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Urinary Tissue Inhibitor of Metalloproteinases-2 and Insulin Like Growth Factor Binding Protein-7 as Early Markers of Cardiorenal Syndrome Type -1 in Patients Hospitalized with Acute Heart Failure

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ABSTRACT

Background: Type 1 Cardiorenal Syndrome (CRS) is defined as an acute worsening of cardiac function—whether in the context of acute decompensated heart failure or acute de novo heart failure—that leads to acute kidney injury (AKI). Acute kidney injury (AKI) during hospitalization is associated with poor prognosis. Urinary [TIMP-2] × [IGFBP-7] has been investigated as early marker which helps to detect early deterioration of the renal function and in turn help to initiate necessary interventions or withhold deleterious medication or interventions which could aggravate acute kidney injury. Aim of the study: The main aim of this study was to demonstrate the usefulness of Urinary [TIMP-2] × [IGFBP7] as early detector of cardiorenal syndrome type 1 in patients with acute heart failure with normal renal function assessed by serum creatinine level on the day of admission (day 1). **Methods & Materials**: This was a prospective observational study which was conducted in the Department of Nephrology, BMU, Dhaka, Bangladesh. The study period ranged from June 2023 to March 2025.First we collected blood for s. creatinine in patients with acute heart failure (acute decompensated heart failure or acute de novo heart failure) on admission day (day 1). Those who had normal renal function (s. creatinine <1.3 mg/dl) were included in the study and urine sample of the patients was collected on day 1 for urinary TIMP-2, IGFBP-7. Then serum creatinine was subsequently followed up on day 3 (48 hours after admission) and day 7 to identify the development of CRS type 1. Patients were classified into AKI and non-AKI groups, and Urinary [TIMP-2] × [IGFBP7] were compared between these groups. Statistical analysis was performed using SPSS-23. **Result**: Among 58 participants, 39.7% (N=23) developed AKI, while 60.3% (n=35) remained Non-AKI. The mean age of AKI patients was higher (67.91±8.66 years) than non-AKI (55.85±10.79 years), but the difference was not statistically significant (p=0.381). Diabetes mellitus was significantly more prevalent in the AKI group (60.9% vs. 31.4%, p=0.027). Urinary [TIMP-2] × [IGFBP-7] levels were significantly higher in AKI patients (1.01±0.56 ng/ml) compared to Non-AKI (0.24±0.11 ng/ml, p<0.001). The ROC analysis showed an AUC of 0.915 (95% CI: 0.842-0.988, p<0.001), indicating strong diagnostic accuracy of urinary [TIMP-2] × [IGFBP-7] for predicting AKI in acute heart failure patients. The optimal cut-off value 0.312 (ng/m1)2/1000 yielded a sensitivity of 87.0%, specificity of 74.3%, and an overall accuracy of 80.7%. **Conclusion**: These findings suggest that urinary [TIMP-2] × [IGFBP-7] is a promising early biomarker for detecting AKI in acute heart failure patients, with good discriminative ability and potential clinical utility in predicting CRS Type 1.

Keywords: *Acute heart failure, Cardiorenal syndrome type 1, Acute kidney injury, TIMP-2, IGFBP-7*

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INTRODUCTION

Heart failure is associated with significant morbidity and mortality, and a substantial number of hospitalized patients experience varying levels of renal impairment [1]. The term cardio-renal syndrome describes the bidirectional relationship between cardiac and renal dysfunction [2]. When acute de novo heart failure or an acute exacerbation of chronic heart failure leads to renal impairment, it is categorized as Type 1 Cardio-renal Syndrome (CRS). The prevalence of Type 1 CRS among patients admitted with acute decompensated heart failure ranges from 24% to 45%. These patients often face prolonged hospital stays, increased readmissions, and a mortality rate that may reach 22% [3]. Several interrelated mechanisms contribute to the development of Type 1 Cardio-renal Syndrome, including venous congestion, reduced cardiac output, anemia, and neurohormonal activation involving the renin-angiotensin-aldosterone system (RAAS), increased sympathetic nervous system activity, and elevated levels of arginine vasopressin [4]. Renal congestion resulting from systemic volume overload plays a key role in the disease process [5]. Chronic reduction in renal blood flow further stimulates RAAS activity [6]. The renin-angiotensin-aldosterone system plays a pivotal role in the pathogenesis of cardio-renal syndrome through several mechanisms. Its activation promotes sodium and water retention, redistributes internal blood flow, and reduces medullary perfusion. These effects contribute to glomerulosclerosis, tubular fibrosis, and vasoconstriction of both efferent and afferent arterioles [7]. In addition to these hemodynamic alterations, oxidative stress and inflammation are implicated in the disease progression. These factors promote phenotypic changes in monocytes, renal interstitial fibrosis, and apoptosis of renal tubular cells [8]. Cardio-renal syndrome in patients with decompensated heart failure is frequently associated with serious cardiovascular and renal complications, including myocardial infarction, cerebrovascular events, the necessity for renal replacement therapy, increased rates of hospital admissions, and elevated mortality [9-11]. Consequently, early identification of the syndrome through emerging biomarkers is crucial for timely intervention and improved clinical outcomes [11]. Serum creatinine (sCr) has traditionally served as a surrogate marker for glomerular filtration; however, it lacks sensitivity and specificity in detecting acute tubular injury, particularly in the

absence of marked reductions in glomerular filtration rate (GFR). Notably, sCr levels typically rise only after approximately 50% of renal function has been compromised, often occurring days after the initial renal insult [12]. Among the emerging biomarkers, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) have shown considerable promise. These are cell stress markers that participate in G1 phase cell cycle arrest, effectively halting cell division to prevent propagation of damaged DNA during cellular injury [13]. IGFBP-7 and TIMP-2 are both expressed, generated, and secreted in renal tubular cells at the early phase of AKI. Urinary [TIMP-2] × [IGFBP-7] had a significantly superior performance in the early identification and diagnosis of AKI compared with classic renal injury biomarkers. Nevertheless, further studies are needed to recommend these new renal biomarkers in ADHF. The study aimed to identify patients who would develop acute renal failure and to assess the role of urinary [TIMP-2] × [IGFBP-7] as an early marker to detect cardio-renal syndrome type 1.

METHODS & MATERIALS

This prospective observational study was conducted under the Department of Nephrology, and the study subjects enrolled from the Department of Cardiology Bangladesh Medical University, Dhaka, Bangladesh. The study was carried out from June 2023 to March 2025 (21 months). The study population consisted of patients with acute heart failure (acute decompensated heart failure or acute *de novo* heart failure) with normal serum creatinine. A total of 58 participants who fulfilled the inclusion criteria and provided informed consent/assent were included through purposive sampling and divided into two groups:

AKI Group (n=23): Patients with serum creatinine <1.3 mg/dl on day 1, with either rise in serum creatinine of 0.3 mg/dl within 48 hours or increase in serum creatinine 1.5 times the base line within 7 days. Here urine output criteria (0.5 mL/kg per hour for 6 hours) were not utilized for AKI diagnosis because of the potential alterations in urine volume induced by therapeutic medication.

Non -AKI Group (n=35): Patients with serum creatinine <1.3 mg/dl without significant increase in serum creatinine.

Inclusion Criteria:

- Patient with feature of acute heart failure (acute decompensated heart failure or acute de novo heart failure) based on history, physical examination and lab findings
- Age ≥ 18years
- Normal serum creatinine (Constantin et al., 2016)

Exclusion Criteria:

- Patients undergoing coronary procedures using contrast (angiography or PCI) within ±7 days of admission
- Patients with surgical plan for valvular heart disease or coronary artery bypass graft within 7 days of admission
- Abnormal thyroid function
- Anticancer drugs
- Evidence of active infection, including: total leukocyte count >11,000/µL or <4,000/µL, C-reactive protein (CRP) level >10 mg/L indicating systemic inflammation (Pepys & Hirschfield, 2003), Clinical signs of infection (e.g., fever, localized symptoms).

Ethical Considerations

Prior to commencement of this study, the research protocol was approved by the Ethical Review Committee of BMU, Dhaka. The aims and objectives of the study along with its procedure, risk and benefits of this study was explained to the patients in easily understandable local language and then informed consent was taken from each patient. It was assured that all information and records will be kept confidential and the procedure will be helpful for both me and the patients in making rational approach of the case management. There were rights of withdrawal of participants any time of thesis work.

Study Procedure

After getting IRB approval, informed written consents were taken from all patients. All patients of age ≥ 18 years with the diagnosis of acute heart failure on the basis of history and clinical examination were noted with serum creatinine level of <1.3 mg/dl. Patient were recruited from Department of Cardiology, BMU, Dhaka, Bangladesh. Subject were selected on the basis of enrollment criteria. Initial information of the patients was collected from hospital records. All biochemical records were collected from the hospital records. Serum creatinine was performed on day 1 and those who have normal renal function (s. creatinine <1.3 mg/dl) were included in the study. Urine for TIMP-2 and IGFBP-7 was collected within the first 24 hours of admission and their levels were measured by the procedure illustrated below. Follow up serum creatinine was performed on day 3 and 7. Patients was divided into AKI and non-AKI on the basis of serum creatinine on day 3 and day 7. Then, urinary [TIMP-2] × [IGFBP-7] level was compared between AKI and non-AKI group.

At least 200 µl of spot urine samples were taken from these patients (two separate urine samples at 72-h intervals). The levels of urinary 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 baseline biochemical and urine samples of patients were measured quantitatively. Follow-up biochemical specimen taken on day 3 and day 7.

Collection of Urine Sample

A clean-catch midstream urine specimen was collected from each participant following standard aseptic procedures. Patients were instructed to wash their hands thoroughly, cleanse the external genitalia, wipe from front to back in female participants, and retract the foreskin in uncircumcised male participants before sample collection. After collection, urine samples were aliquoted and stored at −80°C in the Department of Microbiology, BSMMU, until analysis of urinary TIMP-2 and IGFBP-7.

Processing of Blood Samples

Venous blood samples were collected under aseptic conditions by venepuncture and allowed to clot completely at room temperature before centrifugation. Serum was separated by centrifugation, ensuring that centrifugation was not performed until complete clot formation had occurred to obtain high-quality serum for biochemical analysis.

Measurement of Urinary TIMP-2 and IGFBP-7

Urinary TIMP-2 and IGFBP-7 were measured using a commercially available ELISA kit. Early morning urine samples were collected, centrifuged at 3000 rpm for 5 minutes, aliquoted, and stored at -80°C until analysis. For the assay, urine samples were diluted 10-fold (e.g., 15 µl of urine were mixed with 135 µl of Dilution Buffer for singlets, or preferably 25 µl of urine were mixed with 225 µl of Dilution Buffer for duplicates). The ELISA procedure was carried out as follows: 100 µl of diluted samples, standards, quality controls, and blank were pipetted into appropriate wells in duplicates. The plate was incubated at room temperature (approximately 25°C) for 1 hour with shaking at approximately 300 rpm on an orbital microplate shaker. The wells were washed three times with Wash Solution (0.35 ml per well). After the final wash, the plate was inverted and tapped strongly against a paper towel. Then, 100 µl of Biotin-Labeled Antibody solution were added to each well. The plate

was again incubated at room temperature for 1 hour with shaking. The wells were washed three times as described previously. Next, 100 µl of Streptavidin-HRP Conjugate were added into each well, and the plate was incubated for 30 minutes at room temperature with shaking. The wells were washed three times with Wash Solution. Subsequently, 100 µl of Substrate Solution were added into each well, and the plate was covered with aluminum foil to protect it from direct sunlight. The plate was incubated for 10 minutes at room temperature without shaking. Then, 100 µl of Stop Solution were added to stop the color development. The absorbance of each well was determined using a microplate reader set to 450 nm, with a reference wavelength set at 630 nm (acceptable range: 550–650 nm). The absorbance values at 630 nm (or within 550–650 nm) were subtracted from those at 450 nm. Urinary TIMP-2 and IGFBP-7 excretions were reported individually in ng/ml, and a combined value was calculated as the product of their concentrations divided by 1000, and expressed in units of $(ng/ml)^2/1000$.

Measurement of Serum Creatinine

Serum creatinine was measured using the Jaffe method with the Atellica CH Analyzer (Siemens Healthcare Diagnostics). Approximately 3 mL of venous blood was collected from each participant and centrifuged at 3600 rpm for 15 minutes to separate the serum. One millilitre of serum was mixed with 1 mL of picric acid and 1 mL of sodium hydroxide, and the reaction mixture was analysed using the Atellica CH Analyzer. Serum creatinine concentration was determined by measuring the change in colour intensity at a wavelength of 520 nm.

Data Collection

The study subjects were selected on the basis of enrollment criteria from the CCU in the Department of Cardiology, BMU. The demographic information, relevant history, examination findings and investigation reports of all the study subjects were recorded in pre-tested data collection sheet. Total sample size was 64 but 6 patients were lost during follow up.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation (SD), and qualitative data were expressed as frequency and percentage. Comparisons between categorical variables were performed using the Chi-square test, while continuous variables were analysed using the independent t-test or Mann–Whitney U test, as appropriate. A p-value of <0.05 was considered statistically significant. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of urinary [TIMP-2] × [IGFBP-7] for predicting acute kidney injury (AKI). The area under the ROC curve (AUC) was used to assess the discriminative ability of the biomarker. The optimal cutoff value was determined by maximizing the Youden Index (Sensitivity + Specificity − 1). At the optimal cutoff point, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated. ROC analysis was performed with 95% confidence intervals, and a p-value of <0.05 was considered statistically significant.

RESULT

The mean age was 67.91±8.66 years in the AKI group and 55.85±10.79 years in the non-AKI group (p=0.381). Male participants comprised 65.2% and 74.3% of the respective groups (p=0.458). Mean BMI, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were also similar between groups. Diabetes mellitus was significantly more prevalent in the AKI group than the non-AKI group (60.9% and 31.4%; p=0.027), whereas the prevalence of hypertension did not differ significantly (73.9% and 51.4%; p=0.087) (*Table I*).

Table I
Baseline characteristics of the study participants (*n*=58).

Variable	AKI (n=23)		Non-AKI (n=35)		p-value
	n	%	n	%	
Age (years), Mean ± SD	67.91±8.66		55.85±10.79		0.381
Male Gender	15	65.2	26	74.3	0.458
Female Gender	8	36.8	9	25.7	
BMI (kg/m^2), Mean ± SD	25.86±5.03		23.61±4.33		0.184
Systolic BP (mmHg), Mean ± SD	111.30±33.61		105.42±27.90		0.199
Diastolic BP (mmHg), Mean ± SD	72.17±20.43		66.71±13.77		0.118
Mean arterial pressure (mmHg), Mean ± SD	85.21±24.47		78.85±24.47		0.489
Diabetes mellitus	14	60.9	11	31.4	0.027
History of hypertension	17	73.9	18	51.4	0.087

Figure 1 shows that patients with AKI were predominantly distributed in the older age categories, particularly 60-69 and 70-79 years, whereas non-AKI patients were more frequently represented in the 60-69-year age groups.

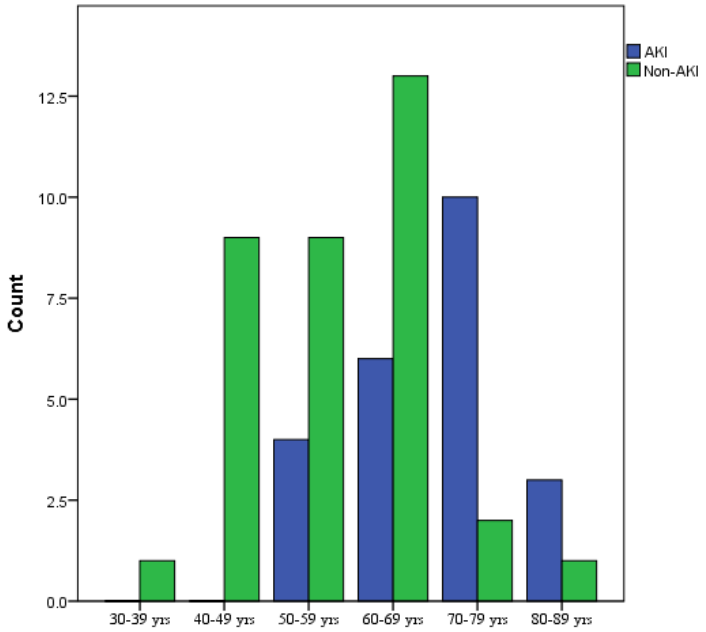

Figure 1 Age distribution of the study patients in AKI and non-AKI groups.

Medication use was comparable between the two groups, with no significant differences in the use of frusemide, inotropes, ACEI/ARB, spironolactone, empagliflozin, ARNI, or daily frusemide dose. Patients with AKI had significantly lower eGFR (67.78±4.13 and 79.00±7.12 mL/min/1.73 m²; p=0.036) and lower serum sodium levels (135.30±6.97 and135.88±4.70 mmol/L; p=0.009) (*Table II*).

Table II
Drug history and laboratory variables between AKI and Non-AKI group (*n*=44).

Variable	AKI (n=23)		Non-AKI (n=35)		p-value
	n	%	n	%	
Drug history					
Frusemide	18	78.3	28	80	0.873
Inotrope	6	26.1	8	22.9	0.779
ACEI /ARB	11	47.8	13	37.1	0.419
Spironolactone	10	43.5	21	60	0.217
Empaglifozin	6	26.1	11	31.4	0.662
ARNI	3	13	9	25.7	0.244
Frusemide dose (mg/day)	60.00±33.57		58.85±34.62		0.93
Laboratory variables (Mean ± SD)					
eGFR (ml/min/1.73m2)	67.78±4.13		79.00±7.12		0.036
Serum urea	18.13± 3.23		14.43±3.74		0.247
S. Sodium (mmol/l)	135.30±6.97		135.88±4.70		0.009
S. Potassium (mmol/l)	4.00±0.70		3.89±0.64		0.657
S. Chloride	98.08±6.11		98.45±6.47		0.811
Pro BNP (U/L)	10534.83±13248.64		11072.34±22592.05		0.893
Troponin I (ng/dl)	3147.59±6231.08		2882.31±6772.07		0.32
CKMB (U/L)	60.86±59.32		69.25±82.78		0.45
Ejection fraction	39.39±8.12		39.68±8.49		0.235
Hemoglobin level (gm/dl)	11.07±2.10		11.92±1.82		0.416
RBS (mmol/l)	9.01±4.51		7.14±3.36		0.212

Ejection fraction categories were comparable between the AKI and non-AKI groups (p=0.488). However, serum creatinine was significantly higher among patients with AKI on both day 3 (2.07±1.54 and 1.10±0.11 mg/dL) and day 7 (2.53±1.31 and 1.05±0.19 mg/dL), indicating persistent renal dysfunction (*Table III*).

Table III
Comparison of cardiac and renal function of patients (*n*=44).

Variable	AKI (n=23)		Non-AKI (n=35)		p-value
	n	%	n	%	
Ejection fraction					
<40%	15	65.2	21	60	0.488
40-49%	6	26.1	7	20	
≥ 50%	2	8.7	7	20	
S. Creatinine (Mean ± SD)					
S. creatinine day 3 (mg/dl)	2.07±1.54		1.10±0.11		<0.001
S. creatinine day 7 (mg/dl)	2.53±1.31		1.05±0.19		0.007

Table IV shows significantly higher concentrations in patients with AKI than in those without AKI (1.01±0.56 and 0.24±0.11 (ng/mL)²/1000; p<0.001).

Table IV
Comparison of Urinary [TIMP-2] × [IGFBP-7] between AKI and non-AKI patients (*n*=58).

Study Groups	Urinary [TIMP-2] × [IGFBP-7] (ng/ml)2/1000	p-value
AKI (n=23)	1.01±0.56	<0.001
Non-AKI (n=35)	0.24±0.11	

Mean values were 0.57±0.39, 1.40±0.29, and 1.47±0.53 (ng/mL)²/1000 in KDIGO stages 1, 2, and 3, respectively (p<0.001), indicating higher biomarker concentrations with advancing AKI stage (*Table V*).

Table V
Comparison of Urinary [TIMP-2] × [IGFBP-7] among different stages of AKI (*n*=23).

KDIGO stage	Frequency (n)	Percentage (%)	Urinary [TIMP-2] × [IGFBP-7] (ng/ml)2/1000, Mean±SD	p-value
Stage 1	11	47.8	0.57±0.39	<0.001
Stage 2	9	39.1	1.40±0.29	
Stage 3	3	13	1.47±0.53	

The ROC curve demonstrated excellent diagnostic performance of urinary [TIMP-2]×[IGFBP-7] for identifying cardio-renal syndrome type 1, with the curve positioned well above the reference line, indicating high discriminatory ability (*Figure 2*).

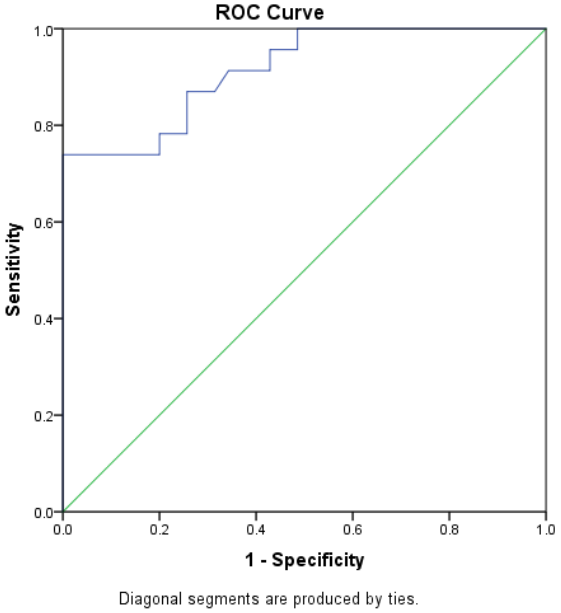

Figure 2 ROC curve of Urinary [TIMP-2] × [IGFBP-7].

Among the evaluated cut-off values, 0.312 (ng/mL)²/1000 provided the highest Youden index (0.613), corresponding to 87.0% sensitivity and 74.3% specificity. Lower cut-off values increased sensitivity but reduced specificity, whereas higher cut-off values improved specificity at the expense of sensitivity (*Table VI*).

Table VI
Yuden Index at different cut off value of Urinary [TIMP-2] × [IGFBP-7] in diagnosis of Cardiorenal Syndrome 1.

Cutoff value Urinary [TIMP-2]× [IGFBP-7] (ng/ml)2/1000	Sensitivity	1−Specificity	Youden Index	Sensitivity	Specificity
0.3	0.913	0.429	0.484	91.3	57.1
0.304	0.913	0.343	0.57	91.3	65.7
0.307	0.87	0.314	0.556	87	68.6
0.312	0.87	0.257	0.613	87	74.3
0.32	0.826	0.257	0.569	82.6	74.3
0.332	0.783	0.257	0.526	78.3	74.3
0.347	0.783	0.229	0.554	78.3	77.1

Table VII shows an AUC of 0.915 (95% CI: 0.842–0.988; p<0.001). The optimal cut-off value was 0.312 (ng/mL)²/1000, yielding 87.0% sensitivity, 74.3% specificity, 69.0% positive predictive value, 89.7% negative predictive value, and 79.4% overall accuracy.

Table VII
ROC analysis of Urinary [TIMP-2] × [IGFBP-7] in diagnosis of Cardiorenal Syndrome 1.

Parameters	Value
Area Under the Curve (AUC)	0.915
95% Confidence Interval (AUC)	0.842-0.988
p-value	<0.001
Optimal Cut-off Value (ng/mL)	0.312
Sensitivity (%)	87
Specificity (%)	74.3
Positive Predictive Value (%)	69
Negative Predictive Value (%)	89.7
Accuracy (%)	79.4

Figure 3 demonstrates a weak positive correlation between urinary [TIMP-2]×[IGFBP-7] and Pro-BNP levels on day 1 (R^2=0.003), suggesting minimal linear association between the biomarker and cardiac natriuretic peptide concentrations.

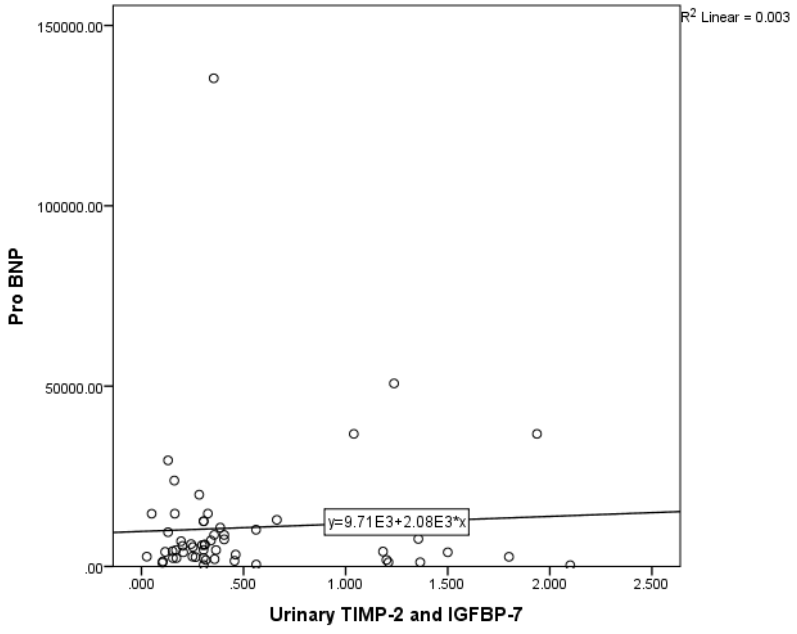

Figure 3 Scatter diagram showing the correlation of Urinary [TIMP-2] × [IGFBP-7] with Pro BNP on day 1.

DISCUSSION

Cardio-renal syndrome type 1 is characterized by acute worsening of cardiac function that precipitates acute kidney injury as a consequence of the bidirectional interaction between the heart and the kidneys [10]. The incidence of AKI in this study was 39.7%, which aligned closely with a study conducted by Manandhar et al, reporting an AKI incidence of 35.3% [16]. However, Schanz et al observed a lower AKI occurrence rate of 27.5% in patients with acute decompensated heart failure (ADHF) [17]. Liu et al reported that the elderly population (mean age >65 years) exhibited an increased AKI incidence, suggesting that age-related renal vulnerability played a crucial role in AKI susceptibility [18]. In this study, the majority of participants were male in both groups with a mean age of

67.91±8.66 and 55.85±10.79 years, respectively. This demographic distribution was consistent with Constantin et al and Zhang et al, which also reported a predominance of older male patients [14,19]. Similarly, Koyner et al observed that their study group predominantly consisted of older male patients with an increased risk of AKI [20]. The mean systolic blood pressure was 111.30±33.61 mm of Hg, the diastolic blood pressure was 72.17±20.43 mm of Hg and a mean arterial pressure was 85.21±24.47 mm of Hg. This finding are similar with findings of Phan (2022) [21]. But studies done by Manandhar et al and Hu et al showed AKI patients were relatively hypotensive [16,22]. 60.9% patients had diabetes mellitus, which was statistically significant. Girman et al found higher diabetes prevalence among AKI patients, indicating diabetes contributes to kidney vulnerability [23]. Oliveria et al emphasized that diabetes, in combination with other factors like hypertension, increases AKI risk in hospitalized patients [24]. None of the drug variables showed a statistically significant association with AKI. Frusemide use and dosage, inotrope use, ACE inhibitors, spironolactone, empagliflozin, and ARNI use did not differ significantly between AKI and Non-AKI groups. Phan (2022) also reported same observations in his study [21]. But, Uduman (2018) reported that in-patients with ADHF, high dose diuretics (>125 mg/d) was associated with higher rate of in hospital worsening of renal function [25]. The AKI group had an eGFR of 67.78±4.13 ml/min/1.73m², while the non-AKI group had a higher eGFR of 79.00±7.12 ml/min/1.73m². This finding was consistent with Hu et al, where the AKI group had an eGFR of 57±15.3 ml/min/1.73m², while the non-AKI group had a significantly higher eGFR of 86±10.7 ml/min/1.73m² [22]. On admission, the mean serum creatinine for all patients had no significant difference between the AKI group and the non-AKI group. In our study, the AKI group showed an increase in creatinine levels by day 3 and day 7, which aligns with the findings of several studies on AKI progression. For instance, studies by Srisawat et al and Schrier et al reported similar findings where serum creatinine levels in patients with AKI progressively increased over time [26,27]. Most participants had a reduced ejection fraction (EF <40%), with a slight predominance in the AKI group (65.2%) over the non-AKI group (60.0%). However, the p-value (0.488) showed no significant difference between groups. Other studies (Manandhar et al., 2022 and Phan, 2022) found the same result [16,21]. In contrast, Schanz et al reported a significant association between lower EF and AKI in a subset of critically ill patients with severe heart failure [17]. In this study, the mean value of Urinary [TIMP-2] × [IGFBP-7] was 1.01±0.56 (ng/ml)²/1000 as compared to 0.24±0.11 (ng/ml)²/1000 in patients who did not develop AKI with a p-value of <0.001 on the day of admission. Similar studies by Schanz et al. and Atici et al. also showed Urinary [TIMP-2] × [IGFBP-7] were higher in patients who developed AKI on the day of admission who subsequently developed AKI [17,28]. Higher urinary [TIMP-2] × [IGFBP-7] levels correlated (p<0.001) with more severe AKI (KDIGO stages 1 to 3). Inotani et al found that [TIMP-2] × [IGFBP-7] levels were significantly higher in patients who developed AKI, particularly in more severe stages, reinforcing its utility in early detection and severity assessment [29]. In present study, AUC of 0.915 indicated good discriminative ability, with a 95% confidence interval of 0.842-0.988 and statistically significant performance (p <0.001). The optimal cutoff of 0.312 (ng/ml)²/1000 achieved a sensitivity of 87.0%, specificity of 74.3%, PPV of 69.0%, NPV of 89.7%, and an overall accuracy of 79.4%. Liu et al reported an AUROC of 0.86 for Urinary [TIMP-2] × [IGFBP-7] in detecting AKI, with sensitivity (0.83) slightly lower than ours (0.87) and comparable specificity (0.72) [18]. Schanz et al reported an AUROC of 0.84 for AKI prediction which aligns closely with our AUROC of 0.915 [17]. From this study it was shown that the patients with acute heart failure who would subsequently develop acute kidney injury had a higher level of Urinary [TIMP-2] × [IGFBP-7] and therefore, Urinary [TIMP-2] × [IGFBP-7] can predict acute kidney injury much earlier than the conventionally used marker for AKI which is serum creatinine.

LIMITATIONS

- Urine output criteria was not utilized for diagnosis of AKI because of potential alteration in urine volume by diuretics.
- Urinary [TIMP-2] × [IGFBP-7] was not compared with other biomarkers in this study due to resource constraints.

CONCLUSION & RECOMMENDATIONS

These findings demonstrate a significant correlation between urinary [TIMP-2] × [IGFBP-7] levels and both the presence and severity of AKI, as classified by the KDIGO criteria. The biomarker shows strong performance in accurately identifying patients at risk for AKI, with a reliable balance between sensitivity and specificity, highlighting its potential for early detection and clinical use.

RECOMMENDATIONS

- This study recommends urinary [TIMP-2] × [IGFBP-7] as a promising biomarker for early AKI detection and risk stratification in ADHF patients due to its high sensitivity and specificity. It could be integrated into clinical practice for early identification and timely intervention.
- Future research should focus on validating its combined diagnostic value with other clinical parameters and expanding studies to diverse patient populations to confirm its clinical utility and establish standardized guidelines for AKI detection.
- Further exploration of its role in monitoring and improving patient outcomes is also encouraged.

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CONFLICT OF INTEREST

None declared

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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