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Clinical Correlations of Biomarkers in Chronic Heart Failure Developed on the Background of Rheumatic Heart Disease

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Annotation: With the increase in life expectancy worldwide, the prevalence and incidence of chronic heart failure (CHF) and cardiovascular diseases (CVD) are also rising. It is well known that CHF and renal dysfunction frequently coexist as comorbid conditions, contributing to the development of adverse outcomes in the cardiovascular continuum and increasing mortality [202, 61, 36, 1]. CHF has a pronounced negative impact on renal and glomerular hemodynamics. In recent years, many literature reviews have emphasized the interrelationship between the heart and kidneys, described by the term "cardiorenal syndrome," which encompasses complex mechanisms of pathophysiological changes.

Keywords: CHF, KIM-1, cystatin C, ischemic heart disease (IHD), rheumatic heart defects, left ventricular ejection fraction, glomerular filtration.

Materials and Methods

The study involved 60 patients diagnosed with renal dysfunction associated with chronic heart failure (CHF) that developed against the background of rheumatic heart disease, and 40 patients with CHF of ischemic origin. All participants were treated at the cardiology and rheumatology departments of the Bukhara Multidisciplinary Medical Center in 2022–2023. All patients received standard therapy with the addition of a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor — empagliflozin. A control group of 20 healthy individuals was also examined.

Renal hemodynamics were assessed using Doppler ultrasound (RI — resistance index, PSV — peak systolic velocity, EDV — end-diastolic velocity). The following blood serum biomarkers were measured: KIM-1, cystatin C, α-TNF (alpha tumor necrosis factor), and IL-6. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI CysC formula. Left ventricular ejection fraction (LVEF) was assessed using Simpson's method via echocardiography. Pearson's correlation coefficient was used for statistical analysis.

Results

Indicators of Renal Hemodynamics Before the Start of Treatment in Chronic Heart Failure Developed Against the Background of Rheumatic Heart Disease and Ischemic Heart Disease

Table 1.

Doppler Ultrasound Parameters	Group 1 (Patients with CHF developed against the background of rheumatic heart disease), n=60	**Group 2 (Patients with CHF developed against the background of IHD and hypertension), n=40**	Control group (healthy individuals), n=20
Main renal artery			
PSV (cm/s)	68,4±3,4***	75,6±4,2**	97.8±5.7
EDV (cm/s)	17,6±1,1***	21,92±2,5*	34,3±3,8
RI	0,74±0,02*	0,71±0,03	0,65±0,03
Segmental artery			
PSV (cm/s)	57,6±2,2***	64,2±3,8***	84,4±4,3
EDV (cm/s)	8,9±1,0***###	15,4±1,3**	21,9±1,8
RI	0,84±0,03**#	0,79±0,02*	0,74±0,04
Interlobar artery			
PSV (cm/s)	49,5±1,1***###	54,2±0,8***	64,3±4,6
EDV (cm/s)	3,96±0,4**#	5,42±0,5*	14,1±3,4
RI	0,92±0,04**	0,90±0,03*	0,80±0,04

Note: PSV – systolic blood flow velocity, cm/sec; EDV – diastolic blood flow velocity, cm/sec; RI – resistance index. * - statistically significant difference compared to the control group: * - p<0,05., ** - p<0,01., *** - p<0,001., # - statistically significant difference compared to the second group: # - p<0,05., ## - p<0,01., ### - p<0,001.

As shown in the table, the peak systolic velocity (PSV) in the main renal artery among healthy individuals (control group) was 97.8 ± 5.7 cm/s, with segmental and interlobar arteries showing values of 84.4 ± 4.3 cm/s and 64.3 ± 4.6 cm/s, respectively. In patients with chronic heart failure (CHF) secondary to rheumatic heart disease, the corresponding PSV values were 68.4 ± 3.4 cm/s, 57.6 ± 2.2 cm/s, and 49.5 ± 1.1 cm/s. These parameters in the first group were significantly lower compared to the control group ($p < 0.001$).

In the second group, consisting of CHF patients with ischemic heart disease (IHD) and hypertension, PSV values were 75.6 ± 4.2 cm/s ($p < 0.01$), 64.2 ± 3.8 cm/s ($p < 0.001$), and 54.2 ± 0.8 cm/s ($p < 0.001$), respectively. A marked reduction in systolic blood flow velocity was observed across all renal arteries in both patient groups. No statistically significant difference ($p > 0.05$) in blood flow velocity was found between the two groups in the main and segmental arteries. However, a significant difference was noted in the interlobar arteries (49.5 ± 1.1 cm/s vs. 54.2 ± 0.8 cm/s, $p < 0.001$).

The primary underlying mechanism is thought to be not only venous congestion in the kidneys due to reduced left ventricular ejection fraction in CHF caused by rheumatic heart disease, but also a persistent inflammatory process associated with rheumatism itself.

The end-diastolic velocity (EDV) in healthy individuals across all renal arteries was 34.3 ± 3.8 cm/s. In the first group (CHF due to rheumatic heart disease), EDV in the main renal artery was 17.6 ± 1.1 cm/s; in the segmental artery — 8.9 ± 1.0 cm/s; and in the interlobar artery — 3.96 ± 0.4 cm/s. Significant differences from the control group were observed ($p < 0.001$).

In the second group (CHF due to IHD), these values were 21.92 ± 2.5 cm/s ($p < 0.05$), 15.4 ± 1.3 cm/s ($p < 0.01$), and 5.42 ± 0.5 cm/s ($p < 0.05$), respectively. When comparing the two patient groups, no significant difference was found in EDV of the main renal artery. However, statistically significant differences were identified in the segmental ($p < 0.001$) and interlobar arteries ($p < 0.05$).

The resistance index (RI) is one of the key Doppler parameters used to assess renal hemodynamics in patients with chronic heart failure (CHF). In CHF, activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system typically occurs, leading to increased systemic and renal vascular resistance. These changes result in vasoconstriction and, consequently, an elevation in renal vascular resistance.

In addition, elevated central venous pressure in CHF causes renal venous congestion, which affects the glomerular pressure gradient and contributes to an increased resistance index. These pathophysiological mechanisms, characteristic of CHF, collectively promote increased vascular resistance in the kidneys.

Monitoring the RI level is valuable for diagnosing renal insufficiency, guiding treatment strategies, and predicting the course of the disease in this patient population.

In our study, Doppler assessment of the renal arteries showed that the RI in the control group was 0.65 ± 0.03. In the first group (CHF due to rheumatic heart disease), the RI in the main renal artery was 0.74 ± 0.02, which was significantly different from that of healthy individuals ($p < 0.05$). In the second group (CHF associated with ischemic heart disease), the RI was 0.71 ± 0.03, showing no statistically significant difference compared to the control group ($p > 0.05$). Furthermore, no significant differences in RI values were observed between the two patient groups ($p > 0.05$).

In patients with CHF due to rheumatic heart disease, RI in the segmental and interlobar arteries was 0.84 ± 0.03 and 0.92 ± 0.04, respectively. Compared to the control group, these values were significantly elevated ($p < 0.01$). In the second group, RI in the segmental arteries was 0.79 ± 0.02, and in the interlobar arteries — 0.90 ± 0.03; both differed significantly from control values ($p < 0.05$).

Patients in the primary study group received standard CHF treatment, including empagliflozin — a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor — for six months. After the treatment course, renal hemodynamic parameters were reassessed via Doppler ultrasound. The results are presented in Table 2.

Table 2. Renal hemodynamic parameters after treatment in patients with chronic heart failure secondary to rheumatic heart disease and ischemic heart disease.

Doppler Parameters	**Group 1** (CHF due to Rheumatic Heart Disease), n=60		**Group 2** (CHF due to IHD and Hypertension), n=40	
	Before treatment	After treatment	Before treatment	After treatment
Main Renal Artery				
PSV (cm/s)	68,4±3,4	78,5±3,2*	75,6±4,2	82.4±3,6
EDV (cm/s)	17,6±1,1	23,6±1,8**	21,92±2,5	26,4±1.6

RI	0,74±0,02	0,70±0,03	0,71±0,03	0.68±0,01
Segmental artery				
PSV (cm/s)	57,6±2,2	70,5±2,6***	64,2±3,8	76,4±3,1*
EDV (cm/s)	8,9±1,0	16,9±1,1***	15,4±1,3	19,1±1,2*
RI	0,84±0,03	0,76±0,02*	0,79±0,02	0,75±0.03
Interlobar artery				
PSV (cm/s)	49,5±1,1	56,3±0,9***	54,2±0,8	60,5±1,0***
EDV (cm/s)	3,96±0,4	9,8±0,3***	5,42±0,5	10,89±0,6***
RI	0,92±0,04	0,825±0,03*	0,90±0,03	0,82±0,02*

Note: PSV – Peak Systolic Velocity (cm/s), EDV – End Diastolic Velocity (cm/s), RI – Resistive Index. *Statistical significance of differences compared to post-treatment values:* *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

As shown in the table, both groups demonstrated significant positive changes after the treatment. In the first group, the systolic blood flow velocity in the main renal artery increased from 68.4 ± 3.4 to 78.5 ± 3.2 cm/s (a 1.14-fold increase), with a statistically significant difference ($p < 0.05$). In the second group of patients with CHF secondary to coronary artery disease (CAD) and hypertension, the parameter improved by 1.04 times (from 75.6 ± 4.2 to 82.4 ± 3.6 cm/s), although the difference was not statistically significant ($p > 0.05$). The diastolic blood flow velocity in the first group significantly increased from 17.6 ± 1.1 to 23.6 ± 1.8 cm/s ($p < 0.01$), while in the second group it increased from 21.92 ± 2.5 to 26.4 ± 1.6 cm/s ($p > 0.05$). The resistance index (RI) improved by approximately 10% in both groups; however, the differences were not statistically significant ($p > 0.05$).

In the first group, systolic and diastolic blood flow velocities in the segmental arteries increased from 57.6 ± 2.2 to 70.5 ± 2.6 cm/s and from 8.9 ± 1.0 to 16.9 ± 1.1 cm/s, respectively. These differences were highly statistically significant ($p < 0.001$). The resistance index improved by 11%, decreasing from 0.84 ± 0.03 to 0.76 ± 0.02, with a significant difference ($p < 0.05$).

In the second group, post-treatment systolic velocity increased from 64.2 ± 3.8 to 76.4 ± 3.1 cm/s ($p < 0.05$), and diastolic velocity rose from 15.4 ± 1.3 to 19.1 ± 1.2 cm/s ($p < 0.05$). The resistance index decreased by 6% (from 0.79 ± 0.02 to 0.75 ± 0.03), although this change was not statistically significant ($p > 0.05$).

Systolic blood flow velocity in the interlobar arteries increased from 49.5 ± 1.1 to 56.3 ± 0.9 cm/s (1.13-fold) in the first group, and from 54.2 ± 0.8 to 60.5 ± 1.0 cm/s (1.11-fold) in the second group, with statistically significant differences ($p < 0.05$). Diastolic blood flow velocity increased in both groups: from 3.96 ± 0.4 to 9.8 ± 0.3 cm/s in the first group, and from 5.42 ± 0.5 to 10.89 ± 0.6 cm/s in the second group, with highly significant differences ($p < 0.001$).

The resistance index in patients with CHF due to rheumatic heart disease decreased from 0.92 ± 0.04 to 0.825 ± 0.03 (12% reduction), and in patients with CHF secondary to CAD and hypertension — from 0.90 ± 0.03 to 0.82 ± 0.02 (11% reduction). A statistically significant difference was found between the two groups ($p < 0.05$).

The observed beneficial effects can be attributed to the stabilizing influence of sodium-glucose cotransporter-2 (SGLT2) inhibitors on renal hemodynamics—not only through improvements in cardiac function and glucose metabolism, but also via reduction of glomerular edema and favorable modulation of the renin–angiotensin system. These pathophysiological processes collectively decrease vascular resistance and stabilize renal perfusion, manifesting as nephroprotective changes and improvement in renal biomarkers.

In chronic heart failure (CHF) secondary to rheumatic heart disease and ischemic heart disease, an analysis of the relationship between renal hemodynamics, glomerular function, and inflammatory markers revealed that, regardless of CHF etiology, systemic hypoxic and

inflammatory processes occur. Prolonged exposure to these processes in the kidney impairs nephron function and ultimately leads to renal dysfunction.

In the next phase of our study, we conducted a comparative correlation analysis between renal hemodynamic parameters, left ventricular ejection fraction, glomerular functional state, and inflammatory cytokines in patients with CHF secondary to rheumatic heart disease versus those with CHF secondary to ischemic heart disease. Table 3.3 presents the results obtained for patients with CHF due to rheumatic heart disease.

Table 3. Correlation coefficients between renal hemodynamics, left ventricular ejection fraction, glomerular functional indices, and inflammatory cytokines in chronic heart failure secondary to rheumatic heart disease.

		RI	PSV cm/s	EDV, cm/s
Left Ventricular Ejection Fraction	**Pearson Correlation**	-0.535**	0.388**	0.357**
	P	0.000	0.002	0.005
	N	60	60	60
KIM-1, pg/mL	**Pearson Correlation**	0.640**	-0.557**	-0.422**
	P	0.000	0.000	0.001
	N	60	60	60
Cystatin C, pg/mL	**Pearson Correlation**	0.575**	-0.417**	-0.358**
	P	0.000	0.001	0.005
	N	60	60	60
Tumor Necrosis Factor-Alpha (TNF-α), pg/mL	**Pearson Correlation**	0.372**	-0.313*	-0.203
	P	0.003	0.015	0.119
	N	60	60	60
nterleukin-6 (IL-6), pg/mL	**Pearson Correlation**	0.386**	-0.231	-0.093
	P	0.002	0.076	0.481
	N	60	60	60
Glomerular Filtration Rate (GFR)	**Pearson Correlation**	-0.486**	0.259*	0.232
	P	0.000	0.045	0.075
	N	60	60	60
Note: *Statistical significance of differences:* * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$.				

As shown in the table, patients with chronic heart failure (CHF) that developed against the background of rheumatic heart disease demonstrated a moderately negative correlation between one of the main indicators of renal hemodynamics—the resistance index (RI)—and the left ventricular ejection fraction (r = -0.535, p<0.001), as well as the estimated glomerular filtration rate (eGFR) (r = -0.486, p<0.001).

A strong positive correlation was established between the resistance index and the pro-inflammatory cytokine KIM-1 (r = 0.640, p<0.001), a moderate positive correlation with cystatin C (r = 0.575, p<0.001), and a weak positive correlation with tumor necrosis factor-alpha (TNF-α) (r = 0.372, p<0.05) and interleukin-6 (IL-6) (r = 0.432, p<0.01).

There was a weak positive correlation between systolic blood flow velocity and left ventricular ejection fraction (r = 0.388, p<0.01); however, no correlation with eGFR was found. Among inflammatory cytokines, a moderate negative correlation was observed with KIM-1 (r = -0.557, p<0.001) and with cystatin C (r = -0.417, p<0.01). No significant correlations were found between systolic blood flow velocity and IL-6 or TNF-α.

A weak positive correlation was also found between diastolic blood flow velocity and left

ventricular ejection fraction (r = 0.357, p<0.01). Among the inflammatory cytokines, a moderate negative correlation was noted with KIM-1 (r = -0.422, p<0.001) and cystatin C (r = -0.358, p<0.01).

The following data were obtained through linear regression analysis to describe the observed results.

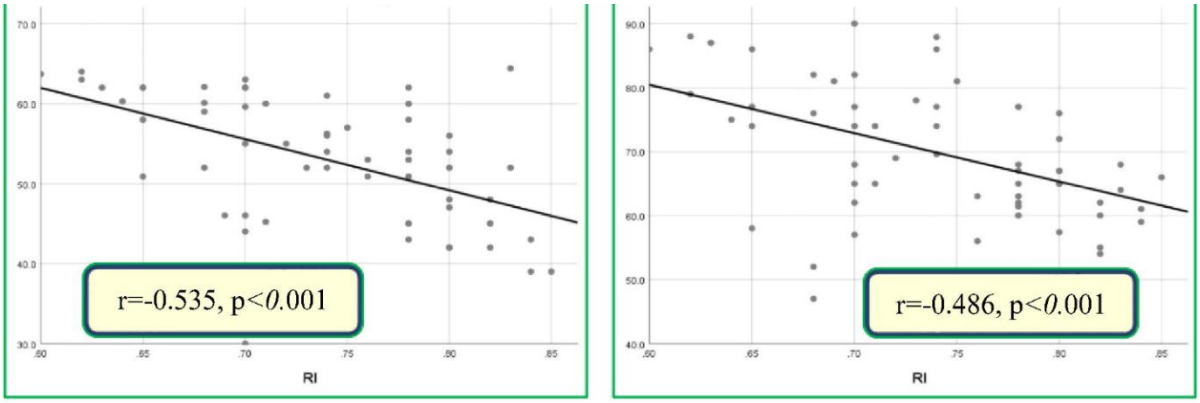

Figure 1. Correlation between renal vascular resistance index (RI) and left ventricular ejection fraction and glomerular filtration rate in chronic heart failure developed against the background of rheumatic heart disease.

As shown in the figure, in patients with CHF, a decrease in left ventricular ejection fraction enhances hypoxic processes in the kidneys, leading to an increase in vascular resistance. As a result, these processes negatively affect nephron function, causing their damage or death. This is manifested by elevated levels of renal biomarkers in the blood and a decrease in the glomerular filtration rate (GFR).

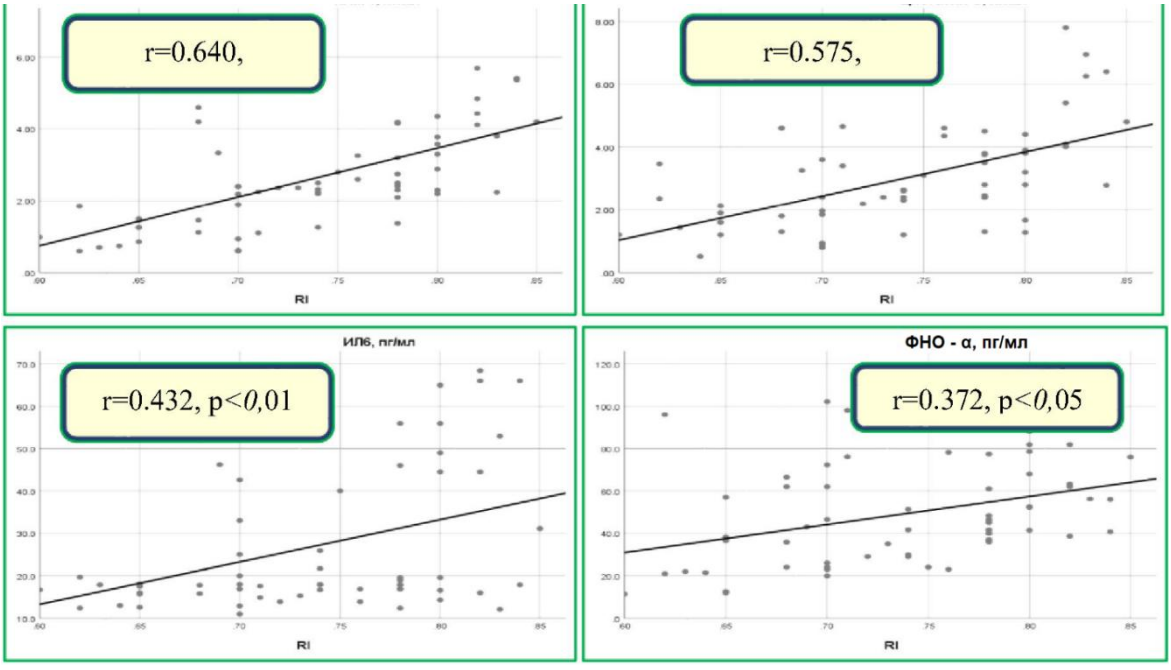

Figure 2. Correlation between the renal vascular resistance index (RI) and pro-inflammatory cytokines in chronic heart failure developed against the background of rheumatic heart disease.

An increased concentration of inflammatory cytokines in the blood serum negatively affects the elasticity of muscular-type arteries, particularly the renal arteries, leading to an increase in the vascular resistance index. As shown in the figure, among these cytokines, KIM-1 and cystatin C have the most significant influence on raising vascular resistance.

The obtained results confirm that in chronic heart failure developed against the background of

rheumatic heart disease, not only the left ventricular ejection fraction (LVEF) and glomerular filtration rate (GFR) play an important role in the development of kidney dysfunction, but also inflammatory cytokines.

Furthermore, the results of the correlation analysis in patients with CHF developed on the background of ischemic heart disease and hypertension (the second group of the study) are presented in Table 4.

Table 4. Correlation between renal hemodynamics, left ventricular ejection fraction, estimated glomerular filtration rate, and pro-inflammatory cytokines in chronic heart failure developed on the background of ischemic heart disease and hypertension.

		RI	PSV, cm/s	EDV, cm/s
Left Ventricular Ejection Fraction	**Pearson correlation**	-0.621**	0.280	0.265
	P	0.000	0.080	0.098
	N	40	40	40
Glomerular Filtration Rate (GFR)	**Pearson correlation**	-0.419**	0.155	0.164
	P	0.007	0.339	0.312
	N	40	40	40
KIM-1, pg/mL	**Pearson correlation**	0.625**	-0.423**	-0.498**
	P	0.000	0.007	0.001
	N	40	40	40
Cystatin C, pg/mL	**Pearson correlation**	0.427**	-0.362*	-0.192
	P	0.006	0.022	0.235
	N	40	40	40
Tumor Necrosis Factor-α (TNF-α), pg/mL	**Pearson correlation**	0.513**	-0.346*	-0.238
	P	0.001	0.029	0.139
	N	40	40	40
Interleukin-6 (IL-6), pg/mL	**Pearson correlation**	0.456**	-0.379*	-0.217
	P	0.003	0.016	0.180
	N	40	40	40
Note: *Statistical significance*: * - p<0,05., ** - p<0,01., *** - p<0,001.				

As shown in the table, in patients with chronic heart failure (CHF) that developed against the background of ischemic heart disease and hypertension, a strong negative correlation was found between the resistance index—one of the main indicators of renal hemodynamics—and the left ventricular ejection fraction ($r = -0.621$, $p < 0.001$), as well as a moderately expressed negative correlation with the estimated glomerular filtration rate (eGFR) ($r = -0.419$, $p < 0.01$).

A strong positive correlation was also established between the resistance index and the inflammatory cytokine KIM-1 ($r = 0.625$, $p < 0.001$), along with moderately expressed positive correlations with cystatin C ($r = 0.427$, $p < 0.01$), TNF-α ($r = 0.513$, $p < 0.01$), and IL-6 ($r = 0.456$, $p < 0.01$).

In this patient group, no significant correlation was found between systolic blood flow velocity and either the ejection fraction of the left ventricle or eGFR. Among the inflammatory cytokines, a moderate negative correlation with KIM-1 ($r = -0.423$, $p < 0.01$) and weak negative correlations with cystatin C ($r = -0.362$, $p < 0.01$), TNF-α ($r = -0.346$, $p < 0.01$), and IL-6 ($r = -0.379$, $p < 0.01$) were observed.

No correlation was found between diastolic blood flow velocity and either the left ventricular ejection fraction or the estimated glomerular filtration rate (eGFR). Among the inflammatory cytokines, only KIM-1 showed a moderate negative correlation ($r = -0.498$, $p < 0.001$).

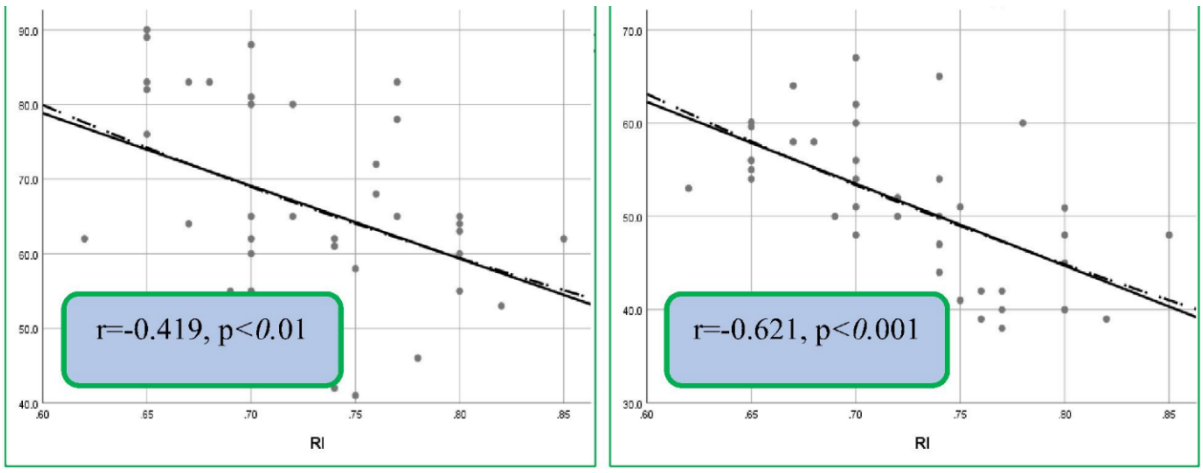

Figure 3. Correlation between the resistance index (RI) and left ventricular ejection fraction and estimated glomerular filtration rate in chronic heart failure developed against the background of ischemic heart disease.

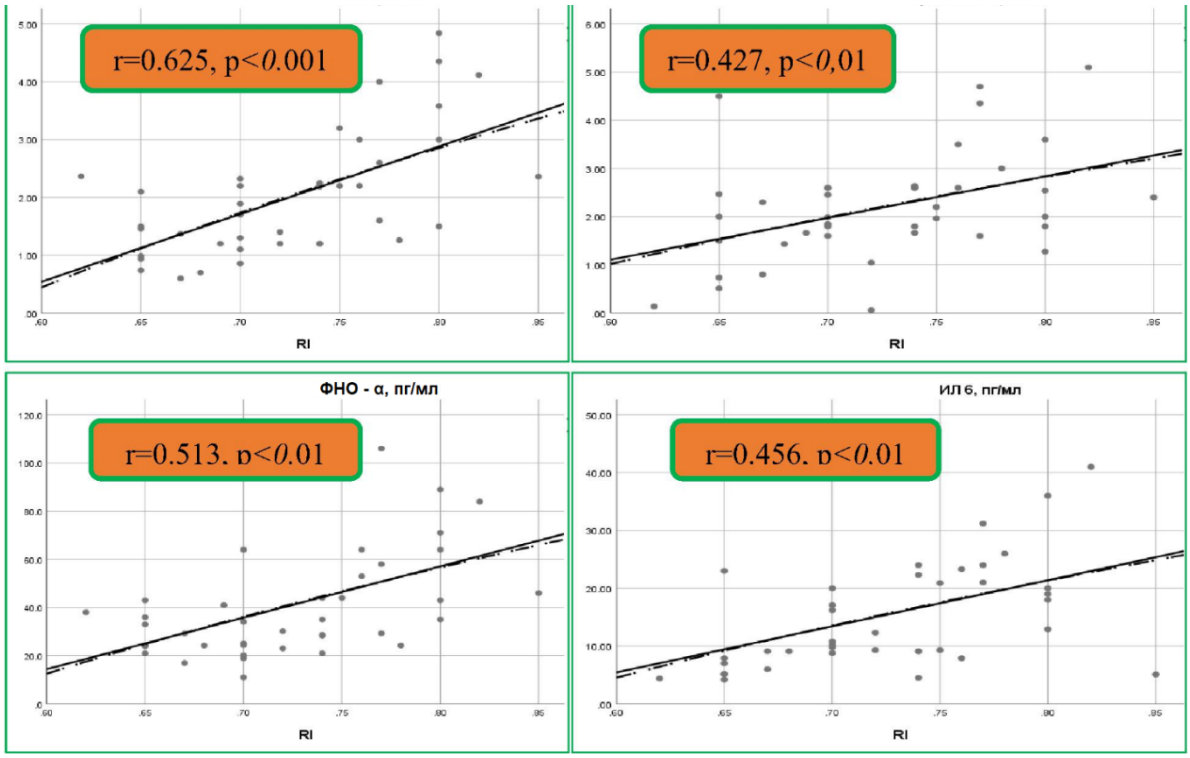

Figure 4. Correlation between the renal resistive index (RI) and pro-inflammatory cytokines in patients with chronic heart failure developed against the background of ischemic heart disease.

The conducted correlation analysis confirms that prolonged inflammatory processes in the presence of chronic heart failure (CHF), developed both against the background of rheumatic heart disease and ischemic heart disease, have a negative impact on renal hemodynamics and kidney function. Among the inflammatory markers studied, KIM-1 was found to have the most significant influence on the renal resistive index in patients with CHF associated with rheumatic heart disease.

Moreover, in this patient group, a decrease in left ventricular ejection fraction had a significantly stronger effect on renal hemodynamics compared to patients with CHF developed due to ischemic heart disease.

Conclusions

1. In CHF associated with rheumatic heart disease (RHD), an increase in the resistive index (RI) and KIM-1 levels is associated with left ventricular dysfunction and a reduction in estimated glomerular filtration rate (eGFR).
2. KIM-1 shows a strong positive correlation with cystatin C, TNF-α, and IL-6, which indicates the presence of early pathological changes in the tubulointerstitial and glomerular interaction.
3. The combined assessment of RI and KIM-1 during cardiorenal monitoring has both diagnostic and prognostic value.

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