Received: 02 May 2025 / Accepted: 23 November 2025 / Published online: 30 December 2025

DOI 10.34689/SH.2025.27.6.003

UDC 616.12:616.37-519.2

ASSESSMENT OF THE PROBABILITY OF DEVELOPING CARDIORENAL SYNDROME TYPE 2 DEPENDING ON POTENTIAL BIOMARKERS IN PEDIATRIC PATIENTS

Almira I. Baygalkanova[1], https://orcid.org/0009-0005-1677-8727

Sagira T. Abdrakhmanova[2], https://orcid.org/0000-0001-9863-6047

Assylzhan M. Messova[2], https://orcid.org/0000-0001-5373-0523

Gulzhan K. Besbayeva[1], https://orcid.org/0009-0008-9623-9142

Aliya A. Tuleubaeva[2], https://orcid.org/0009-0008-8740-1689

[1] CF «University Medical Centre», Astana, Republic of Kazakhstan;
[2] JSC «Astana Medical University», Astana, Republic of Kazakhstan.

Abstract

Introduction. The investigation of cardiorenal syndrome holds significant clinical relevance, as both cardiovascular and renal diseases rank among the leading causes of mortality. Current research efforts are focused on identifying reliable biomarkers for the early detection of acute kidney injury (AKI), which may serve as a valuable predictor for improving prognosis and therapeutic strategies in patients with chronic heart failure.

The study aims to identify biomarkers associated with an increased risk of type 2 cardiorenal syndrome in children.

Materials and methods. We performed a retrospective analysis with a case-control design. From the medical records of the Scientific National Cardiac Surgery Center (NNCC), we identified all pediatric patients with CHF due to DCM who had an initial hospitalization in 2022 and a subsequent re-hospitalization in 2023. Based on their diagnosis at re-hospitalization, patients were classified into two groups: the case group (those with confirmed Type 2 CRS, n=18) and the control group (those with CHF but without CRS, n=21). We then extracted and compared laboratory data from both the 2022 (baseline) and 2023 (follow-up) hospitalizations for all participants.

Results. Reduced serum iron levels were observed at baseline and during follow-up in both the control and case groups (9 and 5.9 μmol/L, respectively). Elevated total bilirubin levels were also detected in both groups (0.41 μmol/L in controls and 0.55 μmol/L in cases). Notably, galectin-3 concentrations were elevated in the case group, showing a 13% increase compared to the control group. Markers of renal dysfunction, including the albumin-to-creatinine ratio (ACR) and the blood urea nitrogen-to-creatinine (BUN/Cr) ratio, were comparable between the two groups (ACR: 31 and 32 mg/g; BUN/Cr: 30 and 32, respectively). Statistically significant correlations were identified between kidney function (as measured by ACR) and levels of serum iron (p=0.05), hemoglobin (p=0.02), and galectin-3 (p=0.02). Galectin-3 was a significant predictor of renal dysfunction, with an 81% increase in the likelihood of renal dysfunction (OR = 1.81, 95% CI). Similarly, the BUN/Cr ratio was associated with a 70% increase in the likelihood of renal impairment (OR = 1.70, 95% CI).

Conclusion. The findings indicate that, despite similar baseline values of key renal markers across groups, galectin-3 levels were significantly elevated in cases and were strongly associated with renal dysfunction. Reduced serum iron and elevated bilirubin levels were observed in both groups, suggesting potential systemic involvement. However, the small sample size limits the statistical power and generalizability of these findings, warranting validation in larger, prospective cohorts.

Keywords: *cardiorenal syndrome type 2, galectin, troponin, potential biomarkers.*

For citation:

Baygalkanova A.I., Abdrakhmanova S.T., Messova A.M., Besbayeva G.K., Tuleubaeva A.A. Assessment of the probability of developing cardiorenal syndrome type 2 depending on potential biomarkers // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol. 27 (6), pp. 21-29. *doi 10.34689/SH.2025.27.6.003*

Резюме

ОЦЕНКА ВЕРОЯТНОСТИ РАЗВИТИЯ КАРДИОРЕНАЛЬНОГО СИНДРОМА 2 ТИПА В ЗАВИСИМОСТИ ОТ ПОТЕНЦИАЛЬНЫХ БИОМАРКЕРОВ У ДЕТЕЙ

Альмира И. Байгалканова[1], https://orcid.org/0009-0005-1677-8727

Сагира Т. Абдрахманова[2], https://orcid.org/0000-0001-9863-6047

Асылжан М. Месова[2], https://orcid.org/0000-0001-5373-0523

Гулжан К. Бесбаева[1], https://orcid.org/0009-0008-9623-9142

Алия А. Тулеубаева[2], https://orcid.org/0009-0008-8740-1689

[1] Корпоративный фонд «University Medical Center», Астана, Республика Казахстан.
[2] АО «Медицинский университет Астана», Астана, Республика Казахстан.

Введение. Исследование кардиоренального синдрома имеет важное клиническое значение, поскольку как сердечно-сосудистые, так и почечные заболевания входят в число основных причин смертности. Текущие исследовательские усилия сосредоточены на выявлении надежных биомаркеров для раннего выявления острого повреждения почек (ОПП), которые могут служить ценным предиктором для улучшения прогноза и терапевтических стратегий у пациентов с хронической сердечной недостаточностью.

Целью исследования является выявление биомаркеров, связанных с повышенным риском кардиоренального синдрома 2 типа.

Материалы и методы. Было проведено ретроспективное исследование типа «случай-контроль» с участием пациентов с подтвержденным диагнозом кардиоренального синдрома (КРС) 2-го типа (n=18) во время первичной госпитализации в 2022 г. и последующей повторной госпитализации в 2023 г., которые составили группу случая. Контрольная группа включала пациентов с хронической сердечной недостаточностью (ХСН), но без клинических или лабораторных признаков КРС 2-го типа (n=21).

Результаты. Снижение уровня сывороточного железа наблюдалось на исходном уровне и во время последующего наблюдения как в группе контроля, так и в группе случая (9 и 5,9) мкмоль/л соответственно). Повышенные уровни общего билирубина также были обнаружены в обеих группах (0,41 мкмоль/л в контрольной группе и 0,55 мкмоль/л в случаях). Примечательно, что концентрации галектина-3 были повышены в группе случая, показывая 13%-ное увеличение по сравнению с контрольной группой. Маркеры почечной дисфункции, включая соотношение альбумина к креатинину (ACR) и соотношение азота мочевины крови к креатинину (BUN/Cr), продемонстрировали сопоставимые значения в обеих группах (ACR: 31 и 32 мг/г; BUN/Cr: 30 и 32 соответственно). Статистически значимые корреляции были выявлены между функцией почек (измеренной по ACR) и уровнями сывороточного железа (p=0,05), гемоглобина (p=0,02) и галектина-3 (p=0,02). Было обнаружено, что галектин-3 является значимым предиктором почечной дисфункции, с 81%-ным увеличением вероятности (OR=1,81, 95% CI). Аналогичным образом, соотношение BUN/Cr продемонстрировало 70%-ную вероятность влияния на почечную недостаточность (OR=1,70, 95% CI).

Заключение. Результаты показывают, что, несмотря на схожие исходные значения ключевых почечных маркеров между группами, уровни галектина-3 были значительно повышены в случаях и продемонстрировали сильную связь с почечной дисфункцией. Снижение уровня сывороточного железа и повышение уровня билирубина наблюдались в обеих группах, что предполагает потенциальное системное вовлечение. Однако небольшой размер выборки ограничивает статистическую мощность и возможность обобщения этих результатов, что требует их подтверждения в более крупных проспективных когортах.

Ключевые слова: *кардиоренальный синдром II типа; галектин; тропонин; потенциальные биомаркеры.*

Для цитирования:

Байгалканова А.И., Абдрахманова С.Т., Месова А.М., Бесбаева Г.К., Тулеубаева А.А. Оценка вероятности развития кардиоренального синдрома 2 типа в зависимости от потенциальных биомаркеров // Наука и Здравоохранение. 2025. Vol.27 (6), С.21-29. *doi 10.34689/SH.2025.27.6.003*

Түйіндеме

БАЛАЛАРДА ПОТЕНЦИАЛДЫ БИОМАРКЕРЛЕРГЕ БАЙЛАНЫСТЫ КАРДИОРЕНАЛДЫ СИНДРОМНЫҢ 2-ТИПІНІҢ ДАМУ ЫҚТИМАЛДЫҒЫН БАҒАЛАУ

Альмира И. Байгалканова[1], https://orcid.org/0009-0005-1677-8727

Сагира Т. Абдрахманова[2], https://orcid.org/0000-0001-9863-6047

Асылжан М. Месова[2], https://orcid.org/0000-0001-5373-0523

Гулжан К.Бесбаева[1], https://orcid.org/0009-0008-9623-9142

Алия А. Тулеубаева[2], https://orcid.org/0009-0008-8740-1689

[1] «University Medical Center» корпоративтік қоры, Астана, Қазақстан Республикасы.
[2] «Астана медициналық университеті» акционерлік қоғамы, Астана, Қазақстан Республикасы.

Кіріспе. Кардиореналдық синдромды зерттеу клиникалық тұрғыдан маңызды, өйткені жүрек-қантамыр және бүйрек аурулары өлімнің негізгі себептерінің қатарына жатады. Қазіргі зерттеулер бүйректің жедел зақымдануын (БЖЗ) ерте анықтауға мүмкіндік беретін сенімді биомаркерлерді айқындауға бағытталған; олар созылмалы жүрек жеткіліксіздігі (СЖЖ) бар науқастарда болжамды жақсартуға және емдік тактиканы жетілдіруге құнды предиктор бола алады.

Мақсаты. Кардиореналдық синдромның (КРС) 2-типі даму қаупінің артуымен байланысты биомаркерлерді анықтау.

Материалдар және әдістер. 2022 жылы алғашқы, 2023 жылы қайталама госпитализация кезінде КРС-2 диагнозы расталған науқастар (n=18) “жағдай” тобына енгізілген, ал КРС-2-нің клиникалық не зертханалық белгілері жоқ СЖЖ-сы бар науқастар (n=21) бақылау тобын құрған, ретроспективті“жағдай–бақылау” типті зерттеу жүргізілген.

Нәтижелер. Сарысулық темір деңгейінің төмендеуі бастапқыда да, кейінгі бақылауда да әрі бақылау, әрі оқиға топтарында байқалды (тиісінше 9 және 5,9 мкмоль/л). Жалпы билирубин деңгейі де екі топта жоғары болды (бақылауда 0,41 мкмоль/л және оқиға тобында 0,55 мкмоль/л). Елеулі жайт - зерттеу тобында галектин-3 концентрациясы жоғарылап, бақылаумен салыстырғанда 13% өсім көрсетті. Бүйрек дисфункциясының маркерлері - альбумин/креатинин арақатынасы (ACR) және қан несепнәрі азоты/креатинин арақатынасы (BUN/Cr) - екі топта да ұқсас мәндер берді (ACR: 31 және 32 мг/г; BUN/Cr: сәйкесінше 30 және 32). Бүйрек қызметі (ACR бойынша) мен сарысулық темір (p=0,05), гемоглобин (p=0,02) және галектин-3 (p=0,02) деңгейлері арасында статистикалық мәнді өзара байланыстар анықталды. Галектин-3 бүйрек дисфункциясының мәнді предикторы болып табылды: бірлестік ықтималдығының 81% артуы байқалды (OR=1,81; 95% сенім аралығы). Сол сияқты BUN/Cr қатынасы да бүйрек жеткіліксіздігіне ықпал ету ықтималдығын 70% арттырды (OR=1,70; 95% сенім аралығы).

Қорытынды. Негізгі бүйрек маркерлерінің бастапқы мәндері топтар арасында ұқсас болғанына қарамастан, зеттелген топта галектин-3 деңгейі айқын жоғары болды және бүйрек дисфункциясымен күшті байланыс көрсетті. Сарысулық темірдің төмендеуі мен билирубиннің жоғарылауы, жүйелік сипаттағы өзгерісті көрсетеді. Дегенмен, іріктеменің шамалы көлемі бұл нәтижелердің статистикалық сенімділігі мен жалпыланған қорытындылар жасау мүмкіндігін шектейді, сондықтан оларды үлкенірек, перспективті когорттарда растау қажет.

Түйін сөздер: *II типті кардиореналды синдром; галектин; тропонин; потенциалды биомаркерлер.*

Дәйексөз үшін:

Байгалканова А.И., Абдрахманова С.Т., Месова А.М., Бесбаева Г.К., Тулеубаева А.А. Потенциалды биомаркерлерге байланысты кардиореналды синдромның 2-типінің даму ықтималдығын бағалау // Ғылым және Денсаулық сақтау. 2025. Vol.27 (6), Б. 21-29. *doi 10.34689/SH.2025.27.6.003*

Introduction

Cardiorenal syndrome (CRS) is characterized by acute or chronic dysfunction of the kidneys or heart, leading to secondary acute and/or chronic dysfunction of the other organ (Acute Dialysis Quality Initiative Group, 2008). The interaction between the heart and kidneys involves several complex cellular, subcellular, and molecular mechanisms. CRS often leads to dysfunction in both organs and is associated with adverse patient outcomes [18]. According to available data, in-hospital mortality among children with chronic heart failure (CHF) and comorbidities, particularly chronic kidney disease, can exceed 20%. Moreover, the risk of mortality remains high even after discharge from the hospital [10,18]. To improve treatment outcomes in CRS, a clear understanding of the pathophysiological interactions between the heart and kidneys, as well as the identification of reliable predictors, is essential [10,18].

Efforts are currently underway to identify biomarkers for the early detection of acute kidney injury (AKI), which could potentially serve as predictors to improve clinical outcomes in CRS [12]. Accordingly, recent research on the diagnosis of CRS has increasingly focused on biomarkers. Among the most commonly used biomarkers in clinical practice are cystatin C, galectin-3, N-acetyl-beta-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), fatty acid-binding proteins (FABPs), and neutrophil gelatinase-associated lipocalin (NGAL). However, their application remains restricted mainly to adult practice [7,22,26]. To date, there is limited evidence supporting the effectiveness of these biomarkers in pediatric CRS, and it remains challenging to classify them by CRS subtypes due to insufficient data [13].

Classical indicators of renal function, such as blood urea nitrogen (BUN) and serum creatinine, remain widely used. However, BUN is an unreliable indicator of renal function, as its levels can be influenced by high protein intake, dehydration, heart failure, increased catabolism, and diuretic use [14,15,24]. Similarly, creatinine is an inadequate early marker of renal dysfunction. Neither BUN nor creatinine alone is effective for the early detection of renal injury. However, the BUN-to-creatinine (BUN/Cr) ratio is a well-established marker of renal failure, and several studies have demonstrated its association with prognosis in heart failure and its role as an independent predictor of all-cause mortality [27].

New diagnostic modalities, such as strain echocardiography and cardiac MRI, offer distinct advantages, particularly for assessing ventricular size, function, and fibrosis. However, the complexity of these methods and their limited availability currently favor the use of traditional echocardiography and ultrasound. At the same time, advances in diagnostic techniques offer opportunities to optimize the algorithms for the timely diagnosis and treatment of CRS in pediatric patients. These topics, however, are insufficiently addressed in the available literature, and the existing data are often contradictory, with most studies originating from abroad. Notably, similar studies have not yet been conducted in Kazakhstan, highlighting the relevance and timeliness of the present research.

Aim: to identify predictors of the development of type 2 cardiorenal syndrome in children with chronic heart failure due to dilated cardiomyopathy (DCM).

Materials and Methods

A retrospective case-control analysis was conducted at the Scientific National Cardiac Surgery Center (hereinafter referred to as NNCC) during 2022-2023. The study design is a longitudinal, observational, case-control study, in which patients with a confirmed diagnosis of type 2 CRS (n=18) were selected. The "control" group included patients (n=21) with chronic heart failure without manifestations of type 2 CRS. Patients with confirmed diagnoses of CRS type 2 for the first time (2022 year) and repeated (2023 year) hospitalizations taken for the "case" group.

The study results were based on medical record extracts from pediatric patients who underwent repeated inpatient treatment at the NCCC in 2022 and 2023.

The study participants were pediatric patients (0-18 years old) with a confirmed diagnosis of cardiorenal

syndrome type 2. *The inclusion criteria were:*

1. Children's age participant (0-18 years);
2. Confirmed diagnosis—cardiorenal syndrome type 2;
3. The presence of cases of hospitalization in the 24-hour hospital of the NNCC in the period 2022 and 2023;
4. Availability of medical documentation indicators selected laboratory tests for each hospitalization.

Exclusion criteria were

1. Exceeding the age of children (older than 18 years);
2. Lack of medical records for laboratory tests. A longitudinal case-control study entails retrospective data collection; our study did not provide for patient contact. Coding is used to copy medical documentation data, thereby preventing loss of confidentiality. Informed agreement was not required.

Laboratory studies were divided into four groups according to the mechanisms of secondary kidney injury, according to international studies:

1. Hematological and biochemical indicators of anemia;
2. Biochemical indicators of kidney function;
3. Biochemical indicators of liver function.
4. Biochemical indicators of damage to cardiac muscles.

Descriptive and inductive statistics were used for qualitative and quantitative analyses, and diagrams and tables were used to visualize the results graphically.

Statistical analysis was used to assess the significance of differences in grouped results, to identify associations between variables, and to predict diagnostic test use at the 95% confidence level.

To determine the distribution of variables, histograms were constructed for each series. Parametric and nonparametric criteria were used to assess the statistical significance of differences, depending on the distribution's normality. The statistical significance of differences was determined using the Student criterion (with a normal distribution of variables) for dependent and independent samples, the Mann-Whitney criterion for independent samples, and the Kruskal-Wallis test for dependent samples (with a non-Gaussian distribution of variables), as well as multivariate analysis of variance (when comparing more than two groups of variables).

The presence of associations between variables was assessed using correlation and regression analyses, and odds ratios were computed when analyzing historical data. The coefficient was calculated using Pearson correlations.

To build a model for predicting the development of type 2 cardiorenal syndrome in pediatric patients with CHF in dilated cardiomyopathy using laboratory tests (serum iron, bilirubin, galectin-3, the ratio of albumin to creatinine in a single portion of urine, and the ratio of blood urea nitrogen to creatinine), ROC analysis (receiver operating characteristic) was used. ROC - the analysis is expressed graphically, where AUC (area under the ROC curve) - the area under the ROC curve characterizes the probability of success. Meanings are interpreted according to classification, where an AUC of 0.5 is considered equally likely for both groups; 0.5-0.75 is a sufficient level of success, and over 0.75 is a significant probability of success. To interpret the ROC, the analysis identified a cutoff threshold for each variable equal to its median value for each test.

Results

Comparative analysis of original and studied levels of potential biomarkers for the development of cardiorenal syndrome type 2 in pediatric patients with CHF in DCM. The study took place in the Department of Pediatric Cardiology at the National Scientific Cardiac Surgery Center. Clinical and laboratory data of 39 pediatric patients with chronic heart failure due to dilated cardiomyopathy, treated in the period from 2022 to 2023.

All study participants were diagnosed with chronic heart failure with dilated cardiomyopathy, with the presence of CRS confirmed in 18 children (46%), which comprised the group "case", and not confirmed in 21 (54%) children, which entered the group "control". In the case group, the distribution of boys and girls was 12 (66.7%) and 6 (33.3%), respectively; in the "control" group, 8 (38.1%) and 13 (61.9%).

We assessed laboratory indicators in both groups at the time of the first and subsequent hospitalizations to determine the initial and current levels of CRS type 2 markers. To conduct the analysis, we constructed histograms to assess the distribution of variables.

It was established that the distribution is non-Gaussian. To determine the presence of statistical significance of differences, we used a non-parametric criterion, the Mann-Whitney test, for comparisons between indicator groups "case" and "control", and the Kruskal-Wallis test for comparing indicators within each group according to the age and sex characteristics of the participants.

We examined indicators by participant gender in laboratory test groups that characterize the main pathogenetic mechanisms underlying the development of cardiorenal syndrome. It was found that the serum iron level in the "case" group was at the lower limit of the norm for both boys and girls. Comparison of indicators within the group was determined using the Kruskal-Wallis criterion. At the 95% confidence level, the indicators hemoglobin, platelets, and serum iron were not statistically significant ($p > 0.05$).

Next, we reviewed the laboratory test results for participants in the control group who were diagnosed with chronic heart failure in DCM but who did not have confirmation of the development of CRS 2nd type. The statistical significance of differences at the 95% confidence level has also not been established. It should be noted that the value of hematological parameters corresponds to the accepted normal values, and the level of serum iron is at the lower limit of the accepted norm.

Table 1 shows that overall hemoglobin levels in the control and case groups were comparable. Minor fluctuations were observed across individual age subgroups; however, no statistically significant differences between the Control and Case groups were identified.

Platelet counts varied across age groups but remained within physiological limits. In contrast, serum iron levels in the Case group were consistently lower than in the Control group. The median serum iron concentration in the Case group was approximately 5.9 μmol/L, compared with 9.0 μmol/L in the Control group, reflecting a nearly 40% reduction. This finding indicates a tendency toward iron-deficiency states in patients in the Case group, warranting further investigation and therapeutic correction.

Comparison of indicators by age groups was not conducted due to the small sample sizes for each age group. It is noteworthy that the serum iron level in the “case” group is 40% lower than that in the “control” group, based on the median value.

Next, we analyzed the liver function indicator, total bilirubin, in participants in the “control” and “case” groups.

High total bilirubin levels were observed in both boys and girls. Despite a three-fold increase in bilirubin levels in girls, by comparison with values in the boys group “case”, and on the contrary, in the “control” group, the statistical significance of differences was not established at a confidence level of 95% (p=0.38, p=0.6, respectively).

Table 1.

Iron metabolism parameters by age group at first hospitalization.

Age (years)	Hb (g/L) Control	Hb (g/L) Case	Platelets (*10⁹/L) Control	Platelets (*10⁹/L) Case	Serum iron (µmol/L) Control	Serum iron (µmol/L) Case
0–1	101.6	115.25	382	496	8.82	4.66
1–2	110	113	486	348	9.3	8.6
2–4	117	104	391	404	8.6	5.3
4–6	114	119	340	356	7.64	5.3
8–10	121	—	—	—	20.5	3.5
12–14	126	124	369	281	13.1	10
14–16	110	122	479	308	8.23	6.51
16–18	135	—	—	—	22.6	9.49

Bilirubin levels across different age groups demonstrate variable fluctuations in both study groups (Table 2). However, of particular note are the elevated bilirubin levels in the Case group with already established persistent renal pathology. Based on the median, bilirubin in the Case group was ~33% higher than in Controls (0.55 vs 0.41 µmol/L; unweighted medians across age groups, missing cells ignored).

Table 2.

Bilirubin levels by age group at first hospitalization.

Age group (years)	Control (µmol/L)	Case (µmol/L)
0–1	0.39	0.55
1–2	0.28	0.60
2–4	0.32	0.65
4–6	0.45	0.50
8–10	—	0.52
12–14	1.01	1.05
14–16	0.43	0.49
16–18	—	0.54

The next group of laboratory tests of interest in the study of type 2 CRS comprises troponin, a particular marker of myocardial injury, and galectin-3, a potential marker of fibrosis in parenchymatous organs [19]. Gal-3 was assessed clinically as a renal disease biomarker to monitor and guide therapeutic strategies [3].

In participants in the "control" group, the level of galectin-3 exceeded the normal value by 110.7% in boys and 47.3% in girls. It was found that troponin levels were within the reference range in participants in the "case" group, whereas galectin-3 levels exceeded reference values by 87.7% and 60.3% in boys and girls, respectively. In both groups, the statistical significance of gender differences was not established (p = 0.7 and p = 0.77 in the "control" and "case " groups, respectively).

The fourth group of laboratory parameters characterizing kidney function in the “control” group comprises urea and blood urea nitrogen levels. It has been established that urea and blood urea nitrogen levels exceed accepted reference values in both boys and girls. The albumin-to-creatinine ratio in a single urine sample is within the upper limits of the reference range. At the same time, the ratio of blood urea nitrogen to creatinine is high compared to normal. There are no statistically significant differences in kidney function indicators at the 95% confidence level across gender groups (p > 0.05).

Given the results indicating an excess of specific laboratory indicators, we conducted a comparative analysis of these indicators between the two groups. We assessed the statistical significance of differences using the nonparametric Mann-Whitney test (Table 3).

It was established that the parameters serum iron (p=0.02), total bilirubin (p=0.03), and galectin-3 (p=0.05) were statistically significant.

Given that galectin-3 levels exceeded normal values in both groups, we conducted correlation and regression analyses to assess associations with other laboratory parameters.

Table 3.

Laboratory test parameters (mean, median) “control” and “case” groups at the time of first hospitalization.

	Control		Case		p-value
	Mean	Median	Mean	Median	
Hemoglobin	112.1	114.0	110.5	111.8	0.41
Platelets	398.2	406.0	415.5	406.9	0.16
Creatinine	0.45	0.3	1.25	1.2	0.53
Urea	29.8	23.4	31.1	30.3	0.8
BUN	13.9	10.9	14.4	14.1	0.9
ACR	30.5	31	32.5	32.0	0.61
Serum iron	9.8	9.0	6.2	5.9	**0.02**
Total bilirubin	0.39	0.41	0.57	0.55	**0.03**
Troponin I	1.22	1	1.35	1.3	0.34
Galectin 3	34.0	19.8	38.5	22.4	**0.05**
BUN/creatinine	30.5	30.0	32.2	32	0.34

It was found that the studied laboratory parameters have very weak and weak associations with the level of galectin-3; the reverse association is with the bilirubin index (r =- 0.3). A linear regression corroborates the correlation analysis results. Regression analysis showed that the effects of the laboratory tests studied were not statistically significant (p > 0.05).

Next, we conducted correlational and regression analyses to assess the influence of the studied parameters on kidney function: the albumin-to-creatinine ratio in a single urine sample and the urea nitrogen-to-creatinine ratio in serum.

It was established that the inverse average correlation links for the increase in the blood serum ratio of urea nitrogen to creatinine in the "control" group are with hematological indicators (hemoglobin: 0.24; platelets: 0.35).

Regression analysis showed that hematological parameters and serum iron levels had a statistically significant effect on ACR and the urea nitrogen-to-creatinine ratio in the serum of the studied "control" group.

During rehospitalization after a 1-year interval, the participants in the case group were confirmed to have type 2 CRS. No statistically significant differences between the case and control groups were observed for any variable at the 95% confidence level (p> 0.05), confirming the diagnosis of type 2 CRS in the studied "case" group.

Our study has established that the development of persistent renal dysfunction in pediatric patients with chronic heart failure is influenced by iron metabolism indices, namely serum iron and hemoglobin (40% higher in the case group) and bilirubin (33% higher in the case group). This indicates more pronounced catabolic processes in the liver and greater iron consumption in the developed form of type 2 CRF. Regression analysis also showed the influence of these indices on renal function. Thus, a decrease in serum iron and elevated total bilirubin indices can be considered prognostic indicators of the development of persistent renal dysfunction.

Evaluation of probabilities for the development of cardiorenal syndrome Type 2, depending on potential biomarkers

To further elucidate the predictive relevance of these biomarkers, logistic regression modeling and receiver operating characteristic (ROC) curve analysis were performed, using the BUN/Cr ratio as the dependent variable. To clarify the effects of serum iron, total bilirubin, and galectin-3 levels on renal impairment, we constructed a logistic regression model and performed ROC analysis. The cutoff threshold was the parameter selected to calculate the odds ratio. The final parameter to which potential biomarkers were assigned was the blood urea nitrogen-to-creatinine ratio. STATA 16E software was used to construct the model.

The area under the curve of the serum iron model was 0.46, indicating insufficient sensitivity for predicting deterioration in the blood urea nitrogen-to-creatinine ratio and, consequently, deterioration in renal function.

For the total bilirubin parameter, the area under the curve was 0.41, indicating low sensitivity of this test as a prognostic indicator for renal dysfunction.

The area under the curve of the galectin-3 model was 0.9, indicating high accuracy in forecasting the increase in the blood urea nitrogen-to-creatinine ratio and supporting the diagnosis of type 2 CRS progression.

1.ROC Analysis of Biomarkers. The AUC for serum iron was 0.46, reflective of poor discriminative capability. The AUC for total bilirubin was 0.41, indicating low sensitivity and specificity. The galectin-3 model exhibited an AUC of 0.9, indicating high diagnostic accuracy and substantial predictive value for CRS2 development.

2. Supplementary ROC Analysis Using ACR as an Endpoint. The serum iron model demonstrated an AUC of 0.6, denoting moderate sensitivity. The total bilirubin model produced an AUC of 0.4, underscoring low sensitivity and specificity. The galectin-3 model achieved an AUC of 0.733, indicating moderate predictive utility for identifying CRS type 2.

3. ROC Analysis of the BUN/Cr Ratio. Subsequent ROC analysis for BUN/Cr produced an AUC of 0.65, indicative of moderate model performance in forecasting CRS type 2 development.

Our analysis establishes that, at the 95% confidence level, elevated galectin-3 levels precede the onset of CRS type 2 in 81% of cases (OR 1.81). While serum iron and total bilirubin showed potential associations with CRS type 2 risk (21% and 50%, respectively), their predictive values were not statistically significant (p > 0.05). The ROC analysis indicates that galectin-3 and the BUN/Cr ratio are promising biomarkers for early identification of declining renal function, with AUC values of 0.9 and 0.733, respectively (Figure 1).

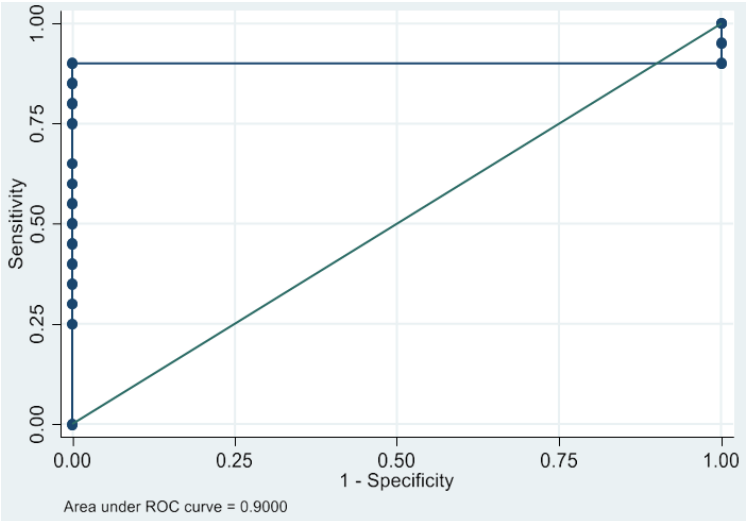

Figure 1. ROC curves for the blood urea nitrogen/creatinine (BUN/Cr) ratio stratified by galectin-3.

Discussion

In the statistical analysis of the data, accounting for the number of children examined, the distributions of the indicators were non-Gaussian. Therefore, to assess the statistical significance of differences, non-parametric methods were used: the Mann-Whitney U test was applied for comparisons between the case and control groups, while the Kruskal-Wallis test was used to analyze differences within each group according to age and gender.

We analyzed laboratory indicators that characterize the main pathogenetic mechanisms underlying the development of cardiorenal syndrome, while accounting for participants' gender.

Laboratory test results were analyzed for participants in the control group with an established diagnosis of chronic heart failure on the background of dilated cardiomyopathy but without confirmed type 2 cardiorenal syndrome. Notably, the serum iron level in the case group was 40% lower than that in the control group, as indicated by the median value.

It was found that the serum iron level in the case group was at the lower limit of normal in both boys and girls. Using the Kruskal-Wallis test for intragroup comparisons, no statistically significant differences were observed in hemoglobin, platelet count, and serum iron levels ($p > 0.05$).

We further analyzed liver function by assessing total bilirubin levels in the control and case groups. Elevated bilirubin levels were observed in both boys and girls. Despite a threefold increase in bilirubin levels in girls compared with boys in the case group, and, conversely, no differences in the case group, these differences were not statistically significant at the 95% confidence level ($p = 0.38$ and $p = 0.6$, respectively).

Of note was also the increased bilirubin level in the case group, in which persistent renal pathology had already developed. The median bilirubin level was 33% higher than in the control group.

The next group of laboratory tests relevant to the study of type 2 CRS included markers of myocardial injury: troponin, a particular marker of myocardial damage, and galectin-3, a potential marker of parenchymal organ fibrosis. It was found that troponin levels were within normal limits in the case group, while galectin-3 levels in both boys and girls exceeded normal values by 87.7% and 60.3%, respectively. In the control group, galectin-3 levels were also elevated above normal by 110.7% in boys and 47.3% in girls. No statistically significant differences by gender were observed within the case and control groups ($p = 0.7$ and $p = 0.77$, respectively).

In the fourth group of laboratory indicators reflecting kidney function in the case group, blood urea and blood urea nitrogen levels exceeded normal values in both boys and girls. The albumin/creatinine ratio in spot urine samples was at the upper limit of normal, while the blood urea nitrogen to creatinine ratio was significantly elevated. There were no statistically significant gender differences in these indicators within the group at the 95% confidence level ($p > 0.05$).

Given the identified excesses of specific laboratory parameters, a comparative analysis of the two groups was conducted, and the statistical significance of differences was assessed using the Mann-Whitney U test. The study revealed statistically significant differences in serum iron ($p = 0.02$), total bilirubin ($p = 0.03$), and galectin-3 ($p = 0.05$).

Upon rehospitalization after a one-year interval, participants in the case group were confirmed to have developed type 2 CRS.

Our study revealed that with the development of persistent renal dysfunction against the background of chronic heart failure in children with dilated cardiomyopathy, iron metabolism indicators such as serum iron and hemoglobin (40% higher in the case group) and bilirubin (33% higher in the case group) play a role. This suggests more pronounced catabolic processes in the liver and higher iron consumption in established type 2 CRS. Regression analysis also demonstrated the influence of these indicators on kidney function.

Thus, decreases in serum iron and an increase in total bilirubin levels may be considered prognostic markers for the development of persistent renal dysfunction. Although ACR is a recognized marker of current kidney function, our study did not establish its predictive value for the development of renal dysfunction, as ACR levels varied from normal to elevated in the case group during both initial and repeated hospitalizations.

Mechanisms of serum iron reduction in chronic heart failure and developed cardiorenal syndrome:

Chronic systemic inflammation increases the level of hepcidin, which suppresses the function of ferroprotein, resulting in decreased iron absorption in the intestine and impaired iron release from macrophage stores [8]; impaired iron absorption due to intestinal edema and hypoperfusion [16]; uremia causes disturbance of erythropoiesis and iron metabolism; activation of neurohormonal systems (renin-angiotensin-aldosterone and sympathetic nervous system) leads to a decrease in iron perfusion and activation of oxidative stress, which negatively affects iron hemostasis [25].

Increased bilirubin levels in patients with chronic heart failure in cardiorenal syndrome are associated with congestion in the inferior vena cava system (impaired liver drainage function, decreased hepatocyte function) [6]. Also, the development of cardiogenic hepatopathy leads to impaired bilirubin excretion [9]. Liver tissue ischemia increases oxidative stress, damages hepatocytes, and contributes to increased bilirubin [11]. Activation of neurohumoral systems exacerbates bilirubin synthesis and utilization [5].

Reduced cardiac output and venous congestion lead to decreased renal perfusion in patients with type 2 CRS and chronic heart failure. BUN/Cr increases as a result of neurohormonal system activation (RAAS, sympathetic nervous system), enhancing urea reabsorption without affecting creatinine. An elevated BUN/Cr ratio may serve as an early indicator of worsening renal function. Previous studies have shown that an elevated BUN/Cr ratio can identify a high-risk, potentially reversible form of renal dysfunction in patients with decompensated heart failure [4]. Another study demonstrated that the BUN/Cr ratio at admission predicts acute kidney injury in acute decompensated heart failure and aids risk stratification [23]. Furthermore, in patients with congestive heart failure, a high BUN/Cr ratio was associated with poor prognosis and predicted all-cause mortality [27]. Additionally, a higher and

more variable BUN/Cr ratio over time was independently associated with an increased risk of hospitalization for heart failure and all-cause mortality in patients with chronic heart failure with preserved ejection fraction [15].

ROC analysis confirmed galectin-3 as a potential biomarker of renal impairment, based on the blood urea nitrogen-to-creatinine ratio and ACR (AUCs of 0.9 and 0.733, respectively). Our results are consistent with previous studies indicating that galectin-3 may be a prognostic marker for the development of cardiorenal syndrome in patients with acute heart failure and reduced left ventricular ejection fraction. Galectin-3 levels were higher in patients who developed CRS compared to those who did not [25].

A meta-analysis of five studies involving 5,226 patients with chronic kidney disease found that elevated galectin-3 levels were associated with an increased risk of all-cause mortality and cardiovascular events. However, the association between galectin-3 and kidney disease progression was inconsistent [28]. Another systematic review failed to confirm a definitive role for serum galectin-3 in predicting the progression of cardiovascular or renal disease.

We acknowledge the small sample size as a limitation of our study, which is due to the severity of the pathology and the challenges associated with patient hospitalization in a single medical institution. Another limitation was the inability to examine other potential biomarkers of cardiorenal syndrome, such as cystatin C, KIM-1, and NGAL, owing to various factors. Nevertheless, our findings provide a foundation for further research and for improving early diagnostic approaches for CRS in children.

Conclusions

1. The laboratory studies conducted in our research, aimed at examining the pathogenetic mechanisms of chronic heart failure (CHF) and the development of type 2 cardiorenal syndrome (CRS), included four groups of indicators reflecting iron metabolism, liver function, myocardial injury, and kidney function.

2. Low serum iron levels were observed both initially and during follow-up in the control and case groups (9 and 5.9 μmol/L, respectively). Elevated bilirubin levels were also noted in both the control and case groups (0.41 and 0.54 μmol/L, respectively), along with increased galectin-3 levels in the case group (13% higher compared to controls). Additionally, markers of reduced kidney function were similar between the groups (ACR: 31 and 32 mg/g; blood urea nitrogen-to-creatinine ratio: 30 and 32, respectively). Statistically significant associations were established between serum iron ($p = 0.05$), hemoglobin ($p = 0.02$), and galectin-3 ($p = 0.02$) levels with markers of kidney function (ACR).

3. It was determined that galectin-3 has an 81% likelihood (OR = 1.81, 95% CI) of influencing the development of renal dysfunction, while the blood urea nitrogen to creatinine ratio has a 70% likelihood (OR = 1.70, 95% CI).

4. The use of the blood urea nitrogen to creatinine ratio and galectin-3 levels can serve as prognostic markers for the development of renal dysfunction in pediatric patients with CHF and dilated cardiomyopathy.

Practical Recommendation

1. Monitoring biomarkers of myocardial injury, particularly troponin and galectin-3, is recommended for the early detection and management of type 2 CRS in children.

2. Regular assessment of serum iron and bilirubin levels is advised to provide insight into systemic processes affecting multiple organs, including the kidneys. Tracking these parameters may also help evaluate the body's overall compensatory capacity during disease progression.

3. Given the limitations of the current study, particularly the inability to assess several potential biomarkers of cardiorenal syndrome (including cystatin C, NGAL, and KIM-1), further research is needed. Future studies should focus on a multimarker approach for the early diagnosis and stratification of CRS in pediatric patients.

Conflict of Interest. *The authors declare that they have no conflict of interest.*

Contribution of authors. *All authors were equally involved in the writing of this article.*

Funding: *No funding was provided.*

Literature:

1. Aronson D., Mittleman M.A., Burger A.J. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. American Journal of Medicine. 2004. Vol. 116, № 7. P. 466–473.

2. Bellos I., Marinaki S., Lagiou P., Benetou V. Galectin-3 in chronic kidney disease. Clinica Chimica Acta. 2024. Vol. 559. Art. 119727. DOI: 10.1016/j.cca.2024.119727.

3. Boutin L., Dépret F., Gayat E., Legrand M., Chadjichristos C. E. Galectin-3 in Kidney Diseases: From an Old Protein to a New Therapeutic Target. International Journal of Molecular Sciences. 2022. Vol. 23, № 6. P. 3124.

4. Brisco M.A., Coca S.G., Chen J., et al. Blood urea nitrogen/creatinine ratio identifies a high-risk but potentially reversible form of renal dysfunction in patients with decompensated heart failure. Circulation: Heart Failure. 2013. Vol. 6, № 2. P. 233–239.

5.Chen Y., Luo X., et al. Bilirubin, Oxidative Stress, and Heart Failure: A Complex Relationship. Frontiers in Cardiovascular Medicine. 2023. Vol. 10. Art. 1095643.

6.Chow S.L., Fonarow G.C., et al. Hepatic Congestion in Heart Failure: Clinical Implications and Emerging Diagnostic Strategies. Journal of the American College of Cardiology. 2023. Vol. 81, № 8. P. 825–838.

7. Emmens J.E., Ter Maaten J.M., Matsue Y., et al. Plasma kidney injury molecule-1 in heart failure: renal mechanisms and clinical outcome. European Journal of Heart Failure. 2016. Vol. 18, № 6. P. 641–649. PubMed+1

8. Ganz T., Nemeth E. Iron homeostasis in host defence and inflammation. Nature Reviews Immunology. 2021. Vol. 21, № 1. P. 26–37.

9. Giallauria F., et al. Cardiac Hepatopathy in Heart Failure Patients: Current Evidence and Future Perspectives. Heart Failure Reviews. 2024. Vol. 29, № 1. P. 55–66.

10. Hatamizadeh P., Fonarow G. C., Budoff M. J., et al. Cardiorenal syndrome: Pathophysiology and potential targets for clinical management. Nature Reviews Nephrology. 2013. Vol. 9, № 2. P. 99–111.

11. Hori M., Okumura T., et al. Bilirubin as a Biomarker

in Heart Failure: Pathophysiology and Prognostic Role. ESC Heart Failure. 2022. Vol. 9, № 6. P. 3720–3732.

12. Kojc T.S., Varda N.M. Novel Biomarkers of Heart Failure in Pediatrics. Children. 2022. Vol. 9, № 5. P. 1–14.

13. Kuster N., Moréna M., Bargnoux A.-S., et al. Biomarkers of cardiorenal syndrome. Annales de Biologie Clinique (Paris). 2013. Vol. 71, № 4. P. 409–418.

14. Lindenfeld J.A., Schrier R.W. Blood Urea Nitrogen: A Marker for Adverse Effects of Loop Diuretics? Journal of the American College of Cardiology. 2011. Vol. 58, № 4. P. 383–385.

15. Matsue Y., et al. Blood urea nitrogen-to-creatinine ratio in the general population and in patients with acute heart failure. Heart. 2017. Vol. 103, № 6. P. 407–413.

16. McDonagh T., Metra M., Adamo M., et al. Iron deficiency in heart failure: an updated consensus statement. European Journal of Heart Failure. 2021. Vol. 23, № 8. P. 141–145.

17. Nikolić T., Radovanovic M., Sreckovic M., Markovic M., Petrovic D. Cardiorenal syndrome type 1: Definition, etiopathogenesis, diagnostics and treatment. Serbian Journal of Experimental and Clinical Research (EABR: Experimental and Applied Biomedical Research). 2018. Vol. 19, № 1. P. 73–80. DOI: 10.1515/sjecr-2016-0051. Paradigm

18. Olowu W.A. Acute Childhood Cardiorenal Syndrome and Impact of Cardiovascular Morbidity on Survival. International Journal of Nephrology. 2011. Vol. 2011. P. 1–6.

19. Ou S.M., Tsai M.T., Chen H.Y., et al. Identification of Galectin-3 as Potential Biomarkers for Renal Fibrosis by RNA-Sequencing and Clinicopathologic Findings of Kidney Biopsy. Frontiers in Medicine (Lausanne). 2021. Vol. 8. Art. 748225.

20. Ozyildirim S., Dogan O., Barman H. A., et al. Galectin-3 as a Biomarker to Predict Cardiorenal Syndrome in Patients with Acute Heart Failure. Acta Cardiologica Sinica. 2023. Vol. 39, № 6. P. 862–870. DOI: 10.6515/ACS.202311_39(6).20230903A.

21. Price J.F., Mott A.R., Dickerson H.A., et al. Worsening renal function in children hospitalized with decompensated heart failure: evidence for a pediatric cardiorenal syndrome? Pediatric Critical Care Medicine. 2008. Vol. 9, № 3. P. 279–284. PubMed+1

22. Ronco C., et al. Neutrophil gelatinase-associated lipocalin: Ready for routine clinical use? An international perspective. Blood Purification. 2014. Vol. 37, № 4. P. 271–285.

23. Sakr A.R.M., Gomaa G.F.E., Wasif S.M.E., Eladawy A.H.H. The prognostic role of urea-to-creatinine ratio in patients with acute heart failure syndrome: a case-control study. Egyptian Heart Journal. 2023. Vol. 75, № 1. Art. 78. DOI: 10.1186/s43044-023-00404-y.

24. Takaya Y., et al. Risk stratification of acute kidney injury using the blood urea nitrogen/creatinine ratio in patients with acute decompensated heart failure. Circulation Journal. 2015. Vol. 79, № 7. P. 1520–1525.

25. Tromp J., Khan M.A., Mentz R.J., et al. Iron Deficiency in Heart Failure: Mechanisms and Therapeutic Approaches. European Heart Journal. 2023. Vol. 44, № 4. P. 292–302.

26. Urbschat A., Obermüller N., Haferkamp A. Biomarkers of kidney injury. Biomarkers. 2011. Vol. 16, Suppl. 1. P. S22–S30.

27. Wang Y., Xu X., Shi S., et al. Blood urea nitrogen to creatinine ratio and long-term survival in patients with chronic heart failure. European Journal of Medical Research. 2023. Vol. 28, № 1. Art. 343.

28. Zhang T, Cao S, Yang H, Li J. Prognostic impact of galectin-3 in chronic kidney disease patients: a systematic review and meta-analysis. Int Urol Nephrol. 2019 Jun.51(6):1005-1011. doi: 10.1007/s11255-019-02123-3. Epub 2019 Apr 8. PMID: 30963453.

Author Information:

Almira I. Baygalkanova – Master of Medical Sciences, the head of pediatric cardiology department of CF «University Medical Centre», Astana, Republic of Kazakhstan, Kerey-Zhanibek khandar 5/1, baigalkanovaalmira@gmail.com, https://orcid.org/0009-0005-1677-8727, +77777346639.

Sagira T. Abdrakhmanova – Professor of the pediatric diseases department No.3 “Astana Medical University”, Astana, Kazakhstan, Beibitshilik str., 49A, abdrakhmanova.a@amu.kz, https://orcid.org/0000-0001-9863-6047, +7(701)7954632

Assylzhan M. Messova – Associate Professor of the pediatric diseases department No.3 “Astana Medical University”, Astana, Kazakhstan, Beibitshilik str., 49A, messova.a@amu.kz, https://orcid.org/0000-0001-5373-0523, +77772138307

Gulzhan K. Besbayeva - Head of the Pediatric Cardioanesthesiology, Resuscitation and Intensive Care Unit of CF «University Medical Centre», Astana, Republic of Kazakhstan, Kerey-Zhanibek khandar 5/1, besbaeva@gmail.com, https://orcid.org/0009-0008-9623-9142, +77015546038.

Alya A. Tuleubayeva – Associate Professor of the pediatric diseases department No.3 “Astana Medical University”, Astana, Kazakhstan, Beibitshilik str., 49A, tuleubayeva.a@amu.kz, Astana, Kazakhstan, Beibitshilik str., 49A, https://orcid.org/0009-0008-8740-1689, +77017674327

Corresponding Author:

Messova Assylzhan Makhmutbayevna, associate professor at the Department of Pediatric Diseases at «Astana Medical University».

Postal Address: 010000, Republic of Kazakhstan, Astana, Beibitshilik street, 49a.

Email: assylzhan2006@mail.ru. https://orcid.org/0000-0001-5373-0523

Phone: 87772138307