Journal of Inflammation Research

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ORIGINAL RESEARCH

The Clinical Value of Systemic Immune Inflammatory Index in Predicting the Prognosis of Patients with Bloodstream Infection

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Introduction: We analyzed the correlation between systemic immune inflammatory index (SII), systemic inflammatory response index (SIRI), systemic inflammatory index (AISI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and mortality in patients with bloodstream infection to determine their application potential in predicting the prognosis of bloodstream infection.

Methods: We calculated SII, SIRI, AISI, NLR, PLR, and MLR in 469 patients with bloodstream infections. Logistic regression modeling, generalized additive modeling (GAM), and smoothed curve fitting were used to investigate the correlation of SII and other inflammatory markers with mortality in patients with bloodstream infections. Area under the curve (AUC) of ROC was used to assess the predictive effect of SII and other inflammatory markers.

Results: Levels of SII, SIRI, AISI, NLR, PLR, and MLR were significantly higher in the mortality group of this study ($P < 0.05$). There were significant differences in gender, age, diabetes, cardiovascular disease, respiratory disease, NEUT and LUMPH between the survival group and the death group ($p < 0.05$). Smooth curve fitting and GAM showed that SII and NLR had a non-linear relationship with death. After adjustment, the breakpoints (K) were 1711 and 7.22, respectively ($P < 0.05$), and there was a positive correlation on both sides of the breakpoint. The comparison of AUC values showed that SII and NLR had higher accuracy in predicting the risk of death in patients with bloodstream infection.

Conclusion: Studies demonstrates that SII and NLR are more predictive of mortality risk in patients with bloodstream infections. Patients with diabetes, cardiovascular disease, or respiratory disease should be monitored regularly for SII and NLR indicators to reduce the risk of death.

Keywords: bloodstream infection, systemic immune inflammatory index, prognosis, smooth curve fitting, neutrophil-to-lymphocyte ratio

Introduction

Bloodstream infection (BSI) is caused by pathogenic microorganisms that invade the blood, reproduce and release a series of metabolites and toxins in the blood, and induce the abnormal release of a variety of cytokines. If not treated in a timely and effective manner, it may lead to the occurrence of systemic inflammatory response, which seriously threatens the life and health of patients.[1–3] In recent years, bloodstream infection has become one of the major public health problems worldwide. According to statistics, bloodstream infections occur in about 30 million patients worldwide each year.[4–6] With the change of people 's lifestyle and living environment, the incidence of BSI is

Received: 29 March 2025
Accepted: 19 July 2025
Published: 30 July 2025

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increasing year by year. Severe cases may even be complicated by sepsis and septic shock. The mortality rate is high, which increases the economic burden of patients' families and society.[7–10] Blood culture is the gold standard for the diagnosis of BSI, but this diagnostic method has limitations such as long examination time, high risk of contamination, and the culture results may be affected by factors such as drugs, which may have adverse effects on the prognosis of critically ill patients.[11–13] Therefore, it is of clinical significance to seek more efficient and accurate indicators, which can provide positive guidance for the prognosis of patients with bloodstream infection. In recent years, with the continuous deepening of related research, more and more scholars have found that inflammatory markers may play a key role in the prognosis of BSI by virtue of their advantages such as simple detection operation, short detection time and good repeatability.

Clinical studies have found that the more severe the condition of patients with bloodstream infection, the more obvious the abnormal hematological parameters, especially the decrease of lymphocytes, the increase of white blood cells and neutrophils, and the decrease of platelets.[14] In recent years, the ratios of these parameters (neutrophil to lymphocyte ratio (NLR), platelet / lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR)) have also been used as biomarkers to assist in the diagnosis of inflammatory diseases and the prediction of prognosis.[15] NLR is a research hotspot in recent years, which is a sensitive indicator for the diagnosis of sepsis, infection and inflammation.[8,16,17] PLR is also a potential prognostic indicator of bloodstream infection.[18,19] However, the reliability of MLR in the diagnosis and prediction of bloodstream infection is still controversial in previous studies.[20,21] Other indicators also include three or more blood parameter ratios such as: systemic immune-inflammation index (SII), which was first proposed by Hu et al in 2014 as a prognostic marker for hepatocellular carcinoma. SII contains parameters such as neutrophils, monocytes and platelets, and may be able to more comprehensively assess the relationship between disease and immune cells and inflammatory response.[22] Systemic inflammatory response index (SIRI) and systemic inflammatory aggregation index (AISI) are also two new immune inflammatory indexes. However, few studies have evaluated their role in bloodstream infection. Therefore, this study collected the levels of SII and other inflammatory indicators (SIRI, AISI, NLR, PLR and MLR) during bloodstream infection in hospitalized patients with bloodstream infection to determine their application potential in predicting the prognosis of bloodstream infection.

Materials and Methods

Study Participants

This was a retrospective case-control study, and the patients with bloodstream infections admitted to the First Hospital of Shanxi Medical University from January 1, 2023 to December 31, 2023 were included. All patients met the diagnostic criteria for bloodstream infection in the "Diagnostic Criteria for Nosocomial Infection (Trial)".[23] Single positive blood culture coagulase-negative Staphylococci (n = 24), age < 18 years (n = 9), incomplete clinical and laboratory data (n = 53), patients who received blood product therapy, long-term immunosuppressive therapy, hematological malignancies or chemotherapy in the near future (n = 123) were excluded. A total of 469 patients with bloodstream infection were included in the study (Figure 1).

Inflammatory Indicators Calculation

Hematological information such as neutrophils, lymphocytes, monocytes, and platelet counts during bloodstream infection were recorded. The counts of lymphocytes, neutrophils, monocytes and platelets were expressed in units of × 109 cells / L. In this study, SII was the main exposure variable, which was calculated according to the counts of neutrophils, platelets and lymphocytes in peripheral blood.[24] In order to further explore the relationship between SII and bloodstream infection, we also studied the relationship between other inflammatory biomarkers and bloodstream infection, including SIRI, AISI, NLR, PLR, MLR. The formula of these inflammatory indicators is: systemic inflammatory response index SIRI = neutrophil count × monocyte count / lymphocyte count, systemic inflammatory composite index AISI = neutrophil count × monocyte count × platelet count / lymphocyte count, NLR = neutrophil count / lymphocyte count, PLR = platelet count / lymphocyte count, MLR = monocyte count / lymphocyte count.[25–27]

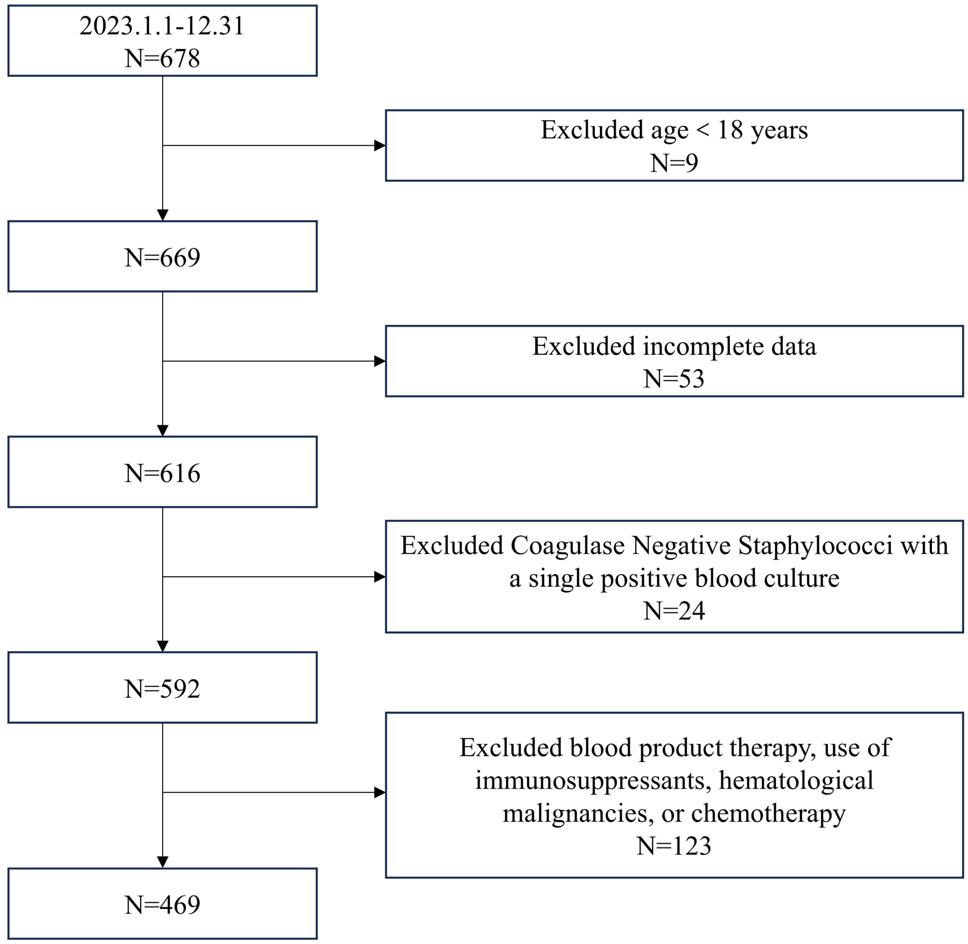

Figure 1 Flow chart.

Covariates

This study included a series of covariates to control potential confounding factors. These confounding factors include age, gender, and other demographic factors. We also included many epidemiological factors and other factors, including drinking, smoking status, diabetes, hypertension, cardiovascular disease, kidney disease, liver disease, respiratory disease.

Statistical Analysis

SPSS Statistics 26.0, Empower software and R version 4.1.3 were used for statistical analysis. Percentage is used to represent categorical variables, and standard error (SE) is used to represent continuous variables. According to the difference between the death group and the survival group, the weighted Student 's *t* test or the weighted X2 test was used. Multivariate logistic regression was used to analyze the correlation between SII, SIRI, AISI, NLR, PLR, MLR and mortality.[28] The robustness of the results was tested by sensitivity analysis of SII, SIRI, AISI, NLR, PLR, and MLR converted from continuous variables to categorical variables (tertiles). Generalized additive model (GAM) and smooth curve fitting are used to solve the nonlinear relationship.[29] In order to further study the threshold effect, the log-likelihood ratio test was used to compare the piecewise regression model (a two-segment linear regression model suitable for each interval) with the non-segmented model. In order to locate the breakpoint, a two-step recursive method is used. In addition, the predictive efficacy of SII, SIRI, AISI, NLR, PLR and MLR was evaluated by the area under the ROC working curve (AUC).[30,31] We used $P < 0.05$ for the difference was statistically significant.

Results

Participants Characteristics at Baseline

A total of 469 patients were analyzed in this study, 331 (70.6%) in the survival group and 138 (29.4%) in the death group. Among them, 294 cases (62.7%) were male and 175 cases (46.7%) were female, 250 cases (53.3%) were under 65 years old and 219 cases (46.7%) were over 65 years old. The prevalence of diabetes, hypertension, cardiovascular disease, kidney disease, liver disease and respiratory disease were 34.5%, 29.9%, 63.5%, 36.5%, 44.8% and 47.1%, respectively. The average levels of SII, SIRI, AISI, NLR, PLR and MLR were 2380.94 ± 121.87, 9.34 ± 0.83, 1330.64 ± 88.20, 17.39 ± 1.25, 319.34 ± 17.84 and 1.01 ± 0.08, respectively. As shown in Table 1, in the death group, the levels of SII, SIRI, AISI, NLR, PLR and MLR were significantly higher ($p < 0.05$). There were significant differences in gender, age, diabetes, cardiovascular disease, respiratory disease, NEUT and LUMPH between the survival group and the death group ($p < 0.05$).

Table 1 Baseline Characteristics According to Survival and Nonsurvival Groups

SII	Overall	Survivor	Non-Survivor	P-value
N	469	331	138	
SII	2380.94±121.87	1749.20±93.11	3896.21±314.02	<0.001
SIRI	9.34±0.83	6.29±0.50	16.66±2.46	<0.001
AISI	1330.64±88.20	1015.30±87.74	2086.98±199.80	<0.001
NLR	17.39±1.25	11.45±0.55	31.64±3.77	<0.001
PLR	319.34±17.84	223.72±10.87	548.71±49.67	<0.001
MLR	1.01±0.08	0.64±0.03	1.92±0.26	<0.001
Age, years, n(%)				<0.001
<65	250(53.3%)	203(61.3%)	47(34.1%)	
≥65	219(46.7%)	128(38.7%)	91(65.9%)	
Sex, n(%)				0.046
Male	294(62.7%)	199(60.1%)	95(68.8%)	
Female	175(37.3%)	132(39.9%)	43(31.2%)	
Smoke, n(%)				0.466
Yes	150(32.0%)	105(31.7%)	45(32.6%)	
No	319(68.0%)	226(68.3%)	93(67.4%)	
Alcohol consumption, n(%)				0.207
Yes	112(23.9%)	83(25.1%)	29(21.0%)	
No	357(76.1%)	248(74.9%)	109(79.0%)	
Diabetes, n(%)				0.277
Yes	140(29.9%)	102(30.8%)	38(27.5%)	
No	329(70.1%)	229(69.2%)	100(72.5%)	
Hypertension, n(%)				0.048
Yes	162(34.5%)	106(32.0%)	56(40.6%)	
No	307(65.5%)	225(68.0%)	82(59.4%)	
Cardiovascular disease, n(%)	298(63.5%)	197(59.5%)	101(73.2%)	0.003
Kidney disease, n(%)	171(36.5%)	122(36.9%)	49(35.5%)	0.433
Liver disease, n(%)	210(44.8%)	152(45.9%)	58(42.0%)	0.252
Respiratory diseases, n(%)	221(47.1%)	130(39.3%)	91(65.9%)	<0.001
NEUT, 10^9/L	8.61±0.27	8.21±0.32	9.56±0.52	0.019
LYMPH, 10^9/L	0.90±0.03	1.03±0.04	0.57±0.04	<0.001
PLT, 10^9/L	177.89±4.47	179.49±5.10	174.05±9.05	0.293
MONO, 10^9/L	0.52±0.02	0.51±0.02	0.54±0.03	0.661

Abbreviations: SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; AISI, Comprehensive index of systemic inflammation; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; NEUT, Neutrophil count; LYMPH, Lymphocyte count; PLT, platelet count; MONO, Mononuclear cell count.

Association Between SII and Survivor

Table 2 shows the correlation between SII, SIRI, AISI, NLR, PLR, MLR and death. For sensitivity analysis, SII, SIRI, AISI, NLR, PLR, and MLR were divided into three equal parts. Participants with higher tertiles had higher mortality than those with lower tertiles ($p < 0.05$). This study shows that when SII, SIRI, AISI, NLR, PLR, MLR are continuous variables, there is a positive correlation with death. After adjusting for the tertiles, there was a positive correlation with death (SII: OR = 1.01; 95% CI: 1.01, 1.01; SIRI: OR = 1.05; 95% CI: 1.03, 1.07; AISI: OR = 1.01; 95% CI: 1.01, 1.01; NLR: OR = 1.07; 95% CI: 1.05, 1.09; PLR: OR = 1.01; 95% CI: 1.01, 1.01; MLR: OR = 2.83; 95% CI: 2. 07, 3. 87). This means that each increase in SII, SIRI, AISI, NLR, PLR, and MLR. Smooth curve fitting and GAM showed that SII, SIRI, AISI, NLR, PLR and MLR had a non-linear relationship with death (Figure 2). After complete adjustment, the breakpoints (K) were 1711, 3.23, 486, 7.22, 866.67 and 1.18, respectively (all log-likelihood ratio tests $P < 0.05$). SIRI, NLR and MLR were positively correlated on both sides of the breakpoint (Table 3).

ROC Analysis

In order to evaluate the predictive ability of SII compared with other inflammatory biomarkers (SIRI, AISI, NLR, PLR, MLR) for the prognosis of patients, we calculated the AUC value (Figure 3). The results showed that the AUC value of NLR was higher than the other five inflammatory biomarkers in predicting the mortality of patients, and SII was second only to NLR. In addition, Table 4 showed that there were statistically significant differences in AUC values of SII, NLR and other inflammatory biomarkers ($p < 0.05$). These results suggest that compared with other inflammatory biomarkers (SIRI, AISI, PLR, MLR), SII and NLR have higher accuracy in predicting the risk of death in patients with bloodstream infection.

Table 2 Associations Between SII and Other Inflammatory Biomarkers with Survivor

Index	Continuous or Categories	OR[a] (95% CI[b])	*P*
SII	SII as continuous variable	1.01 (1.01 ~ 1.01)	<0.001
	Tertile 1	Reference	
	Tertile 2	8.17 (3.85 ~ 17.30)	<0.001
	Tertile 3	15.72 (7.48 ~ 33.02)	<0.001
SIRI	SIRI as continuous variable	1.05 (1.03 ~ 1.07)	<0.001
	Tertile 1	Reference	
	Tertile 2	3.86 (2.11 ~ 7.07)	<0.001
	Tertile 3	6.75 (3.73 ~ 12.22)	<0.001
AISI	AISI as continuous variable	1.01 (1.01 ~ 1.01)	<0.001
	Tertile 1	Reference	
	Tertile 2	2.69 (1.51 ~ 4.77)	<0.001
	Tertile 3	5.31 (3.04 ~ 9.26)	<0.001
NLR	NLR as continuous variable	1.07 (1.05 ~ 1.09)	<0.001
	Tertile 1	Reference	
	Tertile 2	5.50 (2.79 ~ 10.84)	<0.001
	Tertile 3	11.55 (5.93 ~ 22.50)	<0.001
PLR	PLR as continuous variable	1.01 (1.01 ~ 1.01)	<0.001
	Tertile 1	Reference	
	Tertile 2	1.93 (1.07 ~ 3.49)	0.030
	Tertile 3	6.85 (3.93 ~ 11.95)	<0.001
MLR	MLR as continuous variable	2.83 (2.07 ~ 3.87)	<0.001
	Tertile 1	Reference	
	Tertile 2	2.47 (1.34 ~ 4.55)	0.004
	Tertile 3	8.38 (4.68 ~ 15.01)	<0.001

Notes: [a]OR: Odds Ratio. [b]95% CI: Confidence Interval.

 https://doi.org/10.2147/JIR.S531272

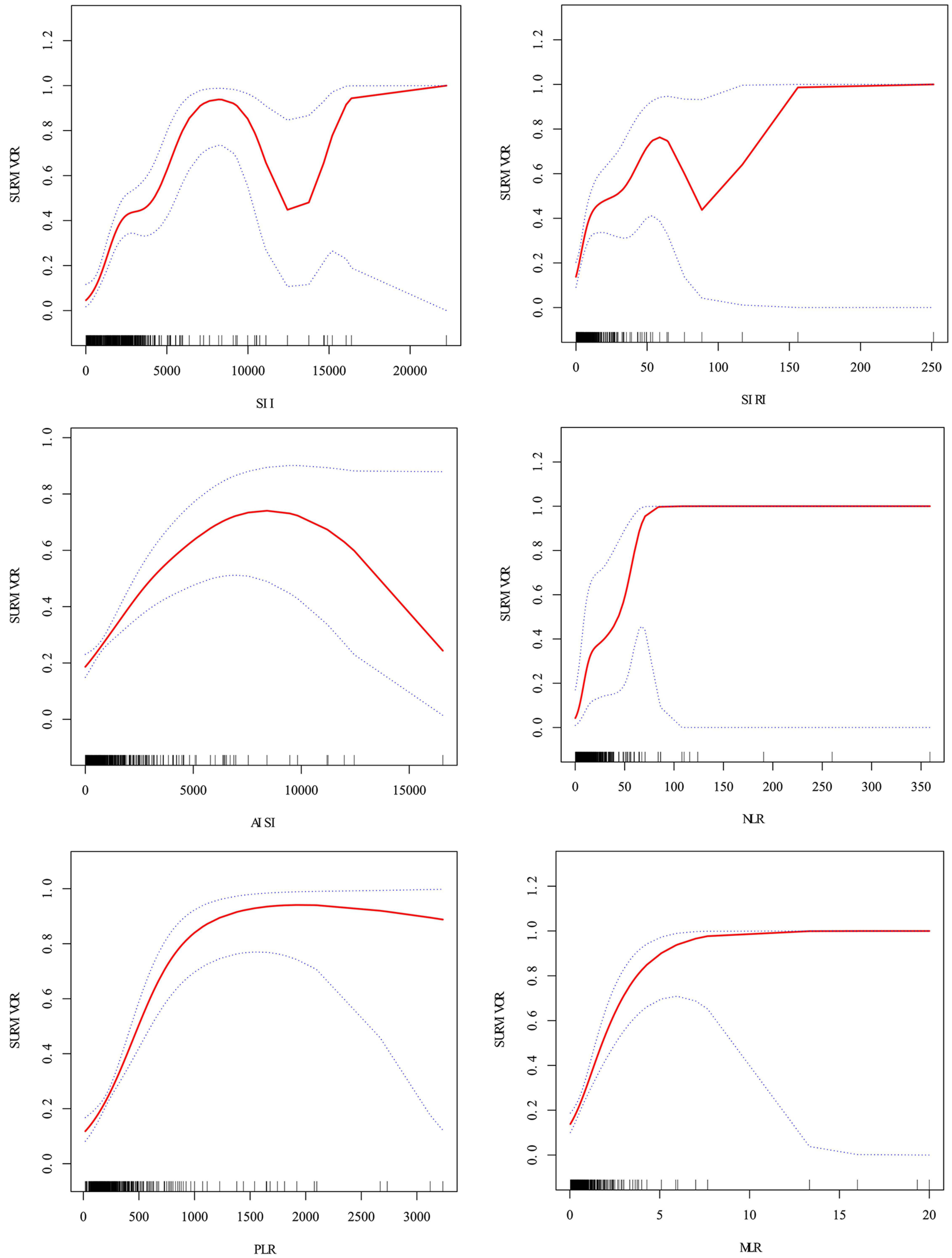

Figure 2 Smooth curve fitting for SII, SIRI, AISI NLR, PLR and MLR with Survivor.

Discussion

In this study, 469 patients with bloodstream infection were retrospectively studied. It was found that SII, SIRI, AISI, NLR, PLR and MLR were positively correlated with mortality. By using smooth curve fitting, it was found that there was a nonlinear relationship between SII, SIRI, AISI, NLR, PLR, MLR and mortality in patients with bloodstream infection. The breakpoints were 1711, 3.23, 486, 7.22, 866.67 and 1.18, respectively. In the sensitivity analysis, the higher the levels of SII, SIRI, AISI, NLR, PLR and MLR, the stronger the correlation with the mortality of patients with bloodstream infection. ROC curve analysis was used to compare SII with other inflammatory biomarkers. The results showed that SII and NLR may be more accurate indicators for predicting mortality in patients with bloodstream infection. In addition, logistics regression analysis showed that older age, diabetes, cardiovascular disease and respiratory disease would increase the mortality of patients with bloodstream infection.

Table 3 Threshold Effect Analysis of SII and Other Inflammatory Biomarkers on Survivor Using a Two-Piecewise Linear Regression Model

Survivor	**OR[a] (95% CI[b])**	**P**
SII		
Fitting by standard linear model	1.01 (1.01 1.01)	<0.0001
Fitting by two-piecewise linear model		
Breakpoint (K)	1711	
OR1(<K)	1.01 (1.01, 1.01)	<0.0001
OR2(>K)	1.01 (1.00, 1.01)	0.0009
OR2/ OR1	1.00 (0.99, 1.00)	<0.0001
Logarithmic likelihood ratio test P		<0.001
SIRI		
Fitting by standard linear model	1.05 (1.03, 1.07)	<0.0001
Fitting by two-piecewise linear model		
Breakpoint (K)	3.23	
OR1(<K)	1.78 (1.32, 2.41)	0.0002
OR2(>K)	1.03 (1.01, 1.05)	0.0073
OR2/ OR1	0.58 (0.42, 0.78)	0.0004
Logarithmic likelihood ratio test P		<0.001
AISI		
Fitting by standard linear model	1.01 (1.01, 1.01)	<0.0001
Fitting by two-piecewise linear model		
Breakpoint (K)	486	
OR1(<K)	1.01 (1.01, 1.01)	0.0003
OR2(>K)	1.01 (1.00, 1.01)	0.0132
OR2/ OR1	1.00 (0.99, 1.00)	0.0007
Logarithmic likelihood ratio test P		<0.001
NLR		
Fitting by standard linear model	1.06 (1.04, 1.08)	<0.0001
Fitting by two-piecewise linear model		
Breakpoint (K)	7.22	
OR1(<K)	1.64 (1.27, 2.11)	0.0001
OR2(>K)	1.04 (1.02, 1.06)	<0.0001
OR2/ OR1	0.64 (0.49, 0.82)	0.0006
Logarithmic likelihood ratio test P		<0.001
PLR		
Fitting by standard linear model	1.01 (1.01, 1.01)	<0.0001
Fitting by two-piecewise linear model		
Breakpoint (K)	866.67	
OR1(<K)	1.01 (1.01 1.01)	<0.0001
OR2(>K)	1.01 (1.00, 1.01	0.8951
OR2/ OR1	1.00 (0.99, 1.00)	0.0002
Logarithmic likelihood ratio test P		0.001
MLR		
Fitting by standard linear model	2.41 (1.77, 3.27)	<0.0001
Fitting by two-piecewise linear model		
Breakpoint (K)	1.18	
OR1(<K)	5.04 (2.45, 10.36)	<0.0001
OR2(>K)	1.68 (1.16, 2.45)	0.0065
OR2/ OR1	0.33 (0.13, 0.85)	0.0220
Logarithmic likelihood ratio test P		0.025

Notes: Adjust: Age, Sex, Hypertension, Cardiovascular disease, Respiratory diseases. [a]OR: Odds Ratio; [b]CI: Confidence Interval.

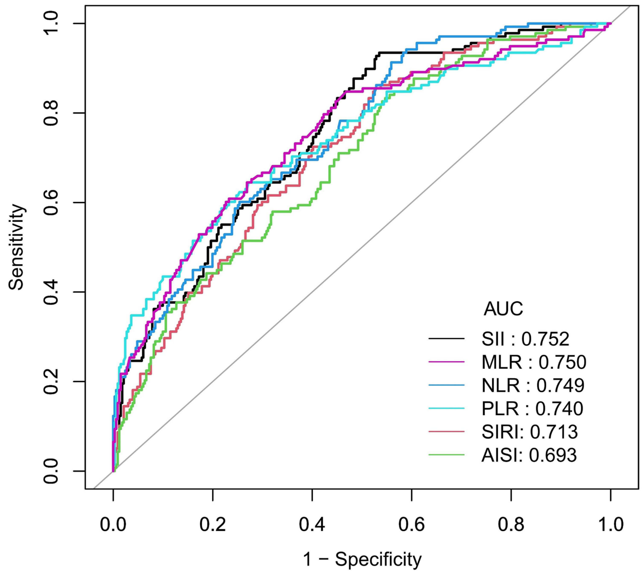

Figure 3 ROC curves and the AUC values of SII, SIRI, AISI, NLR, PLR and MLR.

The inflammatory biomarkers used in this study are new biomarkers related to whole blood cell counts. Inflammatory response can lead to changes in whole blood cell counts including neutrophils, monocytes, and platelets.[32] SII was first described by Hu et al in 2014. Based on three blood parameters, it comprehensively reflects the systemic immune and inflammatory state of the host.[22] Previous studies have found that SII, SIRI and AISI, as three new immune inflammation indexes, have a good predictive effect on tumors, cardiovascular diseases and respiratory diseases, and their predictive ability is better than other conventional ratios.[33–41] NLR, PLR and MLR are new inflammatory biomarkers that have attracted much attention in recent years. They are also fast and convenient parameters that reflect systemic inflammation and stress response. NLR and PLR are effective indicators of blood biochemical indicators that can evaluate the inflammatory state of the body. They are simple to detect and easy to obtain. They have been used in the diagnosis and prediction of systemic lupus erythematosus, influenza and other diseases prognosis.[42–46] On the basis of existing studies, this study further explored the application potential of SII, SIRI, AISI, NLR, PLR and MLR in the prognosis of patients with bloodstream infection.

Recent studies have further confirmed the prognostic role of inflammatory markers in patients with bloodstream infections. A retrospective study found that NLR, PLR and SII had good diagnostic value in neonatal sepsis compared with sepsis neonates and healthy neonates.[47] Another study found that SIRI can be used in conjunction with other parameters as an easy-to-obtain and reliable indicator of systemic inflammation in the diagnosis of early-onset sepsis in very low birth weight preterm infants.[48] In a retrospective study, NLR, MLR, PLR, white blood cell count and neutrophil

Table 4 Comparison of AUC Values Between SII and Other Inflammatory Biomarkers

Test	AUC[a]	95% Ci[b] Low	95% CI Upp	Best Threshold	Specificity	Sensitivity	P for Different in AUC
SII	0.7601	0.7101	0.8042	1344.6961	0.4653	0.9348	<0.0001
SIRI	0.7193	0.6696	0.7648	2.8101	0.4743	0.8551	<0.0001
AISI	0.7005	0.6533	0.7492	471.5757	0.4532	0.8333	<0.0001
NLR	0.7647	0.7193	0.8057	7.1575	0.4411	0.9130	<0.0001
PLR	0.7396	0.6899	0.7888	259.2857	0.7281	0.6449	<0.0001
MLR	0.7445	0.6922	0.7950	0.4976	0.5317	0.8478	<0.0001

Notes: [a]AUC: area under the curve. [b]95% CI: Confidence Interval.

count were significantly higher in patients with sepsis. NLR, MLR and PLR are potential rapid screening tools for detecting sepsis.[49] A recent study has shown that SIRI is a new and effective indicator for early diagnosis of catheter-related bloodstream infections in hemodialysis patients.[50]

This study found that the mortality of patients with bloodstream infection increased with the increase of SII, SIRI, AISI, NLR, PLR and MLR. According to ROC curve analysis, among these inflammatory biomarkers, the AUC values of SII and NLR were relatively high. Therefore, SII and NLR have better predictive ability for mortality in patients with bloodstream infection. In this study, there was a non-linear correlation between SII, NLR and mortality in patients with bloodstream infection. SII and NLR were positively correlated with the mortality of patients with bloodstream infection on both sides of the breakpoint, and the breakpoints were 1711 and 7.22, respectively. This means that the higher the SII and NLR indexes, the higher the risk of death in patients with bloodstream infection. In summary, SII and NLR have great potential in assessing the risk of death in patients with bloodstream infection.

This study did not find the fundamental mechanism of SII and NLR associated with mortality in patients with bloodstream infection. The mechanism of this association may be that SII and NLR are new systemic inflammatory biomarkers based on whole blood cells. After the pathogen invades the blood circulation and grows and reproduces, the toxins and metabolites produced by it can cause systemic inflammatory response syndrome. When the inflammatory response develops to damage its own tissues and organs, it can lead to tissue damage, organ failure and patient death.[51,52] Monocytes can promote this inflammatory response by releasing pro-inflammatory cytokines and interacting with other immune cells such as lymphocytes, platelets, and neutrophils, resulting in increased SII and NLR.[53,54]

This study has the following shortcomings: (1) This study is a retrospective analysis, which cannot determine the causal relationship between exposure and outcome; (2) The research object is limited to the population of Shanxi Province in China, and the number of samples is small. The conclusion has certain limitations and cannot be extended to other regions and other populations. (3) Although this study adjusted for multiple confounding factors, residual confounding factors or other unmeasured factors, such as environmental exposure, diet, lifestyle, etc., cannot be excluded. Therefore, in future studies, more large-scale prospective studies are needed to confirm and expand the results of this study.

Conclusions

In predicting the mortality of patients with bloodstream infection, compared with other inflammatory biomarkers (SIRI, AISI, PLR, MLR), SII and NLR have better predictive ability for the mortality risk of patients with bloodstream infection. Patients with bloodstream infections who have underlying diseases such as diabetes, cardiovascular disease or respiratory disease should regularly monitor SII and NLR indicators to reduce the risk of death in patients with bloodstream infections.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

The studies involving humans were approved by the Ethics Committee of the First Hospital of Shanxi Medical University (KYLL-2025-024) and conducted under the tenets of the Declaration of Helsinki. The studies were conducted in accordance with the local legislation and institutional requirements. The research team promises that any personal information that may be obtained will not be provided to other organizations or individuals; medical records of patients or subjects (including study medical records and physical and chemical examination reports, etc.) will be kept at the hospital as required. Publication of research results at the end of the study will not disclose the personal identity of patients. Written informed consent for participation was not required from the participants or the participants' legal guardians/ next of kin in accordance with the national legislation and institutional requirements.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (NSFC): 82202569; and the Shanxi Province Basic Research Program Project: 202403021212264; Scientific Research Project of Shanxi Provincial Health Commission: 2024067.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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