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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

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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/m². 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 × 10³/μL and 0.7 × 10³/μL, respectively. The mean platelet count, albumin, and CRP were 104.4 × 10⁹/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

Characteristic	Data
No. of patients	1,500
Age (yr)	66.5 ± 14.7
Male sex	943 (62.9)
Systolic blood pressure (mmHg)	112.2 ± 27.6
Diastolic blood pressure (mmHg)	59.6 ± 15.4
Body mass index (kg/m²)	23.0 ± 4.4
Mechanical ventilation	1,108 (73.9)
APACHE II score	27.3 ± 7.8
SOFA score	12.0 ± 3.4
CKRT settings	
Blood flow rate (mL/min)	111.9 ± 25.5
Dialysate flow rate (mL/hr)	1,178.1 ± 432.2
Replacement flow rate (mL/hr)	787.3 ± 611.9
Comorbidities	
CCI score	3.6 ± 2.8
Hypertension	471 (31.4)
Diabetes mellitus	558 (37.2)
Cardiovascular disease	247 (16.5)
Chronic liver disease	255 (17.0)
Laboratory parameters	
Hemoglobin (g/dL)	9.2 ± 2.2
WBC count (×10³/μL)	12.8 (6.4–20.6)
Neutrophil count (×10³/μL)	8.9 (4.0–15.3)
Lymphocyte count (×10³/μL)	0.7 (0.3–1.3)
Platelet count (×10⁹/L)	104.4 ± 92.4
Blood urea nitrogen (mg/dL)	55.1 ± 32.8
Creatinine (mg/dL)	2.8 ± 2.1
eGFR (mL/min/1.73 m²)	33.0 ± 22.9
Albumin (g/dL)	2.6 ± 0.6
C-reactive protein (mg/L)	14.7 ± 11.4

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; eGFR, estimated glomerular filtration rate; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.
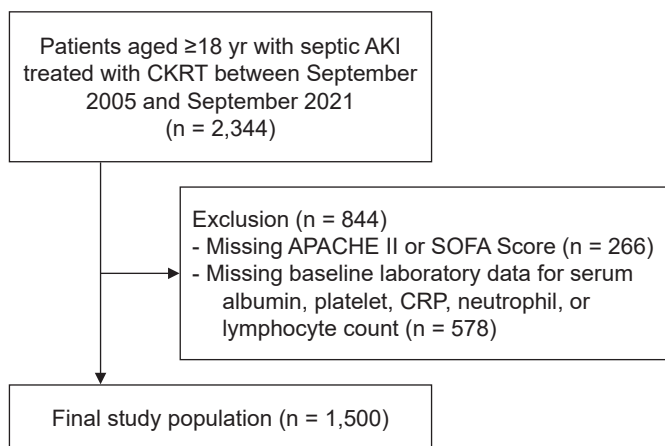

Figure 1. Flow diagram of the study.
AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; CKRT, continuous kidney replacement therapy; CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment.

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, –0.02 to 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, 0.00–0.01), 0.08 (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

Outcome	Total (n = 1,500)
28-Day mortality	940 (62.7)
90-Day mortality	1,048 (69.9)
CKRT duration (day)	3.0 (1.0–6.0)
KRT dependence at discharge[a]	70 (16.4)
Length of ICU stay (day)	7.0 (3.0–16.0)
Length of hospital stay (day)	22.0 (8.0–49.0)

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

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

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.

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

Model	C-statistics (95% CI)	Model performance compared to baseline model					
		ΔC-statistics (95% CI)	p-value	NRI (95% CI)	p-value	IDI (95% CI)	p-value
APACHE	0.65 (0.63–0.66)	-	-	-	-	-	-
APACHE + CAR	0.65 (0.63–0.67)	0.00 (0.00 to 0.01)	0.27	0.05 (0.00 to 0.10)	0.07	0.01 (0.00–0.01)	<0.001
APACHE + PAR	0.66 (0.64–0.68)	0.01 (0.00 to 0.02)	0.004	0.18 (0.11 to 0.22)	<0.001	0.03 (0.01–0.05)	<0.001
APACHE + PCR	0.65 (0.63–0.67)	0.00 (0.00 to 0.01)	0.003	0.08 (−0.19 to 0.14)	0.33	0.00 (0.00–0.02)	0.37
APACHE + CALLY	0.65 (0.63–0.67)	0.00 (0.00 to 0.01)	0.27	0.07 (−0.14 to 0.17)	0.13	0.01 (0.00–0.02)	0.18
APACHE + NAR	0.65 (0.63–0.66)	0.00 (0.00 to 0.00)	0.17	0.04 (−0.09 to 0.09)	0.41	0.00 (0.00–0.00)	0.63
APACHE + LCR	0.65 (0.63–0.67)	0.00 (0.00 to 0.01)	0.41	0.07 (−0.02 to 0.16)	0.05	0.01 (0.00–0.02)	0.07
APACHE + PLR	0.64 (0.63–0.66)	0.00 (0.00 to 0.00)	0.44	0.01 (−0.06 to 0.05)	0.84	0.00 (0.00–0.00)	0.08
APACHE + NLR	0.64 (0.63–0.66)	0.00 (0.00 to 0.00)	0.002	0.05 (−0.08 to 0.10)	0.53	0.00 (0.00–0.00)	0.57
APACHE + SII	0.65 (0.63–0.67)	0.00 (0.00 to 0.01)	0.06	0.08 (0.01 to 0.15)	0.007	0.00 (0.00–0.01)	0.08
APACHE + IBI	0.64 (0.63–0.66)	0.00 (0.00 to 0.00)	<0.001	0.01 (−0.04 to 0.07)	0.55	0.00 (0.00–0.00)	>0.99
APACHE + NCS	0.65 (0.63–0.67)	0.00 (0.00 to 0.00)	0.30	0.04 (−0.02 to 0.09)	0.12	0.00 (0.00–0.01)	0.13
APACHE + NPS	0.66 (0.64–0.68)	0.02 (0.01 to 0.03)	0.001	0.18 (0.10 to 0.23)	<0.001	0.03 (0.01–0.05)	<0.001
APACHE + LAS	0.64 (0.62–0.66)	0.00 (−0.01 to 0.00)	0.41	0.13 (0.00 to 0.18)	0.05	0.01 (0.00–0.02)	0.047

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), 0.24 (95% CI, 0.19–0.29), and 0.06 (95% CI, 0.04–0.09) for platelet count, and 0.02 (95% CI, 0.01–0.03), 0.17 (95% CI, 0.12–0.23), and 0.03 (95% CI, 0.02–0.05) 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).

For NPS, there was an increase in neutrophil count and platelet count with increasing NPS quartiles (all p for trend < 0.05) (Supplementary Table 8, available online). When patients were stratified according to NPS quartiles, the trend towards lower 28- and 90-day mortality at higher NPS was statistically significant (p < 0.001). Regarding KRT dependence at discharge and lengths of ICU and hospital stays, a curvilinear relationship was observed, with the highest KRT dependence rate at discharge, and the longest ICU and hospital stays observed in Q3. However, CKRT duration was comparable across NPS quartiles (Supplementary Table 7, available online).
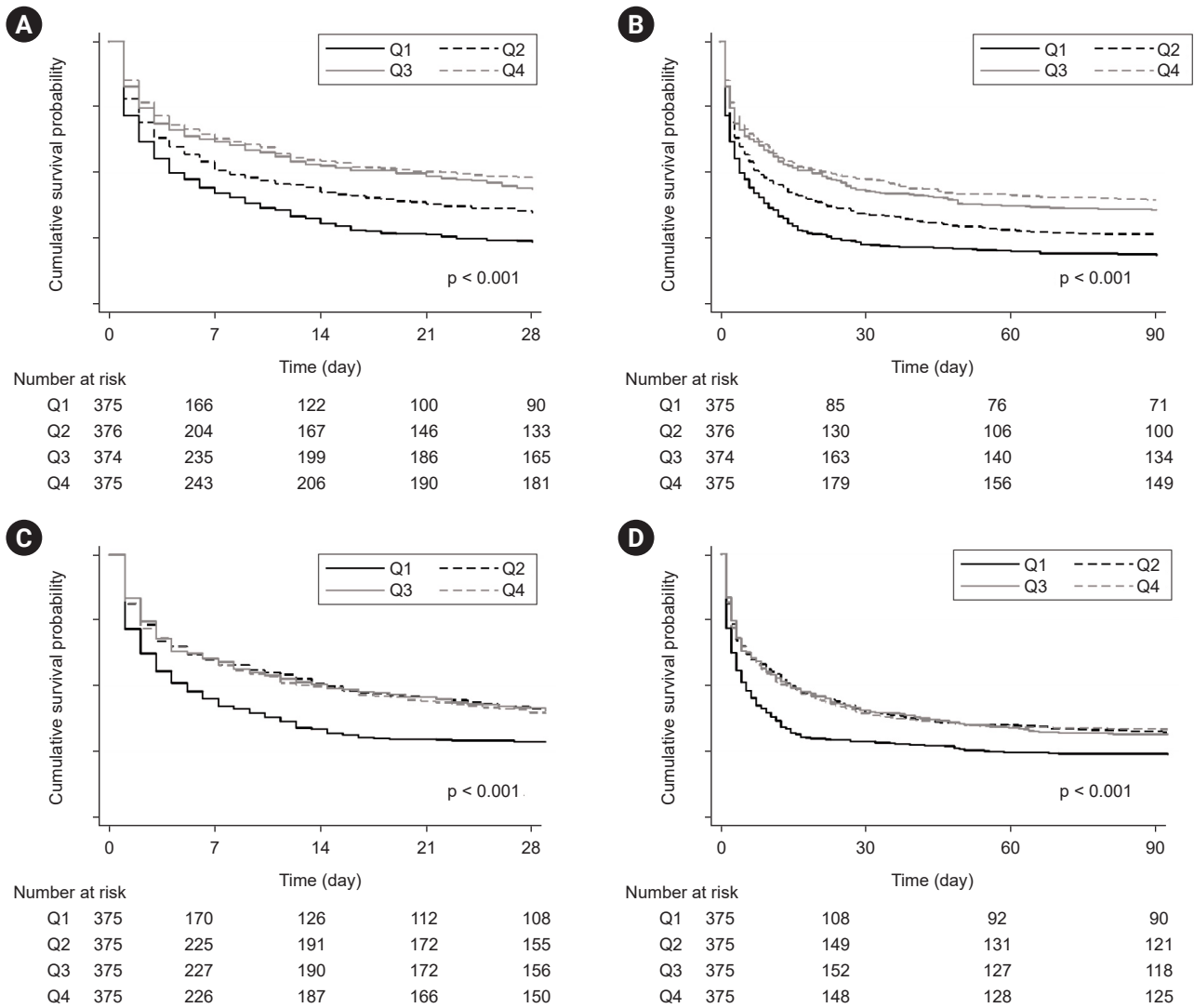
Figure 2. Cumulative survival probability within 28 and 90 days of continuous kidney replacement therapy initiation according to platelet-to-albumin ratio and neutrophil-platelet score quartiles. The Kaplan-Meier curves of (A) 28- and (B) 90-day survival stratified to platelet-to-albumin ratio quartiles, 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-

ticularly 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.

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Conflicts of interest

Tae Hyun Ban is a Deputy Editor of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. All authors have no other 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, Data curation, Formal analysis, Methodology: CYJ, YCK, CHB
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