

Association Between Neutrophil Percentage to-Albumin Ratio, Neutrophil to-Lymphocyte Ratio, Platelet-to Lymphocyte Ratio and in-Hospital Mortality in Elder Patients with Bloodstream Infections

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Background: Bloodstream infections (BSI) is one of the major complications in elder inpatients, which is closely related to inflammation. Neutrophil percentage-to-albumin ratio (NPAR), Neutrophil-to-lymphocyte ratio (NLR), and Platelet-to-lymphocyte (PLR) are convenient predictors of inflammation and poor prognosis for a wide range of diseases. However, the association of NPAR, NLR and PLR with in-hospital mortality in elder inpatients with BSI are unclear. This study aimed to investigate the association and the predictive value of NPAR, NLR and PLR with in-hospital mortality.

Methods: This study included older patients with BSI who were hospitalized in a large healthcare center in Beijing from December 2011 to January 2024. Kaplan-Meier curves and Cox regression analysis were used to explore the association of NPAR, NLR and PLR with in-hospital mortality. Restricted cubic spline analysis and Receiver operating characteristics (ROC) were performed to access the dose-response relationship and predictive value of NPAR, NLR and PLR with in-hospital mortality, respectively.

Results: A total of 511 older patients with BSI were included in this study, with a mean age of 89.9±8.5 years, of which 85 deaths occurred during hospitalization (16.6%). After adjustment, the continuous NPAR level was associated with increased risk of in-hospital mortality (hazard ratio [HR] = 1.08, 95% confidence interval [CI]: 1.05, 1.12). The third tertile group of NPAR significantly increased the risk of in-hospital mortality compared to the first tertile group of NPAR (HR = 3.36, 95% CI: 1.87, 6.02). However, no association between NLR, PLR and in-hospital mortality was found. The area under the ROC curve of NPAR, NLR, and PLR for predicting mortality were 0.681 (95% CI: 0.615–0.747), 0.666 (95% CI: 0.598–0.733), and 0.510 (95% CI: 0.420–0.559), respectively.

Conclusion: Elevated NPAR was associated with higher risk of in-hospital mortality in older patients with BSI. NPAR may serve as a convenient and simple prognostic indicator.

Keywords: biomarkers, neutrophil percentage-to-albumin ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte, bloodstream infections, elder, mortality

Introduction

Bloodstream infections (BSIs) are defined as the presence of microorganisms (eg, bacteria, fungi, or viruses) in the blood, leading to systemic infection or sepsis.¹ The primary types of BSIs include sepsis and bacteremia, with common pathogens

encompassing Gram-negative and Gram-positive bacteria, as well as fungi such as *Candida* species.² Key risk factors for BSIs include immunosuppressed host states, invasive medical procedures, advanced age, prolonged hospitalization, and intensive care unit (ICU) admission.³ The gold standard for diagnosis is the detection of pathogens through blood cultures obtained from multiple sites. Persistent bacteremia often indicates ongoing intravascular infection or infection associated with intravascular devices, whereas intermittent bacteremia typically reflects an extravascular source of infection.⁴ The incidence of BSIs is estimated to range from 100 to 200 cases per 100,000 person-years, with higher rates observed in critically ill patients, particularly those in ICUs, where the incidence can reach up to 500 cases per 100,000 person-years. The population-based estimated incidence rate of BSI (1781/100,000 person-years) was highest among persons ≥ 80 years in a population-based study from southern Sweden.⁵ The case-fatality rate of BSIs generally ranges between 20% and 40%, with elderly and critically ill patients experiencing mortality rates exceeding 50%. Prognosis varies significantly depending on the causative pathogen; fungal infections are associated with the highest mortality rates (40–60%), followed by Gram-negative bacterial infections, while Gram-positive bacterial infections tend to have relatively lower mortality rates.^{6–8}

Biomarkers are important in the prognostic assessment of inpatients with BSI. It has been suggested that serum procalcitonin was a sensitive and specific predictor of 28-day mortality in people over 65 years of age.⁹ Particularly, inflammation-related biomarkers are strongly related to mortality of BSI. Results of a retrospective cohort study based on the MIMIC-IV database suggest that indicators of immune inflammation were associated with in-hospital mortality in critically ill patients.¹⁰ Among various inflammation-related biomarkers, researchers have focused on whole blood inflammatory indicators including neutrophils and lymphocytes, and the association of composite indicators such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte-ratio (PLR) with a variety of diseases has also been explored subsequently.^{11,12} For inpatients with BSI and sepsis, NLR and PLR have been found to be associated with the poor prognosis, including 28-days and in-hospital mortality.^{13–15} In addition, a novel biomarker called neutrophil percentage-to-albumin ratio (NPAR), reflects the body's level of inflammation and immunity by combining neutrophil and albumin.¹⁶ Recent studies have focused on the relationship between NPAR and various diseases or poor prognosis, NPAR was reported to be strongly associated with all-cause mortality or cardiovascular disease-related mortality in the general population and has some predictive value for the risk of mortality in patients with sepsis.^{17,18}

However, there are no studies that have explored the association of NPAR, NLR and PLR with in-hospital mortality in older patients with BSI. Therefore, this study was conducted to estimate the predictive value of NPAR for in-hospital mortality in older patients with BSI, and make comparison with NLR and PLR.

Materials and Methods

Study Population

This retrospective study included older patients over 60 years of age who were hospitalized with BSI from December 2011 to January 2024 in a healthcare center in Beijing, China. Healthcare-associated bloodstream infections (BSIs) were defined as the first positive blood culture obtained at least 48 hours after admission, with no evidence of infection present at the time of admission.^{19,20} Patients with missing information on laboratory tests, including neutrophils, lymphocytes, albumin and platelets, were excluded ($n = 16$), and a total of 511 study participants were finally included. This study was exempt from informed consent as it was a retrospective analysis and did not involve patients' private information. This study was ethically approved by the Ethical Committee of Chinese PLA General Hospital (S2024-359-02). The study was conducted in accordance with the Declaration of Helsinki.

Data Collection

A real-time nosocomial infection surveillance system (RT-NISS) was used to collect information of HAIs in hospitalized patients and to screen inpatients who developed BSI. RT-NISS has been shown by several studies to accurately collect and assess information on HAIs in patients.^{21–23} Furthermore, clinically relevant information about inpatients was provided by the hospital information system and the electronic medical record system, including the following: 1) basic information: age (continuous), gender (male or female), and hospitalize department (internal medicine or surgery medicine); 2) clinical information: smoking (yes or no), diabetes (yes or no), hypertension (yes or no), coronary disease (yes or no), number of

operations (0, 1 or ≥ 2), intensive care unit (ICU) admission (yes or no), dialysis (yes or no), days of ventilator (0, 1–30, 31–90, or >90), days of central venous catheter (0, 1–60, 61–90, or >90), days of urinary catheter (0, 1–60, 61–90, or >90), chemotherapy or radiotherapy (yes or no), blood transfusion (yes or no), and combination of antibacterial drug (yes or no); 3) laboratory test indicators: neutrophil percentage (%), lymphocytes percentage, platelet count ($10^9/L$), and serum albumin levels (g/L); 4) length of hospital stay (continuous) and discharge outcome (death or survival).

Definition of Study Outcome

In this study, we defined in-hospital mortality, namely the death occurring from any cause during hospitalization, as the research outcome. The electronic medical record system was used to access whether deaths occurred during the study subjects' hospitalization. Survival status was defined if the inpatient remained alive until discharge.

Measurement of NLR, PLR and NPAR

Laboratory test indicators were tested and evaluated by the hospital's laboratory department, and were selected from the patient's most recent test results prior to BSI. NLR for each inpatients was calculated as the absolute neutrophil counts divided by the absolute lymphocyte counts. By dividing the platelet counts by the absolute lymphocyte counts, the PLR was computed. The formula for the calculation of NPAR was as follows: $NPAR = \text{neutrophil percentage (\%)} \times 100 / \text{albumin (g/dL)}$. To explore the association of NLR, PLR and NPAR with in-hospital mortality, the NLR, PLR and NPAR were treated not only as continuous variables, but also as categorical variables, expressed as tertiles.

Statistical Analysis

All data processing and analysis were conducted by the R software (version 4.1.3). Continuous variables were expressed as mean and standard deviation (SD) if they were normally distributed, otherwise they were expressed as median and interquartile range (IQR). The Student's *t*-test and Wilcoxon rank sum test were used for comparisons of continuous variables between the death and survival groups. Categorical variables were expressed as frequencies and percentages, and comparisons between groups were made using the Chi-square test or Fisher's exact test. The study subjects were divided into three groups according to the tertiles of NLR, PLR and NPAR respectively, and the differences of in-hospital mortality among the different groups were analyzed and compared by using Kaplan-Meier curves and Log rank test. Multivariate Cox regression analysis was performed to study the associations between in-hospital mortality and NLR, PLR and NPAR, and results were reported as hazard ratio (HR) with its 95% confidence interval (CI). Furthermore, three regression models were conducted to adjust for confounding covariates as following: 1) model 1 adjusted for none variables; 2) model 2 adjusted for age (continuous) and gender; 3) model 3 further adjusted for statistically significant variables in the univariate analysis based on Model 2. The restricted cubic spline (RCS) analysis was used to explore the dose-response relationships between in-hospital mortality and NPAR, NLR and PLR. The receiver operating characteristics (ROC) curve analysis and the area under the ROC curve (AUC) with its 95% CI were used to investigate the predictive value of NPAR, NLR and PLR for in-hospital mortality. In addition, study participants were divided into two groups (≤ 90 or >90 years) based on age, and subgroup analysis was conducted to explore the association between biomarkers and death in different age groups. The *P*-value was set at two side, and a *P*-value of less than 0.05 was considered statistically significant.

Results

Characteristics of the Study Participants

A total of 511 inpatients aged 60 years or older with BSI during hospitalization were included in this study. Among the 511 participants, there were 85 deaths (16.6%) and 426 patients survived (83.4%), summarized in Table 1. The mean (\pm SD) age of the study participants was 89.9 ± 8.5 years and there was no significant difference in age between the death and survival groups (90.1 vs 89.2 , $P = 0.381$). Most of the study subjects were male (97.1%) and mostly were admitted in the internal medicine department (90.0%). No significant difference was found between the death and survival groups in smoking, diabetes, hypertension, coronary disease, number of operations, ICU admissions, dialysis, and blood transfusion (all $P > 0.05$).

Table 1 Baseline Characteristics of Study Participants

Characteristic	Overall (n = 511)	Survive (n = 426)	Death (n = 85)	P value
Age, year (mean±SD)	89.9±8.5	90.1±8.2	89.2±9.7	0.381
Gender, n (%)				
Female	15 (2.9)	11 (2.6)	4 (4.7)	0.479
Male	496 (97.1)	415 (97.4)	81 (95.3)	
Department, n (%)				
Internal medicine	460 (90.0)	384 (90.1)	76 (89.4)	0.995
Surgery medicine	51 (10.0)	42 (9.9)	9 (10.6)	
Smoking, n (%)				
No	313 (61.3)	262 (61.5)	51 (60.0)	0.891
Yes	198 (38.7)	164 (38.5)	34 (40.0)	
Diabetes, n (%)				
No	293 (57.3)	251 (58.9)	42 (49.4)	0.134
Yes	218 (42.7)	175 (41.1)	43 (50.6)	
Hypertension, n (%)				
No	123 (24.1)	103 (24.2)	20 (23.5)	0.997
Yes	388 (75.9)	323 (75.8)	65 (76.5)	
Coronary disease, n (%)				
No	242 (47.4)	201 (47.2)	41 (48.2)	0.953
Yes	269 (52.6)	225 (52.8)	44 (51.8)	
Number of operations, n (%)				
0	332 (65.0)	271 (63.6)	61 (71.8)	0.175
1	111 (21.7)	99 (23.2)	12 (14.1)	
≥2	68 (13.3)	56 (13.1)	12 (14.1)	
ICU, n (%)				
No	432 (84.5)	360 (84.5)	72 (84.7)	0.998
Yes	79 (15.5)	66 (15.5)	13 (15.3)	
Dialysis, n (%)				
No	492 (96.3)	411 (96.5)	81 (95.3)	0.831
Yes	19 (3.7)	15 (3.5)	4 (4.7)	
Days of ventilator, n (%)				
0	251 (49.1)	228 (53.5)	23 (27.1)	<0.001
1-30	58 (11.4)	22 (5.2)	36 (42.4)	
31-90	106 (20.7)	81 (19.0)	25 (29.4)	
>90	96 (18.8)	95 (22.3)	1 (1.2)	
Days of central venous catheter, n (%)				
0	83 (16.2)	74 (17.4)	9 (10.6)	<0.001
1-60	127 (24.9)	79 (18.5)	48 (56.5)	
61-90	137 (26.8)	116 (27.2)	21 (24.7)	
>90	164 (32.1)	157 (36.9)	7 (8.2)	
Days of urinary catheter, n (%)				
0	189 (37.0)	163 (38.3)	26 (30.6)	<0.001
1-60	97 (19.0)	57 (13.4)	40 (47.1)	
61-90	89 (17.4)	75 (17.6)	14 (16.5)	
>90	136 (26.6)	131 (30.8)	5 (5.9)	
Chemotherapy or radiotherapy, n (%)				
No	458 (89.6)	388 (91.1)	70 (82.4)	0.027
Yes	53 (10.4)	38 (8.9)	15 (17.6)	
Blood transfusion, n (%)				
No	311 (60.9)	264 (62.0)	47 (55.3)	0.303
Yes	200 (39.1)	162 (38.0)	38 (44.7)	

(Continued)

Table 1 (Continued).

Characteristic	Overall (n = 511)	Survive (n = 426)	Death (n = 85)	P value
Combination of antibacterial drug, n (%)				
No	71 (13.9)	67 (15.7)	4 (4.7)	0.012
Yes	440 (86.1)	359 (84.3)	81 (95.3)	
Length of hospital stay (median [IQR])	90.0 (65.4, 96.0)	91.0 (82.1, 98.0)	56.4 (34.2, 78.1)	<0.001

Abbreviations: IQR, interquartile range; SD, Standard Deviation; ICU, Intensive Care Unit.

However, there were significant differences between the death and survival groups in the days of ventilator, days of central venous catheter, and days of urinary catheter (all $P < 0.05$). In addition, the proportion of chemotherapy or radiotherapy, and combination of antibacterial drug was higher in the death group than in the survival group (all $P < 0.05$).

Comparison of NPAR NLR and PLR Between Death and Survival Groups

In terms of biomarkers, there were significant differences between the dead and survival groups in the neutrophil percentage, lymphocyte percentage, platelet count, and albumin levels, as shown in [Table 2](#). Furthermore, both NPAR and NLR were significantly higher in the death group than in the survival group (all $P < 0.001$), but there was no significant difference in PLR ($P = 0.761$). After viewing NPAR and NLR as tertiles, it could be seen that the third tertile (T3) has a higher mortality rate than the first tertiles (T1) and second tertiles (T2) in [Figure 1](#). In addition, as shown in [Figure 2](#), RCS analysis showed that there was no non-linear relationship between NPAR, PLR and in-hospital mortality (P for non-linear > 0.05). However, a non-linear dose-response relationship was observed between NLR and in-hospital mortality (P for non-linear < 0.05).

Associations Between NPAR, NLR, PLR and in-Hospital Mortality in Older Patients with BSI

As shown in [Figure 3](#), the Kaplan-Meier curves analysis showed that when NPAR and NLR were divided into tertiles group, there were significant differences in the survival probabilities among the three groups, with the lowest survival

Table 2 Comparison of Blood Inflammation Biomarker in the Study Patients by Survival Status

Characteristic	Survive (n = 426)	Death (n = 85)	P value
Neutrophil percentage (median [IQR])	0.7 (0.6, 0.7)	0.8 (0.6, 0.9)	<0.001
Lymphocytes percentage (median [IQR])	0.2 (0.2, 0.3)	0.2 (0.1, 0.2)	<0.001
Platelet count, $10^9/L$ (median [IQR])	162.5 (118.0, 215.0)	141.0 (91.0, 180.0)	0.001
Albumin, g/L (median [IQR])	34.5 (31.9, 37.1)	33.2 (30.3, 35.9)	0.004
NPAR (median [IQR])	19.0 (16.3, 22.0)	22.7 (18.6, 26.6)	<0.001
T1 (≤ 17.5)	151 (35.4)	18 (21.2)	<0.001
T2 (17.5–21.3)	151 (35.4)	17 (20.0)	
T3 (> 21.3)	124 (29.1)	50 (58.8)	
NLR (median [IQR])	3.1 (2.1, 4.7)	4.8 (3.0, 10.8)	<0.001
T1 (≤ 2.5)	152 (35.7)	17 (20.0)	<0.001
T2 (2.5–4.3)	147 (34.5)	21 (24.7)	
T3 (> 4.3)	127 (29.8)	47 (55.3)	
PLR (median [IQR])	125.6 (85.3, 176.2)	123.1 (87.6, 181.4)	0.761
T1 (≤ 99.3)	140 (32.9)	29 (34.1)	0.886
T2 (99.3–155.0)	142 (33.3)	26 (30.6)	
T3 (> 155.0)	144 (33.8)	30 (35.3)	

Abbreviations: IQR, interquartile range; NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

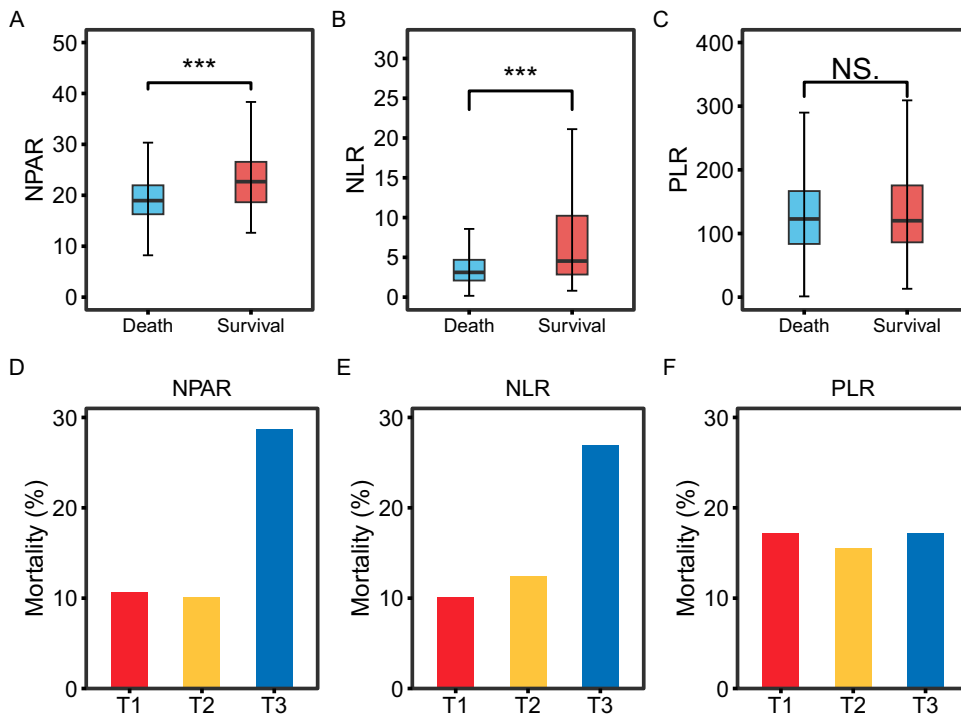


Figure 1 The blood inflammation biomarkers level and in-hospital mortality in older patients with bloodstream infections. **(A)** Boxplots of NPAR in death and survival group. **(B)** Boxplots of NLR in death and survival group. **(C)** Boxplots of PLR in death and survival group. **(D)** In-hospital mortality of older patients with bloodstream infections by tertile of NPAR. **(E)** In-hospital mortality of older patients with bloodstream infections by tertile of NLR. **(F)** In-hospital mortality of older patients with bloodstream infections by tertile of PLR. The main body of a boxplot covers the range between the lower and upper quartiles. The black horizontal line shows the position of the mean. *P*-values were calculated by Wilcoxon test. ****P* < 0.001.

Abbreviations: NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NS, no significant.

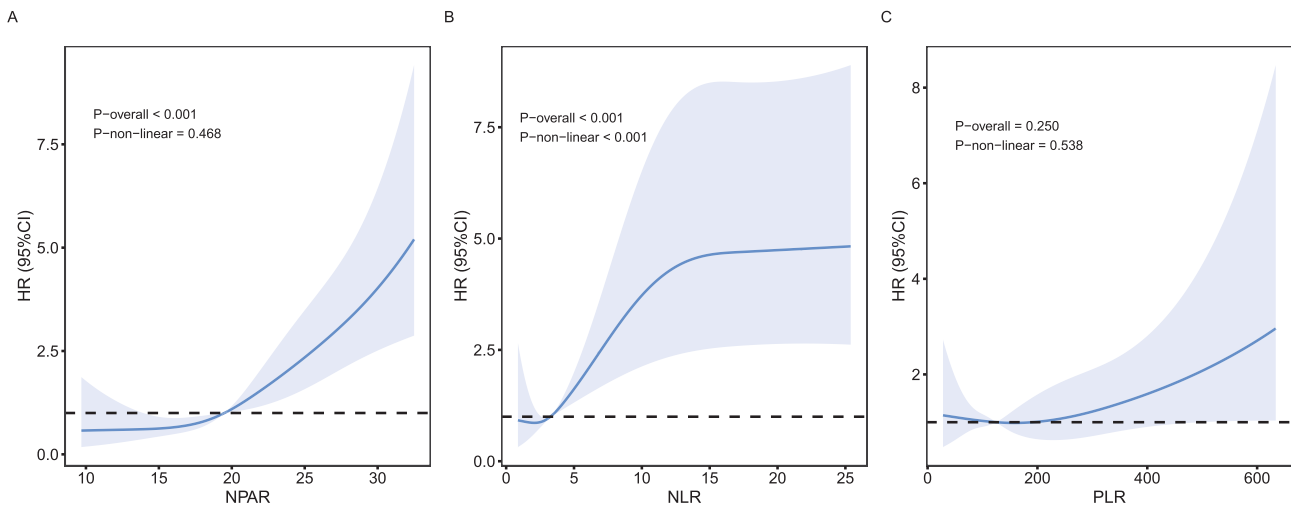
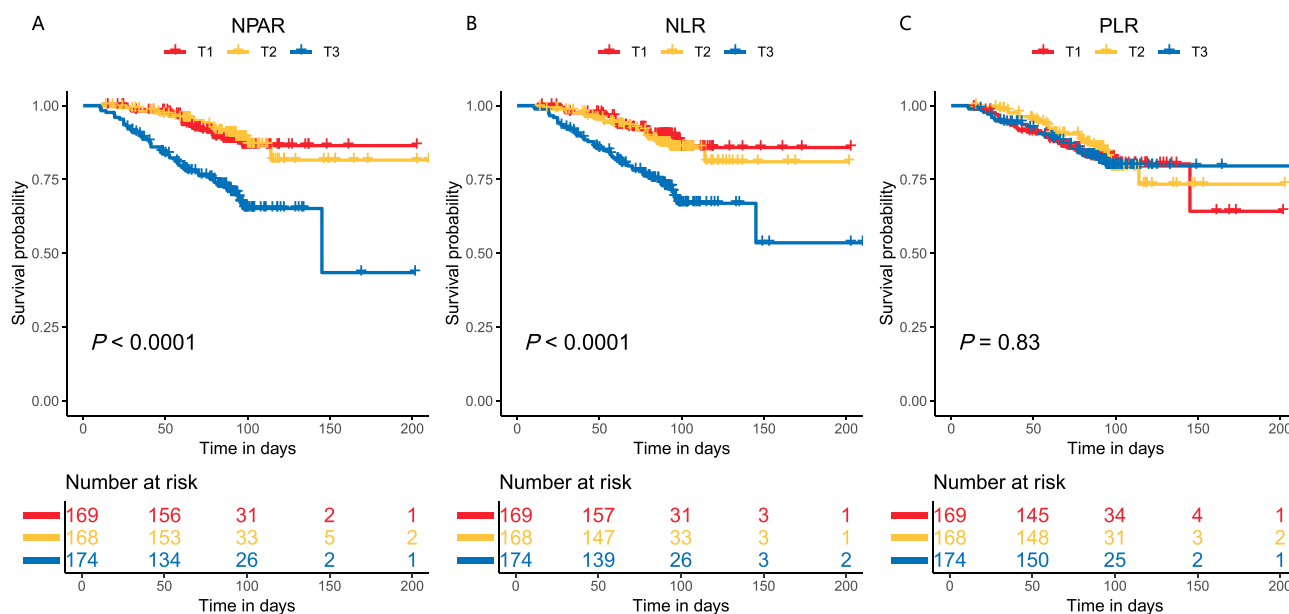


Figure 2 Dose-response relationships between blood inflammation biomarkers and in-hospital mortality in older patients with bloodstream infections. **(A)** Restricted cubic spline analysis of the relationship between NPAR and in-hospital mortality. **(B)** Restricted cubic spline analysis of the relationship between NLR and in-hospital mortality. **(C)** Restricted cubic spline analysis of the relationship between PLR and in-hospital mortality.

Abbreviations: NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; HR, hazard ratios; CI, confidence interval.

probability in the T3 group (all *P* < 0.001). However, no difference was observed in the survival probability between three groups of PLR (*P* = 0.83). **Table 3** shows the results of the Cox regression analysis. When NPAR was considered a continuous variable, each unit of elevated NPAR was associated with an increased risk of in-hospital mortality after adjusting for days of ventilator, days of central venous catheter, days of urinary catheter, chemotherapy or radiotherapy,



and combination of drug (aHR = 1.08, 95% CI: 1.05–1.12, $P < 0.001$). Furthermore, when NPAR was divided into three groups by tertiles, the third tertile of NPAR (T3) was associated with higher risk of in-hospital mortality, compared to the first tertile of NPAR (T1) (aHR = 3.36, 95% CI: 1.87–6.02, $P < 0.001$). In terms of NLR, there was no significant

Table 3 Associations of NPAR, NLR, and PLR with in-Hospital Mortality in Older Patients with Bloodstream Infections

	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
NPAR (continuous)	1.13 (1.09, 1.17)	<0.001	1.13 (1.09, 1.17)	<0.001	1.08 (1.05, 1.12)	<0.001
NPAR (tertiles)						
T1	Reference		Reference		Reference	
T2	0.91 (0.47, 1.77)	0.783	0.85 (0.44, 1.66)	0.636	1.87 (0.90, 3.90)	0.095
T3	3.14 (1.83, 5.39)	<0.001	3.07 (1.79, 5.27)	<0.001	3.36 (1.87, 6.02)	<0.001
P for trend	<0.001		<0.001		<0.001	
NLR (continuous)	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.06)	<0.001	1.01 (1.00, 1.03)	0.200
NLR (tertiles)						
T1	Reference		Reference		Reference	
T2	1.25 (0.66, 2.37)	0.494	1.23 (0.65, 2.33)	0.531	1.32 (0.68, 2.59)	0.415
T3	3.06 (1.76, 5.34)	<0.001	2.94 (1.68, 5.17)	<0.001	2.77 (1.55, 4.95)	<0.001
P for trend	<0.001		<0.001		<0.001	
PLR (continuous)	1 (1.00, 1.00)	0.776	1 (1.00, 1.00)	0.753	1.00 (1.00, 1.00)	0.736
PLR (tertiles)						
T1	Reference		Reference		Reference	
T2	0.88 (0.52, 1.49)	0.635	0.84 (0.49, 1.42)	0.508	0.72 (0.41, 1.27)	0.257
T3	1.03 (0.62, 1.71)	0.917	0.96 (0.57, 1.61)	0.874	0.87 (0.50, 1.52)	0.627
P for trend	0.915		0.881		0.631	

Note: Model 1 adjusted for none. Model 2 adjusted for age (continuous) and gender. Model 3 further adjusted for days of ventilator, days of central venous catheter, days of urinary catheter, chemotherapy or radiotherapy, and combination of antibacterial drug.

Abbreviations: NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; HR, hazard ratios; CI, confidence interval.

Table 4 The Predictive Values of NPAR, NLR, PLR, Neutrophil Percentage and Albumin for in-Hospital Mortality

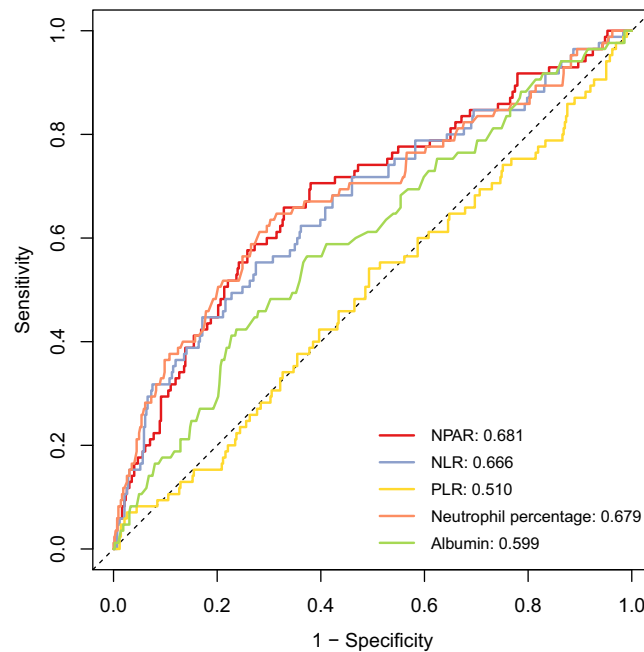
	AUC (95% CI)	Sensitivity	Specificity	Cut-off Value
NPAR	0.681 (0.615, 0.747)	65.9%	67.1%	20.6
NLR	0.666 (0.598, 0.733)	55.3%	72.5%	4.4
PLR	0.510 (0.420, 0.559)	54.1%	50.7%	125.0
Neutrophils percentage	0.679 (0.610, 0.747)	64.7%	68.5%	0.7
Albumin	0.599 (0.532, 0.666)	56.5%	62.7%	33.5

Abbreviations: NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AUC, the area under the receiver operating characteristic curve; CI, confidence interval.

difference in the association between NLR and in-hospital mortality when NLR was considered a continuous variable (aHR = 1.01, 95% CI: 1.00–1.03, $P = 0.200$). But when NLR was considered as tertiles groups, T3 group of NLR was associated with increased risk of in-hospital mortality, compared to the T1 group of NPAR (aHR = 2.77, 95% CI: 1.55–4.95, $P < 0.001$). However, there was no significant difference in the associations between PLR and in-hospital mortality in older patients with BSI (aHR = 1.00, 95% CI: 1.00–1.00, $P = 0.736$).

ROC Analysis of NPAR, NLR and PLR in Predicting in-Hospital Mortality

The predictive value of different biomarkers on in-hospital mortality was shown in demonstrated in Table 4 and Figure 4. Compared with other biomarkers, NPAR demonstrated the highest value of AUC (AUC = 0.681, 95% CI: 0.615–0.747) and the highest value of sensitivity (65.9%), indicating that NPAR maybe a better indicator to predict the in-hospital mortality for older patients with BSI. However, NLR exhibited the highest value of specificity (72.5%) compared to NPAR and other biomarkers.

**Figure 4** ROC curve analysis for blood inflammation biomarkers to predict the in-hospital mortality in older patients with bloodstream infections.

Abbreviations: ROC, Receiver operating characteristic; NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

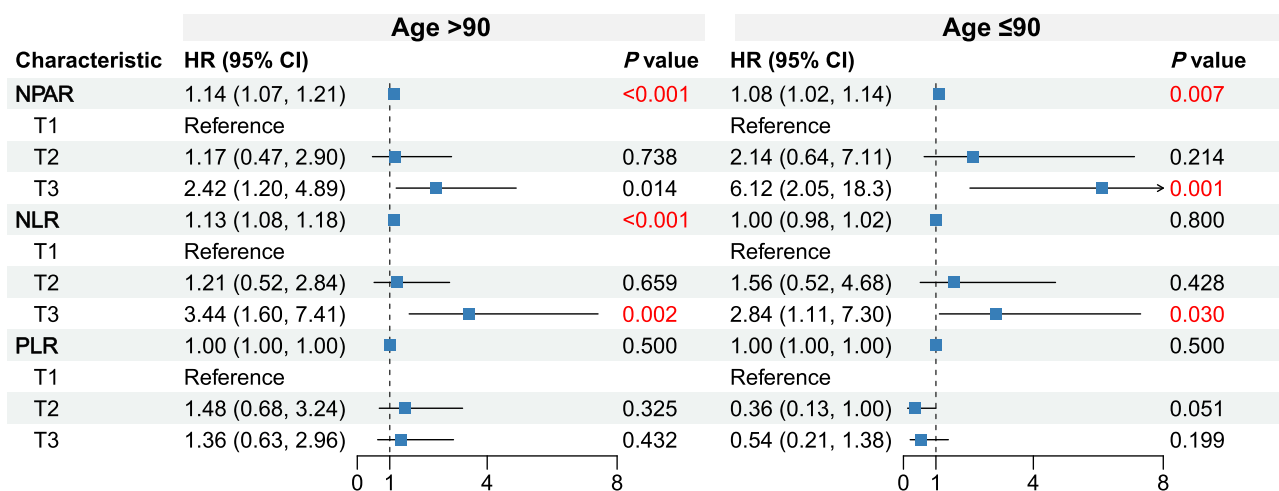


Figure 5 Subgroup analysis of in-hospital mortality by age. Multivariable analyses were adjusted for age (continuous) and gender, days of ventilator, days of central venous catheter, days of urinary catheter, chemotherapy or radiotherapy, and combination of drug. Red *P* values indicate significance.

Abbreviations: NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; HR, hazard ratios; CI, confidence interval.

Subgroup Analysis

Considering that the study population was all over 60 years old, subgroup analyses investigated deeply the association between NPAR and in-hospital mortality in older inpatients with BSI under different age subgroups (≤ 90 years group and > 90 years group). NPAR was associated with in-hospital mortality after adjusting for confounders, both in the > 90 and ≤ 90 age groups (Figure 5). Moreover, the T3 group was significantly associated with in-hospital mortality compared with the T1 group in both age > 90 and ≤ 90 groups. As for NLR, it was found that NLR was associated with in-hospital mortality in the > 90 age group, however no such association was found in the ≤ 90 age group. But when NLR was divided as a tertiles group, there was a significant increase for in-hospital mortality in the T3 group compared to the T1 group, both in the age > 90 and ≤ 90 groups. In terms of PLR, there was no significant association between PLR and in-hospital mortality in older inpatients with BSI.

Discussion

The identification of potential biomarkers for the poor prognosis of inpatients with BSI is of great clinical importance, especially considering the high risk of in-hospital mortality in older patients with BSI. In this study, we focused on the potential association of biomarkers with in-hospital mortality in older patients with BSI, and biomarkers were derived from blood routine laboratory tests, in particular NPAR, NLR and PLR. In addition, we compared the predictive and diagnostic value of NPAR, NLR and PLR for in-hospital mortality in older patients with BSI.

Inflammation serves an important role in the development and prognosis of BSI, which is why indicators of inflammation can demonstrate predictive value of in-hospital mortality for older patients with BSI. BSI releases massive pro-inflammatory cytokines through immune activation during disease progression, leading to a systemic inflammatory response.¹⁴ Especially in severe cases, it causes sepsis and multi-organ failure, which can be fatal consequently. However, there may be a delay in neutrophil apoptosis among some patients with complicated BSI that progress to sepsis.²⁴ It suggests that neutrophil indicator alone has limited predictive value for the death prognosis of patients with BSI.

NLR and PLR were considered to be indicators of the degree of systemic inflammation and immune status. Previous literature has reported that NLR and PLR were associated with all-cause mortality in the general population or older adults.^{25–27} In the present study, we found that NLR and PLR were not independent risk factors for in-hospital mortality in older patients with BSI and had low predictive value for in-hospital mortality. However, the results of a retrospective study in China suggested that NLR was associated with 28-day mortality in patients with BSI and was of great clinical utility in assessing the degree of disease and prognosis in patients with BSI and sepsis.¹³ The opposite conclusion was reported in another study, also from China, which indicated that the NLR was of limited value in predicting 28-day mortality in patients with BSI.²⁸ The

results were inconsistent in different studies, mainly due to differences in the study population and definition of outcomes. In this study, we concluded that the predictive value of NLR and PLR for in-hospital mortality in older patients with BSI was limited. Further study is needed to validate the results in the future. RCS analysis indicated that the relationship between NLR and mortality was non-linear, and this suggested that there was a complex exposure-response relationship between NLR and mortality. Large-scale studies are needed in the future to verify this association.

In this study, NPAR was found to be significantly associated with in-hospital mortality and had a higher predictive value for in-hospital mortality than other biomarkers. Previous studies have shown that NPAR was associated with stroke-associated infection and stroke-associated pneumonia, with some predictive value.^{29,30} There are only two studies reported on the association between NPAR and mortality in patients with sepsis until now, finding that an elevated NPAR was related to an increased risk of death, which was similar to the results of our study.^{18,31} NPAR is a composite marker of systemic inflammation and immune by combining neutrophil percentage and serum albumin level.^{16,17} Neutrophils is a vital indicator of immune function, while albumin reflects the nutritional status, and albumin is proven to have interactions with some inflammatory mediators.^{3,32–34} An increase in NPAR indicates elevated neutrophils percentage or declining albumin level, suggesting that the organism is in an inflammatory state or immune deficiency. And this causes the body to be less resistant to BSI for older inpatients, worsening the damage caused by BSI and causing an increased risk of in-hospital mortality.³ A study from NHANES in the United States reported that NPAR was associated with all-cause mortality in general population, with an HR of 1.46 (95% CI: 1.33–1.61).¹⁷ Another multicentre retrospective study from China found that NPAR was associated with one-year mortality in older patients with hip fractures, with a good sensitivity and specificity.³⁵ Although this study also found that NPAR was associated with in-hospital mortality in older patients with BSI, and had a higher predictive value compared to other indicators. However, considering that the AUC value of NPAR alone was still lower than 0.7, further studies combining NPAR with other indicators are needed in the future. However, we still believed in this study that NPAR, as a convenient and easily accessible biomarker, can be applied even in some areas with insufficient medical resources, which greatly increased its clinical value. What's more, NPAR takes into account the impact of changes in neutrophil percentage and albumin on patients, especially the body of elderly inpatients is more sensitive to such changes. This is the reason why the diagnostic and predictive efficacy of NPAR is higher than that of NLR, PLR, albumin and neutrophil percentage.

Some limitations still exist in this study. Firstly, this study was a single-centre retrospective study, and few hospitals could collect such a large number of older inpatients with BSI. Whether the results of this study can be applied to other regions or hospitals remains to be investigated. Secondly, most of the elderly patients included in this study were male, and further studies are needed to increase representation. Thirdly, older patients with BSI may developed a series of complications, and the potential impact of these complications on in-hospital mortality could not be completely ruled out. Finally, the NPAR was calculated based on a single measurement before BSI, thus the influence of dynamic changes in these blood routine indicator parameters over time may be ignored.

Conclusion

Elevated NPAR was associated with higher risk of in-hospital mortality in older patients with BSI, suggesting that NPAR has a certain clinical value as a convenient and simple indicator. However, the prediction accuracy of NPAR remains to be verified. Further prospective studies should be conducted to explore the predictive value of NPAR combining with other clinical indicators on in-hospital mortality in older patients with BSI.

Abbreviations

NPAR, Neutrophil percentage-to-albumin ratio; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte; BSI, bloodstream infections; HAIs, healthcare associated-infections; RCS, Restricted cubic spline; ROC, Receiver operating characteristics; HR, hazard ratio;; CI, confidence interval;; AUC, area under the ROC curve.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author (Yingzhen Du) upon reasonable request.

Ethics Approval and Informed Consent

This study was ethically approved by the Ethical Committee of Chinese PLA General Hospital (S2024-359-02), and was exempt from informed consent as it was a retrospective analysis and did not involve patients' private information. The study was conducted in accordance with the Declaration of Helsinki.

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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.

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Disclosure

The authors declare that there is no conflict of interest in this work.

References

- Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
- Laupland KB, Church DL. Population-based epidemiology and microbiology of community-onset bloodstream infections. *Clin Microbiol Rev*. 2014;27(4):647–649. doi:10.1128/CMR.00002-14
- Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med*. 2002;28(2):108–121. doi:10.1007/s00134-001-1143-z
- Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the infectious diseases society of America and the American society for microbiology. *Clin Infect Dis*. 2018;67(6):e1–e94. doi:10.1093/cid/ciy381
- Ljungquist O, Blomstergen A, Merkel A, Sunnerhagen T, Holm K, Torisson G. Incidence, aetiology and temporal trend of bloodstream infections in southern Sweden from 2006 to 2019: a population-based study. *Euro Surveill*. 2023;28(10):2200519. doi:10.2807/1560-7917.ES.2023.28.10.2200519
- Kollef M, Micek S, Hampton N, et al. Septic shock attributed to *Candida* infection: importance of empiric therapy and source control. *Clin Infect Dis*. 2012;54(12):1739–1746. doi:10.1093/cid/cis305
- Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1552–1562. doi:10.1007/s00134-020-06151-x
- Markwart R, Saito H, Harder T, et al. Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. *Intensive Care Med*. 2020;46(8):1536–1551. doi:10.1007/s00134-020-06106-2
- Shokouhi B, Bookani KR, Ghasemi H, Khalouei M, Rezaei NJ, Samani SM. Diagnostic and prognostic performances of serum procalcitonin in patients with bloodstream infections: a parallel, case-control study comprising adults and elderly. *Rev Assoc Med Bras*. 2017;63(6):521–526. doi:10.1590/1806-9282.63.06.521
- Jiang D, Bian T, Shen Y, Huang Z. Association between admission systemic immune-inflammation index and mortality in critically ill patients with sepsis: a retrospective cohort study based on MIMIC-IV database. *Clin Exp Med*. 2023;23(7):3641–3650. doi:10.1007/s10238-023-01029-w
- Gong P, Liu Y, Gong Y, et al. The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke. *J Neuroinflammation*. 2021;18(1):51. doi:10.1186/s12974-021-02090-6
- Zhang YR, Wang JJ, Chen SF, et al. Peripheral immunity is associated with the risk of incident dementia. *Mol Psychiatry*. 2022;27(4):1956–1962. doi:10.1038/s41380-022-01446-5
- Liang P, Yu F. Value of CRP, PCT, and NLR in prediction of severity and prognosis of patients with bloodstream infections and sepsis. *Front Surg*. 2022;9:857218. doi:10.3389/fsurg.2022.857218
- Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med*. 2020;38(3):641–647. doi:10.1016/j.ajem.2019.10.023
- Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases. *Int J Mol Sci*. 2022;23(7):3636. doi:10.3390/ijms23073636

16. Wu CC, Wu CH, Lee CH, Cheng CI. Association between neutrophil percentage-to-albumin ratio (NPAR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and long-term mortality in community-dwelling adults with heart failure: evidence from US NHANES 2005-2016. *BMC Cardiovasc Disord.* 2023;23(1):312. doi:10.1186/s12872-023-03316-6
17. Liu Y, Qiu Z, Shen G, et al. Associations between neutrophil-percentage-to-albumin ratio level and all-cause mortality and cardiovascular disease-cause mortality in general population: evidence from NHANES 1999-2010. *Front Cardiovasc Med.* 2024;11:1393513. doi:10.3389/fcvm.2024.1393513
18. Hu C, He Y, Li J, et al. Association between neutrophil percentage-to-albumin ratio and 28-day mortality in Chinese patients with sepsis. *J Int Med Res.* 2023;51(6):3000605231178512. doi:10.1177/03000605231178512
19. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control.* 1988;16(3):128–140. doi:10.1016/0196-6553(88)90053-3
20. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control.* 2008;36(5):309–332. doi:10.1016/j.ajic.2008.03.002
21. Du M, Xing Y, Suo J, et al. Real-time automatic hospital-wide surveillance of nosocomial infections and outbreaks in a large Chinese tertiary hospital. *BMC Med Inform Decis Mak.* 2014;14:9. doi:10.1186/1472-6947-14-9
22. Yu Z, Li X, Lv C, et al. Epidemiological characteristics of ventilator-associated pneumonia in neurosurgery: a 10-year surveillance study in a Chinese tertiary hospital. *Infect Med.* 2024;3(3):100128. doi:10.1016/j.imj.2024.100128
23. Yu ZH, Du MM, Zhang X, et al. The impact of preoperative biliary drainage on postoperative healthcare-associated infections and clinical outcomes following pancreaticoduodenectomy: a ten-year retrospective analysis. *BMC Infect Dis.* 2024;24(1):361. doi:10.1186/s12879-024-09246-8
24. Taneja R, Parodo J, Jia SH, Kapus A, Rotstein OD, Marshall JC. Delayed neutrophil apoptosis in sepsis is associated with maintenance of mitochondrial transmembrane potential and reduced caspase-9 activity. *Crit Care Med.* 2004;32(7):1460–1469. doi:10.1097/01.CCM.0000129975.26905.77
25. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. *Sci Rep.* 2021;11(1):464. doi:10.1038/s41598-020-79431-7
26. Gu L, Xia Z, Qing B, et al. The core role of neutrophil-lymphocyte ratio to predict all-cause and cardiovascular mortality: a research of the 2005-2014 national health and nutrition examination survey. *Front Cardiovasc Med.* 2022;9:847998. doi:10.3389/fcvm.2022.847998
27. Tang Y, Zhai Y, Song W, et al. Association between complete blood count-derived inflammatory markers and the risk of frailty and mortality in middle-aged and older adults. *Front Public Health.* 2024;12:1427546. doi:10.3389/fpubh.2024.1427546
28. Wei Z, Zhao L, Yan J, et al. Dynamic monitoring of neutrophil/lymphocyte ratio, APACHE II score, and SOFA score predict prognosis and drug resistance in patients with *Acinetobacter baumannii-calcoaceticus* complex bloodstream infection: a single-center retrospective study. *Front Microbiol.* 2024;15:1296059. doi:10.3389/fmicb.2024.1296059
29. Zhang H, Wu T, Tian X, Lyu P, Wang J, Cao Y. High neutrophil percentage-to-albumin ratio can predict occurrence of stroke-associated infection. *Front Neurol.* 2021;12:705790. doi:10.3389/fneur.2021.705790
30. Zawiah M, Khan AH, Abu Farha R, et al. Predictors of stroke-associated pneumonia and the predictive value of neutrophil percentage-to-albumin ratio. *Postgrad Med.* 2023;135(7):681–689. doi:10.1080/00325481.2023.2261354
31. Gong Y, Li D, Cheng B, Ying B, Wang B. Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock. *Epidemiol Infect.* 2020;148:e87. doi:10.1017/S0950268820000771
32. Muszynski JA, Thakkar R, Hall MW. Inflammation and innate immune function in critical illness. *Curr Opin Pediatr.* 2016;28(3):267–273. doi:10.1097/MOP.0000000000000352
33. López-Arredondo A, Cruz-Cardenas JA, Cázares-Preciado JA, Timmins NE, Brunck ME. Neutrophils, an emerging new therapeutic platform. *Curr Opin Biotechnol.* 2024;87:103106. doi:10.1016/j.copbio.2024.103106
34. Cabrerizo S, Cuadras D, Gomez-Busto F, Artaza-Artabe I, Marín-Ciancas F, Malafarina V. Serum albumin and health in older people: review and meta analysis. *Maturitas.* 2015;81(1):17–27. doi:10.1016/j.maturitas.2015.02.009
35. Jiao S, Zhou J, Feng Z, et al. The role of neutrophil percentage to albumin ratio in predicting 1-year mortality in elderly patients with Hip fracture and external validation. *Front Immunol.* 2023;14:1223464. doi:10.3389/fimmu.2023.1223464

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