BMC Nephrology

RESEARCH

Open Access

Predictive performance of two types of urinary biomarkers for renal non-recovery in sepsis-associated acute kidney injury: a prospective observational study

Licheng[1], Huimiao Jia[2], Yijia Jiang[2] and Wenxiong Li[2*]

Abstract

Background and purpose Renal non-recovery is known to have negative prognostic implications in patients suffering from acute kidney injury (AKI). Nevertheless, the identification of biomarkers for predicting renal non-recovery in sepsis-associated AKI (SA-AKI) within clinical settings remains unresolved. This study aims to evaluate and compare the predictive ability for renal non-recovery, use of kidney replacement therapy (KRT) in the Intensive Care Unit (ICU), and 30-day mortality after SA-AKI by two urinary biomarkers, namely C-C motif chemokine ligand 14 (CCL14) and [TIMP-2]•[IGFBP7].

Methods We prospectively screened adult patients who met the criteria for AKI stage 2–3 and Sepsis-3.0 in two ICUs from January 2019 to May 2022. Patients who developed new-onset SA-AKI after ICU admission were enrolled and urinary biomarkers including [TIMP-2]•[IGFBP7] and CCL14 were detected at the time of SA-AKI diagnosis. The primary endpoint was non-recovery from SA-AKI within 7 days. The secondary endpoints were the use of KRT in the ICU and 30-day mortality after SA-AKI. The individual discriminative ability of [TIMP-2]•[IGFBP7] and CCL14 to predict renal non-recovery were evaluated by the area under receiver operating characteristics curve (AUC).

Results 141 patients with stage 2–3 SA-AKI were finally included, among whom 54 (38.3%) experienced renal non-recovery. Urinary CCL14 exhibited a higher predictive capability for renal non-recovery compared to [TIMP-2]•[IGFBP7], with CCL14 showing an AUC of 0.901, versus an AUC of 0.730 for [TIMP-2]•[IGFBP7] ($P=0.001$). Urinary CCL14 and [TIMP-2]•[IGFBP7] demonstrated a moderate predictive value for the need for KRT in ICU, with AUC values of 0.794 and 0.725, respectively; The AUC of [TIMP-2]•[IGFBP7] combined with CCL14 reached up to 0.816. Urinary CCL14 and [TIMP-2]•[IGFBP7] exhibited poor predictive power for 30-day mortality, with respective AUC values of 0.623 and 0.593.

Conclusion Urinary CCL14 had excellent predictive value for renal non-recovery in SA-AKI patients. For predicting the use of KRT in the ICU, the predictive capability of urinary [TIMP-2]•[IGFBP7] or CCL14 was fair. However, a combination of [TIMP-2]•[IGFBP7] and CCL14 showed good predictive ability for the use of KRT.

Keywords C-C motif chemokine ligand 14, [TIMP-2]•[IGFBP7], sepsis, Acute kidney injury

*Correspondence:
Wenxiong Li
liwx1126@163.com
[1]Department of Emergent Intensive Critical Unit, Beijing Lu-He Hospital, Capital Medical University, Beijing 101100, China
[2]Department of Surgical Intensive Critical Unit, Beijing Chao-yang Hospital, Capital Medical University, 8 GongrenTiyuchangNanlu, Chaoyang District, Beijing 100020, China

Background

Sepsis, a frequently encountered condition within the intensive care unit (ICU), frequently precipitates organ dysfunction and poses life-threatening complications [1]. Among these complications, acute kidney injury (AKI) emerges as a prevalent concern, exhibiting an incidence rate ranging from 40 to 50% [2]. AKI is characterized by deterioration in renal function, leading to impaired regulation of extracellular volume and clearance of circulating substances [3]. This ultimately contributes to the development of chronic kidney disease (CKD) and cardiovascular events. The impact of AKI on morbidity and mortality is substantial, often resulting in an unfavorable prognosis. It is widely acknowledged that the patient's prognosis is influenced by the severity and duration of AKI [4]. Notably, even a failure to recover renal function within 48 h can significantly affect the patient's prognosis, exerting both short-term and long-term consequences [5, 6].

Sepsis induces renal hemodynamic abnormalities, triggers immune cell activation, releases inflammatory mediators, and suppresses endogenous hormone production, thereby impacting both the glomerulus and renal tubules [7]. The presence of sepsis-associated AKI (SA-AKI) is associated with elevated mortality rates and an augmented incidence of long-term complications [1, 8]. Damaged renal tubules can release biomarkers: tissue inhibitor of metalloproteinase-2 (TIMP-2) is primarily secreted and expressed by distal tubular cells [9], while insulin-like growth factor-binding protein 7 (IGFBP7) is expressed throughout the renal tubules but is mainly secreted by proximal tubular cells [10]. Previous studies have reported that [TIMP-2]•[IGFBP7] (the product of TIMP-2 and IGFBP7) has shown significant predictive ability for the progression of AKI (stages 2–3) within 12 h of sample collection in patients with various diseases, including sepsis [11]. CCL14, a member of the chemokine family, exhibits consistent expression in diverse tissues, including the kidney. Its involvement in pro-inflammatory chemotaxis in multiple diseases is noteworthy, as it activates monocytes and macrophages [12]. Furthermore, CCL14 serves as a novel third-generation biomarker for assessing the risk of renal non-recovery in cases of AKI lasting for 3 days or more [13]. In a comprehensive international cohort study involving medical and surgical intensive care patients, several potential biomarkers were discovered to have predictive value for persistent KDIGO stage 3 AKI lasting for 72 h or more. Among these biomarkers, urinary CCL14 exhibited the highest effectiveness [14]. Our prior investigation revealed that both urinary [TIMP-2]•[IGFBP7] and CCL14 have useful predictive value for renal non-recovery from AKI in such patients; however, CCL14 did not demonstrate a significant advantage over [TIMP-2]•[IGFBP7] in forecasting renal non-recovery [15].

To compare the predictive value of urinary [TIMP-2]•[IGFBP7] and CCL14 for renal non-recovery and to ensure the homogeneity of the included population, this prospective observational study aimed to evaluate and compare the predictive abilities of the urinary [TIMP-2]•[IGFBP7] and CCL14 for renal non-recovery within 7 days, as well as the necessity for KRT in ICU and 30-day mortality. The focus was specifically on ICU patients with Stage 2–3 SA-AKI.

Materials and methods

Study Design and patients

This prospective, observational study was conducted from January 2019 to May 2022 at two tertiary hospitals in China. Approval for the study protocol was obtained from the Ethics Committee of Beijing Chao-Yang Hospital (ethics number 2018−117). The study followed the ethical principles of the Declaration of Helsinki 1964. Informed consent from patients or their next of kin was obtained before patients joined in the study. We prospectively screened patients from two ICUs (Fig. 1). Adult patients were eligible for inclusion if they stayed longer than 24 h in ICU, and met the criteria for AKI stage 2–3 and the Sepsis-3.0. None of the following exclusion criteria was fulfilled: (1) age < 18 years old; (2) patients with KRT use before admission to the ICU; (3) existing AKI before admission to the ICU; (4) insufficient urine samples.

Data collection and biomarkers measurement

At the time of admission to the intensive care unit (ICU), demographic, clinical, and laboratory data, as well as prior health history and chronic comorbidities, were gathered. On the day of the AKI onset, Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE II) score were evaluated. Serum creatinine (SCr) levels were measured and documented upon ICU admission and every 12 h until 7 days following the onset of AKI. Additionally, the hourly urine volume was measured and recorded during the ICU period. Furthermore, information regarding utilization of KRT in ICU, mortality during the ICU stay, duration of hospitalization, and 30-day mortality after the diagnosis of AKI were collected.

Urine samples were obtained upon the diagnosis of AKI. These samples underwent centrifugation at a speed of 3000 revolutions per minute for 10 min. The resulting supernatant urine was extracted and stored at a temperature of -80 °C for subsequent analysis. The concentration of [TIMP-2] and [IGFBP7] were measured using a commercially available NephroCheck Test (Astute Medical, San Diego, CA, USA). Additionally, CCL14 levels were

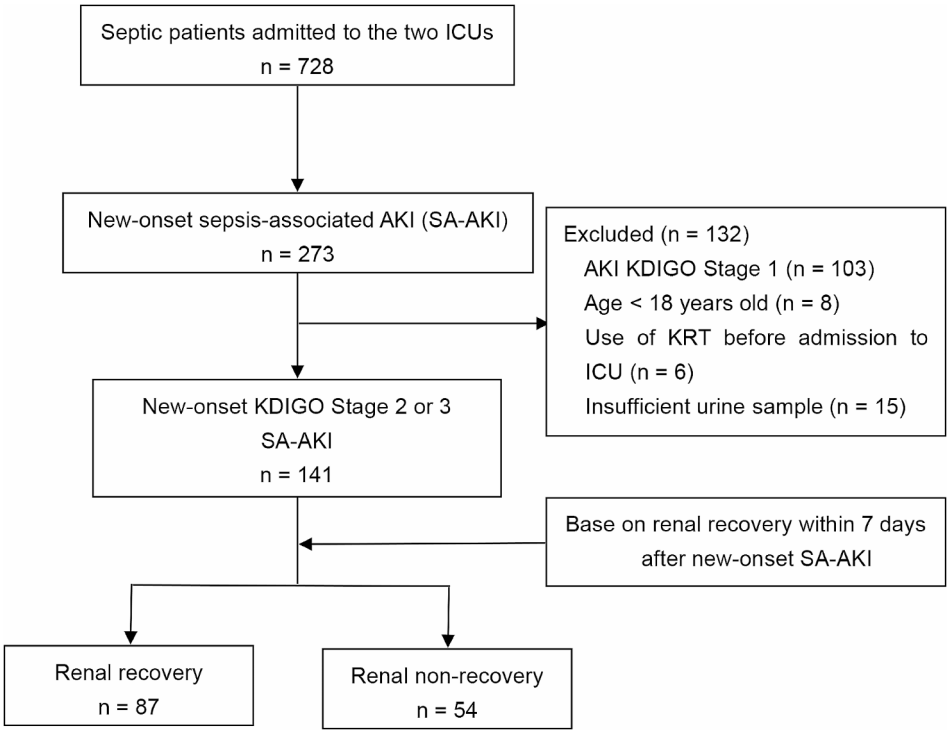

Fig. 1 Study flow diagram. *Abbreviations*: ICU, intensive care unit; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, Renal Replacement Therapy; SA-AKI, sepsis-associated acute kidney injury

quantified through the utilization of an enzyme-linked immunosorbent assay (ab272201, Abcam, UK) by investigators who were unaware of the patient's information. The VITROS 5600 Integrated System reports the product of the two protein concentrations ([TIMP-2]•[IGFBP7]) in units of $(ng/mL)^2/1000$.

Clinical outcomes

The primary outcome of the study was the occurrence of renal non-recovery within a 7-day period following SA-AKI. The secondary outcomes examined included use of KRT in the ICU and 30-day mortality after SA-AKI. Patients who met at least one of the following five indications were given KRT: (1) The presence of acute severe pulmonary edema that did not respond to diuretic therapy. (2) PH below 7.15 in the context of pure metabolic acidosis which was refractory to medical treatment. (3) Serum potassium concentration exceeding 6.5 mmol/L which was refractory to medical treatment. (4) Serum urea nitrogen exceeding 112 mg/dL (40 mmol/L). (5) Oliguria or anuria for more than 72 h [16, 17].

Definitions

Sepsis, a condition characterized by an uncontrolled host response to infection resulting in life-threatening organ dysfunction, has been defined by the Third International Consensus as Sepsis and Septic Shock (Sepsis-3) [18].

AKI is diagnosed based on the criteria established by KDIGO guidelines, meeting any of the following: (1) increase in serum creatinine (SCr) ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 h; (2) increase in SCr to ≥ 1.5 times baseline, which was known or suspected to have occurred within 7 days in the past; (3) urine output (UO) < 0.5 ml/kg/h for more than 6 h. AKI classification criteria were defined as follows: (1) stage 1: 1.5–1.9 times increase of SCr relative to baseline, or increase in SCr ≥ 0.3 mg/dL within 48 h, or UO < 0.5 ml/kg/h for 6–12 h; (2) stage 2: 2.0–3.0 times increase of SCr relative to baseline, or UO < 0.5 ml/kg/h for ≥ 12 h; (3) stage 3: > 3.0 times increase of SCr relative to baseline, or increase in SCr to ≥ 4.0 mg/dL (≥ 353.6 mmol/L), or initiation of KRT (regardless of the change in SCr) or UO < 0.3 ml/kg/h for ≥ 24 h, or anuria for ≥ 12 h [19].

The baseline creatinine was defined as follows: if at least five values were available the median of all values available from 6 months to 6 days before enrollment was used. Otherwise, the lowest value in the 5 days before enrollment was used. If no pre-enrollment creatinine was available or the emergency patient's serum creatinine was abnormal at the time of admission, the baseline creatinine was estimated using the Modification of Diet in Renal Disease (MDRD) equation assuming that baseline eGFR is 75 ml/min per 1.73 m^2 [11].

The criteria to identify patients with stage 2–3 SA-AKI is characterized by the simultaneous presence of

sepsis, as defined in adults according to the Sepsis-3 criteria, and stage 2–3 AKI, as defined by the KDIGO criteria [20]. Renal recovery is operationally defined as the absence of any stage of AKI based on the criteria of either SCr or urine output. Specifically, individuals diagnosed with AKI stage 2 must demonstrate a reduction in SCr to less than 150% of their baseline level and maintain a urine output exceeding 0.5 ml/kg/h for a duration exceeding 6 h. Patients who necessitate KRT or succumb to mortality within 7 days following AKI are classified as experiencing renal non-recovery [21].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on their data distribution. Group comparisons were performed using either a t-test or the rank-sum test. Categorical variables were presented as numbers (n) and percentages (%), and group comparisons were conducted using the chi-square (χ^2) test or Fisher's exact test.

The determinants of renal non-recovery in patients with SA-AKI were investigated using multivariate logistic regression analysis, which was performed with a stepwise forward-selection process. Univariate analysis initially assessed a spectrum of clinical parameters commonly associated with renal non-recovery, including age, serum lactate levels, sepsis severity, SCr at enrollment, and AKI severity. Only those clinical parameters that achieved statistical significance ($P<0.05$) in the univariate analysis were carried forward into the multivariate logistic regression analysis. Ordinal variables were included in the regression analysis without modification. Continuous variables were converted into categorical entities and were employed in the regression model as dummy variables to facilitate the analysis. Variables with $P<0.05$ in the multivariate logistic regression were independent risk factors for renal non-recovery.

We assessed the predictive capacity of various biomarkers in determining renal non-recovery by employing the area under the receiver-operating characteristic (ROC) curve (AUC). The following values were used to describe the AUC: 0.90–1.0, excellent; 0.80–0.89, good; 0.70–0.79, fair; 0.60–0.69, poor; and 0.50–0.59, useless. To evaluate the efficacy of various cutoff values of urinary biomarkers in predicting renal non-recovery, ROC curve analysis was conducted. The optimal cutoff point is identified by finding a balance point that maximizes the sum of sensitivity and specificity. This balance point ensures that the test is as accurate as possible in both identifying patients who will not recover renal function and those who will recover. By maximizing the sum of sensitivity and specificity, the optimal cutoff point serves as a threshold for the most accurate prediction of renal non-recovery. Subsequently, the optimal cut-off values of [TIMP-2]•[IGFBP7] and CCL14 were utilized to estimate Kaplan-Meier survival curves and compare them using the Log-rank test for 30-day mortality following the onset of SA-AKI. Statistical analyses were performed using SPSS Statistics 24, R 3.6.1, and MedCalc software. A significance level of $P<0.05$ was deemed statistically significant.

Results

Baseline characteristics of patients

During the designated study period, a total of 728 sepsis patients were initially screened. Among them, 273 individuals were identified as having newly developed SA-AKI. Subsequently, 132 patients were excluded from the study for various reasons, including 103 patients who exhibited AKI at KDIGO Stage 1, 8 patients who were under the age of 18, 6 patients who had previously undergone KRT before their admission to the ICU, and 15 patients who had insufficient urine samples. Ultimately, a cohort of 141 patients was enrolled for analysis (Fig. 1), and their baseline characteristics are displayed in Table 1. Out of 141 patients, 54 did not show renal recovery. Among these, 31 patients were classified as having renal non-recovery based on the established criterion for renal non-recovery. Additionally, 11 patients were categorized as renal non-recovery due to dependence on KRT at day 7, and 12 patients were defined as non-recovery due to death at day 7. These patients with renal non-recovery exhibited a significantly higher APACHE II score (18 vs. 18.5, $P=0.018$), a higher non-renal SOFA score (8.0 vs. 6.0, $P=0.020$), a higher prevalence of septic shock (31.5% vs. 13.8%, $P=0.012$), higher initial SCr levels at the onset of AKI (2.55 mg/dL vs. 1.69 mg/dL, $P<0.001$), and elevated serum lactate levels (3.7 mmol/L vs. 2.3 mmol/L, $P=0.002$) in comparison to those who experienced renal recovery. Figure 2 showed urinary concentrations of [TIMP-2]•[IGFBP7] and CCL14 at the time of AKI diagnosis; the concentrations of [TIMP-2]•[IGFBP7] and CCL14 were observed to be higher in the non-recovery group compared to the recovery group. The [TIMP-2]•[IGFBP7] concentration was 1.85 $(ng/mL)^2/1000$ versus 1.05 $(ng/mL)^2/1000$ ($P<0.001$), and the CCL14 concentration was 1595.97 pg/mL versus 427.61 pg/mL ($P<0.001$), respectively.

Clinical outcomes

Table 2 presents the clinical outcomes, revealing a significantly higher rate of KRT use (40.7% vs. 19.5%, $P=0.006$) in the renal non-recovery group compared to the recovery group. Additionally, the renal non-recovery group experienced a longer hospital stay (20.5 days vs. 17.0 days, $P=0.028$), higher ICU mortality (22.2% vs. 9.2%, $P=0.031$), higher hospital mortality (29.6% vs. 14.9%, $P=0.036$), and higher 30-day mortality (39.2% vs. 19.3%,

Table 1 Baseline characteristics between patients with renal recovery and non-recovery

Variables	Renal recovery *n* = 87	Renal non-recovery *n* = 54	*p*-value
Patient characteristics			
Age (years)	60 ± 17	59 ± 18	0.658
Male	55 (63.2)	32 (59.3)	0.638
Body mass index (kg/m$^{2)}$	24.4 ± 4.3	25.6 ± 3.7	0.079
APACHE II score	18.0 (15.8, 19.3)	18.5 (18.7, 23.2)	0.018
Non-renal SOFA score	6.0 (5.5, 7.4)	8.0 (6.8, 9.3)	0.020
Baseline SCr (mg/dL)	0.72 (0.70, 0.78)	0.76 (0.74, 0.81)	0.057
SCr at enrollment (mg/dL)	1.69 (1.50, 2.53)	2.55 (2.94, 4.70)	< 0.001
Chronic comorbidities			
Chronic kidney disease	7 (8.0)	7 (13.0)	0.343
Hypertension	31 (47.1)	30 (55.6)	0.330
Diabetes	26 (29.9)	19 (35.2)	0.512
Coronary artery disease	21 (24.1)	6 (11.1)	0.056
COPD	5 (5.7)	5 (9.3)	0.507
Chronic liver disease	24 (27.6)	10 (18.5)	0.221
Sepsis severity			0.012
Sepsis	75 (86.2)	37 (68.5)	
Septic shock	12 (13.8)	17 (31.5)	
Admission type			
Surgical	18 (21.4)	8 (14.8)	0.332
Medical	53 (60.9)	32 (59.3)	0.845
Emergency	16 (18.4)	14 (25.9)	0.288
Characteristics at inclusion			
Hemoglobin (g/L)	102.0 (100.1, 112.6)	106.5 (89.4, 108.1)	0.240
Lactate (mmol/L)	2.3 (2.9, 4.4)	3.7 (4.6, 8.2)	0.002
AKI stage at enrollment			< 0.001
Stage 2	69 (79.3)	15 (34.1)	
Stage 3	18 (20.7)	29 (65.9)	
Mechanical ventilation	74 (85.1)	43 (79.6)	0.404
Use of diuretics	38 (43.7)	29 (53.7)	0.247

Abbreviations AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; SCr, serum creatinine; SOFA, Sequential Organ Failure Assessment.

P=0.011). However, there was no significant difference in the length of ICU stay between the renal recovery and non-recovery groups (10 days vs. 7.0 days, P=0.170).

Risk factors associated with renal non-recovery

Univariate logistic regression analysis demonstrated significant associations between renal non-recovery and several factors, including age, sepsis severity, serum lactate level, SCr at enrollment, AKI stage, as well as urinary levels of [TIMP-2]•[IGFBP7] and CCL14 (all with P<0.05). Subsequent multivariate logistic regression analysis (variables with P<0.05 in the univariate logistic regression analysis) was conducted to evaluate the risk factors influencing renal non-recovery. This analysis confirmed that elevated urinary [TIMP-2]•[IGFBP7] (with an odds ratio [OR] of 1.261, 95% confidence interval [CI] of 1.063–1.495, and P=0.008) and CCL14 (OR 1.003, 95% CI 1.002–1.004, P<0.001) are independent predictors of increased risk for renal non-recovery (Table 3).

[TIMP-2]•[IGFBP7] and CCL14 as biomarkers for the prediction of renal non-recovery

ROC curves were utilized to compare the predictive efficacy of [TIMP-2]•[IGFBP7] and CCL14 concerning renal non-recovery (as shown in Table 4; Fig. 3). The AUC analysis revealed that urinary levels of CCL14 exhibited a superior predictive capacity for renal non-recovery when compared to [TIMP-2]•[IGFBP7] (0.901 vs. 0.730, P=0.001) (as indicated in Table S1). The threshold for CCL14 in predicting renal non-recovery was determined to be 973.95 pg/mL, yielding sensitivity and specificity rates of 90.7% and 80.5% respectively. Similarly, the threshold for [TIMP-2]•[IGFBP7] was established at 1.07 $(ng/mL)^2/1000$, resulting in sensitivity and specificity rates of 85.2% and 52.9% respectively. Furthermore, When [TIMP-2]•[IGFBP7] was combined with CCL14, there was an increase in the AUC to 0.907, indicating enhanced predictive accuracy for renal non-recovery. This combined biomarker approach yielded a

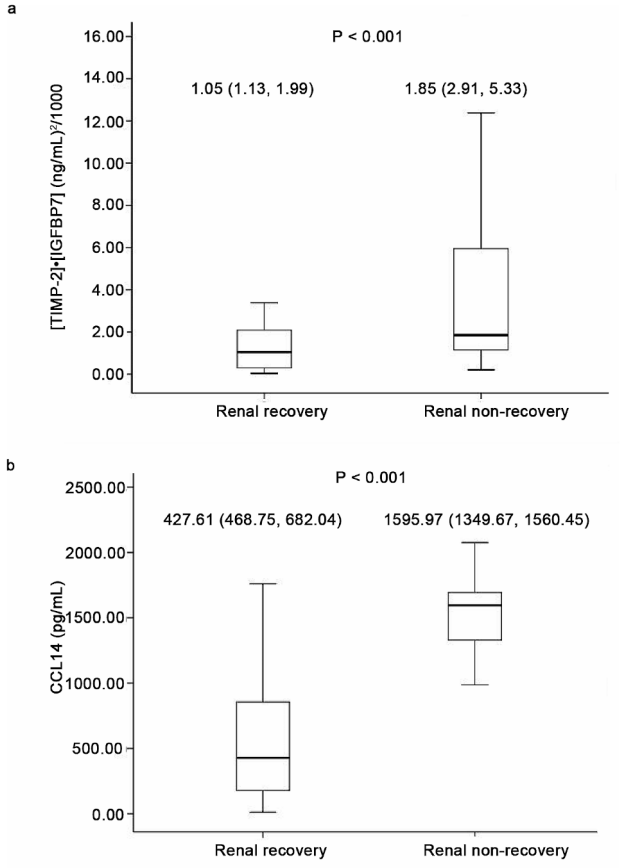

Fig. 2 Urinary [TIMP-2]•[IGFBP7] and CCL14 levels at AKI diagnosis in renal recovery and renal non-recovery group. a: The comparison of urinary [TIMP-2]•[IGFBP7] levels of renal recovery and non-recovery. b: The comparison of urinary CCL14 levels of renal recovery and non-recovery. *Abbreviations*: SA-AKI, sepsis-associated acute kidney injury; TIMP-2, Tissue inhibitor of metalloproteinase-2; IGFBP7, Insulin-like growth factor-binding protein 7; CCL14, C-C motif chemokine ligand 14

Table 2 Clinical outcomes between patients with renal recovery and non-recovery

Variables	Renal recovery *n* = 87	Renal non-recovery *n* = 54	*p*-value
KRT use in ICU	17 (19.5)	22 (40.7)	0.006
ICU stay (days)	7.0 (8.0, 11)	10.0 (10, 16)	0.170
Hospital stay (days)	17.0 (16.2, 19.8)	20.5 (22.6, 43.2)	0.028
ICU mortality	8 (9.2)	12 (22.2)	0.031
Hospital mortality	13 (14.9)	16 (29.6)	0.036
30-day mortality	16 (19.3)	20 (39.2)	0.011

Abbreviations KRT, kidney replacement therapy; ICU, Intensive Care Unit.

high sensitivity of 94.4% and a satisfactory specificity of 78.2%. However, the predictive contributions of CCL14 and [TIMP-2]•[IGFBP7] - CCL14 were not found to be statistically significant as evidenced by Delong analysis (P=0.641), as shown in Table S1.

[TIMP-2]•[IGFBP7] and CCL14 as biomarkers for the prediction of KRT in ICU after AKI

ROC curves were utilized to compare the predictive value of [TIMP-2]•[IGFBP7] and CCL14 for the occurrence of KRT in the ICU following AKI, as presented in Table 5; Fig. 4. The AUC values indicated that the urinary levels of CCL14 and [TIMP-2]•[IGFBP7] exhibited moderate predictive power for the prediction of KRT in the ICU after SA-AKI, with AUC values of 0.794 (95% CI, 0.718–0.858) and 0.725 (95% CI, 0.643–0.796) (P=0.230), respectively, as shown in Table S2. In addition, the AUC of [TIMP-2]•[IGFBP7] combined with CCL14 reached up to 0.816, with a sensitivity of 92.3% and a specificity of 70.6%. The determined threshold for CCL14 in predicting KRT in the ICU after SA-AKI was 1073.61 pg/mL; the sensitivity and specificity values of CCL14 were 82.1% and 72.5%, respectively. the threshold for [TIMP-2]•[IGFBP7] was set at 2.46 $(ng/mL)^2/1000$, with its sensitivity and specificity being 53.8% and 81.4%, respectively.

The correlation between [TIMP-2]•[IGFBP7] and CCL14 with 30-day mortality after AKI

The present study examined the potential association between [TIMP-2]•[IGFBP7] and CCL14 levels with 30-day mortality in patients with SA-AKI. Among the SA-AKI cohort of 141 patients, a total of 36 individuals (25.5%) experienced mortality within 30 days following AKI. ROC curves were utilized to compare the predictive value of [TIMP-2]•[IGFBP7] and CCL14 for 30-day mortality following AKI, as presented in Table 6; Fig. 5. The AUC values indicated that the urinary levels of CCL14 and [TIMP-2]•[IGFBP7] exhibited poor predictive power for 30-day mortality after SA-AKI, with AUC values of 0.623 (95% CI, 0.538–0.704) and 0.593 (95% CI, 0.507–0.675), respectively. Based on the cut-off values of [TIMP-2]•[IGFBP7] and CCL14 for predicting renal non-recovery, the Kaplan Meier curve was used to compare 30-day mortality by Log-rank test; only CCL14≥973.95 pg/mL was associated with a higher risk of 30-day mortality (Fig. 6).

Discussion

TIMP-2 and IGFBP7 are indicators of cellular stress expressed in renal tubule cells [22, 23]. Their concentrations increase when the glomerular filtration rate decreases [22], making them reliable biomarkers for AKI's prediction, diagnosis, and risk stratification [24]. Our previous research indicated the promising potential of urinary [TIMP-2]•[IGFBP7] in predicting non-recovery in critically ill patients with AKI [25]. The investigation conducted by Xie Y et al. focused on the relationship between [TIMP-2]•[IGFBP7] levels and adverse outcomes among ICU patients diagnosed with AKI. The study encompassed all admitted ICU patients 18 years of

Table 3 Risk factors analysis for renal non-recovery

Variables	Univariate			Multivariate		
	OR	95% CI	*p*- value	OR	95% CI	*p*-value
Sepsis severity						
Sepsis	1 [Reference]					
Septic shock	2.765	1.210–6.319	0.016			
SCr at enrollment	1.005	1.002–1.008	0.003			
Serum lactate	1.119	1.036–1.209	0.004			
AKI stage at enrollment						
Stage 2	1 [Reference]					
Stage 3	4.447	2.111–9.368	< 0.001			
[TIMP-2]•[IGFBP7]	1.337	1.151–1.554	< 0.001	1.261	1.063–1.495	0.008
CCL14	1.003	1.002–1.004	< 0.001	1.003	1.002–1.004	< 0.001

Abbreviations AKI, acute kidney injury; CCL14, C-C motif chemokine ligand 14; CI, confidence interval; IGFBP-7, insulin-like growth factor-binding protein 7; OR, odds ration; SCr, serum creatinine; TIMP-2, tissue inhibitor of metalloproteinases-2.

Table 4 The areas under the receiver operating characteristic curves for two kinds of urinary biomarkers to predict renal non-recovery

Variables	AUC	95% CI	*P*- value	Cut-off value	Sensitivity	Specificity
[TIMP-2]•[IGFBP7] ((ng/mL)^2/1000)	0.730	0.649–0.801	< 0.001	1.07	85.2	52.9
CCL14 (pg/mL)	0.901	0.839–0.945	< 0.001	973.95	90.7	80.5
[TIMP-2]•[IGFBP7] - CCL14	0.907	0.847–0.950	< 0.001	0.252	94.4	78.2

Abbreviations AUC, area under the receiver operating characteristic; CCL14, C-C motif chemokine ligand 14; CI, confidence interval; IGFBP-7, insulin-like growth factor-binding protein 7; TIMP-2, tissue inhibitor of metalloproteinases-2.

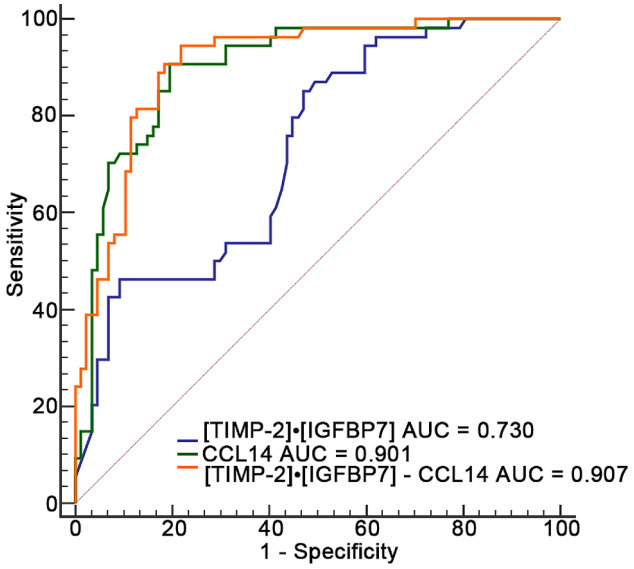

Fig. 3 The predictive value of [TIMP-2]•[IGFBP7], CCL14 at AKI diagnosis and combined model for renal non-recovery. AUCs of [TIMP-2]•[IGFBP7], CCL14, and combined model([TIMP-2]•[IGFBP7] - CCL14) for renal non-recovery. *Abbreviations*: ROC, receiver operating characteristic; AUC, the area under the curve; AKI, acute kidney injury; SA-AKI, sepsis-associated acute kidney injury; TIMP-2, Tissue inhibitor of metalloproteinase-2; IGFBP7, Insulin-like growth factor-binding protein 7; CCL14, C-C motif chemokine ligand 14

age or older, with the exclusion of those on maintenance dialysis or those who were anuric upon ICU admission. Utilizing the established [TIMP-2]•[IGFBP7] cutoff value of 0.3 (ng/mL)^2/1000, which was previously validated in other cohorts, the researchers distinguished patients as having increased [TIMP-2]•[IGFBP7] (+) or not [TIMP-2]•[IGFBP7] (-). Acute kidney injury was identified according to the KDIGO consensus criteria, resulting in patient categorization into four groups: (1) [TIMP-2]•[IGFBP7] (-)/AKI (-), (2) [TIMP-2]•[IGFBP7] (+)/AKI (-), (3) [TIMP-2]•[IGFBP7] (-)/AKI (+), and (4) [TIMP-2]•[IGFBP7] (+)/AKI (+). The study's outcomes indicated that [TIMP-2]•[IGFBP7] is a viable biomarker for pinpointing AKI patients who are at a heightened risk for requiring KRT or facing mortality within the ICU [26]. This aligns with the findings from our current research regarding the link between [TIMP-2]•[IGFBP7] and the necessity for KRT in an ICU setting. The study by Koyner JL et al. encompassed a cohort of critically ill patients, explicitly excluding those with moderate or severe AKI (KDIGO stages 2 or 3). Outcomes were assessed at the 9-month mark post-enrollment, with patients being categorized based on the occurrence of either death or dialysis, or the absence of both. Findings from the study suggest that the early measurement of [TIMP-2]•[IGFBP7] levels in critically ill individuals can serve as a potential indicator for elevated risk of mortality or the necessity for KRT within the subsequent 9 months. It is important to note that the research did not separately explore the relationship between [TIMP-2]•[IGFBP7] levels and the individual outcomes of death or dialysis. Instead, it examined their link to a combined endpoint - either death or dialysis [27]. The research conducted by Godi I et al. also delved into the prognostic capabilities of [TIMP-2]•[IGFBP7] in determining the risk of short-term adverse outcomes in critically ill patients.

Table 5 The areas under the receiver operating characteristic curves for urinary biomarkers to predict use of kidney replacement therapy

Variables	AUC	95% CI	*P*-value	Cut-off value	Sensitivity	Specificity
[TIMP-2]•[IGFBP7] ((ng/mL)^2/1000)	0.725	0.643–0.796	< 0.001	2.46	53.8	81.4
CCL14 (pg/mL)	0.794	0.718–0.858	< 0.001	1073.61	82.1	72.5
[TIMP-2]•[IGFBP7] - CCL14	0.816	0.742–0.876	< 0.001	0.232	92.3	70.6

Abbreviations AUC, area under the receiver operating characteristic; CCL14, C-C motif chemokine ligand 14; CI, confidence interval; IGFBP-7, insulin-like growth factor-binding protein 7; TIMP-2, tissue inhibitor of metalloproteinases-2.

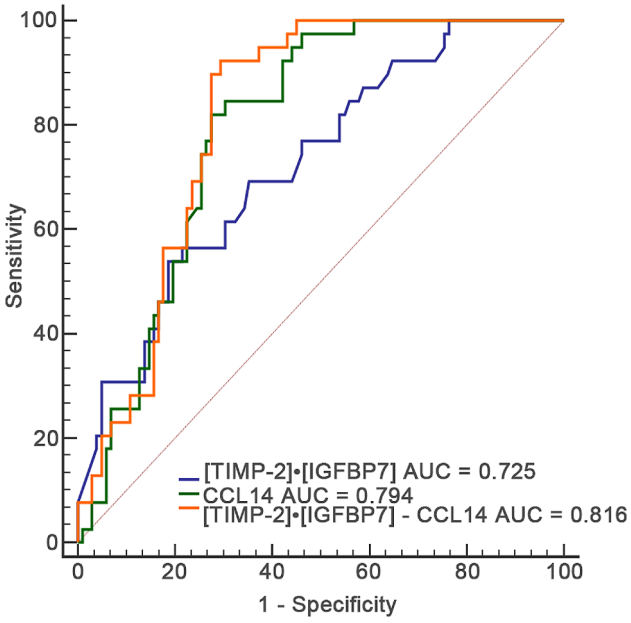

Fig. 4 The predictive value of [TIMP-2]•[IGFBP7], CCL14 and combined model for KRT use in ICU. AUCs of [TIMP-2]•[IGFBP7], CCL14 and combined model ([TIMP-2]•[IGFBP7] - CCL14) for KRT use. *Abbreviations*: ROC, receiver operating characteristic; AUC, the area under the curve; AKI, acute kidney injury; KRT, Kidney Replacement Therapy; TIMP-2, Tissue inhibitor of metalloproteinase-2; IGFBP7, Insulin-like growth factor-binding protein 7; CCL14, C-C motif chemokine ligand 14

Table 6 The areas under the receiver operating characteristic curves for urinary biomarkers to predict 30-day mortality following SA-AKI

Variables	AUC	95% CI	*P*-value
[TIMP-2]•[IGFBP7] ((ng/mL)^2/1000)	0.593	0.507–0.675	0.108
CCL14 (pg/mL)	0.623	0.538–0.704	0.024

Abbreviations AUC, area under the receiver operating characteristic; CCL14, C-C motif chemokine ligand 14; CI, confidence interval; IGFBP-7, insulin-like growth factor-binding protein 7; TIMP-2, tissue inhibitor of metalloproteinases-2.

The findings indicated that both [TIMP-2]•[IGFBP7] and procalcitonin could be instrumental in identifying ICU patients with a high probability of developing septic AKI and encountering short-term complications [28]. This study took the form of a retrospective cohort analysis, suggesting that while the results are noteworthy, they would benefit from verification in a more extensive, prospective trial. Notably, the scope of this study did not cover the association of [TIMP-2]•[IGFBP7] with renal

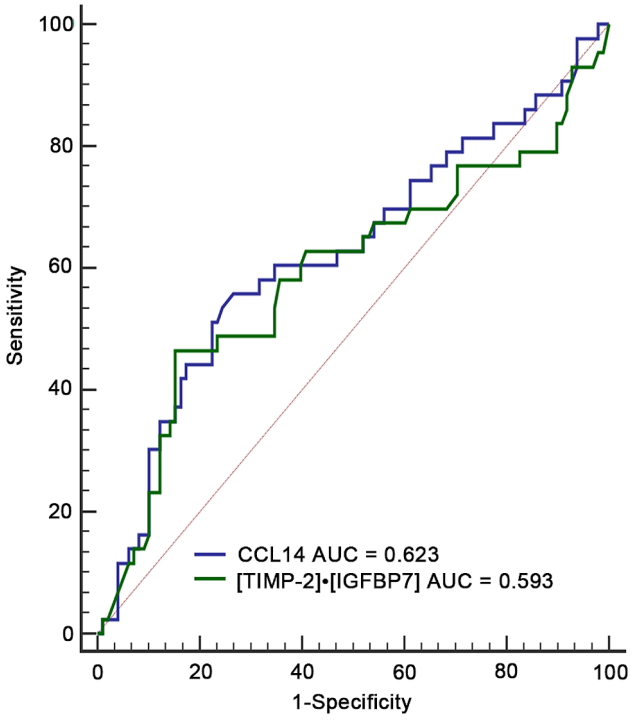

Fig. 5 The predictive value of biomarkers for 30-day mortality after AKI. The ROC curves of urinary [TIMP-2]•[IGFBP7] and CCL14 for predicting 30-day mortality after AKI. *Abbreviations*: ROC, receiver operating characteristic; AUC, area under the ROC. TIMP-2, Tissue inhibitor of metalloproteinase-2; IGFBP7, Insulin-like growth factor-binding protein 7; CCL14, C-C motif chemokine ligand 14

recovery within 7 days post-AKI or mortality at 30 days after the onset of AKI.

CCL14 is a member of the small-molecule chemokine family and was initially thought to play a crucial role in leukocyte chemotaxis. It has also been associated with tissue damage and repair mechanisms. Elevated levels of CCL14 can lead to the substantial recruitment of monocytes and T cells, which have the potential to differentiate into T1 and M1 macrophage cells within an inflammatory injury setting. These macrophage cells possess pathogenic properties and can incite and amplify tissue damage [26]. Urinary CCL14 demonstrated the highest predictive value for persistent stage 3 AKI among the biomarkers studied [14]. However, in our previous study about AKI in critically ill patients [15], CCL14 did not show a significant advantage over [TIMP-2]•[IGFBP7] in

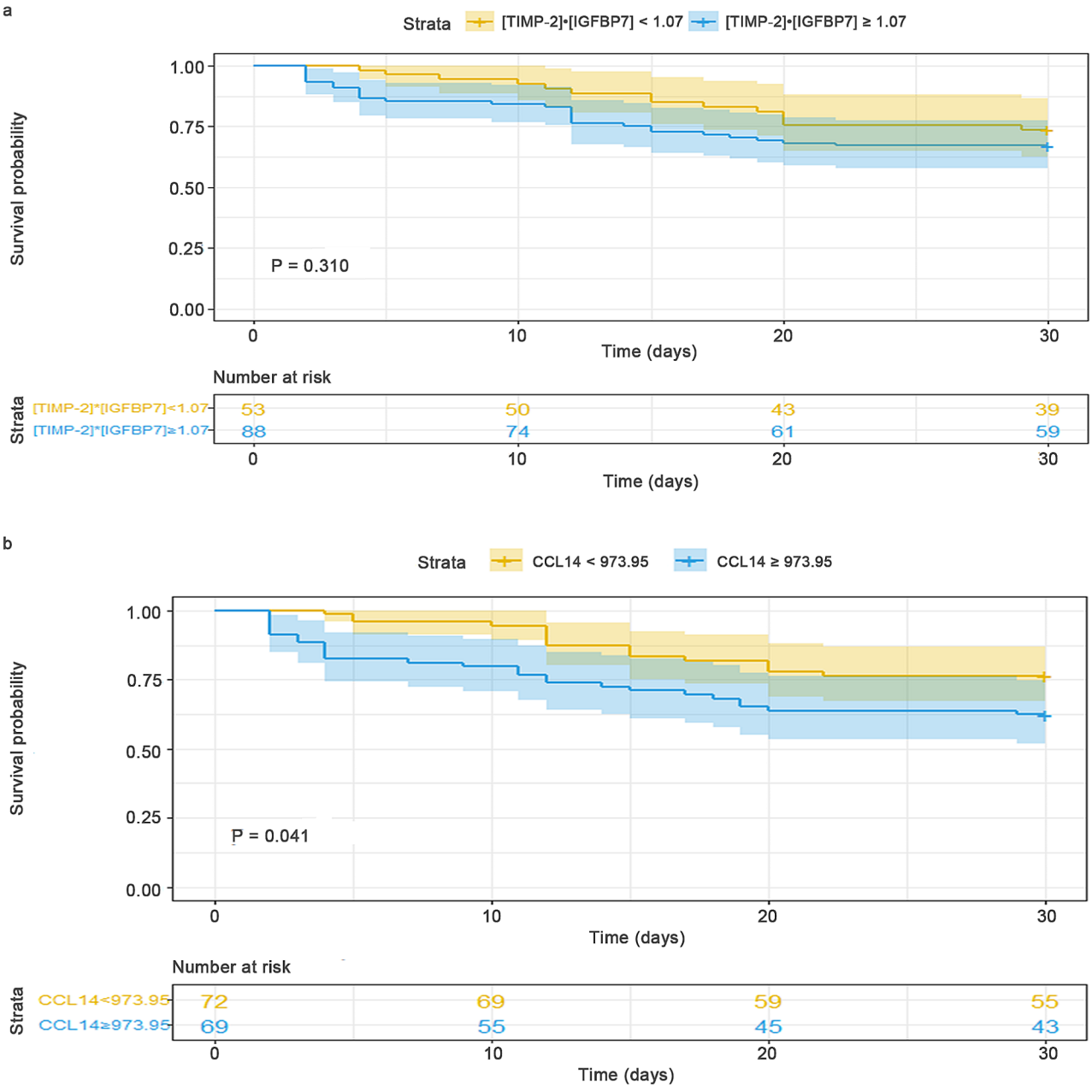

Fig. 6 Association of [TIMP-2]•[IGFBP7] and CCL14 with 30-day mortality after SA-AKI. **a**: The mortality rates were not significantly different when the patients were grouped according to urinary [TIMP-2]•[IGFBP7] level that were higher or less than 1.07 $(ng/mL)^2/1000$. **b**: The mortality rates were significantly different when the patients were grouped according to urinary CCL14 level that were higher or less than 973.95 pg/mL. *Abbreviations*: TIMP-2, Tissue inhibitor of metalloproteinase-2; IGFBP7, Insulin-like growth factor-binding protein 7; CCL14, C-C motif chemokine ligand 14

predicting renal non-recovery within a mixed AKI population. Consequently, we aimed to evaluate and compare the predictive capabilities of urinary biomarkers [TIMP-2]•[IGFBP7] and CCL14 for renal non-recovery, the initiation of KRT in the ICU, and 30-day mortality, focusing specifically on a relatively homogeneous population of patients with SA-AKI. 22 stage 2–3 SA-AKI patients reported in the previous publication [15] and additional 119 stage 2–3 SA-AKI patients were included in current study. It was found in this study that urinary CCL14 exhibited superior predictive ability (AUC=0.901) in comparison to [TIMP-2]•[IGFBP7] (AUC=0.730) for renal non-recovery.

AKI is a widely prevalent condition within ICU, with approximately 40% of cases typically attributed to sepsis [29, 30]. Among patients with SA-AKI, 40% exhibit moderate to severe AKI, while 27% experience severe AKI, necessitating continuous KRT [31]. The pathophysiology

of AKI in critically ill patients is highly heterogeneous, encompassing a variety of underlying causes such as sepsis, surgical interventions, and trauma. In SA-AKI, the pathogenesis is closely associated with the host's inflammatory and immune responses elicited by the infectious insult. As a result, biomarkers like [TIMP-2]•[IGFBP7] and CCL14 may demonstrate different predictive capacities in the context of SA-AKI compared to other critical illnesses, due to specific pathophysiological dynamics. By focusing on SA-AKI patients, our research seeks to create a more homogenized cohort, especially regarding the causes of AKI. A uniform study population in terms of AKI etiology could improve the accuracy of biomarker performance assessment. Applying this focused method might result in more precise and trustworthy prognostic insights related to renal recovery, as the biomarkers' effectiveness could be more directly correlated with the distinctive pathophysiology of this patient subgroup. However, the combination of [TIMP-2]•[IGFBP7] and CCL14 did not enhance the predictive performance beyond that of CCL14 alone.

Our study found that urinary [TIMP-2]•[IGFBP7] or CCL14 exhibited moderate predictive capability in anticipating the need for KRT in the ICU among SA-AKI patients. Furthermore, the predictive model that integrated the concentrations of [TIMP-2]•[IGFBP7] and CCL14 demonstrated a commendable capability, as evidenced by an AUC value exceeding 0.8. Additionally, our study revealed that patients with SA-AKI who exhibited urinary CCL14 levels equal to or exceeding 973.95 pg/mL exhibited a greater likelihood of experiencing 30-day mortality. Unfortunately, elevated levels of [TIMP-2]•[IGFBP7] did not demonstrate a significant correlation with an increased risk of 30-day mortality. KRT is an essential strategy in the treatment of SA-AKI. Nevertheless, there is a lack of universally accepted indicators for KRT in patients with renal non-recovery. The optimal timing for initiating KRT is presently a subject of debate, and there is no definitive tool available to determine its use, resulting in significant variability as the decision ultimately lies with the treating physicians. Our current study suggests that incorporating urinary [TIMP-2]•[IGFBP7] and CCL14 may help clinicians in making informed decisions about initiating KRT, which could potentially reduce renal damage and improve survival rates.

The utilization of specific biomarkers provides clinicians with a powerful tool to classify patients based on their risk levels. This advance in early detection empowers healthcare providers to engage in a more rigorous monitoring and to undertake timely interventions, which holds the potential to halt the furtherance of kidney injury. Enhanced monitoring protocols entail more frequent assessment of renal function and meticulous oversight of fluid and electrolyte equilibrium. The timely interventions could encompass the optimization of hemodynamic status, avoidance of nephrotoxic agents, and the possible use of therapeutic interventions that have shown promise in protecting kidney function, such as hydration protocols, antioxidants, or drugs that target specific pathways involved in AKI [32–34]. Furthermore, it grants enhanced clarity in making pivotal decisions regarding the necessity and the optimal moment to commence KRT. In general, the predictive value of these biomarkers for renal non-recovery offers a powerful tool in the management of SA-AKI patients. By enabling early identification, risk stratification, and the initiation of targeted treatments, these biomarkers hold the potential to significantly improve patient outcomes by preventing or delaying the progression of kidney injury.

Strengths and limitations

This study included stage 2–3 SA-AKI patients with relatively high population homogeneity. However, The study possesses certain limitations. First, further evaluation and validation of urinary [TIMP-2]•[IGFBP7] and CCL14 for renal non-recovery is necessary through extensive sample size studies, despite the inclusion of SA-AKI patients from two ICUs. Second, the lack of continuous monitoring when measuring urinary [TIMP-2]•[IGFBP7] and CCL14 levels solely at the initiation of AKI makes it impossible to determine the changes in [TIMP-2]•[IGFBP7] and CCL14 in SA-AKI patients with renal recovery or non-recovery.

Conclusion

In the prediction of renal non-recovery in cases of stage 2–3 SA-AKI, urinary CCL14 demonstrated superior predictive capacity compared to [TIMP-2]•[IGFBP7] with an AUC value exceeding 0.9. It's worth noting that incorporating [TIMP-2]•[IGFBP7] alongside CCL14 did not markedly improve the predictive accuracy over using CCL14 on its own. When it came to predicting the need for KRT in the ICU, both urinary [TIMP-2]•[IGFBP7] and CCL14 showcased moderate prognostic performance. However, our refined predictive model that combined [TIMP-2]•[IGFBP7] with CCL14 displayed a good predictive power for KRT necessity in the ICU, achieving an AUC greater than 0.8.

Abbreviations

AKI	Acute kidney injury
CCL14	C-C motif chemokine ligand
SA-AKI	Sepsis-associated acute kidney injury
KDIGO	Kidney Disease: Improving Global Outcomes
ICU	Intensive Care Unit
TIMP-2	Tissue inhibitor of metalloproteinase-2
IGFBP7	Insulin-like growth factor-binding protein 7
KRT	Kidney replacement therapy
SOFA	Sequential organ failure assessment
APACHE II	Acute physiology and chronic health evaluation II

SCr	Serum creatinine
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
SD	Standard deviation
AUC	The area under receiver operating characteristics curve
IQR	Interquartile range
ROC	Receiver operating characteristic
AUROC	Area under the receiver operating characteristic
OR	Odds ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03589-9.

Supplementary Material 1

Acknowledgements
We express our gratitude to Professor Fei-fei Zhao from Beijing Lu He Hospital for conducting the statistical analysis.

Author contributions
LC wrote the main manuscript text and prepare Figs. 1, 2, 3, 4, 5 and 6. All authors reviewed the manuscript.

Funding
This study is supported by the Capital Funds for Health improvement and research (approval no. 2020-2-2061) .

Data availability
The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Ethical approval and consent to Participate
The study followed the ethical principles of the 1964 Declaration of Helsinki and was approved by the Hospital Human Ethics Committee of two participating ICUs. Chao-Yang Hospital, Capital Medical University Institutional Review Board granted the study (No. 2018 – 117). Informed written consent is required for participation in the clinical trial.

Received: 24 October 2023 / Accepted: 25 April 2024
Published online: 03 May 2024

References

1. Poston JT, Koyner JL. Sepsis associated acute kidney injury. BMJ. 2019;364:k4891.
2. Gómez H, Kellum JA. Sepsis-induced acute kidney injury. Curr Opin Crit Care. 2016;22:546–53.
3. Huang CY, Güiza F, De Vlieger G, Wouters P, Gunst J, Casaer M. ea ta. Development and validation of clinical prediction models for acute kidney injury recovery at hospital discharge in critically ill adults. J Clin Monit Comput. 2023;37:113–125.
4. Xia WH, Yi F, Qb W. Mortality and differential predictive factors of transient and persistent sepsis-associated acute kidney injury. Clin Nephrol. 2023;99:119–27.
5. Perinel S, Vincent F, Lautrette A, Dellamonica J, Mariat C, Zeni F, et al. Transient and persistent acute kidney injury and the risk of hospital mortality in critically ill patients. Crit Care Med. 2015;43:e269–275.
6. Choi JS, Kim YA, Kim MJ, Kang YU, Kim CS, Bae EH, et al. Relation between transient or persistent acute kidney injury and long-term mortality in patients with myocardial infarction. Am J Cardiol. 2013;112:41–5.
7. Dellepiane S, Marengo M, Cantaluppi V. Detrimental crosstalk between sepsis and acute kidney injury: new pathogenic mechanisms, early biomarkers and targeted therapies. Crit Care. 2016;20:61.
8. Schuler A, Wulf DA, Lu Y, Iwashyna TJ, Escobar GJ, Shah NH, et al. The impact of acute organ dysfunction on long-term survival in Sepsis. Crit Care Med. 2018;46:843–9.
9. Emlet DR, Pastor-Soler N, Marciszyn A, Wen XY, Gomez H, Humphries WH 4th, et al. Insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases-2: differential expression and secretion in human kidney tubule cells. Am J Physiol Ren Physiol. 2017;312:F284–96.
10. Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: the light and the dark sides. Nephrol Dial Transpl. 2016;31:16–22.
11. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013;17:R25.
12. Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med. 2006;354:610–21.
13. Kulvichit W, Kellum JA, Srisawat N. Biomarkers in Acute kidney Injury. Crit Care Clin. 2021;37:385–98.
14. Hoste E, Bihorac A, Al-Khafaji A, Ortega LM, Ostermann M, Haase M, et al. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. Intensive Care Med. 2020;46:943–53.
15. Qian BS, Jia HM, Weng YB, Li XC, Chen CD, Guo FX, et al. Analysis of urinary C-C motif chemokine ligand 14 (CCL14) and first-generation urinary biomarkers for predicting renal recovery from acute kidney injury: a prospective exploratory study. J Intensive care. 2023;11:11.
16. Tandukar S, Palevsky PM. Continuous renal replacement therapy: who, when, why, and how. Chest. 2019;155:626–38.
17. Rachoin JS, Weisberg LS. Renal replacement therapy in the ICU. Crit Care Med. 2019;47:715–21.
18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus definitions for Sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801–10.
19. Kellum JA, Lameire N, KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care. 2013;17:204.
20. Zarbock A, Nadim MK, Pickkers P, Gomez H, Bell S, Joannidis M, et al. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol. 2023;19:401–17.
21. Kellum JA, Sileanu FE, Bihorac A, Hoste EAJ, Chawla LS. Recovery after acute kidney injury. Am J Respir Crit Care Med. 2017;6:784–91.
22. Johnson ACM, Zager RA. Mechanisms underlying increased TIMP2 and IGFBP7 urinary excretion in experimental AKI. J Am Soc Nephrol. 2018;29:2157–67.
23. Gocze I, Koch M, Renner P, Zeman F, Graf BM, Dahlke MH, et al. Urinary biomarker TIMP-2 and IGFBP7 early predict acute kidney Injury after major surgery. PLoS ONE. 2015;10:e0120863.
24. Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R et al. Recommendations on Acute Kidney Injury Biomarkers from the Acute Disease Quality Initiative Consensus Conference: A Consensus Statement. JAMA Netw Open. 2020;3:e2019209.
25. Jia HM, Cheng L, Weng YB, Wang JY, Zheng X, Jiang YY, et al. Cell cycle arrest biomarkers for predicting renal recovery from acute kidney injury: a prospective validation study. Ann Intensive Care. 2022;12:14.
26. Xie Y, Ankawi G, Yang B, Garzotto F, Passannante A, Breglia A, et al. Tissue inhibitor metalloproteinase-2 (TIMP-2)•IGF-binding protein-7 (IGFBP7) levels are associated with adverse outcomes in patients in the intensive care unit with acute kidney injury. Kidney Int. 2019;95:1486–93.
27. Koyner JL, Shaw AD, Chawla LS, Hoste EA, Bihorac A, Kashani K, et al. Tissue inhibitor Metalloproteinase-2 (TIMP-2)•IGF-Binding Protein-7 (IGFBP7) levels are Associated with adverse long-term outcomes in patients with AKI. J Am Soc Nephrol. 2015;26:1747–54.
28. Godi I, De Rosa S, Martino F, Bazzano S, Martin M, Boni E, et al. Urinary [TIMP-2]×[IGFBP7] and serum procalcitonin to predict and assess the risk for short-term outcomes in septic and non-septic critically ill patients. Ann Intensive Care. 2020;10:46.
29. Ninet S, Schnell D, Dewitte A, Zeni F, Meziani F, Darmon M. Doppler-based renal resistive index for prediction of renal dysfunction reversibility: a systematic review and meta-analysis. J Crit Care. 2015;30:629–35.

30. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol. 2007;2:431–9.
31. Peters E, Antonelli M, Wittebole X, Nanchal R, François B, Sakr Y, et al. A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from the Intensive Care Over Nations audit. Crit Care. 2018;22:188.
32. Zarbock A, Küllmar M, Ostermann M, Lucchese G, Baig K, Cennamo A, Prevention of cardiac surgery-associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: The PrevAKI-Multicenter Randomized Controlled Trial. Anesth Analg., Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP et al. Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76:422–427.
33. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76:422–427.
34. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. Sepsis occurrence in acutely ill patients (SOAP) investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12:R74.

Publisher's Note