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Cystatin C and Its Temporal Change May Predict Development and Recovery of Cardio-renal Syndrome Type 1 in Acute Heart Failure

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Abstract

Objectives: Cardio-renal syndrome type 1 (CRS1) complicates 40% of patients hospitalized for acute decompensated heart failure (ADHF) and is associated with poor prognosis. Factors associated with the development and recovery of CRS1 have not been completely understood, and the value of cystatin C in this context has not been studied.

Materials and Methods: We evaluated the predictive value of cystatin C levels at admission and 24th hour and delta-cystatin C (cystatin C change in the first 24 hours of admission) in the development and reversibility of CRS1 in patients hospitalized for ADHF. One hundred ten consecutive patients hospitalized for ADHF were enrolled.

Results: Admission cystatin C [odds ratio (OR): 30.97, confidence interval (CI): 9.28-139.60, p<0.001], delta-cystatin C (OR: 41.26, CI: 7.75-93.55, p<0.001), furosemide dose given in first 24 hours of admission (OR: 1.941, CI: 1.541-4.112, p=0.009), and systolic pulmonary artery pressure (OR: 0.927, CI: 0.874-0.983, p=0.011) were independent predictors of

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Abstract

CRS1. A ROC curve analysis showed that an admission cystatin C level at a cut-off point of 1.385 could detect AKI with 77.1% sensitivity and 77.4% specificity. Among 48 patients in the AKI group, renal function was recovered in 31 (64.6%). Delta-cystatin C (OR: 0.088, CI: 0.018-0.441, p=0.001), systolic pulmonary artery pressure (OR: 0.917, CI: 0.621-0.982, p=0.005), and furosemide dose given in first 24 h of admission (OR: 0.877, CI: 0.541-0.998, p=0.04) were independent predictors of recovery of renal function while admission creatinine and creatinine change in 24 hours were not.

Conclusion: This study demonstrated the potential value of cystatin C and delta-cystatin C in CRS1. Further studies are required to determine the clinical utility of these findings.

Keywords: Cardio-renal syndrome type 1, cystatin C, acute decompensated heart failure, acute kidney injury

Introduction

Cardio-renal syndrome type 1 (CRS1) is a term used to describe acute kidney injury (AKI) due to worsening cardiac functions[1]. It complicates almost 40% of patients hospitalized for acute decompensated heart failure (ADHF) and is associated with higher morbidity and mortality[2]. Although creatinine is the main test to recognize AKI, it is far from being a perfect marker since it increases 48 hours after renal injury when half of the renal function is lost. It is affected by age, muscle mass and many other factors[3,4]. Novel renal markers, such as cystatin C, may detect AKI earlier than serum creatinine when a renal injury is still reversible. However, it remains unclear whether such biomarkers are also suitable for the prediction of recovery after established AKI[5].

Cystatin C is a small protein molecule produced by virtually all nucleated cells in the human body. It is suitable for estimating renal function because its production rate is nearly constant. It is freely filtered from the glomerular membrane and completely reabsorbed without being secreted from the proximal tubular cells. Moreover, its level is not influenced by sex, age, race, muscle mass, infection, liver function, and inflammation. It can be detected earlier than creatinine in renal injury. After renal injury cystatin C level increases in 8 hours, peaks at 24 hours, and decreases at 48 hours[6-10]. In previous studies, cystatin C was found to be associated with contrast-induced nephropathy, renal injury after cardiac surgery, and prognosis in acute or chronic heart failure and acute coronary syndrome[11-15]. Furthermore, Lassus et al.[5] suggested that cystatin C may be a useful marker of early AKI in patients hospitalized for ADHF in their study. However, the predictive value of cystatin C and temporal change in cystatin in AKI recovery in ADHF has not been investigated so far.

The present study aims to evaluate the predictive value of cystatin C levels at admission and 24th hour and cystatin C change in 24 hours in the development and reversibility of acute kidney injury in patients hospitalized for ADHF.

Materials and Methods

Study Population

In this observational study, we prospectively enrolled 110 consecutive patients hospitalized for decompensated heart failure. Patients with acute coronary syndrome in the last 30 days, chronic kidney disease, renal transplant, rheumatologic or auto-immune disease, acute infection, thyroid dysfunction, and malignity were excluded from the study. Patients who received intravenous diuretic therapy or radiopaque contrast media in the last 15 days and who received aminoglycosides, metformin and non-steroid anti-inflammatory drugs in the last 7 days were also excluded. The Institutional Ethics Committee of Gazi University approved the study protocol (09.06.2014/297), and all participants have given informed consent.

Analysis of Patient Data and Laboratory Analysis

Demographic parameters, symptoms, physical examination findings, medications, and the patients' medical history were recorded. A transthoracic echocardiographic examination was performed at admission. The left ventricular ejection fraction was calculated by Modified Simpson's method. Routine serum biochemical parameters including creatinine, blood urea nitrogen, electrolytes, glucose and hepatic transaminases were checked at admission, 24th and 48th hour of admission, and when respective clinicians of the patients required after then. Venous blood samples were taken at admission and 24th hour to measure cystatin C. An immune nephelometric N latex cystatin C assay (Siemens healthcare products, Germany) were used with normal cystatin C levels between 0.53-0.95 mg/L.

Definitions

Acute kidney injury was defined as an increase in serum creatinine level ≥0.3 mg/dL or ≥50% above baseline value during the hospital stay[16]. In patients who developed acute kidney injury, a discharge creatinine value below 125% of admission was defined as recovery from acute kidney injury[17]. Estimated glomerular filtration rate was calculated by the modification of diet in renal disease (MDRD) equation. Creatinine and cystatin C changes in the first 24 h of the admission were defined as delta-creatinine and delta-cystatin C. Patients with ongoing antihypertensive treatment or a systolic blood pressure 140 mmHg or diastolic blood pressure ≥90 mmHg were accepted as hypertensive. Patients on antidiabetic medications or fasting glucose levels >126 mg/dl were defined as diabetic. As ischemic etiology of heart failure was defined as the presence of heart failure with a history of myocardial infarction or coronary revascularization or presence of a ≥50% stenosis in an epicardial coronary artery.

Statistical Analysis

IBM SPSS Statistics version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical calculations. Continuous variables were presented as mean and standard deviation or median and interquartile range as appropriate. Categorical variables were presented as numbers and proportions. Distribution patterns of variables were tested with The Kolmogorov-Smirnov test. The student's t-test was used to compare data with normal distribution, and the Mann-Whitney U test was used for non-normally distributed data. The optimum cut-off level of cystatin C to predict CRS1 was determined with receiver-operating characteristics (ROC) curve analysis. A multivariable stepwise logistic regression analysis was used to examine the association of development and recovery of acute kidney injury with other variables. If a variable has a p value <0.1 in univariate logistic regression analysis, it was included in the multivariate model. A two-tailed p value <0.05 was defined as significant.

Results

The mean age of the 110 participants was 65.06, and 55 (50 %) of them were males. Forty-eight (43.6%) of the participants developed AKI. Age, gender, heart failure etiology, and rates of hypertension (HT) and diabetes mellitus (DM) were similar between patients with and without AKI. Patients in AKI group had higher body mass index (34.12±7.12 vs. 30.32±6.41, p=0.041), higher systolic blood pressure (131.74±26.42 vs. 121.33±17.80, p=0.019) and higher systolic pulmonary artery pressure (38.79±15.89 vs. 37.57±14.00, p=0.003). Daily furosemide dose before admission was significantly higher in the AKI group (94.85±83.49 vs. 50.83±42.56, p=0.036). In AKI group, ALT (20.78±11.16 vs. 15.19±7.94, p=0.003), admission creatinine (1.13±0.25 vs. 1.00±0.17, p=0.002), 24th hour creatinine (1.02±0.46 vs. 1.21±0.92, p<0.001), delta creatinine (0.02±0.01 vs. 0.08±0.06, p=0.001), admission cystatin C (1.32±0.68 vs. 1.24±0.28, p=0.002), 24th hour cystatin C (1.56±0.58 vs. 1.26±0.34, p=0.001) and delta-cystatin C (0.24±0.44 vs. 0.02±0.21, p<0.002) were significantly higher. Furosemide dose given in the first 24 h of admission was also higher in the AKI group (128.47±102.63 vs. 106.55±80.88, p=0.002) (Table 1). In multivariate logistic

Table 1. Demographic, clinical and laboratory characteristics of study patients

Variables	All patients (n=110)	No CRS1 (n=62)	CRS1 (n=48)	p value
Age (years)	65.06±29.65	64.43±31.42	65.86±28.18	0.801
Male gender, n (%)	55 (50)	26 (41.9)	29 (60.4)	0.055
BMI (kg/m^2)	31.51±6.94	30.32±6.41	34.12±7.12	**0.041**
Hypertension, n (%)	92 (83.6)	52 (83.9)	40 (83.3)	0.940
Diabetes, n (%)	59 (53.6)	32 (51.6)	27 (56.2)	0.629
Ischemic etiology, n (%)	80 (72.7)	44 (70.9)	36 (75.0)	0.332
Atrial fibrillation, n (%)	75 (68.2)	42 (67.7)	33 (68.8)	0.853
Previous medication, n (%)				
ACE-I/ARB	89 (80.9)	52 (83.8)	37 (77.1)	0.577
Beta-blocker	83 (75.5)	48 (77.4)	35 (72.9)	0.548
MRA	35 (31.8)	22 (35.5)	13 (27.1)	0.348
Furosemide	81 (73.6)	48 (77.4)	33 (68.8)	0306
Thiazide	27 (24.5)	14 (22.6)	13 (27.1)	0.767
Digoxin	24 (21.8)	12 (19.4)	12 (25.0)	0.477
Daily furosemide dose before admission (mg/day)	70.03±62.28	50.83±42.56	94.85±83.49	**0.036**
HF Hospitalization in last year	1.73±2.05	2.13±2.54	1.24±0.971	0.055
Hospitalization duration (days)	11.77±7.78	12.06±7.22	11.40±8.51	0.657
LVEF (%)	35.95±15.24	36.47±13.32	35.29±16.28	0.146
Systolic PAP (mmHg)	38.10±15.21	37.57±14.00	38.79±15.89	**0.003**
Heart rate (min^{-1})	87.84±21.02	85.74±21.31	90.86±20.45	0.222
Systolic BP (mmHg)	125.68±22.31	121.33±17.80	131.74±26.42	**0.019**
Diastolic BP (mmHg)	74.56±12.74	74.67±13.02	74.42±12.20	0.923
Hemoglobin (g/dL)	11.46±2.27	11.69±2.49	11.16±1.95	0.219
WBC (x1000/µL)	7.74±2.01	7.90±2.19	7.53±1.76	0.351
AST (IU/L)	26.00±11.90	26.03±12.63	25.96±10.94	0.974
ALT (IU/L)	17.54±9.78	15.19±7.94	20.78±11.16	**0.003**
CRP (mg/L)	23.84±46.80	27.41±56.22	19.28±16.28	0.374
Na (mmol/L)	136.69±5.36	135.58±5.54	138.17±4.80	0.052
Cystatin C (mg/L)	1.27±0.34	1.24±0.28	1.32±0.68	**0.002**
Cystatin C 24h (mg/L)	1.39±0.52	1.26±0.34	1.56±0.58	**0.001**
Delta-cystatin C (mg/L)	0.12±0.29	0.02±0.21	0.24±0.44	**<0.001**
BUN (mg/dL)	25.57±9.62	25.04±9.73	25.25±9.18	0.509
BUN 24h (mg/dL)	34.36±14.75	30.42±7.63	39.46±18.04	**0.001**
Maximum BUN (mg/dL)	43.54±1687	37.27±8.13	51.66±21.36	**0.001**
Creatinine (mg/dL)	1.06±0.22	1.00±0.17	1.13±0.25	**0.002**
Creatinine 24h (mg/dL)	1,10±0.68	1.02±0.46	1.21±0.92	**<0.001**
Maximum creatinine (mg/dL)	1.32±0.49	1.09±0.26	1.62±0.54	**<0.001**
Delta-creatinine (mg/dL)	0.04±0.03	0.02±0.01	0.08±0.06	**0.001**
Furosemide dose-first 24 h (mg)	114.94±88.28	106.55±80.88	128.47±102.63	**0.002**

Significant p values are shown in bold.
ACE-I: Angiotensin-converting enzyme inhibitor, ALT: Alanine transaminase, ARB: Angiotensin receptor blocker, AST: Aspartate transaminase, BP: Blood pressure, BMI: Body mass index, BUN: Blood urea nitrogen, CRP: C-reactive protein, CRS1: Cardio-renal syndrome type 1, HF: Heart failure, LVEF: Left ventricular ejection fraction, MRA: Mineralocorticoid receptor antagonist, PAP: Pulmonary artery pressure, WBC: white blood cell

regression analysis, admission cystatin C level [odds ratio (OR): 30.97, confidence interval (CI): 9.28-139.60, p<0.001] and delta-cystatin C (OR: 41.26, CI: 7.75-93.55, p<0.001) were found as independent predictors for development of AKI. Furosemide dose is given in the first 24 h of admission (OR: 1.941, CI: 1.541-4.112, p=0.009), and systolic pulmonary artery pressure (OR: 0.927, CI: 0.874-0.983, p=0.011) were other independent predictors. Although baseline creatinine level and delta-creatinine were predictive of AKI in univariate analysis, they lost their significance in multivariate analysis (Table 2). The receiver-operating characteristic (ROC) curve analysis showed that cystatin C at a cut-off point of 1.385 could detect the occurrence of AKI with 77.1% sensitivity and 77.4% specificity (Figure 1).

Among 48 patients in AKI group, renal function was recovered in 31 (64.6%) during hospital stay. There is not any significant difference between patients with recovered and unrecovered renal function regarding age, gender, heart failure etiology and rates of HT and DM. Admission cystatin C level (1.33±0.72 vs. 1.30±0.60, p=0.661), maximum creatinine level (1.64±0.63 vs. 1.61±0.51, p=0.184) and delta-creatinine (0.08±0.07 vs. 0.08±0.04, p=0.988) were similar between groups. While systolic blood pressure (140.89±26.97 vs. 114.67±14.57, p=0.001) and admission creatinine (1.21±0.23 vs. 0.98±0.19, p=0.001) were higher, hospitalization due to heart failure in last year (0.92±0.58 vs. 1.79±1.25, p=0.006), systolic pulmonary artery pressure (32.48±9.56 vs. 50.29±18.76,p ≤0.001), cystatin C at 24th hour of admission (1.38±0.47 vs. 1.89±0.63, p=0.003), delta-cystatin C (0.05±0.06 vs. 0.59±0.21, p=0.001) and furosemide dose given in first 24 h of admission (124.60±114.18 vs. 135.52±89.92, p=0.001) were significantly lower in patients with recovered renal function. Need for hemodialysis (17.6% vs. 16.1%, p=0.222) and time to hemodialysis (132.4±64.58 h vs. 138.5±78.33 h, p=0.265) were similar between groups (Table 3). In multivariate logistic regression analysis, cystatin c change in 24 h was found as an independent predictor of recovery of renal function in patients with AKI (OR: 0.088, CI: 0.018-0.441, p=0.001). Systolic pulmonary artery pressure (OR: 0.917, CI: 0.621-0.982, p=0.005), p=0.033) and furosemide dose given in first 24 h of admission (OR: 0.877, CI: 0.541-0.998, p=0.04) were other independent predictors (Table 4).

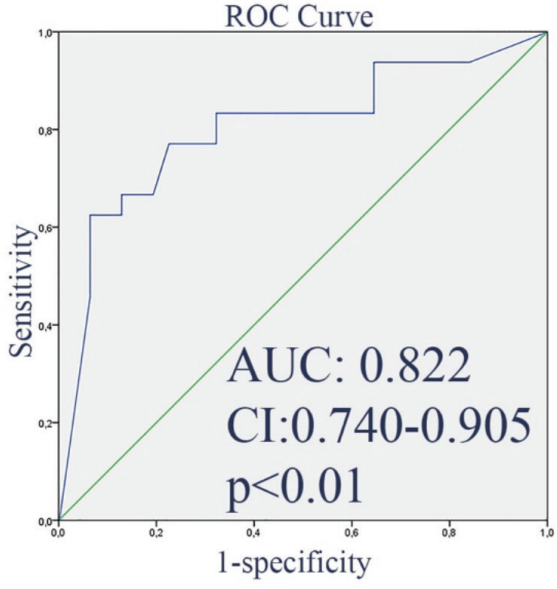

Figure 1. The receiver operating characteristic curve analysis for admission Cystatin C in predicting cardio-renal syndrome type 1

AUC: Area under the curve, CI: confidence interval, ROC: Receiver operating characteristics

Discussion

The present study demonstrated for the first time that the change in cystatin C level in the first 24 h of admission is associated with the development and recovery of CRS1 in patients hospitalized for acute heart failure. In addition, admission cystatin C level was associated with the development of CRS1 in these patients. Admission creatinine and creatinine change in the first 24 h of admission were not independent predictors of CRS1 and its recovery.

Pathophysiological mechanisms underlying CRS1 are not entirely understood. Advanced age and pre-existing chronic kidney disease are essential, but classical risk factors of AKI such as hypotension and hypovolemia are uncommon in this population[18]. Although renal venous HT and renal hypoperfusion are thought to be the major

mechanism of CRS1, previous studies showed that LVEF is not associated with CRS 1 and renal deterioration is not correlated with cardiac output, filling pressures and systemic vascular resistance[19]. It is probably due to the fact that endogenous vasoactive substances such as endothelin, nitric oxide, prostaglandins, natriuretic peptides, and vasopeptidase inhibitors interact with renal perfusion independent of central hemodynamics[20-21]. Even so, it is known that elevated central venous pressure causes increased renal venous and interstitial pressures, leading to the kidney's inability to maintain the glomerular filtration rate resulting in hypoxia renin-angiotensin-aldosterone system activation[22]. Cardio-renal syndrome type1 is rarely seen before hospital admission. It is thought to be a particular evidence of the effect of in-hospital medication on renal function in these patients. High-dose furosemide is associated with a worse renal prognosis. However, it is not clear whether the need for higher doses of furosemide is a cause or a consequence of advanced heart failure or blunt diuretic response due to pre-existing renal failure[23]. In our study, we found out that the furosemide dose given in the first 24 h of admission is associated with CRS1.

Age and chronic kidney disease were shown to be associated with recovery of AKI in different populations. However, it is still unclear whether demographic and clinical factors associated with the development of CRS1 are also helpful for predicting the recovery of CRS1[24,25]. The effect of the presence of chronic kidney disease on the prediction of CRS1 and its recovery was not evaluated in our study since patients with CKD were excluded. However, admission creatinine was not associated with CRS1 and its recovery in our study. We did not find an association between age and development and recovery of CRS1. Schiffl[26] and Alsultan[27] did not find such an association in patients with AKI requiring renal replacement therapy either.

Cystatin C is an important marker of prognosis in AHF[28,29]. Previous studies showed that cystatin C is a

Table 2. Predictors of CRS1 in multivariate logistic regression analysis

Variables	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.995 (0.958-1.033)	0.799	-	
Gender (male)	2.113 (0.981-4.553)	0.56	-	
Hypertension	0.962 (0.348-2.658)	0.940	-	
Diabetes mellitus	1.205 (0.565-2.570)	0.629	-	
Daily furosemide dose before admission	0.642 (0.274-1.505)	0.308	-	
Furosemide dose-first 24 h	2.762 (1.841-3.546)	0.002	1.941 (1.541-4.112)	0.009
Hospitalization (1 year)	0.774 (0.594-1.010)	0.059	0.850 (0.555-1.303)	0.456
Systolic blood pressure	1.023 (1.003-1.044)	0.027	0.958 (0.944-1.026)	0.462
BUN	1.014 (0.974-1.055)	0.506	-	
ALT	1.065 (1.018-1.114)	0.006	1.079 (0.995-1.158)	0.057
Creatinine	23.74 (2.79-201.73)	0.004	16.85 (0.565-502.70)	0.103
Delta-creatinine	27.41 (3.98-321.14)	0.003	18.21 (0.873-345.78)	0.098
Cystatin C	24.59 (6.35-95.23)	<0.001	30.97(9.28-139.60)	<0.001
Delta-cystatin C	22.26 (4.523-109.57)	<0.001	41.26 (7.75-93.55)	<0.001
LVEF	0.981 (0.955-1.007)	0.146	1.028 (0.971-1.089)	0.344
Systolic PAP	0.961 (0.935-0.988)	0.004	0.927 (0.874-0.983)	0.011

ALT: Alanine transaminase, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, PAP: Pulmonary artery pressure, OR: Odds ratio, CI: Confidence interval

Table 3. Demographic, clinical and laboratory characteristics of patients with recovered and non-recovered acute kidney injury

Variables	All CRS1 (n=48)	AKI has not recovered (n=17)	AKI recovered (n=31)	p value
Age (years)	65.86±28.18	66.38±26.48	65.58±28.62	0.564
Gender (male), n (%)	29 (60.4)	10 (58.8)	19 (61.3)	0.867
BMI (kg/m^2)	34.12±7.12	35.42±9.06	31.74±6.01	0.145
Hypertension, n (%)	40 (83.3)	12 (70.6)	28 (90.3)	0.079
Diabetes, n (%)	27 (56.2)	12 (70.6)	15 (48.4)	0.138
Ischemic etiology, n (%)	36 (78.0)	13 (76.4)	23 (74.19)	0.336
Atrial Fibrillation, n (%)	33 (68.8)	11 (64.7)	22 (70.9)	0.165
Previous medication, n (%)				
ACE-I/ARB	37 (77.1)	13 (76.47)	24 (77.41)	0.453
Beta-blocker	35 (72.9)	13 (76.47)	22 (70.96)	0.381
MRA	13 (27.1)	5 (29.4)	8 (25.8)	0.788
Furosemide	33 (68.8)	15 (88.2)	18 (58.1)	0.031
Thiazide	13 (27.1)	6 (29.4)	7 (22.6)	0.601
Digoxin	12 (25.0)	3 (176)	9 (29.0)	0.384
Daily furosemide dose before admission (mg/day)	94.85±83.49	80.00±63.696	107.22±72.75	0.568
HF hospitalization in last year	1.24±0.971	1.79 ±1.25	0.92±0.58	**0.006**
Hospitalization duration (days)	11.40±8.51	12.94±8.70	10.55±8.42	0.357
LVEF (%)	35.29±16.28	34.76 ±17.65	35.58 ±15.76	0.870
Systolic PAP (mmHg)	38.79±15.89	50.29±18.76	32.48±9.56	**<0.001**
Heart rate (min^{-1})	90.86±20.45	91.53±13.4	90.50±± 23.6	0.877
Systolic BP (mmHg)	131.74±26.42	114.67±14.57	140.89±26.97	**0.001**
Diastolic BP (mmHg)	74.42±12.20	70.67±9.61	76.43±13.11	0.142
Hemoglobin (g/dL)	11.16±1.95	11.97±2.10	10.71±1.73	0.051
WBC (x1000/µL)	7.53±1.76	8.11±2.57	7.22±1.03	0.096
CRP (mg/L)	19.28±16.28	31.24±15.98	13.09±17.07	0.055
Na (mmol/L)	138.17±4.80	139.25±5.10	137.61±4.61	0.272
Cystatin C (mg/L)	1.32±0.68	1.30±0.60	1.33±0.72	0.661
Cystatin C 24h (mg/L)	1.56±0.58	1.89±0.63	1.38±0.47	**0.003**
Delta-cystatin C (mg/L)	0.24±0.44	0.59±0.21	0.05±0.06	**0.001**
BUN (mg/dL)	25.25±9.18	30.18±9.83	24.09±8.18	0.26
BUN 24h (mg/dL)	39.46±18.04	46.35±24.37	35.68±12.31	0.49
Maximum BUN (mg/dL)	51.66±21.36	56.12±26.77	49.21±18.49	**0.001**
Creatinine (mg/dL)	1.13±0.25	1.15±0.19	1.12±0.28	**0.02**
Creatinine 24h (mg/dL)	1.21±0.92	1.23±0.76	1.20±0.97	**0.01**
Maximum creatinine (mg/dL)	1.62±0.54	1.64±0.63	1.61±0.51	0.184
Delta-creatinine (mg/dL)	0.08±0.05	0.08±0.07	0.08±0.04	0.988
Furosemide dose-first 24 h (mg)	128.47±102.63	135.52±89.92	124.60±114.18	**0.001**
Hemodialysis	8 (16.7)	3 (17.6)	5 (16.1)	0.222
Time to hemodialysis	136.3±71.26	132.4±64.58	138.5±78.33	0.265

Significant p values are shown in bold.
ACE-I: Angiotensin-converting enzyme inhibitor, AKI: Acute kidney injury, ALT: Alanine transaminase, ARB: Angiotensin receptor blocker, AST: Aspartate transaminase, BMI: Body mass index, BP: Blood pressure, BUN: Blood urea nitrogen, CRP: C-reactive protein, CRS1: Cardio-renal syndrome type 1, HF: Heart failure, LVEF: Left ventricular ejection fraction, MRA: Mineralocorticoid receptor antagonist, PAP: Pulmonary artery pressure, WBC: White blood cell

more reliable marker of renal function than creatinine post cardiopulmonary bypass and detected reduced glomerular filtration rate at an earlier stage after cardiac catheterization[30,31]. Lassus et al.[5] demonstrated that cystatin C is a useful marker of AKI in AHF, and a rise in cystatin C >0.3 mg/L within 48 h after hospitalization was associated with longer hospital stay and higher in-hospital mortality. A study by Carrasco-Sanchez et al.[32] also showed the usefulness of cystatin C in predicting AKI and prognosis in AHF. In contrast, Breidthardt et al.[33] suggested that plasma cystatin C levels cannot adequately predict CRS1 in AHF. Results of the present study confirm the usefulness of cystatin C in predicting CRS1 in AHF. In addition to previous studies, the potential utility of the cystatin C change in the first 24 h in the prediction of CRS was demonstrated.

The value of the novel renal markers in the recovery of AKI has recently been investigated in some studies. In one of them, among neutrophil gelatinase-associated lipocalin (NGAL), the mRNA expressions of kidney injury molecule-1, interleukin-18, alpha-1-microglobulin, sodium/hydrogen exchanger-3, beta-2 microglobulin and N-acetyl-β-D-glucosaminidase, only alpha-1-microglobulin was correlated with the degree of improvement in renal failure[34]. In another, plasma NGAL predicted the failure of renal recovery in community-acquired pneumonia[35]. Urine NGAL and urine hepatocyte growth factor were also showed promise in the prediction of renal recovery[36,37]. Furthermore, Gharaibeh et al.[38] suggested that cystatin C decreases one day earlier than creatinine in most hospitalized patients with AKI, and Leem et al.[39] showed that admission serum cystatin C was associated with recovery of AKI in patients with sepsis-induced kidney injury. In their study on CRS1 patients, Basu et al.[40] suggested that a composite of urine NGAL and plasma cystatin C is superior to serum creatinine for predicting transient AKI in children after cardiopulmonary bypass. Unfortunately, none of the studies above were performed on AHF patients. Results of the present study demonstrated the potential usefulness of cystatin C and

Table 4. Predictors of the recovery from acute kidney injury in multivariate logistic regression analysis

	Univariable		Multivariable	
Variables	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Age	1.055 (0.986-1.127)	0.119	-	
Male Gender	1.108 (0.332-3.703)	0.867	-	
Diabetes mellitus	0.391 (0.111-1.375)	0.143	-	
Body mass index	1.425 (0.998-1.942)	0.174	-	
Atrial fibrillation	3.800 (1.068-13.520)	0.039	2.480 (0.984-15.648)	0.088
Systolic blood pressure	1.092 (1.031-1.158)	0.003	1.088 (1.025-1.188)	0.09
AST	0.990 (0.937-1.046)	0.718	-	
Hemoglobin	0.663 (0.445-0.989)	0.044	0.758 (0.328-1.055)	0.101
WBC	0.741 (0.512-1.073)	0.112	-	
Sodium	0.938 (0.541-1.357)	0.188	-	
LVEF	1.003 (0.967-1.041)	0.867	-	
Systolic PAB	0.908 (0.854-0.965)	0.002	0.917 (0.621-0.982)	0.005
Cystatin	1.228 (0.501-3.012)	0.653	-	
Delta-cystatin C	0.057 (0.008-0.409)	0.002	0.088 (0.018-0.441)	0.001
Creatinine	0.632 (0.319-0.868)	0.032	0.741 (0.289-0.827)	0.063
Delta-creatinine	0.982 (0.241-1.368)	0.122	-	
Furosemide dose-first 24 h	0.842 (0.565-0.922)	0.038	0.887 (0.541-0.998)	0.04

AST: Aspartate transaminase, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, PAP: Pulmonary artery pressure, WBC: White blood cell

its change with time in the prediction of CRS1 and its recovery.

The present study has several limitations. It is a retrospective and single-center study. However, all consecutive patients hospitalized for ADHF in a time frame were included in the study to overcome the limitations of the retrospective design. Moreover, BNP or pro-BNP levels were not measured. Thus, we do not have biochemical evidence about the severity of the heart failure in patients with and without CRS1.

Conclusion

Admission cystatin C may predict CRS1, and a change in cystatin C level in the first 24 h of admission is associated with the development and recovery of CRS1 in patients hospitalized for acute heart failure. Cystatin C may be used as a predictor of renal function beyond creatinine in AHF because neither admission creatinine nor its change in the 24th hour was associated with CRS and its recovery in our study population. Further studies are required to elucidate the role of cystatin C and its temporal change in predicting renal outcomes in ADHF.

Ethics

Ethics Committee Approval: The Institutional Ethics Committee of Gazi University approved the study protocol (decision no: 297, date: 09.06.2014).

Informed Consent: All participants gave informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Design: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Data Collection and/or Processing: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Analysis and/or Interpretation: Açıkgöz E, Açıkgöz SK, Özilhan MO, Özlem G, Özdemir HM, Literature Search: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Writing: Açıkgöz E, Açıkgöz SK, Özdemir HM.

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References

1. Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 2010;31:703-11.
2. Smith GL, Lichtman JH, Bracken MB, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006;47:1987-96.
3. Soni SS, Ronco C, Katz N, et al. Early diagnosis of acute kidney injury: the promise of novel biomarkers. Blood Purif 2009;28:165-74.
4. Kellum JA, Mehta RL, Levin A, et al. development of a clinical research agenda for acute kidney injury using an international, interdisciplinary, three-step modified Delphi process. Clin J Am Soc Nephrol 2008;3:887-94.
5. Lassus JP, Nieminen MS, Peuhkurinen K, et al. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. Eur Heart J. 2010;31:2791-8.
6. Cruz DN, Goh CY, Haase-Fielitz A, et al. Early biomarkers of renal injury. Congestive Heart Failure. 2010;16 Suppl 1:S25-31.
7. Newman DJ. Cystatin C. Ann Clin Biochem 2002;39:89-104.
8. Onopiuk A, Tokarzewicz A, Gorodkiewicz E. Cystatin C: a kidney function biomarker. Adv Clin Chem 2015;68:57-69.
9. Bagshaw SM, Bellomo R. Cystatin C in acute kidney injury. Curr Opin Crit Care 2010;16:533-9.
10. Angelidis C, Deftereos S, Giannopoulos G, et al. Cystatin C: an emerging biomarker in cardiovascular disease. Curr Top Med Chem 2013;13:164-79.
11. Briguori C, Visconti G, Rivera NV, et al. Cystatin C and contrast-induced acute kidney injury. Circulation 2010;121:2117-22.
12. Wang QP, Gu JW, Zhan XH, et al. Assessment of glomerular filtration rate by serum cystatin C in patients undergoing coronary artery bypass grafting. Ann Clin Biochem 2009;46:495-500.
13. Alehagen U, Dahlstrom U, Lindahl TL. Cystatin C and NT-proBNP, a powerful combination of biomarkers for predicting cardiovascular mortality in elderly patients with heart failure: results from a 10-year study in primary care. Eur J Heart Fail 2009;11:354-60.

14. Rafouli-Stergiou P, Parissis J, Farmakis D, et al. Prognostic value of in-hospital change in cystatin C in patients with acutely decompensated heart failure and renal dysfunction. Int J Cardiol 2015;182:74-6.

15. Garcia Acuna JM, Gonzalez-Babarro E, Grigorian Shamagian L, et al. Cystatin C provides more information than other renal function parameters for stratifying risk in patients with acute coronary syndrome. Rev Esp Cardiol 2009;62:510-9.

16. KDIGO Clinical Practice Guidelines for Acute Kidney Injury 2012. Kidney Int Suppl 2012;2:1-138.

17. Pannu N, James M, Hemmelgarn B, et al. Alberta. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. Clin J Am Soc Nephrol 2013;8:194-202

18. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004;43:61-7.

19. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J 1999;138:285-90.

20. Friedrich EB, Muders F, Luchner A, et al. Contribution of the endothelin system to the renal hypoperfusion associated with experimental congestive heart failure. J Cardiovasc Pharmacol 1999;34:612-7.

21. Abassi Z, Gurbanov K, Rubinstein I, et al. Regulation of intrarenal blood flow in experimental heart failure: role of endothelin and nitric oxide. Am J Physiol 1998;274:F766-74.

22. Fiksen-Olsen MJ, Strick DM, Hawley H, et al. Renal effects of angiotensin II inhibition during increases in renal venous pressure. Hypertension 1992;19:137-41.

23. Metra M, Nodari S, Parrinello G, et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. Eur J Heart Fail 2008;10:188-95.

24. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16:3365-70.

25. Macedo E, Zanetta DM, Abdulkader RC. Long-term follow-up of patients after acute kidney injury: patterns of renal functional recovery. PLoS One 2012;7:e36388.

26. Schiffl H. Renal recovery from acute tubular necrosis requiring renal replacement therapy: a prospective study in critically ill patients. Nephrol Dial Transplant 2006;21:1248-52.

27. Alsultan M. The renal recovery of critically ill patients with acute renal failure requiring dialysis. Saudi J Kidney Dis Transpl 2013;24:1175-9.

28. Lassus J, Harjola VP, Sund R, et al. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur Heart J 2007;28:1841-7.

29. Campbell CY, Clarke W, Park H, et al. Usefulness of cystatin C and prognosis following admission for acute heart failure. Am J Cardiol 2009;104:389-92.

30. Zhu J, Yin R, Wu H, et al. Cystatin C as a reliable marker of renal function following heart valve replacement surgery with cardiopulmonary bypass. Clin Chim Acta 2006;374:116-21.

31. Artunc FH, Fischer IU, Risler T, et al. Improved estimation of GFR by serum cystatin C in patients undergoing cardiac catheterization. Int J Cardiol 2005;102:173-8.

32. Carrasco-Sanchez FJ, Galisteo-Almeda L, Paez-Rubio I, et al. Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Card Fail 2011;17:31-8.

33. Breidthardt T, Sabti Z, Ziller R, et al. Diagnostic and prognostic value of cystatin C in acute heart failure. Clin Biochem 2017;50:1007-1013.

34. Luk CC, Chow KM, Kwok JS, et al. Urinary biomarkers for the prediction of reversibility in acute-on-chronic renal failure. Dis Markers 2013;34:179-85.

35. Murugan R, Karajala-Subramanyam V, Lee M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. Kidney Int 2010;77:527-35.

36. Moon SJ, Park HB, Yoon SY, et al. Urinary biomarkers for early detection of recovery in patients with acute kidney injury. J Korean Med Sci 2013;28:1181-6.

37. Srisawat N, Wen X, Lee M, et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol 2011;6:1815-23.

38. Gharaibeh KA, Hamadah AM, El-Zoghby ZM, et al. Cystatin C predicts renal recovery earlier than creatinine among patients with acute kidney injury. Kidney Int Rep 2017;3:337-342.

39. Leem AY, Park MS, Park BH, et al. Value of serum cystatin C measurement in the diagnosis of sepsis-induced kidney injury and prediction of renal function recovery. Yonsei Med J 2017;58:604-12.

40. Basu RK, Wong HR, Krawczeski CD, et al. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. J Am Coll Cardiol 2014;64:2753-62.