Research Square

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Acute Kidney Injury in Pancreatitis: Association and Predictive Performance of Composite Inflammatory Indices

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Research Article

Keywords: Pancreatitis, Acute Kidney Injury, Systemic Immune-Inflammation Index, Neutrophil-to-Lymphocyte Ratio, Nomogram

Posted Date: June 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9562292/v1

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Additional Declarations: No competing interests reported.

Abstract

Objective

To investigate the associations of composite inflammatory indices with acute kidney injury (AKI) in patients with pancreatitis, and to compare their predictive performance for early personalized risk stratification of AKI.

Methods

This was a retrospective cohort study enrolling patients with pancreatitis admitted to the Medical Information Mart for Intensive Care IV (MIMIC-IV). The predictive performance of Systemic Immune-Inflammation Index (SII), Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) was compared using receiver operating characteristic (ROC) curves. Univariate and multivariate logistic regression analyses were performed to evaluate the associations between composite inflammatory indices and AKI. Restricted cubic spline (RCS) analysis was used to explore non-linear relationships. A predictive nomogram was constructed, the predictive performance of these indices was analyzed by comparing the area under the ROC curve (AUC), with external validation performed in the eICU Collaborative Research Database (eICU-CRD) cohort. Additionally, Cox regression and RCS analyses were applied to assess the associations of inflammatory markers with hospital mortality.

Results

A total of 646 patients from the MIMIC - IV cohort were included, and the prevalence of AKI was 76.80%. ROC curve analysis demonstrated that the AUC values of NLR and SII for predicting AKI were 0.608 and 0.580 (both $P < 0.05$). Multivariate logistic regression identified SII ($P = 0.024$) as a positive correlate of AKI. Based on these results, we constructed a nomogram for AKI risk prediction. The model achieved an AUC of 0.907 in the MIMIC-IV cohort and 0.802 in the external validation cohort (eICU-CRD), indicating good discriminative ability. RCS analyses revealed significant non - linear associations of SII and NLR with AKI risk (both P - non - linear < 0.001). In the analysis of hospital mortality, a nonlinear association between NLR and hospital mortality was observed only in the RCS analysis (P - non - linear = 0.016).

Conclusion

This study demonstrated that SII exhibits a significant positive and nonlinear association with AKI risk, along with robust predictive performance. NLR showed a nonlinear relationship with hospital mortality.

Clinical trial number:

not applicable.

1. Introduction

Pancreatitis is a clinical syndrome characterized by pancreatic inflammation and tissue injury, mainly including acute pancreatitis, chronic pancreatitis, and acute-on-chronic pancreatitis[1]. Systemic complications associated with pancreatitis represent one of the leading causes of patient mortality[2, 3]. Among these complications, acute kidney injury (AKI) is one of the most common and severe sequelae in the course of pancreatitis. Clinical studies have reported that the incidence of AKI in pancreatitis patients ranges from 10% to 42%, reaching 69.3% in patients with severe acute pancreatitis[4]. Once AKI occurs, it significantly prolongs hospital stay, increases medical costs, and elevates mortality by 3–5 times in critically ill patients[5–7]. Therefore, early identification of high-risk patients for AKI among pancreatitis patients and optimization of renal protection strategies remain key challenges in critical care and emergency medicine.

However, traditional inflammatory markers used in clinical practice still have obvious limitations. Single inflammatory indices, such as C-reactive protein, white blood cell (WBC) count, and procalcitonin, exhibit limited sensitivity and specificity for predicting AKI due to influences from individual differences, underlying diseases, and therapeutic interventions. Moreover, they are easily disturbed by other infections or inflammatory conditions, failing to meet the clinical demand for early and precise identification of high-risk patients[8]. In recent years, with the widespread application of complete blood count and routine biochemical tests, composite inflammatory indices calculated from these routine parameters, such as neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), and platelet-to-lymphocyte ratio (PLR), have attracted extensive attention in the early risk prediction of pancreatitis and its complications including AKI because of their easy accessibility and low cost[9–12]. Several previous studies have demonstrated that peripheral blood neutrophils, lymphocytes, and platelets, as core components of these composite inflammatory indices, are closely related to the occurrence and progression of AKI[13, 14]. Although these composite indices have shown promising predictive potential, existing studies have mostly focused on the predictive value of a single inflammatory marker such as NLR[10, 15, 16], PLR[17], or SII[9] for AKI, while comparative analyses of the predictive performance of NLR, PLR, and SII are still lacking.

Therefore, based on the Medical Information Mart for Intensive Care IV (MIMIC-IV), this study analyzed the associations of SII, NLR, and PLR with AKI in patients with pancreatitis and evaluated the predictive performance of these indices. To further validate the robustness of the findings, we conducted external validation in the eICU Collaborative Research Database (eICU-CRD). This study aims to provide a clinically applicable tool for early risk stratification of AKI in patients with pancreatitis and to offer high-quality evidence for informing individualized.

2. Materials and methods

2.1 Data source

This study was designed as a retrospective cohort study. Data were extracted from the latest versions of two public critical care databases: the MIMIC-IV and the eICU-CRD. The MIMIC-IV database, developed by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology, is a large-scale publicly accessible repository[18]. It contains comprehensive clinical data for the intensive care unit (ICU) patients admitted between 2008 and 2019, including laboratory results, medication records, vital signs, and length of hospital stay. All personal identifiers were removed to ensure patient privacy, with each patient assigned a unique random code. The eICU-CRD is a multi-center critical care database jointly released by PhysioNet, Philips

Healthcare, and the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. It includes clinical data from 20 hospitals between 2014 and 2015, covering vital signs, nursing notes, severity scores, diagnoses, and treatment information. Similar to MIMIC-IV, all patient data in eICU-CRD were de-identified. Therefore, ethical approval and informed consent were waived for this study.

Inclusion criteria: (1) Aged ≥ 18 years old; (2) Patients admitted to the ICU due to pancreatitis. Diagnosis of pancreatitis (ICD-10: K85, K86.0, and K86.1), including acute pancreatitis and chronic pancreatitis[19, 20]. Acute pancreatitis required meeting at least two of the following three criteria: 1) abdominal pain: acute onset of persistent upper abdominal pain, often radiating to the back; 2) serum lipase activity ≥ 3 times the upper limit of normal; 3) characteristic imaging findings on enhanced computed tomography (CT) or transabdominal ultrasound. Chronic pancreatitis required meeting any one of the following criteria: 1) typical imaging features of chronic pancreatitis (pancreatic calcification, pancreatic duct dilatation/stricture/calculi, pancreatic atrophy) on CT or ultrasound; 2) recurrent upper abdominal pain ≥ 6 months with pancreatic exocrine and endocrine insufficiency; 3) pathologically confirmed chronic pancreatitis. (3) For patients readmitted due to pancreatitis, only the data of the first admission were retained. Exclusion criteria: (1) Missing key variables; (2) Uremia; (3) ICU stay less than 24 hours or death within 24 hours of admission. Finally, a total of 646 pancreatitis patients with complete data from the MIMIC-IV database were finally enrolled for the core analysis, and an additional 515 pancreatitis patients from the eICU-CRD database were included for external validation. The specific process is shown in Fig. 1.

2.2 Variables and Outcomes

2.2.1 Outcome Variables

The primary outcome was AKI, defined according to the Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury. AKI was diagnosed if any of the following criteria was satisfied[21]: an increase in serum creatinine ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours, or an increase in serum creatinine to ≥ 1.5 times the baseline value within 7 days, or urine output < 0.5 mL/(kg·h) within 6 hours. In addition, since renal replacement therapy is one of the diagnostic criteria for stage 3 AKI, all patients were considered to have AKI after excluding uremia[22].

The secondary outcome was hospital mortality, which was defined as death occurring during the hospitalization period after ICU admission due to pancreatitis.

2.2.2 Exposure Variable

The exposure variables were three composite inflammatory indices: SII, NLR, and PLR. All indicators were calculated based on laboratory test results extracted from the database: SII = neutrophil count × platelet count / lymphocyte count; NLR = neutrophil count / lymphocyte count; PLR = platelet count / lymphocyte count.

2.2.3 Covariates

The covariates included in this study are as follows: (1) Demographic information includes gender, age, body mass index (BMI), and race; (2) Clinical parameters includes duration of ICU stay and total hospital stay; (3) Vital signs includes heart rate (HR) and respiratory rate (RR); (4) Laboratory indices includes WBC, red blood cell count (RBC), neutrophil count (NEUT), lymphocyte count (LYM), platelet count (PLT), hemoglobin (HGB), serum

creatinine (Scr), blood urea nitrogen (BUN), albumin (ALB), fasting blood glucose (FBG), serum sodium (Na^+), serum potassium (K^+), calcium (Ca^{2+}), chlorine (Cl^-), bicarbonate (HCO_3^-), international normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP); (5) Admission scores includes Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) score; (6) Comorbidities includes chronic obstructive pulmonary disease (COPD), liver disease, diabetes mellitus, and hypertension; (7) Treatment modalities includes renal replacement therapy (RRT).

2.3 Statistical analysis

Missing values in variables were handled using the multiple imputation by chained equations (MICE) method to reduce potential bias in the analysis results caused by missing data. Outliers in quantitative variables were treated with Winsorization based on 1.5 times the interquartile range (IQR). This method reduces the impact of extreme values on statistical inference while preserving the original sample size. Continuous variables were presented as mean ± standard deviation and compared using the independent-samples t-test or corrected t-test for normally distributed data, or as median (IQR) and compared using the Mann-Whitney U test for non-normally distributed data. Categorical variables were described as n (%) and compared using the chi-square test or Fisher's exact test. Ordinal variables were analyzed using the Mann-Whitney U test. Receiver operating characteristic (ROC) curves were used to construct predictive models for AKI centered on composite inflammatory indices (SII, NLR, and PLR). Univariate and multivariate logistic regression analyses were performed to determine the association between composite inflammatory indices and AKI. To address multicollinearity, variables with a variance inflation factor (VIF) ≥ 5 were excluded from the multivariate analysis[23]. A nomogram was developed based on the multivariate logistic regression results to achieve the visual and quantitative prediction of individual AKI risk. Additionally, we evaluated the predictive performance of composite inflammatory indices based on a multivariate logistic regression model using ROC analysis and performed external validation in the eICU-CRD cohort. Restricted cubic spline (RCS) analysis was applied to explore the potential nonlinear relationship between composite inflammatory indices and AKI risk. With hospital mortality as the secondary outcome, the association between composite inflammatory indices and mortality risk was assessed using cox proportional hazards model and RCS. All statistical analyses in this study were performed using R software (Version 4.5.1), with a two-tailed $P < 0.05$ considered statistically significant.

3. Results

3.1 Baseline characteristics of the study population

In the MIMIC-IV database, a total of 646 patients with pancreatitis were enrolled, including 150 in the non-AKI group and 496 in the AKI group. Compared with the non-AKI group, patients in the AKI group were older, had longer durations of ICU stay and total hospital stay, higher RR, higher BMI, higher levels of WBC, Scr, BUN, K^+, INR, AST, NEUT, FBG, NLR, and SII, and lower levels of ALB and LYM (all $P < 0.05$). The SAPS II score and SOFA score were significantly higher in the AKI group (both $P < 0.001$). The AKI group had a higher proportion of white patients (79.40%, $P = 0.001$). In addition, the proportion of patients receiving RRT and hospital mortality were significantly higher in the AKI group (both $P < 0.001$). See Table 1 for details.

Table 1
Baseline characteristics of the study population

Variable	Level	Non-AKI (N = 150)	AKI (N = 496)	*P*-value
Age, years		53.71 (45.41–63.53)	59.84 (49.24–73.61)	0.001
BMI, kg/m^2		25.63 (22.06–28.62)	29.50 (25.38–34.09)	< 0.001
Gender, n (%)	Female	69 (46.00)	203 (40.90)	0.313
	Male	81 (54.00)	293 (59.10)	
Race, n (%)	Asian	8 (5.30)	15 (3.00)	0.001
	Black	26 (17.30)	32 (6.50)	
	Hispanic/Latino	6 (4.00)	16 (3.20)	
	White	101 (67.30)	393 (79.20)	
	Other	9 (6.00)	40 (8.10)	
Duration of ICU stay, days		1.94 (1.52–2.88)	4.70 (2.32–11.12)	< 0.001
Total hospital stay, days		7.87 (5.25–13.68)	15.23 (8.65–25.95)	< 0.001
HR, bpm		96.00 (84.00-113.00)	102.00 (85.00-116.00)	0.083
RR, breaths/min		20.00 (16.12-24.00)	21.00 (17.00–26.00)	0.006
WBC, ×10^9/L		11.45 (8.30-15.78)	13.80 (9.20-19.92)	< 0.001
RBC, ×10^{12}/L		3.54 (3.06–3.95)	3.60 (3.00-4.30)	0.177
PLT, ×10^9/L		192.50 (138.25–294.00)	187.00 (124.75-270.25)	0.338
HGB, g/dL		10.80 (9.33–12.20)	11.10 (9.30–13.00)	0.118
Scr, mg/dL		0.90 (0.60–1.28)	1.25 (0.80–2.20)	< 0.001
BUN, mg/dL		16.50 (10.00–25.00)	23.00 (14.00–39.00)	< 0.001
ALB, g/dL		3.00 (2.70–3.50)	2.90 (2.40–3.30)	0.002
FBG, mg/dL		116.00 (99.00-162.00)	132.00 (105.00-182.00)	0.012
Na^+, mEq/L		138.00 (135.00-141.00)	138.00 (134.75–141.00)	0.461
K^+, mEq/L		3.90 (3.60–4.30)	4.10 (3.60–4.60)	0.004
Ca^{2+}, mg/dL		8.00 (7.50–8.60)	8.00 (7.40–8.50)	0.119
Cl^-, mEq/L		104.00 (100.00-109.00)	104.00 (99.00-108.00)	0.595

Variable	Level	Non-AKI (N = 150)	AKI (N = 496)	*P*-value
HCO_3^-, mEq/L		22.00 (19.00–24.00)	21.00 (17.00–24.00)	0.098
INR		1.20 (1.10–1.50)	1.30 (1.20–1.60)	< 0.001
ALT, U/L		40.50 (21.00-101.50)	44.50 (23.00-129.50)	0.224
AST, U/L		44.50 (28.25-115.75)	73.00 (34.00-173.00)	0.002
ALP, U/L		87.00 (65.25-145.75)	100.50 (69.00-175.25)	0.182
NEUT, ×10⁹/L		9.41 (5.91–13.55)	11.31 (7.23–17.32)	< 0.001
LYM, ×10⁹/L		1.08 (0.67–1.63)	0.91 (0.56–1.45)	0.028
SAPS II score, points		27.00 (19.00–36.00)	40.00 (31.00–54.00)	< 0.001
SOFA score, points		3.00 (2.00–5.00)	8.00 (5.00–12.00)	< 0.001
NLR		9.09 (4.25–14.19)	12.11 (6.47–22.81)	< 0.001
PLR		185.70 (114.58-302.81)	217.38 (113.68–356.30)	0.201
SII		1674.68 (817.75-3190.80)	2222.12 (947.14-4948.57)	0.003
COPD, n (%)	No	117 (78.00)	394 (79.40)	0.792
	Yes	33 (22.00)	102 (20.60)	
Liver disease, n (%)	No	109 (72.70)	322 (64.90)	0.096
	Yes	41 (27.30)	174 (35.10)	
Diabetes, n (%)	No	105 (70.00)	340 (68.50)	0.814
	Yes	45 (30.00)	156 (31.50)	
Hypertension, n (%)	No	73 (48.70)	283 (57.10)	0.086
	Yes	77 (51.30)	213 (42.90)	
RRT, n (%)	No	149 (99.30)	376 (75.80)	< 0.001
	Yes	1 (0.70)	120 (24.20)	
Hospital mortality, n (%)	No	148 (98.70)	397 (80.00)	< 0.001
	Yes	2 (1.30)	99 (20.00)	

3.2 ROC curves of composite inflammatory indices

The results showed that the AUC with 95%CI for NLR, PLR, and SII were 0.608 (95%CI: 0.557–0.658), 0.534 (95%CI: 0.484–0.585), and 0.580 (95%CI: 0.531–0.629), respectively, with only NLR and SII showing statistical significance (Fig. 2 **and Supplementary Table 1**).

3.3 Correlation between composite inflammatory indices and AKI

Univariate logistic regression analysis revealed that multiple variables were significantly associated with the AKI (Table 2). The results showed that NLR (OR = 1.03, 95%CI: 1.02–1.05, $P < 0.001$) and SII (OR = 1.00, 95%CI: 1.00–1.00, $P = 0.001$) were associated with AKI. In multivariate logistic regression analysis, SII (OR = 1.00, 95% CI: 1.00–1.00, $P = 0.024$) remained positively associated with AKI (Table 3).

Table 2
Univariate logistic regression analysis of AKI

Variable	OR	95%CI Lower	95%CI Upper	*P*-value
Duration of ICU stay	1.54	1.38	1.76	< 0.001
Total hospital stay	1.05	1.03	1.07	< 0.001
Scr	1.73	1.41	2.19	< 0.001
BUN	1.03	1.02	1.04	< 0.001
NEUT	1.06	1.03	1.09	< 0.001
SAPS II score	1.08	1.06	1.09	< 0.001
SOFA score	1.39	1.30	1.49	< 0.001
BMI	1.11	1.08	1.15	< 0.001
RRT	47.55	10.49	840.85	< 0.001
Hospital mortality	18.45	5.75	112.81	< 0.001
WBC	1.05	1.03	1.08	< 0.001
NLR	1.03	1.02	1.05	< 0.001
ALB	0.62	0.47	0.82	0.001
SII	1.00	1.00	1.00	0.001
Age	1.02	1.01	1.03	0.001
INR	2.00	1.31	3.18	0.002
Race (Black)	0.28	0.11	0.65	0.005
Race (Asian)	0.42	0.14	1.31	0.132
Race (White)	0.88	0.39	1.79	0.730
Race (Hispanic/Latino)	0.60	0.18	2.04	0.398
RR	1.04	1.01	1.08	0.007
K^+	1.33	1.06	1.70	0.017
Ca^{2+}	0.82	0.69	0.97	0.021
HGB	1.07	1.00	1.15	0.070
Hypertension	0.71	0.49	1.03	0.071
FBG	1.00	1.00	1.01	0.071
AST	1.00	1.00	1.00	0.078
Liver disease	1.44	0.97	2.17	0.079

Variable	OR	95%CI Lower	95%CI Upper	*P*-value
RBC	1.20	0.97	1.48	0.090
HR	1.01	1.00	1.02	0.094
PLR	1.00	1.00	1.00	0.106
ALP	1.00	1.00	1.00	0.163
LYM	0.87	0.71	1.08	0.206
HCO_3^-	0.98	0.95	1.01	0.220
Gender (Male)	1.23	0.85	1.78	0.271
PLT	1.00	1.00	1.00	0.562
Cl^-	0.99	0.97	1.02	0.638
Na^+	0.99	0.96	1.02	0.686
COPD	0.92	0.59	1.45	0.705
Diabetes	1.07	0.72	1.60	0.737
ALT	1.00	1.00	1.00	0.760

Table 3
Multivariate logistic regression analysis of AKI

Variable	OR	95%CI Lower	95%CI Upper	*P*-value	VIF
Duration of ICU stay	1.56	1.32	1.89	< 0.001	1.34
Total hospital stay	1.01	0.99	1.03	0.617	1.23
BMI	1.09	1.04	1.14	< 0.001	1.26
Age	1.04	1.02	1.06	0.001	2.57
SOFA socre	1.22	1.06	1.42	0.007	2.84
Hypertension	0.51	0.30	0.87	0.014	1.22
SII	1.00	1.00	1.00	0.024	4.31
RBC	1.51	1.05	2.21	0.028	1.47
Hospital mortality	5.66	1.42	38.63	0.032	1.11
Scr	1.61	1.06	2.53	0.032	3.47
AST	1.00	1.00	1.00	0.034	1.31
Liver disease	1.75	0.97	3.24	0.067	1.26
NLR	0.96	0.92	1.01	0.090	4.31
Race (Asian)	0.20	0.04	1.15	0.071	1.51
Race (Black)	0.34	0.09	1.17	0.093	2.53
Race (Hispanic/Latino)	0.47	0.09	2.47	0.377	1.48
Race (White)	1.07	0.39	2.79	0.894	2.96
BUN	0.98	0.96	1.01	0.172	3.24
RRT	4.08	0.58	87.10	0.234	1.24
FBG	1.00	1.00	1.01	0.286	1.15
K^+	1.11	0.79	1.57	0.541	1.19
HR	1.00	0.99	1.02	0.612	1.50
INR	1.17	0.63	2.22	0.619	1.35
RR	0.99	0.95	1.04	0.754	1.30
ALB	1.07	0.68	1.70	0.765	1.49
Ca^{2+}	1.00	0.75	1.35	0.980	1.38
SAPS II socre	1.00	0.97	1.04	0.981	3.21

3.4 Construction of a predictive nomogram model for AKI

The predictive nomogram for AKI was constructed based on the multivariate logistic regression analysis (Fig. 3). The results showed that SOFA score, duration of ICU stay, and BMI were the most influential predictors of AKI, with the highest point contributions among all variables included in the model.

3.5 External validation

In the MIMIC-IV cohort, the multivariate logistic regression model exhibited good discriminative ability, with a sensitivity of 0.796, specificity of 0.880, accuracy of 0.816, F1 score of 0.869, Youden's index of 0.676, and an AUC of 0.907 (95%CI: 0.884–0.931). In the external validation cohort, the model maintained acceptable predictive performance, with a sensitivity of 0.748, specificity of 0.757, accuracy of 0.751, F1 score of 0.783, Youden's index of 0.505, and an AUC of 0.802 (95%CI: 0.764–0.840) (Table 4).

Table 4
Performance of the multivariate logistic regression model in MIMIC-IV and eICU-CRD cohorts

MIMIC-IV	Sensitivity	Specificity	Accuracy	F1 score	Youden's index	AUC	AUC 95%CI Lower	AUC 95%CI Upper	AUC *P*-value
	0.796	**0.880**	**0.816**	**0.869**	**0.676**	**0.907**	**0.884**	**0.931**	**< 0.001**
eICU-CRD	0.748	0.757	0.751	0.783	0.505	0.802	0.764	0.840	< 0.001

3.6 Nonlinear association analysis between composite inflammatory indices and AKI

RCS analysis was conducted to explore the nonlinear association between composite inflammatory indices and the risk of AKI (Fig. 4). RCS analysis showed that SII and NLR exhibited a significant nonlinear association with the risk of AKI (both *P*-overall < 0.001 and *P*-non-linear < 0.001), whereas PLR showed no significant association with the risk of AKI (*P*-overall = 0.105, *P*-non-linear = 0.105).

3.6 Correlation between composite inflammatory indices and hospital mortality

Univariate cox regression analysis revealed that multiple variables were significantly associated with hospital mortality (Table 5). Multivariate cox regression analysis showed that NLR (HR = 0.98, 95%CI: 0.95–1.01, *P* = 0.086), PLR (HR = 1.00, 95%CI: 1.00–1.00, *P* = 0.836), and SII (HR = 1.00, 95%CI: 1.00–1.00, *P* = 0.723) were not significantly associated with hospital mortality (Table 6).

Table 5
Univariate cox regression analysis of hospital mortality

Variable	HR	95%CI Lower	95%CI Upper	*P*-value
SOFA socre	1.18	1.13	1.22	< 0.001
SAPS II socre	1.05	1.03	1.06	< 0.001
RRT	2.61	1.75	3.88	< 0.001
INR	2.08	1.53	2.84	< 0.001
BUN	1.02	1.01	1.02	< 0.001
Age	1.03	1.02	1.04	< 0.001
K^+	1.48	1.22	1.79	< 0.001
Liver disease	2.24	1.51	3.32	< 0.001
Scr	1.22	1.09	1.36	< 0.001
AKI	8.84	2.18	35.93	0.002
AST	1.00	1.00	1.00	0.005
HCO_3^-	0.95	0.92	0.98	0.006
PLT	1.00	1.00	1.00	0.007
ALB	0.66	0.48	0.90	0.009
RBC	0.80	0.65	0.99	0.038
NLR	1.01	1.00	1.03	0.086
HGB	0.93	0.86	1.00	0.043
RR	1.03	1.00	1.06	0.053
Race (Hispanic/Latino)	0.16	0.02	1.23	0.078
Race (Black)	0.60	0.23	1.58	0.301
Race (Asian)	0.81	0.25	2.59	0.724
Race (White)	0.83	0.43	1.59	0.568
Duration of ICU stay	0.98	0.96	1.00	0.086
NEUT	1.01	0.99	1.04	0.231
WBC	1.01	0.99	1.03	0.253
ALP	1.00	1.00	1.00	0.264
LYM	0.87	0.68	1.12	0.283
Cl^-	0.99	0.96	1.01	0.370

Variable	HR	95%CI Lower	95%CI Upper	*P*-value
Na^{+}	0.99	0.96	1.02	0.433
Gender (male)	0.86	0.58	1.27	0.439
ALT	1.00	1.00	1.00	0.532
FBG	1.00	1.00	1.00	0.619
COPD	1.07	0.66	1.74	0.775
BMI	1.00	0.98	1.03	0.787
PLR	1.00	1.00	1.00	0.836
HR	1.00	0.99	1.01	0.853
Diabetes	0.97	0.63	1.48	0.881
Hypertension	1.03	0.69	1.53	0.892
Ca^{2+}	0.99	0.84	1.18	0.932
SII	1.00	1.00	1.00	0.723

Table 6
Multivariate cox regression analysis of hospital mortality

Variable	HR	95%CI Lower	95%CI Upper	*P*-value
SOFA score	1.30	1.20	1.39	< 0.001
SAPS II score	1.00	0.98	1.02	0.776
RRT	1.54	0.81	2.92	0.189
INR	1.59	1.06	2.36	0.024
BUN	1.00	0.99	1.01	0.721
Age	1.04	1.02	1.06	< 0.001
K^+	1.37	1.07	1.74	0.011
Liver disease	1.87	1.09	3.20	0.023
Scr	0.93	0.77	1.11	0.407
AKI	2.68	0.63	11.43	0.183
AST	1.00	1.00	1.00	0.215
HCO_3^-	1.00	0.96	1.05	0.945
PLT	1.00	1.00	1.00	0.315
ALB	0.77	0.55	1.08	0.126
RBC	1.72	0.98	3.03	0.060
NLR	0.98	0.95	1.01	0.191
HGB	0.87	0.72	1.05	0.144
RR	1.05	1.02	1.08	0.003
Race (Asian)	0.29	0.08	1.10	0.068
Race (Black)	0.43	0.15	1.19	0.104
Race (Hispanic/Latino)	0.15	0.02	1.20	0.074
Race (White)	1.00	0.48	2.06	0.992
Duration of ICU stay	0.88	0.85	0.91	< 0.001
PLR	1.00	1.00	1.00	0.569
SII	1.00	1.00	1.00	0.693

3.7 Nonlinear association analysis between composite inflammatory indicators and hospital mortality

RCS analysis was conducted to explore the nonlinear association between composite inflammatory indices and the risk of hospital mortality (Fig. 5). RCS analysis showed that NLR was significantly nonlinearly associated with the risk of hospital mortality (*P*-overall = 0.016, *P*-non-linear = 0.016), while SII (*P*-overall = 0.807, *P*-non-linear = 0.807) and PLR (*P*-overall = 0.782, *P*-non-linear = 0.782) showed no significant association with hospital mortality.

4. Discussion

This study was based on large-scale public ICU databases and investigated the correlations between composite inflammatory indices (SII, NLR, PLR) and the risks of AKI and hospital mortality in patients with pancreatitis, and validated the predictive performance of these composite inflammatory indices for AKI. This study confirms that SII is positively correlated with AKI. The unadjusted RCS model demonstrated a nonlinear relationship between SII and NLR with AKI risk. Additionally, the multivariable logistic regression model exhibits good predictive performance across different cohorts. These findings provide new insights for early risk stratification and personalized interventions in patients with pancreatitis.

This study found that in patients with pancreatitis, SII was positively correlated with AKI. Univariate logistic regression analysis showed that both SII and NLR were associated with AKI; however, after multivariate adjustment, only SII remained statistically significant, suggesting that SII may be a more stable indicator of inflammation assessment than NLR[9, 24, 25]. This finding aligns with previous research, including a study on patients with severe acute pancreatitis reporting a positive correlation between SII levels and AKI (OR = 1.008, 95% CI: 1.002–1.014)[9]. Although the incremental risk per unit increase in SII is minimal, the overall trend as a continuous variable indicates that elevated SII is associated with an increased risk of AKI. Similarly, it demonstrated good predictive performance in a multivariate logistic regression model (AUC = 0.907). Furthermore, RCS analysis revealed a significant nonlinear relationship between SII and AKI (*P*-non-linear < 0.001), suggesting that the impact of SII on AKI is not a simple linear increase and may involve a threshold effect. This indicates that when SII exceeds a certain critical value, the risk of AKI may rise sharply, prompting clinicians to closely monitor pancreatitis patients with significantly elevated SII. Similarly, NLR exhibited a significant nonlinear association with AKI risk (*P*-nonlinear < 0.001), and both SII and NLR outperformed PLR in predicting AKI, with AUCs of 0.580 and 0.608, respectively. Our results are consistent with a previous study reporting high predictive values of SII (AUC = 0.804) and NLR (AUC = 0.742) for AKI in severe acute pancreatitis patients[26]. However, although NLR showed a significant nonlinear trend with hospital mortality, its predictive performance was weak[27], suggesting that the role of inflammatory response in mortality risk may be masked by other organ dysfunctions.

Furthermore, analysis of hospital mortality revealed that cox regression analysis did not identify an association between composite inflammatory markers and hospital mortality; however, further analysis revealed a nonlinear association between the NLR and hospital mortality, suggesting a threshold effect of hospital mortality on prognosis. The presence of such a threshold effect is supported by multiple studies. A study indicates that the NLR exhibits a J-shaped association with the progression and mortality of AKI[28]. However, these findings require further validation through large-scale prospective studies.

In the present study, we constructed a dedicated nomogram for predicting AKI in patients with pancreatitis based on multivariate logistic regression. This visualized prediction tool integrates multiple clinically accessible

indicators to quantitatively assess individual AKI risk, showing good clinical applicability. By early identification of high-risk individuals, this model facilitates timely risk stratification and intensive surveillance. It helps clinicians implement targeted preventive strategies and rationalize clinical decision-making, thereby promoting precise management of acute pancreatitis. Moreover, the intuitive and convenient format of the nomogram improves communication of risk between medical staff and patients. In the future, this predictive model could be embedded in routine clinical workflows to support dynamic risk evaluation and ultimately contribute to better renal protection and clinical prognosis.

This study developed and validated an AKI prediction model for pancreatitis patients utilizing inflammatory markers based on the MIMIC-IV and eICU-CRD databases. The large sample size and external validation enhanced the robustness of the findings. However, several limitations exist. First, as a retrospective study, unmeasured confounders (e.g., extent of pancreatic necrosis, volume of early fluid resuscitation) may have introduced bias despite multivariable adjustment. Second, due to database constraints, key clinical details (e.g., AKI stage, pancreatitis etiology, medication information) were unavailable, potentially affecting predictive accuracy. Third, inflammatory markers (NLR, SII, PLR) were measured only at admission, precluding analysis of their dynamic trends, which may be more valuable for predicting AKI. Fourth, as an observational study, causality cannot be inferred. Finally, although externally validated, both derivation and validation cohorts were from U.S. ICU populations, limiting generalizability to other populations or non-ICU settings.

5. Conclusion

Overall, this study demonstrates that SII exhibits a significant positive and nonlinear association with AKI risk, along with robust predictive performance. NLR shows a nonlinear relationship with hospital mortality. Furthermore, the nomogram provides clinicians with an intuitive, quantitative tool for individualized risk assessment, facilitating early identification of high-risk AKI patients upon ICU admission to optimize clinical decision-making and resource allocation.

Abbreviations

ALB
Albumin
ALT
Alanine Aminotransferase
AKI
Acute Kidney Injury
AST
Aspartate Aminotransferase
AUC
Area Under the ROC Curve
BUN
Blood Urea Nitrogen
Ca^{2+}
Calcium
COPD

Chronic Obstructive Pulmonary Disease
CT
Computed Tomography
eICU-CRD
eICU Collaborative Research Database
FBG
Fasting Blood Glucose
HGB
Hemoglobin
HCO_3^-
Bicarbonate
HR
Heart Rate
ICU
Intensive Care Unit
INR
International Normalized Ratio
IQR
Interquartile Range
K^+
Serum Potassium
LYM
Lymphocyte Count
MICE
Multiple Imputation by Chained Equations
MIMIC-IV
Medical Information Mart for Intensive Care IV
Na^+
Serum Sodium
NEUT
Neutrophil Count
NLR
Neutrophil-to-Lymphocyte Ratio
ALP
Alkaline Phosphatase
PLR
Platelet-to-Lymphocyte Ratio
PLT
Platelet Count
RBC
Red Blood Cell Count
RCS
Restricted Cubic Spline

ROC
Receiver Operating Characteristic
RR
Respiratory Rate
RRT
Renal Replacement Therapy
SAPS II
Simplified Acute Physiology Score II
Scr
Serum Creatinine
Cl^-
Serum Chlorine
SII
Systemic Immune-Inflammation Index
SOFA
Sequential Organ Failure Assessment
VIF
Variance Inflation Factor
WBC
White Blood Cell

Declarations

Ethics approval and consent to participate

This study complies with the ethical principles set forth in the Declaration of Helsinki.

The collection of patient information in the MIMIC-IV database has been reviewed and approved by the Institutional Review Board of Beth Israel Deaconess Medical Center, who granted a waiver of informed consent.

As this study involves secondary analysis of the eICU data, no additional ethical approval or consent was required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the MIMIC-IV (https://physionet.org/content/mimiciv/3.1/) and eICU (https://physionet.org/content/eicu-crd/2.0/) databases.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Youth Program of the National Natural Science Foundation of China (Grant No. 82000509).

Authors' contribution

MS: Writing-original draft, Formal analysis, Conceptualization, Data curation, Methodology. SZ: Writing-review and editing, Software, Visualization, Data curation, Project administration.

All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

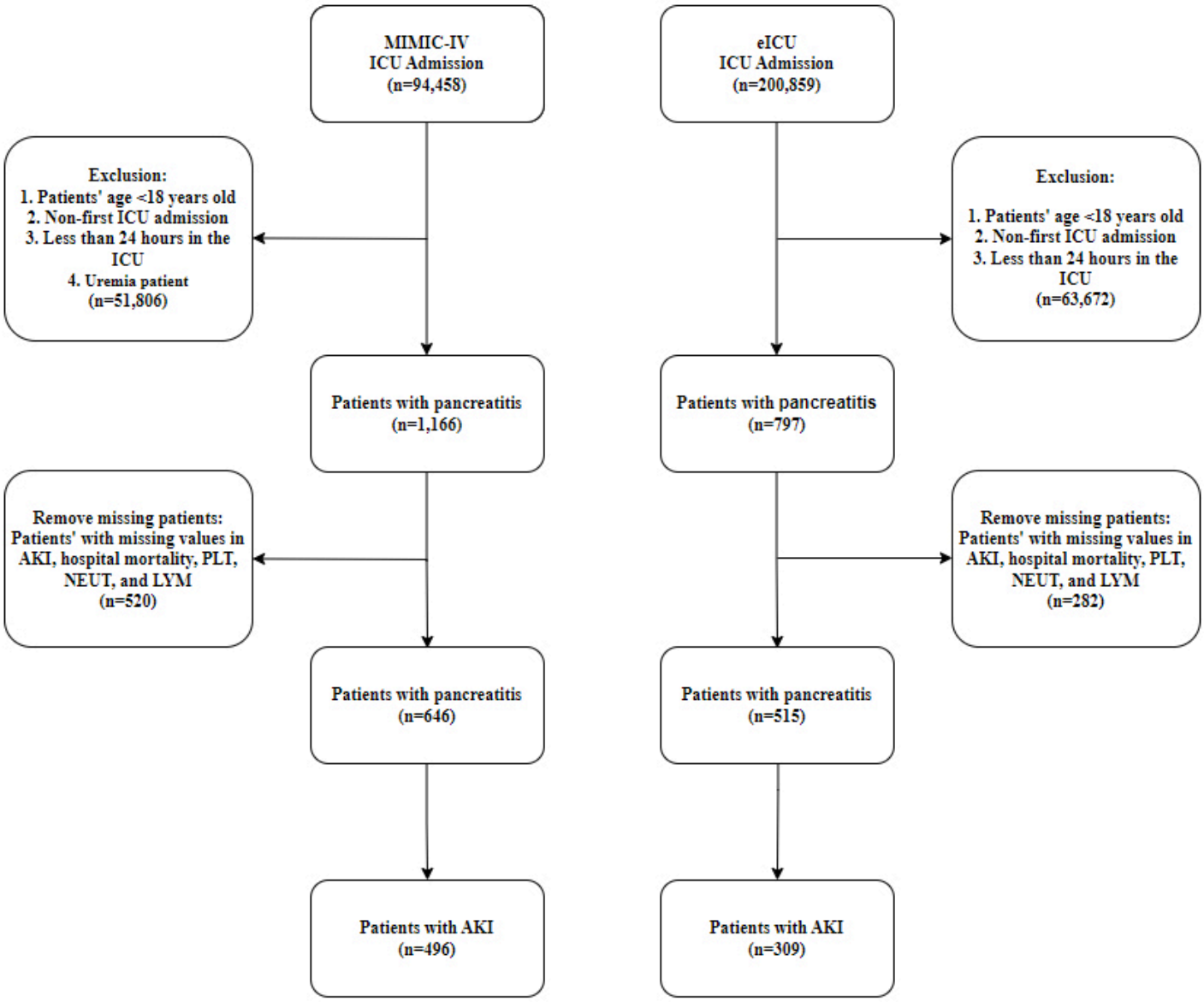


Figure 1

Inclusion and exclusion flowchart

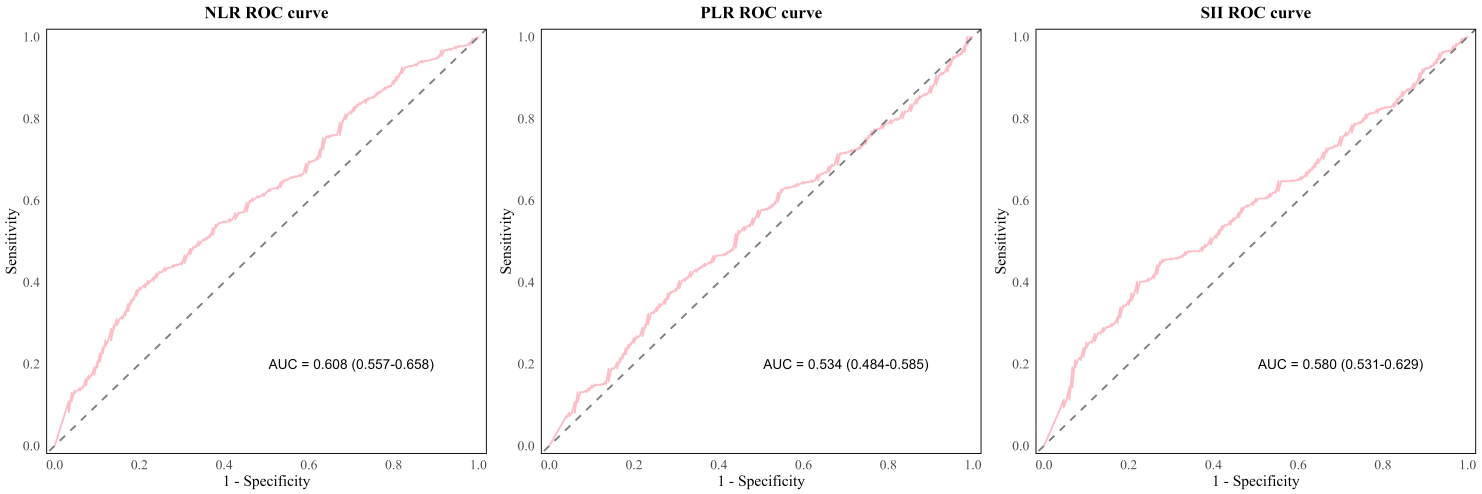


Figure 2

ROC curves for inflammatory indicators

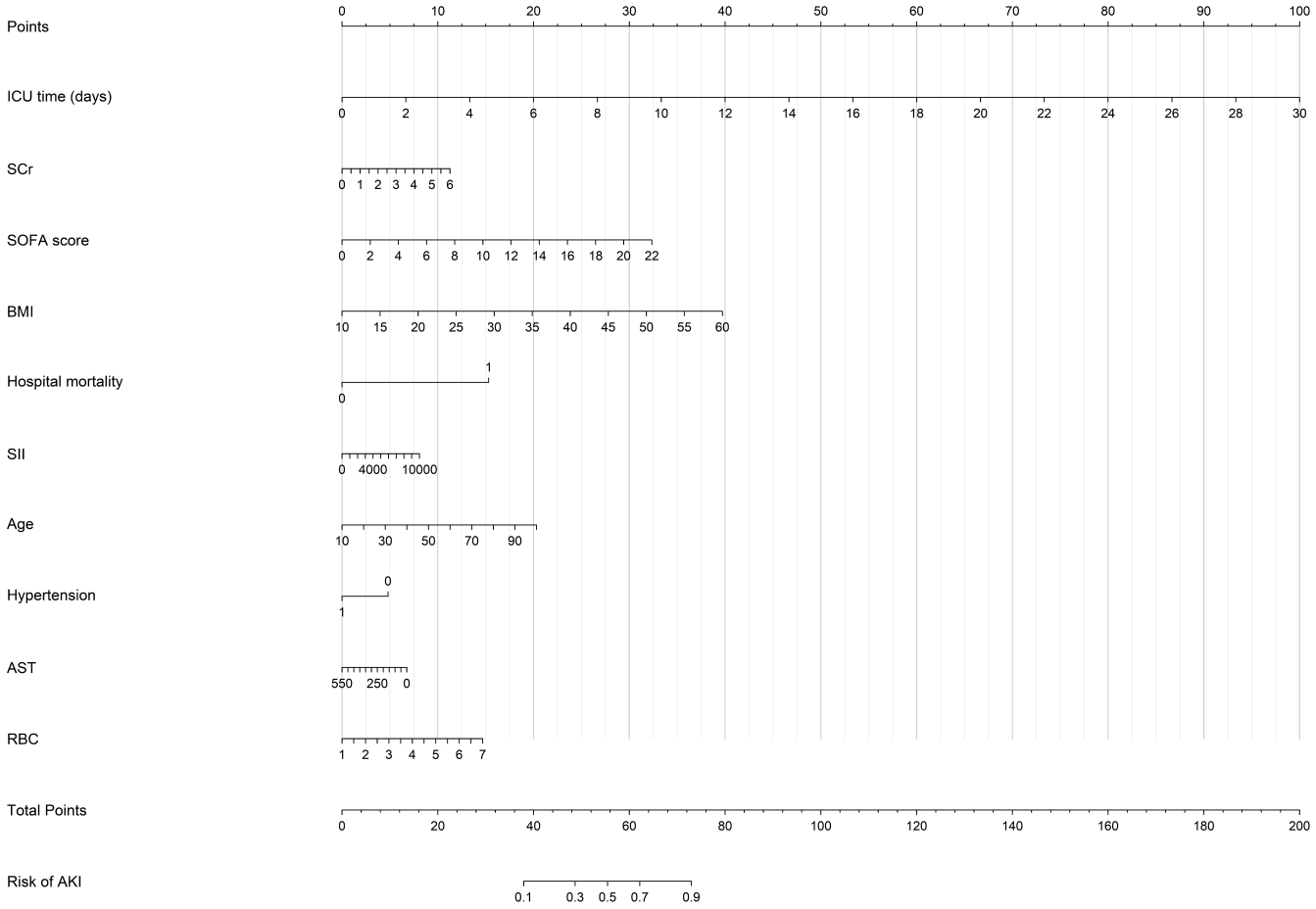


Figure 3

Nomogram for predicting the risk of AKI in patients with pancreatitis

Note: This nomogram was developed to predict the risk of AKI in patients with pancreatitis. Each variable is assigned a point value, and the total points correspond to the predicted probability of AKI. The total score range of this nomogram is 0–300 points, with a predicted risk probability of AKI ranging from 0–100%. Variables with longer axes and wider point ranges contribute more to the overall risk of AKI. Abbreviations as defined in the text.

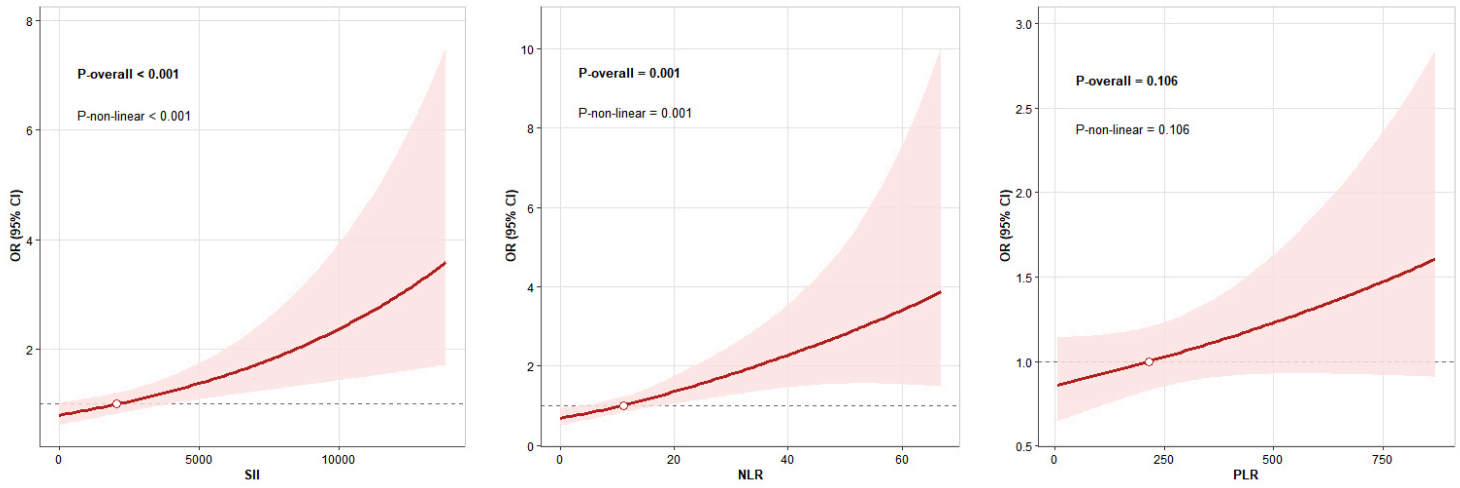


Figure 4

RCS analysis of the association between inflammatory indices and AKI

Note: RCS analysis was performed to evaluate the nonlinear association between inflammatory indices (SII, NLR, PLR) and AKI risk. The solid red line represents the odds ratio (OR) for AKI, and the shaded area represents the 95% confidence interval (CI). The white circle indicates the reference point (OR = 1). *P*-overall: *P*-value for the overall association; *P*-non-linear: *P*-value for the nonlinear trend. *P*<0.05 was considered statistically significant.

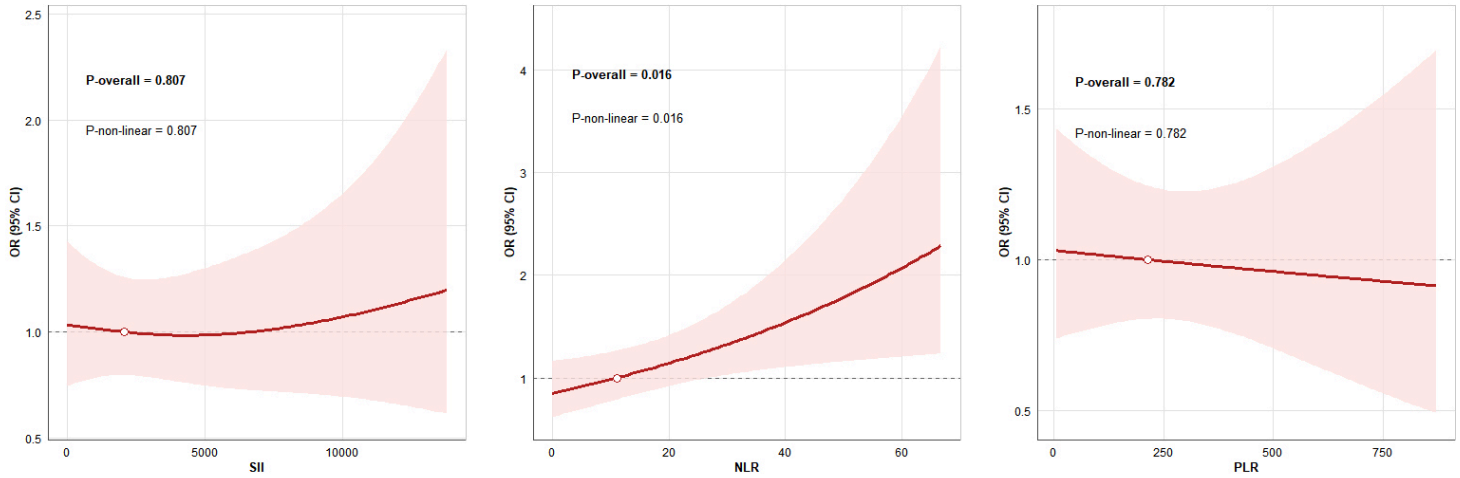


Figure 5

RCS analysis of inflammatory indices and hospital mortality

Note: The solid red line represents the odds ratio (OR) for hospital mortality, and the shaded area represents the 95% confidence interval (CI). The white circle indicates the reference point (OR = 1). *P*-overall: *P*-value for the overall association; *P*-non-linear: *P*-value for the nonlinear trend. $P<0.05$ was considered statistically significant.

Supplementary Files

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- SupplementaryTable1.docx