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Comparative Assessment of Glomerular Filtration Rate Using Cystatin C and Creatinine in Early Cardiorenal Syndrome

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Abstract **Background:** Cardiorenal syndrome is characterized by the coexistence of cardiac and renal dysfunction, significantly worsening patient prognosis. Early detection of renal impairment remains challenging, as creatinine-based estimation of glomerular filtration rate (GFR) lacks sensitivity in early stages. Cystatin C has emerged as a promising biomarker for more accurate assessment of kidney function. **Methods:** This cross-sectional study included 115 patients with chronic heart failure (New York Heart Association [NYHA] class II–III) complicated by early-stage cardiorenal syndrome. Patients were divided into NYHA II (n=30) and NYHA III (n=85) groups. Serum creatinine and cystatin C levels were measured, and GFR was calculated using CKD-EPI equations. Statistical analysis was performed using Student's t-test, with $p<0.05$ considered significant. **Results:** In NYHA II patients, creatinine-based GFR was 88.4±1.57 ml/min/1.73 m², while cystatin C-based GFR was significantly lower at 61.3±3.6 ml/min/1.73 m² ($p<0.001$). In NYHA III patients, the corresponding values were 79.3±1.67 and 53.5±1.06 ml/min/1.73 m², respectively ($p<0.001$). Cystatin C-based GFR was consistently lower than creatinine-based estimates in both groups, indicating earlier detection of renal dysfunction. Additionally, GFR values decreased with increasing NYHA functional class. **Conclusion:** Cystatin C-based estimation of GFR provides a more sensitive assessment of early renal dysfunction in patients with cardiorenal syndrome compared to creatinine-based methods. Its use may improve early diagnosis and clinical management of these patients.

Keywords Cardiorenal syndrome, Cystatin C, Creatinine, Glomerular filtration rate, Chronic heart failure, Renal dysfunction

1. Introduction

Cardiorenal syndrome (CRS) represents a complex pathophysiological condition characterized by the bidirectional interaction between cardiac and renal dysfunction, in which acute or chronic impairment in one organ induces dysfunction in the other. This interplay significantly worsens clinical outcomes and is associated with increased morbidity and mortality among patients with chronic heart failure (CHF). Recent epidemiological data indicate that renal dysfunction occurs in more than 50% of patients with CHF, highlighting the clinical importance of early detection and management of kidney impairment in this population [1,2,3].

Early identification of renal dysfunction in CRS remains a major clinical challenge. Glomerular filtration rate (GFR) is widely used as the standard indicator of kidney function; however, it is most commonly estimated using serum creatinine levels. Despite its widespread use, creatinine-based GFR estimation has important limitations, particularly in the early stages of renal impairment. Serum creatinine is influenced by several non-renal factors, including age, sex, muscle mass, and nutritional status, which may lead to underestimation of early kidney dysfunction [4,5,6].

In recent years, cystatin C has emerged as a more reliable biomarker for assessing kidney function. Cystatin C is a low-molecular-weight protein produced at a constant rate by all nucleated cells and freely filtered by the glomeruli. Unlike creatinine, its concentration is minimally affected by muscle mass and external factors, making it a potentially more sensitive marker of early changes in GFR [7,8]. Several studies have demonstrated that cystatin C-based equations provide improved accuracy and prognostic value compared to creatinine-based estimations, particularly in patients with cardiovascular diseases [9,10,11].

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In the context of CRS, early renal impairment is often subclinical and may not be detected using traditional biomarkers. Neurohormonal activation, including the renin–angiotensin–aldosterone system and sympathetic nervous system, along with hemodynamic alterations and endothelial dysfunction, contribute to progressive kidney injury even in the absence of overt clinical signs [2,12]. Therefore, the use of more sensitive biomarkers such as cystatin C may enhance early diagnosis and improve patient stratification.

Although previous studies have investigated the role of cystatin C in assessing renal function, data specifically focusing on its diagnostic value in early-stage CRS remain limited. In particular, comparative analyses of cystatin C- and creatinine-based GFR across different functional classes of heart failure are insufficiently explored.

Therefore, the aim of the present study was to comparatively assess glomerular filtration rate estimated using cystatin C and creatinine in patients with early cardiorenal syndrome associated with chronic heart failure.

2. Materials and Methods

Study Design

This study was designed as a cross-sectional, observational, and comparative clinical investigation aimed at evaluating renal function in patients with early-stage cardiorenal syndrome.

Study Setting and Period

The study was conducted between 2024 and 2025 in specialized cardiology departments in Tashkent, Uzbekistan.

Ethical Considerations

The study protocol was approved by the local Ethics Committee (Protocol No. 17). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

A total of 115 patients with chronic heart failure (CHF) of New York Heart Association (NYHA) functional class II–III associated with cardiorenal syndrome were included in the study.

Inclusion Criteria

- Age ≥18 years
- Chronic heart failure (NYHA II–III)
- Presence of cardiorenal syndrome
- Written informed consent

Exclusion Criteria

- Acute heart failure
- Chronic kidney disease stage III–V
- Acute infectious diseases
- Malignancy
- Severe hepatic failure
- Pregnancy

Patient Grouping

Patients were stratified into two groups according to NYHA classification:

- NYHA II (n=30; mean age 65.06±2.06 years)
- NYHA III (n=85; mean age 66.74±1.05 years)

All patients had early-stage renal impairment corresponding to chronic kidney disease stages I–II.

Clinical and Laboratory Assessment

All patients underwent standard clinical evaluation, including medical history, physical examination, blood pressure measurement, and heart rate assessment.

Venous blood samples were collected under standardized conditions. The following biomarkers were measured:

- Serum creatinine (μmol/L)
- Serum cystatin C (mg/L)

Biochemical analyses were performed using an automated analyzer (specify model and manufacturer).

Estimation of Glomerular Filtration Rate

Glomerular filtration rate (GFR) was calculated using CKD-EPI equations:

- Creatinine-based CKD-EPI equation
- Cystatin C-based CKD-EPI equation (2012)

Results were expressed in ml/min/1.73 m².

Instrumental Assessment

Cardiac function was evaluated using:

- Electrocardiography (ECG)
- Echocardiography (EchoCG)

Statistical Analysis

Biochemical analyses were performed using Roche Cobas 6000 analyzer (Roche Diagnostics, Germany). Serum cystatin C levels were measured using an immunoturbidimetric assay. Statistical analysis was performed using IBM SPSS Statistics version 26.0.Continuous variables were expressed as mean ± standard error of the mean (SEM). Normality of distribution was assessed using the Shapiro–Wilk test. Comparisons between groups were performed using the independent samples Student's t-test. A p-value <0.05 was considered statistically significant.

The obtained data were used to compare renal function between study groups based on NYHA classification.

3. Results

Baseline Characteristics

A total of 115 patients were included in the study, of whom 30 (26.1%) were classified as NYHA II and 85 (73.9%) as NYHA III. The mean age was 65.06±2.06 and 66.74±1.05 years, respectively. All patients had early-stage cardiorenal syndrome (CKD stages I–II).

Comparison of GFR Between Groups

Table 1. Comparison of GFR values between NYHA II and NYHA III patients

Parameter	NYHA II (n=30)	NYHA III (n=85)	p-value
GFR (creatinine-based) (ml/min/1.73 m²)	88.4 ±1.57	79.3 ±1.67	<0.001
GFR (cystatin C-based) (ml/min/1.73 m²)	61.3 ±3.6	53.5 ±1.06	<0.001

Cystatin C-based GFR values were significantly lower than creatinine-based estimates in both groups (p<0.001).

Functional Class and Renal Function

In NYHA II patients, cystatin C-based GFR was 30.6% lower than creatinine-based GFR, while in NYHA III patients, the difference reached 32.5%.

Patients with NYHA III demonstrated significantly reduced GFR compared to NYHA II:

- Creatinine-based GFR decreased by 10.3%
- Cystatin C-based GFR decreased by 12.7%

Clinical Implications

These findings indicate that:

- Cystatin C detects renal dysfunction earlier than creatinine
- Subclinical renal impairment is present even in early CRS
- Renal function declines with worsening heart failure severity

4. Discussion

The findings of the present study demonstrate a consistent and clinically significant discrepancy between creatinine- and cystatin C-based GFR estimates across different stages of heart failure severity.

Cardiorenal syndrome (CRS) is a complex clinical condition characterized by bidirectional interactions between cardiac and renal dysfunction, leading to progressive deterioration of both organs [1,2]. The coexistence of chronic heart failure (CHF) and renal impairment is common, with epidemiological studies indicating that more than half of patients with CHF develop varying degrees of kidney dysfunction, significantly worsening prognosis [3]. These findings emphasize the importance of early and accurate detection of renal impairment in this population.

In clinical practice, GFR is most commonly estimated using serum creatinine. However, creatinine-based estimation has well-recognized limitations, particularly in the early stages of renal dysfunction. Serum creatinine levels are influenced by multiple non-renal factors, including age, sex, muscle mass, and nutritional status, which may lead to underestimation of kidney impairment [4–6]. In our study, creatinine-based GFR values were consistently higher than cystatin C-based estimates, indicating that creatinine may fail to detect early renal dysfunction in CRS.

Cystatin C has emerged as a more reliable biomarker for kidney function assessment. It is produced at a constant rate by all nucleated cells, freely filtered by the glomeruli, and minimally affected by extrarenal factors, making it a more accurate indicator of true GFR [7,8]. Previous studies have demonstrated that cystatin C-based equations provide improved diagnostic accuracy and prognostic value compared to creatinine-based methods [9–11]. Our findings are consistent with these observations, confirming that cystatin C detects renal dysfunction at earlier stages.

A key finding of our study is the significant discrepancy between cystatin C- and creatinine-based GFR across different NYHA functional classes. In NYHA II patients, cystatin C-based GFR was 30.6% lower than creatinine-based values, while in NYHA III patients, the difference reached 32.5%. This suggests that a considerable proportion of patients with apparently preserved renal function according to creatinine may already have subclinical renal impairment when assessed using cystatin C.

The progressive decline in GFR observed with increasing NYHA class further supports the close interaction between cardiac and renal dysfunction. Worsening heart failure is associated with reduced renal perfusion, increased venous congestion, and sustained neurohormonal activation, all of which contribute to renal impairment [3,9]. In addition, CRS is increasingly recognized as a systemic disorder involving inflammatory pathways and multiorgan interactions [13].

Recent evidence also highlights the prognostic significance of cystatin C beyond renal function assessment. Elevated cystatin C levels have been associated with increased cardiovascular risk and adverse clinical outcomes in patients with heart failure [14]. Furthermore, early detection of renal dysfunction remains a key clinical priority, as timely diagnosis allows for optimization of therapeutic strategies and prevention of disease progression [15].

Advances in heart failure management, including the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, have further underscored the importance of accurate renal function assessment in guiding treatment decisions [16]. Similarly, biomarkers such as natriuretic peptides are widely used in heart failure, but they do not provide direct information on renal function, highlighting the complementary role of cystatin C [17].

Consensus statements and international guidelines increasingly support the use of novel kidney biomarkers in clinical practice. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend cystatin C as an additional or alternative marker for GFR estimation, particularly in cases where creatinine-based assessment may be unreliable [10]. Moreover, recent expert consensus emphasizes the role of multimarker approaches in improving risk stratification and clinical decision-making in cardiorenal syndrome [18,19].

Finally, congestion has been identified as a key determinant of adverse outcomes in heart failure and may further contribute to renal dysfunction through increased venous pressure and reduced renal perfusion [20]. This highlights the importance of integrated cardiorenal assessment in clinical practice.

Clinical Implications

The findings of this study suggest that incorporation of cystatin C into routine clinical evaluation may enable earlier detection of renal dysfunction, improve risk stratification, and facilitate timely therapeutic interventions in patients with cardiorenal syndrome. This may ultimately contribute to improved clinical outcomes and reduced morbidity.

Study Limitations

This study has several limitations. First, its cross-sectional design does not allow assessment of causal relationships or long-term outcomes. Second, the relatively small sample size and single-center nature of the study may limit generalizability. Third, direct measurement of GFR using gold-standard methods was not performed.

5. Conclusions

Cystatin C-based estimation of glomerular filtration rate provides a more sensitive and reliable assessment of early renal dysfunction in patients with cardiorenal syndrome compared to creatinine-based methods. In this study, cystatin C-based GFR consistently identified lower values across all patient groups, indicating the presence of subclinical renal impairment that may not be detected using conventional creatinine-based approaches.

The observed decline in GFR with increasing severity of heart failure further supports the close pathophysiological interaction between cardiac and renal dysfunction. These findings highlight the limitations of relying solely on creatinine for renal assessment in patients with chronic heart failure.

Incorporation of cystatin C into routine clinical evaluation may improve early diagnosis, enhance risk stratification, and facilitate more timely therapeutic interventions in patients with cardiorenal syndrome.

Further large-scale, prospective studies are warranted to confirm these findings and to establish the role of cystatin C as a standard biomarker in the clinical management of cardiorenal syndrome.

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