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Original Article

Cardiovascular-renal-metabolic syndrome in patients with chronic heart failure

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Abstract

Cardiovascular-kidney-metabolic syndrome (CKMS) is characterized by a vicious cycle where each pathogenic link exacerbates the others, contributing to progressive deterioration in cardiac function, renal performance, and metabolic stability. The study aimed to assess kidney, heart, and metabolic functions in chronic heart failure (CHF) patients and examine these characteristics in dependence on endogenous intoxication severity. A number of 110 CHF patients (main group, MG) and 90 patients without CHF (control group, CG) were studied. The MG had a median age of 69.9 years, with 74.5% male patients. Echocardiographic parameters, renal function markers, and endogenous intoxication indices were measured. CKMS subgroups were stratified by estimated glomerular filtration rate (eGFR): GFR1 (>90 mL/min/1.73 m^2), GFR2 (60–90 mL/min/1.73 m^2), and GFR3 (<60 mL/min/1.73 m^2). MG patients exhibited significantly higher serum creatinine (97.7 µmol/L *versus* 72.8 µmol/L) and urea levels (7.1 mmol/L *vs.* 5.3 mmol/L), alongside lower eGFR (67.1 *vs.* 87.0 mL/min/1.73 m^2) compared to CG (p<0.006). Survival analysis revealed a cumulative event-free survival rate of 60.8% in patients with eGFR <60 mL/min/1.73 m^2 *vs.* 75.2% in those with eGFR >90 mL/min/1.73 m^2 (p=0.04). Structural heart abnormalities, including reduced left ventricular ejection fraction and increased left ventricle end-diastolic diameter, correlated with declining eGFR levels. Body mass index was inversely related to eGFR and positively associated with adverse cardiac remodeling, hypertension, and metabolic dysregulation. Patients with eGFR <60 mL/min/1.73 m^2 demonstrated more severe lipid abnormalities and systemic inflammation, reflected in elevated fibrinogen and middle-mass molecules. CKMS in CHF patients is characterized by impaired renal filtration, metabolic instability, and cardiac dysfunction. These changes correlate with systemic inflammation and endogenous intoxication, underscoring the need for integrated therapeutic strategies targeting these interrelated pathologies.

Keywords: cardiovascular-renal-metabolic syndrome, chronic heart failure, eGFR, endogenous intoxication, systemic inflammation

Introduction

In 2023, researchers introduced the concept of cardiovascular-kidney-metabolic syndrome (CKMS), a systemic disorder arising from the interplay of metabolic risk factors, chronic kidney disease, and cardiovascular disorders. CKMS can lead to multi-organ dysfunction and adverse cardiovascular outcomes [1–3]. CKMS is characterized by a vicious cycle where each pathogenic link worsens the others, contributing to a progressive decline in cardiac function, renal performance, and metabolic stability, ultimately resulting in a poorer prognosis [4].

The study aims to assess the functional status of the kidneys, heart, and metabolic background in patients with chronic heart failure (CHF) and analyze

their characteristics in dependence on the severity of endogenous intoxication.

Material and methods

In compliance with the Helsinki Declaration on Human Rights, 110 patients with CHF (main group, MG) and 90 patients without CHF (control group, CG) were included in the study. Patient management followed national standards and international guidelines. Inclusion criteria: CHF of I-IV functional class (FC), additional informed consent for extended examinations spectrum, absence of exclusion criteria (acute infections and exacerbations of chronic inflammatory processes, oncology, severe hepatic failure, grade 3 arterial hypertension (AH), decompensated type 2 diabetes (T2D), systemic and autoimmune disorders, pregnancy, lactation, psychiatric changes, poor compliance). 74.5% of MG patients were male, and 25.5% were female; the median age was 69.9 years. CHF FC distribution in the MG was as follows: I – 11.82%, II – 41.82%, III – 33.64%, and IV – 12.72%. Causes of CHF included ischemic heart disease (90.0%), dilated cardiomyopathy (7.8%), and chronic rheumatic heart disease with valvular defects (2.7%). Cardiac rhythm disorders were detected in 58.2% of cases (atrial fibrillation – in 35.4%). In the CG, the median age was 45 years, and 35% of the patients were female. Renal function parameters, structural and functional heart parameters, and endogenous intoxication indices were evaluated (Table 1).

Cardiac geometry was estimated according to the European Society of Cardiology guidelines [5]. Based on the estimated glomerular filtration rate (eGFR), MG patients were divided into three comparable subgroups: GFR1 (n=34) with eGFR >90 mL/min/1.73 m^2, median age 67 [44; 75] years; GFR2 (n=29) with moderately reduced eGFR (60–90 mL/min/1.73 m^2), median age 74 [66; 80] years; and GFR3 (n=47) with reduced GFR (<60 mL/min/1.73 m^2), median age 73.5 [69; 81] years; all p>0.05.

Lipid metabolism was evaluated using total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C). Reagents produced by "Human" (Germany) and a biochemical analyzer Stat Fax 1940 Plus (USA) were used. Additionally, the atherogenic coefficient (AC = (TC–HDL-C)/HDL-C) and ratios of TG/HDL-C, VLDL-C/TC, TC/TG, and VLDL-C/LDL-C were calculated. Body mass index (BMI) was calculated by dividing weight by the square of height. GFR was estimated using the Cockroft-Gault formula. Fasting glucose was measured using a standard method to screen carbohydrate metabolism. The activity of the endogenous intoxication syndrome (EIS) was assessed by measuring middle mass molecules (MMM) in blood and urine spectrophotometrically at wavelengths of 238, 254, 260, and 280 nm (MMM238, 254, 260, 280). Blood arginine was estimated by the reaction with α-naphthol (CG: 19.84±0.4 μg/ml), and urinary nitrites were measured photometrically (CG: 0.85±0.08 μmol/l). Four hematological indices were additionally calculated, namely, nuclear intoxication index [NII; NII = (monocytes + juvenile neutrophils + band neutrophils) / segmented neutrophils (normal value: 0.05–0.08)], leukocyte shift index LSI; LSI = (eosinophils + basophils + segmented neutrophils + band neutrophils + juvenile neutrophils + myelocytes) / (monocytes+lymphocytes) (normal value: 1.8–2.15), neutrophil-to-lymphocyte ratio (NLR), and neutrophil-to-monocyte ratio (NMR).

Statistical analysis was conducted using parametric methods for Gaussian-distributed data (M±m;

Table 1: Average echocardiographic parameters in the main and control groups (M±m).

Parameter, units	Main group	Control group	p
EF, %	46.7±1.7	56.6±1.2	0.00001
LVEDD, cm	5.76±0.11	4.72±0.51	>0.05
LA, cm	4.49±0.11	3.71±0.14	0.00001
LVWT, cm	1.35±0.03	0.91±0.04	0.00001
IVST, cm	1.37±0.03	0.88±0.02	0.00001
RVEDD, cm	2.72±0.08	2.21±0.07	0.00001
Aorta, cm	4.09±0.53	3.10±0.10	>0.05

Note: EF – ejection fraction; LVEDD – left ventricle end-diastolic diameter; LA – left atrium; LVWT – left ventricle wall thickness; IVST – interventricular septum thickness; RVEDD – right ventricle end-diastolic diameter.

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differences estimated by Student's t-test) and non-parametric methods (median [lower; upper quartile]; differences estimated by Mann-Whitney U-test) for non-Gaussian distributions. Correlation analysis was performed using Kendall's τ. A two-sided P value of 0.05 was used to determine the significance of the composite outcome. The prognosis was assessed by Kaplan-Meier analysis, with significance evaluated by Cox's F-test ($p<0.05$). Events were defined as rehospitalization due to CHF decompensation or patient death.

Results

Evaluation of the renal component of CKMS demonstrated that patients in the MG exhibited changes in renal function, evidenced by significantly higher creatinine levels (97.7 [73.0; 140.0] *vs.* 72.8 [68.3; 78.4] μmol/L) and urea levels (7.1 [5.6; 8.8] *vs.* 5.3 [4.2; 6.3] mmol/L, both $p<0.00001$) together with lower eGFR (67.1 [47.6; 89.5] *vs.* 87.0 [80.0; 89.1] ml/min/1.73 m^2; $p<0.006$). Preserved eGFR was observed in 30.9% of MG patients, moderately reduced eGFR (60–90 ml/min/1.73 m^2) – in 26.4%, which was significantly less frequent than low eGFR levels (<60 ml/min/1.73 m^2) – 42.7% ($p=0.01$).

Renal function was critical for prognosis, as the cumulative event-free survival in patients with low eGFR (<60 ml/min/1.73 m^2) was 60.8%, which was significantly lower than 75.2% in patients with eGFR >90 ml/min/1.73 m^2 (Cox F-test $p=0.04$). The observed poorer prognosis in the case of low eGFR may also be explained by a 6.7-fold higher incidence of severe CHF (21.7% *vs.* 3.2%, $p=0.007$) (Figure 1).

Cardiovascular component of CKMS

CHF FC and the structural and functional cardiac characteristics were associated with eGFR. In the GFR1 subgroup, CHF FC IV was significantly less common than other FCs. In these patients, CHF FC II was most frequently observed (42.0±8.9%), significantly more often than FC IV (3.2±3.1%, $p=0.0001$). In the GFR2 subgroup, CHF FC II was also the most frequent (40.0±8.9%), significantly more often compared to FC I and FC IV (13.3±6.2% each, both $p=0.02$).

In patients with significantly reduced eGFR, the prevalence of severe CHF was the highest, considerably exceeding that of FC I (21.7±6.1% *vs.* 2.2±2.1%, $p=0.003$) and compared to the GFR1 subgroup (3.2±3.1%; $p<0.05$). Thus, as eGFR declined, the frequency of severe CHF increased.

Myocardial contractility was also related to eGFR. The median left ventricular ejection fraction (LVEF) decreased progressively with declining eGFR: in patients with preserved eGFR, the LVEF median was 59.2 [51.5; 64.5]%, in those with reduced eGFR – 45.0 [30.0; 56.0]% ($p=0.03$), and in patients with very low eGFR, it was the lowest – 40.5 [28.0; 51.0]% ($p=0.0003$).

In the GFR1 subgroup, preserved LVEF was significantly more common (82.6±7.9%) than systolic dysfunction (17.4±7.9%, $p=0.00001$). In comparison to GFR1, substantial eGFR reduction was accompanied by significantly smaller interventricular septum thickness (IVST; 1.3 [1.2; 1.4] *vs.* 1.5 [1.3;1.7] cm; $p=0.03$), relative IVST (RIVST; 0.42 [0.35; 0.51] *vs.* 0.53 [0.46; 0.6]; $p=0.03$), and left ventricle relative posterior wall thickness (LVRPWT; 0.42 [0.35; 0.48] *vs.* 0.52 [0.42; 0.57];

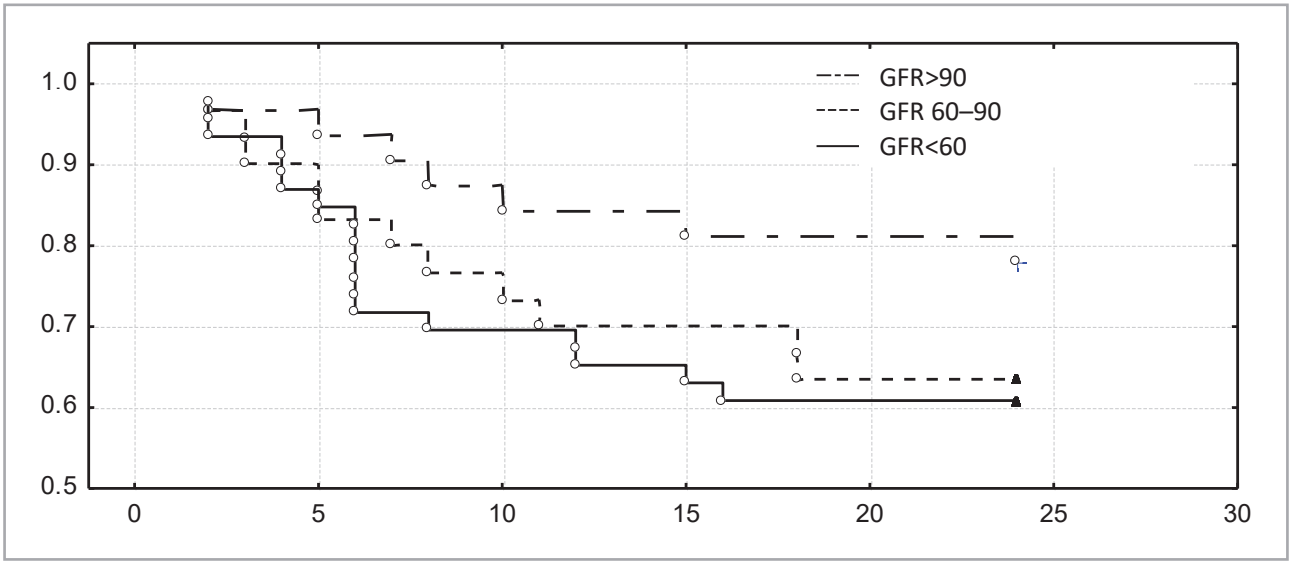

Figure 1: Survival curves of CHF patients during 24 months of follow-up depending on eGFR.

Table 2: Prevalence of different LV geometry types in patients with different eGFR Levels (%; M±m).

LV geometry type	GFR1	GFR 2	GFR 3
Concentric remodeling	21.4±10.9 [1, 2, 3]	9.1±8.7 [2]	0±0 [8]
Concentric hypertrophy	57.2±13.2 [1, 4, 5, 6, 7]	45.4±15.0 [3, 6]	33.3±19.2
Eccentric hypertrophy with dilatation	21.4±10.9 [4, 10]	36.4±14.5	66.7±19.2 [8, 9, 10]
Isolated posterior LV wall hypertrophy	0±0 [5]	9.1±8.7 [7]	0±0 [9, 5]

Note: [1–10] – the difference is significant (p<0.05).

p=0.02), along with pronounced LV dilation (left ventricle end-diastolic volume, LVEDD; 6.1 [5.4; 6.6] *vs.* 5.3 [5.0; 6.2] cm; p=0.02).

In the GFR3 subgroup, the frequency of increased LVEDD was 1.7-fold higher than in GFR1 (65.2±7.0% *vs.* 38.1±8.4%, p=0.05).

Analysis of LV geometry types revealed that the prevalence of various remodeling patterns also depended on eGFR (Table 2). As eGFR declined, the frequency of concentric remodeling and hypertrophy decreased while the frequency of eccentric LV hypertrophy increased.

The metabolic component of CKMS

It was established that patients of the GFR3 subgroup had a significantly lower BMI compared to those in the GFR1 subgroup (26.0 [24.2; 30.1] *vs.* 28.2 [25.1; 32.8] kg/m^2, p=0.03). Correlation analysis revealed that an increase in BMI was associated with a deterioration of the cardiac component of CKMS. This deterioration manifested as AH (both systolic and diastolic), tachycardia, and myocardial hypertrophy (increase of interventricular septum thickness, posterior LV wall thickness, and their relative values). These patients also were characterized by impaired lipid metabolism (evaluated by TG/HDL-C, VLDL-C/TC, TC/TG, and VLDL-C/LDL-C ratios) and a higher prevalence of T2DM (Table 3).

These findings were also supported by absolute data. Indeed, patients of the GFR3 subgroup exhibited the most pronounced proatherogenic lipid changes, characterized by a reduction in HDL-C levels (38.6 [32.1; 50.0] *vs.* 46.4 [41.7; 59.9] mg/dL in the GFR1 subgroup, p=0.006). This reduction was accompanied by a tendency toward hypercoagulation based on the prothrombin index (86.0 [80.0; 90.0]% *vs.* 90.0 [85.0; 96.8]% in the GFR1 subgroup, p=0.04).

Additionally, an increase in BMI was associated with the activation of systemic inflammation syndrome (as indicated by elevated total fibrinogen and band neutrophil count in blood samples) and endogenous intoxication (reflected by elevated urine MMM levels) (Table 3).

Given these findings, we evaluated the main parameters of EIS in dependence of eGFR levels. It was determined that MMM levels were significantly higher in patients with reduced GFR (0.74 *vs.* 0.60 and 0.57 units, p_{2-3}=0.04, p_{1-3}=0.005). Patients in the GFR3 subgroup demonstrated substantially higher blood MMM_{260} and MMM_{280} levels compared to those in the GFR1 subgroup. Urine MMM levels were similar across groups, except for the MMM_{310} level, which was significantly higher in the GFR3 subgroup compared to the GFR2 subgroup.

The GFR3 subgroup was further characterized by the highest urinary nitrate levels and calculated hematologic indices, including LSI, NLR, and NMR, while the NII index was the lowest (Table 4). Consequently, in parallel to the decrease in eGFR, levels of MMM, LSI, NLR, NMR, and nitrites increased, indicating a greater degree of EIS severity and endothelial dysfunction.

Discussion

Our findings underscore the systemic integrity of CKMS. This syndrome originates from adipose tissue excess and dysfunction (abdominal obesity), leading to the hypersecretion of pro-inflammatory and pro-oxidative products. These products, in turn, disrupt arterial, cardiac, and renal functioning [6], promote atherogenesis, myocardial injury, glomerulosclerosis, inflammation of renal glomeruli, renal fibrosis, and activation of the renin-angiotensin-aldosterone system [7, 8].

We confirmed strong correlations between renal function and cardiac structure and function, with a clear progressive decline in LV systolic function in parallel to eGFR decrease. This finding highlights new opportunities for further research in the emerging field of nephrocardiology [9]. The higher mortality rate

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Table 3: Significant correlations between BMI and clinical parameters in CHF patients of MG.

The second correlation component		τ	p
BMI	T2DM	0.2	0.01
	Heart rate	0.2	0.02
	Systolic pressure	0.2	0.01
	Diastolic pressure	0.3	0.005
	Fibrinogen	0.3	0.005
	Band neutrophils	0.5	0.003
	De Ritis ratio	-0.2	0.01
	Interventricular septum thickness	0.4	0.002
	Left ventricle posterior wall thickness	0.4	0.001
	LVRWT	0.4	0.002
	IVSRT	0.4	0.003
	LVPWRT	0.3	0.01
	TG/HDL-C	0.3	0.004
	VLDL-C/TC	0.3	0.0004
	TC/TG	-0.2	0.009
	VLDL-C/LDL-C	0.3	0.0005
	MMM_{288} in urine	0.2	0.03

Note: LVRWT – left ventricle relative wall thickness; IVSRT – interventricular septum relative thickness; LVWRT – left ventricle posterior wall relative thickness.

Table 4: Indicators of endogenous intoxication in accordance with eGFR.

Parameter, units		GFR1	GFR2	GFR3	p_{1-3}	p_{2-3}	p_{1-2}
MMM, units		0.57 [0.43; 0.71]	0.60 [0.43; 0.90]	0.74 [0.58; 1.02]	0.005	0.04	>0.05
MMM in blood	238	1.5 [0.5; 2.1]	1.6 [0.7; 2.1]	1.8 [1.4; 2.2]	>0.05	>0.05	>0.05
	254	0.6 [0.3; 0.9]	0.8 [0.5; 1.2]	0.8 [0.5; 1.4]	>0.05	>0.05	>0.05
	260	0.5 [0.2; 0.8]	0.8 [0.5; 0.9]	0.8 [0.5; 1.2]	**0.04**	>0.05	>0.05
	280	0.5 [0.2; 0.8]	0.8 [0.4; 1.1]	0.9 [0.5; 1.3]	**0.02**	>0.05	>0.05
MMM in urine	238	2.2 [1.8; 2.4]	2.2 [1.8; 2.4]	2.2 [2.0; 2.5]	>0.05	>0.05	>0.05
	254	1.9 [1.8; 2.1]	2.0 [1.9; 2.1]	1.9 [1.9; 2.2]	>0.05	>0.05	>0.05
	266	1.1 [0.7; 1.4]	1.3 [0.9; 1.5]	1.4 [0.9; 2.1]	>0.05	>0.05	>0.05
	282	0.7 [0.5; 1.2]	0.8 [0.5; 1.0]	0.8 [0.5; 1.1]	>0.05	>0.05	>0.05
	288	0.6 [0.4; 1.1]	0.6 [0.4; 0.8]	0.7 [0.5; 1.8]	>0.05	>0.05	>0.05
	310	0.14 [0.04; 0.25]	0.14 [0.09; 0.22]	0.27 [0.14; 0.47]	>0.05	**0.03**	>0.05
L-arginine, mcg/mL		9.0 [6.1; 10.6]	8.6 [5.2; 12.0]	8.2 [5.6; 11.5]	>0.05	>0.05	>0.05
Urine nitrites, mcmol/L		0.28 [0.14; 0.42]	0.48 [0.36; 0.98]	0.52 [0.44; 0.74]	**0.01**	>0.05	**0.04**
NII		0.15 [0.13; 0.18]	0.18 [0.15; 0.28]	0.10 [0.08; 0.13]	**0.0001**	**0.005**	>0.05
LSI		2.1 [1.7; 2.6]	2.3 [1.5; 2.7]	2.7 [2.2; 3.8]	**0.002**	>0.05	>0.05
NLR		2.3 [2.0; 3.4]	3.0 [2.2; 3.8]	3.9 [2.5; 5.4]	**0.03**	>0.05	>0.05
NMR		8.8 [6.5; 12.7]	8.0 [6.78; 9.2]	11.9 [9.3; 22.3]	**0.03**	>0.05	>0.05

associated with a low eGFR (<60 mL/min/1.73 m^2) has been well-documented in the literature [10].

The observed increase in the prevalence of severe CHF in parallel to eGFR decline aligns with the perspectives of the American Heart Association (AHA). Their Task Force has identified eGFR as one of the key predictors of cardiovascular risk in the PREVENT (Prevention of Events with Vasculature in End-Stage Nephropathy Trial) framework [11].

Our results provide valuable insights into the interconnected pathophysiological mechanisms of CRMS and highlight the critical need for integrated management strategies targeting both renal and cardiovascular systems.

The reciprocal impact of renal dysfunction on the heart can be attributed to endogenous intoxication. It has been documented that an increase in creatinine levels with a reduction in eGFR, as well as a decreased uric acid-to-creatinine ratio, is associated with a higher risk of adverse events in older patients with acute myocardial infarction, particularly among men [12]. Additionally, a more frequent occurrence of CHF has been reported in patients with reduced eGFR (odds ratio: 2.49; 95% confidence interval: 2.01–3.08; p<0.001) [9]. These associations highlight the central role of mineralocorticoid receptor antagonists (MRAs) in the management of these patients [13, 14].

MRAs have a dual effect: they increase heart rate variability and improve the function of the sympathetic nervous system. However, they may also cause adverse effects such as gynecomastia and hyperkalemia [15], the latter potentially leading to or exacerbating arrhythmias [16], which is highly undesirable for cardiology patients.

Apart from that, the EIS activity is closely linked to carbohydrate and lipid metabolism, as described in patients with T2DM [17, 18]. Glycated molecules and lipid peroxidation products, classified as MMMs, exhibit nephron- and cardiotoxic properties [19], whereas excess body weight contributes to CHF development, myocardial dystrophic changes, a decrease of cardiac output, and enhanced endogenous intoxication [20, 21]. Obesity is associated with eccentric LV hypertrophy, often leading to acute myocardial infarction, sudden death, and heart failure decompensation, irrespective of arterial pressure [22].

Our findings confirm that in obese patients, increased BMI is associated with AH, tachycardia, myocardial wall hypertrophy, impaired lipid metabolism, and a higher prevalence of T2DM. These effects were even more pronounced in the subgroup with low eGFR, providing a pathogenic rationale for the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors [23]. According to the literature, SGLT2 inhibitors act in the proximal nephron tubules and improve myocardial energy metabolism, calcium balance, and oxygenation while reducing AH. They also enhance erythropoiesis. Favorable effects of SGLT2 inhibitors were demonstrated in large trials such as DECLARE-TIMI, CANVAS, and EMPA-REG OUTCOME [24]. Their diuretic effect makes them particularly beneficial for patients with CHF [25].

The integrative approach to treatment using SGLT2 inhibitors and MRAs helps to mitigate the complex interplay of renal, cardiac, and metabolic dysfunctions, offering substantial benefits in CRMS management.

Conclusion

Cardiovascular-renal-metabolic syndrome in patients with chronic heart failure is characterized by a significantly poorer prognosis and structural and functional cardiac impairments in the context of reduced renal filtration and increased body weight. These changes are closely associated with the activation of endogenous intoxication syndrome.

Prospects for further research include the study of CRMS in patients with another cardiovascular disease.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the Danylo Halytsky Lviv National Medical University (Approval ID: 217).

Consent to participate

Written informed consent was obtained from all the participants.

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