Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock

Yuqiang Gong, Diwen Li, Bihuan Cheng, Binyu Ying and Benji Wang

Department of Anesthesiology, Critical Care and Pain Medicine, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China

Abstract

There has been no study exploring the prognostic values of neutrophil percentage-to-albumin ratio (NPAR). We hypothesised that NPAR is a novel marker of inflammation and is associated with all-cause mortality in patients with severe sepsis or septic shock. Patient data were extracted from the MIMIC-III V1.4 database. Only the data for the first intensive care unit (ICU) admission of each patient were used and baseline data were extracted within 24 h after ICU admission. The clinical endpoints were 30-, 90- and 365-day all-cause mortality in critically ill patients with severe sepsis or septic shock. Furthermore, after adjusting for more confounding factors, higher NPAR remained a significant predictor of all-cause mortality (tertile 3 vs tertile 1: HR, 95% CI: 1.29, 1.04–1.61; 1.41, 1.16–1.72; 1.44, 1.21–1.71). A similar trend was observed in NPAR levels stratified by quartiles. Higher NPAR was associated with increased risk of all-cause mortality in critically ill patients with severe sepsis or septic shock.

Introduction

Sepsis is a syndrome of physiological, pathological and biochemical abnormalities induced by infection [1]. Septic shock causes circulatory and metabolic abnormalities, leading to increased mortality in hospitalised patients, especially in intensive care unit (ICU) patients [2, 3]. Studies showed that once sepsis advanced to septic shock, the mortality rate rose from 25% to 52%, despite adoption of therapeutic strategies according to international sepsis guidelines [4, 5]. Given the poor prognosis of septic shock in critical illness, researchers have found multiple risk factors predicting the prognosis of these patients, with the aim of early intervention to reduce mortality [6, 7]. Nevertheless, the mortality caused by sepsis remains high.

Neutrophils play crucial roles in the innate cellular immune system. Previous studies suggested that early higher neutrophil counts correlated with increased sepsis severity [8, 9], and neutrophil percentage was predictive of bloodstream infection [10]. Albumin is a medium-sized molecule that is the most abundant protein in human plasma. For a variety of physiological mechanisms, albumin is indispensable. It has a variety of functions, including serving as a major buffer, extracellular antioxidant, immunomodulator, antidote and transporter in plasma [11, 12]. Increased capillary leakage of albumin is one of the features of SIRS [13]. This means that lower albumin levels correlate with severe systemic inflammation and organ failure [14]. Moreover, several studies demonstrated that low albumin levels correlated with adverse clinical outcomes [11, 15].

Recently, the neutrophil-albumin ratio has been identified as a prognostic predictor in patients with rectal cancer and palliative pancreatic cancer [16, 17]. Nevertheless, to our knowledge, no previous study has focused on the neutrophil percentage-to-albumin ratio (NPAR). In this study, we hypothesised that NPAR is a novel marker of inflammation associated with all-cause mortality in patients with severe sepsis or septic shock.

Methods

Data source

Similar to our previous studies, we followed the methods of Wang et al., 2019 [18, 19]. The study was based on a publicly accessible clinical database called the Multiparameter Intelligent Monitoring in Intensive Care III version 1.4 (MIMIC-III v1.4). It includes approximately 40 000 critical care patients at the Beth Israel Deaconess Medical Center (Boston, USA).
Table 1. Characteristics of the study patients according to NPARs

| Characteristics          | NPARs          |     |     |     |     |
|-------------------------|----------------|-----|-----|-----|-----|
|                         | <24.4 (n = 722) | ≥24.4, <31.4 (n = 722) | ≥31.4 (n = 722) |     |     |
| Age, years              | 64.9 ± 16.5    | 67.3 ± 16.0    | 66.1 ± 16.6    | 0.022|     |
| Gender, n (%)           | 0.011          |     |     |     |     |
| Female                  | 287 (39.8)     | 318 (44.0)     | 357 (49.4)     |     |     |
| Male                    | 435 (60.2)     | 404 (56.0)     | 365 (50.6)     |     |     |
| Ethnicity, n (%)        | 0.070          |     |     |     |     |
| White                   | 530 (73.4)     | 527 (73.0)     | 538 (74.5)     |     |     |
| Black                   | 89 (12.3)      | 73 (10.1)      | 59 (8.2)       |     |     |
| Other                   | 103 (14.3)     | 122 (16.9)     | 125 (17.3)     |     |     |
| NPAR                    | 18.2 ± 6.0     | 27.8 ± 2.0     | 39.1 ± 7.9     | <0.001|     |
| SBP, mmHg               | 111.1 ± 14.6   | 110.7 ± 14.7   | 109.3 ± 14.6   | 0.048|     |
| DBP, mmHg               | 58.5 ± 9.9     | 57.2 ± 9.5     | 56.7 ± 10.2    | 0.002|     |
| MBP, mmHg               | 74.1 ± 10.2    | 72.9 ± 9.6     | 72.5 ± 10.7    | 0.008|     |
| Heart rate, beats/min   | 92.3 ± 19.2    | 90.9 ± 16.9    | 93.1 ± 16.9    | 0.058|     |
| Respiratory rate, beats/min | 21.2 ± 4.8   | 21.3 ± 4.5     | 21.4 ± 4.7     | 0.753|     |
| Temperature, °C         | 36.9 ± 0.9     | 36.8 ± 0.7     | 36.7 ± 0.8     | <0.001|     |
| SPO2, %                 | 96.1 ± 4.6     | 96.7 ± 3.0     | 96.5 ± 4.1     | 0.016|     |
| Comorbidities, n (%)    |               |     |     |     |     |
| Congestive heart failure| 117 (16.2)     | 183 (25.3)     | 116 (16.1)     | <0.001|     |
| Coronary artery disease | 129 (17.9)     | 154 (21.3)     | 119 (16.5)     | 0.051|     |
| Atrial fibrillation     | 192 (26.6)     | 248 (34.3)     | 230 (31.9)     | 0.005|     |
| Stroke                  | 41 (5.7)       | 39 (5.4)       | 39 (5.4)       | 0.965|     |
| Renal disease           | 117 (16.2)     | 140 (19.4)     | 121 (16.8)     | 0.234|     |
| Liver disease           | 95 (13.2)      | 90 (12.5)      | 91 (12.6)      | 0.916|     |
| Pneumonia               | 321 (44.5)     | 304 (42.1)     | 271 (37.5)     | 0.025|     |
| Malignancy              | 165 (22.9)     | 121 (16.8)     | 182 (25.2)     | <0.001|     |
| Respiratory failure     | 414 (57.3)     | 416 (57.6)     | 447 (61.9)     | 0.141|     |
| COPD                    | 20 (2.8)       | 26 (3.6)       | 14 (1.9)       | 0.157|     |
| ARDS                    | 19 (2.6)       | 21 (2.9)       | 20 (2.8)       | 0.950|     |
| Laboratory parameters   |               |     |     |     |     |
| Neutrophil percentage, %| 62.4 ± 23.9    | 81.8 ± 9.4     | 85.8 ± 7.8     | <0.001|     |
| Albumin, g/dl           | 3.4 ± 0.7      | 3.0 ± 0.4      | 2.3 ± 0.4      | <0.001|     |
| Bicarbonate, mg/dl      | 19.1 ± 5.5     | 19.3 ± 5.6     | 19.1 ± 5.7     | 0.618|     |
| Anion gap, mmol/l       | 14.3 ± 4.2     | 14.2 ± 4.3     | 13.4 ± 4.0     | <0.001|     |
| Creatinine, mEq/l       | 1.7 ± 1.5      | 1.9 ± 1.7      | 1.7 ± 1.5      | 0.006|     |
| Bilirubin, mg/dl        | 2.3 ± 5.4      | 2.2 ± 4.8      | 2.7 ± 5.1      | 0.151|     |
| Chloride, mmol/l        | 100.8 ± 7.5    | 101.5 ± 8.1    | 103.2 ± 8.1    | <0.001|     |
| Glucose, mg/dl          | 144.3 ± 51.4   | 145.3 ± 48.4   | 141.9 ± 50.3   | 0.407|     |
| Haematocrit, %          | 29.5 ± 6.5     | 29.3 ± 5.5     | 27.5 ± 5.5     | <0.001|     |
| Haemoglobin, g/dl       | 9.9 ± 2.2      | 9.8 ± 1.9      | 9.2 ± 1.8      | <0.001|     |
| Platelet, 10^4/l        | 154.1 ± 101.7  | 198.3 ± 133.7  | 200.5 ± 139.3  | <0.001|     |
| Sodium, mmol/l          | 135.9 ± 5.7    | 135.9 ± 6.6    | 136.1 ± 6.6    | 0.770|     |

(Continued)
from 2001 to 2012 [20]. The demographics, vital signs, laboratory tests, medications, nursing progress notes and other clinical variables were recorded in this database. The project was approved by the institutional review boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC). To apply for access to the database, we passed the Protecting Human Research Participants exam and obtained a waiver.

### Data extraction

Structured Query Language (SQL) with the PostgreSQL tool (version 9.6) was used to extract the data from MIMIC-III. Extracted data included demographics, vital signs, comorbidities, laboratory parameters and others upon admission. We extracted comorbidities, including congestive heart failure (CHF), coronary artery disease (CAD), atrial fibrillation (AFIB), stroke, renal disease, liver disease, pneumonia, malignancy, respiratory failure, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). The laboratory parameters included neutrophil percentage, albumin, bicarbonate, anion gap, creatinine, bilirubin, chloride, glucose, haematocrit, haemoglobin, platelet, sodium, potassium, blood urea nitrogen (BUN), white blood cell (WBC), lactate, prothrombin time (PT), international normalised ratio (INR) and activated partial thromboplastin time (APTT). Sequential organ failure assessment (SOFA) scores [22] and simplified acute physiology scores II (SAPSII), Simplified Acute Physiology Score II, were calculated for each patient. The statistical methods used for comparisons were the One-Way Anova (normal distribution), Kruskal-Wallis H (skewed distribution) test and chi-square tests (categorical variables).

### Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or medians and interquartile range, and were tested...
Table 2. HRs (95% CIs) for all-cause mortality across groups of NPARs

| NAR      | Non-adjusted                      |                       |                       | Model I                      |                       |                       | Model II                     |                       |
|----------|-----------------------------------|-----------------------|-----------------------|------------------------------|-----------------------|-----------------------|------------------------------|-----------------------|
|          | HR (95% CIs)                      | P value               | HR (95% CIs)          | P value                      | HR (95% CIs)          | P value               |                              |                       |
|          |                                  |                       |                       |                              |                       |                       |                              |                       |
| 30-day all-cause mortality |                                  |                       |                       |                              |                       |                       |                              |                       |
| Tertiles |                                  |                       |                       |                              |                       |                       |                              |                       |
| <24.4    | 1.0 (ref)                         |                       |                       |                              |                       |                       |                              |                       |
| ≥24.4, <31.4 | 0.92 (0.75, 1.13)             | 0.4356               |                       |                              |                       |                       |                              |                       |
| ≥34.4    | 1.37 (1.13, 1.66)                | 0.0011               |                       |                              |                       |                       |                              |                       |
|          |                                  |                       |                       |                              |                       |                       |                              |                       |
|          | 0.0004                           |                       | 0.0006               | 0.0190                       |                       |                       |                              |                       |
| Quartiles|                                  |                       |                       |                              |                       |                       |                              |                       |
| <22.5    | 1.0 (ref)                         |                       |                       |                              |                       |                       |                              |                       |
| ≥22.5, <27.7 | 0.97 (0.76, 1.23)            | 0.7956               |                       |                              |                       |                       |                              |                       |
| ≥27.7, <33.7 | 1.00 (0.79, 1.27)            | 0.9750               |                       |                              |                       |                       |                              |                       |
| ≥33.7    | 1.61 (1.29, 2.00)                | <0.0001              |                       | 1.55 (1.24, 1.93)            | <0.0001              |                       | 1.37 (1.07, 1.77)            | 0.0139               |
|          |                                  |                       |                       |                              |                       |                       |                              |                       |
|          | <0.0001                           |                       | <0.0001              | 0.0121                       |                       |                       |                              |                       |
| 90-day all-cause mortality |                                  |                       |                       |                              |                       |                       |                              |                       |
| Tertiles |                                  |                       |                       |                              |                       |                       |                              |                       |
| <24.4    | 1.0 (ref)                         |                       |                       |                              |                       |                       |                              |                       |
| ≥24.4, <31.4 | 1.03 (0.87, 1.24)            | 0.7060               |                       | 0.96 (0.81, 1.15)            | 0.6937               |                       | 1.13 (0.93, 1.37)            | 0.2152               |
| ≥34.4    | 1.45 (1.23, 1.72)                | <0.0001              |                       | 1.45 (1.23, 1.72)            | <0.0001              |                       | 1.41 (1.16, 1.72)            | 0.0005               |
|          |                                  |                       |                       |                              |                       |                       |                              |                       |
|          | <0.0001                           |                       | <0.0001              | 0.0004                       |                       |                       |                              |                       |
| Quartiles|                                  |                       |                       |                              |                       |                       |                              |                       |
| <22.5    | 1.0 (ref)                         |                       |                       |                              |                       |                       |                              |                       |
| ≥22.5, <27.7 | 1.00 (0.81, 1.23)            | 0.9912               |                       | 0.92 (0.74, 1.13)            | 0.4073               |                       | 1.03 (0.82, 1.30)            | 0.7740               |
| ≥27.7, <33.7 | 1.11 (0.90, 1.35)            | 0.3352               |                       | 1.03 (0.84, 1.27)            | 0.7506               |                       | 1.14 (0.91, 1.43)            | 0.2464               |
| ≥33.7    | 1.65 (1.36, 1.99)                | <0.0001              |                       | 1.60 (1.32, 1.94)            | <0.0001              |                       | 1.43 (1.15, 1.79)            | 0.0016               |
|          |                                  |                       |                       |                              |                       |                       |                              |                       |
|          | <0.0001                           |                       | <0.0001              | 0.0007                       |                       |                       |                              |                       |
| 365-day all-cause mortality |                                  |                       |                       |                              |                       |                       |                              |                       |
| Tertiles |                                  |                       |                       |                              |                       |                       |                              |                       |
| <24.4    | 1.0 (ref)                         |                       |                       |                              |                       |                       |                              |                       |
| ≥24.4, <31.4 | 1.11 (0.95, 1.29)           | 0.2009               |                       | 1.04 (0.89, 1.21)            | 0.6544               |                       | 1.18 (0.99, 1.40)            | 0.0595               |
| ≥34.4    | 1.47 (1.26, 1.70)                | <0.0001              |                       | 1.50 (1.29, 1.74)            | <0.0001              |                       | 1.44 (1.21, 1.71)            | <0.0001              |
|          |                                  |                       |                       |                              |                       |                       |                              |                       |
|          | <0.0001                           |                       | <0.0001              | <0.0001                      |                       |                       |                              |                       |
| Quartiles|                                  |                       |                       |                              |                       |                       |                              |                       |
| <22.5    | 1.0 (ref)                         |                       |                       |                              |                       |                       |                              |                       |
| ≥22.5, <27.7 | 1.02 (0.85, 1.22)           | 0.8577               |                       | 0.93 (0.77, 1.11)            | 0.4153               |                       | 1.02 (0.83, 1.25)            | 0.8496               |
| ≥27.7, <33.7 | 1.08 (0.91, 1.30)           | 0.3705               |                       | 1.02 (0.85, 1.22)            | 0.8299               |                       | 1.10 (0.90, 1.34)            | 0.3550               |
| ≥33.7    | 1.61 (1.36, 1.91)                | <0.0001              |                       | 1.61 (1.35, 1.90)            | <0.0001              |                       | 1.41 (1.16, 1.73)            | 0.0007               |
|          |                                  |                       |                       |                              |                       |                       |                              |                       |
|          | <0.0001                           |                       | <0.0001              | 0.0003                       |                       |                       |                              |                       |

HR, hazard ratio; CI, confidence interval.

Models were derived from Cox proportional hazards regression models.
Non-adjusted model adjust for: none.
Adjust I model adjust for: age, ethnicity and gender.
Adjust II model adjust for: age, gender, ethnicity, systolic blood pressure, diastolic blood pressure, temperature, SPO2, anion gap, bicarbonate, chloride, haemoglobin, lactate, platelet, APTT, PT, BUN, WBC, vasopressor use, atrial fibrillation, liver disease, respiratory failure, SOFA, SAPSII.

https://doi.org/10.1017/S0950268820000771 Published online by Cambridge University Press
by One-Way ANOVA (normal distribution) and Kruskal–Wallis H (skewed distribution). Categorical data were summarised as number or percentage and were compared using the chi-squared test. The association between NPAR levels and 30-, 90- and 365-day all-cause mortality was evaluated using Cox proportional hazards models. The results of the multivariate analysis were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Two multivariate models were used to evaluate the prognostic values of NPAR for each endpoint. In model I, covariates were only adjusted for age, ethnicity and gender. In model II, we further adjusted for age, gender, ethnicity, SBP, DBP, temperature, SPO2, anion gap, bicarbonate, chloride, haemoglobin, lactate, platelet, APTT, PT, BUN, WBC, vasopressor use, atrial fibrillation, liver disease, respiratory failure, SOFA and SAPSII. We selected these confounders based on a change in effect estimate of more than 10%. The receiver operating curve (ROC) test was performed to measure the sensitivity and specificity of NPAR and other variables (SOFA score, albumin and neutrophils percentage) and calculated the area under the curve (AUC) to ascertain the quality of NPAR as a predictor of 365-day all-cause mortality.

Subgroup analysis of the associations between NPAR and 90-day all-cause mortality was performed to examine whether the effect of the NPAR differed across various subgroups. All statistical analyses were performed using EmpowerStats version 2.17.8 (http://www.empowerstats.com/cn/, X&Y solutions, Inc., Boston, MA) and R software version 3.4.2; 〈0.05 was considered statistically significant.

Results
Subject characteristics
A total of 2166 patients were eligible for this analysis. The demographic characteristics of participants stratified by NPAR tertiles are summarised in Table 1. Of these patients, there were 1204 (55.6%) men and 1595 (73.6%) white. According to NPAR levels, patients were divided into three groups (tertile 1: NPAR < 24.4; tertile 2: NPAR ≥ 24.4, < 31.4; tertile 3: NPAR ≥ 31.4), and the number of patients in each group was 722. Patients in the high tertile of NPAR (NPAR ≥ 31.4) were more likely to use vasopressor, to report a history of malignancy, had lower SBP, DBP, MBP, haematocrit, haemoglobin and had higher values of chloride, BUN, WBC and mortality.

NPAR as a predictor of the clinical endpoints
In multivariate analysis, we stratified NPAR levels by tertiles and quartiles, to assess whether NPAR was associated with 30-, 90- and 365-day all-cause mortality (Table 2). In model I, after adjustments for age, ethnicity and gender, higher NPAR was associated with increased risk of all-cause mortality. In model II, after adjusting for age, gender, ethnicity, SBP, DBP, temperature, SPO2, anion gap, bicarbonate, chloride, haemoglobin, lactate, platelet, APTT, PT, BUN, WBC, vasopressor use, AFIB, liver disease, respiratory failure, SOFA and SAPSII, higher NPAR was still significantly associated with 30-, 90- and 365-day all-cause mortality compared with the low NPAR levels (tertile 3 vs. tertile 1: HR, 95% CI: 1.29, 1.04–1.61; 1.41, 1.16–1.72; 1.44, 1.21–1.71). A similar trend was observed in NPAR levels stratified by quartiles; high-NPAR levels were also independently associated with these clinical endpoints (quartile 4 vs. quartile 1: HR, 95% CI: 1.37, 1.07–1.77; 1.43, 1.15–1.79; 1.41, 1.16–1.73). The generated ROC curves were shown in Figure 1. The AUCs for NPAR, albumin, neutrophil percentage and SOFA scores were 0.655, 0.618, 0.528 and 0.737, respectively.

Subgroup analyses
Subgroup analysis of the associations between NPAR and 90-day all-cause mortality was performed (Table 3), and there were no interactions in most strata (P = 0.0697–0.8841). Patients with a sodium ≥136 mmol/l had a significantly higher risk of 90-day mortality with a NPAR ≥ 31.4 (HR 1.89, 95% CI 1.49–2.40, P = 0.0354). Similarly, patients with a chloride ≥102 mmol/l, WBC ≥ 14.0 × 10^9/l, haematocrit ≥ 28.7% and haemoglobin ≥ 9.5 g/dl showed an increased risk with a NPAR ≥ 31.4 (HR, 95% CI: 1.72, 1.35–2.18; 1.74, 1.34–2.25; 1.81, 1.40–2.35; 1.76, 1.36–2.27, respectively).

Discussion
Our main findings can be summarised as follows. First, higher NPAR was associated with increased risk of 30-, 90- and 365-day all-cause mortality in critically ill patients with severe sepsis or septic shock. The AUCs for NPAR, albumin, neutrophil percentage and SOFA scores were 0.655, 0.618, 0.528 and 0.737, respectively.
Table 3. Subgroup analysis of the associations between the NPARs and 90-day all-cause mortality

|                      | No. of patients | <24.4 | ⩾24.4, <31.4 | ⩾31.4 | P for interaction |
|----------------------|-----------------|-------|--------------|-------|------------------|
| CHF                  |                 |       |              |       | 0.1582           |
| No                   | 1750            | 1.0 (ref) | 1.02 (0.83, 1.24) | 1.37 (1.14, 1.65) |       |
| Yes                  | 416             | 1.0 (ref) | 0.86 (0.57, 1.30) | 1.84 (1.23, 2.76) |       |
| AFIB                 |                 |       |              |       | 0.8613           |
| No                   | 1496            | 1.0 (ref) | 0.94 (0.76, 1.18) | 1.38 (1.12, 1.70) |       |
| Yes                  | 670             | 1.0 (ref) | 1.02 (0.75, 1.38) | 1.56 (1.16, 2.09) |       |
| CAD                  |                 |       |              |       | 0.1415           |
| No                   | 1764            | 1.0 (ref) | 0.95 (0.78, 1.16) | 1.33 (1.11, 1.60) |       |
| Yes                  | 402             | 1.0 (ref) | 1.08 (0.70, 1.65) | 2.07 (1.38, 3.10) |       |
| Stroke               |                 |       |              |       | 0.0882           |
| No                   | 2047            | 1.0 (ref) | 0.96 (0.80, 1.16) | 1.50 (1.26, 1.79) |       |
| Yes                  | 119             | 1.0 (ref) | 1.02 (0.55, 1.88) | 0.76 (0.39, 1.51) |       |
| Malignancy           |                 |       |              |       | 0.6360           |
| No                   | 1698            | 1.0 (ref) | 0.98 (0.80, 1.21) | 1.36 (1.10, 1.66) |       |
| Yes                  | 468             | 1.0 (ref) | 1.01 (0.72, 1.43) | 1.60 (1.19, 2.16) |       |
| Liver disease        |                 |       |              |       | 0.0203           |
| No                   | 1890            | 1.0 (ref) | 1.01 (0.83, 1.24) | 1.62 (1.34, 1.96) |       |
| Yes                  | 276             | 1.0 (ref) | 0.79 (0.54, 1.17) | 0.89 (0.61, 1.30) |       |
| Renal disease        |                 |       |              |       | 0.7984           |
| No                   | 1788            | 1.0 (ref) | 0.95 (0.78, 1.17) | 1.46 (1.21, 1.77) |       |
| Yes                  | 378             | 1.0 (ref) | 0.98 (0.68, 1.43) | 1.36 (0.94, 1.98) |       |
| Respiratory failure  |                 |       |              |       | <0.0001          |
| No                   | 889             | 1.0 (ref) | 1.22 (0.85, 1.74) | 2.66 (1.91, 3.72) |       |
| Yes                  | 1277            | 1.0 (ref) | 0.88 (0.72, 1.08) | 1.10 (0.90, 1.34) |       |
| Pneumonia            |                 |       |              |       | 0.0235           |
| No                   | 1270            | 1.0 (ref) | 0.77 (0.60, 0.99) | 1.29 (1.03, 1.60) |       |
| Yes                  | 896             | 1.0 (ref) | 1.27 (0.98, 1.64) | 1.72 (1.33, 2.23) |       |
| COPD                 |                 |       |              |       | 0.2817           |
| No                   | 2106            | 1.0 (ref) | 0.95 (0.79, 1.13) | 1.44 (1.21, 1.70) |       |
| Yes                  | 60              | 1.0 (ref) | 1.88 (0.63, 5.60) | 4.09 (1.06, 15.71) |       |
| ARDS                 |                 |       |              |       | 0.3307           |
| No                   | 2106            | 1.0 (ref) | 0.96 (0.80, 1.15) | 1.44 (1.22, 1.71) |       |
| Yes                  | 60              | 1.0 (ref) | 1.93 (0.55, 6.78) | 3.61 (1.10, 11.90) |       |
| Vasopressor use      |                 |       |              |       | 0.0019           |
| No                   | 775             | 1.0 (ref) | 1.22 (0.85, 1.74) | 2.41 (1.72, 3.36) |       |
| Yes                  | 1391            | 1.0 (ref) | 0.87 (0.71, 1.07) | 1.15 (0.95, 1.40) |       |
| Albumin, g/dl        |                 |       |              |       | 0.1726           |
| <2.8                 | 963             | 1.0 (ref) | 0.64 (0.45, 0.89) | 0.71 (0.54, 0.93) |       |
| ⩾2.8                 | 1203            | 1.0 (ref) | 1.03 (0.83, 1.27) | 1.44 (0.96, 2.16) |       |
| Neutrophil percentage, % |           |       |              |       | 0.0775           |
| <82                  | 1064            | 1.0 (ref) | 0.94 (0.74, 1.18) | 1.39 (1.08, 1.78) |       |
| ⩾82                  | 1102            | 1.0 (ref) | 1.44 (1.00, 2.07) | 2.29 (1.61, 3.24) |       |

(Continued)
Table 3. (Continued.)

|                      | No. of patients | NPARs | P for interaction |
|----------------------|-----------------|-------|-------------------|
| Sodium, mmol/l       |                 |       |                   |
| <136                 | 915             | 1.0 (ref) | 0.83 (0.64, 1.08) | 1.09 (0.85, 1.38) |
| ≥136                 | 1251            | 1.0 (ref) | 1.15 (0.90, 1.48) | 1.89 (1.49, 2.40) |
| Potassium, mmol/l    |                 |       |                   |
| <3.7                 | 998             | 1.0 (ref) | 0.73 (0.55, 0.98) | 1.29 (1.00, 1.66) |
| ≥3.7                 | 1168            | 1.0 (ref) | 1.15 (0.92, 1.44) | 1.60 (1.28, 2.00) |
| Chloride, mmol/l     |                 |       |                   |
| <102                 | 1006            | 1.0 (ref) | 0.97 (0.76, 1.24) | 1.25 (0.98, 1.59) |
| ≥102                 | 1160            | 1.0 (ref) | 0.97 (0.74, 1.26) | 1.72 (1.35, 2.18) |
| WBC, 10⁹/l           |                 |       |                   |
| <10.3                | 1077            | 1.0 (ref) | 0.79 (0.62, 1.01) | 1.24 (0.97, 1.59) |
| ≥10.3                | 1089            | 1.0 (ref) | 1.24 (0.94, 1.63) | 1.74 (1.34, 2.25) |
| Platelet, 10⁹/l      |                 |       |                   |
| <162                 | 1080            | 1.0 (ref) | 0.98 (0.77, 1.23) | 1.27 (1.02, 1.59) |
| ≥162                 | 1086            | 1.0 (ref) | 1.08 (0.81, 1.43) | 1.86 (1.42, 2.43) |
| Haematocrit, %       |                 |       |                   |
| <28.7                | 1080            | 1.0 (ref) | 0.80 (0.62, 1.04) | 1.16 (0.93, 1.45) |
| ≥28.7                | 1086            | 1.0 (ref) | 1.15 (0.89, 1.48) | 1.81 (1.40, 2.35) |
| Haemoglobin, g/dl    |                 |       |                   |
| <9.5                 | 1046            | 1.0 (ref) | 0.89 (0.69, 1.16) | 1.18 (0.94, 1.48) |
| ≥9.5                 | 1119            | 1.0 (ref) | 1.04 (0.81, 1.34) | 1.76 (1.36, 2.27) |
| Creatinine, mEq/l    |                 |       |                   |
| <1.3                 | 1080            | 1.0 (ref) | 0.97 (0.72, 1.29) | 1.38 (1.06, 1.81) |
| ≥1.3                 | 1086            | 1.0 (ref) | 0.95 (0.75, 1.19) | 1.50 (1.21, 1.86) |
| BUN, mg/dl           |                 |       |                   |
| <28                  | 1050            | 1.0 (ref) | 1.01 (0.75, 1.38) | 1.47 (1.10, 1.96) |
| ≥28                  | 1116            | 1.0 (ref) | 0.89 (0.72, 1.11) | 1.36 (1.11, 1.68) |
| Anion gap, mmol/l    |                 |       |                   |
| <13                  | 856             | 1.0 (ref) | 0.82 (0.58, 1.15) | 1.37 (1.01, 1.86) |
| ≥13                  | 1310            | 1.0 (ref) | 1.04 (0.84, 1.28) | 1.57 (1.28, 1.92) |
| Bicarbonate, mg/dl   |                 |       |                   |
| <19                  | 981             | 1.0 (ref) | 0.81 (0.63, 1.03) | 1.13 (0.90, 1.42) |
| ≥19                  | 1185            | 1.0 (ref) | 1.18 (0.91, 1.54) | 1.84 (1.43, 2.38) |
| Lactate, mmol/l      |                 |       |                   |
| <1.6                 | 887             | 1.0 (ref) | 0.99 (0.71, 1.39) | 1.49 (1.08, 2.05) |
| ≥1.6                 | 1042            | 1.0 (ref) | 1.15 (0.92, 1.44) | 1.62 (1.31, 2.00) |
| Glucose, mg/dl       |                 |       |                   |
| <134                 | 1078            | 1.0 (ref) | 0.92 (0.72, 1.17) | 1.35 (1.07, 1.71) |
| ≥134                 | 1079            | 1.0 (ref) | 1.01 (0.78, 1.31) | 1.55 (1.21, 1.98) |
| Bilirubin, mg/dl     |                 |       |                   |
| <0.7                 | 936             | 1.0 (ref) | 0.79 (0.58, 1.07) | 1.69 (1.28, 2.23) |
| ≥0.7                 | 1060            | 1.0 (ref) | 1.09 (0.87, 1.36) | 1.21 (0.97, 1.52) |

(Continued)
Previous studies focused on the neutrophil-to-albumin ratio, mainly in significantly predicting prognosis of palliative pancreatic cancer treatment and rectal cancer [16, 17]. Neutrophil percentage can be used as a practical marker to assess inflammation, and the serum neutrophil percentage and inflammatory cytokines are increased in infected patients [24, 25]. Moreover, previous studies have described the relationship between hypoproteinemia and mortality in stroke, myocardial infarction and hip fracture [26–28]. These findings suggested that lower albumin values correlated with poorer prognosis of the disease. On the other hand, lower albumin values correlated with higher the values of NPAR. In our study, by comparing changes in NPAR values of patients with severe sepsis or septic shock, we found that increasing values of NPAR predicted poor sepsis prognosis. Russell et al., [29] showed that peripheral blood leucocyte ratios are useful biomarkers for infection. In critical illness due to sepsis, there is a signal

| No. of patients | NPARs | P for interaction |
|-----------------|-------|-----------------|
|                 | <24.4 | ≥24.4, <31.4 | ≥31.4 |
| PT, second      | 1029  | 1.0 (ref) | 0.84 (0.62, 1.15) | 1.72 (1.31, 2.27) |
|                 | 1080  | 1.0 (ref) | 1.03 (0.82, 1.28) | 1.23 (0.99, 1.52) |
| APTT, second    | 0.4212 |
| <31.2           | 1046  | 1.0 (ref) | 1.00 (0.76, 1.33) | 1.64 (1.25, 2.15) |
| ≥31.2           | 1061  | 1.0 (ref) | 0.96 (0.76, 1.21) | 1.20 (0.97, 1.49) |
| INR             | 0.2165 |
| <1.3            | 781   | 1.0 (ref) | 0.85 (0.61, 1.20) | 1.71 (1.25, 2.36) |
| ≥1.3            | 1328  | 1.0 (ref) | 1.01 (0.82, 1.24) | 1.29 (1.06, 1.58) |
| SBP, mmHg       | 0.4607 |
| <108            | 1075  | 1.0 (ref) | 0.85 (0.67, 1.07) | 1.25 (1.00, 1.55) |
| ≥108            | 1082  | 1.0 (ref) | 1.15 (0.88, 1.51) | 1.63 (1.24, 2.13) |
| DBP, mmHg       | 0.2048 |
| <57             | 1077  | 1.0 (ref) | 0.94 (0.74, 1.20) | 1.54 (1.22, 1.93) |
| ≥57             | 1080  | 1.0 (ref) | 0.97 (0.75, 1.27) | 1.26 (0.97, 1.63) |
| MBP, mmHg       | 0.5355 |
| <72             | 1078  | 1.0 (ref) | 1.07 (0.84, 1.37) | 1.71 (1.36, 2.14) |
| ≥72             | 1080  | 1.0 (ref) | 0.83 (0.64, 1.08) | 1.04 (0.80, 1.35) |
| Heart rate, beats/minute | 0.0803 |
| <91             | 1079  | 1.0 (ref) | 1.15 (0.88, 1.49) | 1.91 (1.49, 2.46) |
| ≥91             | 1079  | 1.0 (ref) | 0.83 (0.65, 1.06) | 1.09 (0.87, 1.38) |
| Respiratory rate, beats/minute | 0.0136 |
| <21             | 1078  | 1.0 (ref) | 1.14 (0.86, 1.51) | 1.85 (1.42, 2.41) |
| ≥21             | 1078  | 1.0 (ref) | 0.82 (0.65, 1.03) | 1.18 (0.95, 1.48) |
| Temperature, °C | 0.7159 |
| <36.8           | 1073  | 1.0 (ref) | 0.88 (0.69, 1.12) | 1.52 (1.22, 1.90) |
| ≥36.8           | 1074  | 1.0 (ref) | 1.02 (0.78, 1.33) | 1.25 (0.96, 1.62) |
| SPO2, %         | 0.7942 |
| <97.2           | 1076  | 1.0 (ref) | 0.87 (0.69, 1.10) | 1.35 (1.08, 1.69) |
| ≥97.2           | 1077  | 1.0 (ref) | 1.13 (0.85, 1.50) | 1.71 (1.32, 2.23) |
| RRT             | 0.0292 |
| No              | 1845  | 1.0 (ref) | 0.99 (0.81, 1.21) | 1.59 (1.32, 1.92) |
| Yes             | 321   | 1.0 (ref) | 0.80 (0.54, 1.19) | 0.90 (0.62, 1.32) |

CHF, congestive heart failure; AFIB, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; WBC, white blood cell; BUN, blood urea nitrogen; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalised ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RRT, renal replacement therapy.

The modification and interaction of subgroup were inspected by the likelihood ration test.
and prognosis associated with NLR, and longitudinal measurements of these biomarkers during infection could be informative. Our findings also indicated that NPAR and NLR had similar predictive abilities for poor outcomes.

Neutrophils are part of the differential of WBC counts that are typically sensitive to bacterial and fungal infections [30]. Walling et al., [31] demonstrated that neutrophil percentages above 80% provided a good distinction between positive and negative blood cultures among sepsis patients. However, the role of neutrophils in predicting bloodstream infection remained questionable, because stress, medication, trauma and abnormal bone marrow formation could cause these changes [32, 33]. Therefore, looking for a simple and reliable clinical predictor of mortality in sepsis is significant. Albumin levels reflect nutritional status and organ function, and the underlying inflammatory state give rise to a decrease of albumin production in liver by increasing inflammatory factors, the primary cause of hypoalbuminemia that occurs early in sepsis [34, 35]. Therefore, based on our findings, NPAR, a new biomarker composed of neutrophil percentage and albumin that closely related to the inflammatory response, can significantly predict the prognosis of sepsis.

Our study had some limitations. First, the study was a single-centre retrospective design, and was therefore subject to selection bias. Second, we extracted NPAR in patients only upon admission to the ICU and did not assess changes during the ICU stay. Third, this database does not use the latest sepsis definitions (sepsis 3.0), and severe sepsis no longer forms part of the sepsis 3.0 definitions, this may affect the conclusion. Fourth, missing the aetiology of sepsis and specific cause of death in the MIMIC database failed to the study more detailed and comprehensive. Fifth, although we have done our best to use a multivariate model to control bias, there remain numerous other known and unknown factors. Furthermore, the database contains a few inaccurate data elements. Therefore, multi-centre prospective studies are needed to confirm these findings.

Conclusions

Our findings demonstrated that higher NPAR was associated with increased risk of all-cause mortality in critically ill patients with severe sepsis or septic shock. Nevertheless, the conclusions need to be confirmed in large prospective multicentre studies.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268820000771.

Data. The clinical data used to support the findings of this study were supplied by Monitoring in Intensive Care Database III version 1.4 (MIMIC-III v.1.4). Although the database is publicly and freely available, researchers must complete the National Institutes of Health’s web-based course known as Protecting Human Research Participants to apply for permission to access the database.

Financial support. This research was supported by the Zhejiang Provincial Natural Science Foundation of China (grants No. LY19H150002 and LY13H150007) and the Scientific Research Foundation of Wenzhou (grant No. Y20150038)

Conflict of interest. The authors declare that they have no competing interests.

Ethical standards. The MIMIC-III database has received ethical approval from the institutional review boards (IRBs) at Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology. Because the database does not contain protected health information, a waiver of the requirement for informed consent was included in the IRB approval.

Disclosure. The funders of the project were not involved in study design, collection, data analysis, writing of the report and publication.

Consent for publication. Not applicable.

References

1. Singer M et al. (2016) The Third International Consensus Definitions For Sepsis And Septic Shock (Sepsis-3). Jama 315, 801–810.
2. Mayr FB, Sachin Y and Angus DC (2014) Epidemiology of severe sepsis. Virulence 5, 4–11.
3. Gaiski DF et al. (2013) Benchmarking the incidence and mortality of severe sepsis in the United States. Critical Care Medicine 41, 1167–1174.
4. Rhodes A et al. (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Critical Care Medicine 45, 486–552.
5. Leigidorwich A et al. (2014) Association between source of infection and hospital mortality in patients who have septic shock. American Journal of Respiratory and Critical Care Medicine 189, 1204–1213.
6. Jones AE, Trzeciak S and Kline JA (2009) The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Critical Care Medicine 37, 1649–1654.
7. Gilani MT, Razavi M and Azad AM (2014) A comparison of Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation II and Acute Physiology and Chronic Health Evaluation III scoring system in predicting mortality and length of stay at surgical intensive care unit. Nigerian Medical Journal: Journal of the Nigeria Medical Association 55, 144–147.
8. Shen XF et al. (2017) Neutrophil dysregulation during sepsis: an overview and update. Journal of Cellular and Molecular Medicine 21, 1687–1697.
9. Park I et al. (2019) Neutrophils disturb pulmonary microcirculation in sepsis-induced acute lung injury. The European Respiratory Journal 53, 1800786.
10. Pan Y-P et al. (2017) The diagnostic value of procalcitonin vs. other biomarkers in prediction of bloodstream infection. Clinical Laboratory 63, 277–285.
11. Artigas A et al. (2016) Role of albumin in diseases associated with severe systemic inflammation: pathophysiological and clinical evidence in sepsis and in decompensated cirrhosis. Journal of Critical Care 33, 62–70.
12. Ha CE and Bhagavan NV (2013) Novel insights into the pleiotropic effects of human serum albumin in health and disease. Biochimica et Biophysica Acta 1830, 5486–5493.
13. Gradel KO et al. (2018) Hypoalbuminaemia as a marker of trans-capillary leakage in community-acquired bacteraemia patients. Epidemiology and Infection 146, 648–655.
14. Norberg A et al. (2015) Albumin Kinetics in Patients Undergoing Major Abdominal Surgery. PLoS One 10, e0136371.
15. Arnau-Barres I et al. (2019) Serum albumin is a strong predictor of sepsis outcome in elderly patients. European Journal of Clinical Microbiology & Infectious Diseases 38, 743–746.
16. Tingle SJ et al. (2018) NARCA: a Novel Prognostic Scoring System Using neutrophil-albumin ratio And Ca19-9 to predict overall survival in palliative pancreatic cancer. Journal of Surgical Oncology 118, 680–686.
17. Tawfiq B et al. (2016) The neutrophil to albumin ratio as a predictor of pathological complete response in rectal cancer patients following neoadjuvant chemoradation. Anti-Cancer Drugs 27, 879–883.
18. Wang B et al. (2019) Association of serum total and ionized calcium with all-cause mortality in critically ill patients with acute kidney injury. Clinica Chimica Acta 494, 94–99.
19. Wang B et al. (2019) Relation between red cell distribution width and mortality in critically ill patients with acute respiratory distress syndrome. BioMed Research International 2019, 1942078.
20. Johnson AE et al. (2016) MIMIC-III, a freely accessible critical care database. Scientific Data 3, 160035.
21. Dellinger RP et al. (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Medicine 39, 165–228.
22. Allard J et al. (2007) SOFA – an open source framework for medical simulation. Studies in Health Technology & Informatics 125, 13.
23. Le GJ, Lemeshow S and Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. Journal of the American Medical Association 270, 2957.
24. Sun Y, Jiang L and Shao X (2017) Predictive value of procalcitonin for diagnosis of infections in patients with chronic kidney disease: a comparison with traditional inflammatory markers C-reactive protein, white blood cell count, and neutrophil percentage. International Urology and Nephrology 49, 2205–2216.
25. Lau WY et al. (1989) Leucocyte count and neutrophil percentage in appendicectomy for suspected appendicitis. The Australian and New Zealand Journal of Surgery 59, 395–398.
26. Plakht Y, Gilutz H and Shiyovich A (2016) Decreased admission serum albumin level is an independent predictor of long-term mortality in hospital survivors of acute myocardial infarction. Soroka Acute Myocardial Infarction II (SAMI-II) project. International Journal of Cardiology 219, 20–24.
27. Famakin B et al. (2010) Hypoalbuminemia predicts acute stroke mortality: Paul Coverdell Georgia Stroke Registry. Journal of Stroke and Cerebrovascular Diseases 19, 17–22.
28. Pioli G et al. (2006) Predictors of mortality after hip fracture: results from 1-year follow-up. Aging Clinical and Experimental Research 18, 381–387.
29. Russell CD et al. (2019) The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. The Journal of Infection 78, 339–348.
30. Zarkesh M et al. (2015) Diagnostic value of IL-6, CRP, WBC, and absolute neutrophil count to predict serious bacterial infection in febrile infants. Acta Medica Iranica 53, 408–411.
31. Walling HW and Manian FA (2004) Predictive value of leukocytosis and neutrophilia for bloodstream infection. Infectious Diseases in Clinical Practice 12, 2–6.
32. Pagano L et al. (2009) The role of neutrophils in the development and outcome of zygomycosis in haematological patients. Clinical Microbiology and Infection 15(Suppl 5), 33–36.
33. Murray CK et al. (2007) Evaluation of white blood cell count, neutrophil percentage, and elevated temperature as predictors of bloodstream infection in burn patients. Archives of Surgery (Chicago, Ill.: 1960) 142, 639–642.
34. Churpek MM et al. (2017) Quick sepsis-related organ failure assessment, systemic inflammatory response syndrome, and early warning scores for detecting clinical deterioration in infected patients outside the intensive care unit. American Journal of Respiratory and Critical Care Medicine 195, 906–911.
35. Akirov A, et al. (2017) Low albumin levels are associated with mortality risk in hospitalized patients. The American Journal of Medicine 130, 1465.e11–1465.e19.