BMC Infectious Diseases

RESEARCH

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Association between neutrophil-platelet ratio and 28-day mortality in patients with sepsis: a retrospective analysis based on MIMIC-IV database

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Abstract

Background The immune system and inflammation are intimately linked to the pathophysiology of sepsis. The neutrophil–platelet ratio (NPR), associated with inflammation and immunology, may be useful in predicting sepsis outcomes. According to earlier research, the NPR is linked to the prognosis of several diseases. This study aimed to investigate the connection between the NPR and unfavorable outcomes in patients with sepsis.

Methods We retrieved patient clinical data from the Medical Information Mart for Intensive Care IV database (MIMIC-IV 2.2) based on the inclusion and exclusion criteria. The NPR quartile was used to divide the population into four groups. 28-day mortality was the main result, whereas 90-day mortality was the secondary result. The Cox regression model, Kaplan–Meier survival curve, and limited cubic spline were used to examine the associations between the NPR and the negative outcomes of sepsis. Subgroup analysis was also conducted. At the same time, we used Latent Class Trajectory Model (LCTM) to assess the trajectory of NPR within six days of ICU admission, and to assess the relationship between NPR trajectory and mortality at 28 and 90 days.

Results This study included 3339 patients. Quartile 4 had the greatest 28-day and 90-day mortality rates, according to the Cox regression model and Kaplan–Meier survival curve. A J-shaped relationship between the NPR and mortality was found in restricted cubic spline investigations. This means higher and lower NPRs were linked to higher mortality, with NPR = 3.81 as the tipping point. A total of 434 patients were included in the trajectory analysis, and three trajectory patterns were identified. Patients with sepsis had an increased mortality rate in the slow-decline group compared with the stable development group.

Conclusion The NPR has prognostic value for patients with sepsis, and there is a J-shaped relationship between the two variables. Patients with sepsis who have a slowly declining NPR have an increased mortality rate.

Clinical trial Not applicable.

Keywords Sepsis, Neutrophil-to-platelet ratio, MIMIC-IV, 28-day mortality, Trajectory

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Introduction

Sepsis is a life-threatening condition and one of the leading causes of death worldwide, and it is intimately associated with an aberrant immune response [1]. Despite advances in medical technology, the incidence of sepsis remains high [2]. The danger of death from sepsis is increasing rapidly [3]. Therefore, early detection and treatment are critical. Studying the risk variables associated with sepsis outcomes allows for the development of preventive interventions early on.

An abnormal immunological response and inflammation distinguish sepsis. Patients with sepsis have decreased numbers of B and T cells but increased levels of monocytes and neutrophils [4]. Neutrophils are the most numerous and fast-acting white blood cells in sepsis patients. They are a crucial part of the host's first line of defense against infection and maintain bactericidal action after cell death [5]. Platelets, as inflammatory cells, play a key role in generating inflammation, activating immune cells, and causing damage to numerous organs. Platelets have been linked to survival rates and the immunological state in sepsis patients [6–7]. Therefore, monocytes and platelets can reflect the inflammation and immunity of patients with sepsis and can be used to explore their relationships with prognosis.

The NPR is currently the subject of increasing research. It is a blood-based inflammatory biomarker frequently used to assess patient inflammation and immune function [8]. Research has shown that combining the neutrophil-lymphocyte ratio (NLR) and NPR can better predict 28-day mortality in patients with sepsis [9]. Based on the MIMIC-IV database, this study performed a secondary analysis to investigate the relationship between the NPR and poor outcomes in sepsis patients to advise clinical practice.

Methods

Database

The data for this study were derived from electronic health data in the Medical Information Mart for Intensive Care IV database (MIMIC-IV, version 2.2, data collected between 2008 and 2019). The MIMIC-IV database includes a large amount of information, such as demographics, vital signs, and test results of more than 50,000 patients in the Beth Israel Deacons Medical Center (BIDMC) intensive care unit in Boston, Massachusetts [10]. Since the patient information in the database is anonymous, informed consent was not needed. The author (ZJ) obtained access to the database (certification number: 12338709).

Participants

This study included patients with sepsis who met the definition of the Third International Consensus on Sepsis and Septic Shock (sepsis-3), with a Sequential Organ Failure Assessment (SOFA) score ≥ 2 and suspected infection during the intensive care unit (ICU) stay [11]. The exclusion criteria were age less than 18 years, ICU stay less than 24 h, and lack of neutrophil and platelet markers. In addition, malignant tumors and hematological diseases were excluded according to the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes (Supplementary Material 1). To reduce the deviation of multiple hospitalizations of the same patient, for patients who were admitted to the ICU multiple times, we chose only the information from the first admission.

Data extraction

We used PostgresSQL software (version 13.7.2) and Navicat Premium software (version 16) to extract demographic information (age, sex, body mass index (BMI)), vital signs (heart rate, respiration, body temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SpO2)), laboratory tests (white blood cell (WBC), platelet (PLT), neutrophil, lymphocyte, monocyte, oxygen partial pressure (PO2), lactic acid, blood urea nitrogen (BUN), potassium, sodium, calcium, blood glucose, creatinine, activated partial thromboplastin time (APTT)), comorbidities (congestive heart failure, peripheral vascular disease, chronic lung disease, diabetes, hypertension, acute kidney disease), scoring system (sequential organ failure assessment (SOFA), acute physiology score III (APSIII), Simplified Acute Physiological Score II (SAPSII)), interventions (ventilation, vasopressor, continuous renal replacement therapy (CRRT)) from the MIMIC-IV database. The scoring system selects the highest value within 24 h of admission to the ICU, and other data select the first measurement value within the first day of admission to the ICU. The NPR is defined as the ratio of neutrophils to platelets.

Grouping and outcomes

The primary outcome of this study was 28-day mortality, and the secondary outcome was 90-day mortality. Patients were divided into four groups according to the quartile of the NPR.

Statistical analysis

This study is retrospective, and we choose different statistical methods according to the different types of variables. The numerical variables are expressed as medians and quartiles and were analyzed using the Kruskal–Wallis test. Categorical variables are expressed as counts and percentages and were analyzed using the $\chi 2$ test. For missing variables, we exclude variables with missing values greater than 0.5 [12]. For variables with less than 50% missing data, we use the multiple imputation method.

The variance inflation factor (VIF) is used to delete the variables with a VIF greater than 5 to eliminate the influence of multicollinearity [13]. According to the log-rank test, Kaplan–Meier survival curves were used to compare the 28-day survival rates and 90-day survival rates among the four groups. The hazard ratio (HR) and 95% confidence interval (95% CI) of the NPR and death in patients with sepsis were assessed using a proportional hazard regression model (Cox regression model). Model I only includes NPR variables and does not adjust for covariates. Model II was adjusted for demographic variables (age, sex, BMI) and vital signs (heart rate, respiration, body temperature, SBP, DBP, and SpO2). Model III adds complications to Model II. A time-dependent receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity of the NPR in predicting 28-day mortality and 90-day mortality. In addition, we collected data on the 28-day survival rate and 90-day survival rate (outcome variable), NPR (continuous predictor variable), demographic information (age, sex, BMI), and vital signs (heart rate, respiration, body temperature, SBP, DBP, SpO2) (covariate). The Cox regression model with restricted cubic spline (RCS) was used to study the potential nonlinear relationship between the NPR and survival rate, and 4 nodes were selected as the nodes to obtain the final model. Subgroup analysis was used to explore the effects of the NPR on different subgroups, including age, sex, and BMI, and the corresponding conclusions were drawn. To analyze whether NPR has the value of predicting 28-day mortality in the three risk scores of SOFA, APSIII, and SAPSII, and compare the predictive value of NPR with that of neutrophils and platelets for the risk score.

Trajectory analysis

We selected patients who had at least three measurements of NPR within 6 days after ICU admission, applied the LCTM to evaluate the trajectory of NPR indices, and selected the model based on the Bayesian Information Criterion (BIC), Average posterior probability (AvePP), and clinical rationality. Baseline variables were analyzed according to different trajectory trends. Kaplan-Meier survival curves were used to compare the associations between NPR trajectories and 28-day and 90-day survival rates. Cox regression models were employed to assess the HRs and 95%CIs of NPR trajectories for mortality in septic patients. Model I included only the NPR variable, while Model II was adjusted for demographic variables (age, sex) and vital signs (heart rate, respiration, body temperature, SBP, DBP, SpO2).

All the statistical analyses were performed using SPSS 27 and R version 4.1.2. Statistical significance was defined as two-sided $P < 0.05$.

Results

Baseline data

According to the inclusion and exclusion criteria, 3339 sepsis patients were ultimately extracted from the MIMIC-IV database. The specific flow chart is shown in Fig. 1. Supplementary Table 1 shows the VIF of each variable, indicating that there is no multicollinearity between variables. Table 1 shows the baseline characteristics of the research subjects. We divided the NPR quartiles

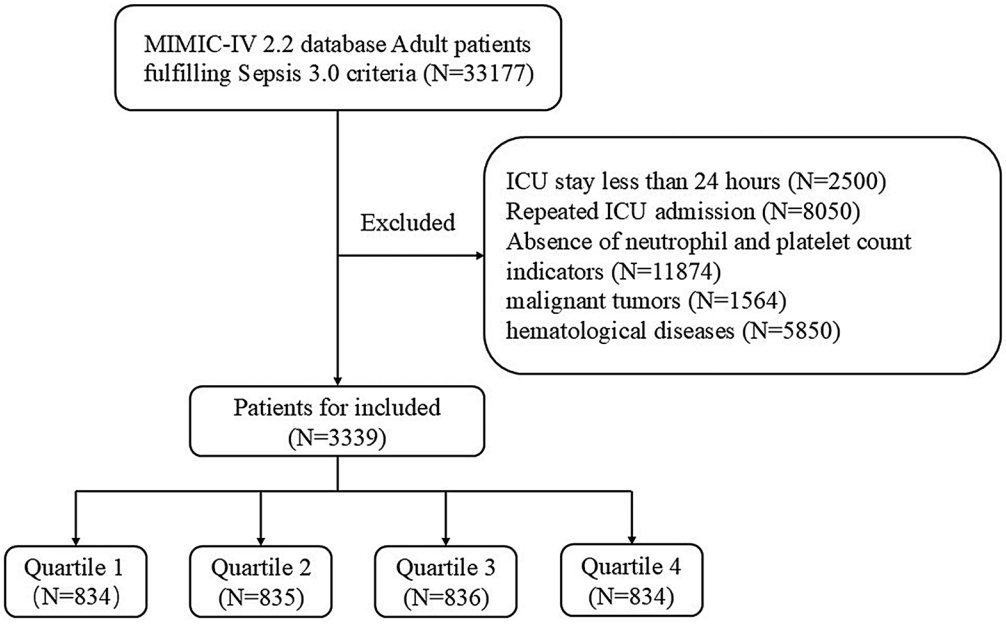


Fig. 1 Flow chart of this study. MIMIC: Medical Information Mart for Intensive Care, ICU: Intensive Care Unit

Table 1 Baseline characteristics of studied population

Variables	Total (*n* = 3339)	Q1 (*n* = 834)	Q2 (*n* = 835)	Q3 (*n* = 836)	Q4 (*n* = 834)	*P* value
Demographic						
Age	67.74 (56.65–78.72)	68.07 (57.14–78.82	67.30 (55.09–78.71)	67.52 (57.10-78.34)	68.13 (56.43–78.83)	0.763
Male (%)	1999 (59.9)	491 (58.9)	482 (57.7)	489 (58.5)	537 (64.4)	0.021
BMI	27.97 (24.22–32.95)	27.96 (24.16–32.85)	28.01 (23.98–33.59)	28.14 (24.45–33.20)	27.79 (24.30-32.27)	0.689
Vital signs						
Heart rate	86.00 (76.00-101.00)	83 (73–99)	87 (76–102)	86 (76–101)	87 (78–101)	0.011
Resp rate	18 (15–22)	18 (16–23)	18 (15–22)	18 (12–22)	18 (14–22)	0.057
Temperature	36.67 (36.22–37.11)	36.72 (36.39–37.11)	36.67 (36.28–37.11)	36.72 (36.20-37.17)	36.56 (36.00–37.00)	< 0.001
SBP	119.00 (105.00-137.00)	121.00 (105.00-138.00)	120.00 (106.00-138.00)	121.50 (107.00-139.75)	115.00 (103.00-133.00)	< 0.001
DBP	65.00 (55.00–77.00)	67.00 (57.00–80.00)	65.00 (55.00–78.00)	66.00 (56.00–77.00)	62.00 (54.00–73.00)	< 0.001
SpO2	99 (96–100)	99 (95–100)	99 (95–100)	99 (96–100)	99 (96–100)	0.088
Laboratory tests						
WBC	11.90 (8.60–16.20)	11.20 (8.50–14.50)	8.80 (6.20–13.80)	11.30 (8.90–14.40)	15.90 (12.60-20.53)	< 0.001
PLT	197.00 (148.00-257.00)	198.00 (151.00-253.00)	216.00 (155.00-295.00)	210.00 (165.00-266.75)	169.00 (132.00-214.00)	< 0.001
Neutrophils	677.25 (15.28-1155.36)	8.85 (6.44–12.13)	452.60 (93.00-667.08)	944.41 (726.55-1183.32)	1391.91 (1080.58-1786.25)	< 0.001
Monocytes	27.56 (1.09–52.92)	0.64 (0.37–0.95)	23.97 (3.20-43.79)	42.91 (26.82–62.40)	50.50 (32.07–78.73)	< 0.001
Lymphocytes	78.09 (2.15–141.60)	1.35 (0.79–2.01)	81.00 (15.00-142.56)	115.67 (78.05–166.70)	120.95 (76.39–186.00)	< 0.001
PO2	155.00 (74.00-321.00)	125.50 (56.00-298.00)	146.00 (77.00-304.00)	160.50 (79.00-318.75)	200.00 (86.00-358.25)	< 0.001
Lactate	1.60 (1.10–2.55)	1.70 (1.20–2.70)	1.60 (1.07–2.50)	1.50 (1.10–2.40)	1.70 (1.10–2.60)	< 0.001
BUN	19.00 (13.00–29.00)	18.00 (13.00–26.00)	19.00 (13.00–31.00)	19.00 (14.00–28.00)	20.50 (14.00–32.00)	< 0.001
Potassium	4.10 (3.80–4.50)	4.20 (3.80–4.60)	4.10 (3.70–4.60)	4.10 (3.70–4.50)	4.10 (3.80–4.50)	0.108
Sodium	139.00 (136.00-141.00)	139.00 (136.00-142.00)	139.00 (136.00-141.00)	139.00 (137.00-142.00)	139.00 (136.00-141.00)	0.385
Glucose	128.00 (106.00-166.00)	126.50 (105.00-165.00)	127.00 (103.00-164.00)	132.00 (108.00-172.00)	127.00 (108.00-162.00)	0.032
Creatinine	1.00 (0.70–1.40)	0.90 (0.70–1.30)	1.00 (0.70–1.40)	1.00 (0.70–1.40)	1.00 (0.80–1.40)	0.003
Calcium	8.30 (7.80–8.80)	8.50 (8.00–9.00)	8.30 (7.80–8.80)	8.30 (7.80–8.80)	8.10 (7.58–8.60)	< 0.001
APTT	30.40 (26.70–36.90)	29.60 (26.40–35.40)	31.30 (27.00–38.00)	30.35 (26.40-37.08)	30.60 (26.98–37.20)	0.004
Comorbidities						
Congestive heart failure (%)	991 (29.7)	245 (29.4)	272 (32.6)	251 (30.0)	223 (26.7)	0.075
Peripheral vascular disease (%)	413 (12.4)	84 (10.1)	97 (11.6)	110 (13.2)	122 (14.6)	0.031
Chronic pulmonary disease (%)	889 (26.6)	190 (22.8)	243 (29.1)	248 (29.7)	208 (24.9)	0.003
Diabetes (%)	1050 (31.4)	251 (30.1)	265 (31.7)	290 (34.7)	244 (29.3)	0.083
Hypertension (%)	2200 (65.9)	576 (69.1)	538 (64.4)	561 (67.1)	525 (62.9)	0.040
Acute kidney failure (%)	1041 (31.2)	254 (30.5)	275 (32.9)	253 (30.3)	259 (31.1)	0.629
Score system						
SOFA	5.00 (3.00–7.00)	5.00 (3.00–7.00)	5.00 (3.00–7.00)	5.00 (3.00–7.00)	5.00 (4.00–8.00)	< 0.001
APSIII	46.00 (33.00–67.00)	44.50 (32.00-63.25)	46.00 (34.00–66.00)	45.00 (34.00–64.00)	51.00 (35.00–73.00)	< 0.001
SAPSII	36.00 (29.00–46.00)	35.00 (28.00–45.00)	37.00 (29.00–46.00)	35.00 (28.00–44.00)	38.00 (30.00–49.00)	< 0.001
Interventions						
Ventilation (%)	2998 (89.8)	733 (87.9)	737 (88.3)	767 (91.7)	761 (91.2)	0.013
Vasopressor (%)	1813 (54.3)	455 (54.6)	429 (51.4)	406 (48.6)	523 (62.7)	< 0.001
CRRT (%)	96 (2.9)	21 (2.5)	21 (2.5)	17 (2.0)	37 (4.4)	0.017

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, SpO2: oxygen saturation, WBC: white blood cell, PLT: platelet, PO2: oxygen partial pressure, BUN: blood urea nitrogen, APTT: activated partial thromboplastin time, SOFA: sequential organ failure assessment, APSIII: Acute physiology Score III, SAPSII: Simplified Acute Physiological Score II, CRRT: continuous renal replacement therapy

Table 2 NPR and 28-day and 90-day mortality

NPR	Q1 ($n=834$)	Q2 ($n=835$)	Q3 ($n=836$)	Q4 ($n=834$)	*P* value
Mortality (n, %)					
28-day mortality	125 (15.0)	124 (14.9)	115 (13.8)	157 (18.8)	0.023
90-day mortality	164 (19.7)	158 (18.9)	159 (19.0)	198 (23.7)	0.036

Quartile 1 ($0.0014 \le NPR < 0.0854$), Quartile 2 ($0.0854 \le NPR < 3.3322$), Quartile 3 ($3.3322 \le NPR < 5.8321$), Quartile 4 ($5.8321 \le NPR \le 49.8836$). NPR: neutrophil-platelet ratio

into four groups: Quartile 1 ($0.0014 \le NPR < 0.0854$), Quartile 2 ($0.0854 \le NPR < 3.3322$), Quartile 3 ($3.3322 \le NPR < 5.8321$), and Quartile 4 ($5.8321 \le NPR \le 49.8836$), which included 834, 835, 836, and 834 patients, respectively. The average age of the patients was 67.74 years, with 1999 males (59.9%) and an average BMI of 27.97. There were 991 patients (29.7%) with congestive heart failure, 413 patients (12.4%) with peripheral vascular disease, 889 patients (26.6%) with chronic lung disease, 1050 patients (31.4%) with diabetes, 2200 patients (65.9%) with hypertension, and 1041 patients (31.2%) with acute renal failure. There were 2998 patients (89.8%) on mechanical ventilation and 1813 patients (54.3%) on vasoactive drugs. Q2 had the lowest white blood cell count and the highest platelet count. Q4 neutrophils, lymphocytes, monocytes, oxygen partial pressure, Bun higher. Q3 had lower lactic acid levels and higher blood glucose levels. Q1 creatinine and APTT were lower, and calcium was greater.

NPR and 28-day and 90-day mortality

Among the 28-day mortality and 90-day mortality rates, Q4 had the highest mortality rate (Table 2). Among them, the 28-day mortality rate was the lowest in Q3; in terms of the 90-day mortality rate, Q2 and Q3 were not very different. In the COX regression model, with Q1 as the reference, the unadjusted model and model I were the highest risk of 28-day and 90-day mortality in the Q4 group ($P<0.05$). In model II, although not statistically significant ($P<0.05$), it can be seen that the risk of death in the Q4 group is higher. The specific information is shown in Tables 3 and 4. The 28-day mortality and 90-day mortality Kaplan–Meier survival curves revealed that Q4 had the lowest survival rate (Figs. 2 and 3). The RCS results revealed that the NPR had a nonlinear relationship with 28-day mortality and 90-day mortality in patients with sepsis, that is, a J-shaped correlation, and that the risk of death decreased first and then increased with the NPR. After adjusting for age, sex, BMI, heart rate, resp rate, temperature, SBP, DBP, and SpO2, RCS analysis revealed that the NPR still had a J-shaped relationship with 28-day mortality ($P=0.032$), but 90-day mortality was $P>0.05$ (Fig. 4). The turning point of the RCS curve is NPR = 3.81. According to the NPR quartile grouping, the turning point is located at Q3, which is consistent with the results of the Cox regression model. We performed a ROC curve analysis of the NPR to determine its predictive value for sepsis mortality, as shown in Supplementary Figs. 1 and 2, and the area under the curve (AUC) was 0.52, which has some predictive significance.

Subgroup analysis

In addition, to confirm the relationship between the NPR and 28-day mortality in patients with sepsis, we conducted a stratified analysis based on age, sex, and BMI. In Fig. 5, in the group defined by BMI < 28, the 28-day mortality rate of Q4 was the highest, which was statistically

Table 3 Cox regression model (28-day mortality)

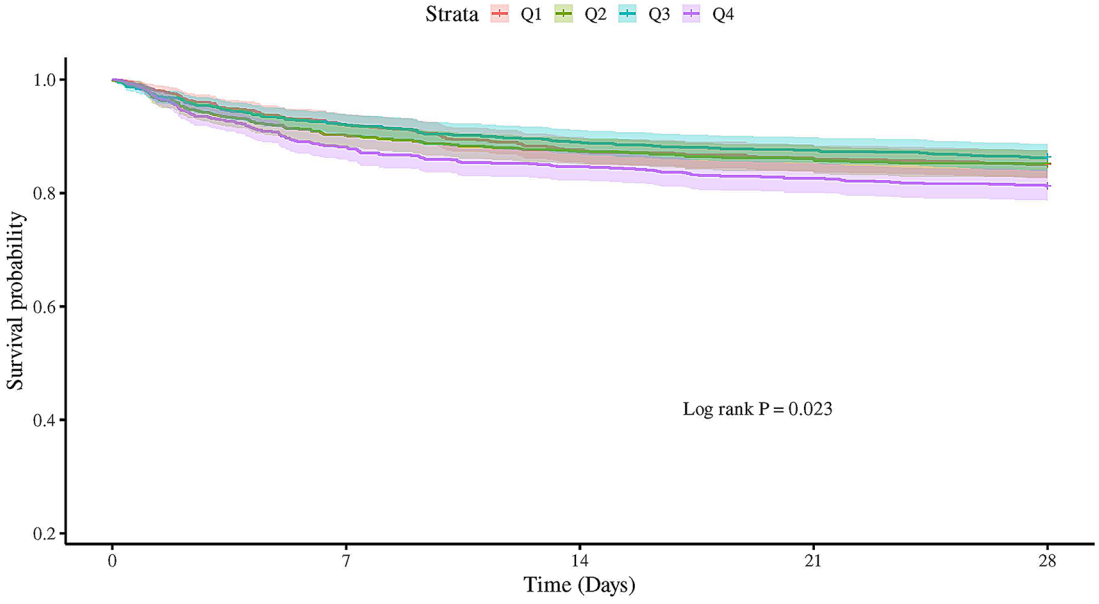
NPR	Model I		Model II		Model III	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Q1 ($n=834$)	Reference		Reference		Reference	
Q2 ($n=835$)	1.00 (0.78–1.29)	0.983	1.02 (0.80–1.32)	0.848	0.98 (0.76–1.26)	0.888
Q3 ($n=836$)	0.92 (0.71–1.18)	0.502	0.96 (0.75–1.24)	0.767	0.95 (0.74–1.23)	0.702
Q4 ($n=834$)	1.29 (1.02–1.64)	0.031	1.29 (1.01–1.63)	0.038	1.24 (0.98–1.58)	0.078

Model I: Crude; Model II: adjusted by age, sex, BMI, heart rate, respiration, body temperature, SBP, DBP, and SpO2. Model III: adjusted by age, sex, BMI, heart rate, respiration, body temperature, SBP, DBP, SpO2 and complications. Quartile 1 ($0.0014 \le NPR < 0.0854$), Quartile 2 ($0.0854 \le NPR < 3.3322$), Quartile 3 ($3.3322 \le NPR < 5.8321$), Quartile 4 ($5.8321 \le NPR \le 49.8836$). NPR: neutrophil-platelet ratio, HR: hazard ratio, CI: confidence interval

Table 4 Cox regression model (90-day mortality)

NPR	Model I		Model II		Model III	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Q1 ($n=834$)	Reference		Reference		Reference	
Q2 ($n=835$)	0.97 (0.78–1.21)	0.790	1.00 (0.80–1.25)	0.999	0.97 (0.77–1.20)	0.753
Q3 ($n=836$)	0.97 (0.78–1.20)	0.751	1.02 (0.82–1.26)	0.892	1.00 (0.80–1.25)	0.985
Q4 ($n=834$)	1.25 (1.02–1.54)	0.035	1.26 (1.02–1.56)	0.030	1.23 (0.99–1.51)	0.058

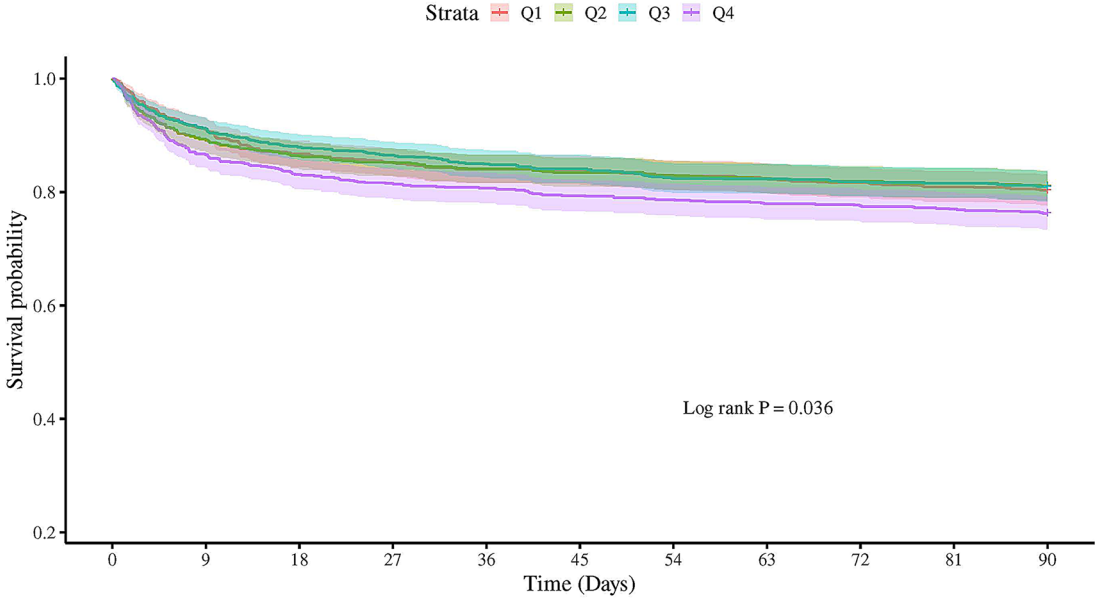
Model I: Crude; Model II: adjusted by age, sex, BMI, heart rate, respiration, body temperature, SBP, DBP, and SpO2. Model III: adjusted by age, sex, BMI, heart rate, respiration, body temperature, SBP, DBP, SpO2 and complications. Quartile 1 ($0.0014 \le NPR < 0.0854$), Quartile 2 ($0.0854 \le NPR < 3.3322$), Quartile 3 ($3.3322 \le NPR < 5.8321$), Quartile 4 ($5.8321 \le NPR \le 49.8836$). NPR: neutrophil-platelet ratio, HR: hazard ratio, CI: confidence interval



Number at risk

Q1	834	767	731	718	709
Q2	835	753	729	718	711
Q3	836	770	744	732	721
Q4	834	735	706	689	677

Fig. 2 28-day Kaplan-Meier survival curve. Quartile 1 (0.0014 ≤ NPR < 0.0854), Quartile 2 (0.0854 ≤ NPR < 3.3322), Quartile 3 (3.3322 ≤ NPR < 5.8321), Quartile 4 (5.8321 ≤ NPR ≤ 49.8836)



Number at risk

Q1	834	760	723	711	701	699	691	687	681	675	670
Q2	835	746	721	712	702	697	692	688	684	681	677
Q3	836	762	735	723	710	703	689	688	684	682	677
Q4	834	722	693	680	673	662	656	650	647	642	636

Fig. 3 90-day Kaplan-Meier survival curve. Quartile 1 (0.0014 ≤ NPR < 0.0854), Quartile 2 (0.0854 ≤ NPR < 3.3322), Quartile 3 (3.3322 ≤ NPR < 5.8321), Quartile 4 (5.8321 ≤ NPR ≤ 49.8836)

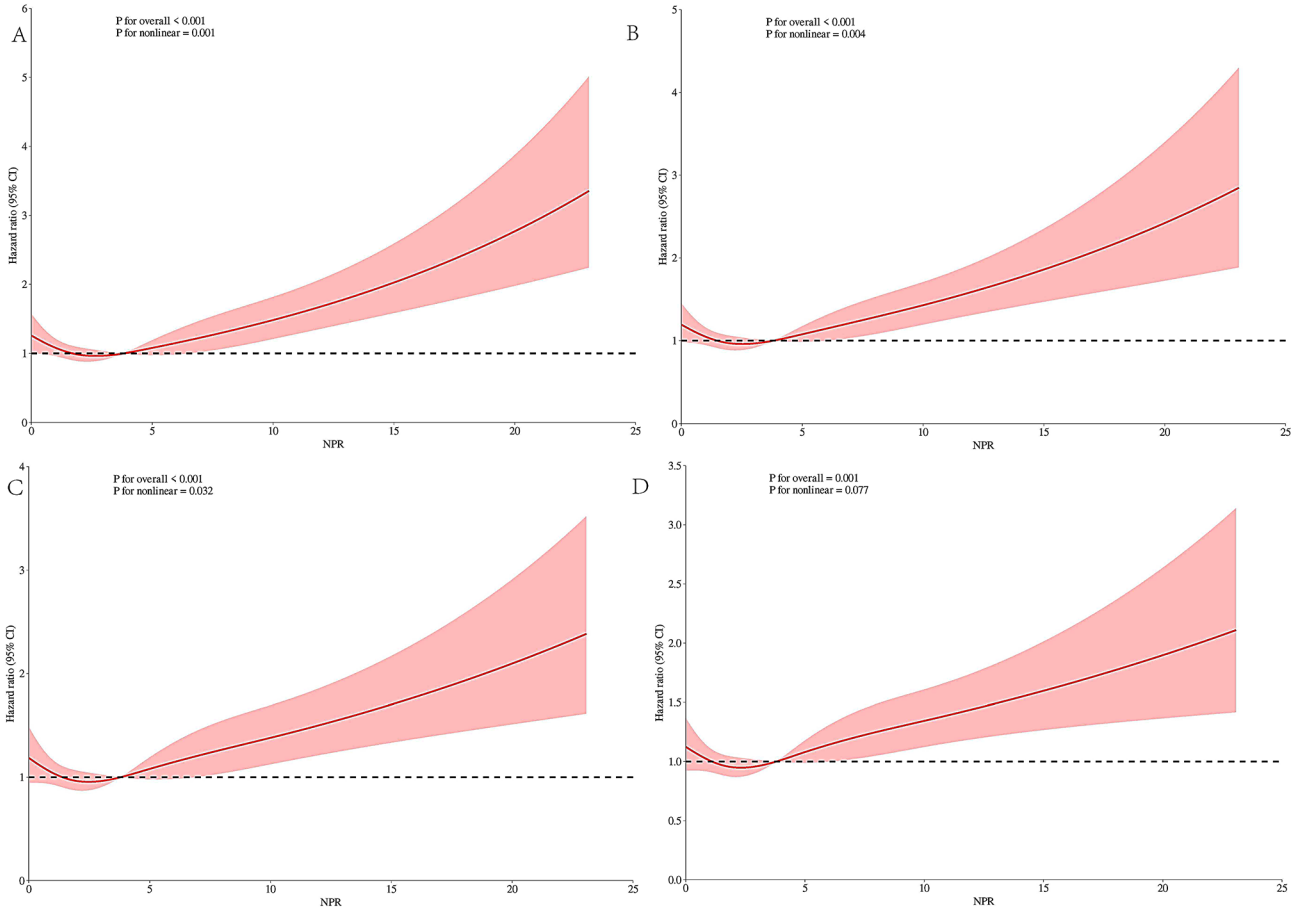


Fig. 4 RCS analysis of NPR and mortality. **A**: Unadjusted 28-day mortality RCS analysis, **B**: Unadjusted 90-day mortality RCS analysis, **C**: RCS analysis of adjusted 28-day mortality, **D**: RCS analysis of adjusted 90-day mortality. The curve represents the estimated adjusted hazard ratio, and the shadow stripe represents a 95% confidence interval. NPR: neutrophil-platelet ratio, CI: confidence interval

significant ($P < 0.05$). However, there was no significant difference in other groups, suggesting that the baseline level may affect the relationship between NPR and 28-day mortality. NPR was then analyzed with 416 patients with septic shock, but the results showed that NPR did not show significant results in predicting 28-day mortality in patients with septic shock, which may be related to sample size and further research is needed (Supplementary Table 2).

The AUC, incremental discrimination improvement (IDI), and net reclassification improvement (NRI) for each risk score alone and after incorporating NPR are shown in Supplementary Table 3. The results suggest that for the SOFA risk score, the AUC value slightly decreased after adding NPR, which may indicate that NPR did not improve the SOFA score's predictive ability for 28-day mortality in this context and may even have had a minor negative impact. In contrast, for the APSIII and SAPSII risk scores, the AUC values showed marginal increases after incorporating NPR, indicating that NPR moderately enhanced the predictive accuracy of these two scores for 28-day mortality, though the magnitude of improvement was relatively modest. ROC curves for the different risk scores are presented in Supplementary Fig. 3. We then calculated and compared the ROC curves, AUC, IDI, and NRI for predicting 28-day mortality using NPR, neutrophils, and platelets within the SOFA, APSIII, and SAPSII risk score frameworks. Details are provided in Supplementary Tables 4 and Supplementary Fig. 4. Overall, NPR did not demonstrate improved ability to predict death risk.

Trajectory analysis

A total of 434 patients were included in the trajectory analysis. Using the LCTM, three distinct developmental trajectories were identified (Fig. 6). Trajectory 1 ($n = 361$, 83.18%), stable development Class, characterized by patients with low baseline values and relatively stable NPR. Trajectory 2 ($n = 27$, 6.22%), rapid-slow increase class, characterized by patients with high baseline values, showing rapid early growth followed by slow late-stage increase in NPR. Trajectory 3 ($n = 46$, 10.60%), slow

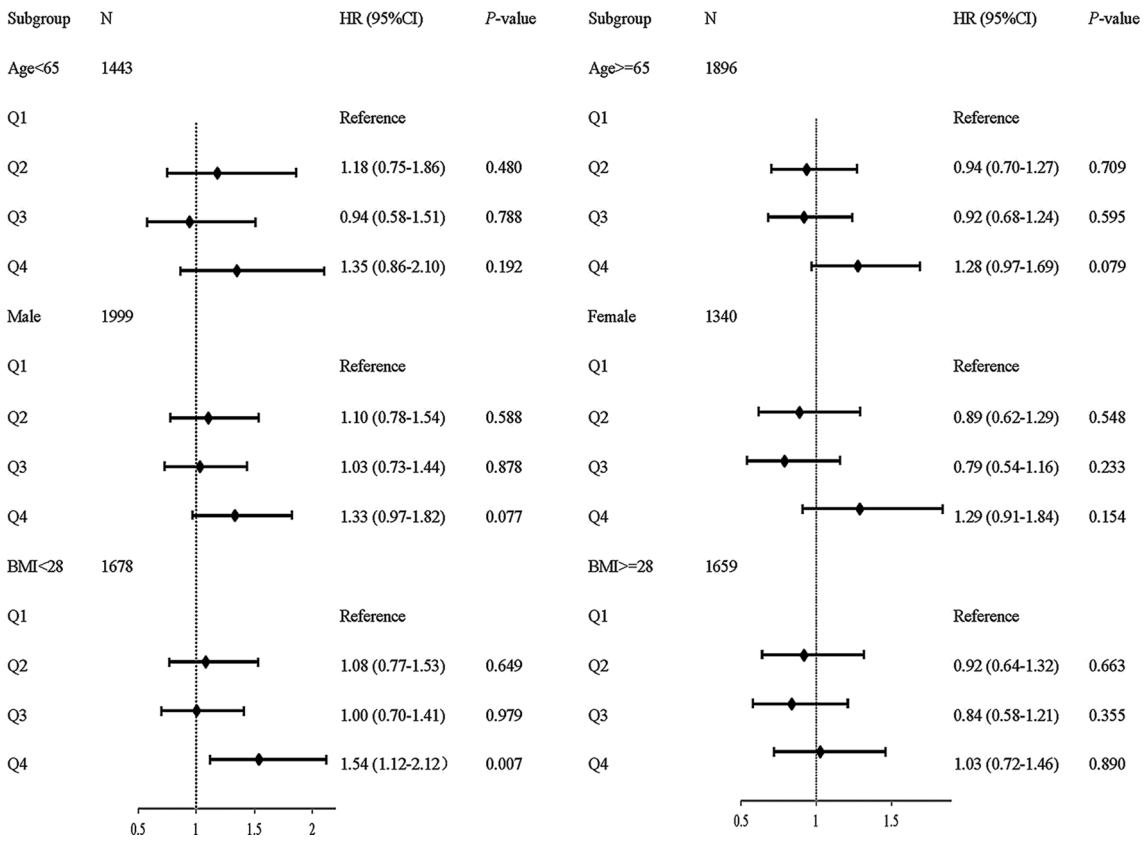


Fig. 5 Subgroup Forest plot for 28-day mortality. Quartile 1 (0.0014 ≤ NPR < 0. 0854), Quartile 2 (0.0854 ≤ NPR < 3.3322), Quartile 3 (3.3322 ≤ NPR < 5.8321), Quartile 4 (5.8321 ≤ NPR ≤ 49.8836). NPR: neutrophil-platelet ratio, BMI: body mass index, HR: hazard ratio, CI: confidence interval

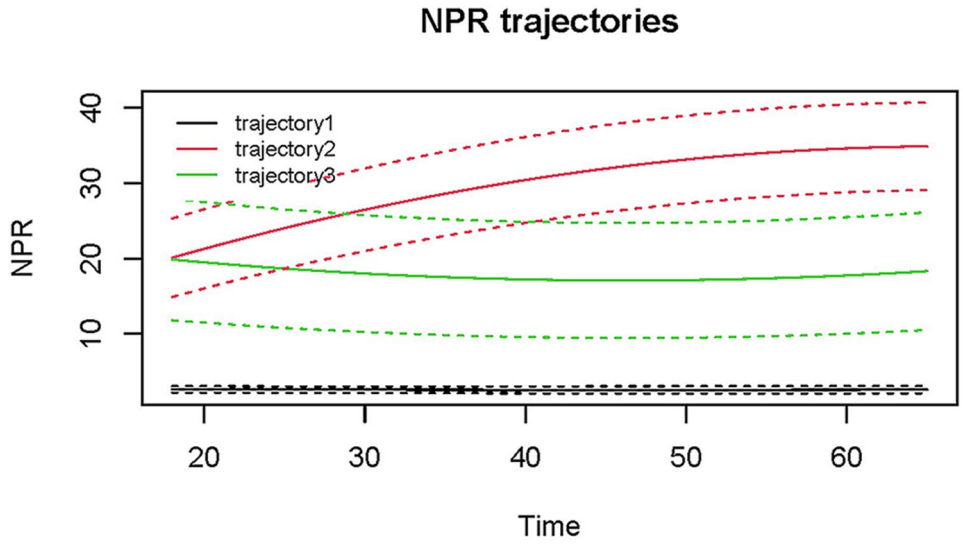


Fig. 6 NPR trajectories over the first 6 days of ICU admission. X-axis (hours): The difference between the NPR measurement time and the time to ICU admission, Y-axis: neutrophil-platelet ratio

decline class, characterized by patients with high baseline values, experiencing slow early decline followed by a plateau in NPR. Demographic and clinical characteristics distributed across NPR trajectories are presented in Supplementary Table 5. Kaplan-Meier survival curve analysis revealed significant differences in mortality rates across trajectories within 28 and 90 days. Compared to Trajectory 1, Trajectory 3 was associated with a higher mortality rate (Fig. 7). Cox regression results were consistent with these findings: after adjusting for confounding

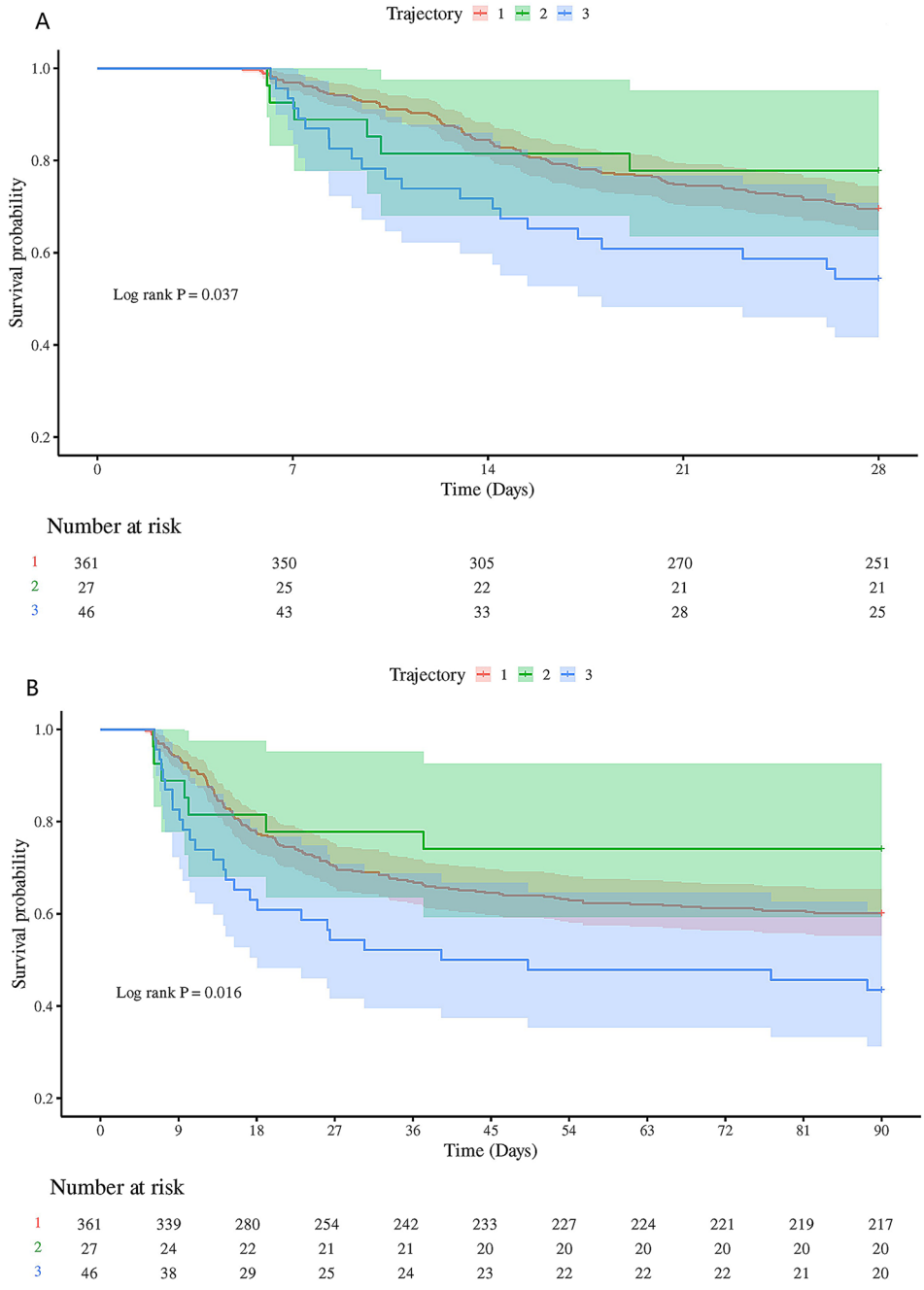


Fig. 7 Kaplan–Meier survival curves of the three trajectories. A: Kaplan–Meier survival curve between three trajectories and 28-day mortality; B: Kaplan–Meier survival curve between three trajectories and 90-day mortality

factors, Trajectory 3 remained an independent risk factor for mortality at both 28 and 90 days, while Trajectory 2 showed no significant association (Tables 5 and 6).

Discussion

This study explored the relationship between the NPR and the risk of death in patients with sepsis, and the results revealed a nonlinear relationship, with the highest survival rate in patients with sepsis when $3.3322 \leq NPR < 5.8321$. To further evaluate the relationship between the NPR and sepsis, the RCS curve revealed that the survival rate of patients with sepsis was highest when the NPR was 3.81, and the two curves were J-shaped. At the same time, NPR trajectory 3 had a higher mortality rate relative to trajectory 1 in patients with sepsis within 6 days of ICU admission.

Neutrophils are the host's front-line preventers of infection [5]. In patients with sepsis, the accumulation of

Table 5 Cox regression analysis of the three NPR trajectories (28-day mortality)

Variables	Model I		Model II	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Trajectory				
1	1.00 (Reference)		1.00 (Reference)	
2	0.74 (0.33 ~ 1.69)	0.477	0.71 (0.31 ~ 1.65)	0.428
3	1.75 (1.10 ~ 2.79)	0.019	1.70 (1.06 ~ 2.73)	0.028

Model I: Crude; Model II: adjusted by age, sex, heart rate, respiration, body temperature, SBP, DBP, and SpO2. NPR: neutrophil-platelet ratio, HR: hazard ratio, CI: confidence interval

Table 6 Cox regression analysis of the three NPR trajectories (90-day mortality)

Variables	Non-adjusted		Adjusted I	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Trajectory				
1	1.00 (Reference)		1.00 (Reference)	
2	0.63 (0.30 ~ 1.36)	0.240	0.61 (0.28 ~ 1.32)	0.209
3	1.69 (1.12 ~ 2.57)	0.013	1.65 (1.08 ~ 2.52)	0.020

Model I: Crude; Model II: adjusted by age, sex, heart rate, respiration, body temperature, SBP, DBP, and SpO2. NPR: neutrophil-platelet ratio, HR: hazard ratio, CI: confidence interval

neutrophils in the vascular endothelium leads to endothelial cell injury, vascular injury, and thrombosis, and many neutrophils migrate to target organs. The body is in an immunosuppressive state, which eventually leads to tissue damage and multiple organ dysfunction. In addition, the regulation of neutrophil activation plays an important role in the management of sepsis [14]. Studies have shown that neutrophil apoptosis in patients with sepsis is significantly reduced. In a rat sepsis model, increasing neutrophil apoptosis improved lung injury [15–16]. Platelets play an important role in sepsis. They can react with pathogenic microorganisms through adhesion, aggregation, and activation to protect the body. Moreover, platelets can also interact with immune cells, such as neutrophils, to participate in the formation of microthrombi and inflammation. Therefore, platelets have antimicrobial effects and can cooperate with other innate immune cells to form a complex intravascular immune defense system that prevents the spread of bacteria. In patients with sepsis, a decrease in platelet count is associated with increased mortality, and a modest increase reduces 90-day mortality [17]. In addition, there was a significant correlation between platelet aggregation and mortality in patients with severe viral infections treated in the ICU [18]. Neutrophils and platelets can be mediated by P-selectin and β (2) and β (3) integrins (CD11b/CD18, CD41/CD61) to promote the recruitment of neutrophils to inflammatory tissues, thereby participating in host defense [19]. In general, sepsis is a complex reaction involving multiple cells and mediators. An increasing number of studies have shown that neutrophils and platelets are involved in the pathological process of sepsis and play synergistic roles.

At present, there are an increasing number of studies on the use of laboratory indicators to predict the survival rate of patients with sepsis, and these studies are no longer limited to a single indicator but rather combine indicators. In this study, the ratio of neutrophils to platelets was used as a new laboratory index to study the relationship between the NPR and mortality in patients with sepsis. Previous studies have shown that the NPR, as a new index, can help clinicians better predict early AKI in critically ill COVID-19 patients. The best cutoff value for predicting AKI is an NPR of 3.9 (AUC = 0.679, 95% CI: 0.622–0.737, $P < 0.001$) [20]. In patients with acute ischemic stroke caused by large vessel occlusion after endovascular treatment, the NPR was independently associated with futile recanalization (FR), and the two were positively correlated; that is, patients with a high NPR had an increased risk of FR [21]. A two-year prospective study showed that the NPR can be used as a good predictor of metabolic syndrome in type 2 diabetes patients (AUC = 0.734) [22]. Another retrospective study revealed that a high NPR may lead to adverse events and poor prognosis after percutaneous coronary intervention in patients with coronary artery disease via the serum creatinine and triglyceride levels [23]. Somaschini A et al. [24] reported that the NPR is a new prognostic biomarker for patients with ST-segment elevation myocardial infarction undergoing direct percutaneous coronary intervention. In addition, the NPR can also be used as a potential prognostic marker for patients with acute aortic dissection [25]. A high NPR at admission is associated with hematoma enlargement in patients with spontaneous intracerebral hemorrhage and is an independent risk factor for early hematoma enlargement in patients with spontaneous intracerebral hemorrhage [26]. Zhang Y et al. [9] reported that the NPR was an independent risk factor for 28-day mortality in patients with sepsis and could be used as a predictor of 28-day mortality (AUC = 0.6284), which was consistent with the results of this study, this study revealed that when the NPR = 3.81, the mortality rate of sepsis patients was the lowest. In general, the NPR, as a new indicator of dynamic contact between neutrophils and platelets, may be used to understand the inflammatory and immune responses in patients with sepsis. Additionally, different NPR trajectories may imply distinct inflammatory and immune characteristics in sepsis patients. Early sepsis is often dominated by inflammatory responses, while the later stage is frequently associated with immunosuppression. A study [27] has found that the lymphocyte count trajectory with a rapid-slow decline is associated with the highest 7-day mortality, and the trajectory with a rapid-slow

increase is associated with the highest 28-day mortality, which is similar to the findings of this study.

In this study, the NPR was divided into four groups according to quartile. The results revealed a J-shaped relationship between the NPR and mortality in sepsis patients. The turning point was NPR = 3.81. When the NPR is greater or less than this value, the mortality of sepsis patients increases. In the subgroup analysis, we found that the results of the study were affected by the age, sex, and BMI of the patients. Furthermore, we found no association between NPR and 28-day mortality in people with septic shock. Unlike previous studies, this study excluded the interference of malignant tumors and hematologic diseases, and performed trajectory analysis. The NPR distribution range is wider, and a more reasonable statistical method is used to process the data, which has certain reference significance for clinical practice. Compared with a single biomarker, the NPR has greater predictive value for the prognosis of sepsis patients. Biomarkers such as the NPR can be used to identify sepsis patients to regulate the immune response and improve patient prognosis [28].

In clinical diagnosis and treatment, NPR can be applied to various aspects such as early disease screening, assessment of disease severity, selection of treatment regimens, and prediction of prognosis. Meanwhile, NPR can be used in combination with other indicators. For example, the neutrophil-to-lymphocyte-to-platelet ratio (NLPR) can be used for risk stratification analysis of sepsis [29]. In future prospective studies, it is possible to conduct research through expanding the sample size and conducting multi-center verification, exploring the specificity of NPR in different disease subgroups, analyzing the association between the dynamic changes of NPR and treatment, and carrying out joint research on NPR and emerging diagnosis and treatment technologies (such as artificial intelligence-assisted diagnosis), such as the use of explainable artificial intelligence models to identify novel platelet metabolites in sepsis [30].

However, it is necessary to acknowledge the limitations of this study. First, our research is retrospective and single-source, which may limit the universality of our research results. Second, although we adjusted for confounding factors, some confounding factors (such as metabolic syndrome parameters and nutritional and metabolic parameters) were not fully considered, and eliminating the influence of confounding factors is a major problem in the study. Third, this study is based on the limitations of observational studies, and we find correlations rather than causalities [31]. Fourth, the MIMIC-IV database used in this study includes sepsis patients from 2008 to 2019, and its clinicians followed different guidelines, which may have had a certain impact on the results of the study [32]. Fifth, causality is important for research and is based on randomization, but in many cases, randomization cannot be easily performed [33]. In this study, there are many factors that are related to the outcome, but their causal relationship is unknown, and future research may need to explore the causal relationship between factors in the context of causal reasoning. Sixth, sepsis is a heterogeneous syndrome, and different clinical phenotypes may lead to different outcomes [34]. Traditional global analysis may dilute or distort the true association between key variables and outcomes due to the mixing of characteristics from different subphenotypes. Within heterogeneous populations, the same variable may exhibit opposite directions of effect or differing magnitudes of effect across different subgroups. Therefore, "subphenotype-guided stratified analysis" should be adopted as a standard procedure in future sepsis research to avoid outcome bias caused by heterogeneity. Finally, there is heterogeneity in neutrophils. The study [35] found that Neu1 component is an important biomarker for the severity of sepsis, which will also have a certain impact on the results of the study. The data included in this study are neutrophil counts in traditional blood tests, and it is impossible to distinguish subtypes with different functions, which is one of the limitations of current research. Therefore, it is necessary to use a larger population sample size, more standardized methods and multicenter clinical studies to further verify this study.

Conclusion

In summary, this study revealed a J-shaped relationship between sepsis mortality risk and the NPR, with a turning point of NPR = 3.81. A lower and higher NPR were significantly associated with increased mortality risk. NPR trajectory 3 is a predictor of 28-day and 90-day mortality. This finding provides an easy-to-obtain and powerful indicator for the early prediction of poor sepsis prognosis, which can enable clinicians to better monitor high-risk patients to reduce mortality.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11064-5.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
Not applicable.

Author contributions
JZ and CRZ had the idea for and designed the study and had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. JZ, CRZ and LFOY wrote and revised the manuscript. LFOY and ZXD contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Funding
Not applicable.

Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 17 December 2024 / Accepted: 30 April 2025
Published online: 09 May 2025

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