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ORIGINAL RESEARCH

Systemic Immune Inflammation Index (SII) and Prognostic Nutritional Index (PNI) Associated with Prolonged Intensive Care Unit (ICU) Stay in Patients with Pneumonia Complicated with Respiratory Failure

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Background: The length of intensive care unit (ICU) stay is an important index reflects the prognosis of severe pneumonia (SP) combined with respiratory failure (RF). Blood transfusion can alleviate tissue hypoxia in ICU patients, but blood transfusion can affect the prognosis of patients. The objective of this study was to evaluate the effect of immune-nutritional indices (pan-immune inflammation value (PIV), systemic immune inflammation index (SII), system inflammation response index (SIRI), neutrophil-to-albumin ratio (NAR), and prognostic nutritional index (PNI)) on length of stay in patients treated with and without transfusion.

Methods: Total of 3425 pneumonia combined with respiratory failure patients were retrospectively analyzed. Medical records (age, gender, body mass index, history of smoking, history of alcohol drinking, hypertension, diabetes mellitus, lung diseases, invasive mechanical ventilation, blood transfusion, APACHE II score, and laboratory test results) were collected, the relationship between this information and prolonged ICU stay was analyzed.

Results: The average length of ICU stay was 5.32 (2.94, 9.36) days, there were 2521 (73.6%) patients with non-prolonged ICU stay (<9 days) and 904 (26.4%) with prolonged ICU stay (≥9 days). The levels of PIV, SII, and SIRI in prolonged ICU stay patients were higher than those of non-prolonged ICU stay in patients with and without blood transfusion, respectively. Multivariate logistic regression analysis showed that high SII (odds ratio (OR): 2.115, 95% confidence interval (CI): 1.428–3.131, $p<0.001$), and invasive mechanical ventilation (OR: 10.205, 95% CI: 5.623–18.524, $p<0.001$) were associated with prolonged ICU stay in patients with blood transfusion; and low PNI (OR: 1.378, 95% CI: 1.073–1.769, $p=0.012$), invasive mechanical ventilation (OR: 3.566, 95% CI: 2.666–4.771, $p<0.001$) were associated with prolonged ICU stay in patients without blood transfusion.

Conclusion: High SII level and invasive mechanical ventilation were independently associated with prolonged ICU stay in patients treated with blood transfusion; and low PNI level and invasive mechanical ventilation were independently associated with prolonged ICU stay in patients without blood transfusion.

Keywords: pneumonia, respiratory failure, intensive care unit stay, systemic immune inflammation index, prognostic nutritional index

Introduction

Pneumonia is the most common respiratory disease worldwide, mainly affecting children and the elderly over 65 years of age.[1] Some patients may develop severe pneumonia (SP) due to aggravation of lung infection and spread of inflammation, with a fatality rate as high as 30–35%, and may be complicated with hypotension, disturbance of consciousness and multiple organ dysfunction, leading to septic shock and respiratory failure (RF) in severe cases, among which acute RF is one of the most dangerous complications of severe pneumonia, which can further increase the fatality rate of patients.[2]

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Acute RF refers to a sudden respiratory dysfunction in which the lungs are unable to effectively exchange oxygen and carbon dioxide, resulting in insufficient oxygen or excessive carbon dioxide in the blood, which affects the normal function of the organs.[3]

SP combined with RF patients are usually intensive care unit (ICU) patients and need mechanical respiratory support treatment.[4] SP combined with RF patients have more serious conditions, heavier economic burden, higher mortality, and significantly poor treatment effect and quality of life.[5,6] The length of hospital stay is an important index that directly reflects the prognosis, medical quality, and utilization of medical resources.[7] Reducing the length of hospital stay can not only reduce the economic burden of patients and improve the quality of life of patients, but also speed up the turnover of hospital beds and enhance social and economic benefits.[8–10] Therefore, the screening of independent risk factors for prolonged ICU stay in patients with SP complicated with RF has a reference value for clinical prediction of ICU stay in such patients and rational optimization of diagnosis and treatment plan. Moreover, anemia is very common in ICU patients, mainly due to insufficient production or excessive loss of red blood cells. Anemia reduces the oxygen supply to tissues, which increases the length of hospital stay and the risk of death.[11] Blood transfusion can alleviate tissue hypoxia in ICU patients, but blood transfusion can lead to a variety of complications and affect the prognosis of patients.[12,13] Are there differences in risk factors for prolonged ICU stay in patients with SP combined with RF who treated with and without blood transfusion? It is of great clinical significance to evaluate the differences in length of stay and influencing factors in ICU patients with or without blood transfusion therapy.

Inflammation, immunity, and nutritional statuses play important roles in the occurrence and development of some diseases.[14,15] In recent years, some comprehensive inflammatory indices have attracted more and more clinical attention, such as pan-immune inflammation value (PIV), systemic immune inflammation index (SII), and system inflammation response index (SIRI). Several studies have suggested that PIV,[16,17] SII,[18–22] and SIRI[21] associated with some respiratory illness, such as occurrence of pneumonia and chronic obstructive pulmonary disease (COPD), treatment outcomes of lung cancer patients, and progression of COVID-19 patients. Neutrophil-to-albumin ratio (NAR) is an important index that comprehensively reflects the level of systemic immunity and nutritional status, and has been proved to be closely related to tumor and cardiovascular and cerebrovascular diseases by many studies.[23,24] Prognostic nutritional index (PNI) is an index calculated on the basis of human lymphocyte count and serum albumin level,[25] which can reflect the immune and nutritional status of the host.[26] Inflammation is the driving factor of the pathophysiological process of pneumonia. Immune function and inflammatory response are closely related to the occurrence and progression of severe pneumonia. The immune response promotes a complex series of host reactions that prevent progressive tissue damage, isolate and destroy pathogens that cause infection, and repair tissues and functions. A series of inflammatory reactions have significant effects on blood circulation, liver metabolism and plasma concentrations of various nutrients.[27,28] There are few studies on the relationship between PIV, SII, SIRI, NAR, and PNI and prolonged ICU stay in patients with SP combined with respiratory failure. The objective of this study was to evaluate the effect of PIV, SII, SIRI, NAR, and PNI on length of stay in patients treated with and without transfusion.

Materials and Methods

Study Cohort

This study retrospectively analyzed 3425 patients with SP combined with RF from the Meizhou People's Hospital, from August 2019 to August 2024. The inclusion criteria of patients were as follows: (1) patients met the diagnostic criteria of pneumonia and respiratory failure; (2) age ≥18 years old; and (3) had complete clinical data and laboratory test results. Exclusion criteria of patients for the following reasons: (1) other serious infections or complications; (2) had immune deficiency or use immunosuppressants; (3) other end-stage diseases; and (4) clinical records incomplete. This study was approved by the Human Ethics Committees of the Meizhou People's Hospital.

Data Collection

The collected clinical data included age, gender, body mass index (BMI), history of smoking, history of alcohol drinking, hypertension, diabetes mellitus, history of lung diseases, invasive mechanical ventilation, blood transfusion, Acute

Physiology and Chronic Health Evaluation (APACHE) II score on admission, and laboratory test results. According to the Chinese standards, BMI was divided into three grades: <18.5 kg/m^2, 18.5–23.9 kg/m^2, and ≥24.0 kg/m^2.[29,30] Blood test data were collected during the first hospital examination. The threshold for prolonged ICU stay was defined based on the third quartile (75th percentile) of ICU length of stay for all patients with SP combined with RF.

Data Processing and Statistical Analysis

The inflammation index PIV, SII, SIRI, NAR, and PNI were calculated according to the following formula:

$$\text{PIV} = \text{monocyte} \times \text{neutrophil} \times \text{platelet} / \text{lymphocyte}$$

$$\text{SII} = \text{platelet} \times \text{neutrophil} / \text{lymphocyte}$$

$$\text{SIRI} = \text{monocyte} \times \text{neutrophil} / \text{lymphocyte}$$

$$\text{NAR} = \text{neutrophil count} / \text{serum albumin}$$

$$\text{PNI} = \text{Serum albumin} + 5 \times \text{lymphocyte count}$$

Data analysis was performed using SPSS statistical software version 26.0 (IBM Inc., USA). Continuous data were compared using the Mann–Whitney *U*-test. Categorical variables are expressed as the number of cases (%), and compared between groups using the χ^2 test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values of APACHE II, PIV, SII, SIRI, NAR, and PNI to distinguish prolonged ICU stay from non-prolonged ICU stay. Logistic regression analysis was applied to analysis the relationship between PIV, SII, SIRI, NAR, and PNI and prolonged ICU stay in patients with SP combined with RF adjusting for other major influencing factors, such as age, gender, BMI, history of smoking, history of alcohol drinking, hypertension, diabetes mellitus, history of lung diseases, invasive mechanical ventilation, and APACHE II.

Results

Characteristics of Subjects

The proportion of male and female was 73.1% and 26.9%, respectively. There were 1166 (34.0%) with overweight (BMI ≥24 kg/m^2). The proportions of patients with history of smoking, history of alcohol drinking, hypertension, diabetes mellitus, and a history of lung diseases was 19.8% (679/3425), 6.3% (217/3425), 45.1% (1545/3425), 25.6% (876/3425), and 13.7% (470/3425), respectively. The proportion of patients treated with invasive mechanical ventilation and blood transfusion during hospitalization was 64.3% (2202/3425), and 30.9% (1060/3425), respectively (Table 1).

The mean PIV, SII, SIRI, NAR, and PNI levels of those patients were 1016.59 (435.82, 2230.40), 1839.90 (976.03, 3532.68), 5.72 (2.82, 11.47), 0.29 (0.20, 0.43), and 35.35 (31.08, 40.35), respectively; the average APACHE II score, and length of ICU stay was 20.00±7.73, and 5.32 (2.94, 9.36) days, respectively (Table 1).

Comparison of the Clinical Characteristics of Patients with Prolonged ICU Stay and Non-Prolonged ICU Stay

In this study, 2521 (73.6%) patients with non-prolonged ICU stay (<9 days) and 904 (26.4%) patients with prolonged ICU stay (≥9 days). The proportion of patients with prolonged ICU stay who were ≥65 years old (68.9% vs 64.3%, p=0.013), invasive mechanical ventilation (86.9% vs 56.2%, p<0.001), and blood transfusion (47.2% vs 25.1%, p<0.001) were higher than those of patients with non-prolonged ICU stay, respectively. The average APACHE II score in patients with prolonged ICU stay was higher than that in patients with non-prolonged ICU stay (20.95±7.59 vs 19.63±7.75, p<0.001). And the levels of PIV, SII, SIRI, and NAR in patients with prolonged ICU stay were higher than those in patients with non-prolonged ICU stay, while the PNI was lower than that in patients with non-prolonged ICU stay (all

Table 1 Clinical Characteristics of Patients and Comparison of the Clinical Characteristics of Patients with Prolonged ICU Stay and Non-Prolonged ICU Stay

Clinical Characteristics	Total (n=3425)	Non-Prolonged ICU Stay (n=2521)	Prolonged ICU Stay (n=904)	*p* values
Age (years)				
<65, n (%)	1181 (34.5%)	900 (35.7%)	281 (31.1%)	0.013
≥65, n (%)	2244 (65.5%)	1621 (64.3%)	623 (68.9%)	
Gender				
Male, n (%)	2505 (73.1%)	1829 (72.6%)	676 (74.8%)	0.205
Female, n (%)	920 (26.9%)	692 (27.4%)	228 (25.2%)	
BMI (kg/m^2)				
<18.5, n (%)	554 (16.2%)	418 (16.6%)	136 (15.0%)	0.439
18.5–23.9, n (%)	1705 (49.8%)	1257 (49.9%)	448 (49.6%)	
≥24.0, n (%)	1166 (34.0%)	846 (33.6%)	320 (35.4%)	
History of smoking				
No, n (%)	2746 (80.2%)	2012 (79.8%)	734 (81.2%)	0.382
Yes, n (%)	679 (19.8%)	509 (20.2%)	170 (18.8%)	
History of alcohol drinking				
No, n (%)	3208 (93.7%)	2350 (93.2%)	858 (94.9%)	0.080
Yes, n (%)	217 (6.3%)	171 (6.8%)	46 (5.1%)	
Hypertension				
No, n (%)	1880 (54.9%)	1403 (55.7%)	477 (52.8%)	0.139
Yes, n (%)	1545 (45.1%)	1118 (44.3%)	427 (47.2%)	
Diabetes mellitus				
No, n (%)	2549 (74.4%)	1882 (74.7%)	667 (73.8%)	0.625
Yes, n (%)	876 (25.6%)	639 (25.3%)	237 (26.2%)	
History of lung diseases				
No, n (%)	2955 (86.3%)	2174 (86.2%)	781 (86.4%)	0.911
Yes, n (%)	470 (13.7%)	347 (13.8%)	123 (13.6%)	
Blood gas analysis				
pH	7.41 (7.35, 7.45)	7.41 (7.35, 7.45)	7.40 (7.34, 7.45)	0.086
PaO_2 (mmHg)	90.80 (67.0, 142.65)	91.10 (67.0, 143.40)	90.05 (66.73, 140.23)	0.582
$PaCO_2$ (mmHg)	31.80 (26.80, 39.10)	31.50 (26.60, 38.90)	32.45 (27.60, 40.0)	0.012
Inflammatory indices levels				
PIV, median (P25, P75)	1016.59 (435.82, 2230.40)	983.25 (406.29, 2093.28)	1138.60 (481.47, 2688.62)	<0.001
SII, median (P25, P75)	1839.90 (976.03, 3532.68)	1765.50 (929.01, 3254.40)	2085.78 (1143.0, 4252.87)	<0.001
SIRI, median (P25, P75)	5.72 (2.82, 11.47)	5.48 (2.74, 10.84)	6.36 (3.03, 13.58)	<0.001
Indexes of immune-nutritional status				
NAR, median (P25, P75)	0.29 (0.20, 0.43)	0.29 (0.19, 0.42)	0.31 (0.21, 0.47)	<0.001
PNI, median (P25, P75)	35.35 (31.08, 40.35)	35.70 (31.55, 40.55)	34.20 (29.65, 39.64)	<0.001
Invasive mechanical ventilation				
No, n (%)	1223 (35.7%)	1105 (43.8%)	118 (13.1%)	<0.001
Yes, n (%)	2202 (64.3%)	1416 (56.2%)	786 (86.9%)	
Blood transfusion				
No, n (%)	2365 (69.1%)	1888 (74.9%)	477 (52.8%)	<0.001
Yes, n (%)	1060 (30.9%)	633 (25.1%)	427 (47.2%)	
APACHE II	20.00±7.73	19.63±7.75	20.95±7.59	<0.001
ICU stay (days)	5.32 (2.94, 9.36)			

Abbreviations: BMI, body mass index; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NAR, neutrophil-to-albumin ratio; PNI, prognostic nutritional index; ICU, Intensive Care Unit; p25, 25th percentile; p75, 75th percentile.

$p<0.05$). There were no statistically significant differences in gender and BMI distribution and proportion of history of smoking, history of alcohol drinking, hypertension, diabetes mellitus, and history of lung diseases between the two groups (Table 1).

Comparison of the Clinical Characteristics of Patients with Prolonged ICU Stay and Non-Prolonged ICU Stay in Patients Treated with and without Blood Transfusion, Respectively

In patients treated with blood transfusion (n=1060), there were 633 patients with non-prolonged ICU stay and 427 patients with prolonged ICU stay. The proportion of patients with prolonged ICU stay had a history of alcohol drinking (3.3% vs 9.0%, $p<0.001$) was lower than that of patients with non-prolonged ICU stay. The proportion of patients with prolonged ICU stay with age ≥65 years old (67.4% vs 59.2%, $p=0.008$), male (75.9% vs 69.4%, $p=0.021$), and treated with invasive mechanical ventilation (95.3% vs 66.7%, $p<0.001$) were higher than those of patients with non-prolonged ICU stay. The levels of PIV, SII, and SIRI in patients with prolonged ICU stay were higher than those in patients with non-prolonged ICU stay, while the PNI was lower than that in patients with non-prolonged ICU stay (all $p<0.05$) (Table 2).

Table 2 Comparison of the Clinical Characteristics of Patients with Prolonged ICU Stay and Non-Prolonged ICU Stay in Patients Treated with and without Blood Transfusion, Respectively

Clinical Characteristics	Blood Transfusion (n=1060)			Non-Blood Transfusion (n=2365)		
	Non-Prolonged ICU Stay (n=633)	Prolonged ICU Stay (n=427)	*p* values	Non-Prolonged ICU Stay (n=1888)	Prolonged ICU Stay (n=477)	*p* values
Age (years)						
<65, n (%)	258 (40.8%)	139 (32.6%)	0.008	642 (34.0%)	142 (29.8%)	0.082
≥65, n (%)	375 (59.2%)	288 (67.4%)		1246 (66.0%)	335 (70.2%)	
Gender						
Male, n (%)	439 (69.4%)	324 (75.9%)	0.021	1390 (73.6%)	352 (73.8%)	0.954
Female, n (%)	194 (30.6%)	103 (24.1%)		498 (26.4%)	125 (26.2%)	
BMI (kg/m^2)						
<18.5, n (%)	134 (21.2%)	62 (14.5%)	0.021	284 (15.0%)	74 (15.5%)	0.270
18.5–23.9, n (%)	299 (47.2%)	225 (52.7%)		958 (50.7%)	223 (46.8%)	
≥24.0, n (%)	200 (31.6%)	140 (32.8%)		646 (34.2%)	180 (37.7%)	
History of smoking						
No, n (%)	541 (85.5%)	361 (84.5%)	0.725	1471 (77.9%)	373 (78.2%)	0.902
Yes, n (%)	92 (14.5%)	66 (15.5%)		417 (22.1%)	104 (21.8%)	
History of alcohol drinking						
No, n (%)	576 (91.0%)	413 (96.7%)	<0.001	1774 (94.0%)	445 (93.3%)	0.595
Yes, n (%)	57 (9.0%)	14 (3.3%)		114 (6.0%)	32 (6.7%)	
Hypertension						
No, n (%)	377 (59.6%)	226 (52.9%)	0.037	1026 (54.3%)	251 (52.6%)	0.504
Yes, n (%)	256 (40.4%)	201 (47.1%)		862 (45.7%)	226 (47.4%)	
Diabetes mellitus						
No, n (%)	466 (73.6%)	316 (74.0%)	0.943	1416 (75.0%)	351 (73.6%)	0.556
Yes, n (%)	167 (26.4%)	111 (26.0%)		472 (25.0%)	126 (26.4%)	
History of lung diseases						
No, n (%)	554 (87.5%)	371 (86.9%)	0.779	1620 (85.8%)	410 (86.0%)	0.942
Yes, n (%)	79 (12.5%)	56 (13.1%)		268 (14.2%)	67 (14.0%)	
Blood gas analysis						
pH	7.40 (7.35, 7.45)	7.40 (7.34, 7.45)	0.441	7.41 (7.36, 7.45)	7.40 (7.34, 7.45)	0.315
PaO_2 (mmHg)	96.30 (68.65, 155.45)	92.30 (67.60, 145.60)	0.468	90.30 (66.33, 139.38)	89.00 (66.65, 132.55)	0.412
$PaCO_2$ (mmHg)	28.80 (24.50, 35.10)	31.60 (27.00, 38.10)	<0.001	32.45 (27.40, 40.20)	33.40 (28.40, 42.20)	0.039
Inflammatory indices levels						
PIV, median (P25, P75)	848.13 (273.41, 1924.83)	1161.71 (436.80, 2728.59)	<0.001	1020.74 (459.83, 2101.15)	1118.33 (550.38, 2666.74)	0.002
SII, median (P25, P75)	1452.44 (668.87, 2849.93)	2048.00 (1127.62, 4509.00)	<0.001	1851.71 (996.25, 3356.96)	2150.63 (1151.17, 4125.84)	<0.001
SIRI, median (P25, P75)	5.98 (2.71, 12.96)	7.09 (3.08, 15.70)	0.032	5.39 (2.76, 10.33)	6.11 (2.99, 12.26)	0.011
Indexes of immune-nutritional status						
NAR, median (P25, P75)	0.32 (0.19, 0.49)	0.34 (0.21, 0.52)	0.208	0.28 (0.19, 0.39)	0.30 (0.22, 0.42)	0.002
PNI, median (P25, P75)	33.70 (29.88, 38.65)	33.05 (28.85, 37.80)	0.041	36.18 (32.20, 41.09)	35.40 (30.78, 40.95)	0.036

(*Continued*)

Table 2 (Continued).

Clinical Characteristics	Blood Transfusion (n=1060)			Non-Blood Transfusion (n=2365)		
	Non-Prolonged ICU Stay (n=633)	Prolonged ICU Stay (n=427)	*p* values	Non-Prolonged ICU Stay (n=1888)	Prolonged ICU Stay (n=477)	*p* values
Invasive mechanical ventilation						
No, n (%)	211 (33.3%)	20 (4.7%)	<0.001	894 (47.4%)	98 (20.5%)	<0.001
Yes, n (%)	422 (66.7%)	407 (95.3%)		994 (52.6%)	379 (79.5%)	
APACHE II	21.58±8.65	22.04±8.06	0.449	18.98±7.32	19.98±7.03	0.018

Abbreviations: BMI, body mass index; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NAR, neutrophil-to-albumin ratio; PNI, prognostic nutritional index; ICU, Intensive Care Unit; p25, 25th percentile; p75, 75th percentile.

In patients without blood transfusion (n=2365), there were 1888 patients with non-prolonged ICU stay and 477 patients with prolonged ICU stay. The proportion of patients with prolonged ICU stay treated with invasive mechanical ventilation (79.5% vs 52.6%, $p<0.001$) was higher than that of patients with non-prolonged ICU stay. The average APACHE II score in patients with prolonged ICU stay was higher than that in patients with non-prolonged ICU stay (19.98±7.03 vs 18.98±7.32, $p=0.018$). The levels of PIV, SII, SIRI, and NAR in patients with prolonged ICU stay were higher than those in patients with non-prolonged ICU stay, while the PNI was lower than that in patients with non-prolonged ICU stay (all $p<0.05$) (Table 2).

Impact of PIV, SII, SIRI, NAR, and PNI on Prolonged ICU Stay

ROC curve analysis was used to determine the optimal cutoff values of APACHE II score, PIV, SII, SIRI, NAR, and PNI to distinguish prolonged ICU stay. When prolonged ICU stay was taken as the endpoint, the critical value of APACHE II score was 19.5 (sensitivity=54.3%, specificity=54.5%, area under the ROC curve (AUC)=0.553), the critical value of PIV was 1564.51 (sensitivity=41.7%, specificity=66.4%, AUC=0.546), the SII cutoff value was 1519.305 (sensitivity=66.9%, specificity=43.6%, AUC=0.566), the SIRI cutoff value was 8.220 (sensitivity=43.3%, specificity=65.0%, AUC=0.545), the NAR cutoff value was 0.285 (sensitivity=57.3%, specificity=49.9%, AUC=0.546), and the PNI cutoff value was 34.025 (sensitivity=49.7%, specificity=59.8%, AUC=0.555) (Figure 1).

The results of univariate analysis indicated that old age (≥65 vs <65 years old, odds ratio (OR): 1.231, 95% confidence interval (CI): 1.046–1.448, $p=0.012$), invasive mechanical ventilation (OR: 5.198, 95% CI: 4.218–6.406, $p<0.001$), blood transfusion (OR: 2.670, 95% CI: 2.278–3.129, $p<0.001$), APACHE II score (OR: 1.420, 95% CI: 1.193–1.690, $p<0.001$), high PIV (≥1564.510 vs <1564.510, OR: 1.411, 95% CI: 1.208–1.649, $p<0.001$), SII (≥1519.305 vs <1519.305, OR: 1.561, 95% CI: 1.331–1.831, $p<0.001$), SIRI (≥8.220 vs <8.220, OR: 1.416, 95% CI: 1.213–1.654, $p<0.001$), NAR (≥0.285/<0.285, OR: 1.339, 95% CI: 1.149–1.560, $p<0.001$), and low PNI (<34.025/≥34.025, OR: 1.467, 95% CI: 1.259–1.709, $p<0.001$) level were significantly associated with prolonged ICU stay (Table 3).

In multivariate logistic regression analysis, invasive mechanical ventilation (OR: 4.524, 95% CI: 3.494–5.856, $p<0.001$), blood transfusion (OR: 2.207, 95% CI: 1.812–2.687, $p<0.001$), high SII (≥1519.305 vs <1519.305, OR: 1.386, 95% CI: 1.087–1.765, $p=0.008$), and low PNI (<34.025/≥34.025, OR: 1.307, 95% CI: 1.074–1.590, $p=0.007$) level were independently associated with prolonged ICU stay (Table 3).

Impact of PIV, SII, SIRI, NAR, and PNI on Prolonged ICU Stay in Patients Treated with and without Blood Transfusion, Respectively

In patients treated with blood transfusion, multivariate logistic regression analysis showed that invasive mechanical ventilation (OR: 10.205, 95% CI: 5.623–18.524, $p<0.001$), and high SII (≥1519.305 vs <1519.305, OR: 2.115, 95% CI: 1.428–3.131, $p<0.001$) were independently associated with prolonged ICU stay (Table 4). In patients without blood

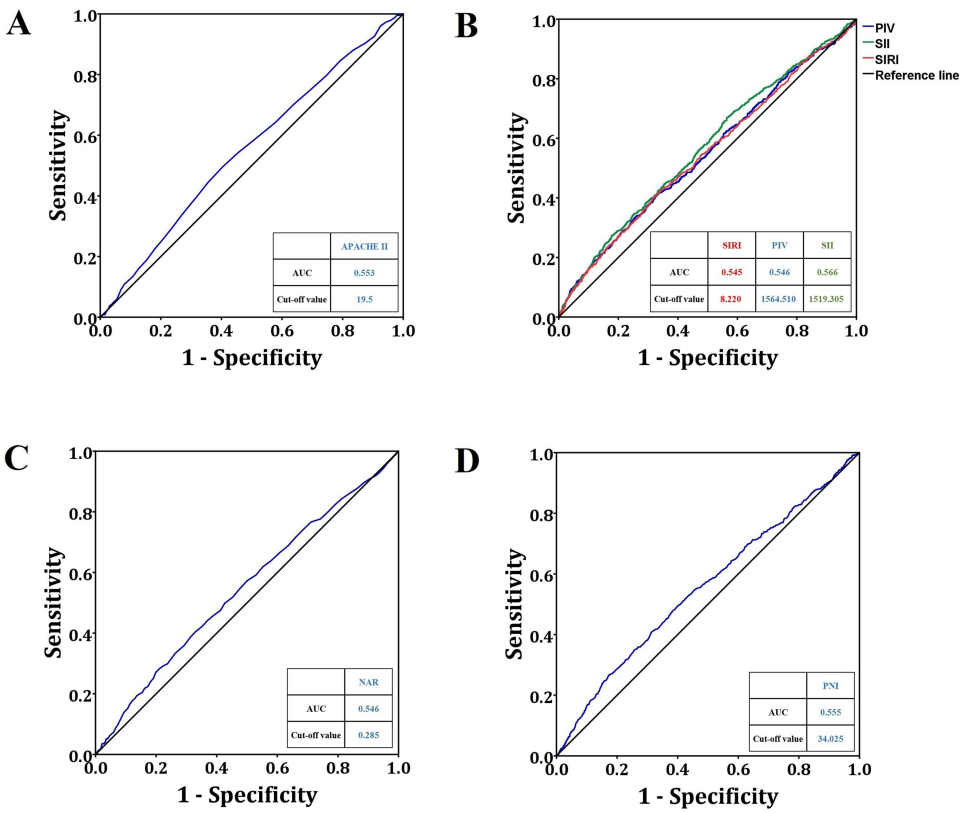

Figure 1 The ROC curve analysis of APACHE II score, PIV, SII, SIRI, NAR, and PNI to distinguish prolonged ICU stay. The ROC curve of APACHE II score (**A**); PIV, SII, and SIRI (**B**); the ROC curve of NAR (**C**); the ROC curve of PNI (**D**).

Abbreviations: ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II score; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NAR, neutrophil-to-albumin ratio; PNI, prognostic nutritional index.

transfusion, multivariate logistic regression analysis showed that invasive mechanical ventilation (OR: 3.566, 95% CI: 2.666–4.771, $p<0.001$), and low PNI (<34.025 vs ≥34.025, OR: 1.378, 95% CI: 1.073–1.769, $p=0.012$) were independently associated with prolonged ICU stay (Table 4).

Table 3 Logistic Regression Analysis of Risk Factors Associated with Prolonged ICU Stay

Variables	Unadjusted Values		Adjusted Values	
	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
Age (≥65 vs <65, years)	1.231 (1.046–1.448)	0.012	1.138 (0.925–1.399)	0.222
Gender (male vs female)	1.122 (0.943–1.335)	0.195	1.048 (0.839–1.309)	0.680
BMI (kg/m^2)				
18.5–23.9	1.000 (reference)	–	1.000 (reference)	–
<18.5	0.913 (0.732–1.139)	0.420	0.983 (0.743–1.300)	0.903
≥24.0	1.061 (0.897–1.255)	0.487	1.089 (0.885–1.339)	0.419
History of smoking (yes vs no)	0.916 (0.755–1.111)	0.370	0.986 (0.755–1.288)	0.919
History of alcohol drinking (yes vs no)	0.737 (0.527–1.030)	0.074	0.719 (0.460–1.125)	0.149
Hypertension (yes vs no)	1.123 (0.965–1.308)	0.135	1.073 (0.875–1.316)	0.499
Diabetes mellitus (yes vs no)	1.047 (0.880–1.244)	0.607	1.153 (0.919–1.446)	0.219
History of lung diseases (yes vs no)	0.987 (0.791–1.231)	0.906	1.041 (0.776–1.398)	0.787
Invasive mechanical ventilation (yes vs no)	5.198 (4.218–6.406)	<0.001	4.524 (3.494–5.856)	<0.001
Blood transfusion (yes vs no)	2.670 (2.278–3.129)	<0.001	2.207 (1.812–2.687)	<0.001

(*Continued*)

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Table 3 (Continued).

Variables	Unadjusted Values		Adjusted Values	
	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
APACHE II (≥19.5 vs <19.5)	1.420 (1.193–1.690)	<0.001	0.948 (0.782–1.148)	0.582
PIV (≥1564.510 vs <1564.510)	1.411 (1.208–1.649)	<0.001	1.303 (0.966–1.759)	0.083
SII (≥1519.305 vs <1519.305)	1.561 (1.331–1.831)	<0.001	1.386 (1.087–1.765)	0.008
SIRI (≥8.220 vs <8.220)	1.416 (1.213–1.654)	<0.001	0.922 (0.696–1.220)	0.568
NAR (≥0.285/<0.285)	1.339 (1.149–1.560)	<0.001	0.913 (0.723–1.154)	0.448
PNI (<34.025/≥34.025)	1.467 (1.259–1.709)	<0.001	1.307 (1.074–1.590)	0.007

Abbreviations: ICU, Intensive Care Unit; BMI, body mass index; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NAR, neutrophil to albumin ratio; PNI, prognostic nutritional index; OR, odds ratio; CI, confidence interval.

Table 4 Logistic Regression Analysis of Risk Factors Associated with Prolonged ICU Stay in Patients Treated with and without Blood Transfusion, Respectively

Variables	Blood Transfusion				Non-Blood Transfusion			
	Unadjusted Values		Adjusted Values		Unadjusted Values		Adjusted Values	
	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values	OR (95% CI)	*p* values	Adjusted OR (95% CI)	*p* values
Age (≥65 vs <65, years)	1.425 (1.102–1.843)	0.007	1.291 (0.919–1.813)	0.141	1.216 (0.977–1.512)	0.079	1.051 (0.805–1.373)	0.714
Gender (male vs female)	1.390 (1.052–1.837)	0.021	1.313 (0.910–1.895)	0.146	1.009 (0.803–1.268)	0.939	0.914 (0.689–1.211)	0.529
BMI (kg/m^2)								
18.5–23.9	1.000 (reference)	–	1.000 (reference)	–	1.000 (reference)	–	1.000 (reference)	–
<18.5	0.615 (0.434–0.870)	0.006	0.578 (0.368–0.906)	0.017	1.119 (0.834–1.503)	0.453	1.415 (0.990–2.021)	0.057
≥24.0	0.930 (0.705–1.227)	0.608	0.877 (0.619–1.243)	0.461	1.197 (0.960–1.492)	0.110	1.226 (0.942–1.597)	0.130
History of smoking (yes vs no)	1.075 (0.763–1.515)	0.679	1.368 (0.831–2.251)	0.218	0.984 (0.771–1.254)	0.894	0.850 (0.609–1.185)	0.338
History of alcohol drinking (yes vs no)	0.343 (0.188–0.623)	<0.001	0.383 (0.177–0.827)	0.015	1.119 (0.746–1.679)	0.587	1.061 (0.608–1.851)	0.834
Hypertension (yes vs no)	1.310 (1.022–1.678)	0.033	1.301 (0.920–1.840)	0.136	1.072 (0.876–1.311)	0.500	1.005 (0.775–1.305)	0.967
Diabetes mellitus (yes vs no)	0.980 (0.741–1.296)	0.888	0.934 (0.635–1.372)	0.727	1.077 (0.857–1.354)	0.525	1.222 (0.917–1.630)	0.171
History of lung diseases (yes vs no)	1.059 (0.734–1.527)	0.761	0.988 (0.585–1.669)	0.965	0.988 (0.740–1.319)	0.934	1.069 (0.745–1.534)	0.718
Invasive mechanical ventilation (yes vs no)	10.175 (6.307–16.416)	<0.001	10.205 (5.623–18.524)	<0.001	3.478 (2.737–4.421)	<0.001	3.566 (2.666–4.771)	<0.001
APACHE II (≥19.5 vs <19.5)	1.225 (0.922–1.629)	0.162	0.871 (0.629–1.205)	0.404	1.353 (1.076–1.702)	0.010	1.019 (0.797–1.301)	0.883
PIV (≥1564.510 vs <1564.510)	1.638 (1.268–2.118)	<0.001	1.270 (0.768–2.101)	0.352	1.353 (1.102–1.661)	0.004	1.268 (0.858–1.874)	0.233
SII (≥1519.305 vs <1519.305)	2.118 (1.642–2.732)	<0.001	2.115 (1.428–3.131)	<0.001	1.413 (1.143–1.746)	0.001	1.018 (0.740–1.401)	0.912
SIRI (≥8.220 vs <8.220)	1.282 (1.000–1.642)	0.050	0.890 (0.560–1.415)	0.623	1.367 (1.112–1.680)	0.003	0.984 (0.681–1.420)	0.930
NAR (≥0.285/<0.285)	1.113 (0.868–1.428)	0.398	0.760 (0.510–1.133)	0.178	1.369 (1.119–1.676)	0.002	1.070 (0.794–1.441)	0.657
PNI (<34.025/≥34.025)	0.827 (0.646–1.059)	0.132	1.137 (0.819–1.579)	0.442	1.346 (1.098–1.651)	0.004	1.378 (1.073–1.769)	0.012

Abbreviations: ICU, Intensive Care Unit; BMI, body mass index; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; NAR, neutrophil to albumin ratio; PNI, prognostic nutritional index; OR, odds ratio; CI, confidence interval.

Discussion

Tissue hypoxia may occur in patients with pulmonary insufficiency such as SP combined with RF.[31] Bleeding requiring blood transfusion is a common adverse complication of ICU stay patients. Thrombocytopenia and anemia can occur in ICU stay patients with SP.[32,33] Inflammation, bleeding, and disseminated intravascular coagulation in patients with severe pneumonia may lead to increased platelet consumption, which may be an important cause of thrombocytopenia.[32,33] The symptoms of hypoxia in partial patients with tissue hypoxia may be effectively improved after blood transfusion of red blood cells.[34,35] However, blood transfusion can activate the immune system and trigger early inflammatory immune response. Fluid resuscitation can cause hypothermia, coagulation dysfunction, acidosis, and aggravate tissue damage. The poor prognosis of transfusion patients may be related to shortened red blood cell life, inflammatory factor production, and decreased erythropoietic cell production in bone marrow.[36,37] The relationship between PIV, SII, SIRI, NAR, and PNI and prolonged ICU stay in SP combined with RF patients was analyzed in this study. And the results showed that high

SII level, and invasive mechanical ventilation were independently associated with prolonged ICU stay in patients treated with blood transfusion; and low PNI level, and invasive mechanical ventilation were independently associated with prolonged ICU stay in patients without blood transfusion.

Studies have found that blood transfusions in patients are equivalent to updating and adjusting the relevant immune functions of the body.[38–40] Parmana et al found that high preoperative SII values were associated with prolonged ICU stay in coronary artery disease (CAD) patients who underwent off-pump coronary artery bypass grafting (OPCAB) surgery.[41] Alsabani et al revealed that high SII values were associated with prolonged hospital stay after orthopedic surgery.[42] SII was found to have association with occurrence and prognosis of some respiratory diseases, such as chronic obstructive pulmonary disease (COPD),[43] respiratory failure,[44] bronchiectasis,[45] and severity of COVID-19.[46] Our findings suggest that high SII level was independently associated with prolonged ICU stay in patients treated with blood transfusion. In the early stage of SP, neutrophils can release a large number of pro-inflammatory cytokines and chemotactic factors, inducing the disorderly expansion of inflammatory response and the generation of "cytokine storm", while progressive inflammation can accelerate the apoptosis of lymphocytes and form immune suppression, resulting in decreased anti-infection ability.[47] In addition, blood transfusion has adverse effects on the immune function of patients, such as the activation and proliferation of immune cells decreased, and the change of immune level in patients treated with blood transfusion can better reflect the extension of hospital stay.

Hogan et al found that preoperative nutrient levels were associated with prolonged hospital stay after pelvic resection.[48] The relationship between PNI and respiratory diseases has been reported. PNI can be used as an indicator of immune nutritional status to predict the severity of COVID-19,[49,50] prognosis of COPD,[51] lung cancer,[52] and mortality risk of community-acquired pneumonia.[53] However, prior to this study, the relationship between PNI levels and prolonged ICU stay in patients with SP combined with RF had not been reported. Our findings suggest that low PNI level is a risk factor for prolonged ICU stay in SP combined with RF patients without blood transfusion. Excessive activation of immune defense in patients with SP may lead to a large amount of energy consumption in the body, exacerbate the loss of nutrients in the body, obtain energy by decomposes its own tissues, and lead to the destruction of its own organs.[54] In non-transfusion-treated patients, changes in nutritional levels were more likely to be reflected in poor patient outcomes, such as prolonged ICU stay.

The key to timely treatment of SP and RF is mechanical ventilation.[55,56] Invasive mechanical ventilation is an important measure in the rescue process of patients with respiratory disorders, which can ensure smooth airway ventilation and maintain life.[57] A study has constructed a predictive model for prolonged ICU stay in COPD patients, with invasive mechanical ventilation as one of the indicators.[58] Another study showed that there was no significant difference between the length of mechanical ventilation and ICU stay in patients with SP.[59] The APACHE II score is a system that classifies the severity of illness in ICU patients based on age, past medical history, and some physiologic measurements.[60] APACHE II score was significantly associated with higher risk of prolonged ICU stay among patients admitted to the ICU in a Japanese study.[61] Some studies have suggested that APACHE II score was associated with prolonged ICU stay.[62,63] On the contrary, another study has suggested that APACHE II score was not a risk factor for prolonged ICU stay.[64]

In conclusion, attention should be paid to the use of mechanical ventilation in ICU patients, but this study did not pay attention to the types and times of use of mechanical ventilation. In the future, it is necessary to conduct more in-depth studies on different types of patients or multiple uses of mechanical ventilation to identify the internal reasons for the influence of mechanical ventilation on the extension of ICU stay.

Although the number of ICU patients with SP combined with RF included in this study is not small, it still has several limitations. First, the data came from data related to a single race, so the results may not be applicable to patients of their race. Second, this is a retrospective analysis, in which retrospective bias is bound to exist, such as all patients may have different detection points for different variables; the AUC values of some ROC curves in this study are generally low, indicating that the predictive ability of the model is flawed. Therefore, a prospective cohort study is needed to further explore the association between these potentially relevant variables and longer ICU stay in patients with SP combined with RF. Third, as has been seen in most past studies, the length of ICU stay varies according to the medical conditions of the hospital itself. Therefore, the applicability of the results of this study to other hospitals is still an open question. All in

all, the risk factors identified in this study for prolonged ICU stay in patients with SP combined with RF have certain clinical significance and are worthy of further exploration in future clinical work and research.

Conclusion

High SII level (≥1519.305), and invasive mechanical ventilation were independently associated with prolonged ICU stay in patients treated with blood transfusion; and low PNI level (<34.025), and invasive mechanical ventilation were independently associated with prolonged ICU stay in patients without blood transfusion. It provides a new method for personalized medicine to guide ICU management of severe pneumonia complicated with respiratory failure. Of course, prospective cohort studies are needed to further explore the relationship between these composite indices and prognosis in patients with severe pneumonia combined with respiratory failure.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals and the study obtained written informed consent from all the participants. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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Author Contributions

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

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Disclosure

The authors declare that they have no competing interests in this work.

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