

Prognostic nutritional index and 28-day mortality in elderly septic patients: A retrospective analysis based on the MIMIC database

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ABSTRACT

OBJECTIVE: Peripheral blood lymphocyte count and serum albumin level are crucial predictors of mortality across various diseases, including sepsis. However, previous studies have focused primarily on individual indicators (lymphocyte count or albumin) in relation to sepsis prognosis. Given the limitations of these single indicators, we investigated the relationship between the Prognostic Nutritional Index (PNI)—a composite indicator combining serum albumin level and lymphocyte count—and 28-day all-cause mortality in elderly septic patients.

METHODS: This retrospective study analyzed data from elderly septic patients in the Medical Information Mart for Intensive Care (MIMIC-IV, v2.2) database from 2008 to 2019. Patients were categorized into survival and mortality groups based on 28-day outcomes, and baseline data were compared between the groups. Restricted cubic spline (RCS) analysis was used to determine PNI values at which the hazard ratio (HR) for 28-day mortality was 1. Patients were then classified into extreme ($PNI < 29.24$ or $PNI > 47.77$) and moderate ($29.24 \leq PNI \leq 47.77$) PNI groups. Kaplan-Meier survival curves were used to analyze cumulative 28-day survival rates, and Cox regression models assessed the relationship between PNI and 28-day outcomes.

RESULTS: The study included 2,121 patients. PNI values were significantly lower in the mortality group compared to the survival group ($p < 0.05$). RCS analysis indicated a nonlinear relationship between PNI and 28-day all-cause mortality risk ($X^2 < 0.001$, $p < 0.001$), with mortality risk decreasing as PNI increased at lower PNI values. Kaplan-Meier survival curves revealed that patients in the extreme PNI groups had significantly lower cumulative 28-day survival rates than those in the moderate PNI group ($p < 0.001$). Cox regression models further confirmed that extreme PNI values (either extremely high or extremely low) were independent risk factors for 28-day all-cause mortality ($HR = 1.349$, $p = 0.004$).

CONCLUSION: To our knowledge, this study is the first to reveal a nonlinear relationship between PNI values and 28-day all-cause mortality in elderly septic patients. Our findings associated extreme PNI values with increased mortality risk, and suggest that PNI may serve as an effective tool for prognostic risk stratification.

Keywords: All-cause mortality; elderly sepsis patients; MIMIC-IV; prognostic nutritional index.

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Sepsis is a common systemic inflammatory response syndrome and a leading cause of mortality among intensive care unit (ICU) patients. It is characterized by a dysregulated host response to infection, resulting in life-threatening organ dysfunction [1]. Despite significant advancements in critical care that have improved the

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understanding and treatment of sepsis and have reduced mortality rates, certain patient populations, particularly elderly patients with prolonged ICU stays, complex comorbidities, and immune dysregulation continue to experience clinical deterioration and poor outcomes [2, 3]. Therefore, the early assessment of disease severity and aggressive treatment are critical for improving outcomes in elderly septic patients.

Numerous studies have confirmed the relationship between C-reactive protein (CRP) and procalcitonin (PCT) levels and the severity and prognosis of sepsis [4]. However, these markers exhibit low diagnostic specificity and predictive value. Multiple studies have associated sepsis with other biomarkers that include complement component proteins, cytokines, chemokines, damage-associated molecular patterns (DAMPs), cell membrane receptors, and cellular proteins [5–7]. However, these markers lack sufficient sensitivity. Thus, the exploration of additional indicators holds significant clinical value.

The Prognostic Nutritional Index (PNI) accurately and comprehensively assesses patient nutritional and immune status [8]. By combining peripheral blood lymphocyte counts and serum albumin levels, PNI reflects the impact of inflammation and related signaling pathways on nutrition and metabolism. In septic patients, invading pathogens initiate immune responses through pathogen-associated molecular patterns and pattern recognition receptors, stimulating the release of numerous inflammatory mediators. Excessive levels of pro-inflammatory cytokines accelerate catabolism, energy and nutritional loss, and protein-energy malnutrition [9]. Consequently, anti-inflammatory and nutritional therapies are imperative to treat sepsis and improve clinical outcomes. Initially used to predict immune status and risks before gastrointestinal surgery, PNI is closely related to the prognosis of various diseases, including cirrhosis and various cancers [10–13]. To our knowledge, no previous studies have applied PNI as a biomarker of sepsis in elderly patients.

Based on the above background, we hypothesized that the PNI is significantly associated with 28-day all-cause mortality in elderly septic patients and that abnormal fluctuations in PNI levels (either elevated or decreased) may be related to higher mortality risks. Therefore, this study aimed to explore the relationship between PNI and 28-day all-cause mortality in elderly septic patients by interrogating data from the MIMIC-IV database, with the goal of providing a new prognostic assessment tool to identify high-risk patients and to optimize treatment strategies.

Highlight key points

- This study aims to explore the relationship between the prognostic nutritional index (PNI) and the prognosis of elderly septic patients.
- In comparison with traditional prognostic indices for the elderly, the PNI introduced in this study places a greater emphasis on immune-inflammatory responses, making it more aligned with clinical practice for elderly patients with sepsis.
- The study pioneers the investigation of PNI's correlation with elderly sepsis prognosis using a large, real-world dataset, offering precise PNI cutoffs for early detection of high-risk patients.

MATERIALS AND METHODS

Data Source

The MIMIC-IV (v2.2) database, developed by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology, provided all data used in this study. The database, available at <https://mimic.mit.edu/>, contains detailed ICU-specific data from all patients treated at the Beth Israel Deaconess Medical Center between 2008 and 2019. To protect patient privacy, all personal identifiers have been replaced with random numbers. Therefore, this study was exempt from ethical review and informed consent requirements.

Population Selection and Inclusion/Exclusion Criteria

The MIMIC-IV database includes data from 180,733 patients admitted to the ICU between 2008 and 2019. Using a retrospective study design, elderly patients with sepsis in MIMIC-IV were enrolled in our research. The diagnosis of sepsis was confirmed according to the Sepsis-3 definition [13], which identifies sepsis as an acute increase in sequential organ failure assessment (SOFA) score by ≥ 2 points attributable to infection. Inclusion criteria were: (1) Age ≥ 65 years old; (2) First admission to the ICU; (3) Meeting Sepsis-3 criteria. Exclusion criteria included: (1) ICU stay < 24 hours; (2) Missing albumin or lymphocyte count data.

Ultimately, 2,121 patients were included in the study.

Data Extraction and Grouping

Main study variable

The PNI was the primary study variable. Based on previous literature [14], PNI was calculated using the formula: $\text{albumin (g/L)} + 5 \times \text{lymphocyte count (} 10^9/\text{L)}$.

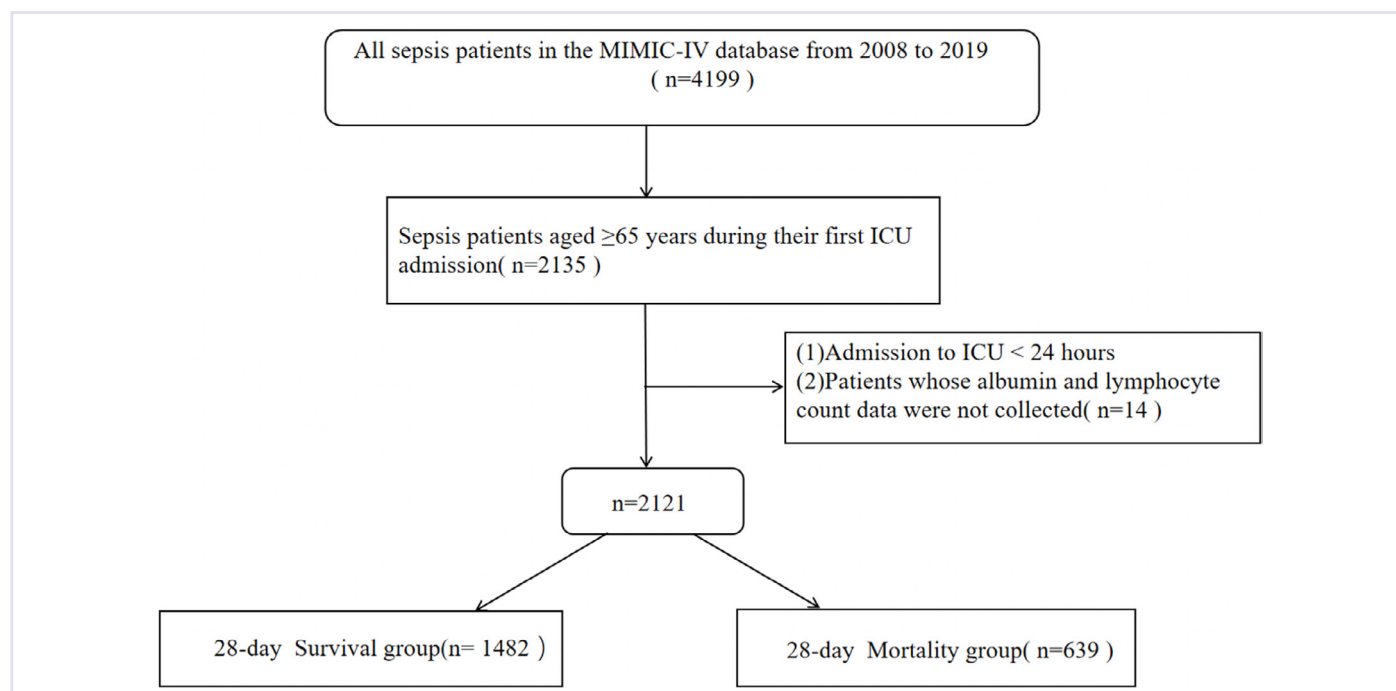


FIGURE 1. Flow chart of the study.

MIMIC-IV: Medical Information Mart for Intensive Care; ICU: Intensive care unit

The first laboratory measurements after ICU admission were selected to minimize potential interference from treatment. Data were extracted from the MIMIC-IV database using PostgreSQL's SQL language. Extracted variables included age, gender, weight, Acute Physiology and Chronic Health Evaluation (APACHE) III score, Sequential Organ Failure Assessment (SOFA) score, laboratory test results, and ICU length of stay. Laboratory data included white blood cell count; red cell distribution width; hemoglobin level; platelet count; lymphocyte count; and serum albumin, creatinine, blood urea nitrogen, and potassium levels.

Grouping

Patients were divided into two groups based on 28-day outcomes: the survival (n=1,482) and mortality (n=639) groups. Additionally, based on RCS analysis, patients were categorized into extreme ($PNI < 29.24$ or $PNI > 47.77$, n=726) and moderate ($29.24 \leq PNI \leq 47.77$, n=1,395) PNI groups (Fig. 1).

Study Outcomes

The primary outcome was 28-day all-cause mortality after hospital admission.

Statistical Analysis

Data analysis was performed using Stata 14.0 and R software. Continuous variables were expressed as mean $\pm$ standard deviation (mean $\pm$ SD) for normally distributed data and as median (interquartile range) (M [QL, QU]) for skewed distributions. Categorical variables were expressed as percentages (%). Intergroup comparisons were made using t-tests for continuous variables, rank-sum tests for skewed data, and chi-square tests for categorical variables. Kaplan-Meier curves were used for survival analysis, with log-rank tests for comparisons. Cox proportional hazards regression models were employed to assess whether PNI was an independent risk factor for mortality within 28 days, with results presented as hazard ratios (HR) and 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 2,121 elderly septic patients were included, with 1,482 in the survival group and 639 in the mortality group. There were no significant intergroup differences in gender and weight ($p > 0.05$). However, the mortality group had significantly higher ages; SOFA

TABLE 1. Patient characteristics

	Total population (n=2121)	Survival group (n=1482)	Death group (n=639)	t/Z/X ²	p
Demographics					
Age, years	77.0 (70.0, 83.0)	76.0 (70.0, 83.0)	77.0 (71.0, 84.0)	-1.977	0.048
Gender, n (%)					
Male	1131 (52.9)	801 (53.83)	330 (51.08)	1.367	0.242
Female	990 (47.1)	681 (46.17)	309 (48.92)		
Weight (kg)	73.7 (62.1, 37.9)	73.8 (62.2, 87.8)	73.4 (61.5, 87.0)	-0.497	0.620
Scoring systems					
SOFA	1 (0, 3)	1 (0, 2)	2 (1, 4)	-9.158	<0.001
APACHE III score	60 (47, 76)	55 (44, 69)	73 (58, 92)	-16.499	<0.001
Laboratory parameters					
WBC count (10 ⁹ /L)	11.3 (7.0, 16.3)	11.4 (7.2, 16.3)	11.2 (6.6, 16.2)	-0.348	0.728
RDW (10 ⁹ /L)	15.1 (14, 16.65)	14.9 (13.8, 16.3)	15.6 (14.5, 17.4)	-1.825	<0.001
Hemoglobin	9.22±1.94	9.25±1.94	1.19±1.93	3.951	<0.001
Lymphocytes (10 ⁹ /L)	0.7 (0.4, 1.2)	0.7 (0.4, 1.1)	0.7 (0.3, 1.3)	-0.467	0.64
Platelet count (10 ⁹ /L)	164 (107, 237)	167 (112, 240)	157 (94, 231)	-3.208	<0.001
Creatinine (mEq/L)	1.3 (0.9, 2.1)	1.2 (0.8, 1.9)	1.5 (1.0, 2.4)	-6.504	<0.001
BUN (mg/dl)	3 (1.9, 4.7)	2.8 (1.8, 4.3)	3.6 (2.3, 5.6)	-7.563	<0.001
Albumin (g/L)	27.79±6.46	28.61±6.19	26.77±6.65	8.136	<0.001
PNI	32.70 (27.90, 37.90)	33.25 (28.90, 38.26)	31.02 (25.40, 36.75)	3.285	<0.001
Anion gap (mmol/L)	10 (8, 13)	10 (8, 12)	12 (9, 15)	-13.278	<0.001
Hemoglobin (g/dl)	25 (21, 28.50)	26 (22, 29)	23 (18, 26)	5.451	<0.001
Potassium (mmol/L)	3.91±0.65	3.88±0.62	3.96±0.89	-4.29	<0.001
Bicarbonate	24.56±6.15	26.11±5.52	22.65±6.34	11.441	<0.001
Chloride (mmol/L)	105.97±7.21	105.89±6.62	105.96±7.78	-0.187	0.852
ICU LOS	3.7 (2.0, 7.8)	3.7 (2.0, 7.9)	3.8 (2.1, 7.7)	-0.645	0.519

SOFA: Sequential Organ Failure Assessment; APACHE III: Acute Physiology and Chronic Health Evaluation III score; WBC: White blood cell; RDW: Red cell distribution width; BUN: Blood urea nitrogen; PNI: Prognostic nutritional index; ICU: Intensive care unit; ICU LOS: length of stay in ICU

scores; APACHE-III scores; red cell distribution width; and serum creatinine, blood urea nitrogen, anion gap, and potassium levels compared to the survival group ($p<0.05$). Additionally, the mortality group had significantly lower platelet counts; PNI values; and hemoglobin, albumin, and bicarbonate levels ($p<0.05$). These findings suggest that higher inflammatory and organ dysfunction indicators are closely related to poor prognosis in elderly septic patients. Detailed data are presented in Table 1.

Restricted Cubic Spline Analysis

To assess the relationship between PNI and 28-day all-cause mortality risk, restricted cubic spline (RCS) analysis was used to determine two critical cutoff values for PNI: 29.24 and 47.77. RCS analysis revealed a signif-

icant nonlinear relationship between PNI and 28-day mortality risk ($X^2<0.001$, $p<0.001$). As PNI increased from lower values, mortality risk significantly decreased. However, when PNI exceeded 47.77, mortality risk began to rise. Based on these findings, patients were divided into three groups: $PNI<29.24$ (extreme group), $29.24\leq PNI\leq 47.77$ (moderate group), and $PNI>47.77$ (extreme group). Survival analysis showed that the cumulative survival curves for the $PNI<29.24$ and $PNI>47.77$ groups were nearly identical and significantly lower than that of the moderate PNI group ($29.24\leq PNI\leq 47.77$). Therefore, the $PNI<29.24$ and $PNI>47.77$ groups were combined into a single extreme PNI group to more clearly illustrate the relationship between PNI and outcome. Detailed analysis results are shown in Figure 2.

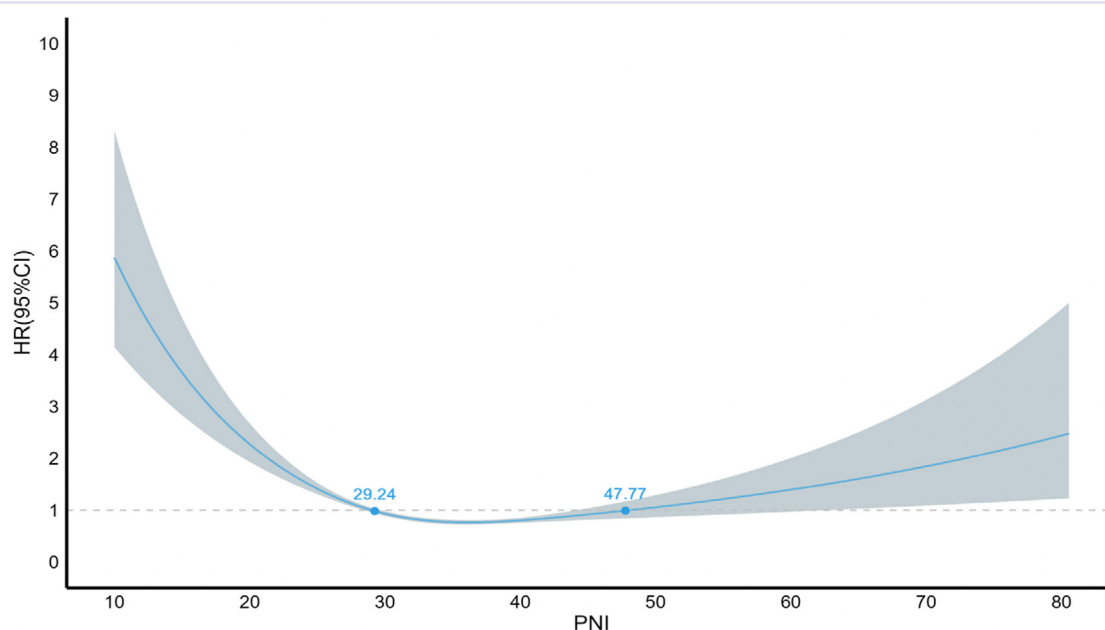


FIGURE 2. PNI Levels and 28-day all-cause mortality risk.

HR: Hazard ratio; CI: Confidence interval; PNI: Prognostic nutritional index

Kaplan-Meier Survival Curves

Kaplan-Meier survival curve analysis demonstrated that patients in the extreme PNI group ($\text{PNI} < 29.24$ or $\text{PNI} > 47.77$) had significantly lower cumulative survival rates at 28 days compared to those in the moderate PNI group ($29.24 \leq \text{PNI} \leq 47.77$) (Log-rank test, $p < 0.001$). This finding further confirmed the importance of PNI in the clinical outcomes of elderly septic patients, indicating that abnormal fluctuations in PNI levels are closely related to higher mortality (Fig. 3).

Cox Regression Analysis

The unadjusted Cox regression analysis model disclosed that the mortality risk was significantly higher in the extreme PNI group than in the moderate PNI group ($\text{HR} = 1.864$, $p < 0.001$). After adjusting for confounding factors such as age, gender, SOFA score, APACHE-III score, serum albumin, and lymphocyte count, the mortality risk in the extreme PNI group remained significantly elevated ($\text{HR} = 1.349$, $p = 0.004$). Additionally, age, serum albumin, red cell distribution width, and lymphocyte count were also associated with mortality risk in the adjusted model ($p < 0.05$). Notably, hemoglobin level shifted from a protective factor to a risk factor after adjustment ($\text{HR} = 1.045$, $p = 0.044$), highlighting the importance of adjusting for confounding factors. Detailed results are presented in Table 2.

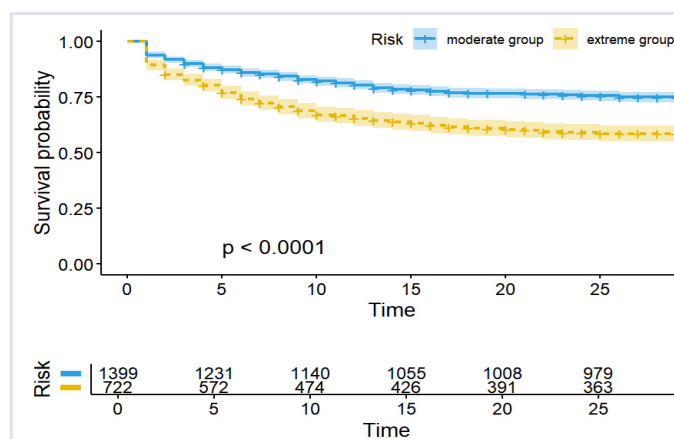


FIGURE 3. 28-day cumulative survival rate curve.

DISCUSSION

The clinical manifestations of sepsis are often atypical in elderly patients and easily overlooked, leading to diagnostic and treatment delays, which in turn expedite further clinical deterioration. Therefore, early diagnosis and prognostic assessment are crucial for improving clinical outcomes in elderly septic patients. To our knowledge, this study is the first to systematically explore the relationship between PNI and 28-day all-cause mortality in elderly septic patients, filling a critical knowledge gap. Our findings suggest that PNI can serve as an indepen-

TABLE 2. Cox regression analysis model

	Model 1			Model 2		
	HR	95% CI	p	HR	95% CI	p
PNI						
Moderate group	Reference			Reference		
Extreme group	1.799	1.460–2.218	<0.001	1.349	1.099–1.656	0.004
Age	1.005	0.992–1.018	0.476			
Albumin	0.946	0.930–0.963	<0.001	0.978	0.955–1.002	0.067
RDW	1.145	1.103–1.187	<0.001	1.060	1.014–1.108	0.010
Lymphocyte	1.085	0.973–1.210	0.143			
WBC	0.992	0.979–1.005	0.226			
Hemoglobin	0.918	0.869–0.969	0.002	1.034	0.974–1.097	0.274
Platelets	0.999	0.999–1.000	0.262			
BUN	1.075	1.039–1.113	<0.001	0.969	0.918–1.022	0.249
Creatinine	1.129	1.056–1.208	<0.001	0.940	0.840–1.052	0.284
Potassium	1.307	1.120–1.526	<0.001	1.097	0.934–1.288	0.260
Weight	1.002	0.997–1.007	0.381			
SOFA	1.290	1.232–1.351	<0.001	1.173	1.116–1.233	<0.001
Gender	0.885	0.719–1.089	0.248			
Total_ICU_stay	1.002	0.988–1.017	0.738			
APACHE-III	1.031	1.027–1.035	<0.001	1.018	1.013–1.022	<0.001
Anion gap	1.164	1.145–1.183	<0.001	1.091	1.065–1.117	<0.001
Bicarbonate	0.897	0.880–0.914	<0.001	0.956	0.936–0.978	<0.001
Chloride	0.987	0.972–1.002	0.086			

HR: Hazard ratio; CI: Confidence interval; PNI: Prognostic nutritional index; RDW: Red cell distribution width; WBC: White blood cell; BUN: Blood urea nitrogen; SOFA: Sequential Organ Failure Assessment; ICU: Intensive care unit; APACHE III: Acute Physiology and Chronic Health Evaluation III score

dent indicator for prognostic risk stratification in elderly septic patients. Its calculation is relatively simple and easily performed, thereby facilitating its clinical application.

Our study identified both high (PNI>47.77) and low (PNI<29.24) PNI levels as independent risk factors for 28-day all-cause mortality. This result indicates that PNI can effectively predict the short-term prognosis of elderly septic patients. Its prognostic value is likely closely related to the pathophysiology of sepsis. Specifically, PNI integrates albumin and peripheral blood lymphocyte count, simultaneously reflecting nutritional status and immune function, thereby providing a comprehensive assessment of the pathodynamics of sepsis.

Albumin is the primary negative acute-phase serum protein, with multiple functions in inflammatory responses that include antioxidant and anticoagulant activities and maintenance of plasma colloid osmotic pressure. Hypoalbuminemia typically indicates hyperinflammation and

malnutrition, which are closely related to poor prognosis in septic patients [15, 16]. As a regulatory adaptation, lymphocytes secrete anti-inflammatory cytokines (e.g., interleukin-10, IL-10) to suppress excessive inflammatory responses. However, hyperinflammation frequently leads to lymphopenia and consequent immune suppression [16].

Although CRP and PCT are currently the most widely used biomarkers for monitoring sepsis, their sensitivity and specificity vary widely between numerous studies [17]. Some reports suggest that PCT and CRP may be more helpful in ruling out rather than ruling in sepsis [18]. Therefore, the use of PNI to comprehensively assess nutritional and immune status is worth consideration. Additionally, compared to the Geriatric Nutritional Risk Index (GNRI) [19], PNI places greater emphasis on immune function assessment, which is significant for the prognosis of septic patients. GNRI can reflect nutritional status, but its

assessment of immune function is insufficient, and its component serum creatinine changes slowly, impeding the rapid identification of disease progression.

Multiple recent studies have explored the prognostic value of PNI in numerous diseases. For example, Wu et al. [20] demonstrated that PNI is an independent prognostic factor for 30-day all-cause mortality in septic patients, consistent with the findings of this study. However, our study further revealed the nonlinear relationship between PNI and 28-day all-cause mortality, suggesting that the prognostic value of PNI in elderly septic patients may be more complex. Moreover, Li et al. [21] found that PNI is independently associated with the presence and severity of neonatal sepsis, indicating that PNI may have universal prognostic significance across age groups of septic patients. Elderly septic patients have more comorbidities and immunodeficiencies than their neonatal counterparts. Therefore, the prognostic value of PNI may be more clinically significant in elderly patients. Our RCS analysis found a nonlinear relationship between PNI and 28-day all-cause mortality, with both high and low PNI levels being risk factors for death. We hypothesize that this may be related to the complex pathophysiology of sepsis: high PNI levels may indicate excessive inflammation, while low PNI levels may reflect malnutrition and immune suppression. This dual relationship suggests that in clinical practice, PNI should not be simply regarded as a single prognostic indicator but rather assessed in combination with individual patient conditions (e.g., nutritional status and severity of inflammation).

Limitations of this study must be acknowledged. First, its retrospective study design may have introduced selection and information biases. Although we used RCS analysis and Cox regression models to minimize the impact of confounding factors, potential biases cannot be completely excluded. Second, the MIMIC database designates all patients aged over 90 years as 90 years old, which may have degraded the precision of age-related analyses. Additionally, the lack of long-term follow-up data precluded the assessment of the impact of PNI on long-term clinical outcomes. Finally, this study did not address all variables that may affect outcomes, such as treatment plans and comorbidities, which may have impacted the study results. Future research should prioritize: (1) directly comparing PNI's prognostic performance against established scores (e.g., APACHE III, SOFA, POSMI) using the same cohort, as demonstrated in Reference 15, to validate its clinical utility; (2) adopting multicenter prospective designs to minimize retrospective biases;

(3) integrating PNI with dynamic biomarkers (e.g., cytokines, DAMPs) to enhance prognostic accuracy; (4) developing comprehensive models that synergize inflammatory, nutritional, and immune indicators; and (5) evaluating PNI's long-term prognostic value to optimize therapeutic strategies for elderly septic patients.

CONCLUSION

To our knowledge, our MIMIC-based study is the first investigation of the relationship between PNI and 28-day all-cause mortality in elderly septic patients. The results suggest that PNI may serve as an independent indicator for prognostic risk stratification in elderly septic patients. The calculation of PNI is relatively simple and easily performed, facilitating its clinical application. However, given the limitations of this investigation, future prospective studies are needed to further validate the prognostic value of PNI.

Informed Consent: The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA), and informed consents were exempted due to all patients' data were anonymized before the data were obtained.

Conflict of Interest: The authors declared that they have no conflict of interest.

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