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Article

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Abstract

Background

Sepsis is a life-threatening syndrome characterized by infection-induced dysregulated host response and multiple organ dysfunction, often requiring various forms of organ support. This study aimed to investigate the association between the prognostic nutritional index (PNI) and 28-day organ support-free days (OSFD-28) in critically ill patients with sepsis.

Methods

A retrospective cohort study was conducted using data extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. The association between baseline PNI and OSFD-28 was evaluated using ordinal logistic regression models and restricted cubic spline (RCS) analyses. Joint risk stratification and multiple sensitivity analyses were further performed to assess the robustness and clinical interpretability of the findings.

Results

A total of 9,619 adult patients with sepsis admitted to the intensive care unit (ICU) were included. After full adjustment for potential confounders, a higher baseline PNI was independently associated with more OSFD-28. For every 10-point increase in PNI, the common odds of achieving a higher OSFD-28 category increased by 19% (common OR, 1.19; 95% CI, 1.13–1.24; $P < 0.001$). RCS analysis demonstrated a significant nonlinear association between PNI and OSFD-28, with the greatest prognostic benefit observed in patients with lower PNI levels. Similar associations were observed for individual organ support-free day outcomes, and multiple sensitivity analyses confirmed the robustness of the primary findings.

Conclusions

Higher baseline PNI was independently associated with more 28-day organ support-free days in adult ICU patients with sepsis, with the strongest association observed in the lower PNI range. PNI may serve as a simple indicator for identifying patients at increased risk of poor overall recovery; however, its clinical utility requires further validation in prospective studies.

Keywords: Sepsis; Prognostic nutritional index; Organ support-free days; Critical care; MIMIC-IV; Restricted cubic spline

Introduction

Sepsis is a life-threatening syndrome characterized by organ dysfunction resulting from a dysregulated host response to infection and remains a major cause of mortality and healthcare resource utilization among critically ill patients[1, 2]. Patients with sepsis frequently develop acute dysfunction of multiple organ systems, including the respiratory, cardiovascular, and renal systems, often requiring invasive mechanical

ventilation, vasopressor therapy, and renal replacement therapy (RRT)[3]. Previous prognostic studies in sepsis have primarily focused on mortality[4, 5]; however, mortality alone does not adequately capture the burden of persistent organ support among survivors or reflect the overall recovery from critical illness. Therefore, outcome measures integrating both survival and dependence on organ support may provide a more comprehensive assessment of prognosis in patients with sepsis.

The prognostic nutritional index (PNI), calculated from serum albumin concentration and peripheral absolute lymphocyte count[6], is an easily obtainable biomarker reflecting nutritional, inflammatory, and immune status. Serum albumin reflects multiple physiological processes, including nutritional reserve, systemic inflammation, hepatic synthetic function, and capillary permeability[7, 8], whereas lymphopenia is closely associated with sepsis-induced immunosuppression and adverse clinical outcomes[9]. Previous studies have demonstrated that a lower PNI is associated with an increased risk of postoperative complications, mortality, and poor clinical outcomes in patients with malignancies[10, 11], major surgery[12], cardiovascular diseases[13], and critical illness[14]. In patients with sepsis, PNI has been shown to facilitate mortality risk stratification[5, 15, 16]; however, whether baseline PNI is associated with subsequent liberation from organ support and overall recovery remains largely unknown.

Twenty-eight-day organ support-free days (OSFD-28), which incorporates both survival status and the duration of dependence on invasive mechanical ventilation, vasopressor therapy, and RRT, has emerged as a clinically meaningful endpoint reflecting short-term overall recovery in critically ill patients[17, 18]. Given that malnutrition, dysregulated inflammation, and immune dysfunction may influence not only mortality but also recovery of organ function and liberation from life-sustaining therapies, we hypothesized that baseline PNI would be associated with OSFD-28. Therefore, using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, this study aimed to investigate the association between early ICU PNI and OSFD-28 in adult patients with sepsis, and further explore its nonlinear relationship and potential value for clinical risk stratification.

Methods

Data source

This retrospective cohort study was conducted using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.0) database, a large publicly available critical care database containing comprehensive clinical information from 94,458 ICU stays/admissions admitted to the intensive care units (ICUs) of Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, USA, between 2008 and 2019[19]. The study author completed the Collaborative Institutional Training Initiative (CITI) program and obtained authorization to access the database (Certification No. 13976153). The use of the MIMIC-IV database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center. All patient information was de-identified before release; therefore, informed consent was waived.

Study population

Adult patients (≥18 years) with a first ICU admission who fulfilled the Sepsis-3 criteria (suspected infection plus an acute increase in SOFA score of ≥2 points) were eligible for inclusion.Patients with hematologic malignancies were excluded because of the potential influence of underlying hematologic disorders on serum albumin concentration, lymphocyte count, and prognosis. Hematologic malignancies were

identified according to the International Classification of Diseases (ICD) diagnosis codes.

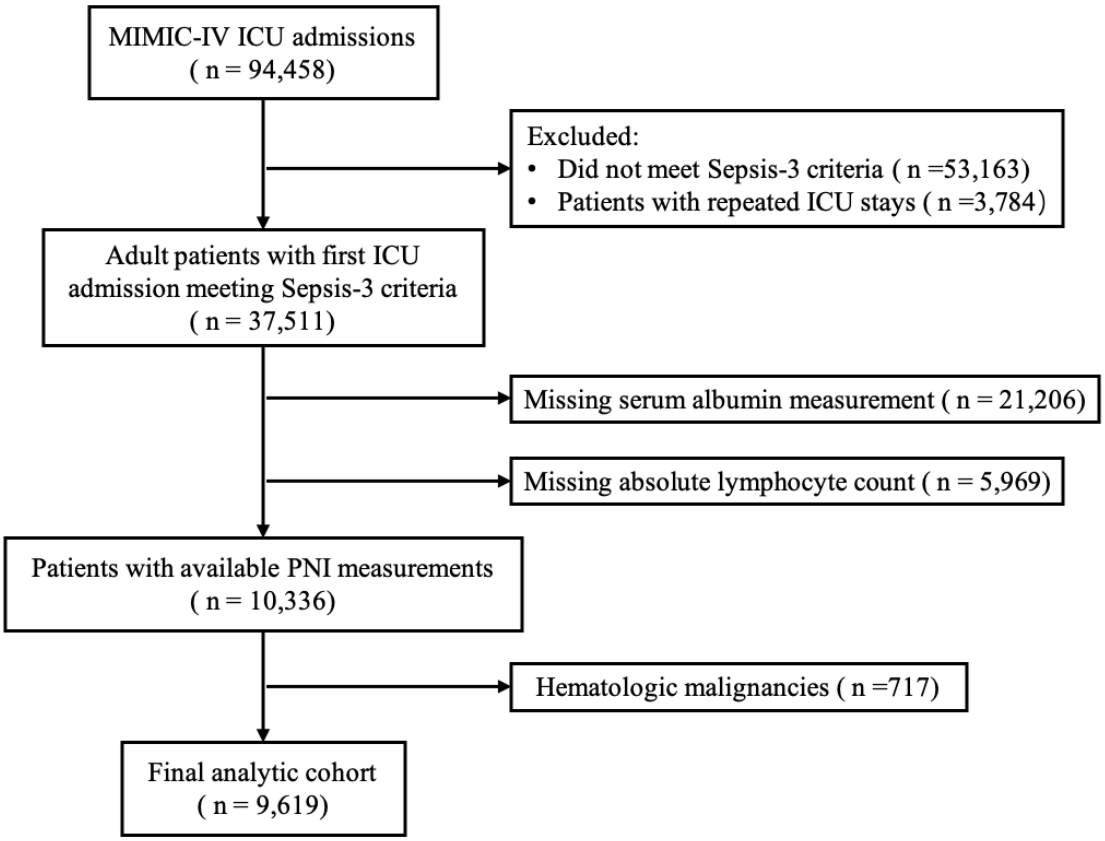


Figure 1. Flowchart of patient selection

Exposure and outcomes

The prognostic nutritional index (PNI) was calculated using the following formula:

$$PNI = 10 \times \text{serum albumin (g/dL)} + 5 \times \text{absolute lymphocyte count(10\^9/L)}$$

Baseline PNI was calculated using laboratory values obtained within the 24-hour window surrounding ICU admission. When two measurements were equally close to ICU admission, the earlier measurement was selected.

The primary outcome was 28-day organ support-free days (OSFD-28), defined as the number of days during the first 28 days after ICU admission that patients were alive and free from invasive mechanical ventilation, vasopressor therapy, and renal replacement therapy (RRT). Patients who died within 28 days after ICU admission were assigned an OSFD-28 value of 0.

Secondary outcomes included 28-day mortality and organ-specific support-free days. Using similar definitions, the number of days during the first 28 days that patients survived without invasive mechanical ventilation, vasopressor therapy, or RRT was calculated separately. Patients who died within 28 days were assigned a value of 0 for all corresponding organ support-free day outcomes.

Study variables

The study variables included age, sex, body mass index (BMI), Charlson Comorbidity Index (CCI), 24-hour Sequential Organ Failure Assessment (SOFA) score after ICU admission, infection source, and admission type.

BMI was calculated based on admission weight and height using the following formula:

BMI = weight(kg)/height(m)^2

If height measurements were unavailable during the current ICU admission, height values from other hospital admissions of the same patient were used.

The CCI, individual comorbidities, and Acute Physiology Score III (APS III) were extracted from the MIMIC-IV derived tables. The SOFA score was defined as the worst SOFA score recorded during the first 24 hours after ICU admission. Infection sources were determined based on ICD diagnosis codes and microbiological specimen sources.

Vital signs and laboratory variables included glucose, mean arterial pressure (MAP), respiratory rate, peripheral oxygen saturation (SpO_2), white blood cell count, platelet count, hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, blood urea nitrogen (BUN), potassium, sodium, calcium, prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR).

All these variables were collected within the first 24 hours after ICU admission. For variables with multiple measurements, the worst value was selected. Early organ support status was also included, including invasive mechanical ventilation, vasopressor therapy, and RRT within the first 24 hours after ICU admission.

Statistical analysis

All statistical analyses were performed using R software (version 4.4.3). A two-sided α level of 0.05 was considered statistically significant.

Baseline clinical characteristics were described according to PNI tertiles. The proportion of missing values for each variable is presented in Supplementary Table 1. Missing covariate data were handled using multiple imputation with 30 imputed datasets, and estimates were pooled using Rubin's rules.

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR), according to their distribution. Categorical variables were summarized as numbers and percentages.

For comparisons of baseline characteristics across PNI tertiles, normally distributed continuous variables were compared using one-way analysis of variance (ANOVA), whereas non-normally distributed continuous variables were compared using the Kruskal–Wallis test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate.

For ordinal outcomes, including OSFD-28 and organ-specific support-free days, ordinal logistic regression models were applied. Results were reported as common odds ratios (common ORs) with 95% confidence intervals (CIs).

Three models were constructed:

Model 1: unadjusted model.

Model 2: adjusted for age, sex, BMI, CCI, 24-hour SOFA score, infection source, and admission type.

Model 3: fully adjusted model, additionally adjusted for glucose, MAP, respiratory rate, SpO_2, white blood cell count, platelet count, hemoglobin, ALT, AST, total bilirubin, creatinine, BUN, potassium, sodium, calcium, PT, APTT, and INR.

To evaluate potential nonlinear associations between PNI and OSFD-28, restricted cubic spline (RCS) analyses with four knots were performed. Overall association and nonlinear association were assessed using corresponding P values. Similar RCS analyses were conducted to explore nonlinear relationships between PNI and 28-day mortality as well as organ-specific support-free days.

For joint risk stratification analyses, PNI ≤30 was defined as low PNI and PNI >30 as high PNI. SOFA ≤6 was defined as low SOFA and SOFA >6 as high SOFA. Based on these two binary variables, four joint risk groups were generated. The group with high PNI and low SOFA was used as the reference group. Multivariable logistic regression was used to estimate the risk of 28-day mortality among different groups, while corresponding regression models were applied to estimate the adjusted probability of achieving higher OSFD-28 levels.

Results

Baseline characteristics

According to the predefined inclusion and exclusion criteria, a total of 9,619 patients with sepsis were included in the final analysis (Table 1). Among them, 4,142 patients (43.06%) were female, and the 28-day all-cause mortality rate was 25.53%.

Patients were categorized into tertiles according to baseline PNI values. Although age distributions were comparable across the three groups, significant differences were observed in sex, BMI, admission type, comorbidity burden, disease severity, infection sources, laboratory parameters, and early organ support requirements.

Patients in the lowest PNI tertile (T1) exhibited greater disease severity and comorbidity burden compared with those in higher PNI tertiles. The median 24-hour SOFA score decreased progressively across PNI tertiles, from 7.00 (5.00–10.00) in the T1 group to 5.00 (3.00–8.00) in the T3 group. Similarly, the median APS III score decreased from 60.00 (47.00–78.00) in T1 to 45.00 (33.00–61.00) in T3 (both $P < 0.001$).

Differences were also observed in infection sources. Patients with lower PNI values had a higher proportion of gastrointestinal/intra-abdominal infections, whereas urinary tract infections were more frequent among patients with higher PNI values.

Regarding laboratory characteristics, increasing PNI levels were associated with progressively higher concentrations of serum albumin, absolute lymphocyte count, hemoglobin, platelet count, and calcium levels, accompanied by overall improvements in liver, renal, and coagulation-related parameters.

Early organ support requirements also differed across PNI tertiles. Patients in the lowest PNI group had a higher proportion of vasopressor use within the first 24 hours after ICU admission (48.92%) and a higher requirement for RRT compared with the highest PNI group (5.14% vs. 2.87%). The proportion of invasive mechanical ventilation use also differed significantly among the three groups.

Regarding clinical outcomes, patients with lower PNI values exhibited poorer short-term outcomes. The median OSFD-28 was 22.00 days (0.00–27.00) in the T1 group,

compared with 25.00 days (3.00–28.00) in the T2 group and 26.00 days (21.00–28.00) in the T3 group. The 28-day mortality rate decreased progressively across increasing PNI tertiles, with mortality rates of 36.20%, 23.46%, and 16.94% in T1, T2, and T3 groups, respectively. A similar trend was observed for in-hospital mortality (30.68%, 19.74%, and 14.60%, respectively; all $P < 0.001$).

Furthermore, patients with higher PNI values had shorter hospital stays. The median hospital length of stay was 7.85 days (5.18–14.26) in the T3 group, compared with 11.12 days (5.99–20.58) in the T1 group.

Overall, patients with lower baseline PNI values demonstrated greater disease severity, higher comorbidity burden, and increased organ dysfunction burden, accompanied by fewer OSFD-28, higher mortality, and prolonged hospitalization.

Table1. Baseline characteristics

variable	level	Overall（n=9619）	T1 (n=3207)	T2 (n=3206)	T3 (n=3206)	P value
Demographics						
Age, years		66.32 [55.17, 77.20]	66.29 [55.58, 76.75]	66.52 [54.58, 78.40]	66.21 [55.44, 76.60]	0.114
Sex	F	4142 (43.06%)	1424 (44.40%)	1422 (44.35%)	1296 (40.42%)	0.001
	M	5477 (56.94%)	1783 (55.60%)	1784 (55.65%)	1910 (59.58%)	
BMI, kg/m2		27.70 [23.73, 32.85]	27.14 [23.15, 32.50]	27.76 [23.61, 33.48]	27.99 [24.45, 32.74]	<0.001
Race	White	5970 (62.06%)	2012 (62.74%)	1997 (62.29%)	1961 (61.17%)	0.044
	Black	1052 (10.94%)	314 (9.79%)	358 (11.17%)	380 (11.85%)	
	Asian	306 (3.18%)	117 (3.65%)	108 (3.37%)	81 (2.53%)	
	Hispanic/Latino	395 (4.11%)	139 (4.33%)	126 (3.93%)	130 (4.05%)	
	Other/Unknown	1896 (19.71%)	625 (19.49%)	617 (19.25%)	654 (20.40%)	
Admission type	Emergency or urgent	7736 (80.42%)	2709 (84.47%)	2683 (83.69%)	2344 (73.11%)	<0.001
	Elective or planned	587 (6.10%)	92 (2.87%)	81 (2.53%)	414 (12.91%)	
	Other/observation	1296 (13.47%)	406 (12.66%)	442 (13.79%)	448 (13.97%)	
Myocardial infarct		1729 (17.97%)	503 (15.68%)	573 (17.87%)	653 (20.37%)	<0.001
Hypertension		6659 (69.23%)	2071 (64.58%)	2274 (70.93%)	2314 (72.18%)	<0.001
Coronary heart disease		3011 (31.30%)	822 (25.63%)	922 (28.76%)	1267 (39.52%)	<0.001
Cerebrovascular disease		1226 (12.75%)	296 (9.23%)	419 (13.07%)	511 (15.94%)	<0.001
Congestive heart failure		3123 (32.47%)	921 (28.72%)	1158 (36.12%)	1044 (32.56%)	<0.001
Chronic pulmonary disease		2460 (25.57%)	770 (24.01%)	906 (28.26%)	784 (24.45%)	<0.001
Diabetes mellitus		3190 (33.16%)	1016 (31.68%)	1103 (34.40%)	1071 (33.41%)	0.064
Renal disease		2575 (26.77%)	835 (26.04%)	966 (30.13%)	774 (24.14%)	<0.001
Liver disease		2352 (24.45%)	951 (29.65%)	832 (25.95%)	569 (17.75%)	<0.001
Cancer		1298 (13.49%)	683 (21.30%)	411 (12.82%)	204 (6.36%)	<0.001
Severity scores						
CCI		5.00 [3.00, 8.00]	6.00 [4.00, 8.00]	5.00 [3.00, 8.00]	5.00 [3.00, 7.00]	<0.001
SOFA		6.00 [4.00, 9.00]	7.00 [5.00, 10.00]	6.00 [4.00, 9.00]	5.00 [3.00, 8.00]	<0.001
APSIII		53.00 [39.00, 70.00]	60.00 [47.00, 78.00]	52.00 [41.00, 68.00]	45.00 [33.00, 61.00]	<0.001
Infection characteristics						
Respiratory		3389 (35.23%)	1169 (36.45%)	1244 (38.80%)	976 (30.44%)	<0.001

Urinary	2336 (24.29%)	579 (18.05%)	626 (19.53%)	1131 (35.28%)	
Gastrointestinal/abdominal	2001 (20.80%)	898 (28.00%)	733 (22.86%)	370 (11.54%)	
Skin/soft tissue	275 (2.86%)	116 (3.62%)	88 (2.74%)	71 (2.21%)	
Central nervous system	205 (2.13%)	46 (1.43%)	75 (2.34%)	84 (2.62%)	
Primary bloodstream	234 (2.43%)	87 (2.71%)	92 (2.87%)	55 (1.72%)	
Other/unknown	1179 (12.26%)	312 (9.73%)	348 (10.85%)	519 (16.19%)	
Laboratory and vital signs					
Albumin	3.10 [2.60, 3.60]	2.40 [2.10, 2.70]	3.10 [2.90, 3.30]	3.80 [3.50, 4.10]	<0.001
Absolute lymphocyte count	0.97 [0.57, 1.55]	0.62 [0.38, 0.98]	0.93 [0.58, 1.34]	1.58 [1.03, 2.29]	<0.001
Glucose (mg/dL)	130.00 [103.00, 178.00]	127.00 [99.00, 174.00]	132.00 [105.00, 178.75]	133.00 [105.00, 181.00]	<0.001
MAP (mmHg)	80.00 [69.00, 92.00]	77.00 [66.00, 89.00]	80.00 [69.00, 93.00]	82.00 [72.00, 95.00]	<0.001
Respiration rate	20.00 [16.00, 24.00]	20.00 [17.00, 25.00]	20.00 [16.00, 24.00]	18.00 [16.00, 23.00]	<0.001
SpO2 (%)	98.00 [95.00, 100.00]	97.00 [94.00, 100.00]	97.00 [94.00, 100.00]	98.00 [95.50, 100.00]	<0.001
WBC (K/uL)	11.90 [7.90, 17.28]	11.70 [7.00, 17.70]	12.00 [8.00, 17.50]	12.00 [8.50, 16.70]	0.003
Platelet (K/uL)	178.00 [117.00, 257.00]	165.00 [100.00, 259.00]	182.00 [120.00, 263.00]	185.00 [128.00, 250.00]	<0.001
Hemoglobin (g/dL)	10.20 [8.70, 11.90]	9.60 [8.20, 11.10]	10.30 [8.90, 11.90]	10.80 [9.10, 12.60]	<0.001
ALT (IU/L)	29.00 [17.00, 67.00]	33.00 [17.00, 75.00]	32.00 [17.75, 78.25]	25.00 [16.00, 49.00]	<0.001
AST (IU/L)	42.00 [24.00, 105.00]	50.00 [26.00, 130.00]	49.00 [26.00, 119.00]	33.00 [21.00, 70.00]	<0.001
Total bilirubin (mg/dL)	0.70 [0.40, 1.80]	0.90 [0.40, 2.55]	0.80 [0.40, 2.00]	0.60 [0.40, 1.10]	<0.001
Creatinine (mg/dL)	1.20 [0.80, 2.10]	1.30 [0.80, 2.30]	1.30 [0.80, 2.20]	1.10 [0.80, 1.70]	<0.001
BUN (mg/dL)	25.00 [15.00, 42.00]	28.00 [17.00, 47.00]	27.00 [17.00, 45.00]	20.00 [13.00, 34.75]	<0.001
Potassium (mEq/L)	4.20 [3.70, 4.70]	4.10 [3.70, 4.70]	4.20 [3.70, 4.70]	4.20 [3.80, 4.70]	0.002
Sodium (mEq/L)	138.00 [135.00, 141.00]	137.00 [134.00, 141.00]	138.00 [134.00, 141.00]	139.00 [136.00, 141.00]	<0.001
Calcium (mmol/L)	8.20 [7.60, 8.80]	7.80 [7.20, 8.30]	8.30 [7.70, 8.80]	8.60 [8.10, 9.10]	<0.001
PT (sec)	15.20 [13.10, 19.00]	16.10 [13.80, 20.30]	14.90 [13.10, 19.50]	14.60 [12.70, 17.60]	<0.001
APTT (sec)	32.10 [27.90, 40.00]	33.70 [29.20, 42.60]	31.80 [27.70, 39.30]	31.10 [27.20, 38.30]	<0.001
INR	1.40 [1.20, 1.70]	1.50 [1.30, 1.90]	1.40 [1.20, 1.80]	1.30 [1.10, 1.60]	<0.001
Early organ support within 24h					
Invasive mechanical ventilation	4908 (51.02%)	1635 (50.98%)	1544 (48.16%)	1729 (53.93%)	<0.001
Vasopressor	4164 (43.29%)	1569 (48.92%)	1235 (38.52%)	1360 (42.42%)	<0.001
RRT	383 (3.98%)	165 (5.14%)	126 (3.93%)	92 (2.87%)	<0.001
Outcomes					
OSFD-28	25.00 [0.00, 28.00]	22.00 [0.00, 27.00]	25.00 [3.00, 28.00]	26.00 [21.00, 28.00]	<0.001
28-day mortality	2456 (25.53%)	1161 (36.20%)	752 (23.46%)	543 (16.94%)	<0.001
In-hospital mortality	2085 (21.68%)	984 (30.68%)	633 (19.74%)	468 (14.60%)	<0.001
Hospital LOS, days	9.58 [5.62, 17.67]	11.12 [5.99, 20.58]	10.03 [5.77, 17.85]	7.85 [5.18, 14.26]	<0.001

238

239 Association of PNI with OSFD-28 and organ-specific support-free days

In ordinal logistic regression analyses, higher baseline PNI was consistently associated with a greater likelihood of achieving higher categories of 28-day organ support-free days (OSFD-28), ventilator-free days, vasopressor-free days, and RRT-free days (Table 2).

Using the lowest PNI tertile (T1) as the reference, the fully adjusted model (Model 3) showed that the adjusted common ORs for OSFD-28 were 1.57 (95% CI, 1.42–1.72) for the middle tertile (T2) and 1.56 (95% CI, 1.40–1.73) for the highest tertile (T3). When PNI was analyzed as a continuous variable, each 10-point increase in PNI was associated with a 19% higher odds of achieving a higher OSFD-28 category (common OR, 1.19; 95% CI, 1.13–1.24; $P < 0.001$). A significant dose–response relationship was also observed across PNI tertiles (P for trend < 0.001).

Component analyses demonstrated similar associations for all organ-specific support-free outcomes. For 28-day ventilator-free days, the adjusted common ORs were 1.55 (95% CI, 1.41–1.71) for T2 and 1.56 (95% CI, 1.40–1.73) for T3, with an adjusted common OR of 1.19 (95% CI, 1.13–1.25) per 10-point increase in PNI. For 28-day vasopressor-free days, the adjusted common ORs were 1.60 (95% CI, 1.45–1.77) and 1.47 (95% CI, 1.32–1.64) for T2 and T3, respectively, while each 10-point increase in PNI was associated with a common OR of 1.14 (95% CI, 1.08–1.20). For 28-day RRT-free days, the adjusted common ORs were 1.84 (95% CI, 1.64–2.08) for T2 and 2.04 (95% CI, 1.78–2.33) for T3, and the adjusted common OR per 10-point increase in PNI was 1.41 (95% CI, 1.32–1.51). All associations remained statistically significant ($P < 0.001$).

Compared with the unadjusted model, the magnitude of the associations was attenuated after sequential adjustment for potential confounders but remained statistically significant in the fully adjusted model.

Table 2. Association between baseline PNI and 28-day organ support-free days and organ-specific support-free days

Exposure	**Model 1**		**Model 2**		**Model 3**	
	OR（95%CI）	**P**	**OR（95%CI）**	**P**	**OR（95%CI）**	**P**
OSFD-28						
T1	Reference		Reference		Reference	
T2	1.69 (1.54-1.84)	<0.001	1.54 (1.40-1.69)	<0.001	1.57 (1.42-1.72)	<0.001
T3	2.22 (2.03-2.42)	<0.001	1.48 (1.35-1.63)	<0.001	1.56 (1.40-1.73)	<0.001
P for trend	-	<0.001	-	<0.001	-	<0.001
As continuous	1.41 (1.35-1.46)	<0.001	1.16 (1.11-1.21)	<0.001	1.19 (1.13-1.24)	<0.001
28-day ventilator free days						
T1	Reference		Reference		Reference	
T2	1.63 (1.49-1.78)	<0.001	1.50 (1.36-1.64)	<0.001	1.55 (1.41-1.71)	<0.001
T3	2.07 (1.89-2.26)	<0.001	1.44 (1.30-1.58)	<0.001	1.56 (1.40-1.73)	<0.001
P for trend	-	<0.001	-	<0.001	-	<0.001
As continuous	1.37 (1.31-1.42)	<0.001	1.14 (1.09-1.19)	<0.001	1.19 (1.13-1.25)	<0.001
28-day vasopressor free days						
T1	Reference		Reference		Reference	
T2	1.81 (1.65-1.98)	<0.001	1.63 (1.48-1.79)	<0.001	1.60 (1.45-1.77)	<0.001
T3	2.18 (1.99-2.38)	<0.001	1.50 (1.36-1.66)	<0.001	1.47 (1.32-1.64)	<0.001
P for trend	-	<0.001	-	<0.001	-	<0.001

As continuous	1.38 (1.33-1.44)	<0.001	1.16 (1.10-1.21)	<0.001	1.14 (1.08-1.20)	<0.001
28-day RRT free days						
T1	Reference		Reference		Reference	
T2	1.84 (1.66-2.04)	<0.001	1.70 (1.52-1.91)	<0.001	1.84 (1.64-2.08)	<0.001
T3	2.85 (2.56-3.19)	<0.001	1.88 (1.66-2.13)	<0.001	2.04 (1.78-2.33)	<0.001
P for trend	-	<0.001	-	<0.001	-	<0.001
As continuous	1.67 (1.58-1.76)	<0.001	1.35 (1.27-1.43)	<0.001	1.41 (1.32-1.51)	<0.001

Model 1: Unadjusted

Model 2: Adjusted for age; sex; BMI; CCI; SOFA_24h; infection_source; admission_type

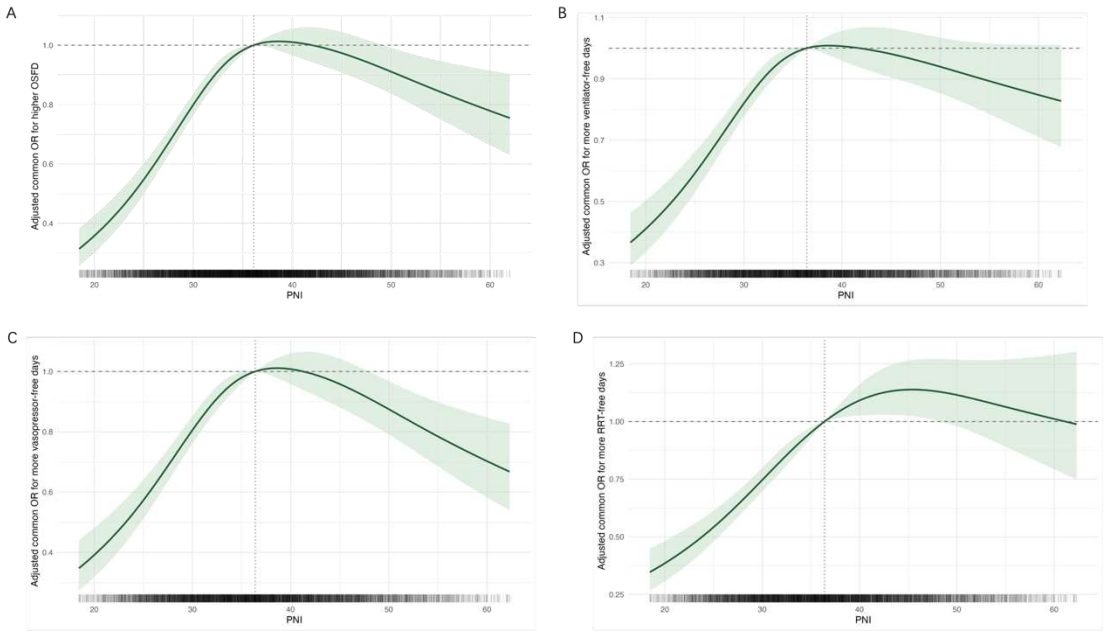
Model 3: Adjusted for age; sex; BMI; CCI; SOFA_24h; infection_source; admission_type; glucose; MAP; respiration rate; SpO2; WBC; platelet; hemoglobin; ALT; AST; total bilirubin; creatinine; BUN; potassium; sodium; calcium; PT; PTT; INR

Nonlinear association between PNI and OSFD-28

Restricted cubic spline (RCS) analyses demonstrated a significant nonlinear association between baseline PNI and 28-day OSFD-28 (Figure 2). As PNI increased, the adjusted common OR for achieving a higher OSFD-28 category increased steeply at lower PNI levels, reached a plateau, and then gradually declined at higher PNI levels. Both the overall and nonlinear association tests were statistically significant ($P<0.001$ for both).

Similar nonlinear associations were observed for 28-day ventilator-free days, vasopressor-free days, and RRT-free days. Although the magnitude of the associations differed across organ-specific outcomes, the overall shapes of the spline curves were comparable to that of OSFD-28, with the steepest increase in adjusted common OR observed within the lower range of PNI values (Figure 2).

Figure 2. Restricted cubic spline analyses of the associations between baseline PNI and 28-day organ support-free days and organ-specific support-free days.



Exploratory segmented regression analysis

An exploratory segmented regression analysis (Supplementary Table S3) identified a change in slope at a PNI value of approximately 33.90. Below this threshold, each 10-point increase in PNI was associated with substantially higher odds of achieving a higher OSFD-28 category (common OR, 2.14; 95% CI, 1.90–2.40; P < 0.001). Above the threshold, the association was attenuated and became inverse (common OR, 0.90; 95% CI, 0.85–0.96; P = 0.001).

Sensitivity analyses

To assess the robustness of the primary findings, the primary analysis was first repeated in the complete-case cohort. Five additional sensitivity analyses were subsequently performed within the complete-case cohort (Supplementary Table S4). These included: (1) repeating the primary analysis using the complete-case cohort; (2) replacing the Charlson Comorbidity Index with individual comorbidities, including malignancy, liver disease, HIV infection, chronic kidney disease, heart failure, and diabetes; (3) replacing the SOFA score with the APS III score; (4) excluding infection source from the adjustment model; (5) additionally adjusting for invasive mechanical ventilation, vasopressor therapy, and renal replacement therapy within the first 24 hours after ICU admission; and (6) excluding patients with baseline PNI values above the 99th percentile.

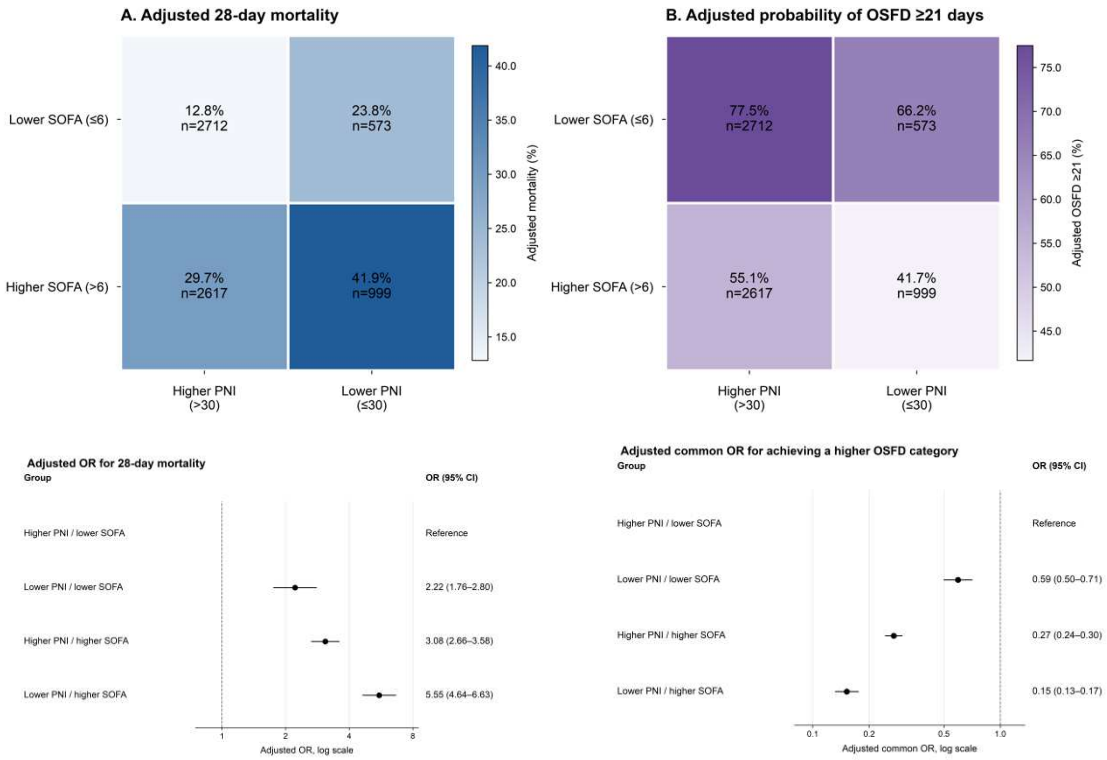
Across all sensitivity analyses, the association between baseline PNI and OSFD-28 remained materially unchanged, supporting the robustness of the primary findings.

Joint risk stratification

Joint risk stratification based on PNI and SOFA score was further performed (Figure 3). Overall, 28-day mortality increased progressively, whereas the probability of achieving higher OSFD-28 levels decreased stepwise with decreasing PNI and increasing SOFA scores.

Patients with PNI >30 and SOFA ≤6 had the most favorable outcomes, with an adjusted 28-day mortality of 12.8% and an adjusted probability of achieving OSFD-28 ≥21 days of 77.5%. Among patients with SOFA ≤6, those with PNI ≤30 had a higher adjusted 28-day mortality (23.8%) and a lower adjusted probability of achieving OSFD-28 ≥21 days (66.2%). Compared with the reference group, the adjusted OR for 28-day mortality was 2.22 (95% CI, 1.76–2.80), whereas the adjusted common OR for achieving higher OSFD-28 categories was 0.59 (95% CI, 0.50–0.71). Outcomes deteriorated further among patients with SOFA >6.

Figure 3. Joint risk stratification according to baseline PNI and SOFA score for 28-day mortality and organ support-free days.



Discussion

In this study, we analyzed 9,619 adult patients with sepsis admitted to the ICU in the MIMIC-IV database and systematically evaluated the association between baseline prognostic nutritional index (PNI) and organ support-free days at 28 days (OSFD-28). Several main findings emerged. First, a higher PNI was significantly associated with more OSFD-28, and this association persisted after adjustment for demographic

characteristics, comorbidity burden, illness severity, source of infection, and multiple vital signs and laboratory parameters. Second, the association between PNI and OSFD-28 was significantly nonlinear. Changes in OSFD-28 associated with increasing PNI were most pronounced within the lower PNI range, whereas further increases in PNI beyond moderate levels were associated with relatively limited differences in outcomes. Third, the associations of PNI with ventilator-free days, vasopressor-free days, and renal replacement therapy (RRT)-free days were directionally consistent with the primary outcome, suggesting that the observed association was not confined to a single form of organ support. Fourth, joint stratification by PNI and Sequential Organ Failure Assessment (SOFA) score showed that, even among patients with lower SOFA scores, lower PNI was associated with higher mortality and fewer OSFD-28. This finding suggests that the host characteristics reflected by PNI may provide clinical information distinct from the severity of acute organ dysfunction. Overall, these findings remained consistent across multiple sensitivity analyses.

Previous studies investigating PNI in patients with sepsis have primarily focused on mortality, with several studies reporting associations between lower PNI and increased short- and long-term mortality[5, 20]. The present study extends these observations by focusing on organ support burden in addition to survival. Although mortality remains one of the most important clinical outcomes in critical care research, it does not characterize the clinical course of survivors with respect to their need for and liberation from life-sustaining therapies. OSFD belongs to the broader family of support-free-day composite outcomes[21] and incorporates both survival and freedom from invasive mechanical ventilation, vasoactive therapy, and RRT. It therefore provides information on the burden of organ support and short-term clinical recovery beyond that captured by mortality alone. Accordingly, the principal contribution of this study is not simply to reaffirm the association between PNI and mortality, but rather to demonstrate that baseline PNI is also associated with a composite outcome reflecting survival and freedom from organ support during the subsequent 28 days. Analyses of the individual components further showed directionally consistent associations across mechanical ventilation, vasoactive therapy, and RRT. Moreover, restricted cubic spline (RCS) analyses demonstrated that these associations were not simply linear, with the most pronounced changes in outcomes occurring within the lower PNI range. Thus, rather than merely categorizing PNI into high- and low-level groups, our findings further characterize the continuous and nonlinear relationship between PNI and organ support-related outcomes. The joint PNI–SOFA analysis provides an additional perspective on this relationship. Whereas SOFA primarily reflects the current severity of acute organ dysfunction in patients with sepsis, PNI may capture aspects of host reserve and inflammatory and immune status. The two measures may therefore characterize different dimensions of the clinical condition of critically ill patients.

PNI is derived from serum albumin concentration and absolute lymphocyte count, and its clinical significance may extend beyond conventional nutritional assessment to encompass several dimensions of host status, including nutritional reserve, systemic inflammation, and immune function[8]. Serum albumin has traditionally been used in the assessment of nutritional status; however, hypoalbuminemia in critically ill patients cannot be attributed solely to malnutrition. Previous studies have demonstrated associations of low serum albumin levels with both increased inflammatory activity and greater nutritional risk[22, 23]. During acute inflammation, increased capillary permeability, altered transcapillary distribution of albumin, and changes in albumin synthesis and catabolism can all contribute to reductions in circulating albumin concentrations[24–26]. Thus, during the early phase of sepsis, serum albumin may reflect information related to both pre-existing nutritional reserve and the current systemic inflammatory response.

The other component of PNI, absolute lymphocyte count, may reflect sepsis-associated alterations in immune function. Lymphopenia is an important feature of immune dysregulation during sepsis[27]. Profound lymphocyte depletion can occur during the course of sepsis, with increased lymphocyte apoptosis representing an important underlying mechanism. In some patients, persistent lymphopenia and impaired immune-cell recovery may also occur[9, 28]. Previous studies have further associated persistent lymphopenia with adverse outcomes, including secondary infections, multiple organ dysfunction, and mortality[29, 30]. Therefore, the lymphocyte component of PNI may, to some extent, capture the immune status of patients responding to severe infection, whereas the albumin component is influenced by both nutritional reserve and the acute inflammatory response. Taken together, PNI may be more appropriately interpreted as a simple composite marker of nutritional–inflammatory–immune host status rather than as a purely nutritional index. In the present study, patients with lower PNI also had higher SOFA and Acute Physiology Score III (APS III) scores, a greater comorbidity burden, higher 28-day mortality, and fewer OSFD-28, findings that are consistent with the interpretation of low PNI as a marker of greater host vulnerability. Accordingly, the association between PNI and OSFD-28 may reflect a broader clinical phenomenon whereby the nutritional, inflammatory, and immune-related host state at the onset of critical illness is associated with the subsequent clinical course of survival and liberation from organ support in patients with sepsis, across varying degrees of acute organ dysfunction. This interpretation also provides a pathophysiological rationale for considering PNI alongside conventional organ dysfunction scores when characterizing patient risk.

Several limitations of this study should be acknowledged. First, this was a retrospective observational study based on a single-center database. Although we adjusted for demographic characteristics, comorbidities, illness severity, and a broad range of clinical and laboratory variables, residual confounding and selection bias cannot be completely excluded. Therefore, the observed association between PNI and

OSFD-28 should not be interpreted as causal, and its generalizability to other healthcare systems and ICU populations requires external validation. Second, host status was assessed using a single PNI measurement obtained early after ICU admission. Consequently, our analyses could not capture dynamic changes in albumin, lymphocyte count, or PNI during the course of sepsis, nor could they distinguish the relative contributions of nutritional, inflammatory, and immune processes to the observed associations. Third, OSFD is a composite outcome incorporating mortality and multiple forms of organ support. Its value may therefore be influenced not only by illness severity and recovery of organ function but also by decisions regarding the initiation and withdrawal of organ support, treatment limitations, and local clinical practice patterns. In addition, the database does not permit continuous assessment of organ support status after hospital discharge. OSFD should therefore be interpreted as an integrated clinical outcome rather than a direct biological measure of organ recovery. Furthermore, because the distributions and death-assignment rules differ across individual organ support-free-day outcomes, the common odds ratios for these component outcomes should not be directly compared as measures of relative effect size. Fourth, the nonlinear patterns identified in the RCS analyses and the inflection points derived from exploratory segmented regression were data-driven. Similarly, the thresholds used in the joint PNI–SOFA stratification have not been validated in an independent cohort. These findings should therefore be regarded primarily as descriptive of the observed association patterns and exploratory for risk stratification rather than as established clinical decision thresholds. Fifth, some covariates contained missing data. Although multiple imputation was used to address missingness and sensitivity analyses were performed to assess the robustness of the primary findings, bias may remain if the underlying missing-data mechanism violated the assumptions required for multiple imputation.

In conclusion, among adult ICU patients with sepsis, higher baseline PNI was associated with more OSFD-28, and this association persisted after multivariable adjustment. The relationship was distinctly nonlinear, with the most pronounced differences in outcomes occurring within the lower PNI range. Directionally consistent associations were also observed for days free from mechanical ventilation, vasoactive therapy, and RRT, while joint stratification by PNI and SOFA provided additional differentiation of outcomes across levels of acute organ dysfunction. Given the clinical information captured by its albumin and lymphocyte components, PNI may serve as a simple marker of nutritional–inflammatory–immune host status that complements conventional assessments of acute organ dysfunction severity. Further studies are warranted to validate these associations and their nonlinear patterns in independent external cohorts and to prospectively investigate the relationship between dynamic changes in PNI and the subsequent course of organ support, as well as their potential clinical relevance.

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