Biomarkers in pursuit of precision medicine for acute kidney injury: hard to get rid of customs

Association between systemic inflammation biomarkers and mortality in patients with sepsis-associated acute kidney injury receiving intensive care and continuous kidney replacement therapy: results from the RENERGY (REsearches for NEphRology and epidemioloGY) study

Time-restricted feeding protects against cisplatin-induced acute kidney injury in mice

Validation of prediction model for successful discontinuation of continuous renal replacement therapy: a multicenter cohort study

A machine learning–based approach for predicting renal function recovery in general ward patients with acute kidney injury
Aims and Scope

Kidney Research and Clinical Practice (KRCP; formerly The Korean Journal of Nephrology; ISSN 1975-9460, launched in 1982), the official journal of the Korean Society of Nephrology, is an international, peer-reviewed journal published in English. Its ISO abbreviation is Kidney Res Clin Pract.

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The 5th Asia Pacific AKI CRRT 2023: Best Movement to Critical Care, Save Lives

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This editorial outlines the proceedings of the 5th Asia Pacific AKI CRRT (APAC 2023): “Best Movement to Critical Care, Save Lives.” This symposium is a valuable educational forum to discuss many critical issues in caring for acute kidney injury (AKI) with continuous renal replacement therapy (CRRT). An eminent international faculty of experts contribute their expertise to the discussion and presentation. This publication has been prepared to present the essential topics of the symposium, providing readers with a helpful overview of the scientific exchange held in Daegu, Republic of Korea.

APAC 2023 shared meaningful clinical experiences and provided an opportunity to review and discuss AKI epidemiology, diagnosis, treatment including CRRT, and novel management for critical care. The symposium begins with the basic practice of CRRT for physicians and nurses, presenting strategies for improving outcomes in AKI, challenges and controversies in renal support and CRRT, including innovative care for AKI patients, and future trends in CRRT and critical care. There are also outstanding basic and clinical research results on AKI, CRRT, general critical care, and nursing issues. Among them, this issue represents a valuable update on many of the critical issues relating to the novel biomarker for AKI patients who underwent CRRT, initiation and discontinuation of CRRT, machine learning or artificial intelligence-based approaches to diagnosis and prediction of the outcomes of AKI, and multidisciplinary approaches to caring for critically ill patients.

In this issue of Kidney Research and Clinical Practice, Lin et al. [1] present the role of biomarkers for AKI to move forward to precision medicine, which promises an early detection and initiation of AKI care. Pan et al. [2] introduce a multidisciplinary team approach to optimize acute kidney disease treatment. Cheungpasitporn et al. [3] present the role of artificial intelligence and machine learning in early diagnosis and management of sepsis-associated AKI, highlighting the potential revolution in this field.

Among original research, Jeon et al. [4] propose a prediction model for successfully discontinuing CRRT using four variables: urine output, blood urea nitrogen, serum potassium, and mean arterial pressure. Interestingly, one cohort performed poorly among multicenter cohorts because attending physicians primarily controlled CRRT prescriptions and discontinuation. Therefore, active engagement of nephrologists and protocolized management for CRRT prescriptions might be helpful in the discontinuation of CRRT in AKI patients.

Three different clinical studies have proposed novel biomarkers or suggested epidemiological data for predicting mortality in patients with AKI requiring CRRT. Plasma presepsin and serum phosphate are related to predicting mortality in patients with AKI requiring CRRT [5,6]. Kim et
al. [7] also suggest that advanced age is not a risk factor for mortality among elderly AKI patients undergoing CRRT.

There are safety concerns about using nafamostat mesylate anticoagulation in patients with bleeding tendencies. Kim et al. [8] have analyzed those concerns and found no differences between using nafamostat mesylate anticoagulation and no anticoagulation in patients with AKI who have bleeding tendencies. These data suggest that nafamostat mesylate is an effective and safe anticoagulant for CRRT in critically ill patients.

This issue, therefore, highlights the 5th Asia Pacific AKI CRRT conference and provides an overview of current expert opinion on the management of AKI patients undergoing CRRT and critical care.

**Conflicts of interest**

The author has no conflicts of interest to declare.

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Biomarkers in pursuit of precision medicine for acute kidney injury: hard to get rid of customs

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Traditional acute kidney injury (AKI) classifications, which are centered around semi-anatomical lines, can no longer capture the complexity of AKI. By employing strategies to identify predictive and prognostic enrichment targets, experts could gain a deeper comprehension of AKI’s pathophysiology, allowing for the development of treatment-specific targets and enhancing individualized care. Subphenotyping, which is enriched with AKI biomarkers, holds insights into distinct risk profiles and tailored treatment strategies that redefine AKI and contribute to improved clinical management. The utilization of biomarkers such as N-acetyl-β-D-glucosaminidase, tissue inhibitor of metalloprotease-2-insulin-like growth factor-binding protein 7, kidney injury molecule-1, and liver fatty acid-binding protein garnered significant attention as a means to predict subclinical AKI. Novel biomarkers offer promise in predicting persistent AKI, with urinary motif chemokine ligand 14 displaying significant sensitivity and specificity. Furthermore, they serve as predictive markers for weaning patients from acute dialysis and offer valuable insights into distinct AKI subgroups. The proposed management of AKI, which is encapsulated in a structured flowchart, bridges the gap between research and clinical practice. It streamlines the utilization of biomarkers and subphenotyping, promising a future in which AKI is swiftly identified and managed with unprecedented precision. Incorporating kidney biomarkers into strategies for early AKI detection and the initiation of AKI care bundles has proven to be more effective than using care bundles without these novel biomarkers. This comprehensive approach represents a significant stride toward precision medicine, enabling the identification of high-risk subphenotypes in patients with AKI.

Keywords: Acute kidney injury, Biomarkers, Dialysis, Precision medicine

Introduction

The burgeoning field of translational science has ushered in a new era in the diagnosis and management of acute kidney injury (AKI), advancing toward the realm of precision medicine [1]. Traditionally, AKI has been perceived as a monolithic entity, often classified along semi-anatomical lines, namely, prerenal, intrinsic, or postrenal AKI. This...
A simplistic classification scheme is gradually making way for more precise categorizations, encompassing conditions like hepatorenal syndrome (HRS), cardiorenal syndrome, and sepsis-related AKI [2].

The prevailing diagnostic criteria for AKI predominantly rely on changes in serum creatinine (sCr) concentration and/or alterations in urine output. However, these criteria primarily reflect alterations in kidney function without necessarily explicitly indicating injury or damage [3]. Furthermore, the current AKI criteria are primarily centered on duration and severity, providing limited insights into the pathophysiology and prognosis of the condition [4].

Relying solely on sCr as a diagnostic marker may lead to diagnostic delays in specific scenarios, such as cases involving muscle wasting, liver diseases, or sepsis [5]. Consequently, the Acute Disease Quality Initiative 2020 has advocated for the concurrent utilization of functional and damage biomarkers in the early diagnosis of AKI [5]. This approach, which amalgamates damage and functional biomarkers, holds the potential to facilitate precise AKI diagnosis, differentiate underlying pathophysiological mechanisms, elucidate the etiology of AKI, and gauge the severity of the condition [6].

Simultaneously, the stratification of critical illness into distinct subphenotypes has emerged as a guiding principle in the quest for individualized medicine, a principle that also extends to the diagnosis of AKI (Fig. 1). Such stratification not only holds promise in the personalized management of AKI but also serves as a conduit for the discovery of distinct endotypes and treatable traits within this multifaceted condition [7]. In this review, we endeavor to synthesize the current methodologies into a comprehensive framework for the management of patients with AKI.

Reconsidering the classification and diagnostic challenges in acute kidney injury

Recent research has consistently demonstrated a notable association between AKI severity or chronic kidney disease (CKD) progression stages and a less favorable prognosis. This encompasses various critical facets, including the potential for renal function recovery, the imperative need for renal replacement therapy (RRT), and the ultimate mortality risk. Nevertheless, the existing definition of AKI portrays it as a solitary diagnostic entity, disregarding the intricate reality that AKI is a multifaceted syndrome influenced by

![Figure 1. Biomarkers for AKI subgrouping—dinosaur parkour illustration.](image)

The clinical use of biomarkers in AKI is influenced by the heterogeneity of patient groups and outcomes. Biomarkers have a range of advantages, including the early detection of kidney injury, the identification of AKI subphenotypes (subsets of clinical features within a shared phenotype), the recognition of AKI endotypes (subsets of patients with distinct biological disease mechanisms), and the predictive enrichment of high-risk patient groups for specific care pathways or interventions.

AKI, acute kidney injury; CCL14, chemokine ligand 14; HJV, hemojuvelin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; PROENK, proenkephalin.
several contributory factors. This underscores the pressing need for the exploration of alternative AKI classifications.

The untimely detection of AKI is a major diagnostic challenge. Notably, sCr levels only become abnormal when much of the patient’s kidney function (often >50%) has already been compromised [8]. This inherent delay in its responsiveness poses a notable hindrance to early diagnosis and intervention.

In contrast, in conditions like angina pectoris, troponin-based diagnostic strategies have led to notable achievements in survival rates by expediting diagnosis and subsequent treatment [9]. However, when considering renal angina, a similar approach that relies on creatinine-based markers may not yield comparable improvements in patient prognosis. The inherent delay in the presentation of elevated creatinine levels in response to kidney injury may explain this disparity. As such, it is imperative to reevaluate the diagnostic criteria for AKI, considering its complex nature and the limitations of current biomarkers.

Redefining acute kidney injury: the imperative of subphenotypes

The prevailing definition of AKI does not sufficiently provide insight into the trajectory of the condition, the utility of measured biomarkers, and the critical question of when a return to baseline renal function may be anticipated. Relying solely on sCr and urine output data does not provide enough information to elucidate the intricate pathophysiological underpinnings and the inherent heterogeneity of AKI [10].

To ensure better prognostic accuracy, it is vital to identify distinct AKI subphenotypes [11]. A subphenotype can be characterized as a discrete subset of AKI patients, who exhibit shared characteristics, risk factors, biomarker profiles, responses to treatment, or outcomes that distinguish them from other patient groups within the broader AKI phenotype [12]. These etiological subphenotypes such as LIION (low perfusion, inflammation/immune, obstruction, nephrotoxin/envenomation) [1] could be delineated based on shared etiological factors (Table 1) [13] or specific outcomes, such as the need for RRT [14]. The process of subphenotyping AKI not only unveils variances in clinical outcomes [15] but also paves the way for the development of treatment strategies tailored to the distinct needs of each patient group.

Table 1. AKI subphenotyping category

<table>
<thead>
<tr>
<th>Subphenotype</th>
<th>Old classification for AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prerenal</strong></td>
<td>1. Absolute decrease in effective blood volume: hemorrhage, volume depletion</td>
</tr>
<tr>
<td></td>
<td>2. Relative decrease in blood volume (ineffective arterial volume): CHF, decompensated liver cirrhosis</td>
</tr>
<tr>
<td></td>
<td>3. Arterial occlusion or stenosis of renal artery</td>
</tr>
<tr>
<td></td>
<td>4. Hemodynamic form: NSAIDs, ACE-I, ARB in renal artery stenosis or CHF</td>
</tr>
<tr>
<td><strong>Intrinsic</strong></td>
<td>Vascular: vasculitis, malignant HTN</td>
</tr>
<tr>
<td></td>
<td>Acute glomerular nephritis; PSGN</td>
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<tr>
<td></td>
<td>AIN: drug-associated</td>
</tr>
<tr>
<td></td>
<td>ATN</td>
</tr>
<tr>
<td></td>
<td>Ischemic</td>
</tr>
<tr>
<td></td>
<td>Nephrotoxic</td>
</tr>
<tr>
<td></td>
<td>Exogenous: cisplatin, contrast</td>
</tr>
<tr>
<td></td>
<td>Endogenous: rhabdomyolysis, myeloma</td>
</tr>
<tr>
<td><strong>Postrenal</strong></td>
<td>Obstruction of collecting system or extrarenal drainage: bladder outlet and ureteral obstruction</td>
</tr>
<tr>
<td><strong>LIION</strong> [1]</td>
<td>Low perfusion subphenotypes</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>Volume: volume depletion, hypervolemia</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td>Dilatation</td>
</tr>
<tr>
<td></td>
<td>Local: hepatorenal syndrome</td>
</tr>
<tr>
<td></td>
<td>Systemic: shock and sepsis</td>
</tr>
<tr>
<td><strong>Constriction</strong></td>
<td>eclampsia, HTN, rhabdomyolysis</td>
</tr>
<tr>
<td><strong>Interruption</strong></td>
<td>IAP↑</td>
</tr>
<tr>
<td><strong>Ventricular</strong></td>
<td>↓ RV output</td>
</tr>
<tr>
<td></td>
<td>↓ LV output</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>Sepsis</td>
</tr>
<tr>
<td><strong>Immune</strong></td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td>Nephritis</td>
</tr>
<tr>
<td><strong>Obstructive</strong></td>
<td>Pressure necrosis</td>
</tr>
<tr>
<td><strong>Nephrotoxin/envenomation</strong></td>
<td>Direct toxin: ATN</td>
</tr>
<tr>
<td></td>
<td>Indirect toxin: AIN</td>
</tr>
</tbody>
</table>

ACE-I, angiotensin-converting enzyme inhibitor; AIN, acute interstitial nephritis; AKI, acute kidney injury; ARB, angiotensin receptor blockers; ATN, acute tubular necrosis; CHF, congestive heart failure; HTN, hypertension; IAP, intraabdominal pressure; LIION, low perfusion, inflammation/immune, obstruction, nephrotoxin/envenomation; LV, left ventricle; NSAIDs, nonsteroidal anti-inflammatory drugs; PSGN, post-streptococcal glomerulonephritis; RV, right ventricle.

Previously labeled “prerenal,” the term “low perfusion” is introduced here to highlight the treatment approaches that are tailored to the pathogenesis of the condition.
Biomarkers and acute kidney injury phenotype

(Fig. 2)

Biomarkers in postcardiac surgery

The PrevAKI randomized controlled trial (RCT) implements the Kidney Disease Improving Global Outcomes (KDIGO) care bundle (optimization of volume status and hemodynamics, functional hemodynamic monitoring, avoidance of nephrotoxic drugs, and prevention of hyperglycemia) in high-risk patients after cardiac surgery. High-risk patients were defined as those with urinary (tissue inhibitor of metalloproteinase-2, TIMP-2)•(insulin-like growth factor-binding protein 7, IGFBP7) > 0.3. The rates of moderate-to-severe AKI were significantly reduced by the intervention compared to standard care [17]. Another multicenter RCT later also demonstrated a lower prevalence of moderate-to-severe AKI in the intervention group [18].

When speaking to the dynamic change in renal function in patients with heart failure, the term (worsening of renal function, WRF) was used [19]. Rao et al. [20] demonstrated that in patients with acute heart failure decompensation who have preexisting WRF, aggressive volume removal with a consequent rise in tubular markers (N-acetyl-β-D-glucosaminidase [NAG], kidney injury molecule-1 [KIM-1], and neutrophil gelatinase-associated lipocalin [NGAL]) did not increase risks of post-discharge mortality or rehospitalization. The extent of the elevation of these tubular “injury” biomarkers is far less than in true AKI [21]. Novel biomarkers such as galectin-3, soluble suppression of tumorigenicity 2 (ST2), fibroblast growth factor 23 (FGF-23), soluble urokinase plasminogen activator receptor (suPAR), microRNA, growth differentiation factor 15, and NAG may have prognostic value in kidney disease progression. Liver fatty acid-binding protein (L-FABP) and suPAR may help predict AKI. ST2 and NAG may be helpful in diuretic resistance [22].

Figure 2. Biomarkers for clinical features in patients sharing a common syndrome or condition.

AKI, acute kidney injury; CXCL9, C-X-C motif chemokine ligand 9; FGF-23, fibroblast growth factor 23; GDF-15, growth differentiation factor 15; IGFBP7, insulin-like growth factor-binding protein 7; IL-9, interleukin 9; KDIGO, Kidney Disease Improving Global Outcomes; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid-binding protein; miRNA, microRNA; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; ST2, suppression of tumorigenicity 2; suPAR, soluble urokinase plasminogen activator receptor; TIMP-2, metalloproteinase 2; TNF, tumor necrosis factor.
Biomarkers in hepatorenal syndrome

AKI in cirrhosis has a spectrum of etiologies, of which HRS carries the worst prognosis [23]. AKI is managed according to its etiology: prerenal AKI is treated with volume resuscitation, HRS is managed using intravenous albumin and vasoconstrictors, and supportive care is used for acute tubular necrosis (ATN).

Fagundes et al. [24] used the levels of urinary tubular markers such as urinary NGAL to predict elevations across the different AKI causes, with prerenal AKI being the lowest, followed by the slightly higher levels seen in HRS and the significantly elevated levels seen in ATN. They also used the cutoff value of 194 g/g creatinine of urinary NGAL to separate type-1 HRS from ATN. If HRS was diagnosed, terlipressin use was recommended [25]. Furthermore, the urinary NGAL can predict the therapeutic response to terlipressin and albumin for HRS-AKI and is an independent predictor of in-hospital mortality [26].

Biomarkers in acute interstitial nephritis

Moledina et al. [27] found that urinary tumor necrosis factor alpha (TNF-α) and interleukin (IL) 9 levels were higher in the patients whose biopsies revealed acute interstitial nephritis (AIN). They concluded that urinary TNF-α and IL-9 were used to differentiate AIN from other causes of acute kidney disease [27]. They also evaluated the relationship between corticosteroid use and 6m-eGFR (the estimated glomerular filtration rate [eGFR] 6 months after the diagnosis of AIN) and concluded that corticosteroid use was associated with higher 6 m-eGFR values in patients with high urinary IL-9 levels [28]. Thus, urinary IL-9 levels could be measured to predict the corticosteroid treatment response. Recently, a diagnostic biomarker for AIN, urinary C-X-C motif chemokine ligand 9 (CXCL9), was identified and validated [29]. They adopted urinary CXCL9-to-creatinine ratios, in which values above 58.9 ng/g were diagnostic of AIN while those below 14.2 ng/g suggested other causes for AKI [30].

Identifying the causes of acute kidney injury subphenotypes (Fig. 3)

1. In the low-perfusion subphenotype, cellular hypoxia is primarily triggered by hypoperfusion, which predominantly affects proximal tubular cells. When tubular injury occurs, certain proteins from the tubular cells, such as L-FABP, NGAL, TIMP-2, and IGFBP7, are released.

2. In the inflammatory subphenotype, both plasma and urine may show elevated levels of inflammatory markers such as IL-6, soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), L-FABP, and KIM-1.

The practical application of these biomarkers can facilitate the timely diagnosis of AKI compared to creatinine-based methods, leading to earlier intervention and better prognoses.

Although several biomarkers have been put forth as potential predictors of AKI, their efficacy varies across distinct trials [31]. Notably, biomarkers incorporating NGAL demonstrated superior predictive accuracy for AKI occurrence, irrespective of whether adjustments were made based on urinary creatinine levels. However, the predictive utility of urinary NGAL was comparatively restrained in surgical patients, with urinary NGAL/creatinine ratios emerging as the most precise biomarkers within this cohort [32].

Acute kidney injury subphenotypes: predictive and prognostic enrichment targets (Fig. 3)

In essence, the subphenotypes of AKI not only enhance our understanding of the underlying pathophysiology but also unveil potential treatment-specific targets. Considering the intrinsic heterogeneity characterizing AKI, there is an ardent call to arms to craft customized clinical study designs, meticulously perform choreograph timing, and meticulously devise robust thresholds for the intervention. In this rigorous journey, we move closer to providing personalized healthcare.

Biomarkers for predicting subclinical acute kidney injury

The utilization of biomarkers to predict subclinical AKI, which is characterized by elevated biomarker levels that do not align with KDIGO classification criteria, has gained considerable attention. Studies by Haase et al. [33] have demonstrated that individuals with subclinical AKI, specifically those with NGAL-positive/sCr-negative profiles, face an elevated risk of subsequent RRT initiation, prolonged
intensive care unit (ICU) and in-hospital stays, and increased mortality.

In a multicenter prospective cohort study [34], it has been established that patients with elevated levels of urinary NGAL and urinary KIM-1 without concurrent sCr elevation are at increased risk of a composite outcome; namely, dialysis initiation or death during hospitalization. This risk is significantly higher than that in patients without elevations in NGAL, KIM-1, or creatinine levels.

Moreover, the incorporation of normalized urinary hemojuvelin and uKIM-1 levels (assessed 3 hours after cardiovascular surgery) into Liano’s score has proven to be a valuable strategy for identifying patients who are predisposed to advanced AKI and adverse composite outcomes [35].

Collectively, these findings emphasize the crucial role of tubular damage biomarkers in clinical practice. Their utilization facilitates the early diagnosis of subclinical AKI, enabling timely and effective interventions to improve patient outcomes [36].

**Biomarkers for predicting the persistence of acute kidney injury (non-recovery of acute kidney injury)**

Urinary motif chemokine ligand 14, in particular, exhibited promising predictive performance, with a pooled sensitivity of 0.81 (95% confidence interval [CI], 0.72–0.87) and specificity of 0.71 (95% CI, 0.53–0.84). Furthermore, the pooled positive likelihood ratio (LR) stood at 2.75 (95% CI, 1.63–4.66), and the negative LR at 0.27 (95% CI, 0.18–0.41) [37]. Establishing standardized cutoff levels for these biomarkers holds significant potential in guiding AKI management and facilitating the design of clinical trials [38].

**Biomarkers for predicting weaning from acute dialysis therapy**

The use of biomarkers to predict the successful weaning of ICU patients with AKI from RRT has been a subject of interest. A retrospective single-center cohort study demonstrated that a daily urinary urea excretion that exceeds 1.35
mmol/kg/24 hr is the most reliable indicator of successful weaning from intermittent hemodialysis in ICU patients with AKI [39]. The urinary L-FABP/creatinine ratio at the time of weaning off RRT has shown promise in predicting both successful weaning from RRT and 90-day mortality [40]. Additionally, in patients with advanced CKD, plasma C-terminal FGF-23 levels have emerged as an independent risk factor for forecasting both 90-day mortality and progression to end-stage kidney failure requiring renal transplantation within the same timeframe [41].

Distinct subgroups in the progression of acute kidney injury

Advanced statistical techniques such as the latent class analysis (LCA) are being employed to subdivide AKI into distinct subgroups. For instance, Bhatraju et al. [42] employed LCA in their analysis of patients with AKI in the VASST trial (Vasopressin and Septic Shock Trial; n = 271), identifying two unique subphenotypes: AKI-SP1 and AKI-SP2. Remarkably, the AKI-SP1 group exhibited lower 90-day mortality rates when vasopressin was introduced early in conjunction with norepinephrine than norepinephrine alone did. Conversely, vasopressin therapy did not significantly impact mortality in the AKI-SP2 subgroup. Furthermore, the authors identified a genetic variant near the ANGPT2 gene, correlating with plasma angiopoietin-2 concentrations and the development of AKI-SP2 in critically ill patients [43]. The utilization of unsupervised consensus clustering to distinguish subphenotypes holds substantial clinical significance, particularly within the context of sepsis-associated AKI requiring dialysis, where it emerges as an invaluable outcome predictor. This method exemplifies a considerable leap forward in the pursuit of precision medicine, offering the capacity to pinpoint high-risk subphenotypes among patients grappling with sepsis-associated AKI [44].

Biomarkers for oliguric acute kidney injury without azotemia

After excluding obstruction, reduced urine output becomes a clinically valuable biomarker for decreased GFR. Consensus definitions of AKI incorporate urine output criteria along with biochemical markers of renal excretory function. Isolated oliguria, even without an increase in sCr, is linked to higher mortality [45]. Despite efforts to enhance risk stratification for poor kidney outcomes using biomarkers like NGAL in oliguric patients [46,47], they did not surpass the predictive performance of sCr [48]. Distinctions in risk among episodes of oliguria were acknowledged, and NGAL successfully differentiated functional oliguria from AKI based on sCr criteria in a separate study [49]. However, assessments of fluid responsiveness using urinary sodium, fractional excretion of sodium, and fractional excretion of urea in oliguric patients lacked significant predictive value [46]. Further research is warranted to refine risk stratification in oliguric patients.

Acute kidney injury subphenotypes: proposed acute kidney injury management flow chart (Fig. 4)

“The less there is to justify a traditional custom, the harder it is to get rid of it” from Mark Twain’s wisdom, as expressed in The Adventures of Tom Sawyer, illustrates this difficulty. It can be challenging for us to transition from using creatinine to adopting novel biomarkers for AKI diagnosis. Due to evolving concepts in critical illness [50], we should adopt a new perspective on AKI management. The incorporation of AKI subphenotyping and corresponding biomarkers into clinical practice should be adopted.

Biomarkers for risk stratification in acute kidney injury

Cartin-Ceba et al. [51] demonstrated that critically ill patients were at increased risk of AKI in the following conditions: older age, diabetes, hypertension, higher baseline creatinine, heart failure, systemic inflammatory response syndrome, use of nephrotoxic drugs, higher severity of disease scores, use of vasopressors/inotropes, high-risk surgery, emergency surgery, use of intra-aortic balloon pump, and more time spent on a cardiopulmonary bypass pump. Thus, the identification of patients at high risk of AKI is vital to AKI management.

The various risk hold prediction models for AKI at ICU admission such as Coritsidis et al. [52], renal angina index [53], and the USCD (the University of California, San Diego) Mayo model [54], were mentioned previously. Recently, Mohebi et al. [55] added four biomarkers (KIM-1, IL-18, osteopontin, and cystatin C) to the contrast-induced AKI
The incorporation of osteopontin and cystatin C into the CA-AKI clinical model significantly increased the c-statistic level from 0.69 to 0.73 (p for change <0.001). Therefore, the application of biomarkers in the risk prediction model could identify high-risk patients and enhance risk classification [56].

**Biomarkers to predict renal recovery**

The amount of irreversible nephron loss determines the long-term outcome of kidney function. However, it is difficult to appreciate nephron loss in clinical practice. Some tools and biomarkers are reported to predict renal recovery. First, the furosemide stress test (FST) can predict AKI progression and the need for RRT [57]. In a study conducted by Chawla et al. [57], 77 patients from two cohorts were administered a single dose of furosemide (1.0 mg/kg for loop diuretic-naïve patients and 1.5 mg/kg for those who had received loop diuretics before). The optimal cut-off for the prediction of AKI progression during the first 2 hours following FST was a urine output of less than 200 mL.

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**Figure 4. Proposed strategies for managing AKI.** The definition of AKI encompasses an escalation in serum creatinine levels, a decrease in urine output, and the presence of kidney damage and stress biomarkers. Various biomarkers, some of which are accessible at the point of care, may assist in the early detection of AKI. These biomarkers can facilitate the timely identification of patients who exhibit potential endotypes, amenable traits for targeted interventions, or suitability for specific preventive measures. AKI subphenotypes, which are delineated by their clinical attributes, have already been integrated into routine clinical practice, including considerations such as etiology, AKI staging, severity, and duration. However, the integration of biomarkers into these subphenotypes may offer a more comprehensive and informative framework, culminating in predictive and prognostic insights. This refined definition of subphenotypes aims to distinguish patient subgroups with comparable outcomes (prognostic enrichment) or similar responses to therapeutic interventions (predictive enrichment). The evolution of treatment strategies requires further development and fine-tuning. Moreover, the nuanced categorization of AKI subphenotypes will advance with the discovery of novel biomarkers and more precise clinical and biomarker-derived subphenotypes.

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**Risk stratification**

- **APACHE II**, Renal angina index / FST
- **KDIGO AKI**
  - Low risk
  - High risk
  - Biomarker (–)
- **Biomarkers for early detection of AKI**
  - Urine NGAL, Urine KIM-1, Urinary [TIMP-2] · [IGFBP7]
- **Sub-phenotypes**
  - AKI (–) sCr, UO
  - AKI (+): sCr, UO
- **Persistent AKI >7 days**
- **Non-recovery of renal function > 90 days**
- **AKD**
- **CKD**

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**KDIGO AKI care bundle**
- 1. Intensified hemodynamic monitoring
- 2. Discontinue nephrotoxins
- 3. Avoid hyperglycemia
- 4. Avoid radiocontrast

**Sub-phenotypes prognosis/predictive enrichment**
- 1. KDIGO AKI care bundle
- 2. AKI Sub-phenotyping LIION, sCr trajectory, electronic biomarkers; AI and machine learning

**AKI Sub-phenotyping LIION, sCr trajectory, electronic biomarkers; AI and machine learning**
- 1. Intensified hemodynamic monitoring
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CA-AKI risk score.

The incorporation of osteopontin and cystatin C into the CA-AKI clinical model significantly increased the c-statistic level from 0.69 to 0.73 (p for change <0.001).

Therefore, the application of biomarkers in the risk prediction model could identify high-risk patients and enhance risk classification [56].
(100 mL/hr) with 87.1% sensitivity and 84.1% specificity. The FST can also predict renal recovery and the cessation of continuous RRT in patients recovering from AKI [58]. Koyner et al. [59] demonstrated that (urinary NGAL of >150 ng/mL [n = 44] or IGFBP7 × TIMP of >0.3 [n = 32]) in whom the 2-hour urine output after FST was analyzed, the area under the curve (AUC) for progression to stage 3 improved to 0.90 ± 0.06 and the AUC for receipt of RRT improved to 0.91 ± 0.08. The above findings suggested that the combination of FST and biomarkers provides higher positive predictive values. Not long ago, Hasson et al. [60] proved that AKI is associated with increased urinary olfactomedin 4 (OLFM4), and urinary OLFM4 is associated with furosemide unresponsiveness. Furthermore, TIMP2 and IGFBP7 demonstrated strong predictive capabilities in the diagnosis of AKI associated with cardiac surgery. It is noteworthy that these biomarkers can also serve as predictors of long-term outcomes.

Biomarkers enhancing acute kidney injury care bundles

Incorporating kidney biomarkers into strategies for early AKI detection and initiating AKI care bundles has shown greater effectiveness than using care bundles without these novel biomarkers. This conclusion stems from a meta-analysis of RCTs [61].

For instance, Halmy et al. [62] divided patients into the following three risk-based groups: low risk (TIMP-2×IGFBP7 of <0.3), moderate risk (TIMP-2×IGFBP7 of 0.3–2.0), and high risk (TIMP-2×IGFBP7 of >2.0). Then, they tailored interventions to align with these risk profiles [62].

Biomarkers identifying treatable endotype

For individuals with high renin levels, the administration of angiotensin II may serve a dual purpose. First, it can effectively reduce the renin concentration. Second, it holds the potential to enhance intra-renal hemodynamics and optimize signaling through the angiotensin II receptor 1. This tailored approach may identify patients for whom treatment with angiotensin II would positively affect clinical outcomes.

In essence, renin levels, when utilized as a biomarker, offer a way of identifying a specific endotype within AKI that is amenable to targeted treatment [63].

Based on the above points, we proposed the management flowchart for AKI (Fig. 4)

Limitations

The ideal characteristics of biomarkers for AKI encompass several key attributes: 1) organ specificity to differentiate between AKI subphenotypes; 2) early detection capability with predictive insights into the course and outcomes of AKI; 3) site specificity, providing information on pathologic changes across various segments of renal tubules during AKI; 4) noninvasive measurability; 5) stability within its matrix; and 6) cost-effectiveness.

However, challenges in the development of biomarkers for kidney injury and toxicity persist, primarily revolving around assay design, validation, and qualification for practical use. Further research is imperative to establish precise cutoff values for specific biomarkers mentioned earlier. Moreover, certain biomarkers present hurdles due to their elevated cost and complexity in clinical application. Addressing these challenges is paramount for the successful clinical integration of biomarkers.

Future directions

Due to the complexity of kidney disease, relying on a single biomarker may be insufficient for early diagnosis, understanding pathophysiology, and predicting outcomes. Combining multiple biomarkers in plasma, urine, or both has proven beneficial. In the future, biomarker test panels are anticipated to serve in diagnosing kidney injury, predicting outcomes, and acting as surrogate endpoints in clinical trials, expediting the evaluation of therapies for kidney diseases.

Conclusions

Within the domain of AKI, the odyssey toward precision medicine unfurls with the pressing necessity of subphenotyping, an approach that not only offers insights into discrete risk profiles but also makes it easier to tailor treatment strategies. This journey not only reshapes our understanding of AKI but profoundly elevates the standards of clinical management. Novel biomarkers are central to this transformative process, and their integration into subphe-
notype heralds the potential to illuminate and enrich our comprehension of AKI’s intricate landscape.

For example, consider the early diagnosis of subclinical AKI and the design of care bundles for interventions, which both profoundly underscore the potency of assimilating biomarkers into the tapestry of clinical practice. Questions surrounding the juxtaposition of traditional AKI criteria naturally arise, hinging on the bedrock of sCr and urine output, against the burgeoning significance of novel biomarkers such as urine NGAL and KIM1. These biomarkers not only demonstrate the potential to bolster AKI subphenotypes but also to guide interventions predicated on a profound grasp of pathophysiological nuances.

The wisdom encapsulated in the proverb “it is hard to get rid of traditional customs” finds contemporary resonance when contemplating the relinquishment of entrenched beliefs tied to the simplicity of creatinine. To boost this transformative potential, biomarkers could assume the role of fortune-tellers, forecasting the responsiveness of treatments.

Conflicts of interest

Vin-Cent Wu was supported by the Mrs. Hsiu-Chin Lee Kidney Research Foundation. All other authors have no conflicts of interest to declare.

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References


Introduction

Acute kidney disease (AKD) was first coined in 2012 to describe abnormal kidney function, defined by either serum creatinine level or estimated glomerular filtration rate (eGFR), for less than 3 months [1]. AKD was proposed to identify patients with kidney injury for less than 90 days with or without preceding acute kidney injury (AKI) events (Fig. 1) [2]. AKD can be viewed as a continuum between AKI (kidney injury within 7 days) and chronic kidney disease (CKD, abnormal kidney function or structure beyond 3 months) [1].

Keywords: Acute kidney injury, Drug therapy, Patient care team, Prognosis

Acute kidney disease (AKD) is a critical transitional period between acute kidney injury and chronic kidney disease. The incidence of AKD following acute kidney injury is approximately 33.6%, and it can occur without identifiable preceding acute kidney injury. The development of AKD is associated with increased risks of chronic kidney disease, dialysis, and mortality. Biomarkers and subphenotypes are promising tools to predict prognosis in AKD. The complex clinical situations in patients with AKD necessitate a comprehensive and structured approach, termed “KAMPS” (kidney function check, advocacy, medications, pressure, sick day protocols). We introduce “MAND-MASS,” an acronym devised to summarize the reconciliation of medications during episodes of acute illness, as a critical component of the sick day protocols at AKD. A multidisciplinary team care, consisting of nephrologists, pharmacists, dietitians, health educators, and nurses, is an optimal model to achieve the care bundle in KAMPS. Although the evidence for patients with AKD is still lacking, several potential pharmacological agents may improve outcomes, including but not limited to angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide 1 receptor agonists. In conclusion, accurate prognosis prediction and effective treatment for AKD are critical yet unmet clinical needs. Future studies are urgently needed to improve patient care in this complex and rapidly evolving field.
A comprehensive systematic review has revealed that, after an episode of AKI, around 33.6% of the patients had AKD [3]. Furthermore, the development of AKD varied significantly across different clinical scenarios, showing a 15.6% incidence in patients with severe malaria-related AKI, 35.9% in patients with postsurgical AKI, and escalating to nearly 40% in patients with myocardial infarction-related AKI [4,5].

It is of paramount importance to highlight that the occurrence of AKD is not solely confined to those with a history of AKI. Specifically, data indicated that the incidence of AKD was 12.3% in hospitalized patients and 4.7% in the general population, irrespective of prior AKI episodes. In line with findings from other investigations, the incidence of AKD in individuals without any previous AKI episodes ranged from 17% to 37.8% [3].

AKI and CKD have been the subject of extensive study, resulting in the formulation of clinical guidelines for patient care [1,6], as expounded in the existing literature. Nevertheless, it is essential to underscore that research concerning AKD remains in its nascent stages. This incipient field confronts several pivotal inquiries that demand further investigation. This review focuses on the intricate domains of AKD prognosis and therapeutic interventions.

**Acute kidney disease and clinical outcomes**

In patients with AKI or AKD, different outcomes may develop, including death, dialysis, CKD, or recovery of renal function [2]. Studies have consistently reported that AKD is...
associated with worse prognosis (mainly subsequent CKD and death) in various disease populations, such as hospitalized patients [7], surgical patients [8], patients with acute decompensated heart failure [9], patients with septic AKI [10], and cirrhotic patients [11]. Importantly, even without identifiable preceding AKI, the prognosis in patients with AKD is still worse than in patients without AKD [3]. This finding justifies the management of AKD as a distinct syndrome other than AKI. Overall, regardless of preceding AKI, the presence of AKD significantly increases the risk of mortality and dialysis [3].

In patients with AKI, the severity of AKI can be staged according to serum creatinine levels [1,12]. A higher AKI stage is associated with poorer outcomes including mortality and dialysis dependence [13-15]. Compared with persistent AKI, early reversal or recovery from an episode of AKI has been consistently associated with better survival [16]. Previous studies have shown that the duration of AKI affects mortality [17]. The longer the duration of AKI, the higher the mortality [17]. In addition, AKD (vs. no kidney disease) was associated with an increased risk of major adverse kidney events (MAKEs), mostly attributed to higher mortality [4].

**Acute kidney disease stages**

Acute Disease Quality Initiative proposed an AKD staging method, the same as AKI staging, based on changes in serum creatinine levels [18]. Specifically, an AKD stage is defined as stage 0, 1, 2, 3, or dialysis when the ratio of serum creatinine level during AKD over baseline serum creatinine level is <1.5 times increase, 1.5-2.0 times increase, 2.0-3.0 times increase, >3.0 times increase, or under dialysis, respectively. Later, AKD staging based on the eGFR level, the same as CKD staging, was also proposed [2]. Specifically, an AKD stage is defined as 0, 3, 4, 5, or dialysis when eGFR is >60, 30-60, 15-30, <15 mL/min/1.73 m², or under dialysis, respectively. Albuminuria may be incorporated into the eGFR-based AKD stages as in the CKD stages.

Several studies have reported a higher serum creatinine-based AKD stage is associated with poorer outcomes [19]. In a retrospective cohort study of 4,741 AKD patients using data from the health information system database of a single tertiary hospital in Taiwan, a higher AKD stage was associated with a higher risk of MAKE (adjusted odds ratio and 95% confidence interval [CI]: AKD stage 1, 1.85 [1.56–2.19]; AKD stage 2, 3.43 [2.85–4.12]; and AKD stage 3, 10.41 [8.68–12.49]; AKD stage 0 as reference) [20].

**Novel biomarkers**

In AKI, in addition to creatinine-based AKI stages, various novel biomarkers have been reported to predict outcomes [21,22]. These biomarkers include but are not limited to neutrophil gelatinase-associated lipocalin (NGAL), liver-type fatty acid-binding protein (L-FABP), tissue inhibitor of metalloproteinase-2 (TIMP-2), insulin-like growth factor binding protein 7 (IGFBP7), cystatin C, and proenkephalin A (PENK) 119-159. These biomarkers can be categorized as biomarkers of tubular injury (NGAL), tubular function (L-FABP), cell cycle arrest (TIMP-2 and IGFBP7), and GFR (cystatin C and PENK) [21].

The level of urinary L-FABP was also known to predict the need for dialysis, weaning from dialysis, or mortality [23]. TIMP-2 and IGFBP7 are both biomarkers of cell cycle arrest, which play an important role in the pathogenesis of AKI and kidney fibrosis [24]. Urinary [TIMP-2] × [IGFBP7] levels were reported to predict dialysis or death in patients with AKI [25]. Cystatin C, a small protein of about 13 kDa, is produced at a constant rate by nucleated cells, freely filtered by the glomerulus, and nearly completely metabolized in the proximal tubule [26]. The formula incorporating serum cystatin C is reported to be better eGFR [27]. The level of serum cystatin C is reported to predict mortality better than serum creatinine [28]. PENK 119–159 was reported to be a predictor of renal recovery after AKI [29].

In patients with AKD, the prognostic value of these biomarkers is less clear. An observational study (French and euRopean Outcome reGistry in ICUs, FROG-ICU) reported that 1-year survival was significantly associated with the levels of biomarkers measured at discharge from the intensive care unit. Among the biomarkers tested in the study (serum creatinine, cystatin C, eGFR, NGAL, and PENK), eGFR estimated by cystatin C had the highest area under the curve for predicting 1-year mortality (0.707; 95% CI, 0.671–0.742) [30]. However, a secondary analysis of the PreCESS (Protocolized Care for Early Septic Shock) trial reported that none of the following five biomarkers—NGAL, L-FABP, [TIMP-2] × [IGFBP7], kidney injury molecule-1, and type 4 collagen—could predict the development of
AKD in patients with septic shock [31]. Recently, AKI subphenotypes have been defined based on a combination of multiple biomarkers and clinical parameters and can be used to predict outcomes in AKI patients [32]. Whether biomarkers or subphenotypes can also be used to predict outcomes in AKD patients remains to be answered.

**Potential management**

Recent studies have proved several therapeutic interventions to improve outcomes in patients with AKI or CKD. These interventions include AKI bundle care [33], sodium-glucose cotransporter 2 (SGLT2) inhibitor [34], glucagon-like peptide 1 receptor agonist (GLP1-RA) [35], renin-angiotensin-aldosterone system (RAAS) inhibitor [36] including nonsteroidal mineralocorticoid receptor antagonist [37], and very-low-protein diet [38]. However, the evidence of pharmacological intervention in AKD is still accumulating. The proper management of patients with AKD may involve non-pharmacological and pharmacological interventions (Fig. 2). Multidisciplinary care is an important approach in non-pharmacological interventions.

KAMPS

The follow-up and care for patients with AKI or AKD should be guided by the comorbidities of the patients and the severity of the AKI or AKD episode. Based on current expert consensus and limited available literature, we proposed a comprehensive bundle of care for post-AKI or post-AKD management, named “KAMPS” (kidney function check, advocacy, medications, pressure, sick day protocols) [39]. This multifaceted approach integrates a range of strategies such as kidney function tests (including eGFR and albuminuria), meticulous blood pressure control, and a thorough review and adjustment of medications (especially over-the-counter and herbal medicine). Communication is vital in this context, not only among healthcare providers but also with the patient, particularly regarding medications requiring close monitoring during acute illness episodes. This category includes drugs predominantly excreted by the kidneys and nephrotoxic agents, collectively termed “KENDS” (kidney-excreted nephrotoxic drugs) [40]. Regular medication reconciliation and vigilant review are imperative components of AKI or AKD management, necessitating implementation at the initial post-discharge consultation and all subsequent clinic visits. This meticulous approach ensures comprehensive care tailored to individual patient needs, enhancing recovery and minimizing the risk of adverse outcomes.

**Sick day protocols and MAND-MASS**

In the context of AKD, the establishment of a clearly defined protocol for the resumption of temporarily discontinued medications is imperative. This protocol should be effectively communicated to both the affected individual and their healthcare providers, with meticulous documentation in the individual’s medical record to ensure continuity of care.

**Figure 2. The four pillars of AKD intervention.** These pillars constitute the cornerstone of current, up-to-date therapy for AKD, including angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blocker (ARB)/mineralocorticoid receptor antagonist (MRA), sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1 RA), and multidisciplinary care (MDC). Nonetheless, it’s essential to acknowledge that the efficacy of this approach may fluctuate according to individual patient necessities and the particular healthcare context.

AKD, acute kidney disease. Icons were created with www.biorender.com and additional icons were made by Freepik from www.flaticon.com.
The widely endorsed practice of “sick day protocols” for individuals with AKD during episodes of acute, dehydrating illnesses offers specific guidance regarding medication management (Fig. 3). These guidelines typically advise the temporary discontinuation of certain medications in AKD periods during acute illness, including mineralocorticoid receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, diuretics and direct renin inhibitors, metformin, angiotensin receptor blockers (ARBs), sulfonylureas, and SGLT2 inhibitors [41]. We propose an acronym “MAND-MASS” to summarize important medications to be reconciled during acute illness (Table 1).

However, it is imperative to acknowledge that the existing body of evidence supporting the effectiveness of sick day protocols in preventing the deterioration of kidney function or other clinically significant outcomes in AKD patients remains notably limited. This is a crucial consideration, given the potential harm that may result if individuals encounter challenges in recognizing dehydrating illnesses or determining which medications should be temporarily discontinued.

In situations resulting in dehydration (such as diarrhea, fever, or vomiting) or when the assurance of food intake is compromised (due to nausea, vomiting, or perioperative conditions), certain antidiabetic medications must be temporarily halted [42]. Patients should be informed about the medications that need to be discontinued in these circumstances. Notably, metformin should be temporarily stopped in all situations leading to relevant dehydration, AKI, or hypoxemia due to the risk of lactic acidosis. For diabetic patients with normal baseline renal function on metformin experiencing severe AKI and AKD, the use of metformin should be discontinued when eGFR falls below 30 mL/min/1.73 m². Consideration for resuming metformin may be given when renal function recovers later [43].

SGLT-2 inhibitors should be temporarily suspended in situations where carbohydrate intake is compromised.

Table 1. An acronym designed for reconciling medications in acute illness and a crucial component of sick day protocols

| M | Mineralocorticoid receptor antagonists |
| A | Angiotensin-converting enzyme inhibitors |
| N | Nonsteroidal anti-inflammatory drugs |
| D | Diuretics or direct renin inhibitors |
| M | Metformin |
| A | Angiotensin receptor blockers |
| S | Sulfonylureas |
| S | Sodium-glucose cotransporter 2 inhibitors |

Figure 3. Exploring ‘sick day protocols’ implementation in acute kidney disease. The sick day protocols comprise several steps. First, identification of sickness. The patient or caregiver should be educated to recognize signs of illness that could lead to further kidney injury, such as vomiting, diarrhea, or fever. Second, identification of dehydration. Dehydration is a common trigger for kidney injury. Patients should be taught to identify signs of dehydration like dry mouth, decreased urine output, and feeling dizzy when standing up. Third, documentation in medical records. All relevant information about the patient’s condition and medication should be documented in their medical record. Fourth, identification and stopping of certain medications. Patients should be advised to temporarily stop certain medications when they are sick. These typically include diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs. However, patients must consult with their healthcare provider before stopping any medication. Fifth, recovery and resuming medications. Once the patient has recovered from the illness and their hydration status is back to normal, they can resume their medications as advised by their healthcare provider.

Readers may also refer to Hall RK et al. [41] for the section on “Safe deprescribing.” Icons were created by Freepik from www.flaticon.com.
such as vomiting, prolonged fasting, perioperative settings, or before gastric or colon endoscopy) due to the risk of ketoacidosis [42]. Because SGLT2 inhibitors can cause natriuresis, a drop in blood pressure, and contraction of the glomerular afferent arteriole, theoretically, they might reduce kidney perfusion [44]. Therefore, it is usually recommended to discontinue SGLT2 inhibitors during AKI [45]. However, meta-analyses of large placebo-controlled trials and real-world data revealed that SGLT2 inhibitors decreased the risk of AKI [34,46]. Medications with a propensity for inducing hypoglycemia (e.g., insulin and sulfonylureas) must be temporarily halted or their doses adjusted when carbohydrate intake cannot be guaranteed [42]. Insulin therapy necessitates dose adjustment during acute illness but should never be completely discontinued [47].

Multidisciplinary care

Multidisciplinary team care involves the coordination of care from different disciplines to establish harmonized and structured patient care (Fig. 4). In patients with kidney disease, the multidisciplinary team usually includes nephrologists, pharmacists, dietitians, and health educators. Multidisciplinary team care is a practical model to achieve the bundle care of KAMPS.

The nephrologist bears the critical responsibility of establishing etiological diagnoses and discerning subphenotypes for AKI and AKD. Nephrologists are pivotal in determining which patients are most likely to benefit substantially from post-AKI and post-AKD follow-up care. When considering kidney biopsy to assist diagnosis, judicious selection of appropriate candidates for this invasive intervention is imperative to avoid complications [48]. Elucidating the etiology of AKD is critical in mitigating the recurrence of AKD episodes. Our meta-analysis substantiates that AKI patients receiving post-hospitalization care from nephrologists exhibit a marked reduction in mortality rates compared to those managed by nonspecialists [49]. Beyond the evaluation of etiological factors, the nephrologist’s responsibilities extend to orchestrating pertinent follow-up assessments of renal function, determining the necessity and timing of kidney replacement therapy, addressing concurrent medical conditions such as diabetes mellitus, hypertension, and dyslipidemia, and adapting medication regimens according to the prevailing and anticipated course of renal function. The pharmacist plays an important role in the proper dosing of medication based on renal function, avoidance of nephrotoxic agents, and

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**AKD health for all**

Nephrologist  
Nurse  
Pharmacist  
Dietitian  
Health education

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**Figure 4. The unfilled gap: multidisciplinary care for preventing deterioration of renal function in AKD.** These professionals work together to provide comprehensive care to patients with AKD, aiming to slow the progression of the disease and improve the patient’s quality of life. The nephrologist leads the team and provides advanced kidney disease treatment. The pharmacist reconciles medication and educates patients about their prescriptions. The dietitian provides dietary guidance tailored to kidney patients’ needs. The health educator or the nurse provides education about lifestyle modifications and self-management strategies to patients. The health educator or the nurse also coordinates patient care with other team members. AKD, acute kidney disease. Icons were created by Freepik from www.flaticon.com.
evaluation of drug-drug interactions. Frequent assessment of medications in AKD patients is necessary. The dietitian is responsible for the assessment of nutrition status and suggestion of dietary interventions. However, the optimal nutritional therapy in AKI or AKD patients is unclear, especially with dietary protein intake. In a recent trial conducted in the intensive care unit (EFFORT Protein trial), a high-protein diet (≥2.2 g/kg per day) resulted in a higher 60-day mortality rate compared with a normal-protein diet (≤1.2 g/kg per day) in patients with AKI [50]. In line with this finding, a retrospective cohort study reported an association between high protein intake and 60-day mortality in patients cared for at the intensive care unit [51]. Future studies are warranted to investigate the optimal dietary protein intake in AKD patients. Follow-up at a nephrologist clinic during the AKD period may improve outcomes after AKI52. However, even in those who sustained critical illness or dialysis-requiring AKI, only 5.0% to 37.3% of AKD patients received nephrology follow-up after discharge [52,53]. The health educator or the nurse in the multidisciplinary AKD team may mitigate the discrepancy between real-world practice and guideline suggestions by enhancing awareness and knowledge of AKD.

A care bundle based on the Kidney Disease: Improving Global Outcomes (KDIGO) guideline has been shown to improve outcomes in patients with AKI [33], and a randomized controlled trial also showed that multidisciplinary team care reduced albuminuria and hypertension in patients with AKD [54]. A retrospective cohort study, based on data from the Taiwan National Health Insurance Research Database, has revealed that the implementation of multidisciplinary care is linked to a decreased risk of chronic dialysis (hazard ratio [HR], 0.55; 95% CI, 0.49–0.52) as well as a reduced mortality risk (HR, 0.79; 95% CI, 0.57–0.88) among individuals with AKD who have survived an episode of dialysis-requiring AKI [55]. At present, at least three randomized controlled trials are enrolling AKD patients to assess the effectiveness of multidisciplinary team care. These trials are identified as NCT05064904, NCT04145609, and NCT05805709.

Renin-angiotensin-aldosterone system blockade for patients with acute kidney disease

ACE inhibitors and ARBs improve renal outcomes in CKD patients with proteinuria and are recommended as the first-line antihypertensive agent in the guideline [6,56]. A recent study also suggested that there is no need for discontinuation of ACE inhibitors or ARBs in patients with advanced CKD [57]. In the AKD period, several observational studies reported that RAAS inhibitors might be associated with improved survival, increased hyperkalemia, and probably increased risks for kidney adverse events (recurrent AKI and hospitalization due to renal causes) [58].

In addition to ACE inhibitors or ARBs [59], mineralocorticoid receptor antagonists were also reported to decrease the risk of dialysis in AKD patients at the cost of increased risk of hyperkalemia [60]. Recently, finerenone, a nonsteroidal mineralocorticoid receptor antagonist, was reported to improve renal and cardiovascular outcomes in patients with diabetes mellitus and CKD [37]. Notably, compared with traditional mineralocorticoid receptor antagonists, finerenone has a lower risk of hyperkalemia leading to discontinuation of the trial regimen (2.3% or 1.2% on finerenone vs. 0.9% or 0.4% on placebo) [37]. The potential benefits of ACE inhibitors, ARBs, and finerenone in patients with AKD warrant further investigation.

Sodium-glucose cotransporter 2 inhibitor

In patients with CKD or heart failure, SGLT2 inhibitors have been proven to effectively retard the decline of kidney function and reduce the risk of death [34]. These protective effects remain even in non-diabetic patients [34,47]. Furthermore, it provides compelling clinical evidence supporting the associations of SGLT-2 inhibitors in reducing the risk of mortality, and cardiovascular and subsequent kidney disease among patients with type 2 diabetes mellitus and AKD [61]. KDIGO 2023 guideline suggests SGLT2 inhibitors as the first-line drug therapy in diabetic CKD patients with an eGFR of more than 20 mL/min/1.73 m² [62].

Currently, at least five trials are testing the effects of SGLT2 inhibitors on the prevention of AKI in patients receiving cardiac surgery (NCT04523064, NCT05852704, and NCT05590143), patients receiving percutaneous coronary intervention (NCT05037695), or patients admitted to the intensive care unit (NCT05468203). Whether SGLT2 inhibitors can accelerate recovery of renal function in patients with AKD is another critical yet unanswered question.
Other potential therapies

GLP-1 RAs constitute an alternative category of therapeutic agents with potential efficacy in managing type 2 diabetes mellitus among patients with AKD. They have exhibited notable cardiovascular benefits in large-scale cardiovascular outcome trials, particularly in the reduction of 3-point major adverse cardiovascular events [63]. Furthermore, GLP-1 RAs confer superior efficacy in terms of lowering A1c levels, reducing lipids, and promoting weight loss, irrespective of the patient’s baseline eGFR. Clinical trials investigating the cardiovascular outcomes and glycemic control effects of GLP-1 RAs have encompassed individuals with type 2 diabetes mellitus, both with and without CKD, and eGFR levels as low as 15 mL/min/1.73 m² [35].

Moreover, the FLOW study, a complementary and conventional kidney-related outcomes trial (NCT03819153), has been structured to assess the safety and effectiveness of semaglutide in diabetic kidney disease. This randomized, interventional, multicountry study aims to ascertain whether the administration of semaglutide, administered via a weekly subcutaneous injection, in addition to standard care, influences the primary composite endpoint. This endpoint is defined as the persistent decline of eGFR by at least 50% from the trial’s initiation, progressing to end-stage kidney disease, death resulting from kidney disease, or cardiovascular-related mortality. Per the trial’s protocol, an interim analysis was performed when a predefined number of primary endpoint events had occurred. We eagerly anticipate the release of these results because of early termination [64].

Tirzepatide is a dual-action agent targeting glucose-dependent insulinotropic polypeptide and GLP-1 receptor activation. In an ongoing trial, it also seeks to investigate the impact of tirzepatide on CKD in patients, whether they have type 2 diabetes mellitus or not. The primary outcome measure in this study is the alteration in kidney oxygenation (TREASURE-CKD, NCT05536804).

Several interventions during the AKI period have been reported to improve outcomes, including sodium bicarbonate [65], recombinant human alkaline phosphatase [66], remote ischemic preconditioning [67], acetaminophen [68], levosimendan [69], and atrial natriuretic peptide [70]. Whether the institution of these interventions at the AKD period can improve outcomes warrants further study.

Conclusion

Accurate prognosis prediction and effective treatment remain unmet needs for patients with AKD. It is essential to compare the performance of serum creatinine-based and eGFR-based AKD staging in predicting outcomes. The integration of clinical information and biomarkers for subphenotype identification and outcome prediction holds promise. To address the complexities of clinical scenarios in AKD patients, a multidisciplinary team-based approach is advisable. The collaboration of diverse healthcare professionals with complementary expertise can offer a more holistic and effective approach to patient care, addressing the complexities and nuances of AKD cases comprehensively. Implementing the widely endorsed practice of sick day protocols for individuals with AKD during episodes of acute illness is recommended. Urgent research is warranted to investigate the efficacy and safety of RAAS inhibitors, SGLT2 inhibitors, and potential GLP-1 RAs. The future holds significant promise in the field of AKD, with these research endeavors poised to contribute to enhanced patient outcomes and the advancement of clinical practice.

Conflicts of interest

Szu-Yu Pan was supported by the Ministry of Science and Technology, Taiwan (MOST, 111-2314-B-002-MY2). All other authors have no conflicts of interest to declare.

Funding

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions

Conceptualization, Funding acquisition: SYP, VCW
Formal analysis, Investigation: ZHJ, LCL, IJT, TLW, HCC
Writing–original draft: SYP
References


Artificial intelligence and machine learning’s role in sepsis-associated acute kidney injury

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Sepsis-associated acute kidney injury (SA-AKI) is a serious complication in critically ill patients, resulting in higher mortality, morbidity, and cost. The intricate pathophysiology of SA-AKI requires vigilant clinical monitoring and appropriate, prompt intervention. While traditional statistical analyses have identified severe risk factors for SA-AKI, the results have been inconsistent across studies. This has led to growing interest in leveraging artificial intelligence (AI) and machine learning (ML) to predict SA-AKI better. ML can uncover complex patterns beyond human discernment by analyzing vast datasets. Supervised learning models like XGBoost and RNN-LSTM have proven remarkably accurate at predicting SA-AKI onset and subsequent mortality, often surpassing traditional risk scores. Meanwhile, unsupervised learning reveals clinically relevant sub-phenotypes among diverse SA-AKI patients, enabling more tailored care. In addition, it potentially optimizes sepsis treatment to prevent SA-AKI through continual refinement based on patient outcomes. However, utilizing AI/ML presents ethical and practical challenges regarding data privacy, algorithmic biases, and regulatory compliance. AI/ML allows early risk detection, personalized management, optimal treatment strategies, and collaborative learning for SA-AKI management. Future directions include real-time patient monitoring, simulated data generation, and predictive algorithms for timely interventions. However, a smooth transition to clinical practice demands continuous model enhancements and rigorous regulatory oversight.

In this article, we outlined the conventional methods used to address SA-AKI and explore how AI and ML can be applied to diagnose and manage SA-AKI, highlighting their potential to revolutionize SA-AKI care.

Keywords: Artificial intelligence, Machine learning, Precision medicine, Acute kidney injury, Sepsis

Introduction

Sepsis-associated acute kidney injury (SA-AKI) is a severe and frequent complication among critically ill septic patients, with reported incidences between 35% and 61% [¹–⁶]. Furthermore, SA-AKI significantly increases the mortality risk, with some studies demonstrating mortality rates of up to 70% in patients with SA-AKI [⁷–⁹]. The clinical course of SA-AKI patients tends to deteriorate, with extended intensive care unit (ICU) stays and increased risks of chronic kidney disease, cardiovascular events, and death [⁹]. Among acute kidney injury (AKI) patients, sepsis has been identified as the primary cause of death [⁴,⁶,¹⁰,¹¹]. The complex pathophysiology of SA-AKI and systemic complications make its management challenging [¹²,¹³]. Keys to therapeutic measures are the meticulous regulation of renal perfusion, targeted inflammation mitigation, and prompt intervention such as fluid management or medica-

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tion adjustments [14,15]. Given SA-AKI’s profound impact, a holistic approach, including preventive protocols, expedited diagnostics, and collaborative treatment, is critical to optimize outcomes [16,17].

Artificial intelligence (AI) and machine learning (ML) are rapidly emerging as transformative tools for diagnosing and managing AKI patients [12–21]. Compared to traditional methods, ML algorithms can reveal patterns beyond human discernment and enhance SA-AKI prediction accuracy by analyzing vast datasets [22–27]. Furthermore, ML enables earlier SA-AKI detection than traditional approaches, allowing timely, appropriate intervention and improved outcomes [12–20,24,28–32]. ML algorithms are designed to accommodate changing patient conditions and integrate new data, continually refining prediction accuracy in a real-time setting [12–20].

Contemporary research increasingly explores AI/ML’s capabilities to advance precision medicine and tailored SA-AKI care. The integration of these technologies promises to usher in a new era of early detection and optimized therapeutic interventions for SA-AKI [22–27]. Several state-of-the-art studies and initiatives are currently underway, highlighting the adoption of these technologies in various clinical settings, each aiming to address the profound challenges posed by SA-AKI with a degree of sophistication previously unattainable [12–20]. However, as with all novel technologies, the advent of AI and ML in SA-AKI diagnosis and management is not without its set of challenges and ethical considerations [33]. While AI can analyze vast datasets and identify patterns beyond human capability, ensuring the accuracy, reliability, scalability, and interpretability of these models is vital. Moreover, the black-box nature of certain ML algorithms poses obscurity, making it challenging for clinicians to justify decisions derived from such systems. Ethical concerns warrant thorough scrutiny, including data privacy, potential biases in AI algorithms, and the subsequent impacts on patient care. The collection and utilization of patient data, especially on sensitive subjects such as SA-AKI, necessitates stringent data protection protocols and informed patient consent mechanisms [22–27].

In this article, we first overview the traditional SA-AKI approach, then discuss AI/ML’s potential applications, connecting foundational and emerging methodologies to showcase AI/ML’s transformative potential for SA-AKI care.

Traditional approach for sepsis-associated acute kidney injury

Predictors and mortality of sepsis-associated acute kidney injury

Traditional statistical analysis has been instrumental in identifying risk factors for SA-AKI across a range of comorbidities, infections, medications, and other determinants [4,34–42]. Key comorbid conditions found to significantly predict SA-AKI include hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease, liver disease, and coronary artery disease [4]. A pooled analysis of 47 observational studies with 55,911 sepsis patients revealed that hypertension, diabetes, and chronic kidney disease increased the odds of AKI, with odds ratios (ORs) of 1.43, 1.59, and 3.49, respectively (Fig. 1) [4]. Furthermore, cardiovascular, liver, and coronary artery diseases emerged as risk factors, with ORs of 1.31, 1.68, and 1.27. Regarding infection sources, pulmonary, abdominal, and undetermined infections were significant SA-AKI predictors, with ORs of 0.77, 1.44, and 2.01, respectively. Medications like vasopressors, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and diuretics also correlated with heightened SA-AKI risk, having ORs of 3.15, 1.61, and 1.40. Other notable risk factors included male sex (OR, 1.22), positive blood culture (OR, 1.60), smoking history (OR, 1.60), septic shock (OR, 1.40), Gram-negative bacteria (OR, 2.19), organ transplantation (OR, 1.96), and mechanical ventilation need (OR, 1.64) [4].

While these findings provide valuable insights, traditional statistical approaches have limitations. Despite identifying these predictors, substantial heterogeneity existed across studies, suggesting potential inconsistencies in outcomes depending on the context of SA-AKI [4].

Prediction model for sepsis-associated acute kidney injury by traditional statistical analysis

Traditional statistical approaches to predicting SA-AKI through various studies have been used [34–42]. These studies (Table 1) utilized well-established methods such as logistic regression analysis, least absolute shrinkage and selection operator (LASSO) regression for variable selection, and calibration plots [34–42]. These models identified
key predictors like diabetes, chronic kidney disease, cardiovascular disease, and specific lab values such as creatinine and procalcitonin. Performance was evaluated using metrics like area under the receiver operating characteristic curve (AUC), sensitivity, and specificity [42].

For instance, Fan et al. [34] developed an SA-AKI prediction model using logistic regression and LASSO, achieving c-statistics of 0.711 and 0.705 in training and validation cohorts. Xin et al. [42] conducted a retrospective cohort study among elderly sepsis patients and achieved an AUC of 0.852 in the training and 0.858 in the validation cohort using logistic regression. Xie et al.’s prospective study [35] of sepsis patients in the ICU resulted in an impressive AUC of 0.9862. In addition, Zhou et al. [36] utilized a randomized clinical trial approach with 16 predictors and achieved an AUC of 0.857 in the validation cohort. While these examples demonstrate traditional statistical methods can effectively predict SA-AKI, recognizing high-risk patients early to guide treatment, these traditional prediction models for SA-AKI come with several limitations (Fig. 2). These limitations include 1) sensitivity to outliers, which may skew results/predictions. Outliers in medical data could be errors or critical rare events that should not be ignored. 2) Multicollinearity among predictor variables complicates the interpretation of individual predictors’ effects on the outcome. 3) Temporal dynamics, as medical time-series data may not meet assumptions of independent and identically distributed points, impacting predictive accuracy. 4) High-dimensional medical data that traditional models can struggle to handle effectively, limiting the identification of complex relationships and predictive capabilities. 5) Calibration, requiring robust procedures to ensure predicted probabilities align closely with observed outcomes, avoiding suboptimal clinical decisions. 6) Potential human bias in feature selection, as choices rely on existing knowledge and practitioner input, possibly introducing limitations.

In essence, while significant, traditional SA-AKI prediction models have inherent challenges around outliers, multicollinearity, temporal dynamics, high-dimensional data, calibration, and bias in feature selection. Continued model updates and refinements alongside technological and research advancements remain important.
<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Sample size</th>
<th>Main Predictors</th>
<th>Outcomes</th>
<th>Statistical analysis approach</th>
<th>C-statistics/AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fan et al. [34]</td>
<td>Patients with sepsis in ICU from MIMIC-III database</td>
<td>Training: 11,008 Validation: 4,718</td>
<td>DM, CKD, CHF, CLD, hyperbicarbonemia, hyperglycemia, low blood pH, prolonged clotting time, hypotension, hyperlactatemia</td>
<td>SA-AKI</td>
<td>LASSO, logistic regression</td>
<td>Training: 0.711 Validation: 0.712 Simplified score Training: 0.712 Validation: 0.705</td>
</tr>
<tr>
<td>Xin et al. [42]</td>
<td>Patients aged ≥65 yr with sepsis in one hospital in China</td>
<td>Training: 637 Validation: 212</td>
<td>Low MAP, albumin globulin ratio, prothrombin time activity, platelet, high serum procalcitonin, and creatinine</td>
<td>SA-AKI, MAKE30, and 30-day mortality</td>
<td>Logistic regression</td>
<td>SA-AKI Training: 0.852 Validation: 0.858 30-day mortality 0.813 MAKE30 0.823</td>
</tr>
<tr>
<td>Xie et al. [35]</td>
<td>Patients with sepsis in ICU in one hospital in China</td>
<td>Not reported</td>
<td>Male sex, low anti-thrombin III, high creatinine, and BUN</td>
<td>SA-AKI</td>
<td>Logistic regression</td>
<td>0.986</td>
</tr>
<tr>
<td>Zhou et al. [36]</td>
<td>Patients with sepsis in ICU</td>
<td>Training: 1,554 Validation: 777</td>
<td>Older age, HTN, CAD, DM, CHF, COPD, acute severe pancreatitis, hypotension, hypoprothrombinemia, lactic acidosis, ICU length of stay, low hemoglobin, other organ failure</td>
<td>SA-AKI</td>
<td>Logistic regression Validation: 0.857</td>
<td></td>
</tr>
<tr>
<td>Xin et al. [37]</td>
<td>Patients with sepsis in one hospital in China</td>
<td>Training: 787 Validation: 264</td>
<td>Cardiovascular disease, high WBC, procalcitonin, thrombin time, low mean arterial pressure, platelet count, prothrombin time activity</td>
<td>SA-AKI, MAKE-30</td>
<td>Logistic regression SA-AKI Training: 0.872 Validation: 0.888 MAKE30 0.843</td>
<td></td>
</tr>
<tr>
<td>Xia et al. [39]</td>
<td>Patients with SA-AKI in ICU from MIMIC-IV database</td>
<td>Not reported</td>
<td>High serum creatinine, change in serum creatinine within 24 hr, CRRT within 48 hr, lactate</td>
<td>Persistent SA-AKI</td>
<td>Logistic regression Training: 0.80 Validation: 0.81</td>
<td></td>
</tr>
<tr>
<td>Hu et al. [40]</td>
<td>Patients with SA-AKI in ICU</td>
<td>Training: 2,066</td>
<td>Older age, admission type, liver disease, metastatic cancer, lactate, BUN/creatinine ratio, creatinine, positive culture, and AKI stage</td>
<td>In-hospital mortality</td>
<td>LASSO, Cox regression</td>
<td>Training: 0.73 Validation: 0.72</td>
</tr>
<tr>
<td>Jiang et al. [41]</td>
<td>Patients aged ≥65 yr with persistent SA-AKI&gt;48 hr in ICU from MIMIC MIMIC-IV database</td>
<td>Training: 1,065 Validation: 454</td>
<td>Male, sex, cancer, AKI stage, low GCS score, high BUN, respiratory rate, CRRT within 48 hr, mechanical ventilation</td>
<td>In-hospital mortality</td>
<td>Logistic regression Training: 0.78 Validation: 0.82</td>
<td></td>
</tr>
<tr>
<td>Li et al. [38]</td>
<td>Patients with SA-AKI in ICU</td>
<td>Training: 1,779 Validation: 344</td>
<td>Age, GCS score, SBP, oxygen saturation, platelet count, WBC, bicarbonate</td>
<td>In-hospital mortality</td>
<td>Logistic regression Training: 0.829 Validation: 0.760</td>
<td></td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; AKD, acute kidney disease; AUC, area under the receiver operating characteristic curve; BUN, blood urea nitrogen; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; DM, diabetes mellitus; GCS, Glasgow coma scale; HTN, hypertension; ICU, intensive care unit; LASSO, least absolute shrinkage and selection operator; MAKE30, major adverse kidney event within 30 days; MAP, mean arterial pressure; MIMIC, Medical Information Mart for Intensive Care; SA-AKI, sepsis-associated acute kidney injury; SBP, systolic blood pressure; WBC, white blood cell count.
Utilization of novel biomarkers for sepsis-associated acute kidney injury

The timely identification of SA-AKI is crucial for preventing further renal complications. Traditional markers like serum creatinine and urea nitrogen have been primary diagnostic tools but present challenges due to delayed responses and susceptibility to external factors, including age, metabolic rate, and the effects of medications [5,43–49]. As a result, recent investigations have uncovered novel biomarkers with heightened sensitivity and specificity for early SA-AKI detection (Fig. 3) [5,9,43–48,50,51]. The identified biomarkers for SA-AKI have shown varying specificity, sensitivity, and AUC degrees [5,43–48]. For example, neutrophil gelatinase-associated lipocalin in urine/serum has a specificity of 0.84/0.79, sensitivity of 0.87/0.83, and an AUC of 0.92/0.87, kidney injury molecule-1 in urine has a specificity of 0.74, sensitivity of 0.84, and AUC of 0.62, cystatin C in serum has a specificity of 0.84, sensitivity of 0.82, and AUC 0.96, interleukin-18 in urine has an AUC of 0.719, liver fatty acid binding protein in urine has a specificity of 0.74, sensitivity 0.78, and AUC of 0.82, and finally tissue inhibitor metalloproteinase-2/insulin-like growth factor binding protein-7 in urine has a specificity of 0.909, sensitivity of 0.67, and AUC of 0.89.

This diverse range of values for specificity, sensitivity, and AUC underlines the complexities inherent in AKI diagnosis. Both traditional statistical approaches and biomarker use for SA-AKI diagnosis have numerous challenges. The classic statistical methods, while foundational in many medical research studies, often operate under specific assumptions about data distributions and might not handle outliers or nonlinear patterns effectively. They also might not be adept at deciphering interactions among multiple variables, especially when dealing with high-dimensional datasets, as is common in modern medicine. Biomarkers, while being indispensable tools in the diagnosis and monitoring of many diseases, have their limitations. For sepsis-associated AKI, the main concerns revolve around their sensitivity, specificity, and their overall predictive value. Not all biomarkers perform uniformly across diverse patient populations [9,50,51]. They might also be influenced by a myriad of other factors, such as comorbid conditions, other medications, or even minor variations in sample handling and storage [9,50,51].

These limitations necessitate more advanced methods like the use of AI/ML. Such technologies can overcome traditional challenges by leveraging larger datasets and more intricate analytical tools. Their proficiency in detecting complex nonlinear relationships and discerning patterns in expansive datasets provides insights beyond the reach of conventional methods. AI/ML represents a promising approach to improving the accuracy and timeliness of SA-AKI diagnosis.
approach to address the diagnostic complexities of SA-AKI.

**Artificial intelligence and machine learning applications in sepsis-associated acute kidney injury**

Recent developments in ML have significantly surpassed traditional AKI prediction methods \[17,52,53\]. Key developments include a deep learning model by Rank et al. \[17\], which effectively uses electronic health records data to predict AKI with high accuracy (AUC, up to 0.893), all while keeping the physician’s workload unchanged. Another study introduced a range of ML models that apply different approaches to estimate baseline serum creatinine, showcasing the importance of error analysis and explainable AI to aid in clinical decisions and prompt AKI treatment \[52\]. Furthermore, a systematic review underlined the value of externally validated ML models that are effective across various patient groups, focusing on the necessity of interpretable models and strong predictors. These advances highlight how ML can be seamlessly integrated into clinical practices, significantly improving the early detection and treatment of AKI, marking a substantial shift from theoretical models to actual clinical use \[53\].

For SA-AKI, ML has emerged as a promising tool in healthcare, presenting innovative solutions to the complexities of medical challenges \[22–27\]. Three key ML branches play pivotal roles: supervised learning, unsupervised learning, and reinforcement learning (Fig. 4). Each approach leverages abundant patient data to address unique aspects of SA-AKI management, including 1) supervised learning, which facilitates risk prediction; 2) unsupervised learning, which enables patient subgroup identification; and 3) reinforcement learning, which optimizes treatment strategy.

These methodologies equip healthcare professionals to enhance precision and efficiency in prediction, identifi-
cation, and optimization for SA-AKI patients. We explore how integrating ML empowers SA-AKI management, from discerning risks early to guiding tailored interventions through continuously optimized protocols. AI/ML represents a transformative approach to tackling the multifaceted difficulties of SA-AKI.

Supervised learning

Supervised learning is a type of ML where the algorithm is trained on labeled data, meaning the input data is paired with corresponding output labels [54]. The primary goal is to learn a mapping function that can accurately predict the output labels for new, unseen data. In the context of SA-AKI, supervised learning can be utilized to predict the risk of AKI in sepsis patients [16,23–31,55]. Researchers can gather historical patient data, including clinical parameters such as vital signs, laboratory results, and patient demographics, as well as information about whether AKI developed during their hospital stay. This data is then used to train a supervised learning model, such as random forest, XGBoost, or artificial neural networks, to predict the likelihood of AKI in sepsis patients [16,23–31]. An example application of supervised learning in SA-AKI is the development of a predictive model that uses patient data from the ICU to identify individuals at high risk of developing AKI as a result of sepsis. The model can provide real-time risk scores, allowing clinicians to intervene early with appropriate interventions, such as fluid management or medication adjustments, to mitigate the risk of AKI [16,23–31].

Supervised learning has emerged as a pivotal tool in predicting outcomes and characteristics related to SA-AKI, according to published studies (Table 2) [16,23–31]. Researchers have successfully employed ML models to predict the onset of SA-AKI, differentiate between persistent and transient AKI, and anticipate in-hospital mortality and acute kidney disease (AKD) occurrence. Notably, models like XGBoost and recurrent neural network (RNN)-long short-term memory (LSTM) were recurrently highlighted for their exceptional performance [16,23–31]. These algorithms often surpassed traditional risk scores such as SOFA (Sequential Organ Failure Assessment) and SAPS II (Simplified Acute Physiology Score II), achieving commendable discrimination metrics [16,23–31]. For instance, in predicting AKI risk in septic patients, an XGBoost model was found to outperform conventional scoring systems, emphasizing the model’s utility in pinpointing high-risk patients for proactive interventions [30]. Furthermore, in another instance, an RNN-LSTM model showcased exemplary predictive ability, with a remarkable AUC of 1.0 (Fig. 5), emphasizing its potential in guiding early AKD interventions [31]. Moreover, the application of ML was not limited to SA-AKI. Zhou et al. [30] explored sepsis-associated acute respiratory distress syndrome patients, aiming

Figure 4. A structured overview of the three primary ML methodologies and their applications in the realm of SA-AKI.

AKI, associated acute kidney injury; ICU, intensive care unit; ML, machine learning; SA-AKI, sepsis-associated AKI.
### Table 2. Examples of Published Supervised Learning for SA-AKI prediction

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Sample size</th>
<th>Outcomes</th>
<th>Machine learning techniques</th>
<th>C-statistics/AUC</th>
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<tbody>
<tr>
<td>Zhang et al. [29]</td>
<td>Patient with sepsis in ICU</td>
<td>Training: 21,308</td>
<td>SA-AKI within 12–48 hr</td>
<td>Ensemble model, combining support vector machine, random forest, neural network, XGBoost via stacking algorithm</td>
<td>eICU-CRD: 0.774–0.788</td>
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<td>Training: MIMIC-IV Validation: eICU-CRD, ZG</td>
<td>Validation: 24,352</td>
<td></td>
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<td>ZG: 0.756-0.813</td>
</tr>
<tr>
<td>Zhou et al. [30]</td>
<td>Patient with SA-AKDS from MIMIC-III database</td>
<td>1,085</td>
<td>SA-AKI</td>
<td>Logistic regression, support vector machine, random forest, XGBoost</td>
<td>Highest C-statistics: XGBoost (0.86)</td>
</tr>
<tr>
<td>Yue et al. [26]</td>
<td>Patient with sepsis in ICU from MIMIC-III database</td>
<td>3,176</td>
<td>SA-AKI</td>
<td>Logistic regression, KNN, support vector machine, decision tree, random forest, XGBoost, artificial neural network</td>
<td>Logistic regression: 0.737</td>
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<td>KNN: 0.664</td>
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<td>Support vector machine: 0.735</td>
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<td>Decision tree: 0.749</td>
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<td>Random forest: 0.779</td>
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<td>XGBoost: 0.817</td>
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<td>Artificial neural network: 0.755</td>
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<tr>
<td>Yu et al. [16]</td>
<td>Various hospitalized patients populations from multiple studies.</td>
<td>87 to over 1 million (varying across studies)</td>
<td>Acute kidney injury</td>
<td>Regression, ensemble tree methods, SVM, neural networks, etc.</td>
<td>AUC ranged from 0.69 to 0.98 across studies.</td>
</tr>
<tr>
<td>Luo et al. [23]</td>
<td>Patients with SA-AKI in ICU from MIMIC-III database</td>
<td>5,984 (70% training, 30% validation set)</td>
<td>Persistent SA-AKI &gt; 48 hours</td>
<td>Logistic regression, random forest, support vector machine, artificial neural network, XGBoost</td>
<td>Logistic regression: 0.76</td>
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<td>Random forest: 0.75</td>
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<td>Support vector machine: 0.74</td>
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<td>Artificial neural network: 0.76</td>
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<td>XGBoost: 0.75</td>
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<tr>
<td>He et al. [31]</td>
<td>Patients with SA-AKI in ICU</td>
<td>Training: 209</td>
<td>Acute kidney disease</td>
<td>RNN-LSTM, decision trees, logistic regression</td>
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</tr>
<tr>
<td></td>
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<td>Validation: 509</td>
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<td>Validation: MIMIC-III</td>
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<td>Decision trees Training: 0.954</td>
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<td>Validation: 0.872</td>
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<td>Support vector machine: 0.680</td>
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<td>KNN: 0.601</td>
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<td>Decision tree: 0.585</td>
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<td>Random forest: 0.778</td>
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<td>XGBoost: 0.794</td>
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<tr>
<td>Li et al. [24]</td>
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<td>Training: 6,503</td>
<td>In-hospital mortality</td>
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<td>Training: 1,626</td>
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<td>Support vector machine: 0.680</td>
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<td>Validation: 509</td>
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<td>KNN: 0.601</td>
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<td>Decision tree: 0.585</td>
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<td>Random forest: 0.778</td>
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<td>XGBoost: 0.794</td>
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<td>Zhou et al. [25]</td>
<td>Patients with SA-AKI in ICU</td>
<td>16,154 (80% training, 20% validation set)</td>
<td>In-hospital mortality</td>
<td>Categorical boosting, gradient boosting decision tree, light gradient boosting, adaptive boosting, XGBoost, KNN, multilayer perception, logistic regression, naive Bayes, support vector machine</td>
<td>Categorical boosting: 0.83, ext - 0.75</td>
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<td>Training/validation: MIMIC-IV</td>
<td>External validation set: 132</td>
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<td>Gradient boosting decision tree: 0.82, ext - 0.62</td>
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<td>External Validation: 2 hospitals in China</td>
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<td>Light gradient boosting: 0.8, ext - 0.61</td>
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<td>Adaptive boosting: 0.82, ext - 0.60)</td>
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<td>XGBoost: 0.81, ext - 0.57</td>
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<td>KNN: 0.80, ext - 0.63</td>
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<td>Multilayer perception: 0.79, ext - 0.63</td>
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<td>Support vector machine: 0.76, ext - 0.68</td>
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(Continued to the next page)
to predict AKI development within a short timeframe post-ICU admission. Here, the XGBoost model once again stood out, indicating its versatility across related medical conditions. A review study by Yu et al. [16] further underlined the importance of ML by summarizing various models tailored for predicting AKI across diverse patient groups and environments. The compiled results suggested that while ML models displayed a range from moderate to superb discrimination for AKI events, there remains room for further refinement and evaluation in real-world clinical settings [16,23–31].

In reflecting upon the strengths of these ML-centered studies, it becomes evident that such methodologies offer several advantages over traditional statistical analysis ap-
proaches. ML models, given their ability to handle large data sets and complex interactions, tend to produce more accurate, robust, and generalizable findings [54]. These models are especially skilled at uncovering nonlinear relationships, thereby providing a more sophisticated understanding of the data’s underlying patterns. Moreover, the ability of ML models to surpass traditional risk scores highlights their transformative potential in patient care. This is particularly relevant for early detection and intervention strategies, which can significantly improve patient outcomes.

Unsupervised learning

Unsupervised learning involves training ML algorithms on unlabeled data to discover patterns, structures, or relationships within the data [56,57]. Clustering is a notable technique in unsupervised learning, where algorithms categorize similar data points into groups. In the specialized context of SA-AKI, unsupervised learning provides invaluable insights by delineating distinct subgroups of sepsis patients, each characterized by unique clinical profiles and outcomes. For instance, an unsupervised learning algorithm like k-means clustering can be employed to analyze clinical data from sepsis patients, including vital signs, laboratory results, and comorbidity information. This can reveal different clusters of patients with similar clinical characteristics. Clinicians can then evaluate whether these specific patient clusters have different risks of developing AKI, thereby facilitating the formulation of more personalized treatment plans.

Recently, Lai et al. [32] conducted a prospective observational cohort study of 999 critically ill patients with dialysis-requiring SA-AKI admitted to surgical ICUs in Taiwan between 2009 and 2018. The mean age was 63.9 years, and 71.5% were male. The authors performed unsupervised consensus clustering based on 23 clinical variables upon initializing renal replacement therapy to identify distinct sub-phenotypes (Fig. 6). Three sub-phenotypes that were identified included 1) cluster 1 (n = 352) with favorable baseline conditions but greatest acute illness severity, 2) cluster 2 (n = 396) with intermediate features, and 3) cluster 3: worst baseline, lowest acute illness.

Figure 6. Flow diagram illustrating the study on SA-AKI sub-phenotypes.
SA-AKI, sepsis-associated acute kidney injury.
Cluster 3 (n = 251) with worst baseline conditions but lowest acute illness severity. Cluster 1 had the highest mortality rate (73.9%) and lowest probability of being dialysis-free at 90 days. Cluster membership and predialysis serum lactate ≥3.3 mmol/L were independent predictors of mortality and dialysis dependence. A clinical prediction model using 11 variables accurately identified cluster 1 as a high-risk sub-phenotype (AUC, 0.99). When applied to an external validation cohort of 898 SA-AKI patients, the model identified a high-risk subgroup with increased mortality. This study demonstrates that ML approaches can identify clinically relevant sub-phenotypes and predictors in heterogeneous syndromes like SA-AKI.

**Reinforcement learning**

Reinforcement learning is a type of ML where an agent learns to make decisions by interacting with an environment. The agent receives feedback in the form of rewards or penalties based on its actions, and its objective is to maximize cumulative rewards over time. In the context of SA-AKI, reinforcement learning can be used to optimize treatment strategies for sepsis patients to minimize the risk of AKI. An example application of reinforcement learning in SA-AKI is developing a treatment recommendation system for sepsis patients in the ICU (Fig. 7). The reinforcement learning agent can learn from historical patient data and clinical guidelines to recommend actions such as fluid administration, antibiotic choices, and vasopressor usage. The agent continually adapts its recommendations based on patient responses and outcomes, aiming to optimize patient care and reduce the incidence of AKI.

Reinforcement learning has been studied with promising findings for potential utilization among critically ill patients with sepsis [58–64]. From optimizing fluid resuscitation strategies to determining when and which antibiotics should be administered, RL agents have showcased their capability to refine treatment strategies based on patient feedback and outcomes continuously. Moreover, the technology presents the appealing possibility of integrating extensive datasets, facilitating a more comprehensive patient management approach that considers a multitude of variables [58–64]. Notwithstanding these advancements, there remains a notable deficiency in data concerning the specific employment of reinforcement learning for SA-AKI, underscoring the need for dedicated future investigations.

**Figure 7.** Reinforcement learning for sepsis treatment optimization to prevent acute kidney injury.

ACLS, advanced cardiac life support; AI, artificial intelligence; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; SA-AKI, sepsis-associated acute kidney injury.
Constraints and ethical considerations

AI and ML have shown tremendous potential in the medical field, including in identifying and managing SA-AKI. However, utilizing these tools is not without challenges and ethical considerations [54,65–67].

Data privacy and security concerns

In medical research using ML models, protecting patient data is critical. This encompasses the challenges of ensuring that AI tools neither inadvertently expose nor misuse this confidential information. Additionally, the secure transfer of such data, which frequently traverses between various databases, servers, and institutions, demands the implementation of robust and encrypted protocols to thwart potential breaches. Concurrently, the ethical imperative of obtaining informed consent cannot be understated, emphasizing the necessity for patients to be comprehensively apprised of the utilization and repercussions associated with their data in AI-driven systems. ML models need to be broadly applicable and independently validated. The challenge is making them effective across various healthcare settings. Federated learning is a new approach that improves these models by learning from spread-out data without compromising privacy. This strategy tackles data silos and fosters the development of robust models delivering consistent results across diverse settings. Promoting federated learning and the standardization of ML models is crucial for achieving trustworthy, universal AI healthcare solutions.

Bias and fairness in artificial intelligence algorithms

Bias can emerge in AI models if the training data lacks representation from the broader population. For example, an algorithm predominately informed by data from a single ethnic group may not be as productive for another, possibly resulting in erroneous predictions or misdiagnoses of SA-AKI risk. Moreover, the opaque nature of “black-box” algorithms, which obscure their decision-making processes, raises ethical quandaries. Healthcare practitioners must discern mechanisms by which these AI models derive their outcomes, especially when these outcomes influence critical medical decisions. Nevertheless, techniques such as SHAP (Shapley Additive exPlanations), Gradient-based Class Activation Mapping (Grad-CAM), and LIME (Local Interpretable Model-agnostic Explanations) can enhance the model's explainability [20]. These methods highlight the features significantly influencing model predictions, offering more profound insights into its decision-making process. Incorporating these techniques not only improves the interpretability of deep learning models but also bolsters trust and reliability in their application to SA-AKI research and clinical practices.

Regulatory and legal aspects

Integrating AI and ML tools in SA-AKI research and therapeutic interventions necessitates the establishment of standardized protocols and guidelines. Alongside standardization, a complex challenge emerges of ascertaining accountability in AI-induced misdiagnoses or mistreatments, raising questions about whether the onus lies with the software developers, the healthcare establishment, or the treating physician. Furthermore, akin to pharmacological agents or medical apparatuses, AI instruments might be subject to rigorous clinical evaluations and requisite regulatory endorsements before widespread adoption.

Future directions

The advancement of AI technologies holds promise in transforming the landscape of SA-AKI research. Notably, the integration of AI facilitates real-time monitoring of susceptible patients, potentially paving the way for instantaneous therapeutic interventions. Reinforcement learning, a specialized subset of ML, can elucidate optimal therapeutic strategies through simulation and iterative learning from diverse clinical scenarios. Furthermore, generative AI models emerge as instrumental tools in generating simulated patient data [68,69], thereby enriching our comprehension of SA-AKI’s pathophysiology and enabling accurate prognostications of its progression. Foundation models and large language models (LLMs) have demonstrated significant progress in healthcare [68,70], notably in analyzing complex data to enhance patient care. They learn from extensive datasets, adapting to specific tasks with minimal manual input, which can lower the costs of AI development and maintenance in hospitals. A recent
study highlighted the effectiveness of LLMs in interpreting continuous renal replacement therapy machine alarms in intensive care [71], suggesting they could be integrated into critical care. Yet, this area is still developing and needs more research to reach its full potential.

As AI continues its innovation trajectory, personalized medicine stands at the forefront of its transformative potential. Through AI’s analytical prowess, treatment regimens can be meticulously tailored, considering an individual’s genetic composition, historical medical data, and myriad other determinants. Additionally, AI-powered predictive modalities are poised to give healthcare practitioners invaluable foresight, facilitating the early identification of patients at high risk of SA-AKI, thus ensuring timely medical interventions. Further amplifying its potential, integrating AI systems across medical establishments might catalyze collaborative learning, refining and enhancing predictive algorithms.

Conclusion

In SA-AKI research and therapeutic interventions, AI emerges as a transformative catalyst, poised to redefine diagnostics, risk stratification, and treatment modalities. The potential of AI to revolutionize early detection through advanced algorithms and real-time monitoring is juxtaposed with multifaceted challenges encompassing data security, biases in algorithmic outcomes, and intricate regulatory frameworks. As we venture further into the AI-driven era of medicine, the confluence of these technologies promises a paradigm shift towards more personalized, predictive, and collaborative healthcare. Therefore, it mandates rigorous ethical, technical, and legal safeguards to utilize its beneficial potential without causing harm.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions

Conceptualization, Investigation: All authors
Supervision: KBK
Visualization: WC, KBK
Writing–original draft: WC, CT, KBK
Writing–review & editing: WC, CT, KBK
All authors read and approved the final manuscript.

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46. Al-Amodi HS, Abdelsattar S, Kasemy ZA, Bedair HM, Elbarbary HS, Kamel HF. Potential value of TNF-α (-376 G/A) polymorphism and cystatin C (CysC) in the diagnosis of sepsis associated acute kidney injury (S-AK I) and prediction of mortality in critically ill patients. Front Mol Biosci 2021;8:751299.


Association between systemic inflammation biomarkers and mortality in patients with sepsis-associated acute kidney injury receiving intensive care and continuous kidney replacement therapy: results from the RENERGY (REsearches for NEphRology and epidemioloGY) study

Chan-Young Jung¹, Jiyun Jung², Jeong-Hoon Lim³, Jin Hyuk Paek⁴, Kipyo Kim⁵, Tae Hyun Ban⁶, Jae Yoon Park⁷, Hyosang Kim⁸, Yong Chul Kim⁹, Chung Hee Baek¹

For further information on the authors’ affiliations, see Additional information.

**Background:** Identifying risk factors and improving prognostication for mortality among patients with sepsis-associated acute kidney injury (AKI) undergoing continuous kidney replacement therapy (CKRT) is important in improving the adverse prognosis of this patient population. This study aimed to compare the prognostic value of existing systemic inflammation biomarkers and determine the optimal systemic inflammation biomarker in patients with sepsis-associated AKI receiving CKRT.

**Methods:** This multi-center, retrospective, observational cohort study included 1,500 patients with sepsis-associated AKI treated with intensive care and CKRT. The main predictor was a panel of 13 different systemic inflammation biomarkers. The primary outcome was 28-day mortality after CKRT initiation. Secondary outcomes included 90-day mortality after CKRT initiation, CKRT duration, kidney replacement therapy dependence at discharge, and lengths of intensive care unit (ICU) and hospital stays.

**Results:** When added to the widely accepted Acute Physiology and Chronic Health Evaluation II score, platelet-to-albumin ratio (PAR) and neutrophil-platelet score (NPS) had the highest improvements in prognostication of 28-day mortality, where the corresponding increases in C-statistic were 0.01 (95% confidence interval [CI], 0.00–0.02) and 0.02 (95% CI, 0.01–0.03). Similar findings were observed for 90-day mortality. The 28- and 90-day mortality rates were significantly lower for the higher PAR and NPS quartiles. These associations remained significant even after adjustment for potential confounding variables in multivariable Cox proportional hazards models.

**Conclusion:** Of the available systemic inflammation biomarkers, the addition of PAR or NPS to conventional ICU prediction models improved the prognostication of patients with sepsis-associated AKI receiving intensive care and CKRT.

**Keywords:** Acute kidney injury, Biomarkers, Continuous renal replacement therapy, Inflammation, Sepsis
Introduction

Acute kidney injury (AKI) is a common and potentially life-threatening complication among critically ill patients and often requires continuous kidney replacement therapy (CKRT) [1,2]. The development of AKI significantly increases the mortality rate of critically ill patients, with the mortality rate ranging from 60% to 80% [3,4]. Due to the high mortality risk associated with AKI, identifying risk factors for patient outcomes is essential in AKI patients treated with CKRT.

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [5]. Among the many etiologies of AKI in critically ill patients, sepsis-associated AKI accounts for 45% to 70% of all cases of AKI [3,4]. Sepsis-associated AKI portends a worse prognosis than either syndrome in isolation and is associated with significantly longer intensive care unit (ICU) and hospital stays, and higher mortality rates [6–8]. Owing to this significantly adverse outcome related to sepsis-associated AKI, identifying risk factors and improving prognostication for mortality is important in improving the adverse prognosis of this patient population.

Several ICU mortality prediction scores are widely used in intensive care medicine for the risk stratification of critically ill patients, of which the most commonly used predictive scoring systems are the Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) [9,10]. Although these predictive scoring systems assist physicians in the prognostication of critically ill patients, they are not without their pitfalls [11,12], and there are ongoing efforts to improve the predictive abilities of current scoring systems [12]. For example, although both the APACHE and SOFA scores incorporate key anthropometric and laboratory parameters such as temperature, blood pressure, and serum creatinine, they do not include inflammation biomarkers such as C-reactive protein (CRP) and differential white blood cell counts [13]. Whether the addition of these inflammation biomarkers to currently used ICU prediction tools improves the predictive abilities of these scoring systems has not been previously tested.

Hence, this study aimed to compare the prognostic value of existing systemic inflammation biomarkers, determine the optimal systemic inflammation biomarker in patients with sepsis-associated AKI receiving CKRT, and assess whether they have additive value to commonly used ICU prediction tools.

Methods

Patient selection

The REsearches for NEphRology and epidemioloGY (RENErGY) study is a multi-center, retrospective, observational cohort study that enrolled non-dialysis patients aged ≥18 years who received CKRT for ≥24 hours at seven tertiary medical centers (Asan Medical Center, Kyungpook National University Chilgok Hospital, Dongsan Hospital, Inha University Hospital, Eunpyeong St. Mary’s Hospital, Dongguk University Ilsan Hospital, and Seoul National University Hospital) in South Korea between September 2005 and September 2021. Patients who met the following criteria were excluded: 1) missing APACHE II or SOFA score, and 2) missing baseline laboratory data for serum albumin, platelet, CRP, neutrophil, or lymphocyte count. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Boards of the participating institutions (Asan Medical Center: S2021-1790–0001; Dongguk University Ilsan Hospital: DUIH 2018–12-010–001; Kyungpook National University Chilgok Hospital: KNUCH 2021–03-024; Keimyung University Dongsan Medical Center: DSMC 2021–06-057; Inha University Hospital: 2021–09-029–000; the Catholic University of Korea, Eunpyeong St. Mary’s Hospital: PC21RI-DI0111; Seoul National University Hospital: H-2111–057-1271). The need for informed consent was waived due to the retrospective study design.

Data collection and measurements

Demographic and laboratory data were collected from the electronic medical records of each participating institution. The time of CKRT initiation was considered baseline. Baseline demographic data included age, sex, cause of AKI (sepsis or non-sepsis), body mass index (BMI), medical history, and the dates of hospital and ICU admission and discharge. Body weight was measured in the supine position using integrated bed scales or patient lift scales at the time of CKRT initiation. BMI was calculated as weight in
kilograms divided by height in meters squared. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, where organ dysfunction was identified as an acute change in total SOFA score ≥2 points consequent to the infection [5]. Sepsis-associated AKI was defined as a life-threatening complication characterized by an abrupt deterioration of kidney function, as indicated by increased serum creatinine, oliguria, or both, associated with infection of sepsis [14].

Laboratory samples were collected immediately before the CKRT circuit connection. Laboratory data included complete blood cell counts with differential counts, serum urea nitrogen, creatinine, albumin, electrolytes, and CRP. Estimated glomerular filtration rate (eGFR) was calculated using the creatinine-based CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [15]. The systemic inflammation biomarkers assessed in this study consisted of pro-inflammatory (neutrophils, platelet, and CRP) and anti-inflammatory (lymphocytes and albumin) parameters (Supplementary Table 1, available online) [16–24]. Disease severity was assessed using the APACHE II score [9], SOFA score [10], and Charlson Comorbidity Index (CCI) [25], which were calculated using medical data recorded at the time of CKRT initiation. Comorbid conditions were defined by diagnosis codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

Continuous kidney replacement therapy protocol

The decisions to initiate CKRT in critically ill patients who developed AKI were made by the attending nephrologists of each participating institution. Common indications included hemodynamic instability, refractory volume overload, metabolic acidosis, refractory hyperkalemia, and oliguria. CKRT was applied using a PRISMAFLEX system (Baxter) with biocompatible AN69 ST membranes or a multiFiltrate device (Fresenius Medical Care) with polysulfone membranes. Continuous venovenous hemodiafiltration mode was used for all patients. CKRT was initiated with an initial blood flow rate ranging from 50 to 250 mL/min that was adjusted based on the patient’s hemodynamic status. Effluent volume was set to achieve a clearance of 40 mL/kg/hr at initiation and adjusted thereafter by the attending nephrologist.

Study outcomes

Patients were followed up until their last visit at their respective hospitals or death. The primary endpoint was the 28-day mortality. The 90-day mortality, CKRT duration, KRT dependence at discharge, and lengths of ICU and hospital stays were also evaluated. Survival data were collected from electronic medical records of in-hospital and outpatient clinics. Survival time was defined as the time between CKRT initiation and either death or last follow-up. Patients who were lost to follow-up were treated as censored in the survival analysis.

Statistical analyses

Baseline characteristics of the study population are described using means with standard deviations for normally distributed continuous variables or medians with interquartile ranges for skewed data. Categorical variables are presented as numbers and percentages. To assess the additive value of systemic inflammation biomarkers in the ICU prediction models, Harrell’s C-statistics, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) for prediction models were calculated. Bootstrap estimation was performed to calculate 95% confidence intervals (CIs). Systemic inflammation biomarkers that showed statistically significant improvements in mortality prediction were then selected, and their associations with 28- and 90-day mortality were assessed using the Cox proportional hazards model. Assumptions were confirmed using Schoenfeld residuals. Cox proportional hazard models were constructed after adjustments for the following variables. Model 1 represents the unadjusted hazard ratios (HRs). Model 2 was adjusted for age and sex. Model 3 was further adjusted for CCI score and BMI. The systemic inflammation biomarkers were evaluated in two forms: as a continuous variable and as a categorical variable. The results are presented as HRs and 95% CIs. Cumulative incidences of the study outcomes were estimated using the Kaplan-Meier analyses and compared using the log-rank test. Statistical significance was defined as p < 0.05. Data were analyzed using STATA (version 15; StataCorp) and R (version 4.1.0; R Foundation for Statistical Computing).
**Results**

**Baseline characteristics**

After excluding participants according to the pre-specified exclusion criteria, a total of 1,500 patients were enrolled in this study (Fig. 1), and their baseline characteristics are presented in Table 1. The mean age was 66.5 years, and 943 patients (62.9%) were male. The mean BMI was 23.0 kg/m$^2$. A total of 1,108 patients (73.9%) were on mechanical ventilation, and the mean APACHE II and SOFA scores were 27.3 and 12.0, respectively. Patients had a mean CCI score of 3.6, and 471 (31.4%), 558 (37.2%), 247 (16.5%), and 255 patients (17.0%) had hypertension, diabetes mellitus, cardiovascular disease, and chronic liver disease, respectively. The median neutrophil and lymphocyte counts were 8.9 × 10$^3$/μL and 0.7 × 10$^3$/μL, respectively. The mean platelet count, albumin, and CRP were 104.4 × 10$^9$/L, 2.6 g/dL, and 14.7 mg/L, respectively.

**Patient outcomes**

A total of 940 (62.7%) and 1,048 deaths (69.9%) occurred within 28 and 90 days of CKRT initiation, respectively (Table 2). The median duration of CKRT was 3.0 days. Median lengths of ICU and hospital stays were 7.0 and 22.0 days, respectively. A total of 70 patients (16.4%) were dependent on the kidney replacement therapy (KRT) at the time of hospital discharge.

**Systemic inflammation biomarkers and mortality risk prediction**

The C-statistic for APACHE II was 0.65 (95% CI, 0.63–0.67) for 28-day mortality (Table 3). The degrees of improvements in C-statistics, NRI, and IDI by adding plate-

*Table 1. Baseline characteristics of patients*

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<td>No. of patients</td>
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<tr>
<td>Male sex</td>
<td>943 (62.9)</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>112.2 ± 27.6</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<tr>
<td>Body mass index (kg/m$^2$)</td>
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<tr>
<td>Mechanical ventilation</td>
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<tr>
<td>APACHE II score</td>
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<td>SOFA score</td>
<td>12.0 ± 3.4</td>
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<td>Blood flow rate (mL/min)</td>
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<td>Comorbidities</td>
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<td>CCI score</td>
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<td>Diabetes mellitus</td>
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<td>Cardiovascular disease</td>
<td>247 (16.5)</td>
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<td>Chronic liver disease</td>
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<td>Hemoglobin (g/dL)</td>
<td>9.2 ± 2.2</td>
</tr>
<tr>
<td>WBC count (×10$^3$/μL)</td>
<td>12.8 (6.4–20.6)</td>
</tr>
<tr>
<td>Neutrophil count (×10$^3$/μL)</td>
<td>8.9 (4.0–15.3)</td>
</tr>
<tr>
<td>Lymphocyte count (×10$^3$/μL)</td>
<td>0.7 (0.3–1.3)</td>
</tr>
<tr>
<td>Platelet count (×10$^9$/L)</td>
<td>104.4 ± 92.4</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>55.1 ± 32.8</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.8 ± 2.1</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m$^2$)</td>
<td>33.0 ± 22.9</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>14.7 ± 11.4</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, number (%), or median (interquartile range). APACHE II, Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; CKRT, continuous kidney replacement therapy; CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.
let-to-albumin ratio (PAR) to APACHE II were 0.01 (95% CI, 0.00–0.02), 0.19 (95% CI, 0.12–0.24), and 0.03 (95% CI, 0.01–0.05), respectively. The addition of neutrophil-platelet score (NPS) to APACHE II showed similar findings, with the corresponding improvements in C-statistics, NRI, and IDI 0.02 (95% CI, 0.01–0.03), 0.18 (95% CI, 0.12–0.22), and 0.03 (95% CI, 0.01–0.05), respectively. In the same analysis for 90-day mortality, the C-statistic for APACHE II was 0.65 (95% CI, 0.63–0.66). Modest improvements in the prediction performance of APACHE II were observed when PAR and NPS were added. The improvements in C-statistics, NRI, and IDI were 0.01 (95% CI, 0.00–0.02), 0.18 (95% CI, 0.11–0.22), and 0.03 (95% CI, 0.01–0.05) for PAR, and 0.02 (95% CI, 0.01–0.03), 0.18 (95% CI, 0.10–0.23), and 0.03 (95% CI, 0.01–0.05) for NPS, respectively (Table 4).

The C-statistic for SOFA was 0.63 (95% CI, 0.61–0.65) for 28-day mortality (Supplementary Table 2, available online). The degrees of improvements in C-statistics, NRI, and IDI by adding NPS to SOFA were 0.01 (95% CI, 0.00–0.01), 0.07 (95% CI, 0.00–0.12), and 0.00 (95% CI, 0.00–0.01), respectively. In the same analysis for 90-day mortality, the C-statistic for SOFA was 0.63 (95% CI, 0.61–0.65) for 90-day mortality (Supplementary Table 3, available online). The degrees of improvements in C-statistics, NRI, and IDI by adding NPS to SOFA were 0.01 (95% CI, 0.00–0.12), and 0.00 (95% CI, 0.00–0.01), respectively.

To provide mechanistic explanations for the improvements in mortality prediction of APACHE II with the addition of PAR or NPS, the additive predictive abilities of

### Table 2. Patient outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n = 1,500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-Day mortality</td>
<td>940 (62.7)</td>
</tr>
<tr>
<td>90-Day mortality</td>
<td>1,048 (69.9)</td>
</tr>
<tr>
<td>CKRT duration (day)</td>
<td>3.0 (1.0–6.0)</td>
</tr>
<tr>
<td>KRT dependence at discharge$^a$</td>
<td>70 (16.4)</td>
</tr>
<tr>
<td>Length of ICU stay (day)</td>
<td>7.0 (3.0–16.0)</td>
</tr>
<tr>
<td>Length of hospital stay (day)</td>
<td>22.0 (8.0–49.0)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) or median (interquartile range). CKRT, continuous kidney replacement therapy; ICU, intensive care unit; KRT, kidney replacement therapy.

$^a$KRT dependence at discharge was defined as a patient being discharged without mortality and receiving KRT within 1 day before discharge.

### Table 3. Improvement of reclassification and discrimination of 28-day mortality with addition of systemic inflammation-related biomarkers to APACHE II scores

<table>
<thead>
<tr>
<th>Model</th>
<th>C-statistics (95% CI)</th>
<th>$\Delta$C-statistics (95% CI)</th>
<th>p-value</th>
<th>NRI (95% CI)</th>
<th>p-value</th>
<th>IDI (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE</td>
<td>0.65 (0.63–0.67)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>APACHE + CAR</td>
<td>0.66 (0.64–0.67)</td>
<td>0.00 (0.00–0.01)</td>
<td>0.22</td>
<td>0.06 (0.00 to 0.11)</td>
<td>0.03</td>
<td>0.01 (0.00–0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE + PAR</td>
<td>0.67 (0.65–0.69)</td>
<td>0.01 (0.00–0.02)</td>
<td>&lt;0.001</td>
<td>0.19 (0.12 to 0.24)</td>
<td>&lt;0.001</td>
<td>0.03 (0.01–0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE + PCR</td>
<td>0.66 (0.64–0.67)</td>
<td>0.00 (0.00–0.01)</td>
<td>&lt;0.001</td>
<td>0.05 (–0.15 to 0.11)</td>
<td>0.32</td>
<td>0.00 (0.00–0.01)</td>
<td>0.33</td>
</tr>
<tr>
<td>APACHE + CALLY</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.01)</td>
<td>0.39</td>
<td>0.05 (0.10 to 0.14)</td>
<td>0.15</td>
<td>0.00 (0.00–0.01)</td>
<td>0.17</td>
</tr>
<tr>
<td>APACHE + NAR</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.02</td>
<td>0.03 (–0.14 to 0.07)</td>
<td>0.61</td>
<td>0.00 (0.00–0.00)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>APACHE + LCR</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.51</td>
<td>0.05 (–0.06 to 0.13)</td>
<td>0.06</td>
<td>0.01 (0.00–0.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>APACHE + PLR</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.30</td>
<td>0.02 (–0.07 to 0.03)</td>
<td>0.498</td>
<td>0.00 (0.00–0.00)</td>
<td>0.15</td>
</tr>
<tr>
<td>APACHE + NLR</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.00)</td>
<td>&lt;0.001</td>
<td>0.02 (–0.03 to 0.07)</td>
<td>0.52</td>
<td>0.00 (0.00–0.00)</td>
<td>0.70</td>
</tr>
<tr>
<td>APACHE + SII</td>
<td>0.66 (0.64–0.68)</td>
<td>0.00 (0.00–0.01)</td>
<td>0.04</td>
<td>0.10 (0.01 to 0.15)</td>
<td>0.01</td>
<td>0.01 (0.00–0.02)</td>
<td>0.03</td>
</tr>
<tr>
<td>APACHE + IBI</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.00)</td>
<td>&lt;0.001</td>
<td>0.02 (–0.05 to 0.09)</td>
<td>0.48</td>
<td>0.00 (0.00–0.00)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>APACHE + NCS</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.23</td>
<td>0.04 (–0.09 to 0.09)</td>
<td>0.19</td>
<td>0.00 (0.00–0.01)</td>
<td>0.17</td>
</tr>
<tr>
<td>APACHE + NPS</td>
<td>0.67 (0.65–0.69)</td>
<td>0.02 (0.01–0.03)</td>
<td>&lt;0.001</td>
<td>0.18 (0.12 to 0.22)</td>
<td>&lt;0.001</td>
<td>0.03 (0.01–0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE + LAS</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00–0.00)</td>
<td>0.49</td>
<td>0.10 (–0.13 to 0.15)</td>
<td>0.20</td>
<td>0.00 (0.00–0.01)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation-II; CALLY, C-reactive protein-albumin-lymphocyte index; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; IBI, inflammatory burden index; IDI, integrated discrimination index; LAS, lymphocyte-albumin score; LCR, lymphocyte-to-C-reactive protein ratio; NAR, neutrophil-to-albumin ratio; NCS, neutrophil-C-reactive protein score; NLR, neutrophil-to-lymphocyte ratio; NPS, neutrophil-platelet score; NRI, net reclassification index; PAR, platelet-to-albumin ratio; PCR, platelet-to-C-reactive protein ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.
the individual laboratory parameters including platelet count, neutrophil count, albumin, CRP, and lymphocyte count were also evaluated (Supplementary Tables 4, 5; available online). Modest improvements in the prediction performance of APACHE II were observed when the platelet count and albumin were added. The improvements in C-statistics, NRI, and IDI were 0.03 (95% CI, 0.02–0.04), 0.27 (95% CI, 0.00–0.10), 0.07 (95% CI, 0.00–0.01) for platelet count, and 0.01 (95% CI, 0.01–0.02), 0.04 (95% CI, 0.11–0.22), <0.001 (95% CI, 0.01–0.05) for albumin, respectively (Supplementary Table 4, available online). Similar degrees of improvements in predictive indices were observed for 90-day mortality (Supplementary Table 5, available online).

### Association between platelet-to-albumin ratio, neutrophil-platelet score, and patient outcomes

When patients were stratified according to PAR quartiles, although there was no observable trend in serum albumin levels (p for trend > 0.05), there was a trend towards higher platelet count with increasing PAR quartiles (p for trend < 0.05) (Supplementary Table 6, available online). Moreover, the trend towards lower 28- and 90-day mortality at higher PAR was statistically significant (p < 0.001). Regarding KRT dependence at discharge, the trend towards KRT dependence was higher with higher PAR (p < 0.001). However, CKRT duration and lengths of ICU and hospital stays were comparable across PAR quartiles (Supplementary Table 7, available online).

**Table 4. Improvement of reclassification and discrimination of 90-day mortality with addition of systemic inflammation-related biomarkers to APACHE II scores**

<table>
<thead>
<tr>
<th>Model</th>
<th>C-statistics (95% CI)</th>
<th>ΔC-statistics (95% CI)</th>
<th>p-value</th>
<th>NRI (95% CI)</th>
<th>p-value</th>
<th>IDI (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE</td>
<td>0.65 (0.63–0.66)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>APACHE + CAR</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00 to 0.01)</td>
<td>0.27</td>
<td>0.05 (0.00 to 0.10)</td>
<td>0.07</td>
<td>0.01 (0.00–0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE + PAR</td>
<td>0.66 (0.64–0.68)</td>
<td>0.01 (0.00 to 0.02)</td>
<td>0.004</td>
<td>0.18 (0.11 to 0.22)</td>
<td>&lt;0.001</td>
<td>0.03 (0.01–0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE + PCR</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00 to 0.01)</td>
<td>0.003</td>
<td>0.08 (−0.19 to 0.14)</td>
<td>0.33</td>
<td>0.00 (0.00–0.02)</td>
<td>0.37</td>
</tr>
<tr>
<td>APACHE + CALLY</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00 to 0.01)</td>
<td>0.27</td>
<td>0.07 (−0.14 to 0.17)</td>
<td>0.13</td>
<td>0.01 (0.00–0.02)</td>
<td>0.18</td>
</tr>
<tr>
<td>APACHE + NAR</td>
<td>0.65 (0.63–0.66)</td>
<td>0.00 (0.00 to 0.00)</td>
<td>0.17</td>
<td>0.04 (−0.09 to 0.09)</td>
<td>0.41</td>
<td>0.00 (0.00–0.00)</td>
<td>0.63</td>
</tr>
<tr>
<td>APACHE + LCR</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00 to 0.01)</td>
<td>0.41</td>
<td>0.07 (−0.02 to 0.16)</td>
<td>0.05</td>
<td>0.01 (0.00–0.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>APACHE + PLR</td>
<td>0.64 (0.63–0.66)</td>
<td>0.00 (0.00 to 0.00)</td>
<td>0.44</td>
<td>0.01 (−0.06 to 0.05)</td>
<td>0.84</td>
<td>0.00 (0.00–0.00)</td>
<td>0.08</td>
</tr>
<tr>
<td>APACHE + NLR</td>
<td>0.64 (0.63–0.66)</td>
<td>0.00 (0.00 to 0.00)</td>
<td>0.002</td>
<td>0.05 (−0.08 to 0.10)</td>
<td>0.53</td>
<td>0.00 (0.00–0.00)</td>
<td>0.57</td>
</tr>
<tr>
<td>APACHE + SII</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00 to 0.01)</td>
<td>0.06</td>
<td>0.08 (0.01 to 0.15)</td>
<td>0.007</td>
<td>0.00 (0.00–0.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>APACHE + IBI</td>
<td>0.64 (0.63–0.66)</td>
<td>0.00 (0.00 to 0.00)</td>
<td>&lt;0.001</td>
<td>0.01 (−0.04 to 0.07)</td>
<td>0.55</td>
<td>0.00 (0.00–0.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE + NCS</td>
<td>0.65 (0.63–0.67)</td>
<td>0.00 (0.00 to 0.00)</td>
<td>0.30</td>
<td>0.04 (−0.02 to 0.09)</td>
<td>0.12</td>
<td>0.00 (0.00–0.01)</td>
<td>0.13</td>
</tr>
<tr>
<td>APACHE + NPS</td>
<td>0.66 (0.64–0.68)</td>
<td>0.02 (0.01 to 0.03)</td>
<td>0.001</td>
<td>0.18 (0.10 to 0.23)</td>
<td>&lt;0.001</td>
<td>0.03 (0.01–0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE + LAS</td>
<td>0.64 (0.62–0.66)</td>
<td>0.00 (−0.01 to 0.00)</td>
<td>0.41</td>
<td>0.13 (0.00 to 0.18)</td>
<td>0.05</td>
<td>0.01 (0.00–0.02)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation II; CALLY, C-reactive protein-albumin-lymphocyte index; CAR, C-reactive protein-to-albumin ratio; CI, confidence interval; IBI, inflammatory burden index; IDI, integrated discrimination index; LAS, lymphocyte-albumin score; LCR, lymphocyte-to-C-reactive protein ratio; NAR, neutrophil-to-albumin ratio; NCS, neutrophil-C-reactive protein score; NLR, neutrophil-to-lymphocyte ratio; NPS, neutrophil-platelet score; NRI, net reclassification index; PAR, platelet-to-albumin ratio; PCR, platelet-to-C-reactive protein ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.
**Figure 2.** Cumulative survival probability within 28 and 90 days of continuous kidney replacement therapy initiation according to platelet-to-albumin ratio and neutrophil-platelet score quartiles. The Kaplan-Meier curves of (A) 28- and (B) 90-day survival stratified to platelet-to-albumin ratio quartiles, and (C) 28- and (D) 90-day survival stratified to neutrophil-platelet score quartiles. Log-rank p < 0.001 for Q1 vs. other groups.

**Association between platelet-to-albumin ratio, neutrophil-platelet score, and mortality**

Kaplan-Meier curves revealed that cumulative 28- and 90-day survival probabilities were significantly lower for patients in the lowest quartiles for both PAR and NPS (p < 0.001) (Fig. 2). There was a graded association between PAR quartiles and cumulative 28- and 90-day survival probability (Fig. 2A, B). For NPS, Q2, Q3, and Q4 showed similar cumulative 28- and 90-day survival probabilities (Fig. 2C, D).

When the associations between PAR, NPS, and mortality were further assessed using multivariate Cox proportional hazards models, higher PAR and NPS quartiles were associated with better 28- and 90-day mortality (Supplementary Table 9, 10; available online). For Q4 of PAR, the HRs for 28- and 90-day mortality were 0.48 (95% CI, 0.40–0.57) and 0.50 (95% CI, 0.42–0.59), respectively; both mortalities were significantly lower compared with Q1 (p < 0.001) (Supplementary Table 9, available online). For Q4 of NPS, the HRs for 28- and 90-day mortality were 0.68 (95% CI, 0.57–0.82).
and 0.69 (95% CI, 0.58–0.82), respectively; both mortalities were lower compared with Q1 (p < 0.001) (Supplementary Table 10, available online). The observed relationships between PAR, NPS, and mortality were maintained even after adjustments for confounding factors.

**Discussion**

In this study of critically ill patients with sepsis-associated AKI receiving CKRT, the addition of PAR or NPS to APACHE II and SOFA scores modestly improved the 28- and 90-day mortality predictive performances of each ICU scoring system. With patients grouped into quartiles according to PAR and NPS measured at the time of CKRT initiation, higher values were significantly associated with reduced risk of 28- and 90-day mortality. The statistical significance of this association was conserved even after adjusting for potential confounding factors. Based on the findings of this study, the additional consideration of PAR or NPS may be useful in the risk stratification of critically ill patients with sepsis-associated AKI receiving CKRT.

Several ICU scoring systems are currently used for risk stratification of critically ill patients, of which the APACHE II and SOFA scores are two of the most commonly used ICU prediction tools [12]. However, even the most widely used ICU scoring systems have their inherent limitations, and they have suboptimal predictive performances [11,12]. In critically ill patients with sepsis-associated AKI, outcome prediction studies have been even more scarce, and there have been efforts to better stratify the risk of this high-risk patient group. According to a recent consensus report of the 28th Acute Disease Quality Initiative Workgroup, it was suggested that sepsis biomarkers such as interleukin-6 and antithrombin III may be used to complement functional and tubular injury-related biomarkers for the prognosis of sepsis-associated AKI [14,26]. However, these biomarkers are not routinely available, and their routine testing may be associated with higher medical costs. The systemic inflammation biomarkers assessed in this study are not only routinely available but given that they reflect the patient's inflammatory burden, they may be able to improve risk stratification of critically ill patients with sepsis-associated AKI undergoing CKRT.

Previous recent studies that have investigated systemic inflammation biomarkers in critically ill patients have reported similar findings. In three studies of critically ill patients with severe sepsis and AKI, a higher CRP-to-albumin ratio (CAR) was significantly associated with 28-, 90-day mortality, and all-cause death [18–20]. In a more recent study of the same cohort, not only was a high CAR associated with a higher risk of in-hospital mortality, but it also improved the predictive performance when combined with conventional ICU severity scoring systems, such as the APACHE II and SOFA scores [27]. Although the CAR did not show improvements in predictive performance in the present study, the baseline characteristics of patients enrolled differed among the aforementioned studies, and therefore the results may need to be interpreted with consideration of the patient population. Nevertheless, the findings of this study add evidence to the current literature by suggesting that in patients with sepsis-associated AKI, among the many systemic inflammation biomarkers, not only are higher levels of PAR and NPS associated with better survival, but they also complement current ICU scoring systems.

A possible explanation for the findings of this study may be that both PAR and NPS have the platelet count included in their respective formulae. Indeed, the results of this study also showed that the addition of platelet count alone improved mortality prediction. Platelets are considered key components in the pathogenesis of sepsis, and the development of severe thrombocytopenia from severe sepsis and disseminated intravascular coagulation is associated with a significantly higher risk of death [28,29]. As suggested by the findings of this study, higher PAR may be associated with better outcomes due to higher platelet counts, and thus, less severity of thrombocytopenia. Furthermore, both PAR and NPS may be able to improve the predictive performance of APACHE II because the platelet count is not included in the calculation of the APACHE II score [9]. Regarding the SOFA score, the improvements in the predictive performance of this scoring system with the addition of PAR or NPS may have been less because in contrast to the APACHE II score, the SOFA score formula already includes the platelet count [10].

However, other systemic inflammatory biomarkers that included the platelet count, such as the platelet-to-CRP ratio and the platelet-to-lymphocyte ratio (PLR) failed to show significant improvements in mortality prediction. A possible explanation for this finding may be that, par-
particularly for CRP, levels above a certain cut-off point [30], rather than in its continuous form, may be associated with a sufficient inflammatory burden to be significantly associated with mortality in patients undergoing intensive care and CKRT. For the PLR, its association with mortality in patients undergoing CKRT has also been explored in a previous study, which indicated a U-shaped relationship between PLR and in-hospital mortality [31]. As a result, this U-shaped relationship may have confounded the assessment of improvements in predictive performances.

This study has several limitations. First, due to the retrospective nature of the study, the independent relationship between systemic inflammation biomarkers and ICU patient outcomes should be interpreted with caution. Although CKRT was applied using a standardized protocol, differences in management may have introduced effects that were not accounted for. Second, the systemic inflammation biomarkers assessed in this study were only measured once at the time of CKRT initiation. Considering that a variety of factors such as ultrafiltration by CKRT, and the use of medications to treat sepsis-associated AKI may have affected the patient’s inflammatory burden, the systemic inflammation biomarkers were likely to be in a state of constant flux; thus, making the application of these biomarkers in outcome prediction less optimal. Third, although this study was confined to patients who developed sepsis-associated AKI, given that this study enrolled patients from tertiary medical centers, the patient characteristics may have been too heterogeneous for testing of systemic inflammation biomarkers. Therefore, further studies that assess the association between these systemic inflammation biomarkers and patient outcomes should be further tested and validated in better-defined patient subgroups. Fourth, as the study cohort did not collect medication data, the differentiation between sepsis-associated AKI and sepsis-induced AKI, a subphenotype of sepsis-associated AKI that excludes injury that primarily develops as the indirect consequence of sepsis or sepsis therapies [14], was not possible. Further distinction of these different disease entities would have made the results more robust. Fifth, given that different etiologies of sepsis have different outcomes, additional consideration of the etiology of sepsis would have provided additional insights into how different systemic inflammatory biomarkers have different prognostic values. Sixth, given that different anticoagulants used for CKRT maintenance may have also affected patient survival, the additional consideration of anticoagulation may have made the results more robust. Finally, this was a cohort consisting of patients from a single ethnic origin. Due to the potential ethnic disparities in sepsis outcomes [32], the findings of this study may be interpreted differently in other ethnic populations.

In conclusion, of the available systemic inflammation biomarkers, the addition of PAR or NPS to conventional ICU prediction models improved the prognostication of patients with sepsis-associated AKI receiving intensive care and CKRT. However, further studies are needed for their generalized applications.

Additional information

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Conflicts of interest

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.
Authors’ contributions

Conceptualization, Data curation, Formal analysis, Methodology: CYJ, YCK, CHB
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Time-restricted feeding protects against cisplatin-induced acute kidney injury in mice

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Background: Time-restricted feeding (TRF), devoid of calorie restriction, is acknowledged for promoting metabolic health and mitigating various chronic metabolic diseases. While TRF exhibits widespread benefits across multiple tissues, there is limited exploration into its impact on kidney function. In this study, our aim was to investigate the potential ameliorative effects of TRF on kidney damage in a mouse model of cisplatin-induced acute kidney injury (AKI).

Methods: Cisplatin-induced AKI was induced through intraperitoneal injection of cisplatin into C57BL/6 male mice. Mice undergoing TRF were provided unrestricted access to standard chow daily but were confined to an 8-hour feeding window during the dark cycle for 2 weeks before cisplatin injection. The mice were categorized into four groups: control, TRF, cisplatin, and TRF + cisplatin.

Results: The tubular damage score and serum creatinine levels were significantly lower in the TRF + cisplatin group compared to the cisplatin group. The TRF + cisplatin group exhibited reduced expression of phosphorylated nuclear factor kappa B, inflammatory cytokines, and F4/80-positive macrophages compared to the cisplatin group. Furthermore, oxidative stress markers for DNA, protein, and lipid were markedly decreased in the TRF + cisplatin group compared to the cisplatin group. TUNEL-positive tubular cells, cleaved caspase-3 expression, and the Bax/Bcl-2 ratio in the TRF + cisplatin group were lower than those in the cisplatin group.

Conclusion: TRF, without calorie restriction, effectively mitigated kidney damage by suppressing inflammatory reactions, oxidative stress, and tubular apoptosis in a mouse model of cisplatin-induced AKI. TRF holds promise as a novel dietary intervention for preventing cisplatin-induced AKI.

Keywords: Acute kidney injury, Apoptosis, Cisplatin, Inflammation, Intermittent fasting, Oxidative stress

Introduction

Acute kidney injury (AKI) is a renal disorder characterized by a rapid decline in kidney function, and its high morbidity and mortality make it a global health problem [1,2]. Among the various causes of AKI, nephrotoxic drugs are responsible for approximately 20% of AKI cases in both hospital and outpatient settings [3]. One of these nephrotoxic agents is cisplatin, an inorganic platinum-based chemotherapeutic agent widely used in the treatment of various solid cancers [4]. However, its use is limited by side effects in normal tissues and organs, and nephrotoxicity is the principal limitation of cisplatin cancer therapy, affecting approximately one-third of patients receiving cisplatin.
therapy [4,5]. Despite significant progress in studying the pathophysiology of cisplatin-induced AKI over the past decades, there is still no effective prophylaxis against it. Therefore, the development of new prophylactic strategies for cisplatin-induced AKI holds great clinical significance.

Calorie restriction, a reduction in caloric intake without malnutrition, has consistently been found to produce reductions in body weight and extend a healthy lifespan across a variety of species [6]. Furthermore, calorie restriction promotes metabolic health and ameliorates chronic metabolic diseases, such as type 2 diabetes mellitus and cardiovascular disorders [7]. Regarding kidney disease, calorie restriction is known to trigger an adaptive defense program to increase resistance to stress and ameliorate renal ischemia-reperfusion injury (IRI) in experimental animals [8–10]. Thus, efforts have been made to pave the way for an alternative, non-pharmacological, diet-based approach to prevent organ injury in both animals and humans [7]. However, although several studies highlight the benefits of calorie restriction in humans, findings from obesity intervention trials over the past decades indicate that the vast majority of humans have significant difficulty sustaining daily calorie restriction for long periods of time [6].

Time-restricted feeding (TRF), a novel dietary intervention where animals have access to food for a defined period of the day, has gained popularity as an alternative to calorie restriction and has shown promise in delivering similar benefits in terms of weight loss and cardiometabolic health [11,12]. TRF does not restrict caloric consumption during the time-restricted window, which is considered an advantage in terms of improving adherence, as no calorie count is needed [13]. Currently, although preclinical and clinical trials have shown that TRF has broad-spectrum benefits for many health conditions such as obesity, diabetes mellitus, cardiovascular disease, cancers, and neurological disorders [12], few studies to date have focused on its effect on the kidney. In the current study, we investigate whether TRF protects against renal injury in a mouse model of cisplatin-induced AKI.

Methods

Animals

All animal experiments were approved by the Institutional Animal Care and Use Committee of Pusan National University (PNU-IACUC, 2021-032) and conducted according to the Guidelines for the Care and Use of Experimental Animals endorsed by the Korean Society of Experimental Animals. Male C57BL/6 mice (8 weeks old) were purchased from the Koatech Technology Corporation (Seoul, Korea) and housed in a specific pathogen-free facility at 22 ± 1 °C, 55% ± 5% humidity under a 12-hour light/dark cycle.

Animal experimental design

After acclimatization for at least 1 week, the mice were randomly divided into four groups as follows (n = 6/group) (Fig. 1A): (a) sham: ad libitum food and vehicle injection, (b) TRF: TRF and vehicle injection, (c) cisplatin: ad libitum food and cisplatin injection, (d) TRF + cisplatin: TRF and cisplatin injection. Mice with ad libitum access had 24-hour availability of food, while the mice on TRF were provided with food for 8 hours daily, starting 3 hours after the beginning of the dark cycles (from 9:00 p.m. to 5:00 a.m.), for a total of 2 weeks. After 2-week of either ad libitum feeding or TRF, the cisplatin (15 mg/kg in 0.9% saline; Sigma-Aldrich) was injected intraperitoneally into the cisplatin group and the TRF + cisplatin group. An equal volume of the vehicle (0.9% saline) was injected intraperitoneally into the sham group and the TRF group. All mice were provided with ad libitum food for 72 hours after cisplatin or vehicle injection. All mice were provided with ad libitum food for 72 hours after cisplatin or vehicle injection.

Blood measurements

Blood glucose and β-hydroxybutyrate (β-HB) levels were measured using a blood glucose and ketone monitoring meter (FreeStyle Optium, Neo; Abbott) in whole blood obtained from the tail vein of mice after 2 weeks of either TRF or ad libitum feeding, immediately before cisplatin administration. Serum creatinine levels were assayed using enzyme-linked immunosorbent assays (#80; Crystal Chem) at the time of mice sacrifice.

Tissue preparation

The mice were euthanized 72 hours after cisplatin administration. The kidneys were perfused with cold (4 °C)
Figure 1. Effect of TRF on metabolic parameters. (A) Experimental design. TRF were provided with food for 8 hours daily for a total of 2 weeks. (B) Food intake. Mice enrolled in TRF for 2 weeks consumed a similar amount of food as the ad libitum control group. (C) Body weight. TRF did not lead to any bodyweight reduction. (D) β-hydroxybutyrate (β-HB) level. TRF-treated mice showed increased levels of β-HB. (E) Glucose level. There was no difference in blood glucose levels between TRF-treated and ad libitum-treated mice. Cis, cisplatin; TRF, time-restricted feeding.

Data are expressed as mean ± standard deviation (n = 6/group; *p < 0.05 compared with sham and cisplatin group).

phosphate-buffered saline and immediately resected. One kidney was stored at ~80 °C for protein and messenger RNA (mRNA) analyses. The remaining kidney was fixed in 10% neutralized formalin at room temperature and embedded in paraffin for histological and immunohistochemical analyses.
**Histological analyses**

The paraffin-embedded kidney samples were cut into 4-μm sections and stained with hematoxylin and eosin (H&E), as described previously [14]. The kidney sections underwent deparaffinization, rehydration in distilled water, staining with Mayer’s hematoxylin for 1 minute, and washing with 4–5 changes of tap water. They were subsequently rinsed with three changes of distilled water, counterstained in alcoholic eosin for 1 minute, and dehydrated through three changes of 95% ethanol and two changes of 100% ethanol. All stained kidney tissues were digitally scanned using a ZEISS Axioscan 7 (Carl Zeiss). Images were captured at 20× magnification using ZEN Lite microscope software (Carl Zeiss), and 10 high power fields (HPFs) were randomly selected. The degree of tubular injury was evaluated by a pathologist in a blinded manner, based on criteria such as tubular dilatation, loss of brush border, vacuolization, epithelial cell shedding, and denuded tubular basement membrane. The scoring scale was as follows: 0, normal; 1, <10%; 2, 10%–25%; 3, 25%–50%; 4, 50%–75%; and 5, 75%–100% [15].

**Immunohistochemical analyses**

Immunohistochemical analyses were performed on 3-μm paraffin-embedded kidney sections, as described previously [14]. In summary, the sections were deparaffinized and rehydrated in an ethanol series. After microwave-based antigen retrieval, the sections were blocked with normal horse serum (Vector Laboratories) and left to incubate overnight with primary antibodies at 4 °C. Subsequently, the sections were treated with secondary antibodies (ImPRESS HRP reagent kit; Vector Laboratories) for 30 minutes at 37 °C. Finally, the slides were developed using 3,3-diaminobenzidine tetrahydrochloride (Vector Laboratories) and counterstained with hematoxylin. Primary antibodies used were anti-F4/80 (#ab111101; Abcam) and anti-phosphorylated nuclear factor kappa B (p-NF-κB) p65 (#sc-136548; Santa Cruz Biotechnology), anti-8-hydroxy-2’-deoxyguanosine (8-OHdG) (JalCA), anti-4-hydroxy-2-nonenal (4-HNE) (JalCA), and anti-nitrotyrosine (#ab125106; Abcam). The stained kidney tissues were captured using a ZEISS Axioscan 7. The images were obtained using the ZEN Lite microscope software, and 10 HPFs were selected randomly for assessment. The image analysis excluded glomeruli, large vessels, and perivascular and subcapsular regions. The average counts of F4/80- and p-NF-κB p65-positive cells per HPF were evaluated in a blinded manner. The staining of 8-OHdG, 4-HNE, and nitrotyrosine was semi-quantitatively graded in a blinded manner using the following scale: 0 for no stained area; 1 for 1%–25% stained area; 2 for 26%–50% stained area; 3 for 51%–75% stained area; and 4 for >75% stained area.

**Western blotting**

Western blotting was performed as described previously [14]. Briefly, proteins were extracted from kidneys with a protein extraction solution (PRO-PREP; iNtRON Biotechnology). Protein concentrations were quantified by the Bradford method (Bio-Rad Protein Assay; Bio-Rad Laboratories Inc.). Proteins were separated by electrophoresis on 12% sodium dodecyl sulfate-polyacrylamide gels and transferred onto nitrocellulose membranes (Hybond ECL; Amersham Pharmacia Biotech Inc.). The membranes were incubated for 2 hours at room temperature with a solution containing 5% (w/v) nonfat dried milk in Tris-buffered saline (10 mM Tris/HCl, pH 8.0, and 150 mM NaCl) supplemented with 0.05% Tween-20. Following this, the membranes were probed using the following specific primary antibodies: anti-Bcl-2 (#ABP50759; Abbkine), anti-Bax (#ABP50752; Abbkine), anti-caspase-3 (#ab13847; Abcam), and cleaved caspase-3 (#9664; Cell Signaling Technology). The secondary antibodies used were anti-rabbit or anti-mouse immunoglobulin G antibodies (#ADI-SAB-300-J, #ADI-SAB-100-J; Enzo Life Science). Immunoreactive bands were visualized using enhanced chemiluminescence (Pierce ECL Western blotting substrate; Thermo Scientific). The protein levels were quantified with ImageJ software (National Institutes of Health). To determine protein expression levels, the relative expression of the target protein was normalized to β-actin (Cell Signaling Technology).

**TUNEL staining**

Tubular apoptosis was assessed using terminal deoxyribonucleotidyl transferase dUTP nick end labeling (TUNEL) staining. Kidney paraffin sections, 3 μm-thick, were deparaffinized in xylene and rehydrated through a series of
ethanol solutions. The TUNEL assay was conducted using the TUNEL Apoptosis Detection Kit (#G3250; Promega), following the manufacturer’s protocol. Nuclei were counterstained with DAPI. Stained kidney tissues were imaged using a ZEISS Axioscan 7. Images were captured using ZEN Lite microscope software at ×20 magnification. TUNEL-positive cell number was quantified in 10 randomly selected HPFs and averaged by an observer blinded to the samples.

Quantitative reverse-transcription polymerase chain reaction analysis

Quantitative reverse-transcription polymerase chain reaction analysis was conducted as previously described [14]. The GAPDH (glyceraldehyde 3-phosphate dehydrogenase) was employed as the housekeeping internal control and was quantified simultaneously with the target gene (tumor necrosis factor alpha [TNF-α], interleukin [IL]-6, IL-1α). All products were confirmed through melting curve analysis (95 °C for 15 seconds, 60 °C for 45 seconds, and 72 °C for 1 minute). Normalization and fold-change values for each gene were calculated by the 2^{-ΔΔCT} method. The primer sequences used are listed in Table 1.

Statistical analysis

Data were presented as the mean ± standard deviation. Analysis of the data was conducted using the Mann-Whitney U test or Kruskal-Wallis test, as deemed appropriate. All statistical analyses were carried out using IBM SPSS version 21.0 (IBM Corp.). A p-value of <0.05 was considered statistically significant.

Table 1. Sequences of the real-time PCR primers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward (5′-3′)</th>
<th>Reverse (3′-5′)</th>
</tr>
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<tbody>
<tr>
<td>GAPDH (mouse)</td>
<td>CATCACTGCACCCAGAGACTG</td>
<td>TGCCAGTGAGCTCCGAGTTAG</td>
</tr>
<tr>
<td>TNF-α (mouse)</td>
<td>GGTGCCATATGCAGCAGCCCTT</td>
<td>GCCATAGAAGCTGGAGAGGAG</td>
</tr>
<tr>
<td>IL-6 (mouse)</td>
<td>TACCACTTCACAAGTGGAGGC</td>
<td>CTGAAATGATGATCAGGAGG</td>
</tr>
<tr>
<td>IL-1α (mouse)</td>
<td>ACGGCTGATTTTGGAGAGCC</td>
<td>CACTTGGTAAAAAGAGGGC</td>
</tr>
</tbody>
</table>

GAPDH, glyceraldehyde 3-phosphate dehydrogenase; IL, interleukin; PCR, polymerase chain reaction; TNF, tumor necrosis factor.

Results

Effect of time-restricted feeding on metabolic parameter

Mice enrolled in TRF for 2 weeks consumed a similar amount of food as the ad libitum control group, confirming that there is no caloric restriction during TRF (Fig. 1B). TRF also did not lead to any body weight reduction (Fig. 1C). Additionally, TRF-treated mice showed increased levels of β-HB, indicating that the TRF regimen induced a state of ketosis (Fig. 1D). There was no difference in blood glucose levels between TRF-treated and ad libitum-treated mice (Fig. 1E).

Time-restricted feeding attenuates renal dysfunction and pathological damage in cisplatin-induced acute kidney injury

The serum creatinine levels of the cisplatin group were higher than those of the sham group 72 hours after cisplatin administration. However, the serum creatinine levels of the TRF + cisplatin group were lower than those of the cisplatin group, indicating that the TRF regimen attenuated renal dysfunction in a mouse model of cisplatin-induced AKI (Fig. 2A). Cisplatin is known to induced tubular injury in humans and rodents [4]. Therefore, we performed a histological assessment of each group using H&E-stained kidney sections. The cisplatin group exhibited prominent histopathological alteration, such as tubular dilation, cast formation, loss of brush border, vacuolization, and epithelial cell shedding than the sham group. However, all these injuries were significantly mitigated in the TRF + cisplatin group (Fig. 2B, C).
Time-restricted feeding attenuates the inflammatory reaction in cisplatin-induced acute kidney injury

Since inflammatory reactions play a pivotal role in cisplatin-induced AKI [16], we investigated the mRNA expression of pro-inflammatory cytokines such as TNF-α, IL-1α, and IL-6, in kidney tissues. The TNF-α, IL-1α, and IL-6 mRNA expression levels in the cisplatin group were significantly higher than those in the sham group. However, TNF-α, IL-1α, and IL-6 mRNA expression levels in the TRF + cisplatin group were significantly lower than those in the cisplatin group (Fig. 3A). Moreover, the number of F4/80-stained cells, a pan-macrophage marker, in the interstitial space of the cisplatin group was higher than that in the sham group. However, the number of F4/80-stained cells in the TRF + cisplatin group was significantly lower than that in the cisplatin group (Fig. 3B).

NF-κB is an important nuclear transcript factor that induces the expression of various pro-inflammatory cytokines [17]. Therefore, we investigated NF-κB expression during inflammation in cisplatin-induced AKI. Immunohistochemical analyses showed that p-NF-κB p65 expression in the cisplatin group was higher than that in the sham group. However, p-NF-κB p65 expression in the TRF
Figure 3. Effect of TRF on inflammatory reaction in cisplatin (Cis)-induced acute kidney injury. (A) The tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-1α messenger RNA (mRNA) levels. The TNF-α, IL-6 mRNA, and IL-1α expression in the TRF + Cis group were significantly lower than those in the Cis group. (B) Representative images of immunohistochemical analysis for F4/80. The F4/80-stained area in the TRF + Cis group was significantly decreased compared to that in the Cis group. (C) Representative images of immunohistochemical analysis for phosphorylated nuclear factor kappa B (p-NF-κB) p65. A p-NF-κB p65 expression in the TRF + Cis group was lower than that in the Cis group.

HPF, high power field; TRF, time-restricted feeding.
Data are expressed as mean ± standard deviation (n = 6/group; *p < 0.05 compared with sham and TRF group; #p < 0.05 compared with cisplatin group).
The pathophysiology of cisplatin-induced AKI is complex. Although the precise mechanisms are not fully elucidated, accumulating evidence suggests the involvement of inflammatory responses, apoptosis of tubular cells, and oxidative stress in the pathophysiology of the disease [4,5]. Among these factors, a robust inflammatory response triggered by cisplatin plays a significant role in the functional and structural deterioration of the kidneys [5]. Previous studies have reported that genetic or pharmacological suppression of pro-inflammatory cytokines can alleviate cisplatin-induced AKI [5]. Moreover, oxidative stress emerges as a pivotal pathogenic element in cisplatin-induced AKI. The increased production of reactive oxygen species during cisplatin treatment activates multiple signaling cascades, leading to damage and demise of renal tubular epithelial cells [20]. Lastly, over the past decades, researchers have paid substantial attention to the apoptosis of renal tubular epithelial cells as a crucial aspect of cisplatin-induced AKI mechanisms. Several studies have indicated that inhibiting tubular cell apoptosis mitigates the impact of cisplatin-induced AKI [4,5,21]. In the context of these well-established mechanisms of cisplatin-induced AKI, our present study highlights that TRF protects against cisplatin-induced AKI by suppressing inflammation, tubular apoptosis, and oxidative stress. To the best of our knowledge, our study is the first to explore the beneficial effects of TRF on cisplatin-induced AKI.

Many studies have explored the benefits of TRF on health and disease [12,22,23]. While some attribute the positive outcomes of TRF to a reduction in overall food intake, others have demonstrated improvements in cardiometabolic markers and protection against pathological conditions, even with the implementation of isocaloric diets [23]. In our research, mice in the TRF groups exhibited similar body weights and consumed comparable amounts of food compared with the sham group, indicating the absence of calorie restriction. This suggests that the favorable effects of TRF on cisplatin-induced AKI in our study were not a result of reduced caloric intake.

One of the key findings in our study is the notable suppression of the inflammatory response by TRF in a mouse model of cisplatin-induced AKI. Although the specific mechanisms governing the anti-inflammatory effect of TRF...
Figure 4. Effect of TRF on oxidative stress in cisplatin (Cis)-induced acute kidney injury. Representative images of immunohistochemical analysis for 8-OHdG (A), 4-HNE (B), and nitrotyrosine (C). The expression of 8-OHdG, 4-HNE, and nitrotyrosine in the TRF + Cis group was markedly decreased compared to that in the Cis group.

HPF, high power field; TRF, time-restricted feeding; 4-HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-hydroxy-2'-deoxyguanosine.

Data are expressed as mean ± standard deviation (n = 6/group; *p < 0.05 compared with sham and TRF group; #p < 0.05 compared with cisplatin group).
on cisplatin-induced AKI were not delineated in this investigation, TRF is recognized for its intrinsic anti-inflammatory properties. In a meta-analysis encompassing 25 human studies, TRF is proposed as an effective approach to diminish TNF-α and leptin levels in the general adult population [24]. Previous research, both in humans and animals, has demonstrated that TRF reduces inflammatory responses in chronic inflammatory conditions, including cardiovascular disease, diabetes mellitus, neurodegenerative disorders, and arthritis [22]. Concerning kidney disease, TRF is reported to decrease renal innate immune cells in a mouse model of hypertension [23].

Despite these findings, the precise mechanism by which TRF mitigates inflammation in our study remains unclear. One potential mechanism is TRF-induced ketosis. We observed elevated levels of β-HB in TRF-treated mice, indicating that the TRF regimen induced a state of ketosis. As the most abundant ketone body in mammals, β-HB is a metabolic byproduct synthesized during fat breakdown in the liver, serving as an alternative energy source in response to carbohydrate or glucose depletion [25]. Beyond its role as an energy substrate, β-HB emerges as a crucial signaling molecule, with a distinct capacity to modulate inflammatory responses [25]. Facilitated by monocarboxylic acid transporters, β-HB reaches cells, contributing to energy generation and enhancing anti-inflammatory signaling [26]. Its anti-inflammatory action extends to the modulation of peroxisome proliferator-activated receptor-gamma co-

Figure 5. Effect of TRF on tubular apoptosis in cisplatin (Cis)-induced acute kidney injury. (A) Representative image of TUNEL staining. The number of apoptotic cells in the TRF + Cis group was lower than that in the Cis group. (B) Representative images of a western blot for cleaved caspase-3, Bax, and Bcl-2. The expression of cleaved caspase-3 (activated caspase-3) and the Bax/Bcl-2 expression ratio in the TRF + Cis group were lower than that in the Cis group.

TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; TRF, time-restricted feeding.

Data are expressed as mean ± standard deviation (n = 6/group; *p < 0.05 compared with sham and TRF group; #p < 0.05 compared with cisplatin group).
activator-1 alpha (PGC-1α) and forkhead box O1 (FOXO1) [27]. In a previous study [28], we examined the impact of pretreatment with exogenous β-HB on inflammation in a mouse model of cisplatin-induced AKI. Our findings indicated that β-HB pretreatment significantly reduced the expression of phosphorylated NF-κB, inflammatory cytokines, and macrophage infiltration. These results suggest that β-HB may play a crucial role in the anti-inflammatory effects of TRF. We posit that further investigations are necessary to elucidate mechanisms other than β-HB that contribute to the anti-inflammatory effect of TRF in cisplatin-induced AKI.

Our study uncovered the inhibitory potential of TRF against oxidative stress in a mouse model of cisplatin-induced AKI. While the precise mechanism underlying the anti-oxidative effect of TRF in cisplatin-induced AKI was not delineated in the present study, accumulating evidence suggests that TRF possesses anti-oxidative properties. A systematic review of randomized controlled studies indicates that TRF has the potential to decrease circulating markers of oxidative stress [29]. Previous animal and human studies have also suggested that TRF decreased oxidative stress markers in chronic disease (obesity, asthma, type 2 diabetes mellitus, cardiovascular disease, and cancer) [12,13,22]. Regarding kidney disease, TRF ameliorated kidney damage by increasing the antioxidant protection and preventing oxidative DNA damage in a mouse model of IRI [7]. Currently, the molecular mechanisms are unclear, but it is possible nuclear factor erythroid 2-related factor 2 (NRF2) and PGC-1α, both redox-sensitive transcriptional regulators are involved in the beneficial effects of TRF on oxidative stress [7]. Moreover, β-HB induced by TRF is also reported to activate FOXO1 and NRF2, controlling cytoprotective genes involved in the oxidative stress response [30]. Moreover, in our previous study [28], we examined the impact of exogenous β-HB on oxidative stress in a mouse model of cisplatin-induced AKI. Our observations revealed that exogenous β-HB decreased oxidative stress markers for DNA, protein, and lipid. These results suggest that β-HB plays a significant role in the anti-oxidative effect of TRF, complementing its anti-inflammatory properties. Further studies are warranted to unveil the mechanisms behind the anti-oxidative effect of TRF in cisplatin-induced AKI.

The present study also demonstrated that TRF suppressed tubular apoptosis in a mouse model of cisplatin-induced AKI. Our findings align with previous research illustrating the anti-apoptotic properties of TRF in diverse animal models. Specifically, TRF has been documented to diminish apoptosis in a mouse model of hepatic IRI [31] and to mitigate apoptosis through the modulation of autophagy in a doxorubicin-induced cardiotoxicity model of albino rats [32]. In the context of kidney disease, preoperative TRF administration demonstrated protective effects against renal IRI by inhibiting apoptosis in a mouse model of aortic aneurysm [33]. Additionally, TRF exhibited the capacity to suppress tubular apoptosis in a rat model of glycercerol-induced AKI [34,35]. Despite these compelling outcomes, the exact mechanism underlying TRF’s attenuation
of tubular apoptosis in a mouse model of cisplatin-induced AKI remains unclear. One plausible hypothesis is that the reduction in inflammatory reactions and oxidative stress induced by TRF contributes to the attenuation of tubular apoptosis. This is because cisplatin-induced tubular cell apoptosis is reported to be aggravated by the concurrent induction of inflammation and oxidative stress caused by cisplatin. Consequently, additional investigations are warranted to elucidate the impact of TRF on tubular apoptosis in the context of cisplatin-induced AKI.

The conclusions of the present study are summarized in Fig. 6. We observed an increase in inflammatory reactions, tubular apoptosis, and oxidative stress in a mouse model of cisplatin-induced AKI. TRF ameliorated cisplatin-induced AKI by attenuating inflammation, tubular cell apoptosis, and oxidative stress. Thus, TRF may represent a new dietary intervention for the prevention of cisplatin-induced AKI. We believe that further studies are necessary to elucidate the mechanism underlying the favorable effects of TRF on inflammation, apoptosis, and oxidative stress.

Conflicts of interest
All authors have no conflicts of interest to declare.

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Data sharing statement
The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions
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Data curation, Formal analysis: All authors
Funding acquisition: IYK
Investigation: KWJ, YSK, SRK, IYK
Writing—original draft: KWJ, IYK
Writing—review & editing: KWJ, IYK
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References
Plasma presepsin for mortality prediction in patients with sepsis-associated acute kidney injury requiring continuous kidney replacement therapy

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Background: The reliability of presepsin as a biomarker of sepsis may be reduced in patients with acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT). This study analyzed the utility of plasma presepsin values in predicting mortality in patients with AKI requiring CKRT, particularly those with sepsis-associated AKI.

Methods: This single-center retrospective study included 57 patients who underwent CKRT, with plasma presepsin measurements, from April 2022 to March 2023; 35 had sepsis-associated AKI. The predictive values of plasma presepsin, as well as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, for 28-day mortality were analyzed using receiver operating characteristic curves. Multivariate Cox regression analysis was performed to identify risk factors for 28-day mortality in the sepsis-associated AKI subgroup.

Results: Overall, plasma presepsin showed a lower area under the curve value (0.636; 95% confidence interval [CI], 0.491–0.781) than the APACHE II (0.663; 95% CI, 0.521–0.804) and SOFA (0.731; 95% CI, 0.599–0.863) scores did. However, in sepsis-associated AKI, the area under the curve increased to 0.799 (95% CI, 0.653–0.946), which was higher than that of the APACHE II (0.638; 95% CI, 0.450–0.826) and SOFA (0.697; 95% CI, 0.519–0.875) scores. In the multivariate Cox regression analysis, a high presepsin level was an independent risk factor for 28-day mortality in sepsis-associated AKI (hazard ratio, 3.437; p = 0.03).

Conclusion: Presepsin is a potential prognostic marker in patients with sepsis-associated AKI requiring CKRT.

Keywords: Acute kidney injury, Continuous renal replacement therapy, Mortality, Presepsin protein, Sepsis

Introduction

Presepsin is a soluble cluster of differentiation (CD) subtype that results from the cleavage of CD14. CD14 is a lipopolysaccharide receptor, mainly expressed in monocytes and macrophages. It is degraded inside the cell during phagocytosis during infection and is released into the blood as a soluble CD14 subtype [1–3]. Presepsin is a novel marker that is highly specific for infections and has been extensively studied. Presepsin is characterized by a faster rise in blood levels during infection compared to other biomarkers, such as procalcitonin (PCT) and C-reactive protein (CRP), and its short half-life is expected to be useful for determination of prognosis [4–6]. Recent clinical studies...
have reported that presepsin is a good indicator for distinguishing between noninfectious organ failure and sepsis, and its utility in clinical practice is expected to increase in the future [7].

Presepsin has a low molecular weight (13 kDa) and is eliminated by the kidneys. Therefore, in patients with reduced kidney function, the cutoff value of presepsin varies and the reliability of the test may decrease [8,9]. In patients with acute kidney injury (AKI), especially those requiring continuous kidney replacement therapy (CKRT), there is a greater risk of a reduction in the reliability of presepsin because kidney function fluctuates very dynamically. Furthermore, there is an additional risk that presepsin may be removed by CKRT machines, further reducing its reliability [10,11]. Therefore, presepsin has not been studied as a diagnostic or prognostic marker in patients with AKI receiving CKRT.

Presepsin is highly specific for infection. Although it is affected by kidney function, we hypothesized that plasma presepsin levels measured before CKRT initiation may be useful as a prognostic marker, especially in patients with sepsis-associated AKI (SA-AKI) undergoing CKRT. Therefore, we analyzed the predictive value of the plasma presepsin level as a prognostic marker for mortality in patients with AKI who underwent CKRT.

**Methods**

**Study design and population**

This single-center, retrospective study included critically ill patients who underwent CKRT for AKI at Konyang University Hospital between April 2022 and March 2023, in addition to plasma presepsin measurements. The exclusion criteria were age of <18 years, already being on maintenance renal replacement therapy (RRT) for end-stage kidney disease (ESKD), and not having a plasma presepsin measurement within the 24 hours prior to CKRT initiation (measurement more than 24 hours prior to CKRT initiation, measurement after CKRT initiation). AKI was diagnosed according to the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) AKI guidelines, and CKRT was initiated in patients with clinical hemodynamic instability with volume overload, electrolyte imbalance, and metabolic acidosis that could not be controlled with conservative treatment [12]. The protocol for CKRT initiation is a continuous veno-venous hemodiafiltration mode with an effluent dose of 30 mL/kg/hr. Half of the total effluent dose is dialysate, the other half are pre- and post-replacement doses in a 2:1 ratio. The blood flow rate is 150 mL/min. The anticoagulation regimen is heparin, nafamostat, or no anticoagulation, depending on the patient’s status and the physician’s consideration of the bleeding risk.

A total of 74 patients were recruited; 57 patients were finally analyzed after excluding three patients who were already undergoing RRT for ESKD and 14 patients whose plasma presepsin measurement was not performed within 24 hours prior to CKRT initiation. The cause of AKI was assessed to establish an SA-AKI subgroup (Fig. 1). This study was approved by the Institutional Review Board (IRB) of Konyang University Hospital, College of Medicine, Konyang University (No. KYUH 2023-09-009). The need to obtain informed patient consent was waived by the IRB because the study was retrospective.

![Figure 1. Study design and population](https://example.com/image.png)

*Figure 1. Study design and population.* Of the 74 patients who underwent CKRT with plasma presepsin measurement at Konyang University Hospital between April 2022 and March 2023, 17 who met the exclusion criteria were excluded. Finally, the data of 57 patients were analyzed; among them, 35 patients who met both the sepsis and AKI criteria were classified into the SA-AKI subgroup.

AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ESKD, end-stage kidney disease; RRT, renal replacement therapy; SA-AKI, sepsis-associated acute kidney injury.
Classification of the sepsis-associated acute kidney injury subgroup

The cause of AKI in each patient was identified through a rigorous review of the electronic medical records. Clinical infection was defined as cases with eminent infection (e.g., pneumonia, urinary tract infection) with or without the identification of specific pathogens, or cases with any organ infection by identified pathogens. Sepsis was defined as the presence of two or more of the following three items from the quick Sequential Organ Failure Assessment (SOFA) criteria, along with a suspected or documented infection according to the Sepsis-3 definition: 1) low blood pressure (systolic blood pressure, ≤100 mmHg), 2) high respiratory rate (≥22 rates per minutes), or 3) altered mental status (Glasgow coma scale [GCS] score, <14) [13]. Patients who met both the sepsis and AKI criteria were classified into the SA-AKI subgroup.

Data collection and primary outcome

The patients’ baseline demographic and clinical data were collected, including age, sex, cause of AKI, and comorbidities. Laboratory test results at the time of CKRT initiation were collected, including complete blood cell counts; coagulation; arterial blood gas; and electrolyte, bilirubin, creatinine, arterial lactate, CRP, and PCT levels. The mean arterial pressure, heart rate, respiratory rate, body temperature, partial pressure of oxygen in the arterial blood/fraction of inspired oxygen (PaO2/FiO2) ratio, GCS score, mechanical ventilator status, and inotropic administration status were recorded at the time of CKRT initiation. Based on the collected data, Acute Physiology and Chronic Health Evaluation II (APACHE II) [14] and SOFA [15] scores were calculated.

The primary outcome was the 28-day mortality, which was defined as death within 28 days of CKRT initiation.

Measurement of plasma presepsin

The plasma presepsin levels were measured using PATH-FAST Presepsin (LSI Science Corp.). Blood samples were collected in ethylenediaminetetraacetic acid tubes and stored at room temperature. Plasma presepsin levels were measured within 4 hours of collection, according to the manufacturer’s instructions. The assay range of plasma presepsin is 20 to 20,000 pg/mL and the coefficient of variation is 4% to 5% [16].

Statistical analysis

All continuous variables are expressed as mean ± standard deviation or median (interquartile range). The Student t test was used to compare variables showing a normal distribution, and the Mann-Whitney U test was used for variables showing a non-normal distribution. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate, and expressed as proportions. The predictive values of plasma presepsin, and APACHE II and SOFA scores, for 28-day mortality were analyzed using receiver operating characteristic (ROC) curve analysis in the overall cohort and the SA-AKI subgroup. The cutoff values were determined to simultaneously represent the highest sensitivity and specificity [17]. The Kaplan-Meier survival curve analysis was performed to compare patient survival between the high- and low-presepsin groups in the SA-AKI subgroup according to the cutoff value of plasma presepsin, which was compared using the log-rank test. Multivariate Cox proportional hazard regression analysis was performed to identify risk factors for 28-day mortality in the SA-AKI subgroup. Patients who were transferred to another medical institution within the 28 days after CKRT initiation were censored. A p-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS version 24 (IBM Corp.).

Results

Comparison of baseline characteristics between the survivor and non-survivor groups in the overall cohort and the sepsis-associated acute kidney injury subgroup

Twenty-eight days after CKRT initiation, 25 survivors and 32 non-survivors were included in the overall cohort. Presepsin measurement was conducted an average of 3.5 hours before CKRT initiation, and there was no significant difference between the survivor and non-survivor groups (3.4 hours in the survivor group vs. 3.6 hours in the non-survivor group, p = 0.86). Table 1 shows the baseline characteristics of the survivor and non-survivor groups.
Table 1. Comparison of baseline characteristics between the survivor and non-survivor groups in the overall cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivor group</th>
<th>Non-survivor group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>77.4 (64.2–84.4)</td>
<td>75.0 (61.8–81.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.0 (19.8–24.1)</td>
<td>24.2 (21.3–27.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male sex</td>
<td>8 (32.0)</td>
<td>14 (43.8)</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>88.0 (76.0–104.3)</td>
<td>72.6 (65.3–80.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>92.0 (82.0–102.0)</td>
<td>100.0 (82.5–121.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Respiratory rate (rates/min)</td>
<td>20.0 (16.5–23.0)</td>
<td>21.0 (17.2–28.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>36.8 (36.3–37.4)</td>
<td>37.0 (36.4–37.6)</td>
<td>0.54</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.308 ± 0.107</td>
<td>7.262 ± 0.146</td>
<td>0.19</td>
</tr>
<tr>
<td>Serum Na (mEq/L)</td>
<td>138.0 (134.0–141.5)</td>
<td>137.5 (132.0–141.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Serum K (mEq/L)</td>
<td>4.56 (3.99–5.55)</td>
<td>4.57 (3.77–6.00)</td>
<td>0.74</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>4.63 (2.79–7.91)</td>
<td>3.18 (1.79–4.26)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>32.7 (29.3–35.3)</td>
<td>34.3 (27.9–39.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>WBC count (×10^3/μL)</td>
<td>9.8 (7.2–13.8)</td>
<td>17.4 (6.0–22.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Platelet count (×10^3/μL)</td>
<td>168.0 (105.5–207.5)</td>
<td>135.0 (39.7–218.7)</td>
<td>0.33</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.62 (0.51–0.88)</td>
<td>1.31 (0.75–2.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>6.23 (5.26–6.74)</td>
<td>5.63 (5.08–6.81)</td>
<td>0.41</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.08 (2.66–3.57)</td>
<td>2.92 (2.58–3.31)</td>
<td>0.25</td>
</tr>
<tr>
<td>Arterial lactate (mmol/L)</td>
<td>1.90 (0.83–3.53)</td>
<td>7.70 (3.35–15.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>8.30 (1.05–22.73)</td>
<td>11.25 (2.65–25.55)</td>
<td>0.14</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>2.42 (0.65–12.80)</td>
<td>7.97 (1.74–37.47)</td>
<td>0.30</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>10.0 (7.0–13.0)</td>
<td>6.0 (3.0–13.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>222 (162–370)</td>
<td>166 (89–370)</td>
<td>0.32</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>11 (44.0)</td>
<td>22 (68.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Inotropes administration</td>
<td>16 (64.0)</td>
<td>30 (93.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>CKRT duration (day)</td>
<td>3.00 (2.00–6.00)</td>
<td>2.00 (1.00–4.75)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cause of AKI requiring CKRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac problem</td>
<td>2 (8.0)</td>
<td>7 (21.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14 (56.0)</td>
<td>21 (65.6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Renal problem</td>
<td>4 (16.0)</td>
<td>2 (6.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hepatic problem</td>
<td>2 (8.0)</td>
<td>0 (0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Pulmonary problem</td>
<td>1 (4.0)</td>
<td>0 (0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0 (0)</td>
<td>2 (6.3)</td>
<td>0.499</td>
</tr>
<tr>
<td>Neurogenic problem</td>
<td>0 (0)</td>
<td>1 (3.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Others</td>
<td>3 (12.0)</td>
<td>1 (3.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (60.0)</td>
<td>12 (37.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (76.0)</td>
<td>13 (40.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>17 (63.0)</td>
<td>10 (31.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cerebro-cardiovascular disease</td>
<td>4 (16.0)</td>
<td>6 (18.8)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>2 (8.0)</td>
<td>0</td>
<td>0.19</td>
</tr>
<tr>
<td>Liver disease</td>
<td>4 (16.0)</td>
<td>7 (21.9)</td>
<td>0.74</td>
</tr>
<tr>
<td>Dementia</td>
<td>3 (12.0)</td>
<td>3 (9.4)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Malignancy</td>
<td>5 (20.0)</td>
<td>9 (28.1)</td>
<td>0.55</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>6.24 ± 2.99</td>
<td>5.25 ± 2.60</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Data are expressed as number only, median (interquartile range), number (%), or mean ± standard deviation.

AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; K, potassium; Na, sodium; PaO₂/FiO₂, partial pressure of oxygen in arterial blood/fraction of inspired oxygen; WBC, white blood cell.
The mean arterial pressure and GCS score were significantly lower in the non-survivor group than in the survivor group, and the total bilirubin, arterial lactate levels, and inotrope administration rates were significantly higher in the non-survivor group than in the survivor group. Among the comorbidities, the prevalence of hypertension and chronic kidney disease was significantly lower in the non-survivor group than in the survivor group, and there was no difference in the Charlson Comorbidity Index (CCI) between the two groups. There were no differences between the two groups regarding other demographics, laboratory findings, or causes of AKI requiring CKRT.

Table 2 shows the baseline characteristics of survivors and non-survivors in the SA-AKI subgroup. Presepsin measurement was conducted an average of 3.7 hours before CKRT initiation, and there was no significant difference be-

### Table 2. Comparison of baseline characteristics between the survivor and non-survivor groups in the SA-AKI subgroup

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivor group</th>
<th>Non-survivor group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>77.0 (64.7–84.3)</td>
<td>74.7 (62.4–80.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.7 ± 2.5</td>
<td>24.0 ± 3.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Male sex</td>
<td>4 (28.6)</td>
<td>8 (38.1)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>89.0 (74.5–103.8)</td>
<td>72.6 (68.6–81.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90.6 ± 18.3</td>
<td>104.0 ± 25.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Respiratory rate (rates/min)</td>
<td>18.5 (16.0–22.0)</td>
<td>26.0 (18.0–30.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>36.9 (36.5–37.4)</td>
<td>37.1 (36.2–37.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.332 ± 0.094</td>
<td>7.272 ± 0.142</td>
<td>0.17</td>
</tr>
<tr>
<td>Serum Na (mEq/L)</td>
<td>139.3 ± 9.9</td>
<td>136.7 ± 6.3</td>
<td>0.35</td>
</tr>
<tr>
<td>Serum K (mEq/L)</td>
<td>4.29 (3.82–5.23)</td>
<td>4.22 (3.54–5.80)</td>
<td>0.40</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>5.13 (3.56–8.01)</td>
<td>3.16 (2.03–5.38)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34.0 (31.9–36.9)</td>
<td>35.3 (26.4–38.6)</td>
<td>0.39</td>
</tr>
<tr>
<td>WBC count (×10³/μL)</td>
<td>11.9 (8.2–16.1)</td>
<td>16.1 (3.65–23.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Platelet count (×10³/μL)</td>
<td>170.0 (94.5–231.5)</td>
<td>102.0 (33.0–207.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.66 (0.52–0.88)</td>
<td>1.47 (0.75–2.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>6.37 (5.04–6.94)</td>
<td>5.27 (4.50–6.78)</td>
<td>0.29</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.07 (2.54–3.65)</td>
<td>2.63 (2.41–3.24)</td>
<td>0.13</td>
</tr>
<tr>
<td>Arterial lactate (mmol/L)</td>
<td>2.2 (0.9–3.7)</td>
<td>6.6 (2.2–15.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>15.60 (2.00–25.05)</td>
<td>11.25 (3.53–27.45)</td>
<td>0.65</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>3.89 (0.73–14.74)</td>
<td>11.11 (1.95–37.79)</td>
<td>0.27</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td>10.0 (6.8–13.3)</td>
<td>6.0 (3.0–13.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>201 (152–268)</td>
<td>101 (87–292)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>6 (42.9)</td>
<td>14 (70)</td>
<td>0.16</td>
</tr>
<tr>
<td>Inotropes administration</td>
<td>10 (71.4)</td>
<td>19 (90.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>CKRT duration (day)</td>
<td>3.0 (2.0–5.25)</td>
<td>1.0 (0.5–5.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (57.1)</td>
<td>8 (38.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (92.9)</td>
<td>9 (62.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>10 (71.4)</td>
<td>8 (38.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cerebro-cardiovascular disease</td>
<td>3 (21.4)</td>
<td>3 (14.3)</td>
<td>0.66</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1 (7.1)</td>
<td>6 (28.6)</td>
<td>0.20</td>
</tr>
<tr>
<td>Dementia</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3 (21.4)</td>
<td>7 (33.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>7.00 (3.75–8.50)</td>
<td>5.00 (4.00–6.00)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Data are expressed as number only, median (interquartile range), mean ± standard deviation, or number (%).

CKRT, continuous kidney replacement therapy; K, potassium; Na, sodium; PaO₂/FiO₂, partial pressure of oxygen in arterial blood/fraction of inspired oxygen; SA-AKI, sepsis-associated acute kidney injury; WBC, white blood cell.
between the survivor and non-survivor groups (3.8 hours in the survivor group vs. 3.6 hours in the non-survivor group, p = 0.70). Similar to the overall cohort results, the mean arterial pressure was significantly lower in the non-survivor group than in the survivor group, and the respiratory rate, total bilirubin, and arterial lactate levels were significantly higher in the non-survivor group than in the survivor group. The prevalence of hypertension was significantly lower in the non-survivor group than in the survivor group, and there was no difference in the CCI between the two groups, similar to the overall cohort results. There were no significant differences in other demographics or laboratory findings between the two groups, other than serum creatinine levels.

Comparison of plasma presepsin levels, and APACHE II and SOFA scores, between the survivor and non-survivor groups in the overall cohort and the sepsis-associated acute kidney injury subgroup

Fig. 2 shows a comparison of the plasma presepsin levels, and the APACHE II and SOFA scores, between the survivor and non-survivor groups in the overall cohort. Plasma presepsin levels were not significantly different between the two groups (1,536 pg/mL in survivor group vs. 2,021 pg/mL in non-survivor group, p = 0.08) (Fig. 2A). In contrast, the APACHE II score (27.0 in survivor group vs. 31.0 in non-survivor group, p = 0.02) (Fig. 2B) and SOFA score (10.0 in survivor group vs. 13.5 in non-survivor group, p = 0.001) (Fig. 2C) were significantly higher in the non-survivor group than in the survivor group.

Fig. 3 shows the plasma presepsin levels, and the APACHE II and SOFA scores, of the survivor and non-survivor groups in the SA-AKI subgroup. In contrast to the overall cohort results, the plasma presepsin level was significantly higher in the non-survivor group than in the survivor group (1,509 pg/mL in survivor group vs. 3,049 pg/mL in non-survivor group, p = 0.002) (Fig. 3A). The APACHE II score tended to be higher in the non-survivor group (28.0 in survivor group vs. 31.0 in non-survivor group, p = 0.12) (Fig. 3B), although this result was not statistically significant. The SOFA score was significantly higher in the non-survivor group than in the survivor group (12.5 in survivor group vs. 14.0 in non-survivor group, p = 0.02) (Fig. 3C).
Comparison of plasma presepsin levels, and APACHE II and SOFA scores, between the survivor and non-survivor groups in the SA-AKI subgroup. Comparison of median (A) plasma presepsin levels, (B) APACHE II scores, and (C) SOFA scores between survivors and non-survivors in the SA-AKI subgroup. The median plasma presepsin level was 1,509 pg/mL in the survivor group and 3,049 pg/mL in the non-survivor group (p = 0.002). The median APACHE II score was 28.0 in the survivor group and 31.0 in the non-survivor group (p = 0.12). The median SOFA score was 12.5 in the survivor group and 14.0 in the non-survivor group (p = 0.02).

APACHE II, Acute Physiology and Chronic Health Evaluation II; SA-AKI, sepsis-associated acute kidney injury; SOFA, Sequential Organ Failure Assessment.

Predictive values of plasma presepsin, and APACHE II and SOFA scores, for 28-day mortality in the overall cohort and the sepsis-associated acute kidney injury subgroup

In the overall cohort, the SOFA score had the highest area under the ROC curve (AuROC) value (0.731; 95% confidence interval [CI], 0.599–0.863), followed by the APACHE II score (0.663; 95% CI, 0.521–0.804). Plasma presepsin showed the lowest predictive value, with an AuROC value of 0.636 (95% CI, 0.491–0.781) (Fig. 4A). However, in the ROC curve analysis performed in the SA-AKI subgroup, the AuROC value of plasma presepsin was 0.799 (95% CI, 0.653–0.946), which was a significantly better predictive value than the APACHE II and SOFA scores; the AuROC value of the APACHE II score = 0.638 (95% CI, 0.450–0.826) and the AuROC value of the SOFA score = 0.697 (95% CI, 0.519–0.875) (Fig. 4B).

In the SA-AKI subgroup, patients were classified into the high- and low-presepsin groups based on a plasma presepsin cutoff level of 1,951 pg/mL. The Kaplan-Meier survival curve analysis showed that the survival rate of the high-presepsin group was prominently decreased (log-rank p < 0.001) (Fig. 5).

Multivariate Cox regression analysis for 28-day mortality in the sepsis-associated acute kidney injury subgroup

Table 3 shows the results of the multivariate Cox proportional hazard regression analysis performed to identify the risk factors affecting 28-day mortality in the SA-AKI subgroup. The analysis included known significant factors (age, PaO2/FiO2 ratio, and the CCI), baseline characteristics that showed statistically significant differences between the two groups (mean arterial pressure, respiratory rate, serum creatinine level, total bilirubin level, presence of hypertension, and presence of chronic kidney disease), high arterial lactate (lactate level ≥3.10 mmol/L), high CRP (CRP level ≥17.45 mg/dL), high PCT (PCT level ≥7.36 ng/mL), and high presepsin (plasma presepsin level ≥1,951 pg/mL) (for cutoff levels of arterial lactate, PCT, and CRP) (Supplementary Fig. 1, available online). The univariate hazard ratio (HR) of a high presepsin level was 4.723 (95% CI, 1.698–13.136); even after adjusting for several confounding factors, it was an independent risk factor with a multivariate HR of 3.437 (95% CI, 1.126–10.491).
Figure 4. Predictive values of plasma presepsin levels, and APACHE II and SOFA scores, for 28-day mortality in the overall cohort and SA-AKI subgroup. (A) the receiver operating characteristic (ROC) curve analysis in the overall cohort. Plasma presepsin showed the lowest area under the ROC (AuROC) value, compared with the APACHE II and SOFA scores. (B) The ROC curve analysis in the SA-AKI subgroup. Plasma presepsin showed the highest AuROC value, compared with the APACHE II and SOFA scores. APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; SA-AKI, sepsis-associated acute kidney injury; SOFA, Sequential Organ Failure Assessment.

Discussion

The plasma presepsin level was not a useful marker for predicting 28-day mortality in the overall study cohort undergoing CKRT for AKI. However, in the SA-AKI subgroup, plasma presepsin levels were superior to the APACHE II and SOFA scores in predicting 28-day mortality. Additionally, there was a significant difference in patient survival between the high- and low-presepsin groups according to the plasma presepsin cutoff value. Furthermore, in the multivariate Cox regression analysis, a high presepsin level was observed to be an independent risk factor for 28-day mortality.

Regarding the baseline characteristics of the overall cohort, non-survivors showed significant differences in mean arterial pressure, GCS score, total bilirubin, arterial lactate, and inotrope administration proportions compared with survivors. These are components of the APACHE II and SOFA scores, which are well-known scoring systems for the evaluation of critically ill patients. The results of this study are consistent with those of previous studies [18–20]. The prevalence of chronic kidney disease was higher in the survivor group than in the non-survivor group. This may be because the rate of CKRT initiation for renal problems was higher in the survivor group than in the non-survivor group (16.0%, survivor group vs. 6.3%, non-survivor group). The prevalence of hypertension was higher in the survivor group than in the non-survivor group; however, it is difficult to provide a clear explanation for this. The number of patients analyzed in this study was small, and since this was a retrospective study, the possibility of bias during the data collection process cannot be ruled out. The baseline characteristics of the SA-AKI subgroup also showed significant differences in the components of the APACHE II and
Figure 5. The Kaplan-Meier survival curve analysis according to plasma presepsin levels in the SA-AKI subgroup. The SA-AKI subgroup was further classified into high- and low-presepsin groups based on the cutoff plasma presepsin level of 1,951 pg/mL observed through receiver operating characteristic curve analysis. The high-presepsin group showed a prominent decrease in the survival rate compared to the low-presepsin group. After 28 days of continuous kidney replacement therapy, the survival rates of the high- and low-presepsin groups were 15.8% and 68.8%, respectively.

SA-AKI, sepsis-associated acute kidney injury.

Table 3. Multivariate Cox regression analysis for 28-day mortality in the SA-AKI subgroup

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR (95% CI)</th>
<th>Multivariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.985 (0.954–1.017)</td>
<td>-</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>0.977 (0.958–0.997)*</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>1.028 (1.007–1.050)*</td>
<td>1.026 (1.002–1.050)*</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.843 (0.712–0.997)*</td>
<td>-</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.140 (1.048–1.241)*</td>
<td>-</td>
</tr>
<tr>
<td>PaO₂/FIO₂ ratio</td>
<td>0.998 (0.995–1.002)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension (Ref., no)</td>
<td>0.333 (0.138–0.806)*</td>
<td>-</td>
</tr>
<tr>
<td>Chronic kidney disease (Ref., no)</td>
<td>0.426 (0.175–1.036)</td>
<td>-</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.969 (0.772–1.216)</td>
<td>-</td>
</tr>
<tr>
<td>High arterial lactate (Ref., &lt;3.10 mmol/L)</td>
<td>3.606 (1.294–10.046)*</td>
<td>-</td>
</tr>
<tr>
<td>High CRP (Ref., &lt;17.45 mg/dL)</td>
<td>1.217 (0.504–2.939)</td>
<td>-</td>
</tr>
<tr>
<td>High PCT (Ref., &lt;7.36 ng/mL)</td>
<td>2.050 (0.817–5.145)</td>
<td>-</td>
</tr>
<tr>
<td>High presepsin (Ref. &lt;1,951 pg/mL)</td>
<td>4.723 (1.698–13.136)*</td>
<td>3.437 (1.126–10.491)*</td>
</tr>
</tbody>
</table>

The multivariate regression model was adjusted for known significant factors and those that showed statistical differences between the survivor and non-survivor groups. The data of 26 patients (74.3%) were included in the regression model. The following parameters were used: age, mean arterial pressure, respiratory rate, serum creatinine level, total bilirubin level, PaO₂/FIO₂ ratio, presence of hypertension, presence of chronic kidney disease, Charlson Comorbidity Index, high arterial lactate, high CRP, high PCT, and high presepsin levels.

CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; PaO₂/FIO₂, partial pressure of oxygen in arterial blood/fraction of inspired oxygen; PCT, procalcitonin; Ref., reference; SA-AKI, sepsis-associated acute kidney injury.

*p < 0.05.
SOFA scores (mean arterial pressure, respiratory rate, total bilirubin, and arterial lactate), similar to those of the overall cohort.

The APACHE II and SOFA scores were observed to have relatively good predictive values for 28-day mortality in both the overall cohort and the SA-AKI subgroup, confirming that they are reliable indicators for evaluating critically ill patients [21–23]. In contrast, plasma presepsin showed poor predictive power for 28-day mortality in the overall cohort; however, in the SA-AKI subgroup, plasma presepsin was a better predictor of 28-day mortality than the APACHE II and SOFA scores. In other words, because plasma presepsin is affected by kidney function, its usefulness may be reduced in cases where kidney function changes dynamically, such as in AKI patients requiring CKRT. In contrast, presepsin is highly specific to infection, rises quickly during infection, and has a short half-life; therefore, in the case of SA-AKI, plasma presepsin measured before CKRT initiation can better reflect the severity of infection [9,24,25]. This study showed that plasma presepsin could be a useful prognostic indicator in patients with SA-AKI undergoing CKRT.

In the SA-AKI subgroup, the Kaplan-Meier survival analysis, performed in the high- and low-presepsin groups according to the plasma presepsin cutoff level of 1,951 pg/mL, showed a clear difference in the survival rate between the two groups. The 28-day survival rates in the high-presepsin and low-presepsin groups were 15.8% and 68.8%, respectively. Furthermore, in the multivariate Cox regression analysis, which included several confounding factors reflecting patient prognosis, plasma presepsin was observed to be an independent risk factor for predicting 28-day mortality in the SA-AKI subgroup. Additionally, in the multivariate Cox regression analysis, performed using the APACHE II and SOFA scores, plasma presepsin remained an independent risk factor (Supplementary Table 1, available online). The results of this study are expected to help determine patient prognosis by measuring plasma presepsin levels before CKRT initiation in patients with SA-AKI in clinical settings. Furthermore, screening patients with high plasma presepsin levels and providing them with more meticulous management can improve patient prognosis.

Arterial lactate, CRP, and PCT levels are widely used laboratory indicators; their correlation with plasma presepsin levels was analyzed. The correlations between plasma presepsin and CRP levels, and between plasma presepsin and PCT levels, showed a moderate correlation (Spearman’s $\rho = 0.482$ and Spearman’s $\rho = 0.546$, respectively). However, plasma presepsin and arterial lactate levels showed no correlation (Spearman’s $\rho = 0.033$) (Supplementary Fig. 2, available online). In particular, arterial lactate showed good AuROC values in both the overall cohort and the SA-AKI subgroup (Supplementary Fig. 1, available online). This appears to be because arterial lactate is not infection-specific and increases in all situations with tissue hypoxia. On the other hand, plasma presepsin showed a notable increase in AuROC value in the SA-AKI subgroup, showing a predictive value comparable to that of arterial lactate, which was superior to CRP or PCT (Supplementary Fig. 1, available online). This result is consistent with those of previous studies that analyzed the prognostic value of plasma presepsin, CRP, and PCT levels in critically ill patients [26,27]. In this study, we observed a novel finding that the 28-day mortality predictive power of plasma presepsin was superior to that of CRP or PCT, even in patients who underwent CKRT for SA-AKI.

This study had several limitations. First, it was a single-center retrospective study and the number of patients analyzed was relatively small. In this study, the highest AuROC value of plasma presepsin was observed in the SA-AKI subgroup, but the Delong test results with the AuROC values of APACHE II and SOFA scores did not show statistical significance (Delong test $p = 0.19$ for plasma presepsin vs. APACHE II score, Delong test $p = 0.30$ for plasma presepsin vs. SOFA score). These results may be due to the small sample size of this study. Second, the Simplified Acute Physiology Score 3 (SAPS 3) was not used as an indicator to evaluate critically ill patients in this study. In a previous study, SAPS 3 was reported to be superior to the APACHE II and SOFA scores [28]. However, the SAPS-3 score is calculated using results at the time of intensive care unit (ICU) admission. Because we had to analyze patient data at the time of CKRT, not at ICU admission, we used APACHE II and SOFA scores. Third, the APACHE II score is already a well-known, reliable indicator for evaluating critically ill patients, but in this study, in the SA-AKI subgroup, although the APACHE II score tended to be higher in the non-survivor group, there was no statistical significance ($p = 0.12$). We are not able to rule out the possibility that this was due to the significantly lower serum creatinine level and the prevalence of hyper-
tension in the non-survivor group. These results imply that several confounding factors may have intervened due to the small sample size of this study. However, despite these limitations, this study is considered valuable in that it identified the potential utility of plasma presepsin in patients requiring CKRT for SA-AKI for the first time.

In conclusion, plasma presepsin levels had the highest predictive power for 28-day mortality compared to the well-known APACHE II and SOFA scores in the SA-AKI subgroup. It was also found to be an independent risk factor after adjusting for other risk factors. Additionally, plasma presepsin was the most useful biomarker of 28-day mortality, compared to PCT and CRP, in the SA-AKI subgroup. Therefore, the plasma presepsin level has the potential to be a strong prognostic indicator in patients with SA-AKI receiving CKRT. The usefulness of plasma presepsin levels in individuals undergoing CKRT should be studied in a larger cohort.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions

Conceptualization, Formal analysis: GBL, YP
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References


The role of nafamostat mesylate anticoagulation in continuous kidney replacement therapy for critically ill patients with bleeding tendencies: a retrospective study on patient outcomes and safety

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Background: Continuous kidney replacement therapy (CKRT) is crucial in the management of acute kidney injury in intensive care units (ICUs). Nonetheless, the optimal anticoagulation strategy for patients with bleeding tendencies remains debated. This study aimed to evaluate patient outcomes and safety of nafamostat mesylate (NM) compared with no anticoagulation (NA) in critically ill patients with bleeding tendencies who were undergoing CKRT.

Methods: This retrospective study enrolled 2,313 patients who underwent CKRT between March 2013 and December 2022 at the third affiliated hospital in South Korea. After applying the exclusion criteria, 490 patients were included in the final analysis, with 245 patients in the NM and NA groups each, following 1:1 propensity score matching. Subsequently, in-hospital mortality, incidence of bleeding complications, agranulocytosis, hyperkalemia, and length of hospital stay were assessed.

Results: No significant differences were observed between the groups regarding the lengths of hospital and ICU stays or the incidence of agranulocytosis and hyperkalemia. The NM group showed a smaller decrease in hemoglobin levels during CKRT (–1.90 g/dL vs. –2.39 g/dL) and less need for blood product transfusions than the NA group. Furthermore, the NM group exhibited a survival benefit in patients who required transfusion of all three blood products.

Conclusion: NM is an effective and safe anticoagulant for CKRT in critically ill patients, especially those requiring transfusion of all three blood products. Although these findings are promising, further multicenter studies are needed to validate them and explore the mechanisms underlying the observed benefits.

Keywords: Acute kidney injury, Anticoagulants, Continuous kidney replacement therapy, Intensive care units, Continuous renal replacement therapy

Introduction

Acute kidney injury (AKI) is observed in 5% to 70% of critically ill patients admitted to the intensive care unit (ICU) [1–4], including 14% to 30% of patients with stage 3 disease requiring kidney replacement therapy [1,2,5]. Despite continuous advancements in intensive care, the mortality rate of ICU patients with AKI remains high [1,6], underscoring
the need for AKI prevention [1,7], early nephrology consultations [8], and more proactive therapeutic approaches. Continuous kidney replacement therapy (CKRT) is frequently applied to ICU patients with AKI, especially to those with hemodynamic instabilities [9,10].

Effective CKRT requires anticoagulation therapy to the extracorporeal circuit [10]. However, while regional citrate anticoagulation is recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) Organization [11], it is not always feasible because of national or institutional circumstances [12,13]. Systemic heparin anticoagulation is an alternative for patients without bleeding tendencies; in cases with bleeding tendencies, no anticoagulation (NA) is suggested because both systemic and regional heparin should be avoided [12]. However, with NA, the filter life is short [14,15]; thus, an anticoagulation strategy is required [11].

Nafamostat mesylate (NM) is a low-molecular-weight synthetic inhibitor of serine proteases that include coagulation factors such as factors VIIa, IXa, Xa, XIIa, and thrombin [16–18]. Due to the short half-life of NM (8–10 minutes) [16,19], it is rapidly eliminated from the blood upon infusion termination. This property allows the use of NM as a circuit anticoagulant for CKRT in patients with bleeding tendencies [20]. In South Korea, NM has been approved as an anticoagulant for CKRT since 2005 and is widely used in patients with bleeding tendencies.

Nevertheless, the 2012 KDIGO guidelines do not recommend NM anticoagulation during CKRT because of possible side effects such as agranulocytosis, hyperkalemia, and anaphylactoid reactions [12,21,22]. To date, several randomized controlled trials (RCTs) and retrospective studies have shown the benefits of NM compared with NA regarding filter life [14,15,23–25]; however, studies exploring the safety of these modalities have not been performed. Herein, we evaluated the safety of NM and NA in critically ill patients undergoing CKRT.

Methods

Study design and population

This retrospective study included data from consecutive adult patients (aged >18 years) who underwent CKRT between March 2013 and December 2022 at the third affiliated hospital in South Korea. Patients with end-stage kidney disease undergoing maintenance dialysis, those with missing information regarding anticoagulation, those who received heparin-based anticoagulation, and those with hospital stays >90 days since the start of CKRT were excluded.

The study protocol was approved by the Institutional Review Board of Pusan National University (No. 2305-023-127), which waived the requirement for informed consent.

Data collection and definition

The parameters examined included patient demographics, comorbidities, disease severity at CKRT initiation, and laboratory findings during CKRT. Demographic information was obtained from nurses’ charts, and comorbidity information was obtained from physicians’ notes. Disease severity was assessed using the Sequential Organ Failure Assessment (SOFA) score [26]. Baseline laboratory parameters at the time of CKRT initiation, laboratory parameters such as hemoglobin and potassium levels and platelet counts, and transfusion records of any blood products during CKRT were extracted from the electronic medical records.

Bleeding complications were indirectly assessed through the delta change of hemoglobin (lowest hemoglobin – initial hemoglobin at start of CKRT, g/dL) and transfusion requirements during CKRT. Hyperkalemia was defined as a serum level of potassium exceeding 5.5 mg/dL at the start of CKRT, and severe hyperkalemia was defined as potassium exceeding 7.0 mg/dL [27]. Absolute neutrophil count (ANC) was calculated in the following way: ANC (cells/µL) = total white blood cell count (×10^9/µL) × percentage of segmented neutrophils [28]. Neutropenia or severe neutropenia was defined as an ANC <1,000 cells/µL or <500 cells/µL, and agranulocytosis as an ANC <100 cells/µL [29].

CKRT data included the mode, prescribed and delivered doses, the anticoagulation method, downtime, actual CKRT time, and the number of filters used. Filter life was defined as the actual CKRT time (in hours) divided by the total number of filters used [30]. Downtime was calculated in the following way: downtime (%) = [1 – (actual CKRT time/total intended CKRT time)] × 100 [31]. Information regarding in-hospital mortality was collected by reviewing the medical charts.
Continuous kidney replacement therapy and nafamostat mesylate anticoagulation

Details of the CKRT procedure have been reported in a previous study [32]. In short, CKRT was initiated at the discretion of the attending physician and implemented and managed by a specialized CKRT team. The decision to terminate CKRT or switch to conventional hemodialysis was made by the attending physician or an experienced nephrologist. A Baxter Prismaflex instrument with an AN69ST membrane (Baxter International Inc.) was used to deliver CKRT, using heparin as the primary anticoagulant. In the event of bleeding tendencies, either NM or NA was chosen. The NM infusion was prepared by dissolving 100 mg NM in 5% dextrose, resulting in a total volume of 20 mL (5 mg NM/mL). The NM solution was administered at an infusion rate of 2 mL/hr (10 mg NM/hr) using an anticoagulant infusion device mounted on the Prismaflex. If filter clotting was frequently observed, the NM concentration was doubled (10 mg NM/mL) and infused at a rate of 2 mL/hr (20 mg NM/hr). In the NA group, the anticoagulant was replaced with 20 mL of normal saline.

Outcomes

The primary outcome was in-hospital mortality. Because not all deaths in hospitals are directly associated with CKRT-anticoagulation methods, we additionally evaluated the deaths observed during CKRT operation (CKRT mortality) and ICU stay (ICU mortality). Secondary outcomes were the safety of NM; incidences of bleeding complications, agranulocytosis, and hyperkalemia; overall length of hospital stay; length of ICU stay; CKRT duration; and filter life.

Statistical analysis

The normality of the data was determined using the Kolmogorov-Smirnov test. Continuous variables are expressed as medians and interquartile ranges or means ± standard deviations. The differences between the two groups were compared using the Student t test, chi-square test, or Mann-Whitney U test, as appropriate. A non-parsimonious multivariate logistic regression model was used for 1:1 propensity score matching (PSM). Rigorous adjustments for significant differences in the patients’ baseline characteristics, including SOFA scores, serum hemoglobin levels, platelet counts, and prothrombin times (PTs) at CKRT initiation, were performed based on a caliper width of 0.05 standard deviations of the propensity score and no replacement. The Kaplan-Meier survival curves were plotted to compare in-hospital mortality. The proportion of patients who received transfusions and the incidence rates of agranulocytosis or hyperkalemia were compared using the Pearson chi-square test. Differences in the time from hyperkalemia to normokalemia between groups were compared using a t test of means. Statistical significance was set at p < 0.05. IBM SPSS version 28.0 (IBM Corp.) was used for statistical analysis.

Results

Patient characteristics

Between January 2013 and December 2022, 3,475 adult patients underwent CKRT at the third affiliated hospital. After excluding 519 patients (14.9%) with end-stage kidney disease, 24 patients (0.7%) without information regarding anticoagulation, 221 patients (6.4%) who underwent heparin anticoagulation, and 79 patients (2.3%) with a hospital stay >90 days after CKRT initiation, the study population consisted of 2,632 patients (Fig. 1), including 1,850 patients (70.3%) who received NM and 782 patients (29.7%) who received NA. In the primary cohort, patients in the NM group were older and had lower SOFA scores, higher serum platelet counts, and shorter prothrombin times compared to those in the NA group; however, after 1:1 PSM, the two groups were well-balanced regarding all baseline characteristics, including comorbidities, disease severity, and laboratory test results, except for the slightly higher proportion of surgical patients in the NA group compared to that of the NM group (Table 1). In the 1:1 PSM model, each group included 245 patients (65.8% males) with a mean age of 63.2 years; 35.6% had diabetes mellitus and 18.4% had cancer. At the time of CKRT initiation, the mean SOFA score was 12.4; sepsis was present in 54.7% and anuria in 68.0% of the patients. Details of the parameters before and after PSM are provided in Table 1, and a specific score for each SOFA parameter is described in Supplementary Table 1 (available online). In both groups, CKRT was performed.
Figure 1. Baseline characteristics of patients. Among the 3,475 patients who required continuous kidney replacement therapy (CKRT), 1,162 patients were excluded based on the exclusion criteria. After 1:1 propensity score matching, 490 patients were included; 245 in the no anticoagulation group and 245 in the nafamostat mesylate group. ESKD, end-stage kidney disease.

Patient outcomes

Information regarding the survival status was available for 489 (99.8%) of the 490 patients. The in-hospital mortality was significantly lower in the NM group (143 of 245, 58.4%) than in the NA group (169 of 244, 69.3%; p = 0.012). The Kaplan-Meier survival plot indicated better survival in patients who received NM than in patients who received NA (Fig. 2).

In the NM group, 121 patients (49.4%) died during CKRT compared with 128 patients (52.7%) in the NA group; the difference was significant (p = 0.003). Deaths in the ICU were less common in the NM group (135 of 245, 55.2%) than in the NA group (164 of 244, 67.4%; p = 0.009).

The lengths of ICU and hospital stays were similar for both groups. The mean length of ICU stay was 12.63 ± 16.40 days for the NM group and 10.80 ± 12.05 days for the NA group (p = 0.16), while the mean length of hospital stay was 25.29 ± 28.24 days for the NM group and 21.46 ± 23.45 days for the NA group (p = 0.11).

Incidences of bleeding complications, agranulocytosis, and hyperkalemia

The delta change in hemoglobin was -2.39 ± 2.14 and -1.90 ± 1.90 g/dL in the NA and NM groups, respectively, being significantly higher in the NA than in the NM group (p = 0.009). During CKRT, any kind of blood product transfusion was required in 353 patients (72.0%), with transfusion being less frequent in the NM group (164 of 245, 66.9%) than in the NA group (189 of 245, 77.1%; p = 0.01). By specific blood product component, the requirements for each red blood cells (RBC), platelet concentrate, or fresh frozen plasma transfusion were significantly higher in the NA group than in the NM group, and the proportion of patients requiring all three types of blood components was significantly higher in the NA group than in the NM group (Fig. 3; Supplementary Table 2, available online).

During CKRT, agranulocytosis (ANC <100 cells/µL) developed in 34.6% (n = 47) of patients; the difference between the two groups was not significant (NM vs. NA, 35.0% vs. 34.1%; p = 0.85). The incidence of neutropenia or severe neutropenia (ANC <1,000 cells/µL or <500 cells/µL) was also similar between the two groups (Fig. 4).

At the time of CKRT initiation, hyperkalemia (serum potassium [serum K] >5.5 mmol/L) and severe hyperkalemia (serum K >7.0 mmol/L) were observed in 19.2% (n = 94) and 5.3% (n = 26) of the patients, respectively. During CKRT, serum K levels gradually decreased in both groups, without any differences between days 2 and 3 of CKRT. The mean time from hyperkalemia (serum K >5.5 mmol/L) to normokalemia (serum K <4.5 mmol/L) was 19.2 ± 13.3 hours in the NM group and 17.9 ± 14.8 hours in the NA group; the difference was not significant (p = 0.72). Similarly, the mean time required to correct severe hyperkalemia (serum K >7.0 mmol/L) to normokalemia (serum K <4.5 mmol/L) showed no significant difference between the two groups (Fig. 5; Supplementary Table 3, available online).

The mean filter life was 21.25 ± 12.01 hours in the NM group, which was not statistically different from the 19.67
### Table 1. Baseline characteristics of patients

<table>
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<tr>
<th>Characteristic</th>
<th>Before PSM</th>
<th>Nafamostat mesylate</th>
<th>p-value</th>
<th>After PSM</th>
<th>Nafamostat mesylate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>782 (29.7)</td>
<td>1,850 (70.3)</td>
<td></td>
<td>245</td>
<td>245</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age (yr)</td>
<td>62.62 ± 14.82</td>
<td>66.49 ± 14.05</td>
<td>&lt;0.001*</td>
<td>63.11 ± 14.43</td>
<td>63.22 ± 14.75</td>
<td>0.93</td>
</tr>
<tr>
<td>Male sex</td>
<td>65.9</td>
<td>62.2</td>
<td>0.07</td>
<td>67.8</td>
<td>63.7</td>
<td>0.34</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 ± 0.10</td>
<td>1.63 ± 0.08</td>
<td>0.45</td>
<td>1.63 ± 0.12</td>
<td>1.65 ± 0.10</td>
<td>0.07</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.32 ± 14.53</td>
<td>63.12 ± 22.38</td>
<td>0.02*</td>
<td>65.39 ± 14.43</td>
<td>64.67 ± 14.51</td>
<td>0.60</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.17 ± 4.46</td>
<td>23.47 ± 9.24</td>
<td>0.07</td>
<td>24.15 ± 4.48</td>
<td>23.38 ± 4.20</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30.5</td>
<td>49.9</td>
<td>&lt;0.001*</td>
<td>36.7</td>
<td>34.4</td>
<td>0.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36.2</td>
<td>57</td>
<td>&lt;0.001*</td>
<td>41.7</td>
<td>50.8</td>
<td>0.31</td>
</tr>
<tr>
<td>Cancer</td>
<td>26.9</td>
<td>18.7</td>
<td>&lt;0.001*</td>
<td>18.4</td>
<td>18.3</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Department</strong></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Medical</td>
<td>65.6</td>
<td>87.4</td>
<td>&lt;0.001*</td>
<td>62.0</td>
<td>88.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Surgical</td>
<td>34.4</td>
<td>12.6</td>
<td>&lt;0.001*</td>
<td>38.0</td>
<td>11.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score</td>
<td>12.48 ± 3.66</td>
<td>9.85 ± 3.81</td>
<td>&lt;0.001*</td>
<td>12.43 ± 3.29</td>
<td>12.68 ± 3.53</td>
<td>0.35</td>
</tr>
<tr>
<td>SOFA score ≥10</td>
<td>78.9</td>
<td>52.8</td>
<td>&lt;0.001*</td>
<td>77.6</td>
<td>79.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Sepsis</td>
<td>44.6</td>
<td>41.7</td>
<td>0.33</td>
<td>49.5</td>
<td>59.8</td>
<td>0.13</td>
</tr>
<tr>
<td>Anuria</td>
<td>65.0</td>
<td>70.0</td>
<td>0.02*</td>
<td>64.9</td>
<td>71.1</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>CKRT treatment mode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVVHDF</td>
<td>100</td>
<td>100</td>
<td>-</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Prescribe dose (mL/kg/hr)</td>
<td>38.46 ± 11.46</td>
<td>38.53 ± 12.68</td>
<td>0.89</td>
<td>38.76 ± 5.35</td>
<td>38.17 ± 5.21</td>
<td>0.23</td>
</tr>
<tr>
<td>Delivered dose (mL/kg/hr)</td>
<td>33.61 ± 6.60</td>
<td>33.44 ± 6.38</td>
<td>0.57</td>
<td>33.94 ± 6.15</td>
<td>34.13 ± 6.10</td>
<td>0.74</td>
</tr>
<tr>
<td>Downtime (%)</td>
<td>4.69 ± 9.95</td>
<td>5.69 ± 11.01</td>
<td>0.04*</td>
<td>4.59 ± 9.82</td>
<td>4.34 ± 9.33</td>
<td>0.78</td>
</tr>
<tr>
<td>Days on CKRT</td>
<td>6.00 ± 7.43</td>
<td>5.47 ± 6.16</td>
<td>0.08</td>
<td>5.73 ± 7.52</td>
<td>5.31 ± 6.47</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Laboratory test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (&gt;10³/μL)</td>
<td>12.83 ± 12.13</td>
<td>14.28 ± 14.05</td>
<td>0.01*</td>
<td>13.05 ± 12.24</td>
<td>12.72 ± 11.73</td>
<td>0.76</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.86 ± 3.39</td>
<td>10.68 ± 4.99</td>
<td>&lt;0.001*</td>
<td>9.94 ± 2.68</td>
<td>10.48 ± 5.44</td>
<td>0.17</td>
</tr>
<tr>
<td>Platelet (&gt;10³/μL)</td>
<td>101.88 ± 86.05</td>
<td>170.65 ± 113.66</td>
<td>&lt;0.001*</td>
<td>104.74 ± 97.57</td>
<td>105.52 ± 71.87</td>
<td>0.92</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>5.02 ± 1.21</td>
<td>5.83 ± 3.83</td>
<td>&lt;0.001*</td>
<td>4.98 ± 1.23</td>
<td>5.32 ± 1.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.96 ± 2.88</td>
<td>3.13 ± 0.97</td>
<td>0.03*</td>
<td>2.78 ± 0.64</td>
<td>2.89 ± 0.65</td>
<td>0.047</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>3.57 ± 5.59</td>
<td>1.66 ± 3.49</td>
<td>&lt;0.001*</td>
<td>2.81 ± 5.82</td>
<td>2.45 ± 2.91</td>
<td>0.66</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>50.82 ± 33.02</td>
<td>58.87 ± 35.96</td>
<td>&lt;0.001*</td>
<td>46.94 ± 33.99</td>
<td>54.82 ± 33.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.88 ± 3.53</td>
<td>4.34 ± 5.93</td>
<td>&lt;0.001*</td>
<td>2.97 ± 5.75</td>
<td>3.67 ± 2.84</td>
<td>0.09</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.71 ± 3.45</td>
<td>7.76 ± 3.71</td>
<td>0.86</td>
<td>8.00 ± 3.13</td>
<td>8.58 ± 4.29</td>
<td>0.40</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>7.87 ± 1.35</td>
<td>8.22 ± 1.31</td>
<td>&lt;0.001*</td>
<td>7.74 ± 1.10</td>
<td>7.94 ± 1.65</td>
<td>0.44</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.85 ± 2.67</td>
<td>5.72 ± 2.61</td>
<td>0.52</td>
<td>6.06 ± 3.05</td>
<td>5.91 ± 2.60</td>
<td>0.77</td>
</tr>
<tr>
<td>PT, INR</td>
<td>2.20 ± 2.00</td>
<td>1.53 ± 0.98</td>
<td>&lt;0.001*</td>
<td>2.05 ± 1.20</td>
<td>1.83 ± 1.56</td>
<td>0.07</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>65.07 ± 42.21</td>
<td>52.52 ± 36.27</td>
<td>&lt;0.001*</td>
<td>75.17 ± 48.81</td>
<td>67.35 ± 46.62</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are expressed as number (%), number only, mean ± standard deviation, or percentage only.
aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; CKRT, continuous kidney replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; INR, International normalized ratio; PSM, propensity score matching; PT, prothrombin time; SOFA score, Sequential Organ Failure Assessment score; WBC, white blood cell.

*Departments refer to the units to which patients were admitted. Medical department includes Departments of Internal Medicine, Emergency Medicine, Neurology, Rehabilitation Medicine, and Pediatrics. Surgical department includes Departments of General Surgery, Neurosurgery, Thoracic Surgery, Obstetrics And Gynecology, Orthopedic Surgery, Urology, Ophthalmology, and Dental Surgery.

*p < 0.05, statistically significant.
± 12.67 hours value in the NA group (p = 0.19) (Fig. 6). The downtime per 24 hours was similar (Table 1).

**Differences in the beneficial effect of nafamostat mesylate on patient outcome by transfusion requirement**

A total of 149 (30.4%), 114 (23.3%), and 90 patients (18.4%) required transfusion of three, two, and one blood product, respectively. In the Kaplan–Meier survival analysis, the survival benefit of NM was the highest in patients who required transfusion of all three blood products (log-rank p = 0.01, Fig. 7A), whereas no significant differences were observed in patients requiring less than three kinds of blood products (any combination of two blood product types: log-rank p = 0.30, Fig. 7B; just one blood product type: log-rank p = 0.74, Fig. 7C).
Differences in the beneficial effect of nafamostat mesylate on patient outcomes between medical and surgical patients

Of 490 patients, 369 (75.3%) were medical and 121 (24.7%) were surgical patients. Surgical patients more frequently required transfusions of all three blood products (63 of 121, 52.1%) compared to medical patients (86 of 369, 23.3%). In the Kaplan-Meier survival analysis, surgical patients showed a higher survival benefit of NM at hospital mortality (log-rank p = 0.03), while the benefit was less pronounced in medical patients (log-rank p = 0.29). CKRT mortality and ICU mortality showed the same trend (Supplementary Fig. 1, available online).

Discussion

Herein, the outcomes of patients treated with NM anticoagulation for CKRT and the safety of NM were evaluated. Both in-hospital mortality and incidences of bleeding complications were significantly lower in the NM group than in the NA group. The incidence of agranulocytosis during CKRT did not differ between the groups, and the time from hyperkalemia to normokalemia was not significantly prolonged by NM anticoagulation therapy. To our knowledge, this is the first study to assess the safety of NM anticoagulation for CKRT following the publication of the KDIGO 2012 anticoagulation guidelines [12].

The survival benefits conferred by NM compared with NA can be attributed to a decrease in the incidence of bleeding complications in patients administered NM. Both the hemoglobin changes during CKRT and transfusion requirements were significantly lower in the NM group than in the NA group. A potential criticism of this result could be selection bias due to the retrospective design of this study. The primary cohort without PSM indicated that younger patients with higher SOFA scores and more pronounced laboratory abnormalities (lower platelet count, longer PT or activated partial thromboplastin time) received NA, whereas patients with milder conditions received NM. Im-

![Figure 4](image1.png)

**Figure 4.** Incidence of neutropenia, severe neutropenia, and agranulocytosis during continuous kidney replacement therapy. ANC, absolute neutrophil count; NA, no anticoagulation; NM, nafamostat mesylate.

![Figure 5](image2.png)

**Figure 5.** Analysis of hyperkalemia. (A) Changes in serum potassium (serum K) levels according to the duration of continuous kidney replacement therapy (CKRT). (B) Time to the correction of serum K levels to <4.5 mmol/L by CKRT. CI, confidence interval; NA, no anticoagulation; NM, nafamostat mesylate.
portantly, we controlled these baseline differences using a PSM model, and analysis was performed with the same baseline characteristics, which strengthened the novelty of our findings. In previous RCTs and meta-analyses, NM did not have a significant effect on patient mortality or bleeding complications [24,25,33]. However, in these studies, in-hospital mortality or bleeding complications were not the primary outcomes, and the study populations were relatively small (20–30 patients per group). In addition, there were differences in the definitions of bleeding complications, RBC transfusion requirements [25,34], or incidences of bleeding events [14,24], which limited the power of evidence in these studies. In contrast, our study included a large number of patients (245 per group), and bleeding complications were objectively determined based on blood product transfusion requirements.

As a serine protease inhibitor, NM has been demonstrated to affect disseminated intravascular coagulation (DIC) [35], which might contribute to better patient outcomes. In our study, 30.4% of patients required transfusions of all three types of blood products; these patients had a greater survival benefit than those who required only one or two types of blood products. We speculate that the group requiring transfusion of all three types of blood products included a larger number of patients with DIC than did the group requiring transfusion of one or two types of blood products; moreover, the survival benefit seen in the NM group might be associated with the DIC treatment effects of NM. Both the higher transfusion requirements in surgical compared to medical patients and the stronger benefit of NM over NA in surgical patients strengthen the likelihood of DIC as a link between NM and improved patient outcomes, considering that surgery itself can cause DIC [36]. This speculation was supported by a study by Kamijo et al. [37] who used data from the nationwide retrospective DIC registry in Japan (J-Septic DIC registry) to evaluate the in-hospital and in-ICU mortality of patients with sepsis who underwent blood purification in the ICU. The patients in the group administered NM had lower in-hospital and in-ICU mortality than those in the NA group. Further RCTs are required to determine the beneficial effects of NM anticoagulation for CKRT on the survival of critically ill patients with DIC.

Hyperkalemia is a well-known side effect of NM [12,21], as both NM and its metabolites (p-guanidinobenzoic acid

![Figure 6. Mean continuous kidney replacement therapy filter life.](image)

CI, confidence interval; NA, no anticoagulation; NM, nafamostat mesylate.

![Figure 7. Kaplan-Meier survival curves for all-cause mortality according to the number of blood product types transfused during continuous kidney replacement therapy.](image)

(A) All three types of products, (B) any two types of products, and (C) any one type of product. NA, no anticoagulation; NM, nafamostat mesylate. *p < 0.05, statistically significant.
and 6-amidino-2-naphthol) inhibit the inward sodium current in the renal collecting duct, thus reducing the driving force for the diffusion of potassium from cells into the lumen, which in turn inhibits urinary potassium secretion [21]. However, in patients receiving CKRT, potassium is eliminated by dialysis and hyperkalemia is less likely to occur. Nevertheless, the speed of hyperkalemia correction may differ. Our study evaluated the effects of NM on the speed of hyperkalemia correction. Hyperkalemia (serum K >5.5 mmol/L) at CKRT initiation was present in 19.2% of the patients, and the time to normokalemia (serum K ≤4.5 mmol/L) in the NM group was 19.2 hours, which was approximately 1 hour (7.3%) longer than that in the NA group (17.9 hours). In patients with severe hyperkalemia (serum K >7.0 mmol/L), the time to normokalemia was 20.3 hours in the NM group and 18.1 hours in the NA group, a difference of approximately 2 hours (12.2%). As the number of patients with hyperkalemia was relatively small, these differences were not statistically significant, and further studies on this issue are required. Therefore, until additional data regarding this becomes available, a higher dose of CKRT may be considered when initiating NM anticoagulation in patients with hyperkalemia.

Herein, agranulocytosis (ANC <100 cells/µL) developed in 34.6% of the patients, without a significant difference between the NM and NA groups. Additionally, there were no cases of anaphylaxis; however, owing to the retrospective nature of this study, relevant records may have been missing. Although infrequent, anaphylaxis is a fatal complication and careful observation is warranted [38].

Unlike previous RCTs, in our study, NM administration did not result in a longer filter life than NA. The mean filter life in our study was 21.25 ± 12.01 hours, which is shorter than those reported in previous RCTs (31.7 ± 24.1 hours [14], 26.63 ± 21.14 hours [25], and 28.73 ± 12.67 hours [33]). This difference might be attributed to our center’s unique CKRT implementation strategies. As the Korean national reimbursement system covers one filter per day for CKRT, we routinely changed the filter every 24 hours, even without evidence of clotting. Therefore, in our center, the filter life is not an appropriate parameter for assessing the efficacy of anticoagulation therapy.

Our study has several limitations. Owing to its retrospective design, there is a potential for systematic error or bias. Despite the use of PSM, unmeasured confounding variables may have remained. In addition, as the study population consisted exclusively of Koreans, the results may not be generalizable to other populations or healthcare settings. Moreover, long-term patient and kidney outcomes in patients administered NM have not been evaluated. Thus, whether NM has other nephroprotective or systemic protective effects in addition to its anticoagulant action should be explored. Some studies have suggested that serine protease inhibitors have anti-inflammatory properties that may be beneficial for critically ill patients [39,40]. Finally, although the in-hospital mortality and adverse events analyzed in our study are important outcomes, long-term sequelae in survivors, including NM-induced renal recovery and long-term mortality, should also be evaluated.

In conclusion, this study provides strong evidence supporting the use of NM as an effective and safe anticoagulant for CKRT in critically ill patients, especially those requiring transfusion of all three blood products. Although our results are promising, they should be interpreted with caution. Multicenter trials, especially in patients with DIC, are still needed, together with an in-depth exploration of the mechanisms underlying the observed benefits. While the quest to find the ideal anticoagulant for CKRT for patients with bleeding tendencies continues, NM may be a step in the correct direction.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions

Conceptualization, Formal analysis: TK, DWK, HJK, EYS, SHS, HR
Funding acquisition: HR
Data curation: DEK, EMJ, YL
Methodology: TK, EYS, SHS, HR
Validation, Visualization: TK, HR
Writing–original draft: TK
Writing–review & editing: HR
All authors read and approved the final manuscript.

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References


Long-term outcomes of acute kidney injury in acute decompensated heart failure: identifying true cardiorenal syndrome and unveiling prognostic significance

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Background: Cardiorenal syndrome (CRS) type 1 defined as acute kidney injury (AKI) in acute decompensated heart failure (ADHF), is complicated due to diverse definitions. Recently, a more precise CRS type 1 definition was proposed, mandating concurrent AKI and signs of unimproved heart failure (HF). Our study explores the incidence, predictors, and long-term outcomes of AKI in ADHF under this new definition.

Methods: A prospective observation study of ADHF patients categorized into the CRS type 1, pseudo-CRS, and non-AKI groups, followed for 12 months. CRS type 1 involved AKI with clinical congestion, while pseudo-CRS included AKI with clinical decongestion (clinical congestion score <2). The primary outcome was a 1-year composite of mortality or HF rehospitalization.

Results: Among 250 consecutive ADHF patients, 46.0% developed CRS type 1; chronic kidney disease (CKD) and blood urea nitrogen were significant risk factors (odds ratios, 1.37; p = 0.002 and OR, 1.05; p < 0.001, respectively). The CRS type 1 group exhibited shorter times to AKI development and peak serum creatinine than the pseudo-CRS group (1 day vs. 4 days and 2 days vs. 4 days, respectively). At 12 months, composite outcomes of mortality or HF rehospitalization and CKD progression were significantly higher in the CRS type 1 group than in the pseudo-CRS and non-AKI groups (63.5% vs. 31.7% vs. 36.1%, p < 0.001; 28.1% vs. 16.2% vs. 11.4%, p = 0.024, respectively).

Conclusion: Distinguishing between CRS type 1 and pseudo-CRS is vital, highlighting significant disparities in short-term and long-term outcomes. Notably, pseudo-CRS exhibits comparable long-term cardiovascular and renal outcomes to those without AKI.

Keywords: Acute kidney injury, Cardio-renal syndrome, Chronic renal insufficiency, Heart failure, Mortality

Introduction

Cardiorenal syndrome (CRS) is a complex medical condition characterized by the bidirectional exacerbation of acute or chronic heart and kidney dysfunction. The consensus definition, introduced by the Acute Dialysis Quality Initiative (ADQI) group, seeks to standardize the classification of disorders where cardiac and renal diseases coexist [1]. CRS encompasses five distinct types, dependent on the sequence and chronicity of organ dysfunction [2,3]. CRS...
type 1 occurs when an acute cardiac event, such as acute heart failure (AHF), precipitates acute kidney injury (AKI). CRS type 2 manifests when chronic heart failure contributes to the development of chronic kidney disease (CKD). CRS type 3 emerges when AKI precedes heart dysfunction. CRS type 4 arises when CKD precedes chronic heart dysfunction, and CRS type 5 occurs when systemic conditions concurrently affect both the heart and kidneys, leading to dysfunction.

According to the ADQI definition, AKI in acute decompensated heart failure (ADHF) is defined as CRS type 1. However, the definition of CRS type 1 varies across the studies, resulting in discrepancies in reported incidences, identified risk factors, and observed outcomes [4]. In earlier research, the term “worsening renal failure (WRF)” was commonly utilized to describe this condition, typically characterized by an increase in serum creatinine (sCr) compared to the first day of admission [5,6]. This definition also had high variation across the studies, in terms of both the marker of renal function (sCr, cystatin C, or estimated glomerular filtration rate [eGFR]) and the magnitude of change that is considered significant [7]. Moreover, the conventional WRF definition may not capture patients who develop AKI on admission [8].

Recent studies have sought to enhance precision by integrating established AKI criteria, such as RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) [9,10], providing a more standardized approach. Nevertheless, it is important to recognize that while these criteria are valuable for identifying AKI and characterizing the extent of renal function impairment, they do not inherently propose a pathophysiological coherent entity. One of the crucial pathophysiological aspects of AKI in AHF is the presence of renal congestion. After fluid removal, the reversal of renal function is often observed [11,12]. Nonetheless, excessive fluid removal can also lead to AKI due to intravascular volume depletion or ischemic AKI. Some studies suggested that as long as decongestion occurs, AKI in AHF can positively impact survival [13,14]. Given these considerations, the European Society of Cardiology (ESC) [15] has proposed a comprehensive definition for CRS type 1, requiring both the concurrent presence of AKI by KDIGO criteria and signs of unimproved heart failure within a 7-day timeframe.

Since no studies adhered to this definition, past information regarding its incidence, risk factors, and outcomes may have been imprecise. We, therefore, conducted a prospective observational study to identify CRS type 1 and assess its long-term prognosis through a combined evaluation of the clinical response and changes in sCr during an AHF episode.

Methods

Study design and participants

A prospective observational study enrolled 250 patients admitted to the Central Chest Institute of Thailand (CCIT), a tertiary medical center specializing in cardiology, pulmonology, and cardiac surgery, with a diagnosis of ADHF between March 1 and October 31, 2022. The diagnostic criteria for ADHF followed the 2021 ESC Guidelines for the diagnosis and management of acute and chronic heart failure [16]. ADHF was defined as the rapid or gradual onset of symptoms and/or clinical signs of heart failure necessitating urgent medical attention. Diagnosis required the presence of either an abnormal electrocardiogram or radiological evidence of pulmonary edema on the chest X-ray, along with an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level equal to or exceeding 2,000 pg/mL.

Patients were excluded from the study if they met specific exclusion criteria, which included a hospital admission duration of less than 48 hours, a diagnosis of acute myocardial infarction, evidence of pulmonary thromboembolism, cardiac tamponade, heart failure following cardiac surgery, multiorgan failure, sepsis or septic shock, or the receipt of contrast-enhancing imaging studies during hospitalization. Additionally, patients with preexisting severe renal dysfunction, including end-stage renal disease (ESRD) requiring dialysis and those with an eGFR of less than 15 mL/min/1.73 m², were excluded. The study also excluded patients with malignancy and those who had potential contributing causes for AKI that may predispose to the development of CRS type 3 including acute glomerulonephritis, postobstructive uropathy, rhabdomyolysis or acute pyelonephritis, and patients who had received nephrotoxic agents, including herbal supplements and nonsteroidal anti-inflammatory drugs, within the 3 months prior to ad-
mission. Patients who had previously participated in the study were also excluded to prevent data duplication and to ensure that each participant contributed unique information.

Study measurement

Data during admission were collected from the electronic medical record (EMR) and paper records. The following variables during admission were collected: demographic data, comorbidities, current medication before admission, clinical parameters, and laboratory parameters. Evaluations of the left ventricular ejection fraction (LVEF) were conducted using transthoracic echocardiography during the index hospitalization or within 6 months after admission. Signs and symptoms of congestion, assessed by a modified clinical congestion score (CCS), were examined daily during the initial 7 days after admission or until discharge, whichever occurred first, by the treating physician. The CCS was calculated by summing the individual scores for orthopnea, jugular venous distension, and leg edema. The scores of <2 indicated mild and ≥3 indicated significant edema [17,18]. SCr levels were also measured daily during the initial 7 days after admission or until discharge, whichever occurred first, by the treating physician. The CCS was calculated by summing the individual scores for orthopnea, jugular venous distension, and leg edema. The scores of <2 indicated mild and ≥3 indicated significant edema [17,18]. SCr levels were also measured daily during the initial 7 days after admission or until discharge, whichever occurred first. AKI was defined and staged in accordance with the KDIGO classification [10]. For the classification of AKI, only sCr was taken into account, since urine output values were difficult to collect. Baseline creatinine levels were determined using the most recent and lowest creatinine value within a range of 7 to 180 days before admission, as documented in the EMR. In instances where baseline creatinine data were unavailable, the lowest sCr level during the admission period was utilized [19]. The eGFR were determined by using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula with sCr. Additionally, data pertaining to in-hospital complications such as mortality, respiratory failure, cardiogenic shock, stroke, ventricular arrhythmia, and renal replacement therapy were collected. Long-term outcomes were scrutinized, encompassing mortality rates, heart failure rehospitalization incidences, incidence of CKD progression (defined as a change in CKD staging based on eGFR criteria), incidence of ESRD, sCr levels at 3 and 12 months, or the nearest values within a 3-month range sourced from EMR or phone calls.

We categorized the patients into three distinct groups: CRS type 1, pseudo-CRS, and no AKI. CRS type 1 was defined by a combination of criteria that included the following: 1) the presence of AKI, as defined by KDIGO criteria, characterized by sCr increase of ≥0.3 mg/dL within 48 hours or 1.5–1.9 times increase from the baseline sCr within 1–7 days during the hospitalization period. Additionally, 2) non-resolving or deteriorating heart failure status, defined as the presence of a CCS of ≥3 or continued radiological evidence of pulmonary congestion (e.g., Kerley B lines, pleural effusion), potentially accompanied by an increase in NT-proBNP levels at two key time points—admission day 1 (admission date) and the day of AKI diagnosis. Lastly, 3) the diagnostic process mandated the exclusion of alternative plausible explanations for AKI, such as volume depletion or exposure to nephrotoxic agents. Pseudo-CRS was defined as 1) the presence of AKI, as defined by KDIGO criteria, and 2) the requirement for confirmation, which involved the presence of signs/symptoms of decongestion (CCS <2) or signs/symptoms of hemoconcentration (defined as an increase in hemoglobin during hospital stay) [20]. The non-AKI group was defined as patients not meeting the criteria for AKI by KDIGO standards. The diagnostic process involved a comprehensive review by both a cardiologist and a nephrologist. Importantly, there were no limitations imposed regarding the treatment of AHF, and the treatment strategy was determined at the discretion of each treating physician.

Outcomes

The primary outcome was a composite outcome encompassing mortality and rehospitalization for heart failure within a 1-year follow-up period. We differentiate between patients with AKI in heart failure with congestion (CRS type 1), patients with AKI in heart failure with decongestion (pseudo-CRS), and patients without AKI (non-AKI).

The secondary outcomes were the incidence and risk factors of CRS type 1, in-hospital complications, and long-term outcomes including mortality, rehospitalization from heart failure, incidence of CKD, incidence of ESRD, and sCr levels at 3 and 12 months. The last follow-up date for survival status was October 30, 2023.
Sample size calculation and statistical analysis

According to a prospective study by Roy et al. [21], the incidence of composite endpoints of heart failure-related readmission, renal replacement therapy, and all-cause mortality at 1 year among ADHF using KDIGO criteria was 67.5% in the AKI group compared to 31.0% in the non-AKI group. To achieve a statistical power of 90% with an alpha level of 0.05 and accounting for a potential dropout rate of 20%, the calculated sample size for each of the CRS and non-AKI groups was approximately 46 patients. Given the lack of specific data for the pseudo-CRS group, we increased the overall sample size to 250 patients to ensure an adequate representation and allow for a meaningful comparison between these groups.

Categorical data were reported in percentage and frequency and analyzed using the chi-square and Fisher exact tests, as appropriate. Continuous data were reported as a mean accompanied by standard deviations or median accompanied by interquartile range (IQR), which represents the 25th to 75th percentiles of the distribution of the data and assessed via analysis of variance or the Kruskal-Wallis test, as appropriate. Risk factors for CRS type 1 were identified through univariate and multivariate logistic regression. All variables with a p-value of <0.05 in the univariate analysis, including hypertension, CKD, receiving furosemide, blood urea nitrogen (BUN), and sCr, were included in the multivariate models.

The primary outcome, a composite of all-cause mortality and rehospitalization from heart failure at 12 months, was analyzed with the Kaplan-Meier survival curves, and the log-rank test was used to calculate the statistical significance of the differences. For the association between variables and the composite of mortality and rehospitalization from heart failure at 12 months, multivariate Cox proportional hazard models were used to evaluate the estimated hazard ratios (HRs) and 95% confidence intervals (CIs). All variables that presented a p-value of <0.05 in the univariate analysis were included in the multivariate analysis. Statistical significance was set at a p-value < 0.05, and all analyses were performed using STATA version 17.0 (StataCorp LLC).

Ethics approval and consent to participate

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board of the CCIT (COA No. 031/2565). Written informed consent was obtained from all patients or their representatives prior to their participation in the study.

Results

Patient characteristics

Between March 1 and October 31, 2022, a total of 250 consecutive patients meeting the study criteria were enrolled. Table 1 illustrates the baseline characteristics. The patient cohort consisted of 56.4% males, with a median age of 68.1 ± 15.9 years. A significant past medical history revealed that 75% had a history of hypertension, while a history of diabetes mellitus, dyslipidemia, prior myocardial infarction, atrial fibrillation, and previous heart failure hospitalization was also prevalent. The mean LVEF was 44.4% ± 19.7%, of which 47.6% had LVEF <40%. The current utilization rates of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ARB), ARB/neprilysin inhibitor, beta-blockers, spironolactone, and sodium-glucose cotransporter-2 inhibitor before admission were 35.6%, 4.8%, 57.2%, 26.8%, and 7.2%, respectively. The mean sCr at the baseline and at the admission were 1.18 ± 0.48 mg/dL and 1.46 ± 1.64 mg/dL, respectively. There was a significant difference in the median intravenous furosemide dosage administered during the first 72 hours of hospitalization across the groups. Specifically, the CRS group received a median dosage of 220 mg (IQR, 120–400 mg), the pseudo-CRS group received 220 mg (IQR, 120–320 mg), and the non-AKI group received 120 mg (IQR, 120–200 mg), respectively (p < 0.001).

Incidence, differentiation, and associated clinical features of cardiorenal syndrome type 1

In this cohort of 250 patients, AKI occurred in 156 patients (62.4%) during AHF. Among these, 115 patients (46.0%) were classified as CRS type 1, while 41 patients (16.5%) were categorized as pseudo-CRS. The CRS type 1 group exhibited significantly higher rates of underlying CKD, prior use of furosemide in current medication, BUN levels at admission, sCr levels at admission, and lower systolic blood
Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>CRS type 1 group</th>
<th>Pseudo-CRS group</th>
<th>Non-AKI group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>250</td>
<td>115</td>
<td>41</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68.1 ± 15.9</td>
<td>68.4 ± 15.2</td>
<td>65.2 ± 18.7</td>
<td>69.0 ± 15.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Male sex</td>
<td>141 (56.4)</td>
<td>68 (59.1)</td>
<td>20 (48.8)</td>
<td>53 (56.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 ± 6.1</td>
<td>24.4 ± 5.5</td>
<td>26.1 ± 6.2</td>
<td>24.0 ± 6.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>100 (40.0)</td>
<td>51 (44.4)</td>
<td>20 (48.8)</td>
<td>29 (30.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>189 (75.6)</td>
<td>94 (81.7)</td>
<td>34 (82.9)</td>
<td>61 (64.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>181 (72.4)</td>
<td>86 (74.8)</td>
<td>34 (82.9)</td>
<td>61 (64.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>122 (48.8)</td>
<td>61 (53.0)</td>
<td>18 (78.3)</td>
<td>43 (45.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>124 (49.6)</td>
<td>58 (50.4)</td>
<td>23 (56.1)</td>
<td>43 (45.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>93 (37.2)</td>
<td>63 (54.8)</td>
<td>11 (26.8)</td>
<td>18 (19.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>28 (11.2)</td>
<td>15 (13.0)</td>
<td>2 (4.9)</td>
<td>11 (11.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Current medication</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ACEi/ARB</td>
<td>89 (35.6)</td>
<td>42 (36.5)</td>
<td>14 (34.2)</td>
<td>33 (35.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>ARNI</td>
<td>12 (4.8)</td>
<td>5 (4.4)</td>
<td>2 (4.9)</td>
<td>5 (5.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>143 (57.2)</td>
<td>68 (59.1)</td>
<td>23 (56.1)</td>
<td>52 (55.3)</td>
<td>0.85</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>67 (26.8)</td>
<td>32 (27.8)</td>
<td>8 (19.5)</td>
<td>27 (28.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>18 (7.2)</td>
<td>8 (7.0)</td>
<td>5 (15.2)</td>
<td>5 (5.3)</td>
<td>0.36</td>
</tr>
<tr>
<td>Furosemide</td>
<td>134 (53.6)</td>
<td>71 (61.7)</td>
<td>16 (39.0)</td>
<td>47 (50.0)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Antplatelets</td>
<td>111 (44.4)</td>
<td>56 (48.7)</td>
<td>20 (48.8)</td>
<td>33 (35.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>93 (37.2)</td>
<td>44 (38.3)</td>
<td>15 (36.6)</td>
<td>34 (36.2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Vital signs and status</td>
<td></td>
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</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128.9 ± 27.6</td>
<td>126.7 ± 25.8</td>
<td>138.7 ± 32.8</td>
<td>127.3 ± 26.7</td>
<td>0.045*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>44.4 ± 19.7</td>
<td>43.3 ± 20.7</td>
<td>45.6 ± 17.7</td>
<td>45.2 ± 19.5</td>
<td>0.73</td>
</tr>
<tr>
<td>EF ≤40%</td>
<td>119 (47.6)</td>
<td>62 (53.9)</td>
<td>16 (39.0)</td>
<td>41 (43.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>72 (28.8)</td>
<td>43 (37.4)</td>
<td>10 (24.4)</td>
<td>19 (20.2)</td>
<td>0.59</td>
</tr>
<tr>
<td>Prior heart failure in 6 mo</td>
<td>120 (48.0)</td>
<td>64 (55.7)</td>
<td>17 (41.5)</td>
<td>39 (41.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Laboratory at admission</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.8 ± 2.7</td>
<td>11.5 ± 2.4</td>
<td>12.2 ± 2.5</td>
<td>12.1 ± 3.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>35.2 ± 7.3</td>
<td>34.3 ± 7.0</td>
<td>37.1 ± 7.1</td>
<td>35.6 ± 7.7</td>
<td>0.09</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>27.7 ± 17.0</td>
<td>34.4 ± 17.4</td>
<td>19.8 ± 6.9</td>
<td>22.4 ± 15.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.46 ± 1.64</td>
<td>1.71 ± 0.93</td>
<td>1.08 ± 0.33</td>
<td>1.09 ± 0.56</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>58.9 ± 25.8</td>
<td>46.6 ± 24.6</td>
<td>64.9 ± 21.6</td>
<td>71.4 ± 21.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>137.5 ± 5.2</td>
<td>136.9 ± 5.4</td>
<td>138.2 ± 5.1</td>
<td>138.1 ± 4.8</td>
<td>0.18</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.0 ± 0.6</td>
<td>4.0 ± 0.6</td>
<td>3.9 ± 0.6</td>
<td>3.9 ± 0.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>24.9 ± 4.9</td>
<td>24.2 ± 5.3</td>
<td>26.6 ± 4.5</td>
<td>25.0 ± 4.5</td>
<td>0.02*</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>6,253</td>
<td>5,937</td>
<td>5,937</td>
<td>6,571</td>
<td>0.10</td>
</tr>
<tr>
<td>Intravenous diuretic dosing in 72 hr (mg)</td>
<td>160 (120–300)</td>
<td>220 (120–400)</td>
<td>220 (120–320)</td>
<td>120 (120–200)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, number (%), or median (interquartile range).

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor blocker/neprilysin inhibitor; BUN, blood urea nitrogen; CRS, cardiorenal syndrome; EF, ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

*p < 0.05, statistically significant.

pressure and bicarbonate levels compared to the pseudo-CRS and non-AKI groups. Notably, NT-proBNP levels did not differ between the groups (Table 1).

During admission, we observed a significant differ-
ence in sCr levels among the CRS type 1, pseudo-CRS, and non-AKI groups. Specifically, patients with CRS type 1 had significantly higher admission sCr, and maximum sCr compared to those in the pseudo-CRS and non-AKI groups. However, sCr at discharge did not differ between the groups. The median time from admission to the development of AKI in the CRS group was 1 day compared to 4 days in the pseudo-CRS group. Similarly, the median time from admission to the peak sCr level was 2 days compared to 4 days. Patients with CRS type 1 also exhibited a higher rate of AKI severity, with 14.8% in stage 3, 14.8% in stage 2, and 70.3% in stage 1. This is in contrast to the pseudo-CRS group, where there was a noticeable absence of AKIN stage 3, predominantly presenting with stage 1 (92.7%) and a smaller proportion in stage 2 (7.3%). Notably, no patients in the pseudo-CRS group required renal replacement therapy (Table 2).

In the univariate analysis, independent predictors of CRS type 1 at admission included comorbid hypertension (OR, 2.07; 95% CI, 1.03–3.43; p = 0.035), CKD (OR, 1.61; 95% CI, 1.35–1.92; p < 0.001), prior furosemide use in current medication (OR, 1.82; 95% CI, 1.10–3.02; p = 0.02), BUN levels (OR, 1.06; 95% CI, 1.03–1.08; p < 0.001), and sCr levels at admission (OR, 1.62; 95% CI, 1.10–2.40; p = 0.003). However, in the multivariate model, only CKD and BUN levels remained independently associated with CRS type 1 (OR, 1.37; 95% CI, 1.13–1.68; p = 0.002 and OR, 1.05; 95% CI, 1.02–1.07; p < 0.001) (Table 3).

In-hospital outcomes

In-hospital mortality rates were notably higher in patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate analysis</th>
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<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p-value</td>
<td>Odds ratio (95% CI)</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical status</td>
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</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99–1.01)</td>
<td>0.80</td>
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</tr>
<tr>
<td>Body mass index</td>
<td>0.81 (0.96–1.03)</td>
<td>0.80</td>
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</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.99 (0.99–1.01)</td>
<td>0.25</td>
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</tr>
<tr>
<td>EF ≤40%</td>
<td>1.60 (0.97–2.97)</td>
<td>0.07</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior heart failure in 6 mo</td>
<td>0.81 (0.48–1.33)</td>
<td>0.42</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.40 (0.84–2.32)</td>
<td>0.19</td>
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<tr>
<td>Hypertension</td>
<td>2.07 (1.03–3.43)</td>
<td>0.04*</td>
<td>1.11 (0.56–2.19)</td>
<td>0.76</td>
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</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.24 (0.83–2.26)</td>
<td>0.22</td>
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<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.61 (1.35–1.92)</td>
<td>&lt;0.001*</td>
<td>1.37 (1.13–1.68)</td>
<td>0.002*</td>
<td></td>
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</tr>
<tr>
<td>Current medication</td>
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<tr>
<td>RAASi</td>
<td>1.09 (0.71–1.66)</td>
<td>0.69</td>
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<tr>
<td>SGLT2i</td>
<td>0.93 (0.35–2.43)</td>
<td>0.88</td>
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<tr>
<td>Spironolactone</td>
<td>1.09 (0.62–1.91)</td>
<td>0.76</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Furosemide</td>
<td>1.82 (1.10–3.02)</td>
<td>0.02*</td>
<td>1.23 (0.07–2.17)</td>
<td>0.48</td>
<td></td>
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</tr>
<tr>
<td>Statin</td>
<td>1.51 (0.90–2.51)</td>
<td>0.12</td>
<td></td>
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</tr>
<tr>
<td>Laboratory at admission</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.91 (0.83–1.00)</td>
<td>0.06</td>
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</tr>
<tr>
<td>Hematocrit</td>
<td>0.97 (0.93–1.01)</td>
<td>0.06</td>
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</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>1.06 (1.03–1.08)</td>
<td>&lt;0.001*</td>
<td>1.05 (1.02–1.07)</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.62 (1.10–2.40)</td>
<td>0.003*</td>
<td>0.92 (0.77–1.11)</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>0.95 (0.91–1.01)</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>0.99 (0.99–1.01)</td>
<td>0.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CRS, cardiorenal syndrome; EF, ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAASi, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

*p < 0.05, statistically significant.
with CRS type 1 at 10.4%, compared to 4.8% in pseudo-CRS and 4.3% in non-AKI. Patients with CRS type 1 also exhibited significantly elevated rates of respiratory failure (22.6% vs. 17.1% vs. 8.5%, p = 0.02), cardiogenic shock (24.4% vs. 17.1% vs. 7.5%, p = 0.005), and renal replacement therapy (8.7% vs. 2.4% vs. 0%, p = 0.008), respectively (Table 2).

Long-term outcomes

The composite outcomes of mortality and rehospitalization from heart failure at 1 year were significantly higher in the CRS group compared with the pseudo-CRS and non-AKI groups, at 63.5%, 31.7%, and 36.1%, respectively (p < 0.001). When considering individual endpoints, the CRS type 1 group demonstrated a markedly elevated 1-year mortality rate of 25.2%, in contrast to the pseudo-CRS (9.8%) and non-AKI groups (12.8%), indicating a statistically significant difference (p = 0.02). Additionally, rehospitalization from heart failure was more prevalent in the CRS type 1 group (43.5%) compared to the pseudo-CRS (24.4%) and non-AKI groups (25.8%) (p = 0.01) (Table 2). Kaplan-Meier curves were used to evaluate estimates of 1-year mortality and rehospitalization from heart failure according to AKI and CRS status. The significance was notably lower in the CRS type 1 group, with p < 0.001 (Fig. 1).

The multivariate Cox proportional hazards analysis for

### Table 3. Renal function and in-hospital outcomes during admission by AKI and CRS status

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRS type 1 group (n = 115)</th>
<th>Pseudo-CRS group (n = 41)</th>
<th>Non-AKI group (n = 94)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine levels during admission (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.16 ± 0.36</td>
<td>1.12 ± 0.44</td>
<td>1.22 ± 0.61</td>
<td>0.43</td>
</tr>
<tr>
<td>Admission date</td>
<td>1.71 ± 0.93</td>
<td>1.08 ± 0.33</td>
<td>1.09 ± 0.56</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Maximum</td>
<td>2.41 ± 1.69</td>
<td>1.56 ± 0.44</td>
<td>1.22 ± 0.55</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Discharge date</td>
<td>1.35 ± 0.61</td>
<td>1.48 ± 0.84</td>
<td>1.26 ± 0.63</td>
<td>0.21</td>
</tr>
<tr>
<td>Time to AKI diagnosis (day)</td>
<td>1 (1-2)</td>
<td>4 (3-5)</td>
<td>-</td>
<td>0.001*</td>
</tr>
<tr>
<td>Time to peak creatinine (day)</td>
<td>2 (1-3)</td>
<td>4 (4-6)</td>
<td>-</td>
<td>0.001*</td>
</tr>
<tr>
<td>AKI staging</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Stage 1</td>
<td>81 (70.3)</td>
<td>38 (92.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>17 (14.8)</td>
<td>3 (7.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>17 (14.8)</td>
<td>0 (0)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>10 (8.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.002*</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>12 (10.4)</td>
<td>2 (4.8)</td>
<td>4 (4.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>26 (22.6)</td>
<td>7 (17.1)</td>
<td>8 (8.5)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>28 (24.4)</td>
<td>7 (17.1)</td>
<td>7 (7.5)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>10 (8.7)</td>
<td>2 (4.9)</td>
<td>2 (2.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Length of stay (day)</td>
<td>11.0 (7-20)</td>
<td>8.0 (6-13)</td>
<td>6.5 (5-12)</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation, median (interquartile range), or number (%).

AKI, acute kidney injury; CRS, cardiorenal syndrome.

*p < 0.05, statistically significant.
Table 4. Long-term outcomes at 1-year by AKI and CRS status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CRS type 1 group (n = 115)</th>
<th>Pseudo-CRS group (n = 41)</th>
<th>Non-AKI group (n = 94)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcomes of mortality and rehospitalization from HF</td>
<td>73 (63.5)</td>
<td>13 (31.7)</td>
<td>34 (36.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>1-yr mortality</td>
<td>29 (25.2)</td>
<td>4 (9.8)</td>
<td>12 (12.8)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Rehospitalization from HF</td>
<td>50 (43.5)</td>
<td>10 (24.4)</td>
<td>24 (25.8)</td>
<td>0.01*</td>
</tr>
<tr>
<td>CKD progression at 1 yr (% among survivors with sCr available)</td>
<td>23 (28.1)</td>
<td>6 (16.2)</td>
<td>9 (11.4)</td>
<td>0.02*</td>
</tr>
<tr>
<td>End-stage renal disease (% among survivors)</td>
<td>3 (3.5)</td>
<td>1 (2.7)</td>
<td>0 (0)</td>
<td>0.38</td>
</tr>
<tr>
<td>SCr</td>
<td>1.47 ± 0.98</td>
<td>1.13 ± 0.47</td>
<td>1.06 ± 0.59</td>
<td>0.99</td>
</tr>
<tr>
<td>1 yr</td>
<td>1.51 ± 1.13</td>
<td>1.26 ± 0.60</td>
<td>1.08 ± 0.68</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) or mean ± standard deviation.
AKI, acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndrome; HF, heart failure; sCr, serum creatinine.

aDefined as a change in CKD staging based on estimated glomerular filtration rate criteria. bAmong 198 patients with 1-year sCr measurement. cAvailable in 202 patients at 3 months and 198 patients at 1 year.
*p < 0.05, statistically significant.

Table 5. Predictors of composite outcomes of mortality or HF rehospitalization at 12 months by multivariate Cox regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS type 1</td>
<td>1.70 (1.07–2.70)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Prior HF in 6 months</td>
<td>1.39 (0.96–2.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.28 (0.85–1.93)</td>
<td>0.24</td>
</tr>
<tr>
<td>BUN levels at admission</td>
<td>1.00 (0.90–1.01)</td>
<td>0.70</td>
</tr>
<tr>
<td>Sodium levels at admission</td>
<td>0.96 (0.93–0.99)</td>
<td>0.02*</td>
</tr>
<tr>
<td>NT-proBNP levels at admission</td>
<td>1.00 (0.99–1.00)</td>
<td>0.13</td>
</tr>
<tr>
<td>Renal replacement therapy during admission</td>
<td>1.07 (0.46–2.47)</td>
<td>0.87</td>
</tr>
<tr>
<td>Respiratory failure during admission</td>
<td>1.69 (1.05–2.71)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

BUN, blood urea nitrogen; CI, confidence interval; CRS, cardiorenal syndrome; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*p < 0.05, statistically significant.

the composite outcomes of mortality and rehospitalization from heart failure at 12 months also showed that CRS type 1 was found to be independently associated with the primary outcomes (adjusted HR, 1.70; 95% CI, 1.07–2.70; p = 0.04). Additionally, other variables independently associated with the outcomes included serum sodium levels at admission (adjusted HR, 0.96; 95% CI, 0.93–0.99; p = 0.02) and respiratory failure during admission (adjusted HR, 1.69; 95% CI, 1.05–2.71; p = 0.03) (Table 5).

At 12 months after an ADHF episode, patients with a history of CRS type 1 exhibited a significantly higher rate of CKD progression compared to those with pseudo-CRS and non-AKI, at 28.1%, 16.2%, and 25.8%, respectively (p = 0.02). Notably, four patients developed ESRD at 12 months, with three in the CRS group and one in the pseudo-CRS group. sCr at 3 and 12 months did not differ significantly between the groups, with only seven patients lacking sCr measurements at 12 months (Table 5).

Discussion

Our study, a prospective evaluation of CRS type 1 among well-characterized ADHF patients, aims to provide a comprehensive understanding of its incidence and long-term implications. We revealed key findings: 1) A high prevalence of AKI in AHF cases, at approximately 62.4%; 2) The distinct association of CRS type 1 with increased occurrences of severe complications such as respiratory failure, cardiogenic shock, and prolonged hospital stays; 3) Identifying AKI in AHF between CRS type 1 and pseudo...
Do-CRS is very important due to substantial differences in prognosis and long-term outcomes; 4) The sCr pattern during AHF admission significantly differentiates CRS type 1 from pseudo-CRS, showing higher AKI staging, a shorter timeline from admission to AKI development, and peak sCr levels, indicating alignment with CRS type 1.

The reported incidence of CRS type 1 has varied widely due to differing definitions and the nature of various studies. Previously, the term “worsening renal function or WRF” was common in AHF publications. However, in recent years, there has been a shift toward utilizing KDIGO criteria for accurate diagnosis and the assessment of AKI’s severity and progression. Our study identified an incidence of AKI in AHF at 62.4%, which aligns with recent research, such as the systematic review and meta-analysis by Vandenberghe et al. [22]. Their study analysis of 64 studies involved 509,766 patients, showing an AKI incidence in AHF using KDIGO criteria at 47.4% (ranging from 39.1% to 63.3%). Their findings also highlighted a higher 28-day mortality rate and prolonged hospital stay associated with AKI in AHF.

While it’s crucial to note that not all AKI or acute decline in GFR in AHF are universally negative. A post-hoc analysis of the EVEREST trial revealed that acute declines in eGFR were not necessarily linked to a higher risk of adverse outcomes, provided there was clear evidence of decongestion. This was evidenced by changes in biomarkers like BNP, NT-proBNP, and weight, as well as hemoconcentration measures such as hematocrit [23]. Similarly, a post-hoc analysis of PROTECT data showed that patients with AKI in AHF experienced adverse outcomes only if they had lingering congestion at the time of renal function assessment [18]. Our findings in the pseudo-CRS group also demonstrated that AKI concurrent with decongestion did not elevate the risk of in-hospital adverse events.

Since the term “pseudo-CRS” is not widely used. However, to the best of our knowledge, there has been no validated terminology to describe the phenomenon of acute declines in eGFR in ADHF occurring concomitantly with decongestion or hemoconcentration, as we now realize that this condition is part of an appropriate response to therapy and not necessarily linked to a higher risk of adverse outcomes.

Martin et al. [24] introduced the term “pseudo-worsening renal function or pseudo-WRF” for AHDF patients with WRF with hemoconcentration, which had a better prognosis than true-WRF and similar prognosis of patients without WRF. Another study by Griffin et al. [20] also defined this phenomenon as “hemoconcentration and worsening creatinine.” Recently, the ESC [15] suggested distinguishing between true AKI in ADHF caused by venous congestion (which is termed as ‘cardiorenal syndrome’ or ‘CRS type 1’), and “pseudo-AKI” caused by decongestion (when only a functional decrease in eGFR is observed). Therefore, our definition of “pseudo-CRS” aligns with this concept and could be less confusing than the term “pseudo-WRF”, which is not uniform and has variation in terminology itself.

Distinguishing between CRS type 1 and pseudo-CRS during patient admission remains a considerable challenge. The presence of AKI in AHF creates a clinical conundrum, often leading physicians to consider halting decongestion early for fear of compromising renal function, inadvertently causing ineffective decongestion and potential adverse outcomes. Our study demonstrated an easy and simple method for identifying CRS type 1 from pseudo-CRS by assessing clinical response and sCr levels. We found that the severity of AKI and the creatinine profile could effectively demarcate these two conditions. Specifically, CRS type 1 frequently displayed AKI upon admission, reaching its peak sCr levels on day 2, while the pseudo-CRS group showed signs of AKI and peak sCr levels on day 4. Moreover, CRS type 1 typically demonstrated more severe AKI than the pseudo-CRS, with the latter rarely exhibiting AKI at AKIN stage 3. This can be understood as the mechanism behind pseudo-CRS arising from aggressive diuresis and excessive fluid removal, resulting in a delayed onset of AKI (Table 6).

Multivariable logistic regression analyses revealed that the presence of CKD and higher BUN levels at admission were independent predictors for CRS type 1. Consistent with many studies, CKD has been consistently associated with a higher likelihood of AKI, particularly within the CRS type 1 context. Notably, Hu et al. [25] emphasized CKD as a significant predictor of WRF. Serum BUN, a well-known biomarker for AKI diagnosis, is influenced by nonrenal factors independent of kidney function, reflecting various aspects of the catabolic state, production, and renal tubular handling [26]. Therefore, a higher BUN level at admission may indicate a patient’s elevated catabolic state and serve
as a predictive factor for CRS type 1. These results highlight the importance of not only monitoring creatinine levels but also paying attention to simple laboratory parameters such as serum BUN in patients with AHF.

Despite numerous pieces of evidence indicating that AKI with decongestion leads to better in-hospital prognosis, some clinicians remain concerned about the long-term outcomes of AKI resulting from excessive dehydration due to aggressive diuresis. Our findings illustrate that as long as decongestion occurs, patients have a lower rate of long-term mortality and rehospitalization due to heart failure. Interestingly, the rate of CKD progression was significantly higher in the CRS group, but not in the pseudo-CRS and non-AKI groups. A recent post-hoc analysis from the EVER-EST study further validates our findings, emphasizing that decongestion in patients with AHF does not increase the risk of adverse kidney outcomes in patients with heart failure [27].

The observed favorable outcomes in both the pseudo-CRS group and the non-AKI group can be attributed to the critical role of decongestion. Numerous studies have highlighted that renal venous congestion, rather than a decrease in cardiac output, constitutes a major pathophysiological factor in acute CRS and is associated with worsened outcomes during AHF [5,28]. Therefore, the maintenance of decongestion emerges as a crucial aspect for optimizing cardiorenal health among heart failure patients, contributing to the amelioration of venous congestion and cardiac refilling pressure. The reduction of renal congestion not only leads to a decrease in intra-renal venous pressure, mitigating the risk of renal venous congestion-related damage but also positively influences systemic hemodynamics. This impact includes a reduction in the activation of neurohormonal pathways known to be detrimental to renal function [29].

Our study had several strengths. Firstly, we provided valuable insights into the relationship of AKI in AHF patients with differences in prognosis by decongestion, an area with limited existing research. Secondly, the prospective design allows for the collection of detailed and real-time clinical data, contributing to the accuracy and reliability of our findings. Thirdly, the comprehensive assessment of AKI, including its severity and pattern during admission, provides a nuanced understanding of the cardiorenal dynamics in AHF. Moreover, the clear differentiation between CRS type 1 and pseudo-CRS based on clinical and laboratory parameters adds depth to our study, addressing the need for precise classification in this complex syndrome.

We acknowledge several limitations in our study. Firstly, its single-center design and a limited number of enrolled patients might impact the generalizability of our findings. A larger, multicenter sample would enhance the robustness of our conclusions. Secondly, the determination of congestion scores relied on a simple method, potentially benefiting from more sophisticated quantitative congestion assessment approaches. Thirdly, the lack of assessment of treatments at discharge hinders the evaluation of pharmacological effects on prognosis in our study design. Fourthly, our study assesses NT-proBNP levels at the time of admission, and these levels alone may not predict renal outcomes in AHF patients. The ESC guideline recommends measuring NT-proBNP both at admission for disease diagnosis and predischarge for the evaluation of disease prognosis [16,30]. Therefore, reassessing NT-proBNP levels before discharge becomes crucial to provide valuable insights

| Table 6. Differentiation between CRS type 1 and pseudo-CRS |
|-----------------|-----------------|-----------------|
| Feature         | CRS type 1      | Pseudo-CRS      |
| Clinical status | Non-resolving or deteriorating | Improvement |
| Volume status   | Congestion      | Dehydration     |
| Serum creatinine change | Large changes | Small changes |
| Time to AKI diagnosis | Shorter duration | Longer duration |
| Time to peak creatinine | Shorter duration | Longer duration |
| Severity of AKI | Higher          | Lower (rarely AKIN 3) |
| Diuretic response | Not appropriate diuretic efficiency | Appropriate diuretic efficiency |
| Prognosis       | Poor            | Favorable       |

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CRS, cardiorenal syndrome.
into patient prognosis. Additionally, our study had a lower rate of sodium-glucose cotransporter-2 inhibitor (SGLT2i) use. Given the established benefits of SGLT2i in reducing the risk of mortality and rehospitalization in heart failure, both with reduced LVEF and preserved LVEF [31–33], the lower usage in our study may be influenced by financial constraints and access to healthcare limitations, limiting our ability to observe the potential benefits of SGLT2i in this study.

In conclusion, AKI during ADHF was prevalent. Differentiating between CRS type 1 and pseudo-CRS is crucial due to marked disparities in both short-term and long-term outcomes. Notably, pseudo-CRS demonstrates comparable long-term cardiovascular and renal outcomes to those without AKI, offering valuable insights for clinicians managing AKI in ADHF with aggressive fluid removal.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

We thank all the investigators, members of the Nephrology Unit at the Central Chest Institute of Thailand, and all patients for participating in this study.

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions

Conceptualization, Methodology: All authors
Data curation, Formal analysis, Investigation: PT, AT
Writing–original draft: PT, AT
Writing–review & editing: All authors
All authors read and approved the final manuscript.

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References


Background: This study investigated the association between serum phosphate level and mortality in acute kidney injury (AKI) patients undergoing continuous kidney replacement therapy (CKRT) and evaluated whether this association differed according to disease severity.

Methods: Data from eight tertiary hospitals in Korea were retrospectively analyzed. The patients were classified into four groups (low, normal, high, and very high) based on their serum phosphate level at baseline. The association between serum phosphate level and mortality was then analyzed, with further subgroup analysis being conducted according to disease severity.

Results: Among the 3,290 patients identified, 166, 955, 1,307, and 862 were in the low, normal, high, and very high phosphate groups, respectively. The 90-day mortality rate was 63.9% and was highest in the very high group (76.3%). Both the high and very high groups showed a significantly higher 90-day mortality rate than did the normal phosphate group (high: hazard ratio [HR], 1.35, 95% confidence interval [CI], 1.21–1.51, p < 0.001; very high: HR, 2.01, 95% CI, 1.78–2.27, p < 0.001). The low group also exhibited a higher 90-day mortality rate than did the normal group among those with high disease severity (HR, 1.47; 95% CI, 1.09–1.99; p = 0.01) but not among those with low disease severity.

Conclusion: High serum phosphate level predicted increased mortality in AKI patients undergoing CKRT, and low phosphate level was associated with increased mortality in patients with high disease severity. Therefore, serum phosphate levels should be carefully considered in critically ill patients with AKI.

Keywords: Acute kidney injury, Continuous kidney replacement therapy, Critical illness, Mortality, Phosphates

For further information on the authors’ affiliations, see Additional information.
Introduction

Acute kidney injury (AKI) is a serious complication commonly observed in critically ill patients. Continuous kidney replacement therapy (CKRT), which is often required for patients with severe AKI to correct for biochemical imbalances and volume status \[1\], has seen increased use over the past decade \[2\]. Despite the advances in CKRT technology and optimization for critically ill patients, mortality rates in AKI patients requiring CKRT remain high, ranging from 30% to 60% \[3\]. Hence, identifying prognostic indicators of morality in these patients is essential for improving their outcomes.

Serum phosphate has emerged as a potential predictor of mortality in patients with AKI. Phosphate is an essential mineral that plays a crucial role in numerous physiological processes, including bone metabolism, energy metabolism, and intracellular signaling \[4\]. Numerous reports have shown that both high and low phosphate levels are associated with adverse outcomes in various clinical conditions, including chronic kidney disease, cardiovascular disease, and critical illness \[5\].

Several studies have investigated the association between serum phosphate and mortality in AKI patients \[6-8\]. Some studies have shown that hyperphosphatemia is associated with poor outcomes given that it can increase cardiovascular events and mortality \[6\]. On the other hand, other studies have shown that hypophosphatemia is also associated with adverse outcomes given that it can cause respiratory muscle weakness \[9,10\], difficulty in weaning off ventilatory support \[11,12\], and increased need for vasopressors \[13\]. The impact of these phosphate levels on patients is more devastating when the severity of the disease is high. Thus, we hypothesized that the effect of phosphate on mortality risk would be more pronounced under high disease severity condition in critically ill patients requiring CKRT.

The current study therefore aimed to investigate the association between serum phosphate level and mortality in critically ill patients with severe AKI requiring CKRT using a large multicenter CKRT cohort. In addition, we evaluated whether this association differed according to disease severity.

Methods

Study participants and data collection

This multicenter retrospective cohort study was conducted on critically ill patients with AKI requiring CKRT. Patients over 18 years of age who received CKRT for over 24 hours were included. Those who were already on maintenance dialysis before CKRT initiation were excluded. Among the 4,995 adult patients who received CKRT between 2006 and 2021 in eight university-based hospitals in South Korea (the Asan Medical Center, Daejeon Eulji Medical Center, Dongguk University Ilsan Hospital, Inha University Hospital, Keimyung University Dongsan Medical Center, Kyungpook National University Chilgok Hospital, Seoul National University Hospital, and the Catholic University of Korea, Eunpyeong St. Mary’s Hospital), 651 were excluded for being on maintenance dialysis. Additionally, those without baseline phosphate data were excluded (n = 1,054). A total of 3,290 patients were included in the analysis (Fig. 1). CKRT was initiated at the discretion of a nephrologist if the patient has persistent oliguria, uncontrolled volume overload, refractory hyperkalemia, or metabolic acidosis unresponsive to conventional therapy.

Patient information at CKRT initiation, including demographics and comorbidities, clinical parameters, and laboratory results, including complete blood counts, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR) obtained using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, electrolytes such as calcium, phosphate, sodium, and potassium, C-reactive protein, albumin, and lactate at CKRT initiation, was retrospectively collected. The Charlson Comorbidity Index (CCI) and disease severity scores, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, were also measured. The causes of AKI were reviewed by nephrologists to determine whether the AKI was septic or non-septic. We also collected information on critical care and mortality at 7, 30, and 90 days.

Definition

The reference range for phosphate used in this study was 2.8 to 4.5 mg/dL (normal phosphate group). Study par-
Participants were divided into four groups (i.e., low, normal, high, and very high phosphate groups) according to their baseline serum phosphate levels. Baseline serum phosphate was defined as the phosphate level measured at the initiation of CKRT. Hypophosphatemia was defined as a phosphate level of <2.8 mg/dL (low phosphate group), hyperphosphatemia was defined as a phosphate level over 4.5 mg/dL but under 7.0 mg/dL (high phosphate group), and severe hyperphosphatemia was defined as a phosphate level over 7.0 mg/dL (very high phosphate group).

Disease severity was classified according to the APACHE II score at CKRT initiation. Patients with an APACHE II score of 28 (median value) or higher were classified into the high severity group, whereas those with a score of <28 were classified into the low severity group.

The CCI weights 19 different diseases to determine the severity of the underlying comorbidities [14]. Septic AKI was defined as the presence of an infection that satisfied the criteria for systemic inflammatory response syndrome [15].

The primary outcome was the 90-day mortality rate, and the secondary outcomes were the 7- and 30-day mortality rates.

**Statistical analyses**

Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as number (percentage). Participants were divided into four groups by serum phosphate level at the time of CKRT initiation. Parameters were compared using a one-way analysis of variance for continuous variables and the Pearson chi-square test or Fisher exact test for categorical variables. We then analyzed the relationship between serum phosphate as a continuous variable and 90-day mortality using a Cox proportional hazard model with restricted cubic spline functions to capture potential nonlinear effects, with the reference value at the lower limit of reference phosphate range. Survival analyses using the Kaplan-Meier curves with log-rank tests were performed to investigate the im-

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**Figure 1.** Flow diagram for the study.

AKI, acute kidney injury; CKRT, continuous kidney replacement therapy; ESKD, end-stage kidney disease.
Impact of phosphate levels on mortality. In addition, subgroup analysis was conducted to determine the relationship between phosphate level and mortality according to disease severity. Outcomes were compared between each group divided according to disease severity. Univariable and multivariable Cox proportional hazard regression models were used to estimate hazard ratios (HRs) for mortality according to phosphate groups and subgroups according to disease severity. The multivariable Cox regression model adjusted for clinically important variables affecting mortality and different baseline characteristics, such as age, sex, body weight, CCI, hypertension, diabetes, chronic kidney disease, congestive heart failure, SOFA score, mechanical ventilator use, vasopressor use, serum creatinine, and serum lactate. In addition, the predictive power of phosphate and traditional prognostic indicators was compared. The ability of prognostic indicators to predict mortality was determined using the area under the curve (AUC) and compared using DeLong’s test [16]. We also confirmed the integrative effects of combining phosphate levels with other prognostic indicators. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were analyzed to measure the integrative effects of combining phosphate levels with other prognostic indicators. Statistical analyses were performed using IBM SPSS for Windows version 22.0 (IBM Corp.) and R software (R Foundation for Statistical Computing). A p-value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study participants and each group based on phosphate levels are presented in Table 1. Participants had a mean age of 65.7 ± 14.7 years, with males accounting for 60.9%. The number of males and body weight were significantly higher in the very high phosphate group than in the rest of the groups (both p < 0.05), but body mass index did not differ among groups. Sepsis accounted for more than half of the AKI cases in all groups. Comorbidity rates and CCI values differed significantly among the groups. Disease severity indexes, such as the APACHE II and SOFA score, were significantly higher in the very high phosphate group than in the other groups (p < 0.001). High and very high phosphate groups exhibited lower hemoglobin, eGFR, calcium, and albumin levels and higher potassium, blood urea nitrogen, creatinine, and lactate levels than did the low phosphate group (all p < 0.05).

Clinical outcomes and in-hospital course

In-hospital information is summarized in Table 2. The 90-day mortality was 63.9%, with the very high and low phosphate groups having the highest and lowest rates (76.3% and 54.8%, respectively; p < 0.001). Short-term (7- and 30-day) mortality rates were also higher in the very high phosphate group and lower in the low phosphate group than in the normal phosphate group (p < 0.001). More patients received mechanical ventilation in the low phosphate group than in the high and very high phosphate groups, whereas the high and very high phosphate groups used more vasopressors than the low phosphate group. The high and very high phosphate groups exhibited shorter hospital length of stay and CKRT duration than did the low phosphate group (p < 0.001).

Association between phosphate level and mortality

Fig. 2 displays the association between phosphate level as a continuous variable and 90-day mortality using Cox regression analysis with restricted cubic splines. After the...
reference value was set at the lower limit of normal for phosphate level (2.8 mg/dL), our results showed that a higher phosphate level was associated with increased 90-day mortality in critically ill AKI patients undergoing CKRT. The Kaplan-Meier curves for 90-day mortality according to phosphate groups are presented in Fig. 3. Accordingly, the high and very high phosphate groups had significantly poorer survival than did the normal phosphate group, with the low phosphate group showing a survival curve similar to that for the normal phosphate group (Fig. 3A).

Table 1. Baseline characteristics in all patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>Very high</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3,290</td>
<td>166</td>
<td>955</td>
<td>1,307</td>
<td>862</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.7 ± 14.7</td>
<td>67.9 ± 16.5</td>
<td>67.2 ± 14.3</td>
<td>65.5 ± 14.6</td>
<td>63.9 ± 14.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>2,004 (60.9)</td>
<td>99 (59.6)</td>
<td>561 (58.7)</td>
<td>782 (59.8)</td>
<td>562 (65.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>ICU admission body weight (kg)</td>
<td>61.7 ± 13.2</td>
<td>60.3 ± 13.8</td>
<td>60.8 ± 12.7</td>
<td>61.4 ± 13.2</td>
<td>63.5 ± 13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission BMI (kg/m²)</td>
<td>23.3 ± 4.5</td>
<td>22.9 ± 4.9</td>
<td>23.0 ± 4.6</td>
<td>23.3 ± 4.4</td>
<td>23.6 ± 4.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>113.3 ± 27.3</td>
<td>115.3 ± 25.8</td>
<td>113.8 ± 25.9</td>
<td>114.8 ± 27.4</td>
<td>112.9 ± 28.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>60.4 ± 15.6</td>
<td>62.0 ± 16.7</td>
<td>60.9 ± 14.9</td>
<td>60.7 ± 15.0</td>
<td>59.2 ± 17.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3.6 ± 2.8</td>
<td>3.2 ± 2.5</td>
<td>3.7 ± 2.8</td>
<td>3.8 ± 2.8</td>
<td>3.3 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cause of AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Septic</td>
<td>1,822 (55.4)</td>
<td>104 (62.7)</td>
<td>528 (55.3)</td>
<td>710 (54.3)</td>
<td>480 (55.7)</td>
<td></td>
</tr>
<tr>
<td>Non-septic</td>
<td>1,467 (44.6)</td>
<td>62 (37.3)</td>
<td>427 (44.7)</td>
<td>597 (45.7)</td>
<td>381 (44.3)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,134 (34.5)</td>
<td>72 (43.4)</td>
<td>386 (40.4)</td>
<td>442 (33.8)</td>
<td>234 (27.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>838 (25.5)</td>
<td>42 (25.3)</td>
<td>240 (25.2)</td>
<td>373 (28.5)</td>
<td>183 (21.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>757 (23.0)</td>
<td>36 (21.7)</td>
<td>232 (24.3)</td>
<td>334 (25.6)</td>
<td>155 (18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>574 (17.4)</td>
<td>27 (16.3)</td>
<td>176 (18.4)</td>
<td>260 (19.9)</td>
<td>111 (12.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>521 (15.8)</td>
<td>23 (13.9)</td>
<td>161 (16.9)</td>
<td>213 (16.3)</td>
<td>124 (14.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>COPD</td>
<td>217 (6.6)</td>
<td>18 (10.8)</td>
<td>66 (6.9)</td>
<td>78 (6.0)</td>
<td>55 (6.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>27.6 ± 8.0</td>
<td>26.1 ± 7.4</td>
<td>25.9 ± 7.6</td>
<td>27.1 ± 7.8</td>
<td>30.5 ± 7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SOFA score</td>
<td>12.1 ± 3.5</td>
<td>11.9 ± 3.3</td>
<td>11.9 ± 3.4</td>
<td>12.1 ± 3.6</td>
<td>12.3 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Laboratory findings at CKRT initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Low</th>
<th>Normal</th>
<th>High</th>
<th>Very high</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count (×10³/μL)</td>
<td>15.0 ± 19.4</td>
<td>13.1 ± 13.2</td>
<td>14.9 ± 21.7</td>
<td>14.5 ± 18.4</td>
<td>16.0 ± 19.1</td>
<td>0.20</td>
</tr>
<tr>
<td>Platelet count (×10³/μL)</td>
<td>109.1 ± 91.4</td>
<td>94.4 ± 75.6</td>
<td>107.5 ± 82.5</td>
<td>110.7 ± 92.4</td>
<td>111.1 ± 101.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.5 ± 2.2</td>
<td>9.8 ± 1.9</td>
<td>9.6 ± 2.0</td>
<td>9.5 ± 2.1</td>
<td>9.2 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>136.9 ± 8.1</td>
<td>138.8 ± 6.8</td>
<td>137.1 ± 7.5</td>
<td>136.4 ± 8.0</td>
<td>137.2 ± 8.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.5 ± 1.1</td>
<td>3.9 ± 0.7</td>
<td>4.2 ± 0.9</td>
<td>4.5 ± 1.0</td>
<td>5.0 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>53.9 ± 32.0</td>
<td>42.9 ± 27.0</td>
<td>47.3 ± 27.1</td>
<td>55.4 ± 30.3</td>
<td>61.2 ± 38.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.9 ± 2.1</td>
<td>2.2 ± 1.4</td>
<td>2.6 ± 1.8</td>
<td>2.9 ± 1.7</td>
<td>3.6 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>31.1 ± 19.0</td>
<td>37.5 ± 21.2</td>
<td>35.2 ± 20.2</td>
<td>30.3 ± 18.3</td>
<td>27.0 ± 16.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>7.8 ± 1.4</td>
<td>8.2 ± 1.1</td>
<td>8.1 ± 1.3</td>
<td>7.9 ± 1.5</td>
<td>7.4 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphate (mg/dL)</td>
<td>5.9 ± 2.5</td>
<td>2.2 ± 0.5</td>
<td>3.8 ± 0.5</td>
<td>5.7 ± 0.7</td>
<td>9.3 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.7 ± 0.7</td>
<td>2.8 ± 0.6</td>
<td>2.7 ± 0.6</td>
<td>2.7 ± 0.8</td>
<td>2.6 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>12.7 ± 10.9</td>
<td>14.5 ± 10.5</td>
<td>12.7 ± 10.4</td>
<td>12.7 ± 10.9</td>
<td>12.4 ± 11.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>18.0 ± 5.8</td>
<td>21.0 ± 6.1</td>
<td>18.9 ± 5.5</td>
<td>17.6 ± 5.1</td>
<td>16.1 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>7.3 ± 5.6</td>
<td>4.8 ± 4.8</td>
<td>5.1 ± 4.2</td>
<td>6.6 ± 5.0</td>
<td>10.5 ± 6.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, or number (%).

AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CKRT, continuous kidney replacement therapy; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.
Table 2. In-hospital information for phosphate groups in all patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 3,290)</th>
<th>Low (n = 166)</th>
<th>Normal (n = 955)</th>
<th>High (n = 1,307)</th>
<th>Very high (n = 862)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-Day</td>
<td>1,146 (34.8)</td>
<td>32 (19.3)</td>
<td>200 (20.9)</td>
<td>464 (35.5)</td>
<td>450 (52.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30-Day</td>
<td>1,818 (55.3)</td>
<td>72 (43.4)</td>
<td>409 (42.8)</td>
<td>728 (55.7)</td>
<td>609 (70.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90-Day</td>
<td>2,101 (63.9)</td>
<td>91 (54.8)</td>
<td>528 (55.3)</td>
<td>824 (63.0)</td>
<td>658 (76.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>278 (8.4)</td>
<td>33 (19.9)</td>
<td>142 (14.9)</td>
<td>86 (6.6)</td>
<td>17 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>1,795 (54.6)</td>
<td>76 (45.8)</td>
<td>481 (50.4)</td>
<td>723 (55.3)</td>
<td>515 (59.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2</td>
<td>735 (22.3)</td>
<td>28 (16.9)</td>
<td>186 (19.5)</td>
<td>299 (22.9)</td>
<td>222 (25.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Target clearance (mL/kg/hr)</td>
<td>40.8 ± 13.5</td>
<td>41.5 ± 14.1</td>
<td>40.6 ± 14.0</td>
<td>40.4 ± 12.8</td>
<td>41.3 ± 13.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Length of hospital stay (day)</td>
<td>14.0 (4.0–35.0)</td>
<td>24.0 (9.0–42.0)</td>
<td>22.0 (9.0–47.0)</td>
<td>16.0 (4.0–34.0)</td>
<td>6.0 (2.0–20.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKRT duration (day)</td>
<td>3.0 (1.0–7.0)</td>
<td>4.0 (2.0–10.0)</td>
<td>4.0 (2.0–8.0)</td>
<td>3.0 (1.0–7.0)</td>
<td>2.0 (1.0–5.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as number (%), mean ± standard deviation, or median (interquartile range).

CKRT, continuous kidney replacement therapy.

Figure 2. Hazard ratios (HRs) for the association between phosphate and 90-day mortality determined using the restricted cubic spline regression model. The reference value was set to the lower limit of normal for phosphate (2.8 mg/dL). The red line indicates the estimated HR; the dashed green line indicates the reference line of the null hypothesis that the HR is 1; the dashed black lines indicate the lower and upper 95% confidence limits (CLs).

In the Cox proportional hazards models, both the high and very high phosphate groups had consistently higher risk for 90-day mortality than did the normal phosphate group (model 4: high phosphate group: adjusted HR [aHR], 1.35, 95% confidence interval [CI], 1.21–1.51, p < 0.001; very high phosphate group: aHR, 2.01, 95% CI, 1.78–2.27, p < 0.001) (Table 3, Fig. 4A). No difference in mortality risk was observed between the low and normal phosphate groups.

Supplementary Table 1 (available online) details the association between phosphate level and short-term (7- and
Figure 3. The Kaplan-Meier curves for 90-day mortality according to phosphate (P) level. (A) All patients, (B) patients with low disease severity, and (C) patients with high disease severity.

Figure 4. HRs and 95% CIs for 90-day mortality among phosphate level groups by Cox proportional hazards models. (A) All patients, (B) patients with low disease severity, and (C) patients with high disease severity. Model 1 was unadjusted. Model 2 was adjusted for age, sex, and body weight. Model 3 was adjusted for age, sex, body weight, Charlson Comorbidity Index (CCI), hypertension, diabetes, and congestive heart failure. Model 4 was adjusted for age, sex, body weight, CCI, hypertension, diabetes, congestive heart failure, mechanical ventilator use, and vasopressor use.

CI, confidence interval; HR, hazard ratio.

Table 3. Cox regression analyses for 90-day mortality among phosphate groups

<table>
<thead>
<tr>
<th>Phosphate</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>aHR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Low</td>
<td>1.02 (0.81–1.27)</td>
<td>0.89</td>
<td>1.01 (0.81–1.27)</td>
<td>0.92</td>
</tr>
<tr>
<td>Normal</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.36 (1.22–1.52)</td>
<td>&lt;0.001</td>
<td>1.37 (1.23–1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Very high</td>
<td>2.18 (1.94–2.44)</td>
<td>&lt;0.001</td>
<td>2.22 (1.97–2.49)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


aHR, adjusted HR; CI, confidence interval; HR, hazard ratio.
30-day) mortality risk. Similar to the results for long-term mortality, the high and very high phosphate groups had greater 7- and 30-day mortality risk (all \( p < 0.001 \)), whereas no difference in mortality risk was observed between the low and normal phosphate groups.

### Association between phosphate level and mortality according to disease severity

The association between phosphate level and mortality was further analyzed according to disease severity upon CKRT initiation. Supplementary Table 2 (available online) summarizes the baseline characteristics of patients with low severity, whereas Supplementary Table 3 (available online) outlines the in-hospital information of the patients. The results of our Kaplan-Meier curve and Cox regression analyses were consistent with those for the overall patient cohort such that the high and very high phosphate groups showed an increased risk of 90-day mortality (Table 4 and Fig. 3B, 4B).

The baseline characteristics and in-hospital information of patients with high severity are shown in Supplementary Tables 4 and 5 (available online), respectively. Among patients with high severity, the normal phosphate group had the lowest 90-day mortality, whereas the low, high, and very high phosphate groups showed significantly increased 90-day mortality in the Kaplan-Meier curve analysis (Fig. 3C). Multivariable Cox regression analysis also showed that both the high and low phosphate groups showed significantly greater risk for 90-day mortality than did the normal phosphate group (model 4: low: aHR, 1.470, 95% CI, 1.09–1.99, \( p = 0.01 \); high: aHR, 1.47, 95% CI, 1.26–1.73, \( p < 0.001 \); very high phosphate group: aHR, 1.97, 95% CI, 1.67–2.32, \( p < 0.001 \)) (Table 4, Fig. 4C).

### Comparison of the ability to predict mortality between phosphate and other prognostic markers

Fig. 5 shows the receiver operating characteristic curves of the prognostic parameters for 90-day mortality. Accordingly, the AUC of phosphate for 90-day mortality was 0.61 (95% CI, 0.59–0.63). The combination of phosphate and other traditional prognostic markers, such as APACHE II score, albumin, and lactate level, demonstrated significantly greater predictive power than any single marker (Table 5). The NRI for the combination of phosphate and APACHE II score or albumin level or lactate level significantly improved predictability. The IDI also revealed that the combination of phosphate and individual markers, such as the APACHE II score, albumin level, and lactate level, demonstrated significantly greater predictive power than any single marker (Table 5).

### Discussion

This study investigated the relationship between serum phosphate levels at the initiation of CKRT and prognosis using nationwide multicenter cohort data of AKI patients.
Table 5. Comparison of the AUCs and predictive power of prognostic markers for 90-day mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC (95% CI)</th>
<th>p-value</th>
<th>NRI (95% CI)</th>
<th>p-value</th>
<th>IDI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate</td>
<td>0.61 (0.59–0.63)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II</td>
<td>0.65 (0.63–0.67)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II + phosphate</td>
<td>0.67 (0.65–0.69)</td>
<td>&lt;0.001</td>
<td>0.24 (0.17–0.31)</td>
<td>&lt;0.001</td>
<td>0.014</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.63 (0.61–0.65)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin + phosphate</td>
<td>0.67 (0.65–0.68)</td>
<td>&lt;0.001</td>
<td>0.32 (0.25–0.39)</td>
<td>&lt;0.001</td>
<td>0.025</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II + albumin</td>
<td>0.69 (0.67–0.70)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II + albumin + phosphate</td>
<td>0.70 (0.68–0.72)</td>
<td>&lt;0.001</td>
<td>0.24 (0.17–0.31)</td>
<td>&lt;0.001</td>
<td>0.012</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate</td>
<td>0.66 (0.65–0.68)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate + phosphate</td>
<td>0.67 (0.65–0.69)</td>
<td>&lt;0.001</td>
<td>0.35 (0.28–0.42)</td>
<td>&lt;0.001</td>
<td>0.053</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under the curve; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

undergoing CKRT. Notably, increased phosphate levels upon CKRT initiation were associated with increased mortality. In addition, we demonstrated that low phosphate level was associated with increased mortality in patients with high disease severity. Previous studies have failed to clearly determine the relationship between phosphate levels and mortality given the limited number of available patients. This study analyzes data from a large CKRT cohort and presents a relationship clearly between phosphate levels at the initiation of CKRT and prognosis.

Hyperphosphatemia, which is mainly caused by decreased renal excretion of phosphate, is common in AKI patients [17]. In this study, more than half of the patients had phosphate levels above the normal range. In a previous study, there were findings indicating an increased mortality rate associated with phosphate levels, particularly when phosphate levels exceeded 7 [18]. Given the number of patients with high phosphate and the reported higher risk...
of mortality with very high phosphate, we divided the high phosphate population into high and very high and identified those patients with very high phosphate in particular who need more attention. Our study found that high and very high phosphate levels were associated with increased mortality risk regardless of disease severity among critically ill AKI patients, and the very high phosphate group had more risk than the high phosphate group. The shorter length of hospital stay observed in patients with higher phosphate levels in this study may be due to the high mortality rate. This is consistent with the findings of previous studies. In a meta-analysis that included 60,358 critically ill patients, hyperphosphatemia at intensive care unit admission was associated with all-cause mortality [19]. Jung et al. [6] also reported that hyperphosphatemia at CKRT initiation increased mortality risk among AKI patients undergoing CKRT, revealing that hyperphosphatemia was positively correlated with disease severity markers, such as APACHE II and the SOFA scores, and negatively correlated with mean arterial pressure and urine output. These findings suggest that phosphate levels reflect disease severity in critically ill patients with severe AKI. The association between phosphate levels at the onset of CKRT and disease severity is also supported by our findings that the group with higher phosphate levels in our study had higher APACHE II scores, SOFA scores, and serum lactate levels. However, this observational study could not prove the causal relationship, so further research is needed.

Interestingly, we also demonstrated that hypophosphatemia was a risk factor for mortality in AKI patients with high disease severity undergoing CKRT. Previous studies in CKRT have not been able to clarify the relationship between low phosphate and mortality risk due to the small number of patients with low phosphate [6,20]. Phosphate is a critical component of bone and cell membranes and plays a vital role in physiological functions requiring energy, especially in nerve and muscle function [21]. Other research has shown that hypophosphatemia can lead to respiratory muscle weakness and difficulty in the process of weaning off ventilatory support [9-12]. In our study, we also found a higher frequency of mechanical ventilator use in the low phosphate group. Various conditions, including sepsis, total parenteral nutrition, gastrointestinal wasting, diuretic usage, and prolonged mechanical ventilation, can cause hypophosphatemia in critically ill patients [8,22,23].

Hypophosphatemia can cause deleterious effects, including diminished myocardial contractility, increased risk of arrhythmia, compromised response to inotropes, and decreased granulocyte phagocytic activity [24-26].

In response to hypophosphatemia, intravenous phosphate administration or the use of phosphate-containing dialysates can reduce the risk of hypophosphatemia and reduce the variability of phosphate levels during CKRT [27,28]. However, there has been no consensus on the appropriate guidelines or protocols for treating hypophosphatemia in critically ill patients undergoing CKRT. This may be due to the lack of large-scale randomized controlled trials confirming the relationship between hypophosphatemia and mortality, as well as the inconsistent findings of retrospective studies. Some studies have indicated that hypophosphatemia increases the risk of mortality in AKI patients undergoing CKRT [7,8], whereas others have found no association between hypophosphatemia and mortality [20,29,30]. Thongprayoon et al. [7] reported that hypophosphatemia before CKRT initiation was an independent predictor of mortality in critically ill AKI patients, whereas Shor et al. [8] reported that severe hypophosphatemia was closely associated with increased mortality risk in patients with sepsis. Low phosphate levels were also associated with an increased risk of infection-related death in patients with dialysis [5]. By contrast, Kim et al. [20] reported that hypophosphatemia was not a risk factor for increased mortality in AKI patients undergoing CKRT. Their study analyzed 492 patients, of whom only 39 (7.9%) had hypophosphatemia. The current study, which analyzed the effects of hypophosphatemia in a large multicenter patient population, was able to confirm the association between hypophosphatemia and prognosis in patients with high severity. Given that patients with greater disease severity are more vulnerable, they may be more susceptible to the detrimental effects of hypophosphatemia. A recent study demonstrated that the use of phosphate-containing dialysate can effectively prevent severe hypophosphatemia in AKI patients undergoing CKRT [21]. Therefore, AKI patients with high disease severity would benefit from regularly monitoring their phosphate levels and actively using phosphate-containing dialysate to correct for low phosphate levels.

The strength of the current study lies in its multicenter cohort design, which allowed us to secure a large sample
size and resulted in significant outcomes after adjusting for various confounders. However, one limitation of our study was our failure to confirm the exact pathophysiologic mechanism for the association between phosphate levels and mortality, despite anticipating the potential mechanisms mentioned earlier. Another limitation is that the causality between phosphate at the initiation of CKRT and disease severity cannot be clearly established. In addition, the causes of AKI and the reasons for initiating CKRT are diverse, and it is expected that there may be differences in outcomes depending on these factors. However, our study was not able to take these aspects into account due to a lack of data. Furthermore, given that no data on serial changes in phosphate levels were available, it remains unclear whether correcting phosphate levels impacts mortality.

In conclusion, hyperphosphatemia was an independent predictor of mortality in critically ill AKI patients undergoing CKRT. Furthermore, hypophosphatemia was associated with increased mortality in patients with high severity. Therefore, healthcare providers must closely monitor serum phosphate levels and pay close attention to critically ill AKI patients, particularly those with greater disease severity.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Funding**

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**Acknowledgments**

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**Data sharing statement**

The data presented in this study are available from the corresponding author upon reasonable request.

**Authors’ contributions**

Conceptualization, Software, Validation: JHL
Data curation: YHL, SL, JJ, JY, JYP, THB, WYP, SWL, KK, KMK, HK, JYC, JHC, YCK, JHL
Formal analysis: YJS, JJ, JHL
Funding acquisition: JYP, JHL
Investigation: YHL, JHL
Methodology: SL, YCK, JHL
Visualization: YJS, JHL
Writing–original draft: YHL, SL, YCK, JHL
Writing–review & editing: YCK, JHL
All authors read and approved the final manuscript.
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References

Mortality of elderly patients with acute kidney injury undergoing continuous renal replacement therapy: is age a risk factor?

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Background: Whether advanced age is associated with poor outcomes of elderly patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is controversial. This study aimed to evaluate age effect and predictors for mortality in elderly AKI patients undergoing CRRT.

Methods: Data of 480 elderly AKI patients who underwent CRRT were retrospectively analyzed. Subjects were stratified into two groups according to age: younger-old (age, 65–74 years; n = 205) and older-old (age, ≥75 years; n = 275). Predictors for 28-day and 90-day mortality and age effects were analyzed using multivariable Cox regression analysis and propensity score matching.

Results: Urine output at the start of CRRT (adjusted hazard ratio [aHR], 0.99; 95% confidence interval [CI], 0.99–1.00; p = 0.04), operation (aHR, 0.53; 95% CI, 0.30–0.93; p = 0.03), and use of an intra-aortic balloon pump (aHR, 3.60; 95% CI, 1.18–10.96; p = 0.02) were predictors for 28-day mortality. Ischemic heart disease (aHR, 1.74; 95% CI, 1.02–2.98; p = 0.04) and use of a ventilator (aHR, 0.56; 95% CI, 0.36–0.89; p = 0.01) were predictors for 90-day mortality. The older-old group did not exhibit a higher risk for 28-day or 90-day mortality than the younger-old group in multivariable or propensity score-matched models.

Conclusion: Advanced age was not a risk factor for mortality among elderly AKI patients undergoing CRRT, suggesting that advanced age should not be considered for therapeutic decisions in critically ill elderly patients with AKI requiring CRRT.

Keywords: Acute kidney injury, Aged, Continuous renal replacement therapy, Mortality
**Introduction**

Elderly individuals conventionally defined as those aged 65 years or older constitute the fastest-growing segment of the population in developed countries [1-3]. Acute kidney injury (AKI) is a common occurrence among geriatric patients with acute illnesses. Its incidence is on the rise among the elderly. This vulnerability to AKI can be attributed to multiple comorbidities, polypharmacy, and age-related structural, functional, and hemodynamic changes in their kidneys [1,3].

Elderly AKI patients face an elevated risk of hemodynamic instability, making them more likely to require continuous renal replacement therapy (CRRT). Nevertheless, the decision to initiate CRRT in elderly individuals is complex, given that these patients might not always benefit from this aggressive, expensive, and life-sustaining therapy [3]. Although there are reports comparing outcomes between elderly and non-elderly critically ill patients with AKI [3-5], not many studies have examined differences in mortality rates based on age in a subpopulation of elderly AKI patients [3,6]. Additionally, there are conflicting results in terms of the impact of age on adverse outcomes of AKI patients [2]. Therefore, this study aimed to evaluate age effect and identify predictors of mortality in elderly AKI patients requiring CRRT.

**Methods**

**Study subjects**

This was a multicenter, retrospective cohort study based on data collected from AKI patients who underwent CRRT in intensive care units (ICUs) at three university hospitals (Seoul St. Mary’s Hospital, Yeouido St. Mary’s Hospital, and Bucheon St. Mary’s Hospital) from 2012 to 2020. Patients with end-stage kidney disease were excluded. Among 892 adults with AKI who underwent CRRT, those who were younger than 65 years old were excluded. A total of 480 patients were included in the analysis. They were stratified into two groups according to age: younger-old (age of 65-74 years) and older-old (age of ≥75 years). The reason for dividing the groups based on the age of 75 years is that the definition of “old-old” population may refer to individuals aged over 75 years [7]. In addition, when conducting propensity score matching (PSM) to control confounding factors, using the age of 75 years as the dividing point ensured that a similar number of individuals were distributed between the two groups, facilitating a balanced comparison.

In line with the principles of the Declaration of Helsinki, this study was approved by the Institutional Review Board of The Catholic University of Korea (No. XC20RIDI0198).

**Data collection**

Baseline demographic data including age, sex, body mass index (BMI), and cause of AKI were collected. BMI was calculated as the patient’s weight in kilograms divided by the square of height in meters (kg/m²). All comorbidities of each patient and biochemical data were collected based on medical chart review. The presence of each disease was defined based on the description in the medical record. Biochemical data included blood levels of hemoglobin, blood urea nitrogen (BUN), creatinine, albumin, bilirubin, alanine aminotransferase (ALT), prothrombin time-international normalized ratio (PT-INR), sodium, potassium, chloride, calcium, phosphorous, magnesium, and uric acid. To assess disease severity at the time of CRRT initiation, data regarding mean blood pressure (MBP), the use of ventilator and vasopressor, and urine output were reviewed. In addition, data on the operation (any surgery or procedure performed during the hospitalization period), use of mechanical cardiac support (intra-aortic balloon pump [IABP], left ventricular assist device, and extracorporeal membrane oxygenation), and medications including renin-angiotensin system (RAS) blockers, diuretics, and statins were collected.

**Patient outcomes**

Outcomes of this study were short-term mortality and long-term mortality. Short-term mortality was defined as 28-day mortality after CRRT initiation. Long-term mortality was defined as 90-day mortality after CRRT initiation.

**Statistical analysis**

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as...
numbers and percentages. Analyses of short- and long-term survival rates for different age cohorts were performed using the log-rank test. Results are presented as a Kaplan-Meier plot. To identify predictive factors for 28-day and 90-day mortality, Cox regression analyses were performed. Variables included in equations were chosen based on the results of univariable analyses if the parameter demonstrated an association with 28-day or 90-day mortality (p < 0.30). The following factors were adjusted in the multivariable Cox regression analysis for short-term mortality: age group, BMI, comorbidities (including hepatobiliary disease, liver cirrhosis, and cancer), ventilator support, urine output at the start of CRRT, any type of operation, cardiac surgery, usage of IABP, and blood levels of bilirubin, PT-INR, sodium, and chloride at the time of CRRT initiation. For long-term mortality, adjusted factors were as follows: age group, comorbidities (including hepatobiliary disease, cancer, and ischemic heart disease), MBP, usage of a ventilator, urine output at the start of CRRT, any type of operation, liver transplantation, and levels of BUN, creatinine, bilirubin, ALT, PT-INR, potassium, chloride, and phosphorous at the time of CRRT initiation. Subgroup Cox regression analysis for 28-day and 90-day mortality was done after excluding patients who received liver transplantation. PSM was additionally used in Cox regression analysis to increase the precision of the estimated effect without increasing bias resulting from the presence of variables potentially associated with survival (confounding factors). Propensity scores were estimated using multiple logistic regression analysis with adjustments for sex, comorbidities including diabetes mellitus, cancer, hypertension, cardiac surgery, and levels of BUN, ALT, bilirubin, and potassium at the time of CRRT initiation. After calculating propensity scores, patients in the younger-old and older-old groups with similar propensity scores were matched at a 1:1 ratio using the nearest-neighbor method with a 0.1-caliper width. Stratified Cox regression analysis was done after PSM. All statistical tests were conducted using a two-tailed 95% confidence interval (CI). A p-value of <0.05 was considered statistically significant. All descriptive and survival analyses were performed using R version 4.3.1 software program (R Foundation for Statistical Computing).

Results

Baseline characteristics of the study population

In the study population, 42.7% (n = 205) belonged to the younger-old group and 57.3% (n = 275) belonged to the older-old group. As shown in Fig. 1, patients aged 79 years were the most prevalent among the study population. The oldest patient was 99 years old. Table 1 summarizes baseline demographics and laboratory data of the study population. Sepsis was the most common cause of AKI, followed by cardiogenic, postoperative, hypovolemic, hepatorenal, and nephrotoxic causes. The mean age was 69.3 ± 2.8 years in the younger-old group and 80.9 ± 4.6 years in the older-old group. There were more male patients in the older-old group than in the younger-old group. There was no significant difference in BMI, prevalence of comorbidities, disease severity indices, proportion of operation and mechanical cardiac support, or medications between the younger-old group and the older-old group. Laboratory data showed that the older-old group had higher BUN but lower bilirubin and ALT levels at the start of CRRT than the younger-old group. The older-old group showed a tendency to have a higher proportion of those with high potassium levels than the younger-old group. There were no significant differences in blood levels of hemoglobin, creatinine, albumin, PT-INR, sodium, chloride, phosphorous, calcium, magnesium, or uric acid at the start of CRRT between the two groups. After 1:1 PSM, the two groups demonstrated a well-balanced distribution across all baseline characteristics. This includes comorbidities, disease severity, operation, utilization of mechanical cardiac support, medications, and biochemical data. The 1:1 PSM model resulted in 170 patients in each group, with a male ratio of 63.5% in both groups. Table 1 presents the specifics of the parameters both before and after the application of PSM.

Comparison of 28-day and 90-day survival rates between the younger-old group and the older-old group

Fig. 2 shows the survival rates of the two groups using the Kaplan-Meier method. There was no significant difference in the 28-day survival rate (log-rank p = 0.09) (Fig. 2A) or 90-day survival rates (log-rank p = 0.07) (Fig. 2B) between
Figure 1. Age distribution of the study group.

Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>205</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69.3 ± 2.8</td>
<td>69.4 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>70 (34.5)</td>
<td>108 (63.5)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.8 ± 4.0</td>
<td>23.6 ± 3.8</td>
<td>0.16</td>
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<td>Cause of acute kidney injury</td>
<td>&gt;0.99</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Septic</td>
<td>82 (40.0)</td>
<td>71 (41.8)</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>37 (18.0)</td>
<td>33 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>29 (14.1)</td>
<td>8 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>24 (11.7)</td>
<td>22 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Hepatorenal</td>
<td>17 (8.3)</td>
<td>7 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Nephrotoxic</td>
<td>8 (3.9)</td>
<td>22 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>8 (3.9)</td>
<td>7 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Period of hospitalization (day)</td>
<td>48.4 ± 37.3</td>
<td>47.7 ± 38.1</td>
<td>0.60</td>
</tr>
<tr>
<td>Period of ICU care (day)</td>
<td>23.6 ± 22.2</td>
<td>24.2 ± 23.6</td>
<td>0.80</td>
</tr>
<tr>
<td>CRRT duration (day)</td>
<td>6.7 ± 4.8</td>
<td>6.7 ± 4.9</td>
<td>&gt;0.99</td>
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<td>Comorbidities</td>
<td></td>
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</tr>
<tr>
<td>Hepatobiliary origin disease</td>
<td>31 (15.1)</td>
<td>18 (10.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>10 (4.9)</td>
<td>7 (4.1)</td>
<td>0.35</td>
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<tr>
<td>Cancer</td>
<td>61 (29.8)</td>
<td>46 (27.1)</td>
<td>0.81</td>
</tr>
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<td>Heart failure</td>
<td>42 (20.5)</td>
<td>34 (20.0)</td>
<td>0.30</td>
</tr>
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<td>Ischemic heart disease</td>
<td>33 (16.1)</td>
<td>28 (16.5)</td>
<td>0.67</td>
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<td>Diabetes mellitus</td>
<td>67 (32.7)</td>
<td>52 (30.6)</td>
<td>0.82</td>
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(Continued to the next page)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>p-value</th>
<th>Before PSM</th>
<th>After PSM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Younger-old group (age 65–74 yr)</td>
<td>Older-old group (age ≥75 yr)</td>
<td></td>
<td>Younger-old group (age 65–74 yr)</td>
<td>Older-old group (age ≥75 yr)</td>
<td></td>
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<tr>
<td>Cerebrovascular disease</td>
<td>18 (8.8)</td>
<td>24 (8.7)</td>
<td>&gt;0.99</td>
<td>16 (9.4)</td>
<td>14 (8.2)</td>
<td>0.85</td>
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<tr>
<td>Hypertension</td>
<td>84 (41.0)</td>
<td>132 (43.0)</td>
<td>0.15</td>
<td>72 (42.4)</td>
<td>75 (44.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Disease severities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>86.8 ± 12.8</td>
<td>85.9 ± 13.0</td>
<td>0.43</td>
<td>85.8 ± 12.6</td>
<td>86.0 ± 12.1</td>
<td>0.93</td>
</tr>
<tr>
<td>Usage of ventilator</td>
<td>95 (46.3)</td>
<td>111 (40.4)</td>
<td>0.22</td>
<td>76 (44.7)</td>
<td>67 (39.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Usage of vasopressor</td>
<td>115 (56.1)</td>
<td>147 (53.5)</td>
<td>0.63</td>
<td>95 (55.9)</td>
<td>88 (51.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Urine output on the day of CRRT initiation (mL/day)</td>
<td>493.1 ± 690.8</td>
<td>493.4 ± 644.8</td>
<td>0.996</td>
<td>91.8 ± 67.6</td>
<td>93.6 ± 65.8</td>
<td>0.80</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any type of operation</td>
<td>77 (37.6)</td>
<td>95 (34.5)</td>
<td>0.56</td>
<td>60 (35.3)</td>
<td>66 (38.8)</td>
<td>0.57</td>
</tr>
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<td>Cardiac surgery</td>
<td>19 (9.3)</td>
<td>13 (4.7)</td>
<td>0.07</td>
<td>13 (7.6)</td>
<td>12 (7.1)</td>
<td>0.57</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>6 (2.9)</td>
<td>1 (0.4)</td>
<td>0.05</td>
<td>2 (1.2)</td>
<td>1 (0.6)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Mechanical cardiac support</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>2 (1.0)</td>
<td>6 (2.2)</td>
<td>0.51</td>
<td>1 (0.6)</td>
<td>5 (2.9)</td>
<td>0.22</td>
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<tr>
<td>Left ventricular assist device</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>&gt;0.99</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>7 (3.4)</td>
<td>7 (2.5)</td>
<td>0.78</td>
<td>7 (4.1)</td>
<td>7 (4.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Renin-angiotensin system blocker</td>
<td>89 (43.4)</td>
<td>138 (50.2)</td>
<td>0.17</td>
<td>77 (45.3)</td>
<td>80 (17.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Diuretics</td>
<td>59 (28.8)</td>
<td>73 (26.5)</td>
<td>0.66</td>
<td>49 (28.8)</td>
<td>51 (30.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Statin</td>
<td>65 (31.7)</td>
<td>91 (33.2)</td>
<td>0.80</td>
<td>54 (31.8)</td>
<td>64 (37.9)</td>
<td>0.29</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.6 ± 1.8</td>
<td>9.5 ± 1.6</td>
<td>0.47</td>
<td>9.8 ± 1.9</td>
<td>9.5 ± 1.5</td>
<td>0.20</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>52.9 ± 29.8</td>
<td>60.1 ± 34.3</td>
<td>0.02</td>
<td>53.3 ± 29.6</td>
<td>54.6 ± 32.5</td>
<td>0.70</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>3.3 ± 2.2</td>
<td>3.2 ± 2.0</td>
<td>0.83</td>
<td>3.4 ± 2.3</td>
<td>3.0 ± 1.9</td>
<td>0.11</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>2.8 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>0.71</td>
<td>2.7 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>0.21</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>3.4 ± 6.7</td>
<td>1.5 ± 2.4</td>
<td>&lt;0.001</td>
<td>1.9 ± 2.8</td>
<td>1.8 ± 2.9</td>
<td>0.62</td>
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<tr>
<td>ALT (U/L)</td>
<td>328.2 ± 926.5</td>
<td>173.0 ± 641.7</td>
<td>0.04</td>
<td>227.6 ± 776.8</td>
<td>233.4 ± 790.6</td>
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<tr>
<td>PT-INR</td>
<td>1.6 ± 0.6</td>
<td>1.5 ± 0.6</td>
<td>0.495</td>
<td>1.5 ± 0.6</td>
<td>1.5 ± 0.5</td>
<td>0.32</td>
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<tr>
<td>Sodium (mmol/L)</td>
<td>136.9 ± 10.7</td>
<td>138.2 ± 4.8</td>
<td>0.12</td>
<td>136.9 ± 11.4</td>
<td>137.9 ± 4.7</td>
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<tr>
<td>Potassium (mmol/L)</td>
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<td>0.04</td>
<td>0.30</td>
<td>0.04</td>
<td>0.04</td>
<td>0.30</td>
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<tr>
<td>&lt;3.5</td>
<td>57 (27.8)</td>
<td>75 (72.3)</td>
<td>0.04</td>
<td>45 (26.5)</td>
<td>50 (29.4)</td>
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<td>3.5–4.5</td>
<td>131 (63.9)</td>
<td>156 (56.7)</td>
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<td>112 (65.9)</td>
<td>100 (58.8)</td>
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<td>&gt;4.5</td>
<td>17 (8.3)</td>
<td>44 (18.0)</td>
<td>0.12</td>
<td>13 (7.6)</td>
<td>20 (11.8)</td>
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<td>Chloride (mmol/L)</td>
<td>101.6 ± 5.3</td>
<td>102.2 ± 5.0</td>
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<td>102.1 ± 5.2</td>
<td>101.7 ± 4.9</td>
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<td>Calcium (mg/dL)</td>
<td>8.1 ± 1.1</td>
<td>8.1 ± 0.9</td>
<td>0.96</td>
<td>8.1 ± 1.1</td>
<td>8.2 ± 0.9</td>
<td>0.36</td>
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<tr>
<td>Phosphorous (mg/dL)</td>
<td>0.13</td>
<td>0.13</td>
<td>0.40</td>
<td>0.13</td>
<td>0.13</td>
<td>0.40</td>
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<tr>
<td>&lt;2.5</td>
<td>19 (10.4)</td>
<td>39 (15.9)</td>
<td>0.15</td>
<td>15 (9.7)</td>
<td>22 (14.7)</td>
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<tr>
<td>2.5–4.49</td>
<td>98 (53.6)</td>
<td>111 (45.3)</td>
<td>0.81</td>
<td>81 (52.6)</td>
<td>72 (48.0)</td>
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<tr>
<td>≥4.5</td>
<td>66 (36.1)</td>
<td>95 (38.8)</td>
<td>0.58</td>
<td>58 (37.7)</td>
<td>56 (37.3)</td>
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<tr>
<td>Magnesium (mg/dL)</td>
<td>2.2 ± 0.5</td>
<td>2.2 ± 0.5</td>
<td>0.91</td>
<td>2.3 ± 0.5</td>
<td>2.2 ± 0.5</td>
<td>0.34</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.5 ± 9.3</td>
<td>6.4 ± 3.7</td>
<td>0.95</td>
<td>6.6 ± 9.7</td>
<td>6.2 ± 4.0</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, or number (%).
ALT, alanine transaminase; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; ICU, intensive care unit; INR, international normalized ratio; PSM, propensity score matching; PT, prothrombin time.
the younger-old group and the older-old group.

**Predictors for 28-day mortality**

Univariable and multivariable analyses were performed to identify independent prognostic factors for 28-day mortality (Table 2). In univariable analysis, hepatobiliary disease, urine output at the start of CRRT, any type of operation, usage of IABP, and serum chloride level were significantly associated with 28-day mortality (all p < 0.05). Multivariable Cox regression analysis showed that urine output at the start of CRRT (adjusted hazard ratio [HR], 0.99; 95% CI, 0.99–1.00; p = 0.04), any type of operation (adjusted HR, 0.53; 95% CI, 0.30–0.93; p = 0.03), and usage of IABP (adjusted HR, 3.60; 95% CI, 1.18–11.00; p = 0.02) were independent prognostic factors for 28-day mortality.

After excluding patients who underwent liver transplantation, a subgroup analysis was conducted. In univariable analysis, factors such as hepatobiliary disease, liver cirrhosis, urine output at the start of CRRT, any type of operation, usage of IABP, and serum bilirubin and chloride level were found to be associated with 28-day mortality (all p < 0.05). Multivariable Cox regression analysis showed that the use of IABP (adjusted HR, 3.95; 95% CI, 1.29–12.12; p = 0.02) was an independent prognostic factor for 28-day mortality (Supplementary Table 1, available online).

**Predictors for 90-day mortality**

Univariable and multivariable analyses were performed to assess independent prognostic factors for 90-day mortality (Table 3). In univariable analysis, hepatobiliary disease, cancer, usage of ventilator, any type of operation, and serum phosphorus level were significantly associated with 90-day mortality (all p < 0.05). Multivariable Cox regression analysis showed that older age (adjusted HR, 0.65; 95% CI, 0.44–0.96; p = 0.03), usage of ventilator (adjusted HR, 0.61; 95% CI, 0.43–0.88; p = 0.007) and liver transplantation (adjusted HR, 0.07; 95% CI, 0.01–0.64; p = 0.02) were significantly associated with a decreased risk of 90-day mortality, whereas ischemic heart disease (adjusted HR, 1.77; 95% CI, 1.04–3.01; p = 0.027) was significantly associated with an increased risk of 90-day mortality.

A subgroup analysis after excluding patients who received liver transplantation was conducted. In univariable analysis, comorbidities such as hepatobiliary disease, cancer, usage of ventilator, serum creatinine, bilirubin, and chloride level were associated with 90-day mortality (all p < 0.05). Multivariable analysis showed that liver cirrhosis (adjusted HR, 0.29; 95% CI, 0.09–0.92; p = 0.04), ischemic heart disease (adjusted HR, 2.250; 95% CI, 1.099–4.608; p = 0.027), usage of ventilator (adjusted HR, 0.54; 95% CI, 0.35–0.83; p = 0.005) and usage of vasopressor (adjusted HR, 2.06; 95% CI, 1.26–3.36; p = 0.004) were independent prognostic factors for 90-day mortality (Supplementary Ta-
Table 2. Cox regression analysis of predictors for 28-day mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger-old</td>
<td>Reference</td>
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</tr>
<tr>
<td>Older-old</td>
<td>0.69 (0.45–1.04)</td>
<td>0.08</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.85 (0.55–1.32)</td>
<td>0.47</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.03 (0.98–1.08)</td>
<td>0.22</td>
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<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
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<tr>
<td>Hepatobiliary origin disease</td>
<td>1.93 (1.18–3.15)</td>
<td>0.008</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1.78 (0.89–3.54)</td>
<td>0.12</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.40 (0.92–2.13)</td>
<td>0.12</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.00 (0.59–1.70)</td>
<td>0.99</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.17 (0.65–2.10)</td>
<td>0.61</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.07 (0.68–1.70)</td>
<td>0.76</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.21 (0.58–2.49)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.04 (0.69–1.59)</td>
<td>0.84</td>
</tr>
<tr>
<td>Disease severities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>1.01 (0.99–1.02)</td>
<td>0.46</td>
</tr>
<tr>
<td>Usage of ventilator</td>
<td>0.75 (0.49–1.14)</td>
<td>0.18</td>
</tr>
<tr>
<td>Usage of vasopressor</td>
<td>1.21 (0.79–1.84)</td>
<td>0.39</td>
</tr>
<tr>
<td>Urine output on the day of CRRT initiation</td>
<td>0.99 (0.99–1.00)</td>
<td>0.01</td>
</tr>
<tr>
<td>Operation</td>
<td>0.56 (0.34–0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Any type of operation</td>
<td>0.51 (0.16–1.61)</td>
<td>0.25</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>0.05 (0.00–35.30)</td>
<td>0.37</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical cardiac support</td>
<td>2.91 (1.07–7.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>IABP</td>
<td>2.19 (0.30–15.76)</td>
<td>0.44</td>
</tr>
<tr>
<td>LVAD</td>
<td>1.13 (0.41–3.07)</td>
<td>0.82</td>
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<tr>
<td>ECMO</td>
<td></td>
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<tr>
<td>Medications</td>
<td>0.99 (0.65–1.50)</td>
<td>0.95</td>
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<tr>
<td>RAS blocker</td>
<td>0.89 (0.56–1.43)</td>
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<tr>
<td>Diuretics</td>
<td>0.90 (0.57–1.41)</td>
<td>0.64</td>
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<td>Statin</td>
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<tr>
<td>Biochemical data at the time of CRRT initiation</td>
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<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.00 (0.87–1.15)</td>
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</tr>
<tr>
<td>BUN</td>
<td>1.00 (1.00–1.01)</td>
<td>0.88</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.00 (0.89–1.13)</td>
<td>0.98</td>
</tr>
<tr>
<td>Albumin</td>
<td>1.02 (0.68–1.52)</td>
<td>0.93</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.02 (1.00–1.05)</td>
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</tr>
<tr>
<td>ALT</td>
<td>1.00 (1.00–1.00)</td>
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<tr>
<td>PT-INR</td>
<td>1.22 (0.92–1.60)</td>
<td>0.17</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.98 (0.95–1.01)</td>
<td>0.23</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td></td>
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<tr>
<td>≤3.5</td>
<td>0.70 (0.43–1.14)</td>
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</tr>
<tr>
<td>&gt;4.5</td>
<td>1.09 (0.60–1.97)</td>
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<tr>
<td>Chloride</td>
<td>0.96 (0.93–1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.01 (0.85–1.21)</td>
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<td>Phosphorous (mg/dL)</td>
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<tr>
<td>≥2.5</td>
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<tr>
<td>Magnesium</td>
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</tr>
<tr>
<td>Uric acid</td>
<td>1.19 (0.76–1.87)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; BUN, blood urea nitrogen; CI, confidence interval; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygen; HR, hazard ratio; IABP, intra-aortic balloon pumps; INR, international normalized ratio; LVAD, left ventricular assist device; PT, prothrombin time; RAS, renin-angiotensin system.
Table 3. Cox regression analysis of predictors for 90-day mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
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<td>Age</td>
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<tr>
<td>Younger-old</td>
<td>Reference</td>
<td></td>
</tr>
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<td>Older-old</td>
<td>0.74 (0.54–1.02)</td>
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<td>Male sex</td>
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<td>Body mass index</td>
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<td>Heart failure</td>
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<td>0.84</td>
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<td>Disease severities</td>
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<tr>
<td>Mean blood pressure</td>
<td>1.01 (1.00–1.02)</td>
<td>0.15</td>
</tr>
<tr>
<td>Usage of ventilator</td>
<td>0.64 (0.46–0.88)</td>
<td>0.005</td>
</tr>
<tr>
<td>Usage of vasopressor</td>
<td>1.16 (0.85–1.59)</td>
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<td>Urine output on the day of CRRT initiation</td>
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<td>Operation</td>
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<tr>
<td>Any type of operation</td>
<td>0.70 (0.50–0.98)</td>
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<td>Cardiac surgery</td>
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<tr>
<td>BUN</td>
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<tr>
<td>Albumin</td>
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<td>Bilirubin</td>
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<td>3.5–4.5</td>
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<td>&gt;4.5</td>
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<tr>
<td>Calcium</td>
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<tr>
<td>Phosphorous (mg/dL)</td>
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<td>1.01 (0.92–1.10)</td>
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<td>&lt;2.5</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>2.5–4.49</td>
<td>0.52 (0.26–1.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>≥4.5</td>
<td>1.15 (0.81–1.61)</td>
<td>0.44</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.07 (0.77–1.49)</td>
<td>0.69</td>
</tr>
<tr>
<td>Uric acid</td>
<td>1.04 (0.96–1.12)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; BUN, blood urea nitrogen; CI, confidence interval; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IABP, intra-aortic balloon pump; INR, international normalized ratio; LVAD, left ventricular assist device; PT, prothrombin time.
**Table 4** shows the results of the Cox proportional hazard regression analysis for the 28-day mortality of the older-old group. In univariable analysis, the risk of 28-day mortality was not higher in the older-old group than in the younger-old group (model 1). In multivariable analysis, the older-old group did not show a higher risk for 28-day mortality than the younger-old group after adjustments for age group, BMI, comorbidities (including hepatobiliary disease, liver cirrhosis, and cancer), ventilator support, urine output at the start of CRRT, any type of operation, cardiac surgery, usage of IABP, and blood levels of bilirubin, PT-INR, sodium, and chloride (model 2). After PSM (model 3), the older-old group was not associated with the risk for 28-day mortality (adjusted HR, 0.92; 95% CI, 0.42–2.00; p = 0.84).

**Table 5** shows the results of the Cox proportional hazard regression analysis for 90-day mortality of the older-old group. In univariable analysis, the risk of 90-day mortality was not higher in the older-old group than in the younger-old group (model 1). In multivariable analysis, the older-old group had a lower risk for 90-day mortality than the younger-old group after adjustments for comorbidities (including hepatobiliary disease, cancer, and ischemic heart disease), MBP, usage of ventilator, urine output at the start of CRRT, any type of operation, liver transplantation, and levels of BUN, creatinine, bilirubin, ALAT, PT-INR, potassium, chloride, and phosphorous. However, after PSM (model 3), the older-old group was not associated with the risk for 90-day mortality (adjusted HR, 1.00; 95% CI, 0.49–2.05; p > 0.99).

**Discussion**

The risk of developing AKI is significantly increased in the elderly [8]. Therefore, we often need to consider CRRT for elderly patients with AKI. There are reports showing that age is a risk factor for mortality in AKI patients [3,4,9], while others have reported that age is not associated with mortality [5,6]. The purpose of this study was to examine whether age affected mortality in elderly patients with AKI undergoing CRRT. Results showed that advanced age did not increase the risk of mortality.

**Table 4. Cox regression analysis of 28-day mortality and individual components**

<table>
<thead>
<tr>
<th>Group</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI) p-value</td>
<td>HR (95% CI) p-value</td>
<td>HR (95% CI) p-value</td>
</tr>
<tr>
<td>Younger-old</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Older-old</td>
<td>0.69 (0.45–1.04) 0.08</td>
<td>0.70 (0.44–1.13) 0.14</td>
<td>0.92 (0.42–2.00) 0.84</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

Model 1: unadjusted. Model 2: adjusted for age group, body mass index, comorbidities including hepatobiliary disease, liver cirrhosis, and cancer, ventilator support, urine output at the start of continuous renal replacement therapy (CRRT), any type of operation, cardiac surgery, usage of intra-aortic ballooning pump, and blood levels of bilirubin, prothrombin time-international normalized ratio, sodium, and chloride at the time of CRRT initiation. Model 3: propensity score-matched covariates: sex, diabetes mellitus, cancer, hypertension, levels of bilirubin, alanine transaminase, blood urea nitrogen, and potassium at the time of CRRT initiation, and cardiac operation.

**Table 5. Cox regression analysis of 90-day mortality and individual components**

<table>
<thead>
<tr>
<th>Group</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI) p-value</td>
<td>HR (95% CI) p-value</td>
<td>HR (95% CI) p-value</td>
</tr>
<tr>
<td>Younger-old</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Older-old</td>
<td>0.74 (0.54–1.02) 0.06</td>
<td>0.65 (0.44–0.96) 0.03</td>
<td>1.00 (0.49–2.05) &gt;0.99</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.

Model 1: unadjusted. Model 2: adjusted for age group, comorbidities including hepatobiliary disease, cancer, and ischemic heart disease, mean blood pressure, usage of ventilator, urine output at the start of continuous renal replacement therapy (CRRT), any type of operation, liver transplantation and blood levels of urea nitrogen, creatinine, bilirubin, alanine transaminase (ALT), prothrombin time-international normalized ratio, potassium, chloride, and phosphorous at the time of CRRT initiation. Model 3: propensity score-matched covariates: sex, diabetes mellitus, cancer, hypertension, levels of bilirubin, ALT, blood urea nitrogen, and potassium at the time of CRRT initiation, and cardiac operation.
not increase short-term or long-term mortality in elderly AKI patients undergoing CRRT. This finding was evident after PSM. These results suggest that it is not reasonable to withhold or hesitate to start CRRT solely because of a patient’s advanced age.

Only a few studies have examined the outcomes of elderly AKI patients undergoing CRRT. There was a prospective multicenter study from South Korea that included 607 patients aged 65 years or older [10], although a detailed age distribution was not described. In a retrospective, single-center study by Rhee et al. [3], 411 patients aged 65 years or older were included, with those aged 75 years or more accounting for 44.3%. Previous studies have also focused on very elderly patients. Conroy et al. [4] have included 118 patients aged 75 years or more. Liu et al. [6] have included 41 patients aged 80 years or more. Funk et al. [5] have included 102 patients aged 80 years or more. These studies indicate that elderly AKI patients undergoing CRRT are common and that application of CRRT in the very elderly group, such as patients with ages more than 75 or 80 years, is not an uncommon finding. Similarly, in this study, the proportion of patients aged ≥75 years was higher than that of patients aged 65 to 74 years (57.3% vs. 42.7%), with patients aged 79 years being the most prevalent among the study population.

In this study, the most common cause of AKI was sepsis, both in the younger-old and older-old groups, similar to the findings of previous studies [10,11]. There was no significant difference in comorbidities, MBP, or urine output at baseline between the two groups, suggesting that hemodynamic or anuric status was not different between the two groups. The baseline BUN level was higher in the older-old group than in the younger-old group. Since BUN is influenced by a range of factors including glomerular filtration, tubular reabsorption of urea, catabolism of endogenous protein, volume status, and upper gastrointestinal bleeding [12], the older-old group might experience reduced glomerular and tubular function, more catabolic and dehydrated state, and increased vulnerability to upper gastrointestinal bleeding than the younger-old group when AKI occurs. Higher levels of bilirubin and ALT in the older-old group than in the older-old group could be potentially attributed to the fact that those in the younger-old group were more likely to have undergone liver transplantation, although there was no significant difference in the prevalence of hepatobiliary disease or liver cirrhosis. Further investigation and analysis are needed to confirm these hypotheses and determine the reasons behind differences in bilirubin and ALT levels between the two groups. An increasing proportion of the older-old group shifting towards a high potassium level compared to the younger-old group might be associated with aging-related disturbance in renal tubular function and RAS activity [13,14]. In this study, serum creatinine levels between the older-old group and the younger-old group did not exhibit a significant difference. However, considering that serum creatinine level can be influenced by factors such as muscle mass, age, and frailty, the actual difference in serum creatinine level might not be apparent [15] and the residual renal function might have been lower in the older-old group than in the younger-old group.

In this study, the older-old group and the younger-old group did not exhibit a significant difference in 28-day or 90-day survival rate, in contrast with the results of a previous study [3]. This difference might be attributed to the fact that, in our study, there was no significant difference in comorbidities or disease severity indices between the younger-old and older-old groups, whereas there were differences in comorbidities and disease severity in the previous study [3]. We speculate that, since the older-old and young-old groups had similar baseline characteristics, survival rates after CRRT initiation were not significantly different between the two groups.

In the 28-day Cox regression analysis, age did not appear to be a significant predictive factor. However, urine output was associated with a reduced risk of 28-day death. This aligns with previous research that considered urine output as a reliable indicator for renal and multiorgan impairment, suggesting that urine output might play a role in reducing the risk of 28-day mortality. When there is a certain amount of urine output in patients who have started CRRT, it can signify a favorable prognosis. Additionally, in some respects, it can be interpreted that early initiation of CRRT in elderly AKI patients is beneficial for their outcomes. A study by Park et al. [10] supports this consideration. In that study, the mortality rate was analyzed according to urine output by categorizing elderly AKI patients undergoing CRRT based on their median 6-hour urine output immediately before CRRT initiation. Their results showed that patients with a higher urine output just before starting CRRT
had better outcomes. In other words, an earlier initiation of CRRT in elderly AKI patients can contribute to improved prognosis. Similar studies suggesting the benefits of early initiation of CRRT have also been reported in AKI patients [16, 17]. In this study, operation appeared to be a variable that reduced the 28-day mortality rate. Since the operation included any surgery or procedure performed during hospitalization, a proactive intervention or the presence of correctable causal factors might have led to a better prognosis. On the other hand, the use of IABP appeared to increase the risk of 28-day death. This suggested that there might have been severe cardiac conditions or multiorgan failure that was significant enough to warrant the application of IABP, which affected the short-term mortality.

In the 90-day Cox regression analysis, the use of ventilator lowered the risk of 90-day mortality. The reason was unclear. It could be speculated that the long-term survival of patients might have benefited from active respiratory support. However, in a previous study, the usage of ventilators was not significantly associated with long-term mortality [3]. Since previous research [3] and the current study did not categorize more specific details such as respiratory diseases, further research is needed to understand how different results were obtained in each study. In our study, ischemic heart disease was not a risk factor for 28-day mortality. However, it was a significant predictor for 90-day mortality. It could be assumed that more patients with ischemic heart disease had cardiac decompensation with AKI, which might have led to an increased risk for long-term mortality. Liver transplantation was also identified as a factor in reducing the risk of 90-day mortality. Previous studies have shown an improvement in the survival rates of liver transplantation over time [18, 19]. Due to this enhancement, liver transplantation appeared as a factor in improving 90-day survival in this study. However, it did not appear to be a prognostic factor in 28-day mortality. The reason is uncertain; it may be associated with acute complications of liver transplantation in the early postoperative period, such as infection, bleeding, and organ failure after surgery. It may also be due to a selection bias, that is, elderly patients with more severe illness might have not been included because they could not even initiate CRRT.

The older-old group seemed to have a lower risk for 90-day mortality in multivariable Cox regression analysis, which might be related to a selection bias in this study. Since this was a retrospective cohort study, we tried to minimize the possible confounding effect by performing PSM. The older-old group had no significant impact of age on 28-day or 90-day mortality after PSM. This suggests that advanced age in elderly patients was neither beneficial nor harmful for survival. A previous report has shown that age is not a risk factor for poor outcomes [4]. This may be because of clinical decisions to perform CRRT in critically ill elderly patients with AKI. ICU physicians might have selected elderly patients with fewer comorbidities and greater likelihood of survival, which has been demonstrated in previous studies [20–22]. On the other hand, it also may be because elderly patients can truly benefit from intensive care, which has been demonstrated by a prospective, observational, multicenter study regarding the effects of ICU triage decisions on mortality and ICU benefit in elderly patients [23]. Its results showed that elderly patients had more ICU rejections and higher mortality than younger patients. However, the mortality benefit appeared to be greater for the elderly.

In this study, liver transplantation was performed on younger-old patients rather than older-old patients. Despite the improved survival rates associated with liver transplantation, the inevitability of potential complications such as infection, bleeding, and organ failure after surgery makes it evident that adjustments for post-liver transplantation mortality may be necessary. Therefore, we conducted a subgroup Cox regression analysis after excluding liver transplant recipients and the results consistently showed age was not a significant risk factor for 28- and 90-day mortality.

Our study has several limitations. First, this study did not include variables such as scores indicating the severity of illness because data such as APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sequential Organ Failure Assessment) score were lacking. Second, the dose of CRRT was not analyzed because those data were not collected. However, until now, there has been no randomized controlled trial demonstrating the optimal CRRT dose in elderly patients. Third, variables such as comorbidities and disease severity indices did not exhibit significant differences between the older-old and younger-old groups. This might be due to a selection bias, that is, elderly patients with more severe illness might have not been included because they could not even initiate CRRT.

Fourth, resulting in due to the retrospective manner of this research, bias and several uncharted comorbidities or
events could play a role in the interpretation of short- and long-term mortality in this study. Despite these limitations, the number of elderly patients in this study was not small. In addition, the use of PSM enabled control of confounding variables, which could stand as a strength of this study.

In conclusion, an older age was not a risk factor for short-term or long-term mortality in elderly patients with AKI undergoing CRRT. This supports the importance of active management and application of CRRT in critically ill elderly patients with AKI.

Conflicts of interest
All authors have no conflicts of interest to declare.

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Data sharing statement
The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions
Conceptualization, Methodology, Funding acquisition: HEY
Formal analysis: JHK, SHE, HWK, HEY
Investigation, Resources: JWM, ESK, EJK, HDK, BHC, SJS, CWY, HEY
Writing–original draft: JHK, HEY
Writing–review & editing: All authors
All authors read and approved the final manuscript.

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References


Differences in the incidence, characteristics, and outcomes of patients with acute kidney injury in the medical and surgical intensive care units

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²Department of Internal Medicine, Pusan National University School of Medicine, Yangsan, Republic of Korea

Introduction

Acute kidney injury (AKI) is a common condition among patients in the intensive care unit (ICU). It is associated with longer hospital stays, and a two-to three-fold increased risk of death [1–3]. The prevalence of AKI among patients in the ICU varies widely, ranging from 10% to 70% [1,4–8]. This variation has been attributed to inconsistencies in the definition of AKI. However, even after the adoption of a unified definition by the Kidney Disease: Improving Global Outcomes (KDIGO) group in 2012 [9], the prevalence of AKI remains variable across studies. Critical-
ly ill patients can be broadly categorized into medical and surgical groups, with distinct patient characteristics, co-morbidities, and reasons for ICU admission. Consequently, the frequency and impact of AKI are also expected to differ between these groups.

Epidemiologic studies on AKI were conducted without distinguishing between medical and surgical patients. Limited studies have compared the prevalence or impact of AKI on patient mortality between medical and surgical ICU patients \[10,11\]. Previous research has shown that medical ICU patients have a higher incidence of AKI and comorbid conditions, such as sepsis and cardiovascular disease \[1,10,11\]. Among surgical patients, AKI was commonly complicated after cardiovascular or trauma surgery \[12\], and AKI patients have been shown to have a higher mortality rate than non-AKI patients.

With the differences in baseline characteristics and etiologies of AKI between medical and surgical patients, we hypothesized that the courses of AKI, clinical outcomes, and the influence of AKI may differ between both groups. If it does, differentiation and well characterization of medical and surgical AKI patients will help us to find the reasons for AKI, predict clinical courses, and plan the management of AKI at the time of diagnosis. It may also help us to plan personalized prevention of AKI in critically ill patients depending on the department.

However, there is a lack of studies directly comparing the characteristics of AKI in medical and surgical patients. This study aims to address this gap by analyzing data from the ICU-AKI cohort of two hospitals in South Korea from 2011 to 2020.

**Methods**

**Design and setting**

This is a multicenter, retrospective cohort study based on the electronic medical record (EMR)-extracted ICU cohorts in two tertiary care hospitals in South Korea: the Pusan National University Hospital (PNUH) and Pusan National University Yangsan Hospital (PNUYH).

Data of patients admitted to ICUs (medical, pulmonary, surgical, trauma, neurosurgery, and emergency) in PNUH and PNUYH, between January 2011 to December 2020, were reviewed. Patients were excluded if they had end-stage kidney disease (ESKD) on maintenance dialysis, lacked prior information on baseline kidney function, and were younger than 18 years old. Patients were divided into medical and surgical groups, based on the attending physician’s department at ICU admission. Information on comorbidities, laboratory findings at ICU admission, and survival status was retrieved from the EMR. Details about cohort construction are described in our previous reports \[12\].

The study protocol was approved by the Institutional Review Board of Pusan National University (No. 2306-028-128), which waived the requirement for informed consent.

**Data collection and definition**

AKI was retrospectively defined based on the modified KDIGO serum creatinine (SCr) criteria (changes in SCr by $\geq 0.3$ mg/dL [$\geq 26.5$ μmol/L] within 48 hours; or changes in SCr to $\geq 1.5$ times the baseline, which is known or presumed to have occurred within the prior 7 days) \[9\]. AKI was categorized according to the AKI developing time, baseline kidney function status, and severity. We defined community-acquired AKI (CAAKI) as AKI diagnosed within 48 hours of hospital admission, and hospital-acquired AKI (HAAKI) as those that developed after 48 hours. AKI on chronic kidney disease (CKD) was defined as AKI diagnosed in previously diagnosed CKD patients. AKI severity was assessed based on the fold changes in peak SCr level, during the patient’s ICU stay, using the KDIGO AKI staging criteria \[9\]. Information on the causes of AKI was obtained by retrospective chart review. AKI causes were categorized as sepsis, volume-related, drug-related, cardiac dysfunction, hepatorenal syndrome, and obstruction of the urinary tract \[4,13\]. While many patients had overlapping causes of AKI, we adopted and described the single most predominant cause as the cause of AKI. Details of the criteria of each etiology were summarized in Supplementary Table 1 (available online) \[14-16\].

**Outcomes**

The primary outcome was the incidence of AKI. The secondary outcome was in-hospital mortality.
Statistical analysis

Data normality was assessed using the Kolmogorov-Smirnov test. Continuous variables are expressed as medians with interquartile ranges (IQR) or means ± standard deviations, as appropriate. Differences between the two groups were compared using the Student t test. Categorical variables are expressed as percentages, and proportions were compared using the chi-square test.

The effects of AKI on in-hospital mortality were analyzed using univariable and multivariable Cox proportional hazards models. The full model was adjusted for age, diabetes mellitus (DM), hypertension, CKD status, chronic obstructive pulmonary disease (COPD) and asthma, cancer, Sequential Organ Failure Assessment (SOFA) score, sepsis, AKI stage, and serum level of albumin. All the covariates included in the analyses are known factors associated with AKI, some of them were included in the final model. In the final model, covariates were selected by backward selection based on the Wald test, with a threshold of 0.2 for all predictors. The Cox proportional hazards model was plotted to compare the effect of AKI on mortality between medical and surgical patients who had AKI and those who did not, respectively. All analyses were restricted to the subjects with complete data on the variables involved in each analysis.

All statistical tests were two-sided, and p-values less than 0.05 were considered significant. Data analysis and plotting were performed using IBM SPSS software (ver. 29.0; IBM Corp.).

Results

Baseline characteristics

Between January 2011 and December 2020, 48,834 patients were admitted to the ICU. After excluding 100 patients (0.2%) with ESKD, 40,720 patients (97.6%) without information on their baseline kidney function status, and 861 patients (2.0%) younger than 18 years old, a total of 7,150 ICU patients were included in this study (Fig. 1). The mean age was 63.9 ± 13.4 years, and 4,289 (60.0%) were male. Among them, 3,625 (50.7%) were medical patients, and 3,525 (49.3%) were surgical patients. DM, hypertension, CKD, ischemic heart disease (IHD), lung disease, liver disease, and stroke were more prevalent among medical patients, while cancer was more common in surgical patients. At ICU admission, the mean SOFA score was 5.8 ± 3.8, which was significantly higher in medical patients (6.6 ± 3.9), who also had a higher prevalence of sepsis (43.8%) (Table 1).

Differences in acute kidney injury epidemiology among medical and surgical intensive care unit patients

AKI was observed in 2,459 patients (34.4%), and it was more prevalent in medical (1,765 out of 3,625, 48.7%) than in surgical patients (694 of 3,525, 19.7%) (Fig. 2). Table 2 summarizes the differences in AKI characteristics between medical and surgical ICU patients. Stage 1 AKI was more common in surgical patients, whereas severe (stage ≥ 2) (68.4% vs. 48.7%, p < 0.001) or dialysis-requiring AKI (25.0% vs. 12.2%, p < 0.001) was more frequent in medical patients. Among patients with AKI, 1,073 (43.6%) had HAAKI, and 1,386 (56.3%) had CAAKI. HAAKI was more prevalent in surgical patients than in medical patients (49.0% vs. 41.5%, p < 0.001), while CAAKI was more common in medical patients compared to surgical patients (58.5% vs. 51.0%, p < 0.001). AKI on CKD was observed in 784 patients (31.9%) and was more frequent in medical patients than in surgical patients.
### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Medical group</th>
<th>Surgical group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>7,150 (100)</td>
<td>3,625 (50.7)</td>
<td>3,525 (49.3)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63.88 ± 13.38</td>
<td>63.93 ± 13.91</td>
<td>63.83 ± 12.82</td>
<td>0.32</td>
</tr>
<tr>
<td>Male sex</td>
<td>4,289 (60.0)</td>
<td>2,191 (60.4)</td>
<td>2,098 (59.5)</td>
<td>0.43</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3,265 (45.7)</td>
<td>1,908 (52.6)</td>
<td>1,360 (38.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4,791 (67.0)</td>
<td>2,730 (75.3)</td>
<td>2,062 (58.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1,464 (20.5)</td>
<td>1,004 (27.7)</td>
<td>461 (13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1,098 (15.4)</td>
<td>637 (17.6)</td>
<td>462 (13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lung disease</td>
<td>349 (4.9)</td>
<td>235 (6.5)</td>
<td>115 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver disease</td>
<td>696 (9.7)</td>
<td>381 (10.5)</td>
<td>314 (8.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke</td>
<td>729 (10.2)</td>
<td>396 (10.9)</td>
<td>333 (9.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Malignancy</td>
<td>3,088 (43.2)</td>
<td>1,375 (37.9)</td>
<td>1,715 (48.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Severity of disease at ICU admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score</td>
<td>5.77 ± 3.75</td>
<td>6.61 ± 3.93</td>
<td>4.91 ± 3.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2,440 (34.1)</td>
<td>1,586 (43.8)</td>
<td>856 (24.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of AKI</td>
<td>2,461 (34.4)</td>
<td>1,765 (48.7)</td>
<td>694 (19.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) or mean ± standard deviation.
AKI, acute kidney injury; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

The causes of AKI were reviewed only in patients treated at PNUH (1,673 of 2,461, 67.9%). Among these patients, sepsis (44.8%) was the most common cause of AKI, followed by volume-related AKI (34.5%), cardiac dysfunction (9.8%), and nephrotoxin-induced AKI (3.9%). In medical patients, sepsis (616 out of 1,252, 49.2%) was the leading cause of AKI, followed by volume-related AKI (349 out of 1,252, 27.9%), while in surgical patients, volume-related AKI (228 out of 421, 54.2%) was most common. Drug-related AKI was more prevalent in medical patients (63 out of 1,252, 5.0%), whereas AKI related to cardiac dysfunction was more frequent in surgical patients (49 out of 421, 11.6%) (Table 3).

### Differences in patient outcomes by acute kidney injury status between medical and surgical intensive care unit patients

The average length of stay (LOS) at the hospital was 16 days (IQR, 9–30 days). Medical ICU patients had a longer LOS of 18 days, while surgical ICU patients had a LOS of 15 days. Both medical and surgical patients with AKI stayed longer in the hospital than those without, even after being transferred from the ICU (Supplementary Table 2, available online).

Out of the total patient population, 819 (11.5%) died in the hospital. The in-hospital mortality rate was higher in medical patients (612 out of 3,620, 16.9%) compared to sur-
Table 2. Differences in AKI characteristics between medical and surgical ICU patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 2,459)</th>
<th>Medical group (n = 1,765)</th>
<th>Surgical group (n = 694)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2,459 (34.4)</td>
<td>1,765 (48.7)</td>
<td>694 (19.7)</td>
<td></td>
</tr>
<tr>
<td>AKI stage at peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI stage 1</td>
<td>915 (37.2)</td>
<td>558 (31.6)</td>
<td>356 (51.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI stage 2</td>
<td>481 (19.5)</td>
<td>341 (19.3)</td>
<td>140 (20.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>AKI stage 3</td>
<td>538 (21.8)</td>
<td>425 (24.1)</td>
<td>113 (16.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI stage 3D</td>
<td>527 (21.0)</td>
<td>441 (25.0)</td>
<td>85 (12.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI developing time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>1,073 (43.6)</td>
<td>733 (41.5)</td>
<td>340 (49.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Community-acquired</td>
<td>1,386 (56.3)</td>
<td>1,032 (58.5)</td>
<td>354 (51.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI on CKD</td>
<td>784 (31.9)</td>
<td>637 (36.1)</td>
<td>147 (21.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as number (%).
AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit.

Table 3. Cause of AKI (Pusan National University Hospital)

<table>
<thead>
<tr>
<th>Cause of AKI</th>
<th>Total (n = 1,673)</th>
<th>Medical group (n = 1,252)</th>
<th>Surgical group (n = 421)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>749 (44.8)</td>
<td>616 (49.2)</td>
<td>133 (31.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume overload/depletion</td>
<td>577 (34.5)</td>
<td>349 (27.9)</td>
<td>228 (54.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>164 (9.8)</td>
<td>115 (9.2)</td>
<td>49 (11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drug-related</td>
<td>65 (3.9)</td>
<td>63 (5.0)</td>
<td>2 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>44 (2.6)</td>
<td>38 (3.0)</td>
<td>6 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstruction of urinary tract</td>
<td>10 (0.6)</td>
<td>7 (0.6)</td>
<td>3 (0.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Others</td>
<td>19 (1.1)</td>
<td>19 (1.5)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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AKI, acute kidney injury.

gical patients (207 in 3,525, 5.9%; p < 0.001). In medical patients with and without AKI, in-hospital mortality rate was 21.6% and 12.6% and in surgical patients, it was 18.9% and 2.7%, respectively (Fig. 3A; Supplementary Table 2, available online). The influence of AKI on mortality differed between medical and surgical patients. In medical patients, the risk of in-hospital mortality was 1.239 (95% confidence interval [CI], 1.051–1.461; p = 0.01) fold higher in AKI patients compared to no AKI, whereas it was 4.778 (95% CI, 3.577–6.382; p < 0.001) in surgical patients (Table 4). Other factors associated with in-hospital mortality included old age, DM, hypertension, COPD, malignancy, sepsis, and low serum albumin levels at ICU admission (Table 4). Higher SOFA score and higher AKI stage were AKI-specific risk factors for in-hospital mortality in patients with AKI admitted to the ICU (Supplementary Table 3, available online). Patients with CKD showed better survival, regardless of AKI, during ICU stay (Table 4; Supplementary Table 3, available online).

Table 2. Differences in AKI characteristics between medical and surgical ICU patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 2,459)</th>
<th>Medical group (n = 1,765)</th>
<th>Surgical group (n = 694)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2,459 (34.4)</td>
<td>1,765 (48.7)</td>
<td>694 (19.7)</td>
<td></td>
</tr>
<tr>
<td>AKI stage at peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI stage 1</td>
<td>915 (37.2)</td>
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Data are expressed as number (%).
AKI, acute kidney injury.

The proportion of comorbidities and mortality rate increased with increasing AKI severity in both medical and surgical patient groups (Supplementary Fig. 1, available online).

In the multivariable Cox proportional hazard model, using surgical patients without AKI as the reference group, medical patients without AKI had a 2.5-fold higher risk of mortality, surgical patients with AKI had a 2.7-fold higher risk, and medical patients with AKI had a 2.9-fold higher risk (Table 4). Other factors associated with in-hospital mortality included old age, DM, hypertension, COPD, malignancy, sepsis, and low serum albumin levels at ICU admission (Table 4). Higher SOFA score and higher AKI stage were AKI-specific risk factors for in-hospital mortality in patients with AKI admitted to the ICU (Supplementary Table 3, available online). Patients with CKD showed better survival, regardless of AKI, during ICU stay (Table 4; Supplementary Table 3, available online).

Discussion

While previous epidemiologic studies have established the association between AKI and high nosocomial mortality [17–21] and substantial healthcare costs, particularly in dialysis-requiring cases [22–24], studies on the epidemiology of AKI in ICU patients in South Korea remain limited. Even less is known about the differences in characteristics between heterogeneous patient groups.
Figure 3. In-hospital mortality. (A) It shows differences in in-hospital mortality rates between medical and surgical patients by the presence of acute kidney injury (AKI). (B) Cox proportional hazards model of patients by department and presence of AKI.

Table 4. Multivariate Cox regression analysis for in-hospital mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.85 (1.61–2.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.05 (2.47–3.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.22 (1.04–1.43)</td>
<td>0.02</td>
</tr>
<tr>
<td>COPD, asthma</td>
<td>1.40 (1.33–2.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.59 (1.39–1.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.25 (1.96–2.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin level</td>
<td>0.48 (0.42–0.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total SOFA score</td>
<td>1.14 (1.12–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical department</td>
<td>4.04 (3.11–5.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical department</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical department</td>
<td>4.53 (3.41–6.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical department</td>
<td>5.05 (3.94–6.48)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.
There were a few studies that categorized ICU patients into medical and surgical groups, but these were at the level of baseline characteristics. Patients were stratified by AKI status to analyze final outcomes such as incidence or mortality of AKI [10,11].

We aimed to conduct simple and intuitive phenotype of medical and surgical AKI patients in ICU, including clinically important factors such as reasons, courses, severity, and mortality outcomes. We created this ICU-AKI cohort using EMR-extracted data from 2011 to 2020, to allow this analysis. This study investigated how patient characteristics vary across departments, and whether and how these characteristics influence the incidence of AKI. Furthermore, the mortality outcomes of patients, considering the presence of AKI and other risk factors including AKI severity, were also evaluated.

Medical patients exhibited a higher prevalence of co-morbidities, such as DM, hypertension, CKD, IHD, lung disease, and liver disease, along with a more severe illness at ICU admission. In contrast, surgical patients had a higher incidence of underlying malignancy. AKI was more prevalent in medical patients (48.1%) compared to surgical patients (19.7%). The severity of AKI was higher in medical patients, with sepsis being a major contributing factor. In surgical patients, volume status played a more significant role in the development of AKI. In-hospital mortality was substantially higher in AKI patients (20.8%) compared to non-AKI patients (6.5%). The mortality gap between surgical patients with and without AKI was more pronounced (18.9% vs. 2.7%) compared to that observed in medical patients. The incidence of AKI in our cohort aligns with previous reports. Hoste et al. [4] reported an AKI incidence of 56.7% among ICU-admitted patients, 18.4% in stage 1, 8.9% in stage 2, 30.0% in stage 3. Bagshaw et al. [25] reported an AKI incidence of 36.1% in ICU patients, while this study found an overall AKI incidence of 34.4% in ICU patients.

The incidence and mortality of AKI in medical patients are higher than in surgical patients due to the high frequency of co-morbidities such as chronic hypertension, DM, or CKD which can lead to tissue hypoperfusion and inflammation. Hoste et al. [26] demonstrated that AKI contributes to a higher mortality rate in ICUs due to complications arising from AKI and renal replacement therapy, which can lead to the deterioration of other vital organs. Other studies have shown an increase in ICU mortality associated with increasing disease severity and the presence of AKI [27,28]. AKI systemically affects the body through inflammatory pathways, increasing the risk of infection and potentially causing sepsis or worsening preexisting sepsis [3,29]. Inflammation, rather than an ischemic component, results in renal endothelial dysfunction, leading to microvascular disturbances [30,31]. Consistent with this pathogenesis, this study highlights that sepsis was the primary cause of AKI in both medical and surgical groups, contributing more significantly to mortality and the need for renal replacement therapy, as reported in several studies [32,33].

In surgical patients, volume overload/depletion was the main etiology of AKI (54.2%). Shock related to bleeding plays a major role, with some other mechanisms affecting the development of AKI. Even if we did not categorize the anatomical type of surgery in this study, it has been suggested that direct injury to kidney and/or urinary tract leads to reduced kidney function. Furthermore, intra-abdominal packing, which is usually used for bleeding control, may also deteriorate kidney function [34]. However, with the development of trauma centers, adequate volume management, and perioperative management such as prophylactic treatment of complications such as rhabdomyolysis in high-risk patients might be a factor in lowering the incidence and mortality of AKI in surgical patients compared to medical patients.

The LOS in the hospital was longer, and the mortality rate was higher in patients with AKI compared to those without AKI. Some previous studies have reported a positive correlation between prolonged LOS and mortality [35,36], due to an increased risk of various AKI-associated complications. Among the AKI patients, in-hospital mortality was higher in medical patients compared to surgical patients. Nevertheless, the contribution of AKI to mortality was greater in surgical patients. The prevalence of AKI had a greater impact on mortality (18.9% in the surgical AKI group vs. 2.7% in the surgical non-AKI group) in surgical patients than in medical patients. This can be explained by several factors.

First, AKI-related fluid imbalance is a challenging issue, especially if it coexists with perioperative fasting or a bleeding condition, which is inevitable with major surgery [34]. Second, even though we did not differentiate between types of surgery in this present study, the higher
rate of underlying cancer in surgical patients implies that it is more difficult for them to recover from AKI. Third, AKI itself played a critical role in in-hospital mortality. Surgical patients had fewer comorbidities and a lower SOFA score compared to medical patients, and surgical patients without AKI showed the best survival rate. Meanwhile, medical patients without AKI had a 2.5-fold higher risk of mortality, possibly associated with their comorbidities and higher disease burden. Once surgical patients developed AKI, their probability of mortality was higher than that of medical patients without AKI. We speculate that AKI has a more significant contribution to mortality than other comorbidities in critically ill patients. Therefore, preventing AKI is essential even in surgical patients with fewer comorbidities.

Consistent with previous studies [5,13,25,28,32,37], this multivariate analysis identified old age, multiple comorbidities, a higher SOFA score, and the presence of sepsis as risk factors for in-hospital mortality. Mortality is lower in patients with pre-diagnosed CKD (hazard ratio, 0.831 referenced by surgical ICU patients without AKI). Oppert et al. [38] previously reported that patients with septic AKI and preexisting non-dialysis-dependent CKD had a lower mortality rate than those without preexisting CKD. This finding led to the suggestion by Parmar et al. [37] that preexisting CKD might modify the response to stressful conditions, including sepsis. Additionally, we speculate that awareness of CKD by physicians might have influenced their limited prescription of nephrotoxic drugs (e.g., analgesics or antibiotics) and cautious regulation of fluids in CKD patients than in patients with previously normal kidney function, potentially leading to lower rates of mortality.

This study has several limitations. First, we did not identify overlapping causes of AKI since it was a retrospective review of medical charts and blood, urine, and imaging studies before and after the AKI. Therefore, in cases of multiple causes, one etiology was selected as the most likely cause. Second, within the surgical department, we did not distinguish between patient characteristics that vary by type of surgery, such as trauma or cancer surgery. Third, although the SOFA score is a reliable and relatively accurate indicator for assessing organ dysfunction and predicting the prognosis of patients admitted to ICU, indicators such as simplified acute physiology score and multiple organ dysfunction score are more commonly used to assess the severity of illness and should be further quantified and analyzed.

The incidence of AKI among critically ill patients was 38%, with a higher prevalence in medical patients compared to surgical patients. In medical patients, CAAKI was more common whereas in surgical patients, HAAKI was more frequent. This difference may be attributed to the higher prevalence of comorbidities or disease severity in medical patients and differences in reasons for AKI between medical and surgical patients. While the incidence and mortality of AKI itself were higher in medical patients, the impact on mortality was more pronounced in surgical patients. These findings emphasize the need for active monitoring of kidney function during hospital stays, regardless of a patient’s baseline kidney status. Furthermore, prevention of AKI should be prioritized in both medical and surgical departments.

Conflicts of interest
All authors have no conflicts of interest to declare.

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Data sharing statement
The data presented in this study are available from the corresponding author upon reasonable request.

Authors’ contributions
Conceptualization: YL, DWK, HJK, EYS, SHS, HR
Data curation, Formal analysis, Investigation, Methodology: YL, TK, DEK, EMJ, HR
Funding acquisition: HR
Supervision: DWK, HJK, EYS, SHS, HR,
Writing–original draft: HR, YL.
Writing–review & editing: HR, YL
All authors read and approved the final manuscript.

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References


Validation of prediction model for successful discontinuation of continuous renal replacement therapy: a multicenter cohort study

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1Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
2Division of Nephrology, Department of Internal Medicine, The Catholic University of Korea, Bucheon St. Mary’s Hospital, Bucheon, Republic of Korea
3Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
4Division of Nephrology, Department of Internal Medicine, Myongji Hospital, Hanyang University Medical Center, Goyang, Republic of Korea
5Division of Nephrology, Department of Internal Medicine, The Catholic University of Korea, Eunpyeong St. Mary’s Hospital, Seoul, Republic of Korea
6Division of Nephrology, Department of Internal Medicine, The Catholic University of Korea, Yeouido St. Mary’s Hospital, Seoul, Republic of Korea
7Division of Nephrology, Department of Internal Medicine, The Catholic University of Korea, Seoul St. Mary’s Hospital, Seoul, Republic of Korea

**Background:** Continuous renal replacement therapy (CRRT) has become the standard modality of renal replacement therapy (RRT) in critically ill patients. However, consensus is lacking regarding the criteria for discontinuing CRRT. Here we validated the usefulness of the prediction model for successful discontinuation of CRRT in a multicenter retrospective cohort.

**Methods:** One temporal cohort and four external cohorts included 1,517 patients with acute kidney injury who underwent CRRT for >2 days from 2018 to 2020. The model was composed of four variables: urine output, blood urea nitrogen, serum potassium, and mean arterial pressure. Successful discontinuation of CRRT was defined as the absence of an RRT requirement for 7 days thereafter.

**Results:** The area under the receiver operating characteristic curve (AUROC) was 0.74 (95% confidence interval, 0.71–0.76). The probabilities of successful discontinuation were approximately 17%, 35%, and 70% in the low-score, intermediate-score, and high-score groups, respectively. The model performance was good in four cohorts (AUROC, 0.73–0.75) but poor in one cohort (AUROC, 0.56). In one cohort with poor performance, attending physicians primarily controlled CRRT prescription and discontinuation, while in the other four cohorts, nephrologists determined all important steps in CRRT operation, including screening for CRRT discontinuation.

**Conclusion:** The overall performance of our prediction model using four simple variables for successful discontinuation of CRRT was good, except for one cohort where nephrologists did not actively engage in CRRT operation. These results suggest the need for active engagement of nephrologists and protocolized management for CRRT discontinuation.

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*Junseok Jeon and Eun Jeong Ko contributed equally to this study as co-first authors.
†Byung Ha Chung and Hye Ryoun Jang contributed equally to this study as co-corresponding authors.

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Introduction

Acute kidney injury (AKI) is a common condition among critically ill patients. A recent multicenter study reported that the incidence of AKI at all stages was 57% while that of stage 3 AKI was 30%; the mortality rate increased as AKI severity increased in critically ill patients [1]. Although continuous renal replacement therapy (CRRT) has not been proven superior to intermittent renal replacement therapy (RRT) in critically ill patients [2,3], CRRT is the preferred and mainly used RRT in critically ill patients because of its hemodynamic stability and high capacity to remove solutes or fluids. Meanwhile, CRRT has disadvantages including the risk of catheter-related complications, risk of bleeding associated with continuous anticoagulation, increased length of intensive care unit (ICU) stay, delayed rehabilitation, and removal of undesired substances such as antibiotics [4].

Therefore, it is important to discontinue CRRT for patients who no longer require it. However, consensus is lacking regarding the optimal timing of CRRT discontinuation. Urine output is reportedly the most consistent and important predictor of successful discontinuation of CRRT [5,6]. Some studies presented regression equations of urine output, serum creatinine, or sequential organ failure assessment score and showed excellent discriminative ability for successful discontinuation of CRRT [5,7,8]. However, no externally validated prediction models are simple or easy to apply.

We previously developed a prediction model derived from four clinical parameters for successful discontinuation of CRRT that was simple and showed good performance [9]. This study aimed to validate a prediction model for successful discontinuation of CRRT using temporal and external cohorts.

Methods

Study setting and population

This retrospective cohort study consisted of one temporal cohort and four external cohorts. All cohorts included adults (>18 years) who received CRRT for at least 3 days and survived for at least 7 days after its discontinuation between January 1, 2018 and November 31, 2020. Excluding patients with preexisting end-stage kidney disease (n = 345) or patients in hopeless condition or with insufficient data (n = 29), 1,517 patients were included in the final analysis: 540 in the temporal cohort from Samsung Medical Center and 977 from Seoul St. Mary’s Hospital, Yeouido St. Mary’s Hospital, Bucheon St. Mary’s Hospital, and Myongji Hospital.

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center (No. 2021-01-052, December 31, 2020; titled “Investigation of evidence-based optimal management strategies for continuous renal replacement therapy”), which waived the requirement for informed consent because of the minimal risk and retrospective nature of the collected data.

Variables

Data were extracted from the electronic medical records. Age, sex, primary diagnosis at admission, variables of the prediction model (urine output, blood pressure, blood urea nitrogen [BUN], and serum potassium), and reinitiation of RRT (CRRT or intermittent RRT) after CRRT discontinuation were obtained.

Prediction model

The prediction model was composed of four variables [9]: 24-hour urine output (mL/day) on the day before CRRT discontinuation (D−1), mean arterial blood pressure (MAP) (mmHg), BUN (mg/dL), and serum potassium (mmol/L) on the day of CRRT discontinuation (D0). Each variable was scored as follows: 4 points with a urine output on D−1 ≥300 mL/day; 1 point if MAP on D0 was 50 to 78 mmHg; 2 points with BUN on D0 <35 mg/dL; and 1 point if serum potassium <4.1 mmol/L. The total score, which was the sum of the scores, was 0 to 8 points. The patients were divided into three groups according to their total scores: low (0–2 points), intermediate (3–5 points), and high (6–8 points).
Validation of model performance

Discrimination performance was evaluated using the area under the receiver operating characteristic curve (AUROC) and calibration performance was evaluated by comparing the predicted probability of each score or group of scores to the observed probability.

Outcome

Successful discontinuation of CRRT was defined as the absence of RRT reinitiation within 7 days of CRRT discontinuation. Resumption of RRT with transition to intermittent hemodialysis (HD) within 7 days after CRRT discontinuation was considered as failure of CRRT discontinuation. Patients were divided into success and failure groups according to successful discontinuation of CRRT.

Statistical analysis

Descriptive summaries are presented as frequencies (percentages) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. The discrimination performance was assessed using the area under the AUROC, and the calibration performance was assessed by comparing the predicted probability of each score or score group to the observed probability. Data were analyzed using SAS version 9.4 (SAS Institute). The p-values of <0.05 were considered statistically significant.

Results

Patients’ characteristics

The median patient age was 65 years (interquartile range, 54–76 years), and 61.8% were male (Table 1). The primary diagnoses upon admission were cancer (57.2%), heart failure (27.2%), and others (15.6%). Approximately 45% of patients (677 of 1,517) successfully discontinued CRRT. A higher proportion of patients had heart failure in the success versus failure group. Urine output was larger, and BUN and serum potassium levels were lower in the success versus failure group. However, MAP was comparable between the two groups. Age, proportion of primary diagnoses, and values of major variables on the day of CRRT discontinuation differed among institutions (Table 2). The rate of successful discontinuation of CRRT was 40% to 51%.

Table 1. Characteristics of all patients of the pooled cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Failure</th>
<th>Success</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1,517</td>
<td>840</td>
<td>677</td>
<td>0.44</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65 (54–76)</td>
<td>65 (55–75)</td>
<td>66 (53–77)</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Male</td>
<td>938 (61.8)</td>
<td>528 (62.9)</td>
<td>410 (60.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>579 (38.2)</td>
<td>312 (37.1)</td>
<td>267 (39.4)</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Cancer</td>
<td>868 (57.2)</td>
<td>484 (57.6)</td>
<td>384 (56.7)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>412 (27.2)</td>
<td>242 (28.8)</td>
<td>170 (25.1)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>237 (15.6)</td>
<td>114 (13.6)</td>
<td>123 (18.2)</td>
<td></td>
</tr>
<tr>
<td>CRRT duration (day)</td>
<td>7.09 ± 5.66</td>
<td>7.64 ± 6.12</td>
<td>6.39 ± 4.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Values at CRRT discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output, D–1 (mL/24 hr)</td>
<td>205 (845–11,250)</td>
<td>65 (11–323)</td>
<td>615 (180–1,430)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MAP on D0 (mmHg)</td>
<td>83 (72–94)</td>
<td>83 (72–94)</td>
<td>83 (73–94)</td>
<td>0.62</td>
</tr>
<tr>
<td>BUN on D0 (mg/dL)</td>
<td>23.0 (16.1–31.0)</td>
<td>24.0 (17.0–33.0)</td>
<td>21.8 (15.1–29.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Potassium on D0 (mmol/L)</td>
<td>3.9 (4.2–5.6)</td>
<td>3.9 (3.6–4.3)</td>
<td>3.8 (3.5–4.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are expressed as number only, median (interquartile range), or number (%). Patients were divided into success and failure groups according to the successful discontinuation of CRRT defined as not initiating renal replacement therapy within 7 days after CRRT discontinuation. D0 and D–1 were defined as the day of and the day before CRRT discontinuation, respectively. BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; MAP, mean arterial blood pressure.
Performance of prediction model

The predicted and observed probabilities of successful discontinuation of CRRT in the entire cohort matched well according to each score (Fig. 1A) and the low- (0–2 points), intermediate- (3–5 points), and high-score (6–8 points) groups (Fig. 1B). The overall differences between the observed and predicted incidence were 3.0% (17.7% observed and 16.9% predicted probabilities), 3.6% (35.2% and 34.8%), and 2.0% (69.3% and 70.3%) in the low-, intermediate-, and high-score groups, respectively. The overall AUROC of the prediction model was 0.74 (95% confidence interval [CI], 0.71–0.76) (Fig. 1C). We assessed the AUROC according to the primary diagnosis at admission. Regardless of primary diagnosis, the prediction model showed good performance (AUROC [95% CI]: 0.76 [0.68–0.83] in heart failure, 0.75 [0.69–0.81] in cancer, and 0.73 [0.67–0.76] in others) (Fig. 2).

Performance of prediction model at each hospital

We further assessed the performance of the prediction model according to the institution. One temporal cohort and three external cohorts showed good discriminative ability (AUROC [95% CI]: 0.77 [0.73–0.81], 0.73 [0.69–0.77], 0.72 [0.63–0.82], and 0.73 [0.63–0.84]), but one external cohort (Hospital C) showed poor discriminative ability (0.56 [0.45–0.67]) (Fig. 3). This cohort, with poor discriminative ability, showed little association between the scores and the CRRT discontinuation success rate. The predicted and observed probabilities of successful discontinuation of CRRT in each cohort according to the score groups and scores are presented in Fig. 4 and Supplementary Fig. 1 (available online), respectively.

We analyzed each variable separately to elucidate what variable in the model caused the difference in performance between cohorts. Hospital C (AUROC 0.539 for urine output) showed very low discriminative ability for urine output compared to other hospitals (AUROC 0.698, 0.715, 0.665, and 0.683 for urine output in each hospital) (Supplementary Fig. 2, available online). Hospital C also tended to show lower or similar discriminative ability for BUN and serum potassium, but higher discriminative ability for MAP compared to other hospitals (Supplementary Figs. 3–5, available online).

### Table 2. Patients’ characteristics in temporal and external validation set by cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SMC</th>
<th>Hospital A</th>
<th>Hospital B</th>
<th>Hospital C</th>
<th>Hospital D</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>540</td>
<td>678</td>
<td>113</td>
<td>100</td>
<td>86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64 (53–72)</td>
<td>64 (52–75)</td>
<td>73 (66–82)</td>
<td>67 (54.5–78)</td>
<td>77 (62–83)</td>
<td>0.65</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>342 (63.3)</td>
<td>419 (61.8)</td>
<td>66 (58.4)</td>
<td>63 (63.0)</td>
<td>48 (55.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>198 (36.7)</td>
<td>259 (38.2)</td>
<td>47 (41.6)</td>
<td>37 (37.0)</td>
<td>38 (44.2)</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cancer</td>
<td>240 (44.4)</td>
<td>405 (59.7)</td>
<td>77 (68.1)</td>
<td>80 (80.0)</td>
<td>66 (76.7)</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>189 (35.0)</td>
<td>184 (27.1)</td>
<td>28 (24.8)</td>
<td>7 (7.0)</td>
<td>4 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>111 (20.6)</td>
<td>89 (13.1)</td>
<td>8 (7.1)</td>
<td>13 (13.0)</td>
<td>16 (18.6)</td>
<td></td>
</tr>
<tr>
<td>CRRT duration (day)</td>
<td>7.31 ± 6.74</td>
<td>7.19 ± 5.22</td>
<td>6.02 ± 3.93</td>
<td>7.31 ± 4.85</td>
<td>6.01 ± 3.95</td>
<td>0.08</td>
</tr>
<tr>
<td>Variables at CRRT discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output on D–1 (mL/day)</td>
<td>114 (20–482.5)</td>
<td>263 (35–1,120)</td>
<td>235 (50–665)</td>
<td>275 (35–1,062.5)</td>
<td>418 (140–1,045)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MAP on D0 (mmHg)</td>
<td>78 (69–88)</td>
<td>85 (73–95)</td>
<td>90 (77–101)</td>
<td>83 (74–99)</td>
<td>93 (81–103)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BUN on D0 (mmol/L)</td>
<td>20.9 (14.3–27.9)</td>
<td>25.2 (18.4–34.5)</td>
<td>25.4 (17.5–33.9)</td>
<td>17.15 (11.7–25.9)</td>
<td>21.1 (15.9–31.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Potassium on D0 (mmol/L)</td>
<td>4.1 (3.8–4.4)</td>
<td>3.8 (3.4–4.1)</td>
<td>3.9 (3.7–4.3)</td>
<td>3.6 (3.4–3.8)</td>
<td>4.0 (3.7–4.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Score</td>
<td>4 (3–6)</td>
<td>4 (3–7)</td>
<td>4 (2–6)</td>
<td>4 (3–7)</td>
<td>6 (3–7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Success</td>
<td>216 (40.0)</td>
<td>324 (47.8)</td>
<td>47 (41.6)</td>
<td>46 (46.0)</td>
<td>44 (51.2)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data are expressed as number only, median (interquartile range), number (%), or mean ± standard deviation.

D0 and D–1 were defined as the day of and the day before CRRT discontinuation, respectively.

BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; MAP, mean arterial blood pressure; SMC, Samsung Medical Center.
Figure 1. Performance of prediction model for CRRT discontinuation. The observed and predicted probabilities of successful discontinuation of CRRT were well-matched (A) in each score group and (B) in the low- (0–2), intermediate- (3–5), and high-score (6–8) groups. (C) The ROC curve of the prediction model. AUROC, area under the curve of receiver operating characteristics; CI, confidence interval; CRRT, continuous renal replacement therapy; ROC, receiver operating characteristics.

Figure 2. Performance of prediction model according to primary diagnosis at admission or cohorts. The performance of the prediction model was good in all subgroups according to the primary diagnosis at admission. AUROC, area under the curve of receiver operating characteristics; CI, confidence interval.

Figure 3. Performance of prediction model according to each cohort. The prediction model performed well in four cohorts but poorly in one cohort. AUROC, area under the curve of receiver operating characteristics; CI, confidence interval; SMC, Samsung Medical Center.
Differences in the strategies of continuous renal replacement therapy operation

We compared differences in the overall steps of CRRT operation to elucidate the cause of the differences in model performance between hospitals. Table 3 shows CRRT operation strategies regarding nephrology engagement and CRRT-dedicated nursing staff of each hospital. In Samsung Medical Center and the three hospitals where the performance of the prediction model was good, nephrologists determined all important steps of CRRT operation including initiation, prescription with monitoring the adequacy
of CRRT, and screening the possibility or final decision of CRRT discontinuation by multidisciplinary care with critical care physicians. On the other hand, both prescription and discontinuation of CRRT were primarily controlled by attending physicians in the Hospital C although only initiation of CRRT was determined by nephrologists under on-demand consultation.

**Discussion**

Here we validated our simple prediction model for successful discontinuation of CRRT. The prediction model showed good discriminating ability for one temporal cohort and three external cohorts but showed poor performance for one external cohort. Our prediction model was based on urine output, MAP, BUN, and serum potassium levels. This is simple and easy to apply in clinical practice; however, as shown in one external cohort, its usefulness can be affected by the strategies of CRRT operation.

Consensus is currently lacking on CRRT discontinuation criteria. The prolonged maintenance of CRRT increases the length of ICU stay and overall costs, delays mobility, and exposes patients to CRRT-associated complications [4]. On the other hand, whether reinitiating RRT per se after CRRT discontinuation adversely affects mortality or renal outcomes has not been sufficiently studied. Previous observational studies demonstrated that 40%–50% of patients with AKI requiring RRT failed to discontinue it and had higher mortality rates and a lower chance of renal recovery than those who successfully discontinued RRT [6,10–12]. These differences may reflect the overall disease severity of patients rather than the adverse effects of RRT reinitiation. However, if kidney function does not sufficiently recover after CRRT is discontinued, the patient is at risk of recurrent volume overload, uremia, and electrolyte imbalance. In addition, approximately 50% of patients experience intradialytic hypotension when CRRT is switched to intermittent RRT, which can cause additional ischemic injury and aggravate organ dysfunction [13]. Therefore, the appropriate timing of CRRT discontinuation is important.

Urine output was the only common significant factor associated with successful discontinuation of CRRT across several previous studies and in our study [5–9,14]. Although most previous studies were small-scale, the largest multicenter study reported urine output, increased urine output, serum creatinine, history of chronic kidney disease, and CRRT duration as significant factors for successful discontinuation of CRRT [6]. Two previous studies presented calculation formulas using a regression model [5,7]. However, despite their high AUROC, they did not provide a simplified scoring system; thus, these models could be less practical for clinical decisions. One study presented a simple scoring system and a high AUROC with kinetic estimated glomerular filtration rate and urine output; however, kinetic estimated glomerular filtration rate itself requires serial serum creatinine values and a complex calculation formula [8]. In addition, the prediction models reported in previous studies have not been validated. Our prediction model, which is based on a simple scoring system with clinical parameters that can be easily obtained daily, has a relatively good AUROC value and good discriminative ability [9]. Furthermore, we validated the model in both temporal and external cohorts.

Four clinical variables were selected for our model and applied regardless of the patient’s medical condition or diagnosis. However, the relative importance of each variable may vary depending on the patient’s underlying disease or

| Table 3. The strategies of CRRT operation for each hospital |
|-------------------------|-------------|-------------|-------------|-------------|-------------|
| Strategy               | SMC         | Hospital A  | Hospital B  | Hospital C  | Hospital D  |
| Nephrology engagement  |             |             |             |             |             |
| Initiation             | 0           | 0           | 0           | 0           | 0           |
| Daily monitoring       | 0           | 0           | 0           | X           | 0           |
| Discontinuation        |             |             |             |             |             |
| Screening              | 0           | 0           | 0           | X           | 0           |
| Decision               | 0           | 0           | 0           | 0           | 0           |
| CRRT-dedicated nursing staff | 0           | 0           | X           | X           | X           |

CRRT, continuous renal replacement therapy; SMC, Samsung Medical Center.
clinical setting. Although the performance of our simple model did not depend on primary diagnoses, more accurate and differential weighting of each variable according to the patient’s condition or clinical setting may improve the universality and optimality of the model. On the other hand, complex model may be less clinically useful. Further research is needed to improve the performance and universality of our model with simple clinical variables.

It is worth noting that the performance of our prediction model was good in the four cohorts but poor in one external cohort. This discrepancy can be caused by differences in CRRT application, operation policies, and patient characteristics. Only one institution demonstrated poor model performance, whereas the other two institutions with similar numbers of patients demonstrated good model performance. In addition, urine output, which has been reported as an important factor predicting CRRT discontinuation or kidney recovery in most previous studies [5–9,14], was not helpful in predicting successful discontinuation of CRRT in one institution with poor model performance. Therefore, poor performance of prediction model in one institution seems to be attributed to CRRT operation strategy rather than patient characteristics. In one institution showing poor performance of the model, the nephrology staffs or team played only a limited role in deciding the initiation of CRRT as consultants and did not actively engage to control and discontinue CRRT. Therefore, our study strongly supports the necessity of active intervention by nephrology team or specialized CRRT team for optimal CRRT management and good performance of our prediction model. On the other hand, our prediction model may also help clinicians make appropriate decisions regarding CRRT discontinuation even in institutions without active participation of nephrology staffs. Further prospective studies are needed to verify whether our prediction model can effectively assist the adequate discontinuation of CRRT in institutions with limited nephrological resources.

In South Korea, switching CRRT to intermittent HD is actively attempted in patients whose overall hemodynamic status has been relatively stabilized even during ICU stay, and this effort for the transition of the RRT modality has been driven by the Korean National Health Insurance Service. This policy makes a significant portion of CRRT discontinuation in South Korea aimed at transitioning to intermittent HD before sufficient renal recovery, rather than complete discontinuation of RRT. Therefore, our findings should be interpreted with caution in countries or institutions whose primary goal of CRRT discontinuation is to discontinue RRT completely. Nevertheless, our prediction model is still useful when attempting to use a scoring system to aid clinical decisions regarding transitioning from CRRT to intermittent HD or maintaining CRRT.

This study had several limitations. First, it was a retrospective cohort study. However, several cohorts were used to validate the prediction model, which may minimize or overcome potential bias. Second, our multicenter study included only Korean ICU patients covered by the Korean National Health Insurance Service. Therefore, our prediction model requires validation in other races or countries. Third, our prediction model showed poor performance in one external cohort, suggesting the necessity of active intervention by nephrology team supporting the entire process as a prerequisite for applying our prediction model. However, as mentioned above, if our prediction model is applied appropriately in an institution with limited involvement of nephrology team, it has the potential to help decisions regarding CRRT discontinuation. Fourth, detailed causes of AKI requiring RRT were not included in the analyses. The retrospective data collection inevitably limits the accurate capture of such data. To overcome this limitation, we conducted a subgroup analysis based on the primary diagnosis at admission and demonstrated that the model was effective for each group.

In conclusion, the good performance of our prediction model for successful discontinuation of CRRT was validated in all four cohorts, except for one cohort in which nephrologists did not actively engage in CRRT operation. This model can help discriminate between patients with a high or low probability of successful discontinuation of CRRT depending on the active engagement of nephrologists in CRRT operation. Further prospective multicenter studies with protocolized CRRT management considering the active engagement of nephrologists in CRRT operation are required to validate and improve our predictive model.

Conflicts of interest

All authors have no conflicts of interest to declare.
**Funding**

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**Data sharing statement**

The data presented in this study are available from the corresponding author upon reasonable request from the corresponding author.

**Authors’ contributions**

Conceptualization: JJ, HRJ  
Data curation: JJ, EJK, SIB, HDK, JWM, ESK, HRJ  
Formal analysis: HP, DK, JC  
Funding acquisition: HRJ  
Investigation: JJ, EJK, HP, HDK, JWM, ESK, KL, DK, BHC, HRJ  
Methodology: JJ, HP, DK, JC, HRJ  
Supervision: JC, JEL, WH, BHC, HRJ  
Visualization: JJ, HP, DK  
Writing—original draft: JJ  
Writing—review & editing: JJ, EJK, BHC, HRJ  
All authors read and approved the final manuscript.

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**References**


A machine learning-based approach for predicting renal function recovery in general ward patients with acute kidney injury

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**Background:** Acute kidney injury (AKI) is a significant challenge in healthcare. While there are considerable researches dedicated to AKI patients, a crucial factor in their renal function recovery, is often overlooked. Thus, our study aims to address this issue through the development of a machine learning model to predict restoration of kidney function in patients with AKI.

**Methods:** Our study encompassed data from 350,345 cases, derived from three hospitals. AKI was classified in accordance with the Kidney Disease: Improving Global Outcomes. Criteria for recovery were established as either a 33% decrease in serum creatinine levels at AKI onset, which was initially employed for the diagnosis of AKI. We employed various machine learning models, selecting 43 pertinent features for analysis.

**Results:** Our analysis contained 7,041 and 2,929 patients’ data from internal cohort and external cohort respectively. The Categorical Boosting Model demonstrated significant predictive accuracy, as evidenced by an internal area under the receiver operating characteristic (AUROC) of 0.7860, and an external AUROC score of 0.7316, thereby confirming its robustness in predictive performance. SHapley Additive exPlanations (SHAP) values were employed to explain key factors impacting recovery of renal function in AKI patients.

**Conclusion:** This study presented a machine learning approach for predicting renal function recovery in patients with AKI. The model performance was assessed across distinct hospital settings, which revealed its efficacy. Although the model exhibited favorable outcomes, the necessity for further enhancements and the incorporation of more diverse datasets is imperative for its application in real-world.

**Keywords:** Acute kidney injury, Hospital records, Machine learning, Recovery of function, Creatinine

**Introduction**

Despite treatment advancements in recent years, acute kidney injury (AKI) remains a significant concern in the medical field. AKI independently contributes to the escalation of healthcare costs and prolongation of hospitalization...
periods, while also elevating the incidence of in-hospital complications and mortality rates [1–3]. This condition is recognized as one of the most prevalent diseases, exhibiting incidence rates of 10% to 15% in general hospital admissions and escalating to 50% to 60% within intensive care unit (ICU) settings. The duration of renal function recovery is increasingly recognized as a pivotal factor in predicting patient outcomes [4]. Studies have shown a correlation between prolonged AKI and heightened risks of complications and mortality [5,6].

Nevertheless, the crucial role of renal function recovery in the prognosis of patients with AKI has been largely overlooked [7]. Consequently, this research area experiences a significant dearth of research, necessitating the need for new investigations. Prior efforts to predict renal function recovery have been hindered by limitations, such as small sample sizes [8–10], exclusive focus on ICU patients, and the absence of an all-encompassing definition for renal function recovery, which impedes the application of these research outcomes in clinical settings [11–15]. Therefore, this study aimed to fill this gap by developing a machine learning-based approach that includes validation in external settings, aimed to predict renal function recovery in patients with AKI, with a particular focus on patients in general wards.

**Methods**

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The Institutional Review Boards (IRBs) of Soonchunhyang University Cheonan Hospital and Korea University Anam Hospital and Guro Hospital approved the study protocol (No. 2019-10-023, 2023AN0145, and 2023GR0425). The need for informed consent was waived by the IRB as the current study was a retrospective review of anonymized clinical data.

**Study population**

For model development, patient datasets were extracted from the Korea University Anam Hospital (Hospital A) and Guro Hospital (Hospital B) from January 1, 2015, to December 31, 2021. These datasets were used as an internal cohort. Additional datasets were extracted from Soonchunhyang University Cheonan Hospital (Hospital C), specifically from patients who were admitted to the general wards from March 1, 2016, to March 31, 2021 for an external cohort. We only considered admissions for individuals aged 19 years and older. Using these data, we constructed a retrospective cohort and applied the following exclusion criteria.

1) Patients with a hospital stay of less than 24 hours.
2) Patients with no blood pressure measurement recorded within 24 hours of admission or with fewer than two measurements during their hospital stay.
3) Patients without serum creatinine (Cr) measurement or estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m² on the first day.

Patients with an eGFR of less than 60 mL/min/1.73 m² were excluded from this research due to the unavailability of comprehensive blood test results prior to hospitalization, which precluded accurate assessment of baseline renal function in these individuals. In other words, the eGFR at the time of hospital admission could represent the patient’s baseline renal function or the eGFR following the onset of AKI. To exclude such ambiguity and focus exclusively on in-hospital AKI, only patients with an eGFR of 60 mL/min/1.73 m² or above upon admission were included in this study, indicating relatively preserved renal function.

**Acute kidney injury definition**

AKI was defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines. AKI was diagnosed based on the following criteria.

1) An increase in Cr by 0.3 mg/dL (or 26.5 μmol/L) or more within 48 hours. The baseline value is defined as the lowest Cr value measured in the preceding 2 days.
2) A Cr level that is 1.5 times or more and the baseline. The baseline value is defined as the lowest Cr value measured in the preceding 7 days.

Baseline Cr was determined as the lowest Cr value measured in the preceding 2 or 7 days. If no Cr value was measured for definition 2, the most recent measurement within the last 180 days was used as the baseline. Urinary output criteria were not utilized for AKI diagnosis because of the predominance of missing data in the patient records.

**Acute kidney injury recovery definition**

To define AKI recovery, we referred to previous studies [4,16] and used the following criteria; AKI recovery was de-
termined based on the following two criteria for Cr:

1) A decrease of 33% or more compared to the Cr at the time of AKI onset.
2) A decrease below the baseline used for AKI diagnosis.

We established a recovery period of 7 days to evaluate AKI recovery. If recovery does not occur within this period, the patient was categorized as suffering from acute kidney disease rather instead of AKI [17].

Cohort organization and outcome labeling
After applying these exclusion criteria, we established a research cohort consisting of 140,636 cases from Hospital A and 114,893 cases from Hospital B. Among these data, 5,456 and 8,532 cases of AKI cases during hospitalization were selected from Hospitals A and B, respectively. 94,816 cases of research cohort from hospital C were collected and 5,716 AKI cases during hospitalization were selected. The process of dataset construction is depicted in Fig. 1, and the distribution of AKI cases according to hospitalization period is presented in Supplementary Fig. 1 (available online). The data from Hospitals A and B were utilized for training and internal validation, and the data from Hospital C was utilized for external validation.

For labeling purposes, patients who satisfied AKI recovery criteria were labeled with 1, others were labeled with 0. Patients were excluded from this study if, following the onset of AKI, Cr levels were not measured or, even if measured, recovery could not be definitively determined within 7 days. Examples regarding this process are shown in Supplementary Fig. 2 (available online).

Statistical analysis
For continuous variables, the median and interquartile values were provided when a normal distribution could not be assumed; otherwise, the mean and standard deviation (SD) were presented. Categorical variables were represented by the number and percentage of patients. To assess the differences between recovery and non-recovery, t tests were performed for continuous variables showing a normal distribution, the Mann-Whitney U tests for non-normally distributed continuous variables, and the chi-square tests for categorical variables, all at a significance level of 0.05.

**Figure 1.** The data composition process.
AKI, acute kidney injury.
Data preprocessing

Data collected from the electronic health records included measurements, measurement times, and specific variables, resulting in numerous missing values. To address this issue, we adopted a method of summarizing the data at 24-hour intervals. This approach has been validated for its efficacy in prior studies, providing benefits in terms of simplicity of deployment and utilization of the developed model. By summarizing the data at 24-hour intervals, we maintained consistency and facilitated data analysis.

Variables with multiple measurements within 24 hours were summarized as maximum, mean, minimum, and the number of measurements, for vital signs data. The laboratory test results were based on recent measurements. Additionally, variables such as the prescription of nephrotoxic drugs (e.g., nephrotoxic antibiotics, nonsteroidal anti-inflammatory drugs [NSAIDs], and cytotoxic chemotherapeutic agents), vascular imaging studies, surgery with general anesthesia, contrast-enhanced computed tomography (CT), and transfer to the ICU, were considered influential within 7 days of the corresponding measurement times. Next, eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2021 Cr equation \(^1\). We also added a variable named “Increased amount of Cr” by subtracting the baseline Cr from Cr at the time of AKI occurrence. Finally, the “BUN/Cr ratio” represents the value obtained by dividing blood urea nitrogen (BUN) by Cr. Subsequently, robust scaling was applied to all the continuous variables. For categorical variables, one-hot encoding was applied.

Feature selection

Approximately 120 features were extracted from the electronic health records, covering basic patient information, vital signs, laboratory test results, and other relevant factors. Following a comprehensive literature review and consultation with domain experts, a two-step feature selection process was undertaken. Initially, the LASSO (Least Absolute Shrinkage and Selection Operator) was utilized to examine the regression coefficients and SHapley Additive ExPlanations (SHAP) values for all features. Simultaneously, the outcomes were assessed using a stepwise method with logistic regression as the criterion. Subsequently, based on correlation coefficients and missing value ratios, the feature set was refined to 43 features. Details of the selected 43 features are provided in Supplementary Table 1 (available online).

Outlier and missing value handling

To address outliers, the data distribution for each feature was thoroughly examined, and individual patient records were reviewed. Detection thresholds for certain numerical variables were established in collaboration with clinical experts, utilizing histograms and quantile-quantile plots.

To address missing values in the data, two methods were employed: imputation with preceding values, and the use of missing value indicators. For variables with available preceding values, the missing values were replaced with the preceding values to maintain data continuity. Additionally, for variables with low missing value rates (<20%), the multiple imputation by chained equations (MICE) method was used to handle missing values from the three hospitals. MICE is widely used to generate imputations that closely resemble true distributions when the rate of missing values is low \(^1\). The choice between the missing indicator method and MICE was determined based on the extent of missing values for each variable. The missing indicator method was used for variables with missing value rates exceeding 20%, where missing values were marked as ‘unknown.’ This approach allowed us to identify and distinguish the patterns of missing values within the variables. Supplementary Table 2 (available online) presents the missing value rates before and after handling missing values with preceding values in each hospital. Additionally, Supplementary Table 3 (available online) provides an explanation of the application of the missing indicator method, where missing values are marked as ‘unknown.’

Machine learning models

Deep learning models generally exhibit superior performance compared to traditional machine learning models, but due to the amount of data required for training and high time and space complexities \(^1\), traditional machine learning models were selected in this study. Various machine learning models were used in this study, including logistic regression (LR), random forest (RF), eXtreme Gradient Boosting (XGB), Light Gradient Boosting Model (LGBM), and Categorical Boosting (CAT). CAT was utilized...
as an effective model for handling categorical variables, negating the need for separate one-hot encoding procedure for such variables [23].

For model training purposes, the dataset was randomly divided into 10 groups, ensuring an equal outcome ratio across them. The last group (group 10) was utilized for internal validation, while the remaining nine groups were used for cross-validation to conduct hyperparameter tuning and model selection. During the nine cycles of iteration, seven groups served for training purposes, one group was used to set early stopping criteria, and the remaining group was employed for performance evaluation. Grid search was applied for hyperparameter tuning, and the range of hyperparameters adjusted according to the model is detailed in Supplementary Table 4 (available online). The processes of early stopping, hyperparameter tuning, and model selection were all based on the area under the receiver operating characteristic curve (AUROC). A graphical representation of the training process can be found in Supplementary Fig. 3 (available online).

**Model evaluation and interpretation**

For the evaluation metrics, accuracy, precision, recall, specificity, F1 score, AUROC, and area under the precision-recall curve (AUPRC) were utilized. Internal validation was conducted using group 10 from the internal cohort, which has not been employed in the training phase, while external validation utilized all data from the external cohort at Soonchunhyang University Cheonan Hospital. The evaluation of metrics such as accuracy, precision, recall, specificity, and F1 score, which vary according to the threshold, involved adjusting the threshold in increments of 0.01 from 0.01 to 0.99, and the results were presented in Supplementary Fig. 4 (available online). The performance metrics of this manuscript are reported based on a threshold of 0.5. Evaluations were carried out on both internal and external validation datasets.

An in-depth sub-cohort analysis was conducted to gain a deeper understanding of early renal function recovery using the developed model. The criteria for the sub-cohort included patients with an eGFR less than 60 mL/min/1.73 m² and those with an eGFR of 60 mL/min/1.73 m² or above at the time of AKI onset, female and male patients, patients aged 65 years and over versus those under 65 years, and the use of cytotoxic chemotherapeutic agents. To enhance the interpretability of the models, SHAP values were provided for each analysis.

**Results**

**Baseline characteristics**

The final analysis included 7,041 patients from the internal cohort and 2,929 patients from the external cohort. The labeling ratios for recovery in these hospitals were 46.9% and 51.8%, respectively. Among recovered patients, the mean time to recovery post-AKI was 5.05 days (SD, 2.26) in the internal cohort and 4.75 days (SD, 2.20) in the external cohort. The distribution of recovery in patients with AKI is illustrated in Supplementary Fig. 5 (available online). The baseline characteristics of the recovery and non-recovery groups from each hospital are presented in Supplementary Table 5 (available online). Although Cr was not utilized in the actual model training, it is included in the table. Supplementary Table 6 (available online) shows the result after applying the missing indicator.

Numerous variables exhibited statistically significant differences between the renal function recovery group and the non-recovery group. Among continuous variables, vital signs such as blood pressure, heart rate, respiratory rate, along with white blood cell count, BUN, increased amount of Cr, glucose, blood sugar test, uric acid, phosphorus, chloride, and urine specific gravity (SG) were higher in the recovery group compared to the non-recovery group in both hospitals. Conversely, platelet, eGFR, alkaline phosphatase, pH, and total CO₂ levels were higher in the non-recovery group than in the recovery group across both hospitals. For categorical variables, the proportion of patients using nephrotoxic antibiotics in the non-recovery group was higher, while the incidence of contrast-enhanced CT and general anesthesia showed the opposite trend. Even when applying a missing indicator, variables that showed statistically significant differences among continuous variables largely maintained their disparities. Additionally, C-reactive protein and pro-brain natriuretic peptide, which did not exhibit statistically significant differences before applying the missing indicator, showed differences afterward. Some variables demonstrated statistical differences in only one of either the internal or external cohort. Total
cholesterol showed statistical differences in both cohorts, but with the non-recovery group showing higher levels in the internal cohort, whereas in the external cohort, the recovery group had higher levels. These differences between hospitals could potentially impact the model’s generalizability and suggest that analyzing a larger patient population is necessary to enhance generalization performance.

**Model performance**

Table 1 presents the performance outcomes of internal and external validation, evaluating five machine learning models: LR, RF, XGB, LGBM, and CAT. The CAT model demonstrated strong predictive capability with the highest AUROC of 0.7816. The RF model also performed well, with an AUROC of 0.7727, whereas the XGB model exhibited commendable performance with an AUROC of 0.7543. LR showed a moderate performance, with an AUROC of 0.7402. The LGBM displayed relatively lower predictive power, with an AUROC of 0.7254. The external validation results indicated a general decrease in performance across all models. The performance degradation in external validation, as measured by AUROC ranged from a minimum decrease of 0.0168 to a maximum decrease of 0.0456. The CAT model consistently outperformed the other models in terms of internal validation. The RF model demonstrated the highest performance in external validation. However, external validation data were not considered in the model selection process, and the CAT model was ultimately chosen. Supplementary Fig. 6 (available online) shows the AUROC and AUPRC curves for internal and external validation.

**Model evaluation and interpretation**

The SHAP values for the model are depicted in Fig. 2. In the figure, the red color indicates higher values of the respective feature, while the blue color signifies lower values. The position of the dots placed towards the right signifies a greater contribution by the feature value to the model’s prediction of non-recovery for the patient. For categorical variables, red dots represent a value of 1, and blue dots signify a value of 0. The variables that the model considered important include increased amount of Cr, the use of anti-SG, activated partial thromboplastin time, sex, heart rate, BUN, alkaline phosphatase, respiratory rate, systolic blood pressure, total carbon dioxide, white blood cell count, body temperature, age, triglycerides, platelet count, and albumin (Alb). When AKI occurs, all patients tend to have increased Cr. In cases where there was a greater change in Cr, it appeared to have an extreme impact, resulting in recovery. Patients with a high BUN/Cr ratio or high SG typically raise suspicions of dehydration. Patients who were dehydrated tended to have a more favorable prognosis for recovery. Variables such as high Alb, BUN, heart rate, and body temperature are positively associated with better recovery. The use of NSAIDs contributes to improved renal function recovery, whereas nephrotoxic antibiotics or cytotoxic chemotherapeutic agents hinder renal recovery.

<table>
<thead>
<tr>
<th>Validation</th>
<th>Model</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Recall</th>
<th>F1</th>
<th>AUROC</th>
<th>AUPRC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internal</strong></td>
<td>LR</td>
<td>0.6805</td>
<td>0.6881</td>
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<td>0.7402</td>
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<td>0.7258</td>
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<td>0.7360</td>
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</tbody>
</table>

AUROC, area under the receiver operating characteristic curve; AUPRC, area under the precision-recall curve; CAT, Categorical Boosting; LGBM, Light Gradient Boosting Model; LR, logistic regression; RF, random forest; XGB, eXtreme Gradient Boosting.
Figure 2. SHapley Additive exPlanations (SHAP) value.
BUN, blood urea nitrogen; Cr, creatinine; CT, computed tomography.

Table 2. Subgroup analysis of internal and external validation outcomes

<table>
<thead>
<tr>
<th>Validation</th>
<th>Group</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Recall</th>
<th>F1</th>
<th>AUROC</th>
<th>AUPRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal</td>
<td>eGFR ≥60 a</td>
<td>0.7298</td>
<td>0.7507</td>
<td>0.7833</td>
<td>0.7667</td>
<td>0.7846</td>
<td>0.8183</td>
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<tr>
<td></td>
<td>eGFR &lt;60 a</td>
<td>0.6863</td>
<td>0.6875</td>
<td>0.3667</td>
<td>0.4783</td>
<td>0.7486</td>
<td>0.6284</td>
</tr>
<tr>
<td></td>
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<td>0.7538</td>
<td>0.6901</td>
<td>0.7206</td>
<td>0.7783</td>
<td>0.8003</td>
</tr>
<tr>
<td></td>
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<td>0.7442</td>
<td>0.7844</td>
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<tr>
<td></td>
<td>Age ≥65 yr</td>
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<td>0.7366</td>
<td>0.7173</td>
<td>0.7268</td>
<td>0.7783</td>
<td>0.7698</td>
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<tr>
<td></td>
<td>Age &lt;65 yr</td>
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<td>0.7541</td>
<td>0.7188</td>
<td>0.7360</td>
<td>0.7838</td>
<td>0.8247</td>
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<td>0.7036</td>
<td>0.7279</td>
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<td>0.7205</td>
<td>0.7547</td>
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<tr>
<td></td>
<td>No b</td>
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<td>0.8133</td>
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<td>0.722</td>
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<tr>
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<td>0.6719</td>
<td>0.6410</td>
<td>0.8754</td>
<td>0.7401</td>
<td>0.7435</td>
<td>0.7503</td>
</tr>
<tr>
<td></td>
<td>eGFR &lt;60 a</td>
<td>0.6597</td>
<td>0.5137</td>
<td>0.3357</td>
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<td>0.7607</td>
<td>0.6664</td>
</tr>
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</table>

AUPRC, area under the precision-recall curve; AUROC, area under the receiver operating characteristic curve; eGFR, estimated glomerular filtration rate.

"The unit is mL/min/1.73 m². It means general anesthesia surgery."
Subgroup analysis

Table 2 presents the results of subgroup analyses based on four criteria at the onset of AKI: eGFR levels, sex, age, and whether the patient underwent general anestheisa. Only internal and external validations were conducted for the model previously trained. While the models’ performance did not significantly differ by sex and age, it exhibited higher efficiency in groups with an eGFR of 60 mL/min/1.73 m² or above at the onset of AKI and in those who did not undergo surgery under general anesthesia compared to their counterparts. These findings suggest that the model developed in this study may perform better in patients with relatively good renal function and those who have not received general anesthesia, indicating its potential superiority in milder cases.

Discussion

In this study, we introduced a method to predict recovery after AKI. The model achieved a moderate performance level with an AUROC of 0.7816 (internal) and 0.7360 (external). Despite its significant relevance to patient prognosis, AKI recovery remains unclear, making predictions challenging for clinicians, the model that demonstrated the highest performance is CAT. CAT is known as a tree-based ensemble model specialized in handling categorical variables through mechanisms such as categorical feature combination [23]. It is speculated that the increase in the number of categorical variables, due to the use of the missing indicator, contributed to CAT’s superior performance. We utilized SHAP values to identify the factors contributing to AKI recovery and quantify their significance. As expected, patients with low Alb or high blood pressure, showed a tendency toward poorer renal function recovery. Conversely, patients with elevated white blood cell counts and high body temperatures tended to have better renal function recovery. For patients where AKI might be associated with infection, resolution of the causative infection also led to AKI recovery. Although the use of NSAIDs is related to better renal recovery, the use of chemotherapeutic agents or nephrotoxic antibiotics tends to hinder recovery. The use of NSAIDs can be easily discontinued in AKI patients; however, agents such as chemotherapy may be challenging to cease depending on the patient’s condition and are also presumed to act as negative factors, potentially causing more severe damage. Furthermore, in dehydrated patients with a high BUN/Cr ratio or urine SG, a more favorable recovery trend was observed as the state of dehydration improved, high BUN had a positive impact on recovery. This suggests that AKI caused by prerenal factors tends to lead to a relatively good recovery.

It was observed that patients who underwent surgery under general anesthesia exhibited more substantial recovery in statistical analysis. However, this trend was not evident in the SHAP analysis. While the tendency to predict recovery or non-recovery was not distinct for patients who had undergone general anesthesia, the absolute value of SHAP values was larger compared to those who had not received general anesthesia. The outcomes following surgery under general anesthesia could vary greatly depending on the cause and type of surgery, and this complexity seems to be reflected in the model. For patients who did not undergo surgery, the model demonstrated a very high performance with a score of 0.8714. Future research may benefit from distinguishing characteristics based on the purpose and type of surgery rather than categorizing all patients uniformly based on the administration of general anesthesia.

Interpreting the model through SHAP values offers various advantages over relying solely on statistics. By quantifying the factors contributing to AKI recovery in each patient, this approach provides insights into the crucial elements influencing AKI recovery. Predicting whether and when patients with AKI recover in real-life situations is challenging. The model proposed in this study could serve as an effective tool to assist clinicians in situations where clinical judgment alone may be insufficient.

Another objective of this study was to evaluate the clinical applicability of the machine learning model. To achieve this, we conducted various studies on renal function recovery using data from three hospitals. We observed a trend of decreased external validation performance compared to internal validation, which was attributed to differences in patient populations, disease severity, and hospitalization patterns among institutions. Additionally, the inability to precisely match the features used in the model and potential overfitting of the training data may have contributed to this trend [24]. Therefore, limited data and patient numbers may interfere with the model’s ability to learn generalized patterns.

It is important to note that almost all medical artificial in-
elligence studies have been retrospective. Therefore, several biases (e.g., biases stemming from data loss, label definitions based on operational definitions, and selection of Cr baseline or reference values) occurred during patient selection and cohort formation owing to the exclusion of a substantial number of patients. These factors are critical and contribute to the uncertainty in the general performance of the developed model. Additionally, the process of organizing data on a daily basis was intended for the convenience of model development and application but might have introduced biases into the model. This underscores the need for model calibration when applied to clinical settings and the importance of including diverse patient populations with sufficient sample sizes in multi-institutional studies [25].

This study is subject to certain limitations. First, the lack of consensus on AKI recovery criteria necessitated reliance on existing research findings to establish a definition. Moreover, recovery status was evaluated using the initial Cr level at the time of AKI onset as a fixed reference point, an approach that may not fully account for the clinical context of peak Cr levels when evaluating Cr stages. Further, limitations in data utilization precluded the incorporation of additional clinical evidence related to AKI beyond Cr levels [16]. As a result, this criterion was omitted from the AKI definition, potentially leading to unidentified AKI cases and introducing bias. Secondly, the absence of data on dialysis or kidney transplantation was noted, and this was addressed by excluding patients with an eGFR of less than 60 mL/min/1.73 m², an issue that warrants attention in future research. Thirdly, the study did not account for the differences in interventions post-AKI occurrence. The nature of interventions following AKI can significantly influence patient prognosis, and considering this through additional data collection could be highly significant [26]. Lastly, while the model’s performance was commendable, its adequacy for seamless real-world application is acknowledged to be limited. Future efforts should aim at enhancing performance by securing more diverse and extensive datasets and refining the machine learning methodology for predicting renal function recovery in patients with AKI.

In conclusion, our study introduced a machine learning-based approach for predicting recovery after AKI, revealing key factors influencing renal function recovery. This approach will be helpful in aiding clinical decision-making and further future research.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

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Data sharing statement

The data set used in this study is not publicly available. However, the data of this study can be obtained upon reasonable request from the corresponding author. The code to generate the result of this study can be accessed at https://github.com/5454dls/AKI_recovery, upon reasonable request.

Authors’ contributions

Conceptualization: NJC, IJ
Data curation: NJC, SHK, HWG
Formal analysis: NJC, IJ, YK, HWG
Funding acquisition, Project administration, Resources: HL
Investigation: IJ, YK, DOK
Methodology: IJ
Supervision: HWG, HL
Validation: SJA, SHK
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References


The effect of pharmacist-led medication therapy management in the multidisciplinary care of acute kidney injury survivors

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Background: The Acute Disease Quality Initiative advocates multidisciplinary care for the survivors of acute kidney injury (AKI). The bundled care strategy recognizes the role of pharmacists. However, their specific contributions in this context remain underexplored.

Methods: This retrospective study examined the efficacy of pharmacist-led post-AKI pharmaceutical care in outpatient settings at a single center. Adults with recent AKI during hospitalization, maintaining an estimated glomerular filtration rate <45 mL/min/1.73 m² postdischarge, were enrolled in a multidisciplinary team care program from March 2022 to January 2023, with a 6-month follow-up period. Pharmacist-delivered care adhered to international multidisciplinary consensus guidelines. Efficacy was evaluated by analyzing medication-related recommendations, medication adherence, nephrotoxic drug utilization, and renoprotective medication usage before and after the intervention.

Results: A total of 40 patients were referred to the pharmacist-managed clinic. Of these, 33 patients (mean age, 63 ± 15 years; 60.6% male) attended the clinic. Nineteen patients completed follow-up visits. The pharmacist provided 14 medication-related recommendations to relevant physicians, with 10 of these recommendations (71.4%) being accepted. There was a significant decrease in the use of modifiable nephrotoxic drugs (p = 0.03). However, no significant improvements were noted in medication adherence or the utilization of renoprotective medications.

Conclusion: Our study underscores the potential benefits of pharmacist-led post-AKI bundled care strategy in outpatient settings. We observed a significant reduction in the utilization of modifiable nephrotoxic drugs, indicating the effectiveness of pharmacist interventions in optimizing medication regimens to mitigate renal harm.

Keywords: Acute kidney injury, Medication therapy management, Pharmaceutical services
**Introduction**

Acute kidney injury (AKI) is a common and complex clinical syndrome, frequently manifesting as a complication in hospital settings, and its etiology involves diverse underlying factors [1]. The transitional phase between AKI and the onset of chronic kidney disease (CKD) is medically defined as acute kidney disease (AKD) [2]. A comprehensive systematic review has revealed that approximately 33.6% of all patients with AKI subsequently develop AKD [3]. AKI survivors have elevated risks of recurrent AKI incidents and adverse drug reactions [4,5]. Meticulous reconciliation of medications following discharge is paramount given the likely alterations in patients’ current medication regimens due to AKI [4]. Medications that undergo renal processing, possess renoprotective attributes, or have nephrotoxic potential are modifiable elements that can substantially affect post-AKI outcomes [6–8]. Consequently, the management of medications for AKI survivors must be optimized.

In 2018, the Acute Disease Quality Initiative recommended the inclusion of a comprehensive care bundle for AKI survivors. This bundle, denoted as “KAMPS” (an acronym for kidney function check, advocacy, medication, pressure, and sick-day protocols) (Table 1), pertains to the careful evaluation and subsequent intervention in the context of medications [9]. Recently, the evolving roles and prospective contributions of pharmacists in post-AKI care have garnered increasing attention [10–13]. Pharmacists play crucial roles, such as educating patients on medication management throughout the course of AKD; calibrating drug dosages; ensuring no unnecessary nephrotoxic drug exposure in the post-AKI phase; exercising caution in reintroducing indispensable drugs with potential nephrotoxic effects during acute illness settings, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs); managing comorbidities; and monitoring patients and collaborating with their care teams [10,13]. Pharmacist interventions have been effec-

### Table 1. KAMPS framework and MTM for AKI survivors

<table>
<thead>
<tr>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KAMPS framework</strong></td>
<td></td>
</tr>
<tr>
<td>Kidney function check</td>
<td>Measure kidney function</td>
</tr>
<tr>
<td>Advocacy</td>
<td>Educate patients and caregivers on AKI and CKD</td>
</tr>
<tr>
<td></td>
<td>Communicate with other care providers</td>
</tr>
<tr>
<td>Medication</td>
<td>Reconcile, review, and manage medications</td>
</tr>
<tr>
<td></td>
<td>Discuss the risks and benefits of medications, particularly angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and diuretics</td>
</tr>
<tr>
<td>Pressure</td>
<td>Review KENDs and over-the-counter medications</td>
</tr>
<tr>
<td>Sick-day protocols</td>
<td>Ensure patients’ understanding of blood pressure goals and targets</td>
</tr>
<tr>
<td></td>
<td>Discuss fluid status, ideal weight, and diuretics’ functions</td>
</tr>
<tr>
<td></td>
<td>Educate patients on medications that require monitoring during acute illness</td>
</tr>
<tr>
<td></td>
<td>Consider protocols to withhold KENDs</td>
</tr>
<tr>
<td><strong>Focal points of MTM for AKI survivors</strong></td>
<td></td>
</tr>
<tr>
<td>Medication reconciliation</td>
<td>Review current prescription, nonprescription medications, herbal medicines, and dietary supplements</td>
</tr>
<tr>
<td></td>
<td>Identify medication discrepancies before and after admission</td>
</tr>
<tr>
<td>Comprehensive medication assessment</td>
<td>Assess renally processed or eliminated drugs, renoprotective medications, and potential drug interactions</td>
</tr>
<tr>
<td></td>
<td>Identify medication-related problems</td>
</tr>
<tr>
<td></td>
<td>Identify potentially harmful drugs</td>
</tr>
<tr>
<td>Medication adherence</td>
<td>Assess medication adherence using the Adherence to Refills and Medications Scale</td>
</tr>
<tr>
<td></td>
<td>Describe medication nonadherence in detail</td>
</tr>
<tr>
<td>Education</td>
<td>Provide information on AKI, avoiding nephrotoxic agents, and sick-day protocols</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; CKD, chronic kidney disease; KAMPS, kidney function check, advocacy, medication, pressure, and sick-day protocols; KEND, kidney-eliminated and nephrotoxic drug; MTM, medication therapy management.
ative in enhancing medication adherence among both patients with CKD and those with AKD [14,15]. A pioneering pilot study in the United States that included pharmacists in post-AKI care teams in primary care settings highlighted pharmacists’ engagement in discerning medication-related problems (MRPs) and offering effective recommendations [13].

In 2006, Taiwan initiated a multidisciplinary team care program for pre-end-stage renal disease (pre-ESRD) patients. By 2021, the program expanded its ambit to include patients with AKD and integrated pharmaceutical care services. However, the precise scope of pharmacists’ contributions within this evolving landscape remains unclear. To date, very few studies have investigated the efficacy of multidisciplinary post-AKI care; moreover, limited data are available on pharmacist-led outpatient pharmaceutical care for AKI survivors, particularly in Asian populations. Therefore, the present study aimed to evaluate the efficacy of pharmacist-delivered outpatient pharmaceutical care for AKI survivors by assessing pharmacist-provided MRP recommendations, changes in patient medication adherence, and the usage of renoprotective and nephrotoxic medications during their AKD period.

**Methods**

**Patients**

This retrospective study was conducted at a single medical center and involved survivors of AKI who were enrolled in a multidisciplinary outpatient AKI care program and subsequently referred to a pharmacist-managed clinic (PMC) at National Taiwan University Hospital between March 2022 and January 2023. The participants were followed up for 6 months after enrollment. Eligible participants included adults (≥18 years) who had developed AKI during hospitalization and exhibited an estimated glomerular filtration rate of <45 mL/min/1.73 m² within 1 month after discharge. AKI was defined and graded by a nephrologist following the KDIGO (Kidney Disease: Improving Global Outcomes) framework, with criteria including an increase in serum creatinine (S_{Cr}) by ≥0.3 mg/dL within 48 hours or an increase in S_{Cr} to ≥1.5 times baseline [2]. Baseline S_{Cr} was defined as the lowest value within the preceding 180 days before hospital admission, or if this information was lacking, as the lowest S_{Cr} level during hospitalization. In addition, individuals requiring dialysis for less than 3 months due to AKI and deemed by physicians to have the potential to discontinue dialysis were eligible for inclusion. To alleviate the risk of information bias, individuals who had previously participated in our institution’s pre-ESRD program or similar multidisciplinary care programs for multidisciplinary CKD care before AKI onset were excluded from the study.

This study was approved by the Research Ethics Committee of National Taiwan University Hospital (No. 202207142RINB; 2022). Written informed consent was waived due to the retrospective nature of the study.

**Multidisciplinary team**

The AKD multidisciplinary team comprised various specialized professionals, such as nephrologists, nurses, dietitians, and a pharmacist. Each specialist conducted an initial consultation with patients within 30 days after discharge, with all specialists meeting on the same day; this was followed by a revisit after 3 months. The nephrologists assumed a central role in the team, offering advanced kidney disease treatment. The nurses coordinated patient care within the team, and the dietitians offered personalized dietary guidance for the patients. The pharmacist, in accordance with the KAMPS framework (Table 1), engaged in medication therapy management (MTM), which included tasks such as ensuring medication reconciliation, performing comprehensive assessments, evaluating medication adherence, and delivering medication-related education [9]. Pharmaceutical care was provided before or after physician consultations. Following each consultation, a succinct personal medication record was generated, outlining current medications, MRPs, and action plans for each patient. Notably, each care session was meticulously documented within the patients’ electronic medical records.

**Outcomes of pharmaceutical care**

Pharmaceutical care outcomes were assessed across four key dimensions: MRP recommendations, changes in patient medication adherence, usage of renoprotective medications, and exposure to nephrotoxic agents. MRP recommendations provided by pharmacists were quantified and
organized, while medication adherence was evaluated using the Adherence to Refills and Medications Scale (ARMS) [16], with scores ranging from 12 (optimal adherence) to 48 (extremely poor adherence). Instances of nonadherence, particularly regarding renoprotective medications and nephrotoxic drugs, were documented. Renoprotective medication evaluation encompassed ACEIs, ARBs, and sodium-glucose cotransporter 2 (SGLT2) inhibitors. The assessment of nephrotoxic drug usage was guided by previous literature [17], with a comprehensive list provided in Table 2. Nephrotoxic agents were categorized into modifiable and non-modifiable types based on patient usage circumstances. Modifiable agents encompassed medications for which non-nephrotoxic alternatives were available, those lacking clear indications, and drugs that patients self-administered. On the other hand, non-modifiable nephrotoxic agents referred to medications deemed essential for treatment, for which substitutions or alterations were not feasible. The assessment of both renoprotective and nephrotoxic agents was conducted across four stages (pre-AKI, before discharge, first visit, and second visit), tracking patients' medication profiles before and after AKI onset and during subsequent follow-up visits.

### Statistical analysis

Data on the patients’ characteristics and clinical outcomes were manually extracted from their electronic medical records. Categorical data are presented as the number and percentage values, whereas continuous data are presented as the mean ± standard deviation or median (interquartile range) values. The change in ARMS score was assessed using a paired t test, while categorical variables, such as ARMS categorization (=12 or >12), as well as the utilization of nephrotoxic and renoprotective medications, were analyzed using the McNemar test. Statistical significance was set at p < 0.05. All statistical analyses were performed using STATA (version 14.0; StataCorp).

<table>
<thead>
<tr>
<th>Table 2. List of potentially nephrotoxic medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication class</strong></td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>Beta-lactam drugs</td>
</tr>
<tr>
<td>Antifungals</td>
</tr>
<tr>
<td>Antivirals</td>
</tr>
<tr>
<td>Acyclovir</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Antiangiogenic drugs</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Immunosuppressants</td>
</tr>
<tr>
<td>Immunotherapies</td>
</tr>
<tr>
<td>Avelumab</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Diclofenac</td>
</tr>
<tr>
<td>Etoricoxib</td>
</tr>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
</tr>
<tr>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Bisphosphonates</td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drugs; TMP/SMX, Trimethoprim/sulfamethoxazole.

*All medications investigated were in systemic formulations. Topical routes and inhalation were not evaluated.*
Results

Patient attendance and characteristics

During the study period, 40 patients were referred to the PMC. Of them, 33 adults (82.5%) attended the PMC. Nineteen patients (57.6%) completed the follow-up visits (Fig. 1). The patients’ absence at follow-up visits was attributed to various factors, including loss to follow-up at a nephrology clinic (21.4%), admission or referral to an emergency department (14.3%), death within 3 months (7.1%), administrative oversight (14.3%), and patient-related factors (42.9%).

The demographic characteristics of the cohort are summarized in Table 3. The mean age was 63 years, with 60.6% being men. Notably, 20 patients (60.6%) had CKD before the onset of AKI. Common comorbidities associated with AKI included diabetes mellitus (54.5%), heart failure (39.4%), and malignancy (24.2%). Among the cohort, 25 patients (75.8%) had stage 3 AKI, with 14 patients requiring dialysis during hospitalization and three patients remaining on dialysis upon discharge. The primary etiological factors contributing to AKI were categorized as cardiorenal syndrome (33.3%), infection (27.3%), and medication-related causes (21.2%). Duplicates of etiology were allowed, indicating that patients might have more than one contributing factor to their AKI. After 6 months of follow-up, 17 individuals achieved a Scr level lower than 1.3 times the baseline, two patients discontinued dialysis, three patients were on long-term dialysis, and three patients passed away. Additionally, 14 patients were still receiving multidisciplinary pharmaceutical care for CKD under the purview of the nephrology department.

Pharmacist intervention

The pharmacist involved in this study provided 14 medication-related recommendations to relevant physicians, of which 10 recommendations (71.4%) were accepted and implemented (Table 4; Supplementary Table 1, available online). These recommendations primarily centered on medication reconciliation, comprising 57% of all suggestions. Specifically, these medication reconciliation-related suggestions predominantly pertained to the cessation and resumption of chronic disease medications prescribed long-term for patients during their hospitalization for AKI. Other MRPs included inappropriate dosage based on current renal function, indication (requiring additional therapy), nephrotoxic medication usage, and inadequate medication efficacy (due to low dosage). Four recommendations were not accepted, likely due to concerns regarding the resumption of ezetimibe and valsartan, management of a potential overdose of erythropoiesis-stimulating agents such as methoxy polyethylene glycol-epoetin beta, and an increase in the dosage of valsartan. For the 19 individuals who completed follow-up visits, the average ARMS score before and after the pharmacist’s consultation showed a nonsignificant change (from 13.4 ± 1.5 to 13.2 ± 1.3, p = 0.72) (Fig. 2). Specifically, among those with an ARMS score of 12 (indicating full adherence to the medication regimen and prescription refills in the past month), the number of patients decreased from 9 (47.4%) to 8 (42.1%). Four individuals showed an improvement in adherence (ARMS score decreased to 12), while five individuals ex-
Table 3. Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Summary</th>
<th>Patients with 1 visit</th>
<th>Patients with 2 visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63 ± 16</td>
<td>66 ± 15</td>
<td>61 ± 16</td>
</tr>
<tr>
<td>Male sex</td>
<td>20 (60.6)</td>
<td>7 (50.0)</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>20 (60.6)</td>
<td>9 (64.3)</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (54.5)</td>
<td>9 (64.3)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (69.7)</td>
<td>9 (64.3)</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13 (39.4)</td>
<td>4 (28.6)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (18.2)</td>
<td>2 (14.3)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>4 (12.1)</td>
<td>2 (14.3)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (24.2)</td>
<td>3 (21.4)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>eGFR* (mL/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>44.9 ± 31.0</td>
<td>45.6 ± 31.5</td>
<td>44.5 ± 33.9</td>
</tr>
<tr>
<td>At the time of discharge</td>
<td>23.7 ± 11.7</td>
<td>26.1 ± 14.8</td>
<td>22.1 ± 9.3</td>
</tr>
<tr>
<td>At inclusion (1st visit)</td>
<td>23.3 ± 9.8</td>
<td>23.6 ± 11.6</td>
<td>23.1 ± 8.7</td>
</tr>
<tr>
<td>After 3 mo (2nd visit)</td>
<td>29.1 ± 18.6</td>
<td>26.9 ± 10.4</td>
<td>30.2 ± 21.8</td>
</tr>
<tr>
<td>After 6 mo (follow-up)</td>
<td>30.8 ± 21.0</td>
<td>28.0 ± 5.7</td>
<td>31.9 ± 24.6</td>
</tr>
<tr>
<td>No. of medications used at inclusion</td>
<td>9 (7–11)</td>
<td>10 (7–11)</td>
<td>9 (7–10)</td>
</tr>
<tr>
<td>AKI staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KDIGO stage 1</td>
<td>6 (18.2)</td>
<td>4 (28.6)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>KDIGO stage 2</td>
<td>2 (6.1)</td>
<td>1 (7.1)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>KDIGO stage 3</td>
<td>25 (75.8)</td>
<td>9 (64.3)</td>
<td>16 (84.2)</td>
</tr>
<tr>
<td>Received RRT due to AKI during admission</td>
<td>14 (42.4)</td>
<td>7 (50.0)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Still under RRT at inclusion</td>
<td>3 (9.1)</td>
<td>2 (14.3)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Etiology of AKI§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiorenal syndrome</td>
<td>11 (33.3)</td>
<td>4 (28.6)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Infection</td>
<td>9 (27.3)</td>
<td>4 (28.6)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Drug</td>
<td>7 (21.2)</td>
<td>3 (21.4)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Obstructive nephropathy</td>
<td>4 (12.1)</td>
<td>1 (7.1)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Underlying diseases</td>
<td>4 (12.1)</td>
<td>2 (14.3)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1 (3.0)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>1 (3.0)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hospital length of stay (day)</td>
<td>19 (9–30)</td>
<td>21 (13–27)</td>
<td>15 (8–30)</td>
</tr>
<tr>
<td>Days from onset of AKI to follow-up visit</td>
<td>41 (33–51)</td>
<td>40 (34–47)</td>
<td>41 (31–53)</td>
</tr>
<tr>
<td>Days from hospital discharge to follow-up visit</td>
<td>19 (14–24)</td>
<td>16 (14–22)</td>
<td>20 (14–24)</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, number (%), or median (interquartile range).

AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RRT, renal replacement therapy.

*Exclude patients undergoing dialysis from the calculation. §Duplicates of etiology were permitted.

hibited worsened adherence (ARMS score changed from 12 to >12). The findings suggest no significant difference in adherence change (p = 0.99) (Fig. 2). Further exploration of characteristics associated with poor adherence (ARMS >12) based on AKI stage, PMC visit frequency, and polypharmacy (number of medications ≥5) revealed that individuals with AKI stage 1, those who visited the PMC only once, and those using five or more medications had poorer medication adherence (Supplementary Fig. 1, available online). Additionally, the pharmacist identified 16 instances of medication nonadherence among all the 33 patients, including one patient who self-administered
A nephrotoxic drug (nonsteroidal anti-inflammatory drug, NSAID) and three patients who voluntarily reduced their intake of renoprotective medications, specifically ARBs. After the pharmacist-led MTM, nonsignificant increases were observed in the numbers of patients using ACEIs or ARBs (p = 0.13) and those using SGLT2 inhibitors (p = 0.99) (Fig. 3). Two patients refrained from resuming ACEIs or ARBs due to low blood pressure or unstable kidney function after

Table 4. Medication-related recommendations to physicians

<table>
<thead>
<tr>
<th>Medication-related problem</th>
<th>Summary</th>
<th>Acceptance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication reconciliation(^a)</td>
<td>8</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>4</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Anti-hypertensives (including RASi)</td>
<td>2</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Urate lowering therapy</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Dosage or frequency</td>
<td>2</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Indication (need additional therapy)</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Contraindication (nephrotoxic medication)</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Efficacy of medication (dose too low)</td>
<td>2</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>10 (71.4)</td>
</tr>
</tbody>
</table>

Data are expressed as number only or number (%).
\(^a\)A single medication recommendation may encompass multiple categories of drugs.

Figure 2. Comparing medication adherence before and after pharmacist intervention using the ARMS.
ARMS, Adherence to Refills and Medications Scale.

![Figure 2](image-url)

Figure 3. Trends in renoprotective medication utilization: prevalence of renoprotective medications at pre-AKI, discharge, and follow-up stages. (A) Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. (B) Sodium-glucose cotransporter 2 inhibitor. PMC 1 represents patients who attended the PMC only once (n = 14); PMC 2 represents patients who attended the PMC twice (n = 19).
AKI, acute kidney injury; PMC, pharmacist-managed clinic.

![Figure 3](image-url)
AKI, while one patient refrained from resuming SGLT2 inhibitors because of poor kidney function. Overall, there was no reduction observed in the number of patients who had been exposed to at least one nephrotoxic drug before and after AKI, with a usage rate of 63.6% before AKI and 60.6% to 63.6% during the follow-up period after discharge (Fig. 4). The highest proportion of nephrotoxic drug usage was seen in the antibiotic category (particularly beta-lactam drugs) and proton-pump inhibitors. When analyzing modifiable nephrotoxic agents alone, a significant reduction was observed between pre-AKI and after pharmacist intervention (p = 0.03), with the decrease in NSAID usage being the primary contributing factor (reduced from 27.3% to 3.0%).

Discussion

Our findings highlighted that pharmacists involved in caring for AKI survivors can assist in postdischarge medication reconciliation, provide recommendations for minimizing medication discrepancies, and reduce nephrotoxic drug exposure. Our care team is consistent with multidisciplinary teams formed in other post-AKI studies [11,12]. Our pharmacist delivered post-AKI pharmaceutical care in line with the international consensus, offering services similar to those described in other studies [11–13].

Pharmacists bring a wealth of expertise to the realm of health care. They recognize potential drug interactions, determine necessary drug dosage adjustments, formulate monitoring plans, and limit nephrotoxic drug exposure, thereby optimizing the selection and dosage of medications [18]. Key components of pharmaceutical care encompass vital tasks such as ensuring medication reconciliation, performing comprehensive medication assessments with a focus on drugs eliminated through the renal route and those known to be nephrotoxic, and providing drug-related education. Notably, our unique approach integrates the routine evaluation of medication adherence.

Previous studies assessing the efficacy of multidisciplinary post-AKI care have predominantly focused on team-based interventions with results of optimizing blood pressure management, reducing the urine albumin-to-creatinine ratio, and enhancing patient knowledge [11,12]. However, limited data are available on the efficacy of interventions targeting medication-related behaviors and MRPs. A Mayo Clinic study on post-AKI pharmaceutical care reported that pharmacists, when working closely with primary care providers, can identify and address MRPs [13]. However, in our study, a relatively low number of medication-related recommendations were provided by the pharmacist. This discrepancy may be attributable to the timing of pharmacist consultation in our study, which predominantly occurred after physician consultation; by contrast, in the aforementioned Mayo Clinic study, pharmacist consultation preceded physician consultation. In this study, a substantial proportion of MRPs was associated with medication discrepancies before and after AKI. However, a considerable percentage of omitted medications were not medications that undergo renal processing or have nephrotoxic potential, such as lipid-lowering agents, levothyroxine, and febuxostat. This underscores the importance of comprehensive assessment.

Research on medication adherence in AKI survivors or patients with AKD is either limited or of low quality [15]. CKD studies have indicated that poor adherence increases the risks of kidney function deterioration and mortality [19,20]. Medication adherence is crucial, regardless of the advancement of kidney disease. In our study, we focused on short-term postdischarge adherence since we includ-
ed patients within the first month after discharge. Most patients demonstrated good adherence, making it challenging to discern the effects of pharmacist intervention. Upon further investigation, we observed that individuals with lower clinic attendance and those with polypharmacy exhibited poorer adherence, consistent with previous findings [21]. However, the subset of individuals who did not attend follow-up visits after 3 months could not be evaluated for differences before and after pharmacist intervention, potentially introducing selection bias into the interpretation of results. Additionally, there was a slight increase in the proportion of individuals with suboptimal adherence (ARMS >12) at the second visit, suggesting a decline in adherence over time since discharge, highlighting the potential necessity for more frequent interventions and longer follow-up periods. Future research should focus on assessing sustained intervention impact and employ larger sample sizes for comprehensive understanding.

An observational post-AKI study revealed that 87% of all AKI survivors were exposed to at least one nephrotoxin; these individuals had higher risks of de novo CKD, readmission for AKI, and mortality than nonexposed individuals [22]. Few post-AKI outpatient studies have evaluated the rate of success for nephrotoxin avoidance. In our study, approximately 60% of patients had used at least one nephrotoxic medication, and pharmacist-delivered MTM led to a significant reduction in the use of modifiable nephrotoxic drugs, such as NSAIDs. However, the overall rate of nephrotoxic exposure did not decrease significantly due to the use of essential nephrotoxic drugs such as antibiotics, proton-pump inhibitors, immunosuppressants, and cancer therapies. Extended observation is necessary to assess the sustainability of the effects of pharmacist intervention.

Patients with AKI typically discontinue long-term prescription medications, such as ACEIs, ARBs, and SGLT2 inhibitors, during their hospital stay [5,23]. Observational studies have reported a reduction in the mortality rate among AKI survivors using renin-angiotensin-aldosterone system (RAAS) inhibitors, without any increase in the rate of AKI recurrence [6,24]. Nonetheless, the risks of hyperkalemia and hemodynamically mediated AKI necessitate the personalized assessment of medication re-administration [6,10,17,24]. The effects of SGLT2 inhibitors on post-AKI or AKD outcomes remain unclear; however, long-term studies conducted in high-risk patients, such as those with type 2 diabetes, heart failure, or CKD, have demonstrated that SGLT2 inhibitors can delay kidney function decline and reduce AKI risk [25,26]. Hence, pharmacist-mediated postdischarge medication reconciliation is indispensable for AKI survivors. In the pharmaceutical care for AKI survivors, the pharmacist routinely assessed the usage of these medications. At the second visit, there were increases in the number of users of RAAS inhibitors and SGLT2 inhibitors. However, the resumption of medication use could not be solely attributed to pharmacist intervention. Pharmacists’ assistance in educating patients on monitoring blood pressure, blood sugar, and fluid status might have had an indirect impact. Furthermore, since the number of individuals using these two types of medications before AKI was low, it was challenging to observe significant differences in this regard.

Individuals with a history of AKI are at high risk of unfavorable kidney-related outcomes and adverse drug reactions; therefore, effective MTM is crucial [7,9,27,28]. In Taiwan, post-AKI care is an emerging domain of health care. This study presents a practical model for AKD pharmaceutical care and has yielded preliminary results. However, the small sample size, retrospective study design, and lack of a control group may limit the generalizability of our findings. Therefore, extensive studies are required to elucidate the advantages and multifaceted implications of outpatient pharmacist interventions.

In conclusion, the role of pharmacists in AKD bundled care strategy is paramount given the high risks of kidney-related complications and adverse drug reactions in AKI survivors. Our study clarifies the potential benefits of outpatient pharmacist intervention. Further studies are warranted to comprehensively assess the long-term advantages and implications of pharmacist involvement in AKD care.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Acknowledgments**

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**Data sharing statement**

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

**Authors’ contributions**

Conceptualization, Formal analysis, Investigation, Methodology: TW

Resources: TLW, CFH

Writing–original draft: TW

Writing–review & editing: HCK, CCW, VCW

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**References**


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For the control of hyperphosphatemia in adult patients with chronic kidney disease undergoing hemodialysis

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[제품명] 파시톨주 (PACITOL Injection) [분류번호] 311(비타민 A 및 D제) [성상] 무색 투명한 바이알에 든 무색 투명한 액상 주사제 [원료약품 및 분량] 1 mL 중, 유효성분(주성분) : 파리칼시톨(USP) 5 μg 기타 첨가제 : 에탄올, 프로필렌글리콜, 주사용수 [효능·효과] 만성신부전과 관련된 이차적 부갑상샘기능항진증의 치료 및 예방 [용법·용량] 이 약의 적절한 용량은 각 환자에 따라 주의 깊게 결정되어야 한다. 만성신부전 환자에서 현재 인정되는 완전한 부갑상샘호르몬(intact PTH) 수치의 목표 범위는 요독증이 없는 정상치 상한의 1.5~3 배보다 높지 않다. 이 약의 권장 초기 용량은 2일 1회 또는 이보다 반번하지 않은 빈도로 투석 시 0.04~0.1 μg/kg(2.8~7 μg)을 일시 주사한다.(상세 내용은 제품 설명서 참조) [포장정보] 5바이알/상자 [사용기간] 제조일로부터 24 개월

Ref.) 제품 허가사항. 식약처 의약품안전나라. accessed on 2022.06.20

CKD 환자의 질환 치료를 위해\(^1\)\(^2\) 미쎄라\(^\circledR\)와 렌벨라\(^\circledR\)가
한독으로 하나가 되었습니다.

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미쎄라\(^\circledR\)과 렌벨라\(^\circledR\)가
한독으로 하나가 되었습니다.

CKD 환자의
안정적인 Hb level
관리를 위해\(^3\)

References

CKD, chronic kidney disease; Hb, hemoglobin

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2. Based on IQVIA MAT 3Q 2023, V03G
* Kalimate® Powder is the 1st released calcium polystyrene sulfonate agent in 1984 in Korea, through the licensing with the originator, Nikken(now Kowa) from Japan.
† Based on IQVIA MAT 3Q 2023, V03G (Oral administration)
Patients with aHUS can be at continuous risk of the life-threatening consequences of unpredictable complement-mediated TMA.\textsuperscript{1,2}

Chronic, uncontrolled complement activity in aHUS leads to ongoing endothelial injury, organ damage, and sudden death.\textsuperscript{2,3}


aHUS, atypical Hemolytic Uremic Syndrome; TMA, Thrombotic Microangiopathy

[Table 1]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose (mg/kg)</th>
<th>Maintenance Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Soliris</td>
<td>600</td>
<td>600</td>
</tr>
</tbody>
</table>

[Table 2]

<table>
<thead>
<tr>
<th>Blood volume exchange (plasmapheresis)</th>
<th>Initial Dose (mg/kg)</th>
<th>Maintenance Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

[Table 3]

<table>
<thead>
<tr>
<th>Fresh frozen plasma infusion</th>
<th>Initial Dose (mg/kg)</th>
<th>Maintenance Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

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AstraZeneca

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