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RESEARCH

Association between admission systemic immune-inflammation index and mortality in critically ill patients with sepsis: a retrospective cohort study based on MIMIC-IV database

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Abstract

Systemic immune-inflammation index (SII) has been identified as a prognostic biomarker for various diseases. Our study aimed to investigate the association between SII and mortality risk in critically ill patients with sepsis, thus exploring possible tools for rapid screening. This retrospective cohort study was conducted using clinical data extracted from the Medical Information Mart for Intensive Care Database. The study included only patients diagnosed with sepsis admitted to the intensive care unit for the first time. We used the restricted cubic splines to explore the relationship between SII and 28-day mortality. Kaplan–Meier curve and Cox regression models were performed to evaluate the association between SII and mortality. Subgroup analysis was performed to explore the stability of the primary results. A total of 16,007 patients with sepsis were eligible in the final analysis. We found a J-shaped relationship between SII and mortality risk. The SII level associated with the lowest mortality risk was 774.46*10^9/L. Compared with the reference group (second SII quartile), the 28-day mortality was increased in the highest quartile and third quartile groups of SII levels; fully adjusted HRs were 1.16 (1.02 to 1.32) and 1.40 (1.23 to 1.58), respectively. However, although the lower SII (Q1 group) also showed a trend toward a higher hazard of 28-day mortality, there was no statistical difference, with a fully adjusted HR of 1.05 (0.92 to 1.21). In the population of critically ill patients with sepsis, low and high SII levels were associated with an increased risk of short-term mortality. The 28-day mortality risk was lowest at SII levels of 774.46*10^9/L.

Keywords Sepsis · Mortality · Systemic inflammatory immune index · Biomarkers

Abbreviations

SII	Systemic immune-inflammation index
MIMIC-IV	The Medical Information Mart for Intensive Care IV
ICU	Intensive care unit
SPO2	Percutaneous oxygen saturation
COPD	Chronic obstructive pulmonary disease
SOFA	Sequential organ failure assessment
SAPS II	Simplified acute physiology score II
BUN	Blood urea nitrogen
CRRT	Continuous renal replacement therapy
RCS	Restricted cubic splines
HR	Hazard ratio
CI	Confidence interval

Introduction

Sepsis is a clinical syndrome with physiologic, biologic, and biochemical abnormalities caused by a dysregulated host response to infection [1], which can lead to multiple organ dysfunction syndrome and death. The latest sepsis guidelines have highlighted the importance of early screening of patients with sepsis. They have stated that given the poor sensitivity of qSOFA, the panel strongly recommended against its use as a single screening tool [2].

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The emergency department (ED) is often the first medical contact of patients with sepsis [3], but the medical conditions available are often quite limited. Therefore, the rapid screening of septic patients and identification of critically ill patients is a challenge that needs to be urgently addressed. Blood cell component testing is widely performed in EDs as a routine, rapid examination, even in primary care hospitals in rural areas. The utility of various components of the complete hemogram in sepsis has been investigated. Previous studies have reported the utility of absolute neutrophil and lymphocyte counts, platelet count, red blood cell distribution width, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, and platelet index [4–8]. The systemic immune-inflammation index (SII) is a novel parameter based on lymphocyte, neutrophil, and platelet counts, which has the benefit of economics and convenience and can simultaneously reflect patients' inflammatory and immune status [9]. The role of SII in predicting the survival of patients with cardiovascular disease [10], malignancy [11], and acute kidney injury [12] has been reported. We hypothesized that SII is associated with the prognosis of critically ill patients with sepsis and may be a potential early screening tool. However, scarce studies have evaluated the prognostic effect of SII on critically ill patients with sepsis, especially in large samples. Therefore, we aimed to investigate the relationship between SII and mortality in patients with sepsis with data extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV version 1.0) database after adjusting for potential confounders.

Methods

Data source and study design

Data were extracted from the MIMIC-IV database, an updated MIMIC-III approved by an institutional review board [13]. From 2008 to 2019, patients admitted to intensive care units (ICUs) at Beth Israel Deaconess Medical Center (BIDMC) were included in the MIMIC-IV; a comprehensive and high-quality dataset developed by the computational physiology laboratory of Massachusetts Institute of the MIMIC-IV database includes desensitization data for over 50,000 critically ill patients at BIDMC between 2008 and 2019 and contains demographics, laboratory indicators, vital signs, and medications. For permission to access the database, the author (DJ) has accomplished a recognized course in the Protecting Human Research Participants (certification number: 31591048). This retrospective cohort study aimed to investigate the association between SII and mortality risk in critically ill patients with sepsis.

Population selection criteria

A total of 53,150 adult patients admitted to the ICU for the first time were recorded in the MIMIC-IV database. Only patients diagnosed with sepsis were included. Study participants met the Sepsis-3 criteria from the Third International Consensus Definitions for Sepsis and Septic shock for the diagnosis of sepsis [1]. The exclusion criteria were: (1) length of stay in hospital was less than 48 h; (2) patients died within 48 h of admission; (3) missing platelets or neutrophils or lymphocyte counts within 24 h of admission. (4) The recorded value of platelets, neutrophils, or lymphocytes was zero. The flowchart of this study is presented in Fig. 1.

Variables extraction

Patient data within the first 24 h after admission were extracted from MIMIC-IV using Structured Query Language and were collected as follows: (1) Comorbidities: congestive heart failure, myocardial infarction, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), severe liver disease, chronic kidney disease, malignant cancer, and Charlson comorbidity index; (2) Vital signs: temperature, heart rate, respiratory rate, mean blood pressure, and percutaneous oxygen saturation (SPO2); (3) Laboratory parameters: white blood cell count, hemoglobin, platelets count, total bilirubin, albumin, anion gap, blood urea nitrogen (BUN), serum creatinine, glucose, potassium, sodium, chloride, calcium, and lactate; (4) Scoring systems: sequential organ failure assessment (SOFA) score, and simplified acute physiology score II (SAPS II); (5) Organ function support: vasopressors, invasive ventilation, and continuous renal replacement therapy (CRRT).

Definition and endpoint

The SII calculated equation: Platelet Count ($*10^9$/L) * Neutrophil Count ($*10^9$/L) ÷ Lymphocyte Count ($*10^9$/L)[9]. The primary endpoint was the 28-day mortality. Survival data were extracted from the MIMIC-IV database.

Statistical analysis

The SII quartiles stratified the baseline characteristics of all patients. Categorical variables were established as frequencies or percentages, and we used the Chi-square test for categorical data comparison. Continuous variables were summarized as the medians and interquartile range. Nonparametric methods were used regardless of the distributions

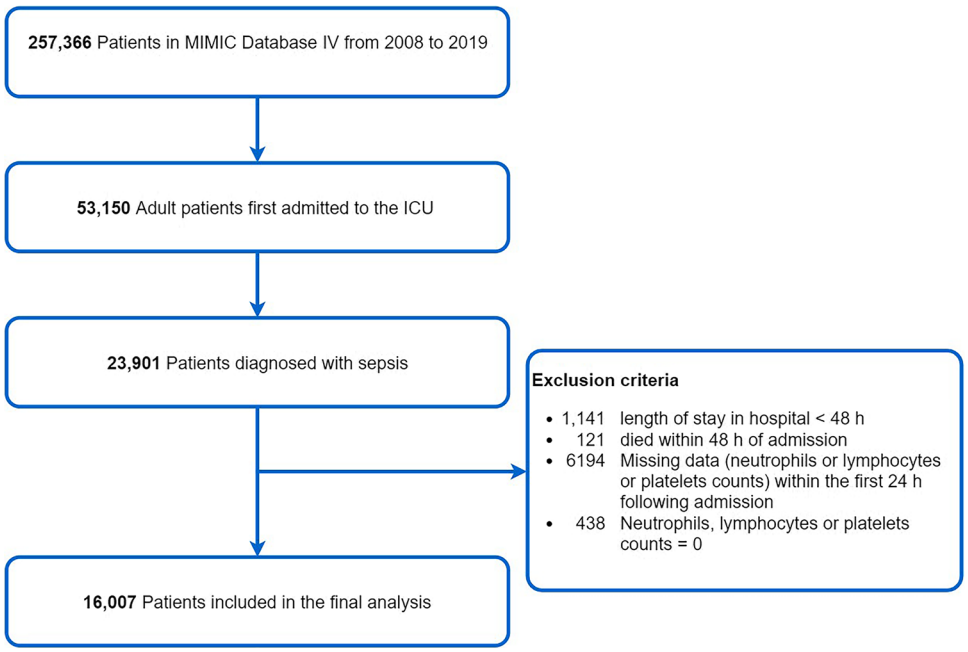

Fig. 1 Flow chart showing patient screening and inclusion

to provide robust comparisons. The Kruskal–Wallis H test tested differences for continuous measurements.

We used restricted cubic splines (RCS) with five knots, corresponding to the 5, 35, 50, 65, and 95th percentiles, to explore the relationship between SII and mortality in critically ill patients with sepsis. The Kaplan–Meier survival curve was performed to estimate patients' survival status, and the differences between the curves were compared using the log-rank test. Cox proportional hazards models were performed to evaluate the association between the SII and 28-day mortality, and the results were presented as hazard ratio (HR) with 95% confidence intervals (CIs). To improve the robustness of the analysis results, we constructed two different multivariable models based on the SII quartiles, including minimally adjusted (Model 1) and fully adjusted (Model 2) models. We used the backward stepwise method of selecting covariates to construct Model 1. Covariates in Model 1 were adjusted for age, gender, congestive heart failure, myocardial infarction, severe liver disease, malignant cancer, respiratory rate, temperature, hemoglobin, total bilirubin, albumin, BUN, serum glucose, anion gap, lactate, vasopressors, invasive ventilation, and CRRT. We assessed the multicollinearity problem by calculating variance inflation factors (VIF). The VIF of all covariates was less than 3 (Table S1). The missing values of all variables were less than 20%, and we used multiple imputations to impute the missing data. The details of the missing values are shown in the supplementary material (Table S2).

Analyses of the primary endpoint were also performed in several prospectively defined subgroups. The subgroups included age and gender, as well as patients with and without a history of congestive heart failure, myocardial infarction, hypertension, diabetes mellitus, COPD, severe liver disease, chronic kidney disease, malignant cancer, SOFA, and SAPS II. All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software (version 1.7.1); a *P* value of less than 0.05 indicated statistical significance; all tests were two-tailed. Reporting of this study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [14].

Results

Baseline characteristics

A total of 16,007 critically ill patients with sepsis were eligible for the present study according to the inclusion and exclusion criteria, including 9178 men (57.3%) and 6829 women. Patients were divided into four groups according to SII ($*10^9$/L) quartiles (Q1: ≤ 739.7, Q2: 740.2~1617.9, Q3: 1618.1~3450, Q4: ≥ 3452.5). The baseline characteristics are summarized in Table 1. Patients with higher SII values were more likely to be elderly, female, and have a history of congestive heart failure, hypertension, diabetes mellitus, COPD, chronic kidney disease, and malignant cancer. They also had higher hemoglobin levels, platelets, white blood cells, anion gap, serum creatinine, BUN, and serum glucose. Furthermore, patients with higher SII values are more likely to have higher SAPS II scores and to have received vasopressors and invasive ventilation. In contrast, patients with lower SII values were more likely to have severe liver disease and lower total bilirubin, albumin, and lactate levels.

Table 1 Baseline characteristics

Variables	Systemic immune-inflammation index				*P* value
	Q1	Q2	Q3	Q4	
N	4002	4001	4002	4002	
SII, 10^9/L	≤739.7	740.2 ~ 1617.9	1618.1 ~ 3450	≥3452.5	
Age, years	65 (55, 77)	67 (56, 78)	68 (55, 80)	69 (57, 80)	< 0.001[a]
Gender, n (%)					< 0.001[b]
Male	2374 (59.3)	2389 (59.7)	2268 (56.7)	2147 (53.6)	
Female	1628 (40.7)	1612 (40.3)	1734 (43.3)	1855 (46.4)	
Vital signs					
Heart rate, beats/min	84 (75, 99)	86 (76, 101)	90 (77, 105)	94.0 (80, 108)	< 0.001[b]
Mean blood pressure, mmHg	80 (70, 91)	81 (71, 93)	81 (70, 94)	80 (70, 93)	0.023[b]
Respiratory rate, breaths/min	18 (15, 22)	18 (15, 23)	20 (16, 23)	20 (17, 25)	< 0.001[b]
Temperature, ℃	36.7 (36.3, 37.0)	36.7 (36.4, 37.1)	36.8 (36.4, 37.2)	36.8 (36.4, 37.2)	< 0.001[b]
SPO2, %	99 (96, 100)	98 (95, 100)	98 (95, 100)	97 (94, 100)	< 0.001[b]
Comorbidities, n (%)					
Congestive heart failure	987 (24.7)	1190 (29.7)	1364 (34.1)	1278 (31.9)	< 0.001[b]
Myocardial infarction	593 (14.8)	714 (17.8)	742 (18.5)	711 (17.8)	< 0.001[b]
Hypertension	1724 (43.1)	1699 (42.5)	1582 (39.5)	1602 (40.0)	0.002[b]
Diabetes mellitus	1148 (28.7)	1239 (31.0)	1289 (32.2)	1202 (30.0)	0.006[b]
COPD	875 (21.9)	1024 (25.6)	1081 (27)	1236 (30.9)	< 0.001[b]
Severe liver disease	552 (13.8)	314 (7.8)	217 (5.4)	138 (3.4)	< 0.001[b]
Chronic kidney disease	755 (18.9)	858 (21.4)	971 (24.3)	944 (23.6)	< 0.001[b]
Malignant cancer	587 (14.7)	401 (10.0)	438 (10.9)	662 (16.5)	< 0.001[b]
Scoring					
Charlson comorbidity index	5.0 (4.0, 7.0)	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	< 0.001[a]
SOFA	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	< 0.001[a]
SAPS II	36.0 (29.0, 46.0)	37.0 (30.0, 46.0)	38.0 (30.0, 48.0)	40.0 (32.0, 50.0)	< 0.001[a]
Laboratory parameters					
White blood cell, 10^9/L	7.9 (5.4, 11.3)	10.8 (8.0, 14.3)	12.8 (9.7, 16.8)	16.4 (12.1, 21.5)	< 0.001[a]
Neutrophils, 10^9/L	1.47 (0.06, 5.33)	5.15 (0.10, 8.99)	7.60 (0.14, 11.76)	9.90 (0.18, 15.92)	< 0.001[a]
Lymphocytes, 10^9/L	0.46 (0.02, 1.67)	0.74 (0.02, 1.50)	0.67 (0.01, 1.18)	0.36 (0.01, 0.77)	< 0.001[a]
Monocytes, 10^9/L	0.10 (0.01, 0.35)	0.22 (0.01, 0.50)	0.30 (0.01, 0.58)	0.27 (0.01, 0.62)	< 0.001[a]
Hemoglobin, g/dL	10.2 (8.6, 12.0)	10.9 (9.2, 12.7)	11.4 (9.7, 13.1)	11.1 (9.5, 12.8)	< 0.001[a]
Platelets, 10^9/L	122 (81, 169)	177 (134, 228)	219 (168, 282)	273 (203, 371)	< 0.001[a]
Total bilirubin, mg/dL	0.8 (0.5, 2.1)	0.7 (0.4, 1.4)	0.7 (0.4, 1.2)	0.6 (0.4, 1.2)	< 0.001[a]
Albumin, g/dL	3.1 (2.6, 3.6)	3.2 (2.7, 3.6)	3.2 (2.7, 3.6)	3.0 (2.6, 3.5)	< 0.001[a]
Anion gap	14 (12, 17.0)	15 (12, 18)	16 (14, 19)	16 (14, 20)	< 0.001[a]
BUN, mg/dL	19 (13, 30)	21 (14, 33)	23 (15, 39)	25 (16, 41)	< 0.001[a]
Serum creatinine, mg/dL	1.0 (0.7, 1.4)	1.0 (0.8, 1.6)	1.2 (0.8, 1.8)	1.2 (0.8, 1.9)	< 0.001[a]
Serum glucose, mg/dL	127 (104, 160)	130 (107, 168)	135 (110, 181)	138 (110, 184)	< 0.001[a]
Serum lactate, mmol/L	2.5 (1.7, 3.7)	2.3 (1.5, 3.4)	2.1 (1.4, 3.6)	2.0 (1.4, 3.3)	< 0.001[a]
Curing, n (%)					
Vasopressor	1288 (32.2)	1412 (35.3)	1518 (37.9)	1666 (41.6)	< 0.001[b]
Invasive ventilation	365 (9.1)	372 (9.3)	384 (9.6)	443 (11.1)	0.013[b]
CRRT	130 (3.2)	114 (2.8)	131 (3.3)	147 (3.7)	0.230[b]
Mortality, n (%)					
28-day	417 (10.4)	424 (10.6)	546 (13.6)	723 (18.1)	< 0.001[b]
90-day	499 (12.5)	508 (12.7)	638 (15.9)	834 (20.8)	< 0.001[b]

SII, systemic immune-inflammation index; SPO2, percutaneous oxygen saturation; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy

[a]Kruskal–Wallis H test

[b]Pearson's Chi-squared test

Restricted cubic splines analysis

We used RCS to investigate and visualize the relationship between SII and mortality in critically ill patients with sepsis. After adjusting full variables, we found a nonlinear association between SII and 28-day mortality (nonlinear $P = 0.049$, Fig. 2). Regarding the J-shaped relationship between SII and 28-day mortality, the breakpoint analysis showed that the risk reduction occurred in the lower part of the SII range, reaching the lowest risk around SII = 774.46*10^9/L, after which it began to rise rapidly (Figure S1). Therefore, in the subsequent Cox regression analysis, we set the Q2 group (SII: 740.2*10^9/L~1617.9*10^9/L) as a reference group.

Kaplan–Meier analysis

The Kaplan–Meier curve for the SII quartile is shown in Fig. 3. The survival rates of groups Q1 and Q2 were higher than those in Q3 and Q4 groups, even though the Q4 group described the lowest survival probability at the time point of 28 days ($P < 0.001$ by log-rank test). Similar trends were found in 90-day mortality (Figure S2).

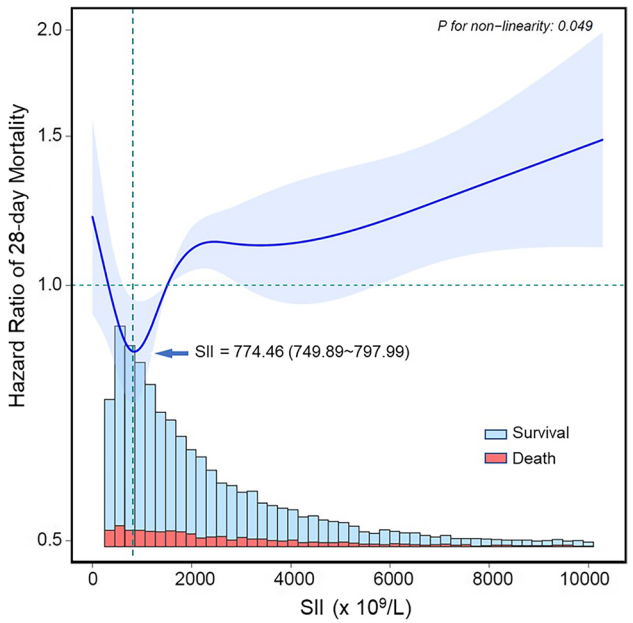

Fig. 2 Restricted cubic spline for the association between SII and mortality. The lines represent adjusted hazard ratios based on restricted cubic splines in the Cox regression model for the SII. Adjusted factors were age, gender, comorbidities, vital signs, laboratory parameters, vasopressors, invasive ventilation, and CRRT. Shaded areas around the curves depict a 95% confidence interval. SII, Systemic immune-inflammation index; CRRT, continuous renal replacement therapy

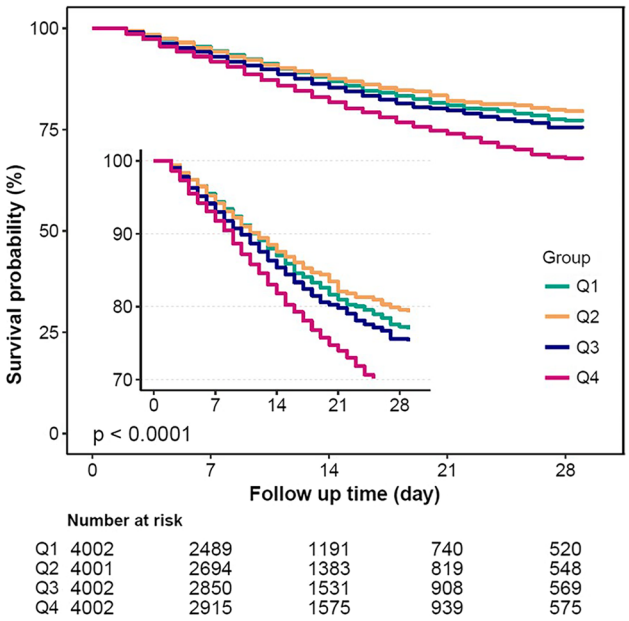

Fig. 3 Kaplan–Meier survival curve for mortality according to SII. SII, Systemic immune-inflammation index; HR, hazard ratio; CI, confidence interval

Cox regression analysis

Among all enrolled patients, the 28-day mortality was 2110 (13.2%). We performed the Cox regression model to evaluate the association between SII and 28-day mortality risk (Table 2). We set the Q2 group as a reference based on the RCS results. Compared to the Q2 group, higher SII (Q4 group) was associated with an increased risk of 28-day mortality (unadjusted model: 1.59 (1.41~1.79); minimally adjusted model: 1.38 (1.22~1.56); and fully adjusted model: 1.40 (1.23~1.58)). A similar trend was found in the Q3 group. However, although lower SII (Q1 group) also showed a trend toward a higher 28-day mortality hazard, there was no statistical difference (unadjusted model: 1.06 (0.93~1.22); minimally adjusted model: 1.04 (0.91~1.20); and fully adjusted model: 1.05 (0.92~1.21)). The detailed results of the univariable Cox regression analyses are shown in the supplementary material (Table S1).

Subgroup analyses

Considering the considerable intergroup variation in baseline characteristics, we conducted subgroup analyses to estimate the association between SII and 28-day mortality across age, gender, comorbidities, SOFA, and SAPS II, as shown in Table 3. In the fully adjusted model, the primary endpoint trended similarly in most subgroups, except for significant interactions observed for severe liver disease (P for interaction = 0.033).

Table 2 Multivariable Cox regression analysis for 28-day mortality

Variable	Event, *n* (%)	Model 1		Model 2	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
SII					
Q1	417 (10.4)	1.04 (0.91–1.2)	0.529	1.05 (0.92–1.21)	0.471
Q2	424 (10.6)	1	Reference	1	Reference
Q3	546 (13.6)	1.15 (1.01–1.31)	0.029	1.16 (1.02–1.32)	0.025
Q4	723 (18.1)	1.38 (1.22–1.56)	< 0.001	1.40 (1.23–1.58)	< 0.001
Covariates					
Age		1.03 (1.02–1.03)	< 0.001	1.03 (1.02–1.03)	< 0.001
Respiratory rate		1.02 (1.01–1.03)	< 0.001	1.02 (1.01–1.02)	< 0.001
Temperature		0.88 (0.84–0.92)	< 0.001	0.88 (0.84–0.92)	< 0.001
SPO2		0.99 (0.98–1.00)	0.052	0.99 (0.98–1.00)	0.090
Congestive heart failure		0.99 (0.90–1.09)	0.836	0.97 (0.88–1.08)	0.588
Myocardial infarction		1.15 (1.04–1.29)	0.009	1.18 (1.06–1.32)	0.003
Malignant cancer		1.42 (1.27–1.58)	< 0.001	1.40 (1.25–1.56)	< 0.001
Severe liver disease		1.59 (1.37–1.84)	< 0.001	1.55 (1.34–1.80)	< 0.001
Hemoglobin		1.03 (1.02–1.05)	< 0.001	1.03 (1.01–1.05)	0.004
Total bilirubin		1.03 (1.02–1.03)	< 0.001	1.03 (1.02–1.03)	< 0.001
Albumin		0.85 (0.79–0.91)	< 0.001	0.86 (0.79–0.95)	0.003
Anion gap		1.02 (1.01–1.03)	0.001	1.02 (1.01–1.03)	< 0.001
BUN		1.00 (1.00–1.00)	0.066	1.01 (1.00–1.01)	< 0.001
Serum glucose		1.00 (1.00–1.00)	0.559	1.00 (1.00–1.00)	0.353
Serum lactate		1.03 (1.01–1.04)	< 0.001	1.02 (1.01–1.04)	0.003
Vasopressor		1.61 (1.45–1.78)	< 0.001	1.63 (1.47–1.81)	< 0.001
Invasive ventilation		1.68 (1.48–1.91)	< 0.001	1.66 (1.46–1.89)	< 0.001
CRRT		1.21 (1.03–1.42)	0.018	1.30 (1.11–1.53)	0.001
Gender				1.04 (0.95–1.14)	0.359
Heart rate				1.00 (1.00–1.00)	0.297
Mean blood pressure				1.00 (1.00–1.01)	0.006
Hypertension				0.86 (0.77–0.95)	0.004
Diabetes mellitus				0.89 (0.80–0.99)	0.030
COPD				1.05 (0.95–1.16)	0.309
Chronic kidney disease				0.96 (0.84–1.09)	0.496
Serum creatinine				0.90 (0.86–0.94)	< 0.001

Model 1: adjusted for age, respiratory rate, temperature, congestive heart failure, myocardial infarction, severe liver disease, malignant cancer, hemoglobin, total bilirubin, albumin, serum glucose, BUN, anion gap, serum lactate, vasopressors, invasive ventilation, and CRRT

Model 2: fully adjusted Cox regression model; adjusted for model 2, additionally adjusted for gender, hypertension, diabetes mellitus, COPD, chronic kidney disease, mean blood pressure, heart rate, SPO2, and serum creatinine

Discussion

In this study of 16,007 individuals from a cohort of critically ill patients with sepsis from the MIMIC database, our analysis results indicated a J-shaped relationship between SII and short-term mortality, with low and high levels associated with an increased hazard. The SII level with the lowest risk of 28-day mortality was $774.46*10^9$/L. Since sepsis is a time-dependent disease, the importance of rapid identification of critically ill patients is indisputable. Our findings have clinical significance, and SII may contribute to early identification and prognostic stratification.

SII integrates the predictive value of the three indicators, which may reflect the balance of the patient's inflammatory, immune, and thrombotic pathways. It was first described as an indicator of prognosis in patients with resected hepatocellular carcinoma [9]. Subsequently, SII was shown to have prognostic value for various cancers [15–22]. Previous studies in adult patients with sepsis are consistent with our results [23, 24]. SII could be used not only to predict death in patients with sepsis but also to synergize clinical scores

Table 3 Subgroup analysis of the association between SII and 28-day mortality

Subgroups	*n*	Fully adjusted HR (95%CI)				*P* for interaction
		Q1	Q2	Q3	Q4	
Age (years)						0.259
≤65	6928	0.93 (0.72–1.21)	Ref	0.98 (0.76–1.27)	1.16 (0.90–1.49)	
>65	9079	1.15 (0.91–1.45)	Ref	1.39 (1.14–1.71)	1.55 (1.27–1.89)	
Gender						0.440
Male	9178	0.97 (0.78–1.22)	Ref	1.10 (0.89–1.35)	1.24 (1.02–1.52)	
Female	6829	1.22 (0.92–1.60)	Ref	1.43 (1.11–1.83)	1.62 (1.28–2.06)	
Congestive heart failure						0.780
No	11,188	1.04 (0.84–1.30)	Ref	1.26 (1.03–1.54)	1.37 (1.13–1.67)	
Yes	4819	1.08 (0.81–1.46)	Ref	1.13 (0.87–1.46)	1.36 (1.06–1.75)	
Myocardial infarction						0.667
No	13,247	1.07 (0.88–1.3)	Ref	1.28 (1.06–1.53)	1.45 (1.21–1.72)	
Yes	2760	1.11 (0.76–1.62)	Ref	1.04 (0.75–1.44)	1.26 (0.92–1.74)	
Hypertension						0.235
No	9400	1.00 (0.81–1.24)	Ref	1.05 (0.86–1.29)	1.27 (1.05–1.54)	
Yes	6607	1.15 (0.86–1.55)	Ref	1.51 (1.16–1.97)	1.55 (1.20–2.01)	
Diabetes mellitus						0.455
No	11,129	1.07 (0.87–1.32)	Ref	1.29 (1.07–1.56)	1.38 (1.15–1.65)	
Yes	4878	0.97 (0.70–1.35)	Ref	1.04 (0.78–1.40)	1.41 (1.06–1.87)	
Chronic kidney disease						0.290
No	12,479	1.07 (0.87–1.30)	Ref	1.31 (1.09–1.57)	1.45 (1.22–1.73)	
Yes	3528	1.01 (0.71–1.44)	Ref	0.96 (0.69–1.33)	1.17 (0.86–1.60)	
COPD						0.423
No	11,791	1.01 (0.83–1.24)	Ref	1.12 (0.93–1.34)	1.28 (1.07–1.54)	
Yes	4216	1.16 (0.81–1.65)	Ref	1.48 (1.08–2.01)	1.67 (1.24–2.23)	
Severe liver disease						**0.033**
No	14,786	1.07 (0.88–1.31)	Ref	1.35 (1.13–1.60)	1.49 (1.26–1.76)	
Yes	1221	0.88 (0.61–1.27)	Ref	0.65 (0.43–0.99)	0.79 (0.50–1.24)	
Malignant cancer						0.718
No	13,919	1.05 (0.87–1.28)	Ref	1.25 (1.05–1.49)	1.39 (1.17–1.65)	
Yes	2088	1.12 (0.75–1.67)	Ref	1.04 (0.68–1.59)	1.39 (0.95–2.03)	
SOFA						0.565
≤4	9562	0.93 (0.69–1.27)	Ref	1.27 (0.99–1.63)	1.43 (1.13–1.81)	
>4	6445	1.1 (0.89–1.37)	Ref	1.18 (0.95–1.45)	1.36 (1.11–1.67)	
SAPS II						0.182
≤40	8747	0.71 (0.47–1.06)	Ref	0.99 (0.7–1.4)	1.33 (0.96–1.84)	
>40	7260	1.15 (0.94–1.39)	Ref	1.26 (1.05–1.51)	1.4 (1.18–1.67)	

SII, systemic immune-inflammation index; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II

Bold values indicate statistical significance ($P < 0.05$)

of sepsis severity, thus improving the accuracy of diagnosis. The role of SII in the early diagnosis of neonatal sepsis in neonatal heart disease has also been recently investigated [25].

In the present study, the mortality risk was significantly higher in the third and fourth quartile groups than in the first and second groups. It suggested that significantly higher SII levels correlate with poorer prognosis in critically ill patients with sepsis. Similarly, Tang Y et al. reported that higher SII levels effectively predicted 30- and 90-day mortality and in-hospital mortality, and an increased risk of major adverse cardiovascular events, in a retrospective cohort study of 4606 critically ill patients with cognitive heart failure [10]. Higher SII has also been associated with an elevated hazard of contrast-induced nephropathy in patients with acute coronary syndrome [26, 27], increased severity of acute kidney

injury in patients with acute pancreatitis [28], and elevated mortality risk in critically ill COVID-19 patients [29].

However, because SII is calculated with neutrophil and platelet counts included in the numerator, a lower neutrophil or platelet count will translate to a lower value of the SII. Neutropenia [30, 31] and thrombocytopenia [32] are common among critically ill patients. Moreover, sustained platelet activation amplifies the inflammatory response and favors the development of endothelial dysfunction and multiple organ failure [33, 34]; marked thrombocytopenia is associated with a worse prognosis [35, 36]. Therefore, lower SII theoretically indicates that the body may be in disorder with severe inflammation or myelosuppression and could usually associate with poor prognosis, thus helping to explain the J-shaped relationship we observed. However, compared with the second quartile group, we found no statistically significant difference in the increased mortality hazard in the lowest quartile group. The relationship between SII levels and prognosis in other populations has also been controversial in previous studies. Jia L et al. found a similar J-shaped relationship in patients with acute kidney injury [12]. However, a recent study found a linear positive association in patients with acute ischemic stroke [37]. The controversy may be related to the cutoff values for the grouping and different study populations. So, analyzing the dynamic changes in SII occurring during the clinical course of sepsis may help better assess the prognosis of patients [38, 39].

In our subgroup analysis, SII appears to have weaker prognostic value in patients with co-morbid severe liver disease. The liver is considered one of the essential organs in infection. During severe liver disease, neutrophil responses are modified over time, and the balance between immunotolerance and effective immune responses could be impaired [40]. Therefore, the severe liver disease could affect the coordinated response of the liver to infections. It may explain why SII had less prognostic value in patients with sepsis with concomitant severe liver disease in our study. However, the prognostic value of SII was found in hepatocellular carcinoma and liver-only metastasis of rectal cancer [41, 42]. It may be related to the presence or absence of infection and specific liver function.

Strengths and limitations

To our knowledge, only two studies have reported the diagnostic value of SII in adult patients with sepsis [23, 24]. Our study is the most extensive retrospective cohort study exploring the association between SII and prognosis in patients with sepsis. We also reported a J-shaped nonlinear relationship between them for the first time. However, our study has some limitations. First, the data were collected retrospectively, and some crucial variables may need to be included due to insufficient data. Our study lacked some other drugs use, such as the use of steroids and nonsteroidal anti-inflammatory drugs, some information at the time of participants' blood sample collection, including indicators of the acute inflammatory state, and information about the site of infection and pathogenic tests, such as blood cultures. Second, SII was calculated using only the first test results after admission and did not assess the changes during hospitalization. The optimal time point needs to be investigated. Finally, this is a single-center retrospective study, and selection bias cannot be disregarded. We only use short-term mortality, which may influence prognostic assessments.

Conclusions

Low and high SII levels were associated with an increased short-term mortality risk in critically ill patients with sepsis. In addition, patients with SII levels of $774.46*10^9$/L had the lowest mortality risk. SII may be a potentially cost-effective and accessible prognostic biomarker for patients with sepsis. However, the clinical application still needs to be validated by extensive prospective studies.

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Authors' contribution DJ took part in conceptualization, methodology, software, formal analysis, writing—original draft. TB involved in data curation, validation, investigation. YS involved in supervision, writing—reviewing, and editing. ZH took part in supervision, project administration. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate Institutional Review Board Statement: The MIMIC-IV database has received ethical approval from the Institutional Review Boards of the Massachusetts Institute of Technology and BIDMC. Because the database does not contain protected health information, this study did not require written informed consent for participation.

Consent for publication Informed consent was obtained from all participants for publication.

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