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Type I cardiorenal syndrome in patients with acutely decompensated heart failure: the importance of new renal biomarkers

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Abstract. – OBJECTIVE: Type 1 cardiorenal syndrome (CRS) is an acute renal failure in patients with acute decompensated heart failure with an incidence of 24% to 45%. The aim of our study was to investigate the significance of new renal biomarkers to predict type 1 CRS.

PATIENTS AND METHODS: The study included 111 patients with acute decompensated heart failure diagnosed at the Istanbul Medical Faculty Emergency Department between 2014 and 2016, and 24 healthy volunteers. All urine samples were stored at -80°C after centrifugation. Samples were run according to the instructions of TIMP-2, ILGF-7, KIM-1, and IGFBP-7 ELISA kits. Diuretic treatments were then administered with intravenous administration of at least 80 mg furosemide per day. Follow-up biochemical and spot urine specimens were taken after 72 hours. For statistical analysis, SPSS version 21.0 statistical software was used. Significance was evaluated at $p<0.05$.

RESULTS: The baseline creatinine level was measured as 1.33 ± 0.39 mg/dL in the heart failure group. It was seen that 67% (75) of the patients had increased creatinine levels and developed type 1 CRS. ILGF-7, TIMP-2, and (ILGF-7 * TIMP-2) values were significantly higher in patients with cardiorenal syndrome when we separated the two groups as patients with and without cardiorenal syndrome (0.40 (0.25-0.71), p1: 0.049/2.40 (1.42-3.70), p2: 0.003/1.15 (0.29-2.43), p3: 0.001).

CONCLUSIONS: Renal tubular markers reveal promising developments in the pathophysiology of cardiorenal syndrome in light of recently obtained data. Renal tubular biomarkers may have the potential to be a predictor of heart failure and cardiorenal syndrome.

Key Words
Cardiorenal syndrome, Acute decompensated heart failure, Renal biomarkers.

Introduction

Cardiac and renal diseases are common, serious health problems that frequently occur together and increase morbidity, mortality, and healthcare expenditure[1,2]. There are complex physiologic, biochemical, and hormonal interactions between the heart and kidneys[3], and problems with these interactions are collectively referred to as cardiorenal syndrome (CRS)[4]. The frequency of type 1 CRS is 24% to 45% in patients with acutely decompensated heart failure. Hospitalization and hospital admissions increase in patients with type 1 CRS and the mortality rate can reach up to 22% in these patients[5].

Diuretics are used to rapidly correct acutely decompensated heart failure; however, treatment is often complicated by a deterioration of renal function[6]. On the other hand, in cases of diuretic resistance, tubular damage might result from excessive diuretic doses, leaving physicians unsure of how best to proceed[7,8].

Early diagnosis can prevent the emergence of acute renal failure. Serum creatinine measurement is inadequate for the early detection of kidney damage because it requires 48-72 h for elevation and has low sensitivity[9]. Kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinase-2 (TIMP-2), and insulin-like growth factor binding protein (IGFBP-7) have also been shown to be present early in the course of renal damage, typically resulting from the presence of inflammation, ischemia, oxidative stress, drugs or toxins [0-12]. KIM-1 can also be used to distinguish between ischemic acute kidney injury (AKI) and pre-renal azotemia[13]. These molecules have been

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shown to be effective in the diagnosis of AKI in many clinical situations, such as coronary bypass surgery[14-17], heart failure[18], and contrast-dependent renal failure[17,19].

Here, among patients with acutely decompensated heart failure, we aimed to identify patients who would develop acute renal failure after diuretic use, and to assess the role of new biomarkers in predicting the development of type I CRS according to blood urea nitrogen (BUN) and creatinine levels.

Patients and Methods

Patients

One-hundred-eleven patients who were diagnosed as having acute decompensated CHF between 2014 and 2016 at the Istanbul Medical Faculty Emergency Department and 24 healthy volunteers were included in the study. Written and oral consents were obtained. Heart failure was defined using the criteria of the European Society of Cardiology. The study group consisted of patients between 50- and 75-years-old with decompensated heart failure symptoms with a preserved or low ejection fraction. Patients with acute myocardial infarction, recent stroke, severe pulmonary disease, immunosuppressive chemotherapy treatment, sepsis or end-stage renal failure were excluded from the study.

Acute cardiorenal syndrome (type-1) was defined as acute dysfunction in the heart due to complicated pathophysiologic disorders caused by the kidney. An increase of 35% or 0.5 mg/dL in baseline creatinine was considered acute renal failure.

Functional capacity, medication, diuretic dose, and physical examination findings (edema, rheumatism, jugular venous fullness) were evaluated in all patients. Experts with similar experience levels made these evaluations. Simpson method was used to measure election fractions. Glomerular filtration rates (GFR) were calculated according to the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Written informed consents were taken from all patients. The Local Ethics Committee of Istanbul Medical Faculty approved the study.

Sample Taking and Biochemical Analysis

Patients who were hospitalized and were not scheduled to be discharged in less than 72 h were selected. At least 200 µl of spot urine samples were taken from these patients (two separate urine samples at 72-h intervals). All urine samples were stored at -80°C after centrifugation. The levels of urinary KIM-1, TIMP-2, and IGFBP-7 were determined by enzyme-linked immunosorbent assay (ELISA). All ELISAs were performed by a single investigator using commercial kits following the manufacturer's instructions. The sensitivity and specificity of the ELISAs were both 98%. The baseline biochemical and urine samples of patients were measured quantitatively. Diuretic treatments were intravenously administered with at least 80 mg furosemide per day. Follow-up biochemical and spot urine specimens were taken after 72 h.

Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a transmembrane protein that originates from the tubules of nephrons. In animal experiments, it has been shown that KIM-1, which cannot be determined in normal kidney tissue or urine, increases significantly in proximal tubule epithelial cells in response to ischemic or toxic AKI[13]. The rate of excretion of KIM-1 from the kidneys seems to be affected during ischemic or toxic acute renal damage. Therefore, kidney damage seems a more sensitive marker than BUN or creatinine because no expression is observed in other organs. It is thought that KIM-1 is particularly effective in the diagnosis of AKI[20].

Tissue Inhibitor of Metalloproteinases 2 (TIMP-2)

TIMP-2 is a member of the TIMP gene family. Proteins encoded by this gene family are natural inhibitors of matrix metalloproteinases. In addition to its inhibitory effect on metalloproteinases, TIMP-2 can directly inhibit endothelial cell proliferation and, therefore, has a more dominant role than other members of the TIMP family.

As a result, TIMP-2 suppresses the proliferation of silent tissues in response to angiogenic factors and inhibits protease activity, which leads to remodeling of the extracellular matrix in these tissues, thereby playing a critical role in tissue homeostasis. TIMP-2 can work as both an inhibitor and activator of metalloproteinases[21].

Insulin-like Growth Factor Binding Protein 7 (IGFBP-7)

Insulin-like growth factor-binding protein 7 (IGFBP-7) is encoded by the IGFBP7 gene in humans[22,23]. The major function of this protein is to regulate the binding of insulin-like growth factors

to IGF-binding receptors. IGFBP-7 binds to IGF with high affinity[24] and stimulates cell adhesion.

TIMP-2 and IGFBP-7 are biomarkers that occur early in the course of tubular damage, such as damage arising from inflammation, ischemia, oxidative stress, drugs, and toxins [25]. Both TIMP 2 and IGFBP7 are released in the G1 phase of the cell cycle, which is early in the cellular stress response [25]. TIMP 2 and IGFBP7 have been detected in the G1 phase of cell cycle arrest, especially in renal tubular cells following various stresses [26]. Induction of the cell cycle is associated with an increased risk of AKI, and might also be a sign of a mechanical link between CKD of AKI[27]. Continuous cell cycle arrest might result in an aging-cell phenotype and the progression of fibrosis. Interestingly, various TIMP protein subgroups might be involved in various roles in the kidney. Price et al[28] have shown that TIMP-3 can protect cells against damage. On the other hand, TIMP-2 can induce damage through the activation of matrix metalloproteinases. Also, increased urine TIMP-2 and IGFBP-7 levels are strongly associated with death and need of dialysis[29].

Echocardiographic Evaluation

In all patients, myocardial function was assessed by echocardiography. Echocardiographic examination was performed at least 15 min after rest, in the left lateral position (2-dimensional, M-mode, Doppler echocardiography) using a Philips IE33 instrument and an X5-1 parasternal transducer, and apical windows using a transthoracic probe. Echocardiography was performed on each participant according to standard imaging techniques in the American and European Echocardiography Society (AEC) guidelines. All images were recorded digitally and then analyzed.

Statistical Analysis

SPSS (version 21.0, Chicago, IL, USA) statistical software was used for all statistical analyses. The Kolmogorov-Smirnov test was used to determine the normality of the distribution. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used for data evaluation. The Mann-Whitney U test was used to compare two groups of nonparametric parameters in the comparison of quantitative data. *p*-values less than 0.05 were considered statistically significant. The Kolmogorov-Smirnov test was used to determine the normality of the distribution.

Results

General Characteristics of the Groups

The clinical and demographic characteristics of the 111 patients with acutely decompensated heart failure and 24 healthy volunteers are shown in Table I. The mean age of the patients with chronic heart failure was 65.0 ± 5.5 years, and 56% (n = 63) were men. 60% (n = 67) of the heart failure group had type 2 diabetes mellitus (DM), 51% (n = 57) had coronary artery disease, and 14% (n = 16) had a cerebrovascular accident. 48% (n = 54) of all patients were using ACEI/ARB, 41% (n = 46) were using spironolactone, and 29% (n = 33) were using oral anti-diabetic drugs. 42% (n = 47) of the patients were smokers. The functional capacity of all patients was measured as ≥ III according to the New York Heart Association (NYHA) classification. When we classified the ejection fraction (EF) as below and above 50%, 54% of patients (n = 60) had an EF of less than 50%, and 46% (n = 45) had an EF of greater than 50%. The subjects included in the study were divided into patients with heart failure and healthy volunteers. In the heart failure group, ILGF-7, TIMP-2, ILGF-7+TIMP-2, and KIM-1 levels were significantly higher than in the healthy volunteers (Figure 1). The baseline creatinine level was measured as 1.33 ± 0.39 mg/dL in the heart failure group. 67% of patients (n = 75) developed CRS. When we divided patients into those with or without cardiorenal syndrome, we found that ILGF-7, TIMP-2, and ILGF-7+TIMP-2 values were significantly higher in patients with CRS (0.40, 71), p1: 0.049/2.40 (1.42-3.70), p2: 0.003/1.15 (0.29-2.43), p3: 0.001) (3.88 (2.72–5.38), p4: 0.615) (Figure 2). Using receiver operating characteristic (ROC) curve analysis, we assessed the specificity and sensitivity of ILGF-7, TIMP-2, ILGF-7+TIMP-2, and KIM-1 levels to predict the development of type 1 CRS. The blue line color indicates TIMP-2 and its area under the curve (AUC) was 0.73 (0.59-0.87). The red line represents ILGF7+TIMP2, and its AUC was 0.75 (0.61-0.88). The purplish line represents ILGF7, and its AUC was 0.64 (0.48-0.79). The green line represents KIM-1, and its AUC was 0.54 (0.37-0.70). The AUC of ILGF-7+TIMP-2 was 0.75 (0.61–0.88), which is significantly higher than for other parameters (Figure 3).

Patients were divided into two groups according to their ejection fractions, and the differences between their ILGF-7, TIMP-2, ILGF-7+TIMP-2, and KIM-1 levels were evaluated. We detected no

Table I. Baseline characteristics of study group and healthy volunteers.

	Patients (n=111)	Control (n=24)	*p*-value
Age (year)	65±5.5	66.7±4.8	0.155
Gender (male %)	63 (% 56)	14 (% 58)	0.887
HT	67 (% 60)		
DM	52 (% 46)		
CAD	57 (% 51)		
SVA	16 (% 14)		
Smoking	47 (% 42)		
AF	55 (% 49)		
NYHA [III/IV n (%)]	59 (% 53) / 52(% 46)		
LVEF	45.41±16.07	64.83±6.90	<0.001
LVEF [≥ 50%/< % 50, n (%)]	51(% 45) / 60(% 54)		
Pro BNP (pg/mL)	4292 (2264-7852)	79 (56-110)	<0.001
Creatinine basal (mg/dl)	1.33±0.39	0.83±0.20	<0.001
Creatinine control (mg/dl)	1.52±0.54	0.82±0.16	<0.001
GFR (ml/dk/1.73 m^2)	55 (44-74)	85 (74-113)	<0.001
Renal Biomarkers			
KIM-1 (ng/ml)	4.41 (3.07-5.66)	3.24 (2.49-3.85)	0.003
TIMP-2 (ng/ml)	2.66 (1.68-4.24)	1.54 (0.49-2.95)	0.009
IGFBP-7 (ng/ml)	0.44 (0.29-0.87)	0.34 (0.19-0.39)	0.027
(IGFBP-7*TIMP-2) (ng/ml)	1.44 (0.57-3.50)	0.47 (0.14-0.89)	<0.001
Medication			
ACE-I/ARB	54 (48%)		
Spironalactone	46 (41%)		
OAD	33 (29%)		
Statin	25 (22%)		
Thiazide diuretic	28 (25%)		
Loop diuretic	111 (100%)		

HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, SVA: Serebrovascular accent , AF: Atrial fibrillation, KIM-1: Kidney injury molecule 1, TIMP-2: Tissue inhibitor of matrix metalloproteinase-2, IGFBP-7: Insulin-like growth factor binding protein-7, NYHA: New York Heart Association, GFR: Glomerular Filtration Rate, SBP: Sistolic blood pressure, DBP: Diastolic blood pressure, LVEF: Left ventricular ejection fraction, BNP: Brain natriuretic peptide, ACE-I: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker, OAD: Oral anti-diabetes.

statistically significant differences between the two groups. No significant differences were detected when the development ratios of acute renal failure of these groups were compared using the x^2-test (p = 0.502). Spearman correlation analysis detected a statistically significant inverse correlation between the EF and creatinine value (p = 0.017); the EF value decrease as the creatinine

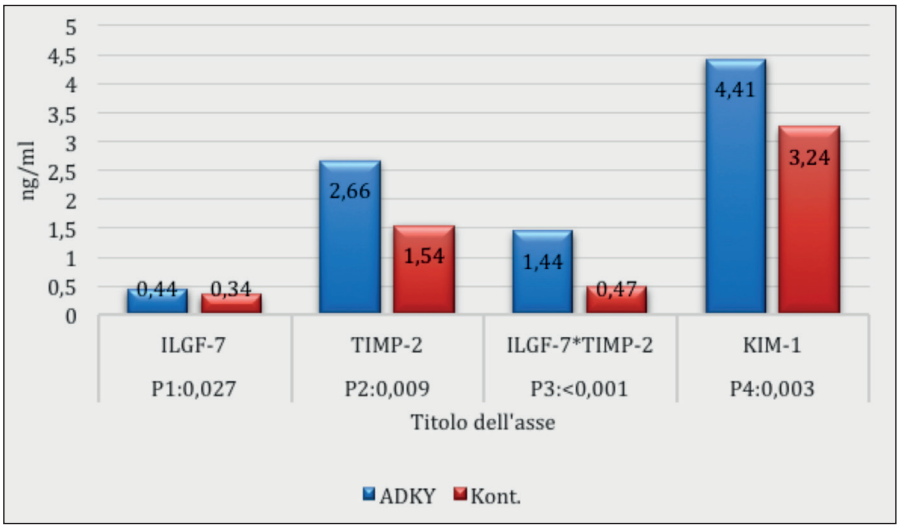

Figure 1. Levels of new renal biomarkers in study group and healthy volunteers.

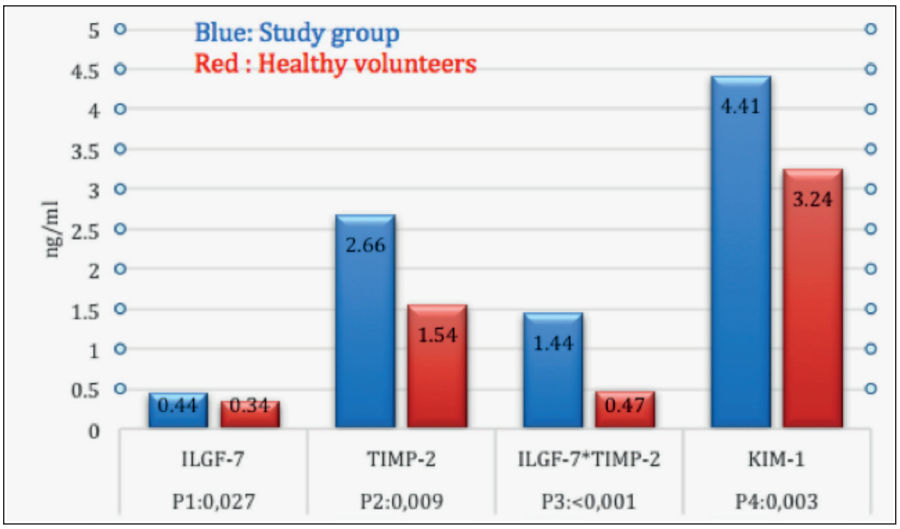

Figure 2. Levels of new renal biomarkers in patients with and without cardio-renal syndrome.

level increased (Figure 4). There was a correlation between the GFR and renal biomarkers. The GFR value was used to divide the participants into two groups, those with values above or below 60 mL/min/1.73 m^2. Although the ILGF-7 and ILGF-7+TIMP-2 levels were higher (p1 = 0.035; p2 = 0.044; and p3 = 0.002) in those patients with GFR values below 60 mL/min/1.73 m^2, there were no significant differences between the TIMP-2 and GFR values of these groups (p = 0.569). There was a moderate negative correlation between GFR and KIM-1 levels (r = -334, p = 0.002); the level of KIM-1 increased as GFR decreased (Figure 5).

We assessed the relationship between proBNP values and ILGF-7, TIMP-2, ILGF-7+TIMP-2, and KIM-1 using Spearman correlation analysis. A moderate relationship was detected between the proBNP and KIM-1 levels (p = 0.04) (Figure 6). However, we detected no correlation between IL-7, TIMP-2, ILGF-7+TIMP-2, and proBNP levels (p1: 0.277, p2: 0.384, p3: 0.066). During the 2-year follow-up, 34% (n = 38) of patients died. When the relationship between mortality and renal biomarkers was evaluated, we detected no statistically significant relationships (p1 = 0.984; p2 = 0.168; p3 = 0.292; p4 = 0.826).

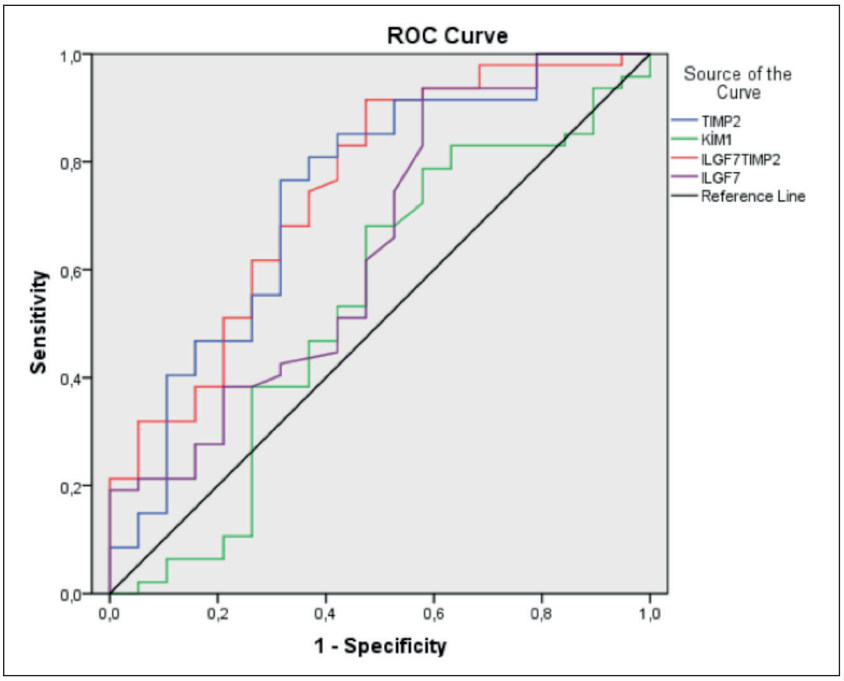

Figure 3. Values of renal biomarkers in the ROC curve for predicting cardiorenal syndrome.

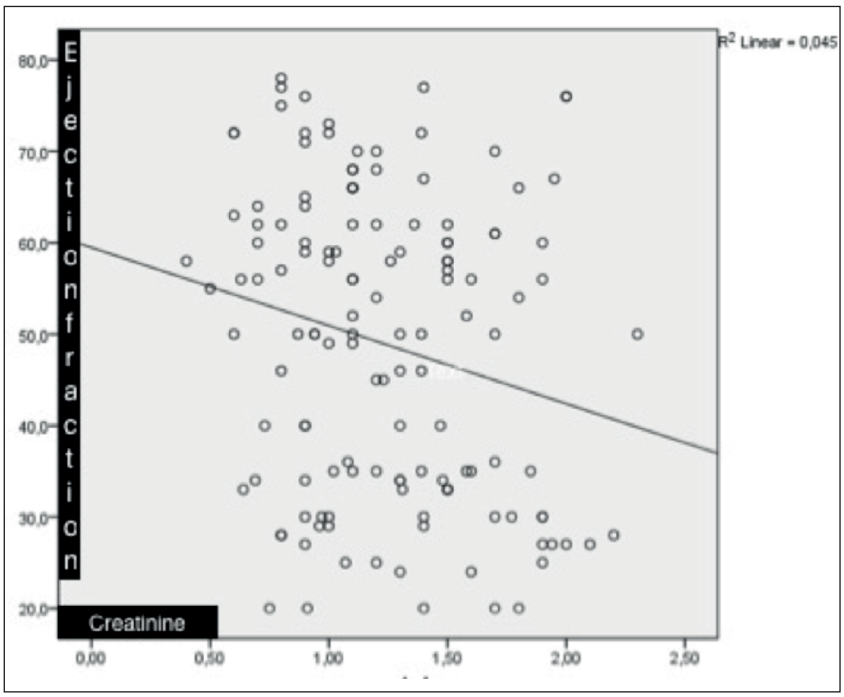

Figure 4. Correlation curve between creatinine values and ejection fraction

Discussion

The use of urea, creatinine, and urine, which are traditional diagnostic methods for the diagnosis of CRS, raise various problems in terms of early and effective diagnosis. Therefore, novel biomarkers are being tested for their ability to diagnose CRS earlier and more accurately in patients with diabetes who have cardiac insufficiency [30-32]. Positive results have been obtained as a result of these studies [20]. Here we assessed a series of novel urinary biomarkers (KIM-1, TIMP-

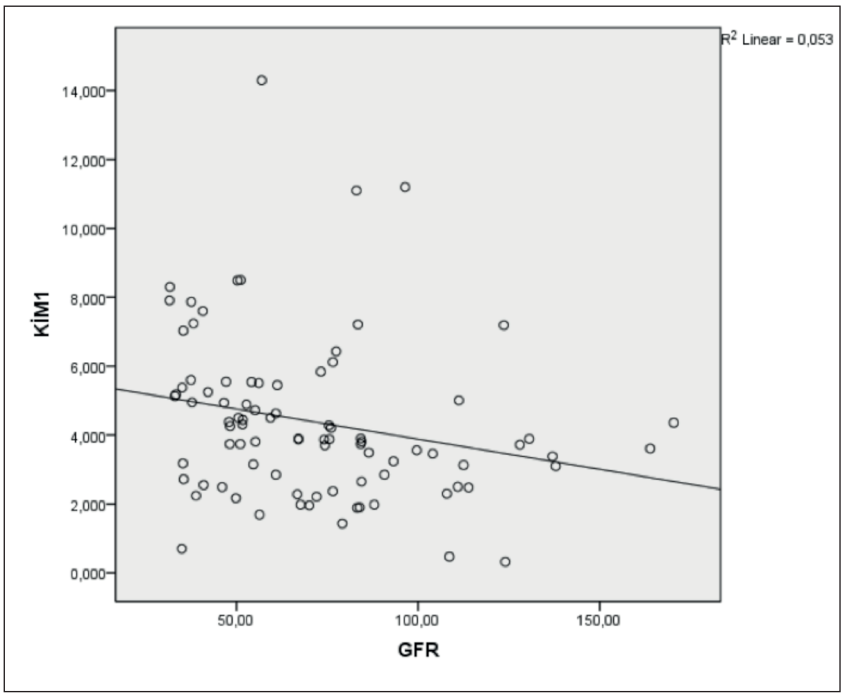

Figure 5. The curve of the correlation analysis between KIM-1 levels and glomerular filtration rate (GFR).

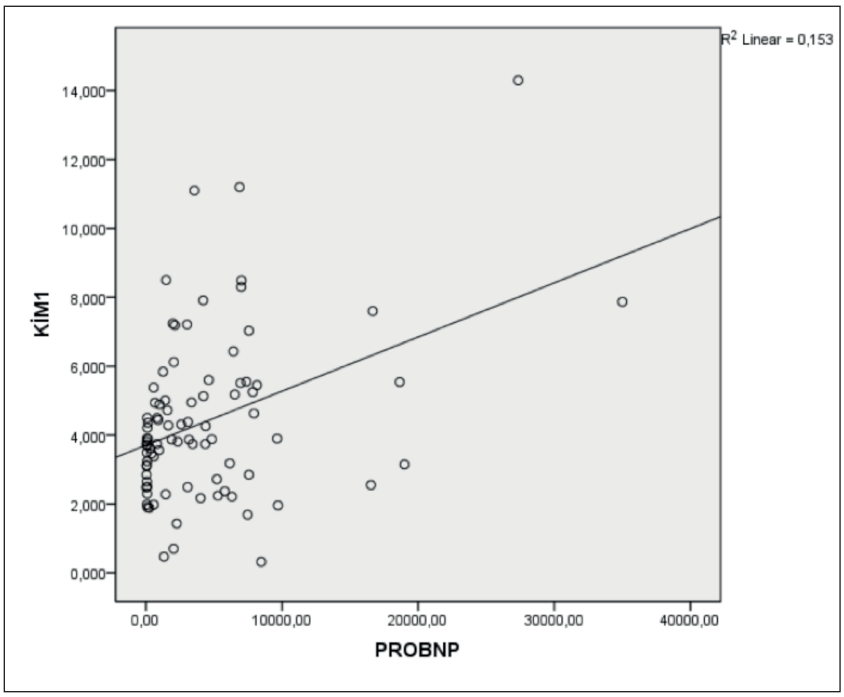

Figure 6. The curve of the correlation analysis between KIM-1 value and pro-BNP value.

2, and ILGFB-7) because we believe that the use of creatinine as a standard method for predicting the development of CRS in patients with acute heart failure is insufficient. Jungbauer et al[33] studied KIM-1 levels in patients with cardiac insufficiency and detected higher KIM-1 levels in their patient group than control group (4.41 [3.07-5.66] *vs*. 3.24 [2.49-3.85], $p = 0.003$), as we found in our study. Similarly, in our study, a moderate positive correlation was detected between proBNP and KIM-1 ($r = 0.304$, $p = 0.004$). This suggests that kidney tubular damage is a sign of heart failure or cardiac decompensation. Renal tubular damage in heart failure is not completely understood, although the over-activation of the renin-angiotensin system is considered an important mechanism. Activation of this system triggers ischemia in renal tubular cells [7,8,34]. It has been suggested that urine KIM-1 is a biomarker for the activation of the renin-angiotensin-aldosterone system [25]. Also, renal tubular ischemia in patients with heart failure can be explained by multiple mechanisms that increase levels of vasoconstrictor mediators, such as epinephrine and endothelium, hypoperfusion, renal congestion, and an over-active sympathetic nervous system [35-37].

In contrast to the study of Jungbauer et al[33], in our study, we detected no correlation between EF, NYHA, and KIM-1 ($p = 0.07$ and $p = 0.807$, respectively). This might be related to the different methodologies used in these studies; Jungbauer et al[33] divided patients into two groups with an EF limit of 40% and NYHA 1, 2, and NYHA 3, 4. Also, although KIM-1 is secreted from the proximal tubule epithelial cells of the kidney, it is not known by how much KIM-1 is affected by predisposing factors that cause decompensated heart failure. This is because it is different for many patients. In conclusion, although patients with type-1 CRS have a higher level of KIM-1, the available evidence does not support the superiority of KIM-1 over creatinine in predicting the development of type-1 CRS.

Several mechanisms play a role in acute renal failure, including the occurrence of G1 cell cycle arrest following renal tubular ischemia[34]. ILGF-7 and TIMP-2 are involved in this cycle and arrest the G1 cell cycle in the early phase during cell damage [30,31,38]. Kashani et al[39] found these molecules to be more sensitive and more specific than other renal markers (e.g., KIM-1, NGAL, and IL18) in predicting acute renal failure [39]. This suggests that the cell cycle arrest biomarkers, urinary IGFBP-7, and TIMP-2, might lead to a clinical benefit for predicting the development of type 1 CRS after renal ischemia in patients with decompensated heart failure. In this pilot study, ILGF-7 and TIMP-2 have been evaluated in the development of the CRS. ILGF-7, TIMP-2, and ILGF-7+TIMP-2 values were significantly higher

than those of patients who did not develop type 1 CRS. These findings suggest that ILGF-7, TIMP-2, and ILGF-7+TIMP-2 values are effective for predicting type 1 CRS. The superiority of these over KIM-1 is in their sensitivity and specificity in predicting type 1 CRS [39-41].

Gandhi et al[42] found that IGFBP-7 levels were significantly higher in patients with heart failure than in the control group, which is in line with our findings. Gandhi et al[42] detected a weak relationship between proBNP and ILGF-7, which was not detected in our study. Cell loss, interstitial fibrosis, and diastolic stiffness are the principal mechanisms in the pathophysiology of heart failure[43]. Previous studies[44] have shown a correlation between the concentration of ILGF-7 and the presence of colloid fibers. The increase in ILGF-7 level observed in patients with heart failure was thought to be associated with increased collagen accumulation and consequent myocardial stiffness and contractile myocardial tissue loss. Also, Polyakova et al[45] found that TIMP-2 (ng/mL) values were higher in patients with heart failure than in the control group, which is consistent with our findings. TIMP-2 has been identified as a contributor to the development of fibrosis in the heart [45,46]. It is thought that the loss of cardiac tissue and fibrosis are associated with ILGF-7 levels, with similar pathophysiology like galectin-3, a fibrosis marker in cardiac and renal tissue, mechanism shown in a previous study [47].

Given the data obtained from our study, renal tubular markers show promise as developments in the pathophysiology of CRS. Renal tubular markers might help to regulate diuretic treatment and fluid balance, especially in patients with heart failure. Also, renal tubular markers might contribute to the early detection of fluid accumulation in heart failure, which is likely to lead to CRS. Preventing CRS will create new concepts and contribute to the management of the disease. Thus, further understanding of cardiorenal interactions is required. Prevention, early diagnosis, and effective treatment need to be developed to achieve the desired health outcomes.

Our study has some limitations. First, our study was single-centered and included a relatively small number of patients. Second, the results were obtained only from patients with acutely decompensated heart failure, and their functional capacity was NYHA 3-4. Therefore, these results might not translate to patients with chronic heart failure with functional capacity of NYHA 1-2. Third, no biopsies were performed to evaluate tubulointerstitial pathology and possible morphologic changes in the kidneys in chronic heart failure. Finally, the instantaneous urine specimens we studied might produce statistically different results when compared to 24-h urine. This is because there is insufficient information about the diurnal change of urinary renal biomarkers, as in some biomarkers.

Conclusions

We investigated the usefulness of a series of novel renal biomarkers in patients with acute decompensated heart failure to predict cardiorenal syndrome. Except for KIM-1, we detected a statistically significant correlation between renal biomarker levels and the occurrence of cardiorenal syndrome. We detected no correlation between patient mortality and renal tubular biomarker levels. Based on our findings, we propose that renal tubular biomarkers have potential as predictors of heart failure and cardiorenal syndrome.

Conflict of interest

The Authors declare that they have no conflict of interests.

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