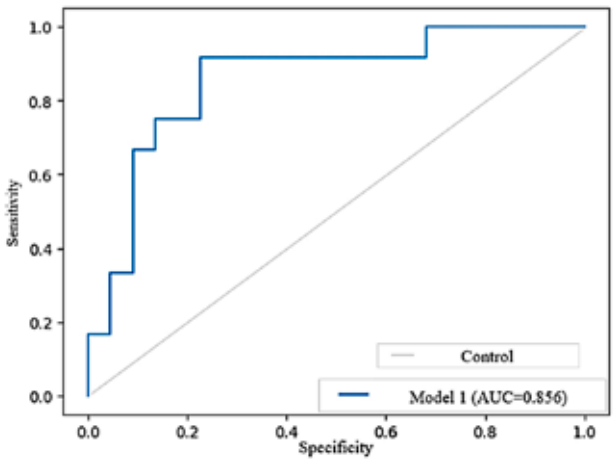

Fig. 4. ROC curve for baseline Model 1 including NT-proBNP

When assessing the prognostic capability of the studied biomarkers, cystatin C and galectin-3 concentrations were sequentially added to the baseline model and the performance of the resulting models was analyzed. Incorporating cystatin C into the original model (Model 2) improved the prognostic properties of Model 1, increasing the area under the ROC curve (AUC=0.867; 95 % CI: 0.808–0.923, p<0.001; sensitivity 86.3 %, specificity 75 %) (Fig. 5, Table 4).

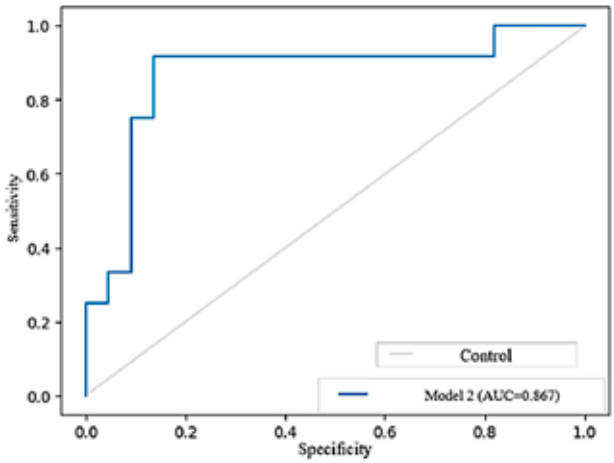

Fig. 5. ROC curve for Model 2 including NT-proBNP and cystatin C

Model 3, which included galectin-3 concentration (AUC=0.866; 95 % CI: 0.809–0.923, p<0.001; sensitivity 84.9 %, specificity 83.3 %), demonstrated a larger AUC compared to baseline Model 1 but did not significantly differ in prognostic significance from the model containing cystatin C (Fig. 6, Table 5).

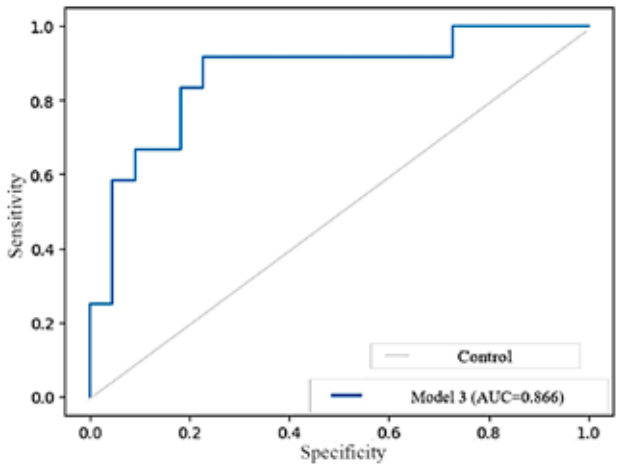

Fig. 6. ROC curve for Model 3 including NT-proBNP and galectin-3

The inclusion of all studied biomarkers further improved the predictive properties of the model (AUC=0.879; 95 % CI: 0.845–0.913, p<0.001; sensitivity 87.5 %, specificity 88.8 %) (Fig. 7, Table 5).

Thus, compared to the baseline model incorporating NT-proBNP concentration, the addition of cystatin C

Table 5. **Risk factors for HF decompensation in multivariate regression models (Models 3, 4)**

Parameter	Model 3 (AUC=0.866; p<0.001)		Model 4 (AUC=0.879; p<0.001)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
NT-proBNP	1.01 (1.00–1.02)	0.01	1.01 (1.0–1.02)	0.004
ShOKS	1.07 (0.77–1.49)	0.647	1.01 (0.7–1.43)	0.966
SV	0.98 (0.94–1.02)	0.516	0.99 (0.95–1.03)	0.74
LVMMI	0.96 (0.93–0.99)	0.016	0.96 (0.94–0.99)	0.021
E/e`	1.08 (0.9–1.3)	0.363	0.99 (0.83–1.18)	0.965
Galectin-3	1.1 (0.92–1.31)	0.26	1.14 (0.92–1.4)	0.21
Cystatin C	No data	No data	1.47 (0.35–6.13)	0.592

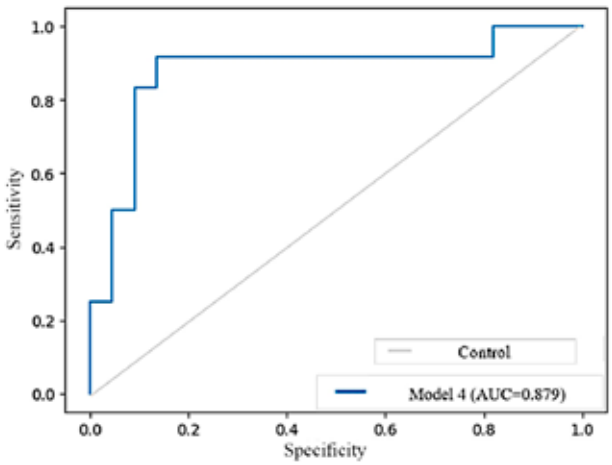

Fig. 7. ROC curve for Model 4 including NT-proBNP, cystatin C, and galectin-3

and/or galectin-3 enhances the predictive capability for assessing the risk of HF decompensation and CVD in post-COVID-19 patients with HFpEF, T2DM, and CKD.

Discussion

The comprehensive algorithm for HF patients' diagnosis and treatment efficacy evaluation involves the use of biomarkers and EchoCG data. Extensive evidence has established NT-proBNP as a reference-standard biomarker in HF [13]. Study results confirmed the reasonably high prognostic value of NT-proBNP (ROC AUC=0.787; 95% CI 0.633–0.942, p<0.001) in HFpEF patients with cardiovascular disease, T2DM, CKD, and a history of COVID-19. The biomarker was a significant predictor in the multivariate model (p=0.001).

Given the scarcity of studies evaluating long-term prognosis using markers reflecting different aspects of HFpEF pathogenesis in patients with T2DM and CKD after COVID-19, this work investigated the prognostic influence of established markers such as cystatin C and galectin-3 in comorbid HFpEF patients.

The study revealed correlations of varying strength between cystatin C levels and cardiac structural and functional parameters, indicating a close connection of cardiorenal dysfunction in HFpEF and CKD patients. The observed increase in cystatin C concentration corresponding to declining eGFR levels and severity of prior COVID-19 likely reflects more severe renal impairment and inflammation. In previous studies, cystatin C has proven to be an ideal marker for GFR, with its levels also associated with acute kidney injury and inflammatory status severity during the COVID-19 pandemic [4, 14, 15]. Elevated cystatin C in COVID-19 patients alongside reduced GFR may result from its involvement in the release of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-12 (IL-12), interleukin-10 (IL-10), and nitric oxide (NO) [16]. Cystatin C activates the inducible isoform of nitric oxide synthase (iNOS), which generates higher NO concentrations compared to endothelial NOS (eNOS) and neuronal NOS (nNOS) during local and systemic inflammatory responses. This leads to the formation of highly reactive derivatives that cause irreversible alterations in intracellular structures and cellular apoptosis. This process represents one of the pathophysiological mechanisms underlying cytokine storm development and severe COVID-19 progression [17–19].

In prognostic assessment, cystatin C demonstrated predictive capability for the CEP development comparable to NT-proBNP. The established cystatin C cut-off value of ⩾1.683 mg/L in the univariable model identified high-risk individuals for HF decompensation and CVD among clinically stable HFpEF patients with T2DM and CKD after COVID-19. Adding this biomarker to baseline parameters, which included NT-proBNP, improved prediction accuracy. Previous studies associated cystatin C levels >0.80–1.6 mg/L with increased mortality risk [20–22]. The higher cut-off value observed in this study may reflect the more severe clinical profile of our patient cohort.

In this study, galectin-3, being a biomarker of inflammation and fibrosis, exhibited correlations with T2DM duration, HF duration, patient comorbidity burden and functional status, left ventricular remodeling and diastolic dysfunction parameters, NT-proBNP levels, renal dysfunction markers (ACR, creatinine, and eGFR). Prolonged systemic exposure to risk fac-

tors evidently activates proinflammatory processes, oxidative stress, and fibrosis in target organs, leading to progressive functional decline. Similar but stronger correlations were reported in a Turkish study of HFpEF patients, where galectin-3 correlated with NT-proBNP (r=0.90, p<0.0001), left atrial volume index (r=0.75, p=0.0001), LVMMI (r=0.86, p=0.0001), E/e' ratio (r=0.80, p=0.0001) [23]. A weaker galectin-3/NT-proBNP correlation (r=0.21, p=0.048) was observed in another HFpEF cohort [24]. Association between galectin-3 and LV diastolic dysfunction was documented in HFpEF patients with ST-segment elevation myocardial infarction as well [25]. The observed link between galectin-3 and renal impairment severity aligns with prior research [8]. Impaired renal clearance, particularly in patients with kidney dysfunction, is presumed to contribute to elevated galectin-3 in HF [26].

In this study, a galectin-3 level ⩾13.08 ng/mL (sensitivity 84.1%, specificity 72.7%, p<0.001) was associated with increased risk of the CEP. Previous studies also established statistically significant associations between galectin-3 and mortality in CHF patients [27]. Elevated galectin-3 levels were linked to worse outcomes regardless of treatment or NT-proBNP concentration [28]. Furthermore, in patients from CHF-risk groups, galectin-3 independently predicted HF development and 10-year mortality [29].

Model 4, which incorporated NT-proBNP, cystatin C, and galectin-3 in addition to baseline parameters, demonstrated the strongest predictive performance. Multimarker risk assessment for HF decompensation and CVD enhanced model performance, increasing the ROC AUC to 0.879 (p<0.001). Thus, biomarkers reflecting core pathophysiological mechanisms of cardiorenal interactions in post-COVID-19 HFpEF patients with T2DM and CKD enable precise identification of high-risk individuals, facilitating timely therapeutic management for subclinical disease control and prevention of potential complications.

Conclusion

Analysis of this HFpEF cohort with T2DM and CKD demonstrated that measuring cystatin C and galectin-3 alongside NT-proBNP enhances risk stratification, addressing the urgent unmet need for more precise prediction tools for HF decompensation and CVD in comorbid post-COVID-19 patients. These findings reveal the potential clinical utility of inflammation and fibrosis biomarkers in comorbid HFpEF populations. Prospectively, serial monitoring of cystatin C and galectin-3, particularly, in post-COVID patients, combined with multimarker assessment would provide refined prognostic insights and enable therapy efficacy evaluation. Extended follow-up of comorbid HFpEF patients using biomarkers reflecting diverse pathophysiological pathways, alongside developing specialized diagnostic and prognostic panels, may facilitate timely treatment correction. The stronger association between galectin-3 levels and COVID-19 severity warrants further investigation for objectively assessing post-infectious sequelae in critically ill patients.

Conflict of interest: none declared.

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