Clinical value of the red blood cell distribution width to albumin ratio in the assessment of prognosis in critically ill patients with sepsis: a retrospective analysis

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Background: Red blood cell (RBC) distribution width (RDW) to albumin ratio is a novel biomarker and its prognostic effect on critically ill patients with sepsis has not been extensively investigated. The objective of this study was to identify the prognostic value of the RDW to albumin ratio in these patients.

Methods: Data were extracted from the Medical Information Mart for Intensive Care III (MIMIC-III) database. A Cox proportional hazards model and restricted cubic spline model were used to determine the association of RDW to albumin ratio with mortality. Receiver operating characteristic (ROC) curves and Kaplan-Meier survival curves were applied, and the area under the curve (AUC) was used to compare the predictive value.

Results: A total of 3,969 eligible patients were enrolled. The median RDW to albumin ratio was significantly higher in non-survivors than in survivors at 30 and 90 days. Patients were divided into groups according to the RDW to albumin ratio, and the risk of 30- and 90-day mortality markedly increased in the group with a higher ratio. The relationship between the RDW to albumin ratio as a continuous variable and 30-day mortality also showed an upward trend in the restricted cubic spline. The AUC of the RDW to albumin ratio was 0.633 in discriminating 30-day mortality which was similar to that of the lactate to albumin ratio (AUC =0.617; P=0.133) and higher than that of the neutrophil percentage to albumin ratio (AUC =0.559; P<0.001).

Conclusions: The RDW to albumin ratio is a promising biomarker for assessing the prognosis of critically ill patients with sepsis. Its predictive value in determining mortality was found to be similar to that of the lactate to albumin ratio and superior to that of the neutrophil percentage to albumin ratio.

Keywords: Sepsis; red blood cell distribution width (RDW); albumin; prognosis

Introduction

Sepsis remains a major challenge in critically ill patients accounting for approximately 30–50% of short-term mortality (1,2). Early diagnosis and timely treatment of sepsis can greatly improve outcomes and reduce the rate of fatality (3). In recent years progress has been made in the identification of sepsis based on complex biological characteristics and auxiliary examinations, but these are still highly time-consuming and thus unsatisfactory for identifying high-risk patients (4-6). There is therefore, a demand for simpler and more cost-effective biomarkers for predicting the prognosis of patients with sepsis and identifying those at high risk of death (7).

Red blood cell (RBC) distribution width (RDW) is a hematological index that reflects the volume heterogeneity of RBCs and is one of the more commonly used hematologic indices in clinics. As part of complete blood count, the RDW may be biased by variables in the preanalytical and analytical phases of the total testing process. The heterogeneous algorithms for calculating the RDW applied by different instrumentation suggest that harmonization may still be regarded as an unmet need (8). RDW has been shown to increase during systemic inflammation and infection and is associated with poor prognosis (9,10). Accumulating evidence supports the prognostic role of RDW in several clinical conditions, such as pneumonia, cardiovascular diseases, and critically ill patients with sepsis and those with coronavirus disease 2019 (COVID-19) (9-12).

Serum albumin plays critical physiological roles, including maintaining oncotic pressure, transporting various substances such as hormones, fatty acids, and drugs, and contributing to antioxidant defense, making it a multifunctional protein with significant implications for overall health (13). Studies have demonstrated that the serum albumin level is inversely associated with severity of illness and the extent of hypoalbuminemia correlates with the degree of sepsis (14,15). Moreover, serum albumin has been used as a marker of poor prognosis in critically ill patients, and, along with other hematologic parameters, such as the lactic acid to albumin ratio and neutrophil percentage to albumin ratio, can also predict the severity of sepsis in patients and their associated prognosis (16-18).

The RDW to albumin ratio is a novel biomarker based on both RDW and albumin levels and is associated with short-term mortality in critically ill patients with acute respiratory distress syndrome and pneumonia (19,20). Additionally, the RDW to albumin ratio can also predict mortality in patients with diabetic ketoacidosis, stroke, cancer, or aortic aneurysm (21-24). However, only few studies have been conducted on the clinical value of the RDW to albumin ratio in evaluating the prognosis of patients with sepsis in the intensive care unit (ICU) suggesting a predictive role for acute kidney injury (AKI) development in sepsis (25,26). Moreover, it remains unclear whether the RDW to albumin ratio is more valuable than are other albumin-based indicators in predicting mortality.

Therefore, this study aimed to investigate the relationship between the RDW to albumin ratio and the prognosis of critically ill patients with sepsis and to compare its performance with that of the lactate to albumin ratio and neutrophil percentage to albumin ratio. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1696/rc).

Highlight box

Key findings

- The red blood cell distribution width (RDW) to albumin ratio was independently associated with mortality in patients with sepsis, even after a broad array of potential confounders were considered. The area under the curve of the RDW to albumin ratio in discriminating 30-day mortality was similar to that of the lactate to albumin ratio and higher than that of the neutrophil percentage to albumin ratio.

What is known and what is new?

- To date, some studies have shown that the RDW-albumin ratio is related to increased mortality from several disease.
- To our knowledge, this is one of the first studies to examine the association between the RDW to albumin ratio and the risk of mortality in critically ill patients with sepsis and to demonstrate that the RDW to albumin ratio may be a useful and easy-to-use marker for clinical prognosis.

What is the implication, and what should change now?

- The RDW to albumin ratio may be a convenient and reliable marker that can be used to predict mortality in critically ill patients with sepsis. This perspective opens new approaches for personalized sepsis management.

Methods

Data source

Patient data were obtained from the publicly available Medical Information Mart for Intensive Care III (MIMIC-

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III) database version 1.4. The database holds the records of deidentified health data for more than 50,000 patients admitted to the ICU at the Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2001 to 2012 (27). To ensure robustness of our findings, the sample size was guided by precedent in similar biomarker studies in sepsis, although a formal calculation was not performed due to the retrospective nature of our analysis and reliance on existing clinical data.

This database was approved by the institutional review boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA). All personal data were anonymized to protect the privacy of the enrolled patients. Author CY Ma obtained access to the MIMIC-III database (record ID: 34907227). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data extraction

The selection criteria in our study included adult ICU patients with sepsis at their first hospital admission and a length of ICU stay longer than 24 hours. We identified a sepsis population according to the Martin criteria, a widely used approach for identifying sepsis in administrative health data (28,29). Sequential imputation using chained equations (SICE) method was used to address any missing data (<5%) (30). SICE is a robust multiple imputation technique that allows for the imputation of missing values in a dataset with different types of variables, such as continuous, binary, and ordinal. The process involves imputing missing values multiple times to create several complete datasets. Each variable with missing data is imputed sequentially, with the method taking into account the distribution of the observed data. By employing this technique, we aimed to minimize bias and improve the reliability of our analysis, ensuring that the missing data did not significantly skew the results. The imputed datasets were then analyzed separately, and the results were combined to produce estimates that reflect the uncertainty due to the missing data. Patients were excluded if they had no data on RDW or albumin within the first 24 hours of admission, or if more than 5% of the data were absent.

Structure query language (SQL) was used to extract the following admission data in the first record within 24 hours after their ICU admission: demographic information, including sex, age, ethnicity, and service

units; disease severity, as assessed by the Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) score; vital signs, including heart rate, respiratory rate, temperature, mean blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and percutaneous oxygen saturation (SpO$_2$); laboratory parameters, including white blood cell (WBC) count, hemoglobin concentration, platelet count, RDW, and levels of hematocrit, bicarbonate, chloride, serum creatinine, blood urea nitrogen (BUN), serum potassium, serum sodium, albumin, and serum lactate; comorbidities, including congestive heart failure, chronic renal disease, liver disease, chronic obstructive pulmonary disease (COPD), stroke, and malignancy; and ICU intervention measures, including mechanical ventilation (MV) use, renal replacement therapy (RRT) use, and vasopressor use.

Study outcome and definitions

The study outcome was 30- and 90-day mortality. The start date was the date of the patient's admission.

We used a previously proposed equation to calculate the RDW to albumin ratio: RDW (%) divided by albumin concentration (g/dL). The lactate to albumin ratio was calculated as serum lactate (mmol/L) divided by albumin concentration (g/dL); the neutrophil percentage to albumin ratio was calculated as the neutrophil percentage (%) divided by albumin concentration (g/dL).

We identified a sepsis population according to the Martin criteria, a widely used approach for identifying sepsis in administrative health data (28,29). Patients were excluded if: (I) they were not first ICU admission; (II) age less than 18 years old; (III) length of ICU stay less than 1 day; (IV) without sepsis diagnosis; and (V) they had no data on RDW or albumin within the first 24 hours of admission, or if more than 5% of the data were absent.

Statistical analysis

The study population was subdivided into three groups based on the RDW to albumin ratio. Data conforming to a normal distribution are presented as the mean ± standard deviation (SD); they are presented as the median and interquartile range (IQR) for continuous variables not conforming to a normal distribution, and as the number and frequency for categorical data. The logarithmic transformation Mann-Whitney test was used for comparisons between the survivor and non-survivor groups,
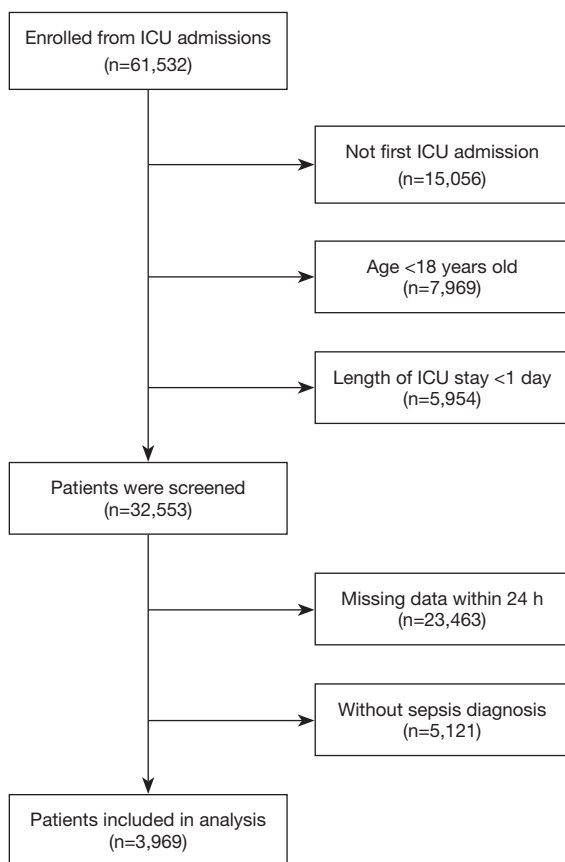
Figure 1 Flowchart of patients enrolled from the MIMIC-III database. ICU, intensive care unit; MIMIC-III, Medical Information Mart for Intensive Care III.

the Kruskal-Wallis test was used for continuous variables, and the χ^2 test or Fisher exact test (expected frequency <10) was used for categorical variables.

Cox proportional risk models were used to determine factors associated with 30- and 90-day mortality, expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The RDW to albumin ratio values were divided into tertiles or quintiles, and the first tertile or quintile was selected as the reference group. The variables with P<0.1 in the univariate model were subjected to multivariate Cox regression analysis. The following models were used for covariance correction: model 1 was adjusted for the confounders of age, sex, ethnicity, and service units; model 2 was adjusted for model 1 and other confounders, including vital signs (heart rate, SBP, DBP, MBP, respiratory rate, SpO_2, and temperature), laboratory parameters (WBC, hemoglobin, platelet count, bicarbonate, sodium, glucose, BUN, creatinine, and lactate level), severity scores (SOFA

and SAPS II), comorbidities (congestive heart failure, chronic renal disease, liver disease, stroke, and malignancy), and ICU intervention measures (MV use, RRT use, and vasopressor use) as covariates. The associations between the crude and adjusted HR (95% CI) and RDW to albumin ratio as a continuous variable were evaluated using a restricted cubic spline with 5 knots (29,31), and the confounders were adjusted as shown in model 2.

Receiver operating characteristic (ROC) curves were generated to calculate the area under the curve (AUC), and the predictive values of the RDW to albumin ratio, lactate to albumin ratio, and neutrophil percentage to albumin ratio for all-cause mortality were compared. The Youden index was used to determine the optimal cutoff value. The population was divided into low (<5.246) and high (≥5.246) RDW to albumin groups, and the survival difference between the two groups was indicated with a Kaplan-Meier curve. The participants in this study were for analysis of the influence of patient characteristics including disease severity then subdivided into the following three groups based on the RDW to albumin ratio: <4.915, 4.915–6.405, and >6.405.

All analyses of data were performed using Stata 14.0 (StataCorp, College Station, TX, USA), SPSS software version 22.0 (IBM Corp., Armonk, NY, USA), and R software (https://www.r-project.org/). A two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 3,969 patients who met the screening criteria were ultimately included in this study (*Figure 1*). The comparison of baseline characteristics of survivors and non-survivors at 30 and 90 days is shown in Tables S1,S2, respectively. The overall median RDW to albumin ratio at 30 days in the non-survivor group was significantly higher than that in the survival group (6.24 *vs.* 5.39, P<0.001), and the same trend was observed at 90 days (6.19 *vs.* 5.27, P<0.001) (*Figure 2*).

The participants in this study were then subdivided into the following three groups based on the RDW to albumin ratio: <4.915 (n=1,325), 4.915–6.405 (n=1,322), and >6.405 (n=1,322). *Table 1* shows the baseline and clinical characteristics of the different RDW to albumin ratio groups. Patients with sepsis and a higher RDW to albumin ratio tended to have a higher heart rate, respiratory rate, WBC count, RDW, and chloride, BUN, creatinine,
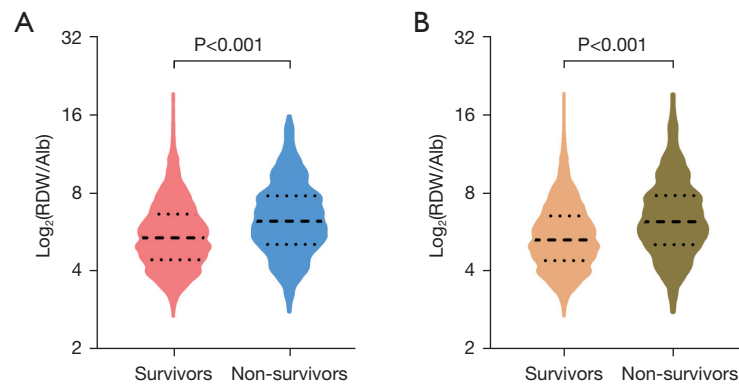
Figure 2 Comparison of RDW to albumin ratio between non-survivors and survivors at 30 and 90 days. The overall median RDW to albumin ratio at both 30 and 90 days in the non-survivor group was significantly higher than that in the survivor group. RDW, red blood cell distribution width; Alb, albumin.

Table 1 Baseline characteristics of the included patients

Characteristics	RDW to albumin ratio			P value
	<4.915	4.915–6.405	>6.405	
RDW to albumin ratio	4.267±0.476	5.603±0.427	8.289±1.856	<0.001
Number	1,325	1,322	1,322	
Age (years)	66.16 [52.62–78.72]	66.92 [54.17–79.32]	65.04 [53.64–77.13]	0.044
Male	701 (52.9)	708 (53.6)	703 (53.2)	0.945
Ethnicity				0.383
White	951 (71.8)	912 (69.0)	914 (69.1)	
Black	97 (7.3)	106 (8.0)	117 (8.9)	
Others	277 (20.9)	304 (23.0)	291 (22.0)	
Service unit				<0.001
MICU	622 (46.9)	819 (62.0)	816 (61.7)	
SICU/TSICU	378 (28.5)	283 (21.4)	334 (25.3)	
CCU/CSRU	325 (24.5)	220 (16.6)	172 (13.0)	
SOFA score	5 [3–7]	6 [4–9]	7.5 [5–11]	<0.001
SAPS II score	38 [29–47]	43 [34–53]	48 [37–59]	<0.001
Interventions				
MV use (first 24 h)	780 (58.9)	76 (5.7)	872 (66.0)	<0.001
RRT use (first 24 h)	50 (3.8)	93 (7.0)	119 (9.0)	<0.001
Vasopressor use (first 24 h)	386 (29.1)	540 (40.8)	694 (52.5)	<0.001
Vital signs				
Heart rate (bpm)	86.8 [75.3–98.4]	90.7 [78.2–104.0]	93.1 [81.3–106.0]	<0.001
SBP (mmHg)	117.8 [106.9–133.3]	112.2 [104.1–123.5]	108.1 [100.8–118.2]	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	RDW to albumin ratio			P value
	<4.915	4.915–6.405	>6.405	
DBP (mmHg)	60.9 [54.6–68.7]	58.7 [52.6–65.5]	56.4 [50.6–63.0]	<0.001
MBP (mmHg)	77.9 [71.5–86.4]	74.5 [69–82.5]	72.2 [67.0–79.1]	<0.001
Respiratory rate (bpm)	19.3 [16.8–22.2]	20 [17.3–23.3]	20.3 [17.4–23.8]	<0.001
SpO$_2$ (%)	97.5 [96.0–98.8]	97.2 [95.8–98.5]	97.5 [96.0–98.7]	0.008
Temperature (℃)	37.0 [36.6–37.4]	36.9 [36.4–37.4]	36.8 [36.3–37.3]	<0.001
Laboratory tests				
WBC (×10^9/L)	13.2 [10.1–18.1]	14.1 [9.3–19.9]	14.9 [9.5–22.1]	<0.001
Hemoglobin (g/dL)	11 [9.6–12.3]	9.6 [8.5–10.8]	8.8 [7.9–9.9]	<0.001
Platelet count (×10^9/L)	191 [140.5–251]	164.5 [102–262]	141.5 [71–240.3]	<0.001
RDW (%)	14.2 [13.4–14.9]	15.4 [14.5–16.7]	17.1 [15.6–19.1]	<0.001
Bicarbonate (mmol/L)	22 [19–25]	20 [17–24]	19 [15–23]	<0.001
Potassium (mmol/L)	3.6 [3.3–4.0]	3.7 [3.3–4.1]	3.7 [3.3–4.1]	0.196
Sodium (mmol/L)	137 [134–140]	137 [133–140]	136 [132–140]	<0.001
Glucose (mg/dL)	138 [116.8–167.3]	134.3 [112.0–167.0]	131.1 [107.6–159]	<0.001
Albumin (g/dL)	3.4 [3.2–3.7]	2.8 [2.6–3.0]	2.2 [1.9–2.5]	<0.001
BUN (mg/dL)	24 [16–40]	33 [20–54.3]	34 [20–56]	<0.001
Creatinine (mg/dL)	1.2 [0.9–1.9]	1.5 [1.0–2.6]	1.5 [0.9–2.6]	<0.001
Chloride (mmol/L)	107 [103–110]	108 [103–113]	109 [104–114]	<0.001
Lactate level (mmol/L)	2.33 [1.57–3.51]	2.56 [1.6–4.0]	3.0 [1.9–5.1]	<0.001
Comorbidities				
Congestive heart failure	449 (33.9)	472 (35.7)	363 (27.5)	<0.001
Chronic renal disease	162 (12.2)	215 (16.3)	189 (14.3)	0.012
Liver disease	98 (7.4)	174 (13.2)	266 (20.1)	<0.001
COPD	190 (14.3)	206 (15.6)	174 (13.2)	0.207
Stroke	183 (13.8)	82 (6.2)	63 (4.8)	<0.001
Malignancy	132 (10.0)	283 (21.4)	389 (29.4)	<0.001
Mortality				
30-day mortality	224 (16.9)	337 (25.5)	500 (37.8)	<0.001
90-day mortality	288 (21.7)	448 (33.9)	633 (47.9)	<0.001

Data are presented as mean ± SD, n, median [IQR], or n (%). RDW, red blood cell distribution width; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma/surgical intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; RRT, renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO$_2$, percutaneous oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; SD, standard deviation; IQR, interquartile range.

and lactate levels; however, they had lower blood pressure, temperature, and hemoglobin, platelet count, bicarbonate, sodium, glucose, and albumin levels. They were also more likely to exhibit higher critical scores of SAPS II and SOFA, and to require a greater degree of ICU intervention, including MV, RRT, and vasopressor use. The prevalence of liver disease and malignancy was also significantly increased in patients with a high RDW to albumin ratio.

Association between RDW to albumin ratio and 30- and 90-day mortality

To investigate the relationship between the RDW to albumin ratio and the outcomes of patients with sepsis, we performed the Cox regression analysis, the results of which are shown in *Table 2*. The RDW to albumin ratio was found to be an independent predictor for 30- and 90-day mortality in patients with sepsis. For 30-day mortality, the HR for the second (4.915–6.405) and the third (>6.405) tertiles was 1.597 (95% CI: 1.348–1.890) and 2.598 (95% CI: 2.219–3.042), respectively, compared to the first tertiles (<4.915). For model 1, after adjustments were made for age, sex, ethnicity, and service units, the HR (of 30-day mortality for the second and third tertiles) was 1.505 (95% CI: 1.270–1.784) and 2.558 (95% CI: 2.181–2.999), respectively, compared to the first tertile. After further adjustment of potential covariates in model 2 (model 1 plus other multiple confounders), the trend was similar to that of previous models. The HR for the second and third tertiles was 1.169 (95% CI: 0.976–1.331) and 1.521 (95% CI: 1.263–1.833), respectively, compared to the reference. In quintile analyses, a similar trend was observed, and the fifth quintile (>7.40) had the highest HR compared with the reference (<4.35) in the three models. The tendency of the all-cause mortality rate in all models showed significant increases in HR (95% CI) values in tertile and quintile analyses. For the 90-day all-cause mortality rate, the same association was detected when the RDW to albumin ratio was divided into three and five categories, and a similar association with mortality was also observed.

The crude and adjusted HR for 30-day mortality was further investigated when the RDW to albumin ratio was used as a continuous variable based on restricted cubic spline analysis of the Cox model, as shown in *Figure 3*. From the figure, it is evident that an increased RDW to albumin ratio is associated with the risk of death in patients with sepsis.

Subgroup analysis

Subgroup analysis revealed the relationship between the RDW to albumin ratio and 30-day mortality in critically ill patients with sepsis with different comorbidities (*Figure 4*). After adjustments were made for confounding factors in model 1, there was no significant difference in other subgroup factors except chronic heart failure (P=0.015) and chronic renal disease (P=0.014).

Predictive value of RDW to albumin ratio for 30-day mortality in patients with sepsis

The value of the RDW to albumin ratio for predicting 30-day mortality in critically ill patients with sepsis was analyzed through the ROC curve and compared to that of the other two albumin-based indicators: the lactate to albumin ratio and neutrophil percentage to albumin ratio (*Figure 5*, *Table 3*). The AUC value of the RDW to albumin ratio in all patients was 0.633 (95% CI: 0.614–0.653), this was similar to the lactate to albumin ratio (AUC =0.617; 95% CI: 0.597–0.636; P=0.133) but higher than that of the neutrophil percentage to albumin ratio (AUC =0.559; 95% CI: 0.539–0.580; P<0.001). According to the Youden index, the optimal cutoff point of the RDW to albumin ratio was 5.246, with a sensitivity of 72.48% and a specificity of 47.39%. Accordingly, the study population was divided into a high RDW to albumin ratio group (≥5.246) and a low RDW to albumin ratio group (<5.246), with the Kaplan-Meier curve showing that the 30-day all-cause mortality in the high RDW to albumin ratio group was significantly higher than that in the low group (log-rank P<0.001; *Figure 6*).

Discussion

To the best of our knowledge, this is one of the first studies to examine the association between the RDW to albumin ratio and the risk of mortality in critically ill patients with sepsis and to demonstrate that the RDW to albumin ratio may be a useful and easy-to-use marker for clinical prognostic prediction.

Sepsis is a heterogeneous clinical disorder defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (32). The inflammatory response plays an important role in the occurrence and development of sepsis, and early identification of new inflammatory biomarkers or combined indicators is crucial for the timely

Table 2 The association between RDW to albumin ratio and mortality of patients with sepsis

Exposure	Non-adjusted			Model 1			Model 2		
	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend
30-day mortality									
Tertile			<0.001			<0.001			<0.001
<4.915	1			1			1		
4.915–6.405	1.597 (1.348–1.890)	<0.001		1.505 (1.270–1.784)	<0.001		1.169 (0.976–1.331)	0.089	
>6.405	2.598 (2.219–3.042)	<0.001		2.558 (2.181–2.999)	<0.001		1.521 (1.263–1.833)	<0.001	
Quintile									
<4.35	1		<0.001	1		<0.001			<0.001
4.35–<5.15	1.132 (0.894–1.432)	0.303		1.093 (0.863–1.385)	0.459		0.973 (0.765–1.238)	0.825	
5.15–<6.04	1.718 (1.382–2.134)	<0.001		1.602 (1.287–1.994)	<0.001		1.232 (0.977–1.552)	0.077	
6.04–7.40	1.988 (1.607–2.459)	<0.001		1.919 (1.549–2.378)	<0.001		1.232 (1.045–1.672)	0.020	
>7.40	3.071 (2.510–3.758)	<0.001		3.044 (2.483–3.733)	<0.001		1.649 (1.300–2.091)	<0.001	
90-day mortality									
Tertile			<0.001			<0.001			<0.001
<4.915	1			1			1		
4.915–6.405	1.685 (1.453–1.953)	<0.001		1.607 (1.384–1.865)	<0.001		1.212 (1.039–1.413)	0.014	
>6.405	2.679 (2.330–3.080)	<0.001		2.691 (2.338–3.098)	<0.001		1.522 (1.301–1.779)	<0.001	
Quintile			<0.001			<0.001			<0.001
<4.35	1			1			1		
4.35–<5.15	1.255 (1.021–1.543)	0.031		1.231 (1.001–1.515)	0.049		1.080 (0.874–1.334)	0.477	
5.15–<6.04	1.848 (1.523–2.242)	<0.001		1.753 (1.443–2.130)	<0.001		1.346 (1.095–1.653)	0.005	
6.04–7.40	2.100 (1.737–2.540)	<0.001		2.065 (1.705–2.500)	<0.001		1.402 (1.137–1.728)	0.002	
>7.40	3.346 (2.794–4.008)	<0.001		3.438 (2.865–4.126)	<0.001		1.829 (1.478–2.264)	<0.001	

Model 1 was adjusted for the confounder of: age, sex, ethnicity, and service units; model 2 was adjusted for model 1 plus other factors (heart rate, SBP, DBP, MBP, respiratory rate, SpO_2, temperature, WBC, hemoglobin, platelet count, bicarbonate, sodium, glucose, BUN, creatinine, chloride, lactate level, SOFA score, SAPS II, congestive heart failure, chronic renal disease, liver disease, stroke, malignancy, MV use, RRT use, and vasopressor use). RDW, red blood cell distribution width; HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO_2, percutaneous oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; RRT, renal replacement therapy.
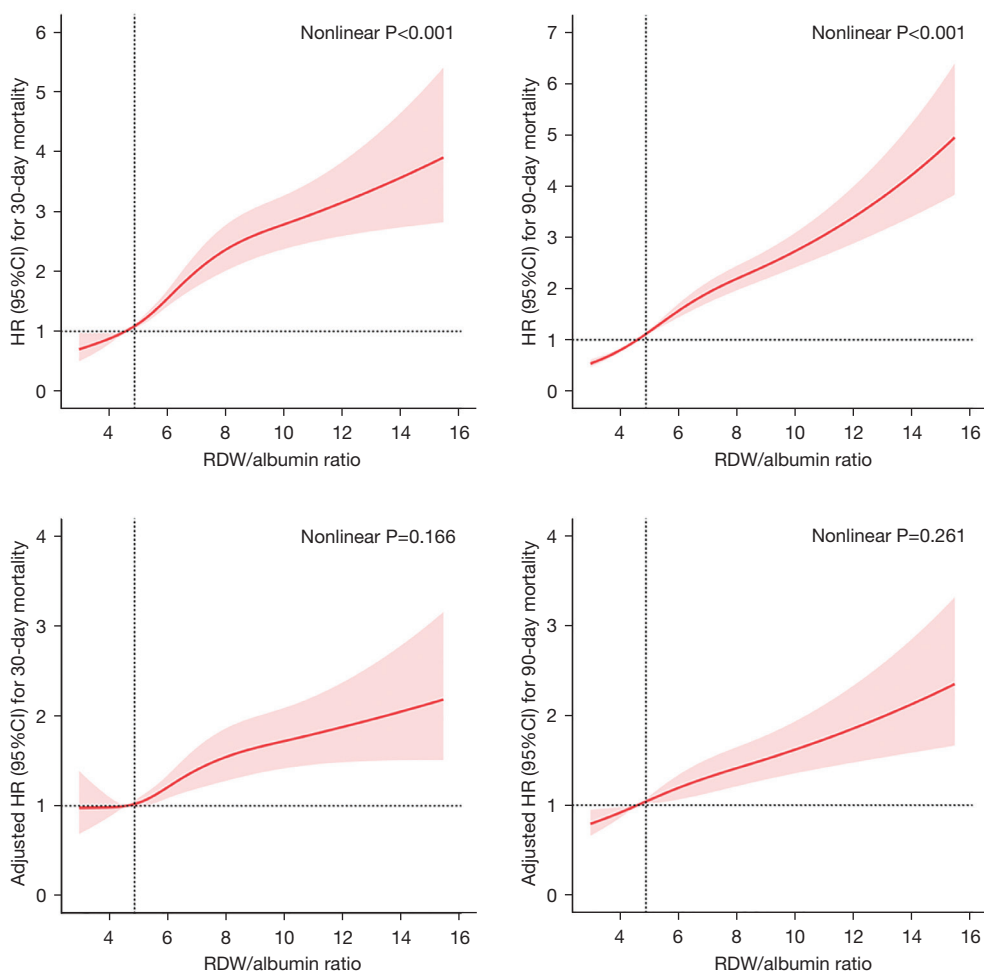
Figure 3 The association between RDW to albumin ratio as a continuous variable and mortality in critically ill patients with sepsis. Crude and adjusted HR and 95% CI for the RDW to albumin ratio in 30- and 90-day mortality. The adjusted confounding factors are shown in model 2 (*Table 2*), and it is evident that an increased RDW to albumin ratio is associated with the risk of death in patients with sepsis. HR, hazard ratio; CI, confidence interval; RDW, red blood cell distribution width.

initiation of treatment and prediction of progression and outcome. Previous studies have suggested that identifying new markers of inflammation or combining already existing indicators, such as the lactate to albumin ratio and neutrophil percentage to albumin ratio, may be valuable in determining the severity or predicting the clinical prognosis of patients with sepsis (18,33-35).

RDW expresses changes in the size of RBCs and has been identified as a novel prognostic factor in many pathophysiological conditions, including severe inflammation and sepsis (9,36,37). Hu *et al.* (9) conducted a narrative review to summarize the relationship between RDW and sepsis and found that increased RDW on

admission, both in adults and neonates, may be associated with unfavorable outcomes in the short- and long-term. The mechanisms underlying the association between increased RDW and poor outcomes remain largely unknown. Previous studies have shown that RDW is positively associated with some inflammatory biomarkers, suggesting that RDW may reflect the existence of an inflammatory response (37). In sepsis, erythrocyte heterogeneity and morphological changes are more prominent due to high oxidative stress and alterations in erythrocyte membrane glycoproteins and ion channels, leading directly to an increase in RDW (36). In addition, RDW is involved in the function of different organs in the body. Therefore, in
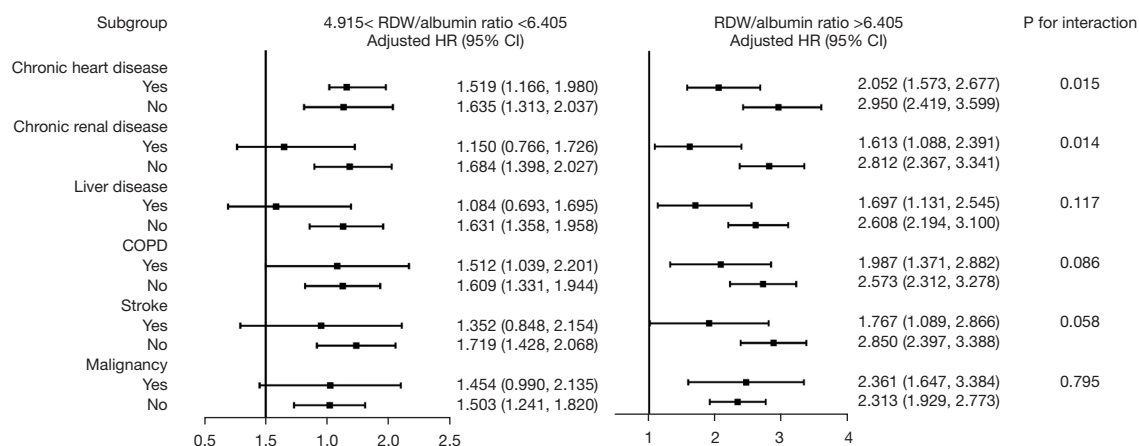
Figure 4 Adjusted HR and 95% CI of the RDW to albumin ratio for 30-day mortality subgroup. Confounding factors were adjusted as shown in model 1 (*Table 2*), and the adjusted HR and 95% CI were calculated and compared to those of the RDW to albumin ratio <4.915 group. RDW, red blood cell distribution width; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
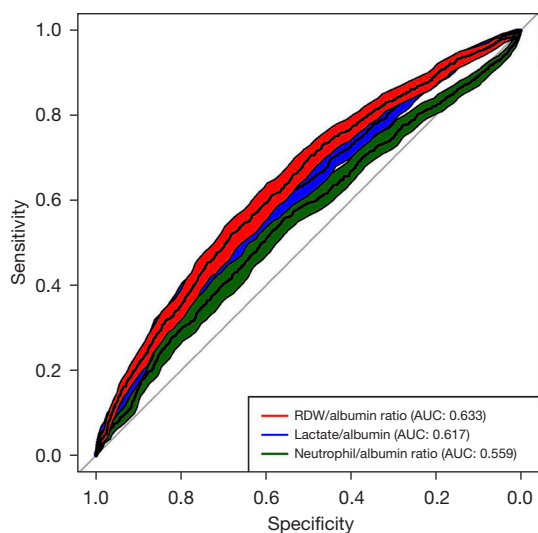

Figure 5 Prognostic value of indicators for predicting 30-day mortality in patients with sepsis (*Table 3*). RDW, red blood cell distribution width; AUC, area under the curve.

patients with sepsis, an increase in RDW suggests possible organ dysfunction and poor outcomes (36).

Serum albumin, a biochemical marker of nutritional status, plays a role in the acute response to inflammation and in sepsis (38). In sepsis, acute and chronic states of low serum albumin are independently associated with an increased risk of mortality (39). Previous studies also showed that serum albumin level over time, serum albumin level at admission, and the lowest serum albumin level were

significant unique predictors of mortality in ICU patients with sepsis (40). The increased vascular permeability in sepsis may increase albumin loss, accelerate the onset of hypoalbuminemia and compound the negative effects of hypoproteinemia in sepsis. Ultimately, a vicious cycle exists between the adverse outcomes of hypoproteinemia and sepsis (41).

The RDW to albumin ratio is a novel combined inflammatory-related indicator, and several studies have shown that the RDW to albumin ratio has predictive value in disease prognosis. Yoo *et al.* (20) evaluated an adult medical ICU and found that the RDW to albumin ratio was associated with 60-day mortality in patients with acute respiratory distress syndrome. Jeong *et al.* (19) recently conducted a prospective study in critically ill patients with pneumonia receiving invasive MV, and they found that a high RDW to albumin ratio has similar predictability in determining 28-day mortality to that of the lactate to albumin ratio. In addition, the RDW to albumin ratio was found to be a potential prognostic biomarker for predict mortality in patients afflicted with diabetic ketoacidosis, stroke, cancer, or aortic aneurysm (21-25). To the best of our knowledge, our study is one of the first studies to focus on the relationship between the RDW to albumin ratio and the prognosis of patients with sepsis. We found that the median RDW to albumin ratio was significantly higher in non-survivor patients with sepsis than that in survivors at 30 and 90 days. As the RDW to albumin ratio increased, the risk of both 30- and 90-day mortality increased, and

Table 3 Prognostic value of indicators for predicting 30-day mortality in patients with sepsis

Variables	AUC	95% CI	Cutoff value	P_1	P_2
RDW to albumin ratio	0.633	0.614–0.653	5.246	<0.001	
Lactate to albumin ratio	0.617	0.597–0.636	1.301	<0.001	0.133
Neutrophil percentage to albumin ratio	0.559	0.539–0.580	28.41	<0.001	<0.001

P_1: P value for the AUC of each variable; P_2: P value compared to RDW to albumin ratio. According to the AUC, the predictive ability of the RDW to albumin ratio for 30-day mortality was similar to that of the lactate to albumin ratio (P=0.133) and was better than that of the neutrophil percentage to albumin ratio (P<0.001). AUC, area under the curve; CI, confidence interval; RDW, red blood cell distribution width.
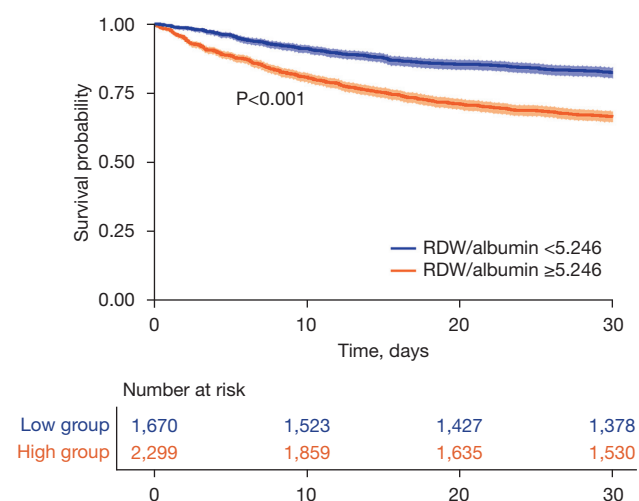

Figure 6 Kaplan-Meier survival curve at 30 days between the low and high RDW to albumin ratio groups. The 30-day mortality rate in the high RDW to albumin ratio group (≥5.246) was significantly higher than that in the low RDW to albumin ratio group (<5.246) (P for log rank test <0.001). RDW, red blood cell distribution width.

the RDW to albumin ratio was independently associated with mortality. In addition, the AUC of the RDW to albumin ratio showed that it was comparable to the lactate to albumin ratio in predicting 30-day mortality while being superior to that of the neutrophil percentage to albumin ratio. Finally, patients with a high RDW to albumin ratio (≥5.246) had a significantly higher risk of 30-day mortality than patients with a low RDW to albumin ratio (<5.246). We found that a high RDW to albumin ratio was independently associated with increased 30- and 90-day mortality of patients with sepsis, even after a broad array of potential confounders were considered. This result suggests that the RDW to albumin ratio is a promising biomarker that can readily predict mortality in patients with sepsis.

To contextualize our findings within the broader scope of existing research, it is noteworthy that elevated RDW-albumin ratios have been associated with increased mortality in heart failure and acute myocardial infarction, suggesting potential parallels in the systemic inflammatory and stress responses observed in our septic patient cohort.

Previously, albumin-based ratios, including the lactate to albumin ratio and neutrophil percentage to albumin ratio, were identified as prognostic factors for evaluating the outcome of patients with sepsis (18,33-35). Thus, we further compared the diagnostic value of these indicators to predict mortality. Notably, the RDW to albumin ratio has the same utility as the lactate to albumin ratio in assessing the 30-day mortality of patients with sepsis and a superior utility to that of neutrophil percentage to albumin ratio. In addition, given that regular monitoring of arterial lactic acid in critically ill patients is difficult to achieve, RDW and albumin are feasible measurements that can be obtained from venous blood and routine laboratory tests. Therefore, the RDW to albumin ratio is less restrictive in clinical practice and more easily used for risk stratification of patients with sepsis, serving as a reference for early recognition and intervention. Our findings suggest that the RDW/albumin ratio, beyond reflecting disease severity, might also have potential in guiding therapeutic strategies. Specifically, it could aid in the future identification of sepsis patients who are likely to benefit from albumin supplementation, akin to the targeted use of albumin in cirrhosis. This perspective opens new approaches for personalized sepsis management, where biomarkers are not only prognostic indicators but also guide therapeutic interventions.

However, several limitations of this study should be noted. First, we employed a single-center, retrospective study design, using observational data from the MIMIC-III database. As this was a retrospective analysis of the database, the database is not up to date and includes patients from the

first decade of the year 2000. Besides, some data we were unable to extract, such as the infection origin of sepsis and types of etiological agent, etc. Nonetheless, the conclusions are still reliable because of the large sample data analysis. Further multi-center prospective studies are required to validate our findings. Second, the RDW to albumin ratio was obtained from RDW and albumin within the first 24 hours of ICU admission, and the possible effects of different processes and dynamic changes on the RDW to albumin ratio were not addressed. Third, this was a retrospective cohort study, these results could be reinforced by prospective observational studies. Despite the deficiencies in this study, we have demonstrated that the RDW to albumin ratio is a statistically significant prognostic marker in critically ill patients with sepsis.

Conclusions

In summary, the RDW to albumin ratio was found to be an independent predictor for 30- and 90-day mortality in patients with sepsis, and its prognostic value was similar to that of the lactic acid to albumin ratio and superior to that of the neutrophil percentage to albumin ratio. According to our findings, the RDW to albumin ratio may be a convenient and reliable marker that can be used to predict mortality in critically ill patients with sepsis; it would thus be worthwhile to further verify these findings using a prospective, multicenter study.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1696/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1696/coif). C.J.W.

reports fees for speaking and/or consulting from Biotest, CSL Behring, and Grifols. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Table S1 Comparison of baseline characteristics between survivor and non-survivor critically ill patients with sepsis at 30 days

Characteristics	All patients	Survivors	Non-survivors	P value
Number	3,969	2,908	1,061	
Age (years)	66.1 [53.5–78.4]	63.7 [51.6–77.1]	70.8 [59.1–80.9]	<0.001
Male	2,112 (53.2)	1,526 (52.5)	586 (55.2)	0.124
Ethnicity				<0.001
White	2,777 (70.0)	2,070 (71.2)	707 (66.6)	
Black	320 (8.1)	251 (8.6)	69 (6.5)	
Others	872 (22.0)	587 (20.2)	285 (26.9)	
Service unit				<0.001
MICU	2,257 (56.9)	1,586 (54.5)	671 (63.2)	
SICU/TSICU	995 (25.1)	780 (26.8)	215 (20.3)	
CCU/CSRU	717 (18.1)	542 (18.6)	175 (16.5)	
SOFA score	6 [4–9]	5 [3–8]	8 [5–11]	<0.001
SAPS II score	43 [33–53]	39 [31–49]	52 [42–62]	<0.001
Interventions				
MV use (first 24 h)	2,413 (60.8)	1748 (60.1)	665 (62.7)	0.143
RRT use (first 24 h)	262 (6.6)	173 (5.9)	89 (8.4)	0.006
Vasopressor use (first 24 h)	1,620 (40.8)	1,096 (37.7)	524 (49.4)	<0.001
Vital signs				
Heart rate (bpm)	90.8 [78.1–102.7]	89.3 [77.5–101.6]	92.3 [79.6–106.0]	<0.001
SBP (mmHg)	112.4 [103.5–125.8]	114.1 [104.8–127.4]	108.6 [100.5–120.6]	<0.001
DBP (mmHg)	58.8 [52.5–65.8]	59.7 [53.2–66.7]	56.4 [50.6–62.6]	<0.001
MBP (mmHg)	74.9 [69.0–83.0]	75.7 [69.9–84.0]	72.3 [66.4–79.8]	<0.001
Respiratory rate (bpm)	19.9 [17.1–23.1]	19.6 [16.9–22.6]	20.6 [17.7–24.4]	<0.001
SpO$_2$ (%)	97.4 [96.0–98.7]	97.5 [96.1–98.7]	97.1 [95.4–98.5]	<0.001
Temperature (℃)	36.9 [36.4–37.4]	36.9 [36.5–37.5]	36.7 [36.2–37.2]	<0.001
Laboratory tests				
RDW to albumin ratio	5.59 [4.57–6.98]	5.39 [4.43–6.63]	6.24 [5.08–10.2]	<0.001
WBC (×10^9/L)	13.9 [9.7–19.9]	13.6 [9.7–19.5]	14.9 [9.5–21.5]	0.010
Hemoglobin (g/dL)	9.7 [8.5–11.1]	9.8 [8.6–11.2]	9.4 [8.3–10.8]	<0.001
Platelet count (×10^9/L)	172 [104–251]	178 [111–255]	148 [76.5–237]	<0.001
RDW (%)	15.3 [14.2–17.0]	15 [14–16.6]	16.3 [14.9–18.2]	<0.001
Bicarbonate (mmol/L)	20 [17–24]	21 [17–24]	19 [16–23]	<0.001
Potassium (mmol/L)	3.7 [3.3–4.1]	3.6 [3.3–4.0]	3.8 [3.4–4.2]	<0.001
Sodium (mmol/L)	137 [133–140]	137 [133–140]	136 [133–140]	0.022
Glucose (mg/dL)	134.4 [112–164.1]	133.7 [112.0–162.2]	136.1 [110.8–168.5]	0.230

Table S1 (*continued*)

Table S1 (*continued*)

Characteristics	All patients	Survivors	Non-survivors	P value
Albumin (g/dL)	2.8 [2.4–3.3]	2.9 [2.4–3.3]	2.6 [2.2–3.1]	<0.001
BUN (mg/dL)	29 [18–50]	27 [17–45]	39 [24–62]	<0.001
Creatinine (mg/dL)	1.4 [0.9–2.3]	1.3 [0.9–2.2]	1.7 [1.0–2.8]	<0.001
Chloride (mmol/L)	108 [103–112]	108 [104–112]	107 [102–112]	0.002
Lactate level (mmol/L)	2.6 [1.7–4.1]	2.5 [1.6–3.7]	3.1 [1.9–5.1]	<0.001
Comorbidities				
Congestive heart failure	1,284 (32.4)	920 (31.6)	364 (34.3)	0.111
Chronic renal disease	566 (14.3)	401 (13.8)	165 (15.6)	0.160
Liver disease	538 (13.6)	331 (11.4)	207 (19.5)	<0.001
COPD	570 (14.4)	383 (13.2)	187 (17.6)	<0.001
Stroke	328 (8.3)	227 (7.8)	101 (9.5)	0.083
Malignancy	804 (20.3)	473 (16.3)	331 (31.2)	<0.001
Length of stay (days)	5.1 [2.6–11.2]	5.0 [2.6–11.8]	5.2 [2.7–10.2]	0.093

Data are presented as n, median [IQR], or n (%). MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma/surgical intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; RRT, renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO_2, percutaneous oxygen saturation; RDW, red blood cell distribution width; WBC, white blood cell; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table S2 Comparison of baseline characteristics between the survivor and non-survivor critically ill patients with sepsis at 90 days

Characteristics	All patients	Survivors	Non-survivors	P value
Number	3,969	2,600	1,369	
Age (years)	66.1 [53.5–78.4]	62.8 [51.0–75.9]	72.0 [59.3–81.2]	<0.001
Male	2,112 (53.2)	1,342 (51.6)	770 (56.2)	0.005
Ethnicity				<0.001
White	2,777 (70.0)	1,851 (71.2)	926 (67.6)	
Black	320 (8.1)	225 (8.7)	95 (6.9)	
Others	872 (22.0)	524 (20.2)	348 (25.4)	
Service unit				0.001
MICU	2,257 (56.9)	1,421 (54.7)	836 (61.1)	
SICU/TSICU	995 (25.1)	696 (26.8)	299 (21.8)	
CCU/CSRU	717 (18.1)	483 (18.6)	234 (17.1)	
SOFA score	6 [4–9]	5 [3–8]	7 [5–11]	<0.001
SAPS II score	43 [33–53]	39 [30–48]	51 [41–61]	<0.001
Interventions				
MV use (first 24 h)	2,413 (60.8)	1,564 (60.2)	849 (62.0)	0.253
RRT use (first 24 h)	262 (6.6)	143 (5.5)	119 (8.7)	<0.001
Vasopressor use (first 24 h)	1,620 (40.8)	966 (37.2)	654 (47.8)	<0.001
Vital signs				
Heart rate (bpm)	90.8 [78.1–102.7]	89.6 [77.5–101.7]	90.8 [79.1–105.0]	0.001
SBP (mmHg)	112.4 [103.5–125.8]	114.3 [105.0–128.0]	109.3 [100.7–121.1]	<0.001
DBP (mmHg)	58.8 [52.5–65.8]	60.0 [53.6–67.1]	56.4 [50.4–62.8]	<0.001
MBP (mmHg)	74.9 [69.0–83.0]	76.0 [70.1–84.4]	72.6 [66.7–79.8]	<0.001
Respiratory rate (bpm)	19.9 [17.1–23.1]	19.6 [16.9–22.6]	20.4 [17.5–24.0]	<0.001
SpO$_2$ (%)	97.4 [96.0–98.7]	97.5 [96.1–98.7]	97.2 [95.6–98.6]	<0.001
Temperature (℃)	36.9 [36.4–37.4]	37.0 [36.5–37.5]	36.7 [36.2–37.2]	<0.001
Laboratory tests				
RDW to albumin ratio	5.59 [4.57–6.98]	5.27 [4.39–6.52]	6.19 [5.06–7.80]	<0.001
WBC (×10^9/L)	13.9 [9.7–19.9]	13.5 [9.8–19.4]	14.7 [9.4–21.3]	0.017
Hemoglobin (g/dL)	9.7 [8.5–11.1]	9.9 [8.6–11.3]	9.4 [8.2–10.7]	<0.001
Platelet count (×10^9/L)	172 [104–251]	180 [113–256]	153 [82–240]	<0.001
RDW (%)	15.3 [14.2–17.0]	14.9 [13.9–16.4]	16.2 [14.8–18.1]	<0.001
Bicarbonate (mmol/L)	20 [17–24]	21 [17.3–24.0]	19 [16–23]	<0.001
Potassium (mmol/L)	3.7 [3.3–4.1]	3.6 [3.3–4.0]	3.7 [3.4–4.2]	<0.001
Sodium (mmol/L)	137 [133–140]	137 [133–140]	136 [133–140]	0.013
Glucose (mg/dL)	134.4 [112–164.1]	134.2 [112.7–163.2]	134.6 [110.6–166.7]	0.823

Table S2 (*continued*)

Table S2 (*continued*)

Characteristics	All patients	Survivors	Non-survivors	P value
Albumin (g/dL)	2.8 [2.4–3.3]	2.9 [2.5–3.4]	2.7 [2.2–3.1]	<0.001
BUN (mg/dL)	29 [18–50]	26 [15–44]	37 [23–60.5]	<0.001
Creatinine (mg/dL)	1.4 [0.9–2.3]	1.3 [0.9–2.1]	1.6 [1.0–2.8]	<0.001
Chloride (mmol/L)	108 [103–112]	108 [104–112]	107 [102–112]	0.005
Lactate level (mmol/L)	2.6 [1.7–4.1]	2.4 [1.6–3.7]	3.0 [1.9–4.9]	<0.001
Comorbidities				
Congestive heart failure	1,284 (32.4)	794 (30.5)	490 (35.8)	0.001
Chronic renal disease	566 (14.3)	333 (12.8)	233 (17.0)	<0.001
Liver disease	538 (13.6)	283 (10.9)	255 (18.6)	<0.001
COPD	570 (14.4)	343 (13.2)	227 (16.6)	0.004
Stroke	328 (8.3)	196 (7.5)	132 (9.6)	0.022
Malignancy	804 (20.3)	391 (15.0)	413 (30.2)	<0.001
Length of stay (days)	5.1 [2.6–11.2]	5.0 [2.5–11.1]	5.4 [2.8–11.2]	0.141

Data are presented as n, median [IQR], or n (%). MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma/surgical intensive care unit; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; MV, mechanical ventilation; RRT, renal replacement therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO_2, percutaneous oxygen saturation; RDW, red blood cell distribution width; WBC, white blood cell; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.