The association between neutrophil-to-albumin ratio and mortality in patients with cardiogenic shock: a cohort study

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Abstract

Background Cardiogenic shock (CS) is a lethal complication. Given the poor outcome of CS, we performed a retrospective cohort study to identify whether the neutrophil-to-albumin ratio (NAR) was significantly associated with mortality from CS. **Methods** All patient data were extracted from the MIMIC III version 1.3. Comparisons between groups was made using the chi-square or Fisher's exact tests for categorical variables and the variance analysis or the Kruskal-Wallis test was used for continuous variables. The primary outcome was 30-day mortality and the secondary ones were 90-day and 365-day mortality. We used Cox proportional hazards models to evaluate the association between the various categories of NAR and survival. To further identify the association, subgroup analyses were performed. **Results** A total of 475 patients with CS were enrolled. A significant positive correlation between NAR levels and 30-day, 90-day or 365-day mortality was observed. For the primary outcome of 30-day mortality, the HR (95% CI) values given NAR levels 23.54–27.86 and > 27.86 were 1.72 (1.17, 2.53) and 1.96 (1.34, 2.87) compared with the reference (NAR < 23.47) in tertile analysis. In multivariate analyses, the HR (95% CI) values were still of statistical significance [1.98 (1.25, 3.15) and 2.03 (1.26, 3.26)]. When quintiles were applied to grouping patients according to NAR level, similar associations were also observed. For the secondary outcomes, the upward trend remained statistically significant. **Conclusions** NAR level was associated with survival from CS. NAR appeared to be an independent and readily-available prognostic biomarker of mortality in patients with CS.

Background

Cardiogenic shock (CS), a lethal complication of cardiac emergencies, is traditionally thought to begin with depression of myocardial contractility, followed by intractable hypotension, coronary insufficiency and further loss of cardiac output, causing multiple organ failure and eventually death ^{1,2}. For decades, the prevalence of CS has risen from 4.1% to 7.7% of all admissions to the intensive care unit (ICU) ³, of which approximately 6.4% to 40% were reported to have died despite intensive care ^{4,5}. Although less frequent than other fatal diseases, CS has had even higher mortality rates and poorer short-term survival, remaining a clinical challenge for medical personnel throughout the world ⁶⁻⁸.

Previous studies have shown that a systemic inflammatory response, release of cytokines, activation of complement, expression of inducible nitric oxide synthase and improper vasodilatation might exert an influence both on the occurrence and the outcome of shock ⁹. Further evidence suggested that inflammation played an important role in the pathogenesis and outcome of CS, a devastating complication of cardiovascular diseases ¹⁰. Among the inflammatory mediators, the neutrophil is well-known as a marker of inflammation ¹¹. Several studies indicated that low serum albumin levels were associated with high mortality because of all-cause or cardiovascular mortality ^{12,13}.

Based on these studies, we put forward a hypothesis that neutrophil-to-albumin ratio (NAR) would be associated with mortality from CS. To our knowledge, to date, no study has explored the prognostic

significance of NAR in patients with CS. Therefore, we performed a retrospective cohort study to identify the associations between NAR and mortality in patients with CS so as to assess prognosis.

Methods

2.1 Data source

All data in our study were extracted from the Medical Information Mart for Intensive Care Database III version 1.3 (MIMIC-III v1.3), a large, open, free and single-centered database including information from more than 50,000 adult patients admitted to various critical care units at Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2001 to 2012 ¹⁴. The setting and use of this database were approved by the institutional review boards of the Massachusetts Institute of Technology (Boston, MA) and Beth Israel Deaconess Medical Center (Cambridge, MA). All personal information included in the database have been de-identified to safeguard privacy.

2.2 Population selection criteria

More than 50,000 ICU admissions to the MIMIC-III database were recorded, and only patients diagnosed with CS were extracted. Among these patients, we selected those who attained more than 16 years of age at first admission while remaining in the hospital for more than 48 hours. Exclusion criteria were as follows: (1) patients who were diagnosed with hematologic neoplasms, including leukemia, multiple myeloma, and others; (2) more than 10% individual data were missing; (3) individual data values exceeded the mean $\pm$ 3 times the standard deviation (SD).

CS was determined on the grounds of International Classification of Diseases, Ninth Revision (ICD-9), the definitions in the clinical practice guidelines including the ESC Guidelines ¹⁵ as well as clinical trials, including SHOCK ¹⁶ and IABP-SHOCK II ¹⁷.

2.3 Data extraction

Data were extracted through Structured Query Language (SQL) ¹⁸ with MySQL tools (version 5.6.24) from MIMIC-III. The extracted data contain demographic parameters, basic vital signs, laboratory indicators and scoring systems.

Demographic parameters included age, gender and ethnicity, while basic vital signs included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), respiratory rate (RR), temperature and percutaneous oxygen saturation (SPO₂). The following laboratory indicators were extracted: neutrophils, albumin, platelets, partial thromboplastin time (PTT), prothrombin time (PT), international normalized ratio (INR), serum bicarbonate, serum sodium levels, serum potassium levels and serum glucose levels. We defined the NAR as the ratio of the neutrophil percentage to the serum albumin level. We additionally extracted relevant comorbidities, for example, coronary heart disease (CAD), congestive heart failure (CHF), atrial fibrillation (AF), stroke, chronic obstructive pulmonary

disease (COPD), pneumonia, acute respiratory distress syndrome (ARDS) and other diseases listed in Table 1. Severity-of-illness scores, including the Sequential Organ Failure Assessment (SOFA) ¹⁹ score and the Simplified Acute Physiology Score II (SAPS II) ²⁰ were also calculated for every individual. The SOFA score, designed to describe a sequence of complications in the critically ill, is the sum of points obtained from evaluation of respiration, coagulation, liver, cardiovascular system, central nervous system and kidney. The SAPS II, a scoring system developed to estimate the risk of death, included 12 physiology variables (HR, SBP, body temperature, partial pressure of arterial oxygen or fraction of inspired oxygen ratio, urinary output, serum urea or serum urea nitrogen level, WBC count, serum potassium level, serum sodium level, serum bicarbonate level, bilirubin level and Glasgow Coma Score ²¹), age, type of admission (scheduled surgical, unscheduled surgical or medical) and three underlying disease variables (acquired immunodeficiency syndrome, metastatic cancer and hematologic malignancy). All scores were assessed and calculated on the basis of published recommendations and accepted formulas.

The initiation of our study was the time when the patient admitted to ICU. The outcomes were 30-day, 90-day and 365-day mortality, in which 30-day mortality was the primary outcome. Baseline characteristics were all recorded within 24 hours after admission to the ICU.

2.4 Statistical analysis and modeling strategy

Baseline characteristics delaminated by NAR were presented in Table 1. Categorical data were shown as frequency (percent), while continuous ones as mean (SD) or median(IQR). We did comparisons between groups by the chi-square test ²² or Fisher's exact test ²³ for categorical variables and the variance analysis or the Kruskal-Wallis test ²⁴ for continuous ones.

To examine the associations between NAR and outcomes (30-day, 90-day and 365-day mortality), we used Cox proportional hazards models ²⁵. The outcomes were respectively analysed according to the tertiles or the quintiles of the NAR level. The first tertile or quartile group was regarded as the reference group. The results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). To further identify the association between NAR and mortality, multivariate analyses were performed using two adjusted models. The confounders selected in our models were based on their associations with mortality or a mutation exceeding 10% ²⁶. In model I, we adjusted covariates for age, gender and ethnicity. In model II, covariates were adjusted further for length of stay in ICU, HR, SBP, DBP, RR, SPO₂, anion gap, serum bicarbonate, serum potassium, SCr, BUN, hematocrit, platelet count, WBC count, PTT, PT, INR, stroke, pneumonia, COPD, chronic liver disease, chronic renal disease, RRT, malignancy, vasoactive agent, SOFA score and SAPSII score. Building further on this foundation, we performed stratified analysis to confirm whether the effect of NAR differed across each of the subgroups that were classified by stay in ICU, vital signs (HR, SBP, DBP, RR, temperature, SPO₂), laboratory parameters (anion gap, serum bicarbonate, serum sodium, serum potassium, serum chloride, serum bilirubin, serum glucose, SCr, BUN, hematocrit, hemoglobin, platelet count, WBC count, PTT, PT, INR), comorbidities (CAD, CHF,

stroke, pneumonia, COPD, respiratory failure, chronic liver disease, chronic renal disease, RRT, malignancy), vasoactive drug use and scoring systems (SOFA and SAPSII scores).

A two-tailed P value < 0.05 was deemed statistically significant. EmpowerStats version 2.17.8 (<http://www.empowerstats.com/cn/>) and R software version 3.42 were used for all statistical analysis.

Results

3.1 Subject characteristics

Patient records from more than 50,000 subjects treated in the ICU at Beth Israel Deaconess Medical Center were originally extracted from the MIMIC-III database. After subjects who did not meet the inclusion criteria were excluded, a total of 475 patients with CS remained. As shown in Table 1, among the patients included, 272 (57.3%) were men and 328 (69.1%) were white.

All patients included in the study were equally divided into three groups according to NAR: 158 patients were in the low-NAR group (< 23.47), 158 patients were in the mid-NAR group (23.54–27.86), and 159 patients were in the high-NAR group (> 27.86). Patients in the higher NAR group (34.1 ± 8.0) tended to be white and had higher serum chloride, BUN, WBC count, PTT, PT, INR and lower serum bicarbonate, hematocrit, hemoglobin. Participants with higher NAR also had a higher SOFA and SAPSII scores than did those with lower NAR (< 23.47). These patients, however, had no apparent differences in age, gender, vital signs, vasoactive drug use or comorbidities listed in the Table 1.

3.2 NAR levels and mortality

A total of 180, 218 and 264 deaths were recorded in the 30-day, 90-day and 365-day follow-up periods, respectively. As shown in Table 2, we observed a positive relationship between NAR and mortality from CS.

For the primary outcome of 30-day mortality, we observed that higher NAR was associated with increased risk of mortality in tertile analysis and the HR values of the three models were all significant compared to the reference group (NAR < 23.47). The HR (95% CI) values of the mid tertile (NAR 23.54–27.86) and the upper tertile (NAR > 27.86) were 1.72 (1.17, 2.53) and 1.96 (1.34, 2.87), respectively, when compared with the reference of lower tertile (NAR < 23.47). When adjusted for age, gender and ethnicity in model I, an increasing trend was also observed and the adjusted HR (95% CI) values for 30-day mortality given NAR of 23.54–27.86 and > 27.86 were 1.63 (1.10, 2.40) and 1.99 (1.36, 2.92), respectively. After further adjustment for potential confounders, including HR, SBP, DBP and RR in model II, the upward trend remained statistically significant and the upper tertile (NAR > 27.86), even revealing the highest HR (95% CI) of 2.03 (1.26, 3.26).

When stratifying the NAR levels into quintiles and defining the extremely low (NAR < 21.74) NAR as a reference, we further confirmed the upward trend between NAR levels and 30-day mortality (P trend 0.0034 in model II). However, the HRs of the second quintile (NAR 21.76 - 24.29) in the three models and the third quintile (NAR 24.35 - 26.91) in model I didn't have statistical significance compared to the reference group (NAR < 21.74).

Furthermore, the similar trends were also observed for the secondary outcomes of 90-day and 365-day mortality. In tertile analysis, the adjusted HR (95% CI) values for 90-day mortality given NAR of 23.54–27.86 and > 27.86 were 1.71 (1.14, 2.55) and 1.93 (1.27, 2.93) in model II, while those for 365-day mortality were 1.93 (1.34, 2.77) and 2.36 (1.61, 3.47). In quintile analysis, the upward trend between NAR and 90-day or 365-day mortality continued to make sense. The HRs of the second quintile (NAR 21.76–24.29), however, also showed no statistical significance.

The results are presented in Table 2 and Figures 1 and 2.

3.3 Subgroup analyses

Subgroup analyses were conducted to determine the consistency of association between NAR and 90-day mortality in patients with CS (Table 3).

Most subgroup factors showed weak significance with 90-day mortality, except for the length of stay in ICU (p = 0.0465), the serum sodium (p = 0.0270), the serum bilirubin (p = 0.0343), respiratory failure (p = 0.0102) and RRT (p = 0.0044). NAR particularly showed significant interactions in patients without RRT. Patients without the therapy of RRT had a significant higher 90-day mortality risk for NAR > 27.86 [HR (95% CI) 2.29 (1.58, 3.32)]. While patients without respiratory failure had higher risks with NAR > 27.86 [HR (95% CI) 3.14 (1.89, 5.20) vs HR (95% CI) 1.19 (0.75, 1.90)] and NAR 23.54 - 27.86 [HR (95% CI) 1.73 (1.02, 2.95) vs. HR (95% CI) 1.22 (0.76, 1.94)]. In the subgroups of the length of stay in ICU, the serum sodium and the serum bilirubin, however, the interactions were of relatively weak significance. All of the subgroup analyses were demonstrated in Table 3.

Discussion

In our study, we observed a significant positive correlation between NAR levels and 30-day, 90-day or 365-day mortality in patients with CS. In particular a high level of NAR was associated with growing risk of mortality. After adjusting for potential confounders, the differences in each outcome retained statistical significance.

CS is a lethal complication of cardiovascular diseases with an extremely high mortality. Inflammation has been shown to play a vital role in the pathogenesis and outcome of CS. Studies in recent decades have suggested the prognostic value of inflammatory mediators in CS, including blood cells²⁷, cytokines^{28,29}, complement³⁰ and enzymes^{31,32}. Furthermore, the use of albumin, the main serum protein, to predict the mortality of cardiovascular disease as well as all-cause mortality has already been

described^{12, 33, 34}. As blood cells and serum albumin can directly indicate the host environment, recent studies have combined them, just as the NAR, to predict the outcome of diseases. The NAR, a combination of the neutrophil percentage and the serum albumin level, is a novel and readily-available biomarker. Prior to our work, the prognostic value of NAR was recently shown. Samuel et al.³⁵ demonstrated that NAR was a significant prognostic hallmark in patients with palliative pancreatic cancer. Tawfik et al.³⁶ investigated the association between NAR and pathological complete response in rectal cancer patients after neoadjuvant chemoradiation. Based on this evidence, an inference may be put forward that NAR levels could predict the mortality in patients with CS.

It remains unclear why NAR, the combined biomarker, could have such a significant prognostic value in patients with CS. On the one hand, neutrophils, which are vital leukocytes, have been well-studied regarding the generation and development of various diseases, including CS. Sionis et al.³⁷ recently found that distinct microparticles released by neutrophils (CD15+) significantly increased in patients with CS. This result suggested high activation of neutrophils in CS and further indicated the significance of inflammation in that condition. Given the severe systemic inflammatory response in CS, it was demonstrated that patients with higher leukocyte count had a higher mortality in cardiogenic shock³⁸. However, whether the increase of inflammatory mediators in CS results from the heart itself, from intestinal bacterial translocation, or from ischemia-reperfusion injury remains unknown¹⁰. On the other hand, serum albumin, synthesized in the liver, is the major plasma protein in human blood. Albumin has already been used to predict mortality especially in critically ill patients in ICUs^{39, 40}, and even has been a part of major risk scores, for example, the Acute Physiology and Chronic Health Evaluation (APACHE) III Prognostic system and the Framingham risk score for cardiovascular risk. Low albumin levels were demonstrated to be related to some inflammatory mediators^{41, 42}; therefore, the association between serum albumin and mortality may result from subclinical inflammation, as Mutsert et al.⁴³ found in their study. However, whether the prognostic value of albumin only reflects inflammation or whether there is an independent role of albumin itself remains to be turned determined. As albumin plays an important role in maintaining the plasma colloid osmotic pressure, low albumin levels may disorganize the fluid distribution in the internal environment so as to destroy the balance of the hemodynamics, resulting in poor outcomes⁴⁴. Another interpretation may involve the state of nutrition because lower albumin is possibly related to malnutrition, emaciation or cachexia⁴⁵. Furthermore, as the most abundant carrier protein in plasma, albumin can change the existing form of some toxins by binding to them, leading to changes in their biological effects. The recent study of Watanabe et al.⁴⁶ indicated that, when combined with lower albumin levels, levels of indoxyl sulfate, a protein-bound uremic toxin, might be a prognostic marker for cardiovascular diseases, because lower albumin levels might increase free indoxyl sulfate levels, possibly activating a signal transduction pathway and subsequently exerting toxic effects. Further studies are needed to confirm these hypotheses.

CS in critically ill patients has an extremely high mortality. This poor outcome may be affected by a number of factors, including basic vital signs (i.e., DBP⁴⁷, MBP⁴⁸), some laboratory parameters (i.e.,

serum bicarbonate levels ⁴⁹), cardiac power index ⁴⁸, vasopressor support ⁵⁰, severity-of-illness scores (i.e., SAPSII ⁴⁸), as well as other comorbidities. In subgroup analyses, patients were stratified according to potential confounders and statistically significant interactions were observed for some factors, such as respiratory failure and RRT. Patients without a history of respiratory failure or without the therapy of RRT might have a higher risk of 90-day mortality. In patients with the therapy of RRT, prognosis might be meliorated through metabolites clearance. While in patients with a history of respiratory failure, the improved survival might contribute to the systemic antimicrobial therapy and advanced assisted ventilation strategies. The real mechanism, however, remained unclear.

Our study was the first study to explore the prognostic effect of NAR in patients with CS. The period of follow-up in our study was quite long. To further confirm the significant association between NAR and outcomes, we applied quintiles to grouping patients and performed subgroup analyses. The limitations of this study, however, cannot be ignored. First and foremost, it was a retrospective observational study in a single center. The biases inherent in this type of study and selection bias in this design should be highlighted. Therefore, we should further perform studies based on multiple centers. Second, owing to the relatively low incidence of CS, the sample size of patients selected in our study was small, suggesting that larger prospective studies are needed. Third, the NAR was measured only when patients first admitted to the ICU, possibly causing errors to a certain extent. Therefore, the dynamic evaluation of NAR during the ICU stay can make a difference. Furthermore, merely measuring NAR does not adequately reflect genuine levels of inflammation. Therefore, simultaneous measurement of other inflammatory factors would make a better demonstration of our conclusions. Last but not the least, to set up NAR as a prognostic biomarker, its clinical significance must further be verified.

Conclusions

We found that NAR level was associated with survival of CS. Furthermore, NAR appeared to be an independent and readily available prognostic biomarker of outcomes in patients with CS. However, further prospective studies with larger sample size are needed to confirm our findings.

Declarations

6.1 Ethics approval and consent to participate

Not applicable.

6.2 Consent for publication

Not applicable.

6.3 Competing interests

The authors have no competing interests to declare.

6.4 Funding

No funding.

6.5 Authors' contributions

Yangpei Peng, Jie Wang and Cong Lin conceived and designed the research. Yangjing Xue, Jinsheng Wang and Huaqiang Xiang performed the studies and participated in data collection. Jie Wang, Yangjing Xue and Kangting Ji completed data processing and statistical analysis. Yangpei Peng, Yangjing Xue and Cong Lin drafted the manuscript. All authors read and approved the final manuscript.

6.6 Acknowledgements

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6.7 Availability of data and materials

All data in our study were extracted from a freely accessible database, the Medical Information Mart for Intensive Care Database III version 1.3 (MIMIC-III v1.3). The setting and use of this database were approved by the institutional review boards of the Massachusetts Institute of Technology (Boston, MA) and Beth Israel Deaconess Medical Center (Cambridge, MA). Data are available from MIMIC-III for researchers who meet the criteria for access to the database.

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Tables

Table 1. Baseline characteristics of the study population

	Neutrophil-albumin ratio			P-value
	< 23.47	23.54 - 27.86	> 27.86	
n	158	158	159	
NAR	19.8 ± 3.8	25.6 ± 1.2	34.1 ± 8.0	<0.001
Neutrophil	72.6 ± 15.4	83.2 ± 9.6	85.8 ± 7.8	<0.001
Albumin	3.7 ± 0.5	3.3 ± 0.4	2.6 ± 0.5	<0.001
Death, n (%)				
30-Day	42 (26.6)	67 (42.4)	71 (44.7)	0.001
90-Day	54 (34.2)	76 (48.1)	88 (55.3)	<0.001
365-Day	63 (39.9)	93 (58.9)	108 (67.9)	<0.001
Age	69.2 ± 14.9	70.1 ± 13.3	70.9 ± 13.8	0.661
Gender, n(%)				0.065
Female	57 (36.1)	68 (43.0)	78 (49.1)	
Male	101 (63.9)	90 (57.0)	81 (50.9)	
Ethnicity, n (%)				0.039
White	112 (70.9)	107 (67.7)	109 (68.6)	
Black	13 (8.2)	3 (1.9)	13 (8.2)	
Other	33 (20.9)	48 (30.4)	37 (23.3)	
LOS_ICU	7.1 ± 7.7	8.6 ± 9.1	8.7 ± 9.6	0.196
Vital signs				
HR, beats/min	86.6 ± 17.5	90.1 ± 17.3	90.4 ± 18.0	0.077
SBP, mmHg	108.3 ± 15.2	106.0 ± 13.3	104.7 ± 13.9	0.058
DBP, mmHg	58.7 ± 9.9	57.5 ± 8.9	57.5 ± 11.5	0.303
MBP, mmHg	75.2 ± 9.5	74.4 ± 9.3	73.3 ± 10.0	0.114
RR, beats/minute	19.9 ± 4.2	20.1 ± 3.9	20.2 ± 4.1	0.554
Temperature, °C	36.8 ± 0.8	36.8 ± 0.9	36.7 ± 0.9	0.442
SPO2, %	96.3 ± 4.6	96.5 ± 4.5	96.4 ± 5.2	0.089
Laboratory parameters				
Anion gap, mmol/l	14.6 ± 4.0	14.7 ± 4.1	14.7 ± 3.9	0.942
Serum bicarbonate, mmol/l	20.2 ± 5.4	19.6 ± 5.3	18.6 ± 5.3	0.042
Serum sodium, mmol/l	134.7 ± 5.4	135.0 ± 6.6	135.3 ± 5.3	0.632
Serum potassium, mmol/l	3.8 ± 0.6	3.8 ± 0.6	3.8 ± 0.6	0.616
Serum chloride, mmol/l	99.5 ± 7.0	101.2 ± 7.6	101.9 ± 6.2	0.010
Serum glucose, mg/dl	119.7 ± 43.6	123.6 ± 46.3	121.4 ± 52.4	0.433
Serum bilirubin	1.0 ± 1.7	0.9 ± 1.0	1.3 ± 2.9	0.625
BUN, mg/dl	33.2 ± 23.0	35.2 ± 24.9	38.5 ± 23.9	0.031
SCr, mg/dl	1.7 ± 1.5	1.7 ± 1.3	1.8 ± 1.4	0.629
Hematocrit	32.4 ± 7.6	30.4 ± 6.1	28.0 ± 6.3	<0.001
Hemoglobin, g/dl	11.0 ± 2.6	10.2 ± 2.1	9.3 ± 2.0	<0.001
Platelet count, 10 ⁹ /l	195.3 ± 91.3	207.6 ± 118.3	209.3 ± 113.4	0.712
WBC count, 10 ⁹ /l	9.9 ± 5.5	12.3 ± 5.9	12.6 ± 5.7	<0.001
PTT, s	35.3 ± 18.6	36.8 ± 18.0	41.7 ± 24.3	0.005
PT, s	15.5 ± 5.8	16.3 ± 5.7	16.5 ± 5.1	<0.001
INR	1.6 ± 1.8	1.6 ± 1.1	1.6 ± 0.7	<0.001
Comorbidities, n (%)				
CAD	89 (56.3)	91 (57.6)	79 (49.7)	0.315
CHF	58 (36.7)	58 (36.7)	61 (38.4)	0.940
AF	65 (41.1)	68 (43.0)	67 (42.1)	0.943
Stroke	6 (3.8)	6 (3.8)	9 (5.7)	0.752
COPD	1 (0.6)	0 (0.0)	4 (2.5)	0.133
Pneumonia	50 (31.6)	60 (38.0)	53 (33.3)	0.471
ARDS	2 (1.3)	3 (1.9)	0 (0.0)	0.214
Respiratory failure	69 (43.7)	82 (51.9)	84 (52.8)	0.200
Chronic liver disease	5 (3.2)	11 (7.0)	6 (3.8)	0.250

Chronic renal disease	30 (19.0)	28 (17.7)	42 (26.4)	0.122
RRT	16 (10.1)	27 (17.1)	30 (18.9)	0.074
Malignancy	21 (13.3)	15 (9.5)	18 (11.3)	0.568
Vasoactive drug, n (%)	113 (71.5)	126 (79.7)	126 (79.2)	0.151
Scoring systems, mean (Q1-Q3)				
SOFA	6.7 ± 3.6	6.8 ± 4.0	7.9 ± 3.7	0.005
SAPSII	45.5 ± 15.3	46.5 ± 15.1	52.8 ± 16.1	<0.001

NAR: neutrophil-to-albumin ratio; N: number; LOS_ICU: length of stay in intensive care unit; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; RR: respiratory rate; SPO2: percutaneous oxygen saturation; BUN: blood urea nitrogen; SCr: Serum creatinine; WBC: white blood cell; PTT: partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; CAD: coronary heart disease; CHF: congestive heart failure; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; RRT: renal replacement therapy; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score. Normally distributed data are presented as the mean±SD, non-normally distributed data are presented as median (IQR) and categorical variables are presented as n(%).

Table 2. HRs (95% CIs) for mortality across groups of neutrophil-to-albumin ratio

		Non-adjusted		Model I			Model II		
	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend
30-day mortality									
Tertiles			0.0008			0.0005			0.0096
< 23.47	1.0			1.0			1.0		
23.54 - 27.86	1.72 (1.17, 2.53)	0.0060		1.63 (1.10, 2.40)	0.0139		1.98 (1.25, 3.15)	0.0036	
> 27.86	1.96 (1.34, 2.87)	0.0006		1.99 (1.36, 2.92)	0.0004		2.03 (1.26, 3.26)	0.0036	
Quintiles			0.0001			0.0002			0.0034
< 21.74	1.0			1.0			1.0		
21.76 - 24.29	1.13 (0.65, 1.97)	0.6524		1.01 (0.58, 1.76)	0.9695		1.21 (0.64, 2.29)	0.5632	
24.35 - 26.91	1.82 (1.10, 3.02)	0.0201		1.63 (0.98, 2.71)	0.0610		2.08 (1.14, 3.80)	0.0170	
26.97 - 30.65	2.06 (1.25, 3.38)	0.0045		2.12 (1.29, 3.49)	0.0031		2.17 (1.21, 3.91)	0.0094	
> 30.67	2.29 (1.39, 3.76)	0.0011		2.11 (1.29, 3.47)	0.0032		2.36 (1.29, 4.30)	0.0051	
90-day mortality									
Tertiles			0.0001			<0.0001			0.0037
< 23.47	1.0			1.0			1.0		
23.54 - 27.86	1.56 (1.10, 2.22)	0.0122		1.50 (1.06, 2.13)	0.0229		1.71 (1.14, 2.55)	0.0092	
> 27.86	1.95 (1.39, 2.73)	0.0001		1.99 (1.42, 2.80)	<0.0001		1.93 (1.27, 2.93)	0.0022	
Quintiles			<0.0001			<0.0001			0.0010
< 21.74	1.0			1.0			1.0		
21.76 - 24.29	1.15 (0.71, 1.86)	0.5825		1.03 (0.63, 1.67)	0.9152		1.17 (0.68, 2.02)	0.5771	
24.35 - 26.91	1.60 (1.01, 2.54)	0.0447		1.46 (0.92, 2.32)	0.1074		1.75 (1.03, 2.97)	0.0402	
26.97 - 30.65	1.97 (1.26, 3.07)	0.0028		2.03 (1.30, 3.17)	0.0019		1.94 (1.17, 3.24)	0.0107	
> 30.67	2.28 (1.47, 3.54)	0.0002		2.12 (1.37, 3.30)	0.0008		2.26 (1.33, 3.86)	0.0026	
365-day mortality									
Tertiles			<0.0001			<0.0001			<0.0001
< 23.47	1.0			1.0			1.0		
23.54 -	1.69	0.0013		1.65	0.0022		1.93	0.0004	

27.86	(1.23, 2.33)		(1.20, 2.28)		(1.34, 2.77)	
>	2.17	<0.0001	2.24	<0.0001	2.36	<0.0001
27.86	(1.59, 2.97)		(1.64, 3.06)		(1.61, 3.47)	
Quintiles		<0.0001		<0.0001		<0.0001
<	1.0		1.0		1.0	
21.74						
21.76 -	1.32	0.2290	1.20	0.4259	1.33	0.2627
24.29	(0.84, 2.07)		(0.76, 1.89)		(0.81, 2.20)	
24.35 -	1.97	0.0017	1.84	0.0052	2.33	0.0006
26.91	(1.29, 3.02)		(1.20, 2.82)		(1.44, 3.79)	
26.97 -	2.41	<0.0001	2.51	<0.0001	2.64	<0.0001
30.65	(1.59, 3.66)		(1.66, 3.81)		(1.65, 4.24)	
> 30.67	2.59	<0.0001	2.44	<0.0001	2.78	<0.0001
	(1.71, 3.93)		(1.61, 3.70)		(1.69, 4.58)	

HR: hazard ratio; CI: confidence interval.

Models I and II were derived from Cox proportional hazards regression models: model I covariates were adjusted for age; gender; ethnicity; model II covariates were adjusted for age; gender; ethnicity; length of stay in ICU; HR; SBP; DBP; RR; SPO2; anion gap; serum bicarbonate; serum potassium; SCr; BUN; hematocrit; platelet count; WBC count; PTT; PT; INR; stroke; pneumonia; COPD; chronic liver disease; chronic renal disease; RRT; malignancy; vasoactive agent; SOFA; SAPSII.

Table 3. Subgroup analysis of the associations between the NAR and 90-day mortality

	N	NAR of in-hospital mortality			P for interaction
		< 23.47	23.54 - 27.86	> 27.86	
Neutrophils					0.1289
0 - 83.3	235	1.0	1.38 (0.85, 2.26)	1.94 (1.17, 3.21) ^a	
83.6 - 97.6	240	1.0	1.87 (0.98, 3.56)	2.32 (1.23, 4.37) ^b	
Albumin					0.1034
1 - 3.1	223	1.0	0.88 (0.45, 1.74)	0.95 (0.52, 1.77)	
3.2 - 4.7	252	1.0	1.61 (1.05, 2.48) ^a	1.77 (0.62, 5.04)	
LOS_ICU					0.0465
0.15 - 5.04	237	1.0	1.68 (1.00, 2.80) ^a	3.13 (1.97, 4.99) ^c	
5.04 - 67.97	238	1.0	1.35 (0.83, 2.20)	1.14 (0.68, 1.89)	
Vital signs					
HR					0.2793
45.27 - 87.24	236	1.0	1.99 (1.16, 3.38) ^a	2.89 (1.74, 4.80) ^c	
87.46 - 139.48	237	1.0	1.15 (0.71, 1.84)	1.40 (0.88, 2.24)	
SBP					0.3579
61.09 - 104.48	235	1.0	1.71 (1.03, 2.84) ^a	1.81 (1.10, 2.98) ^a	
104.48 - 153.02	237	1.0	1.32 (0.80, 2.17)	2.08 (1.26, 3.43) ^b	
DBP					0.4170
17 - 57.84	236	1.0	1.84 (1.11, 3.04) ^a	2.54 (1.57, 4.12) ^c	
58.03 - 94.5	236	1.0	1.33 (0.80, 2.21)	1.50 (0.91, 2.49)	
MBP					0.1870
37.92 - 73.56	236	1.0	1.29 (0.79, 2.09)	1.61 (1.02, 2.53) ^a	
73.65 - 116.5	237	1.0	1.98 (1.16, 3.38) ^a	2.47 (1.46, 4.18) ^c	
RR					0.8981
11.48 - 19.53	236	1.0	1.55 (0.93, 2.59)	1.95 (1.19, 3.20) ^b	
19.54 - 33.87	237	1.0	1.58 (0.97, 2.58)	2.10 (1.30, 3.40) ^b	
Temperature					0.1493
33.33 - 36.76	231	1.0	1.35 (0.84, 2.18)	1.68 (1.05, 2.69) ^a	
36.76 - 39.72	232	1.0	1.73 (1.01, 2.97) ^a	2.57 (1.51, 4.37) ^c	
SPO2					0.7774
56.8 - 97.39	236	1.0	1.31 (0.81, 2.10)	1.71 (1.07, 2.73) ^a	
97.41 - 100	237	1.0	1.93 (1.13, 3.31) ^a	2.60 (1.54, 4.36) ^c	
Laboratory parameters					
Anion gap					0.7581
6 - 13	199	1.0	1.75 (0.94, 3.25)	1.52 (0.83, 2.79)	
14 - 39	276	1.0	1.44 (0.94, 2.22)	2.44 (1.60, 3.70) ^c	
bicarbonate					0.9570
5 - 18	206	1.0	1.48 (0.88, 2.49)	1.98 (1.20, 3.25) ^b	
19 - 36	269	1.0	1.50 (0.91, 2.46)	1.85 (1.14, 3.00) ^a	
Serum sodium					0.0270
95 - 134	192	1.0	1.11 (0.66, 1.88)	1.23 (0.74, 2.03)	
135 - 150	283	1.0	2.01 (1.24, 3.27) ^b	2.90 (1.81, 4.67) ^c	
Serum potassium					0.3218
1.8 - 3.6	211	1.0	1.71 (0.94, 3.11)	1.94 (1.08, 3.46) ^a	
3.7 - 5.7	264	1.0	1.44 (0.93, 2.24)	2.24 (1.45, 3.45) ^c	
Serum chloride					0.0702
61 - 100	206	1.0	1.59 (0.97, 2.61)	1.44 (0.86, 2.39)	
101 - 120	269	1.0	1.50 (0.91, 2.48)	2.56 (1.59, 4.12) ^c	
Serum bilirubin					0.0343
0.1 - 0.5	192	1.0	1.91 (1.07, 3.42) ^a	2.87 (1.63, 5.05) ^c	
0.6 - 24.7	239	1.0	1.46 (0.89, 2.37)	1.75 (1.08, 2.84) ^a	
Serum glucose					0.7638
16 - 112	233	1.0	1.48 (0.90, 2.43)	1.59 (0.98, 2.60)	

113 - 356	242	1.0	1.48 (0.88, 2.48)	2.25 (1.36, 3.72) ^b	0.5793
SCr					
0.2 - 1.2	236	1.0	1.85 (1.04, 3.31) ^a	2.14 (1.20, 3.80) ^b	
1.3 - 12.6	239	1.0	1.45 (0.92, 2.28)	1.87 (1.22, 2.86) ^b	0.5891
BUN					
4 - 28	235	1.0	1.88 (1.07, 3.30) ^a	1.78 (1.01, 3.16) ^a	
29 - 152	240	1.0	1.42 (0.89, 2.28)	2.15 (1.38, 3.33) ^c	0.2874
Hematocrit					
7.3 - 29.9	233	1.0	1.93 (1.09, 3.41) ^a	1.95 (1.13, 3.39) ^a	
30 - 53	242	1.0	1.26 (0.80, 2.00)	2.78 (1.73, 4.47) ^c	0.1307
Hemoglobin					
2.8 - 10	233	1.0	1.81 (1.03, 3.21) ^a	1.96 (1.14, 3.38) ^a	
10.1 - 17.1	242	1.0	1.40 (0.88, 2.23)	2.90 (1.78, 4.71) ^c	0.2390
Platelet count					
7 - 188	235	1.0	1.96 (1.20, 3.20) ^b	2.22 (1.37, 3.60) ^b	
189 - 948	240	1.0	1.14 (0.68, 1.89)	1.77 (1.10, 2.87) ^a	0.8677
WBC count					
0.1 - 10.7	234	1.0	1.31 (0.79, 2.15)	1.80 (1.12, 2.90) ^a	
10.8 - 52.7	241	1.0	1.80 (1.06, 3.04) ^a	2.23 (1.33, 3.75) ^b	0.9137
PTT					
17.1 - 31.5	231	1.0	2.00 (1.19, 3.35) ^b	2.03 (1.16, 3.56) ^a	
31.6 - 150	238	1.0	1.10 (0.67, 1.80)	1.62 (1.04, 2.53) ^a	0.3765
PT					
9.1 - 14.2	229	1.0	1.94 (1.11, 3.38) ^a	2.93 (1.67, 5.14) ^c	
14.3 - 58.8	235	1.0	1.11 (0.69, 1.78)	1.30 (0.84, 2.03)	0.5209
INR					
0.7 - 1.2	199	1.0	1.88 (1.03, 3.42) ^a	2.58 (1.39, 4.81) ^b	
1.3 - 22.8	265	1.0	1.24 (0.79, 1.95)	1.56 (1.02, 2.39) ^a	0.4651
Comorbidities					
CAD					
NO	216	1.0	1.20 (0.71, 2.02)	1.68 (1.03, 2.73) ^a	0.8517
YES	259	1.0	1.87 (1.15, 3.01) ^a	2.14 (1.31, 3.50) ^b	
CHF					
NO	298	1.0	1.59 (1.02, 2.46) ^a	2.04 (1.33, 3.13) ^b	0.3994
YES	177	1.0	1.33 (0.74, 2.41)	1.81 (1.00, 3.28) ^a	
AF					
NO	275	1.0	1.21 (0.74, 1.99)	1.93 (1.22, 3.04) ^b	0.0742
YES	200	1.0	1.87 (1.13, 3.10) ^a	2.08 (1.25, 3.47) ^b	
Stroke					
NO	454	1.0	1.44 (1.01, 2.05) ^a	1.85 (1.31, 2.61) ^c	0.7460
YES	21	1.0	NA	NA	
Pneumonia					
NO	312	1.0	1.47 (0.96, 2.27)	2.15 (1.43, 3.24) ^c	NA
YES	163	1.0	1.58 (0.85, 2.94)	1.88 (0.99, 3.55)	
COPD					
NO	470	1.0	1.52 (1.07, 2.17) ^a	1.97 (1.40, 2.79) ^c	NA
YES	5	1.0	NA	NA	
ARDS					
NO	470	1.0	1.47 (1.03, 2.09) ^a	1.97 (1.40, 2.77) ^c	0.0102
YES	5	1.0	NA	NA	
Respiratory failure					
NO	240	1.0	1.73 (1.02, 2.95) ^a	3.14 (1.89, 5.20) ^c	0.3705
YES	235	1.0	1.22 (0.76, 1.94)	1.19 (0.75, 1.90)	
Chronic liver disease					
NO	453	1.0	1.49 (1.04, 2.14) ^a	1.98 (1.40, 2.81) ^c	

YES	22	1.0	0.50 (0.09, 2.75)	3.26 (0.66, 16.14)	0.4300
Chronic renal disease					
NO	375	1.0	1.69 (1.11, 2.57) ^a	2.22 (1.47, 3.36) ^c	
YES	100	1.0	1.17 (0.60, 2.26)	1.47 (0.80, 2.73)	0.0044
RRT					
NO	402	1.0	1.42 (0.96, 2.11)	2.29 (1.58, 3.32) ^c	
YES	73	1.0	0.87 (0.36, 2.09)	0.45 (0.18, 1.11)	0.3513
Malignancy					
NO	421	1.0	1.53 (1.05, 2.25) ^a	2.15 (1.48, 3.12) ^c	
YES	54	1.0	1.58 (0.59, 4.26)	1.08 (0.41, 2.85)	0.3256
Vasoactive drug					
NO	110	1.0	0.83 (0.35, 1.96)	1.78 (0.87, 3.64)	
YES	365	1.0	1.63 (1.10, 2.42) ^a	2.02 (1.36, 2.98) ^c	0.2866
Score systems					
SOFA					
0 - 6	216	1.0	1.66 (0.94, 2.96)	2.47 (1.37, 4.46) ^b	0.1969
7 - 21	259	1.0	1.26 (0.80, 1.99)	1.46 (0.95, 2.24)	
SAPSII					
10 - 46	231	1.0	1.56 (0.86, 2.82)	3.01 (1.67, 5.42) ^c	0.1969
47 - 110	244	1.0	1.49 (0.95, 2.34)	1.41 (0.92, 2.15)	

NAR: neutrophil-albumin ratio; LOS_ICU: length of stay in intensive care unit; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; RR: respiratory rate; SPO2: percutaneous oxygen saturation; BUN: blood urea nitrogen; SCr: Serum creatinine; WBC: white blood cell; PTT: partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; CAD: coronary heart disease; CHF: congestive heart failure; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; RRT: renal replacement therapy; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score.

Pvalue: ^a P < 0.05, ^b P < 0.01, ^c P < 0.001

Figures

Figure. 1 HRs (95% CIs) for mortality across tertile groups of NARs (Tertiles: model I and model II)

Figure 1

Figure 2