

Association Between Red Cell Distribution Width and Hospital Mortality in Patients with Sepsis

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Abstract

Objective: Sepsis is the leading cause of death in patients admitted to adult intensive care units (ICUs). We aimed to determine the predictive value of red blood cell distribution width (RDW) in patients with sepsis in a large cohort.

Methods: This retrospective observational study used data from the eICU Collaborative Research Database. The prognostic value of RDW was investigated using the receiver operating characteristic (ROC) curve, multiple logistic regression model, integrated discriminatory index (IDI), and net reclassification index (NRI).

Results: In total, 9743 patients were included. The area under the ROC curve of the RDW for predicting hospital mortality was 0.631 (95% confidence interval [CI]: 0.616–0.645). Based on the multiple logistic regression model, an RDW of $\geq 14.5\%$ was correlated with hospital mortality, regardless of Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation IV (APACHE IV) scores (odds ratio [OR]: 1.838, 95% CI: 1.598–2.119). Using SOFA and APACHE IV scores as reference, the IDI and continuous NRI of RDW for hospital mortality was about 0.3 and 0.014, respectively.

Conclusions: The RDW may be useful in predicting hospital mortality in patients with sepsis, offering extra prognostic value beyond SOFA and APACHE IV scores.

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Keywords

Red cell distribution width, eICU Collaborative Research Database, sepsis, hospital mortality, intensive care unit, Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation IV

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Introduction

Red blood cell distribution width is a measure of the spectrum of discrepancy in red blood cell volume and is commonly assessed as part of a complete blood count. The normal reference range for red cell distribution width in adults is 11.5% to 14.5%.¹ An increase in red cell distribution width suggests that some red blood cells are either too large or too small, which is indicative of several abnormalities, such as oxidative stress, hypertension, poor nutritional status, inflammation, erythrocyte fragmentation, dyslipidemia, and alteration of erythropoietin function.² This measure can also be used as a predictor of poor outcomes in several diseases, such as cardiovascular diseases,^{3–5} peripheral artery disease,⁶ cerebrovascular disease,^{7,8} pulmonary embolism,⁹ cancers,^{10,11} kidney disease,¹² and chronic obstructive pulmonary disease.¹³ Red cell distribution width is a widely used laboratory indicator and is increasingly valued.

Sepsis is a potentially life-threatening condition caused by the body's response to an infection. Sepsis is the most expensive condition treated in hospitals in the United States, accounting for more than \$23 billion (6.2%) of the total hospital costs in that country in 2013.¹⁴ One report showed that no significant changes were observed in the sepsis mortality rate from 2002 to 2016, after controlling for severity.¹⁵ The severity of sepsis can range from mild to fatal. Hence, a reliable method for clinical practitioners to predict mortality in patients with sepsis is

urgently needed. In addition to several scoring systems, such as the quick Sequential Organ Failure Assessment (qSOFA),¹⁶ and New York Sepsis Severity Score,¹⁷ several markers have been found to be effective in predicting the prognosis of sepsis, including procalcitonin, presepsin, galectin-3, soluble suppression of tumorigenicity-2, fibroblast growth factor 21, interleukin-8, and soluble tumor necrosis factor- α receptor 1.^{18–20} However, the tools required to measure some of these biomarkers are not available in most hospitals. Even the use of lactate level, as a classical predictor of sepsis, remains controversial.²¹ Hence, a new and simple predictor with satisfactory outcomes must be identified.

Several authors have explored the relationship between red cell distribution width and mortality in patients with sepsis. However, the participants in previous studies were neonates^{22,23} or older adults,²⁴ and some studies were limited by a small sample size.^{25–27} Thus, in the present study, we aimed to determine the predictive value of red cell distribution width in patients with sepsis using a large cohort.

Materials and Methods

Database

Philips Healthcare has developed a remote health system called the eICU Program, which uses a large amount of data to support the management of critically ill patients.

These data are archived and then transformed into a structured query language database, to be used for further research by the eICU Research Institute (eRI).²⁸ The Laboratory for Computational Physiology at the Massachusetts Institute of Technology (LCP-MIT) has partnered with the eRI to establish the eICU Collaborative Research Database (eICU-CRD), which is a large, multicenter intensive care unit (ICU) database with high-granular data on over 200,000 ICU admissions monitored by eICU Programs across the United States in 2014 and 2015. The database comprises 208 hospitals, including 19 teaching hospitals; 70 of these hospitals are located in the Midwestern United States, 56 in the South, and 43 in the West. The data are deidentified and include information on, for example, vital signs, diagnosis, disease severity measures, treatment information, and care plan documentation. Data on the clinical outcomes are available until patients are discharged from the hospital. The database is constantly updated, and the current version is v2.0 (17 May 2018). In this study, we used the current version of the database, and PostgreSQL v11.2 was used to query and manage the data (<http://www.postgresql.org/>).

After completing a training course of the Collaborative Institutional Training Initiative (CITI Program), one author (YL) was authorized to access the data from the eICU-CRD for medical research purposes. The database was released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. The reidentification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (HIPAA certification no. 1031219-2). Because this study was a retrospective analysis of a third-party anonymized publicly available database with pre-existing institutional review board (IRB) approval, IRB approval from our institution and patient consent were not required.

Study population

The inclusion criteria were as follows:

1. Patients with a primary diagnosis of sepsis upon admission to the ICU
2. Patients aged older than 16 years and younger than 89 years

The exclusion criteria were as follows:

1. Patients who had been repeatedly admitted in the ICU
2. Patients whose length of ICU stay was <4 hours
3. Patients whose SOFA score was <2
4. Patients whose key information was unavailable (sex, Acute Physiology and Chronic Health Evaluation IV [APACHE IV] score, mortality, and red cell distribution width assessed within the first 24 hours in the ICU)

The eICU-CRD includes patients who were admitted to the ICU from 2014 to 2015. The inclusion of patients was carried out before publication of the third definition of sepsis.²⁹ Thus, we included SOFA scores in our inclusion criteria.

Data, including demographic characteristics, severity-of-disease scores, mortality, red cell distribution width, other laboratory results, cause of ICU admission, length of ICU stay, and vital signs, were obtained from the eICU-CRD. If additional laboratory results were recorded for the same patient within the first 24 hours of ICU admission, only the first set of laboratory results was included in the study. In addition, the initial vital signs upon ICU admission were included. Severity-of-disease scores included SOFA and APACHE IV scores. The SOFA source code was shared by Alistair Johnson.³⁰

Statistical analysis. The distribution of continuous variables was assessed using the

Shapiro–Wilk test, and none of these variables showed a normal distribution. Data were expressed as either frequency and percentage for categorical variables or median and interquartile range (IQR) for continuous variables. The Kruskal–Wallis H test was used to compare continuous data. Categorical variables were compared using the Fisher’s exact test. The receiver operating characteristic (ROC) curve and two multivariable logistic regression models were used to investigate the possible association between red cell distribution width and hospital mortality. Approximately <12.5% of the covariates were missing; hence, multiple imputation by chained equations was adopted to replace the missing values. The net reclassification index (NRI) and integrated discriminatory index (IDI) were used to measure improvement in the predictive performance of red blood cell distribution when added to the classical severity-of-disease scores.^{31,32} We performed a subgroup analysis for each etiology of sepsis. All significance tests were two-sided, and a p value <0.05 was considered statistically significant. All analyses were conducted using R 3.6.0 with the mice, pROC,³³ PredictABEL, and ggplot2 packages (The R Project for Statistical Computing, Vienna, Austria).

Sensitivity analyses. Sensitivity analyses were performed to evaluate the effect of missing data in multivariable logistic regression model 2. Ten different random numbers between 1 and 10,000, generated using the R command, were used as seed values in the multiple imputations. We also performed a sensitivity analysis using complete case analysis.

Results

Participants

Figure 1 shows the process of selecting participants who were eligible for the study.

Finally, 9743 patients from 177 hospitals were included in the study.

Baseline characteristics of participants

The baseline characteristics of the study population are shown in Table 1. The median age of the 9743 study participants was 65 years. Of these, 48% were women. Participants were categorized into two identical groups according to the normal reference values for red cell distribution width (normal: $\leq 14.5\%$ and high: $>14.5\%$). The group with a higher red cell distribution width had higher APACHE IV scores and higher hospital mortality rates ($p < 0.001$). It also had older age and a higher percentage of women ($p < 0.001$).

Association between red blood cell distribution width and hospital mortality. We performed multiple logistic regression analysis to explore the association between red cell distribution width and hospital mortality. In model 1, after adjusting for SOFA and APACHE IV scores, a significant correlation was still observed between a high red cell distribution width and hospital mortality, with an odds ratio (OR) of 1.838 (95% confidence interval [CI]: 1.598–2.119). There were no missing values in the variables used in this model. We ran an alternative model to determine the relationship between red cell distribution width and hospital mortality, in which the covariates were adjusted for SOFA and APACHE IV scores; age; albumin, creatinine, glucose, hematocrit, hemoglobin, platelet, and potassium levels; white blood cell count; mean arterial pressure; and body mass index. Approximately <12.5% of the covariate data were missing. These missing covariates were then imputed by multiple imputation using the mice package in R. Moreover, a high red cell distribution width was significantly associated with hospital mortality, after adjusting for potential

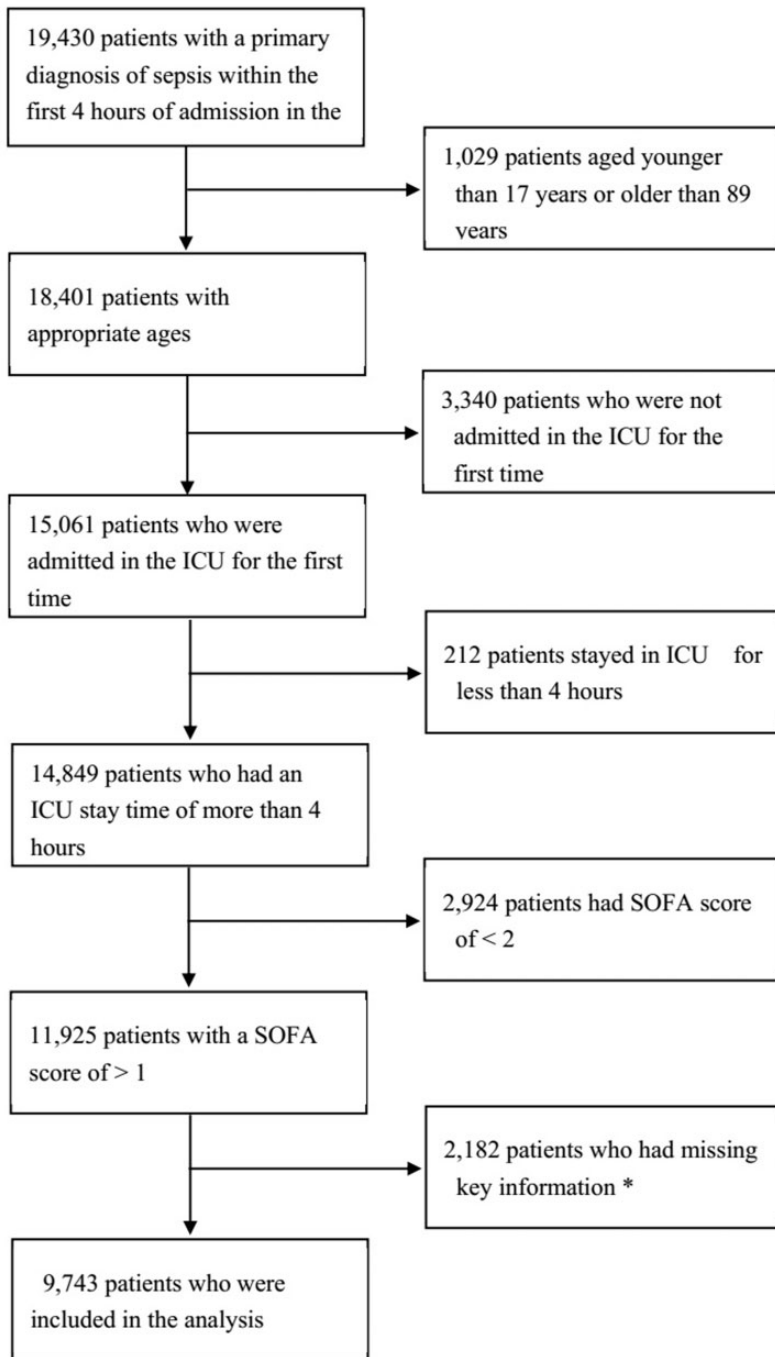


Figure 1. Patient selection process.

* Key information refers to sex, Acute Physiology and Chronic Health Evaluation IV (APACHE IV) scores, mortality, and red blood cell distribution assessed within the first 24 hours after admission to the intensive care unit (ICU).

SOFA, Sequential Organ Failure Assessment.

Table 1. Baseline characteristics of the study population.

	RDW		p [#]
	Overall	Normal ($\leq 14.5\%$)	
N	9743	3218	6525
Age (years), median [IQR]	67.00 [56.00, 77.00]	65.00 [54.00, 76.00]	68.00 [58.00, 78.00]
Type of sepsis, n (%)			
Sepsis, cutaneous/soft tissue	797 (8.2)	242 (7.5)	555 (8.5)
Sepsis, GI	1137 (11.7)	385 (12.0)	752 (11.5)
Sepsis, gynecologic	26 (0.3)	12 (0.4)	14 (0.2)
Sepsis, other	647 (6.6)	182 (5.7)	465 (7.1)
Sepsis, pulmonary	3535 (36.3)	1208 (37.5)	2327 (35.7)
Sepsis, renal/UTI	2424 (24.9)	814 (25.3)	1610 (24.7)
Sepsis, unknown	1177 (12.1)	375 (11.7)	802 (12.3)
Female sex, n (%)	4680 (48.0)	1476 (45.9)	3204 (49.1)
Ethnicity, n (%) *			
African American	1084 (11.2)	240 (7.5)	844 (13.0)
Asian	141 (1.5)	47 (1.5)	94 (1.5)
White	7565 (78.2)	2564 (80.0)	5001 (77.2)
Hispanic	373 (3.9)	167 (5.2)	206 (3.2)
Native American	57 (0.6)	16 (0.5)	41 (0.6)
Other/Unknown	460 (4.8)	169 (5.3)	291 (4.5)
Death in ICU, n (%)	1218 (12.5)	240 (7.5)	978 (15.0)
Length of ICU stay (hours), median [IQR]	55.00 [30.00, 104.00]	51.00 [29.00, 97.00]	58.00 [31.00, 107.00]
Death in hospital, n(%)	1623 (16.7)	319 (9.9)	1304 (20.0)
SOFA score, median [IQR]	5.00 [3.00, 8.00]	5.00 [3.00, 7.00]	5.00 [3.00, 8.00]
APACHE IV score, median [IQR]	67.00 [53.00, 85.00]	63.00 [49.00, 79.00]	70.00 [55.00, 88.00]
BMI (kg/m ²), median [IQR]	27.12 [22.90, 33.15]	26.88 [22.97, 32.26]	27.29 [22.86, 33.59]
MAP (mmHg), median [IQR]	74.30 [64.30, 86.70]	75.70 [65.70, 88.70]	73.70 [64.00, 86.00]
Heart rate, median [IQR]	97.00 [82.00, 112.00]	98.00 [84.00, 113.00]	96.00 [82.00, 112.00]
Temperature (°C), median [IQR]	36.90 [36.50, 37.40]	36.90 [36.60, 37.60]	36.80 [36.40, 37.40]
RDW (%), median [IQR]	15.40 [14.10, 17.30]	13.70 [13.20, 14.10]	16.50 [15.40, 18.20]
MCH (pg), median [IQR]	29.90 [28.10, 31.40]	30.70 [29.40, 31.90]	29.40 [27.50, 31.10]

(continued)

Table 1. Continued.

	Overall	RDW		p [#]
		Normal (\leq 14.5%)	High ($>$ 14.5%)	
MCHC (g/dL), median [IQR]	32.80 [31.70, 33.70]	33.40 [32.60, 34.20]	32.40 [31.40, 33.30]	<0.001
Albumin (g/dL), median [IQR]	2.90 [2.40, 3.40]	3.20 [2.70, 3.60]	2.80 [2.30, 3.30]	<0.001
Creatinine (mg/dL), median [IQR]	1.50 [0.99, 2.56]	1.38 [0.94, 2.20]	1.60 [1.00, 2.76]	<0.001
Glucose (mg/dL), median [IQR]	131.00 [104.00, 177.00]	135.00 [109.00, 187.00]	128.00 [102.00, 173.00]	<0.001
WBC ($\times 10^9/L$), median [IQR]	13.60 [8.70, 19.30]	13.70 [9.00, 19.10]	13.58 [8.60, 19.48]	0.674
Hematocrit (%), median [IQR]	34.90 [29.70, 39.80]	37.60 [33.23, 42.00]	33.30 [28.50, 38.50]	<0.001
Hemoglobin (g/dL), median [IQR]	11.40 [9.60, 13.10]	12.60 [11.10, 14.00]	10.70 [9.10, 12.50]	<0.001
Platelet ($\times 10^9/L$), median [IQR]	202.00 [139.00, 283.00]	198.00 [145.00, 267.25]	205.00 [136.00, 292.00]	0.023

*Owing to missing data, the sum of patients was not equal to the total cohort number.

[#]Continuous data were compared using the Kruskal–Wallis H test. Categorical variables were compared using the Fisher's exact test.

GI, gastrointestinal; UTI, urinary tract infection; ICU, intensive care unit; BMI, body mass index; MAP, mean arterial pressure; RDW, red blood distribution width; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cell; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV.

confounders (OR: 1.608, 95% CI: 1.455–1.762) (Table 2).

ROC analysis was performed to investigate the relationship between red cell distribution width and hospital mortality. The ROC curves for red cell distribution width

and classical severity-of-disease scores are illustrated in Figure 2, and the area under the ROC curve (AUC) values are presented in Table 3.

The AUCs of the three curves were > 0.6, and the AUC of the red cell distribution

Table 2. Multivariable logistic regression analysis of the relationship between RDW and hospital mortality.

	Model 1		Model 2	
	OR (95% CI)	p	OR (95% CI)	p
RDW (high group)	1.838 (1.598–2.119)	<0.001	1.608 (1.455–1.762)	<0.001
SOFA (per 1 score)	1.109 (1.083–1.135)	<0.001	1.140 (1.112–1.168)	<0.001
APACHE IV (per 1 score)	1.030 (1.027–1.033)	<0.001	1.025 (1.021–1.028)	<0.001

Model 1 adjusted for SOFA and APACHE IV scores.

Model 2 adjusted for SOFA and APACHE IV scores; age; albumin, creatinine, glucose, hematocrit, hemoglobin, platelet, and potassium levels; white blood cell count; mean arterial pressure; and body mass index.

RDW, red blood distribution width; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV.

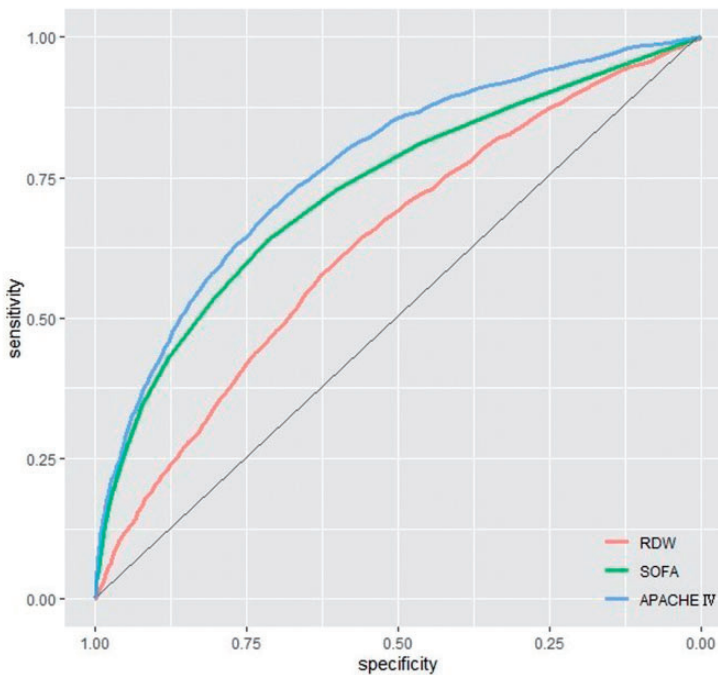


Figure 2. Receiver operating characteristic curves of red blood cell distribution (RDW) and classical severity scores for hospital mortality.

SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV.

width was lower than that of the SOFA and APACHE IV scores. To determine whether red cell distribution width had a higher prognostic value than the classical severity-of-disease scores, we analyzed the data using both the IDI and NRI, as presented in Table 4. Red cell distribution width significantly improved the predictive efficacy of the classical severity-of-disease scores ($p < 0.001$).

Subgroup analyses

We conducted a series of subgroup analyses to examine the effect of red cell distribution width across various subgroups, which were classified according to the cause of sepsis. The distribution of red cell distribution width in each subgroup is shown in Figure 3. Logistic regression analysis model 1 was used in each group, except for the gynecologic sepsis group, which only had 26 participants. The ORs and 95% CIs are summarized in Table 5.

Table 3. Area under the receiver operating characteristic curve (AUC) for red blood cell distribution width and severity scores.

Name	AUC (95% CI)
RDW	0.631 (0.616–0.645)
SOFA	0.727 (0.712–0.741)
APACHE IV	0.769 (0.757–0.782)

RDW, red blood distribution width; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV scores; CI, confidence interval.

Table 4. Extra predictive value of RDW over classical severity scores.

	Continuous NRI		IDI	
	Estimates (95% CI)	p	Estimates (95% CI)	p
SOFA	0.308 (0.256–0.361)	<0.001	0.015 (0.012–0.019)	<0.001
APACHE IV	0.305 (0.252–0.358)	<0.001	0.013 (0.010–0.017)	<0.001

IDI, integrated discriminatory index; NRI, net reclassification index; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV scores; CI, confidence interval.

Subgroup analyses also revealed a significant association between high red cell distribution width and hospital mortality.

Sensitivity analyses. Figure 4 summarizes the results of sensitivity analyses using various seeds in multiple imputation and complete case analysis. As shown in Figure 4, the OR for high red cell distribution width and hospital mortality was >1.5 for all random seeds and complete case analyses. The results of all analyses were statistically significant ($p < 0.05$).

Discussion

This retrospective study showed that red cell distribution width was an independent predictor of mortality in critically ill patients with sepsis. Although the AUC for red cell distribution width was lower than that of APACHE IV and SOFA scores, it showed significant predictive performance. The group with a high red cell distribution width had a higher risk of death (OR: 1.838, 95% CI: 1.598–2.119). Han initially explored the relationship between red cell distribution width and mortality in patients with sepsis using the data obtained from the Medical Information Mart for Intensive Care III (MIMIC III), a single-center database, during 2001 to 2012.³⁴ In the present study, we used multicenter data, a contemporary definition of sepsis, and patients who were newly diagnosed with sepsis. In addition to the classical severity scores, the red blood cell distribution width can also yield a

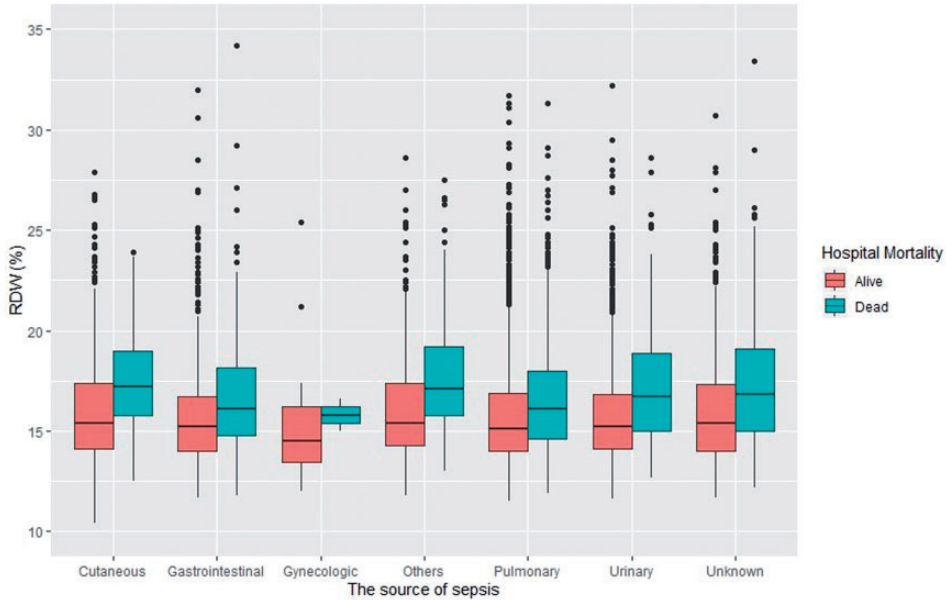


Figure 3. Red blood cell distribution width (RDW) across all subgroups, classified by source of sepsis.

Table 5. Multivariable logistic regression analysis of the relationship between RDW and hospital mortality in each sepsis subgroup.

	Cutaneous (n = 797)	Gastrointestinal (n = 1137)	Other (n = 647)	Pulmonary (n = 3535)	Urinary (n = 2424)	Unknown (n = 1177)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
RDW	2.415**	1.883***	2.946***	1.538***	2.630***	1.886**
(High group)	(1.298–4.862)	(1.301–2.767)	(1.631–5.648)	(1.255–1.890)	(1.829–3.880)	(1.246–2.912)
SOFA	1.117*	1.102**	1.073	1.080***	1.140***	1.140***
(per 1 score)	(1.014–1.229)	(1.038–1.170)	(0.974–1.182)	(1.042–1.121)	(1.076–1.210)	(1.060–1.228)
APACHE IV	1.028***	1.032***	1.037***	1.028***	1.026***	1.036***
(per 1 score)	(1.016–1.040)	(1.024–1.041)	(1.025–1.050)	(1.023–1.033)	(1.019–1.034)	(1.027–1.046)

*p < 0.05, **p < 0.01, ***p < 0.001.

RDW, red blood distribution width; OR, odds ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; APACHE IV, Acute Physiology and Chronic Health Evaluation IV.

prognostic value. Using the classical severity-of-disease scores as covariates, the continuous NRI and IDI of the red cell distribution width for hospital mortality was approximately 0.3 and 0.014, respectively. This suggests that incorporation of the red cell distribution width into classical

severity-of-disease scoring systems would provide more information about the patients' prognosis. Subgroup analysis showed that high red cell distribution width had a significant predictive value in each subgroup with different sepsis etiologies, particularly those with cutaneous

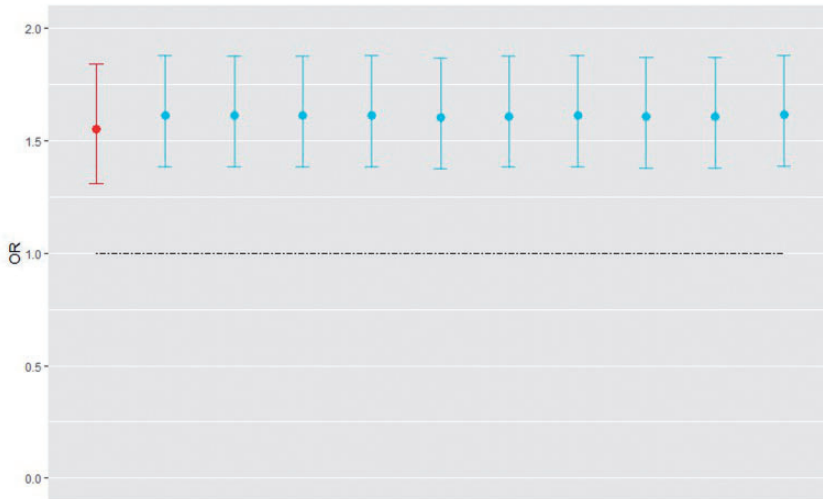


Figure 4. Sensitivity analyses of complete case analysis and various random seeds in multiple imputations. The red dot indicates the OR of the complete case analysis. Blue dots represent the OR of different multiple imputation seeds. Vertical lines indicate the 95% CI. The horizontal dotted line represents the position of OR = 1.

OR, odds ratio; CI, confidence interval.

sepsis (OR: 2.415, 95% CI: 1.298–4.862) and other sources of sepsis (OR: 2.946, 95% CI: 1.631–5.648).

Recently, some novel biomarkers have been found to be effective in predicting mortality in critically ill patients with sepsis, such as apoptosis inhibitor of macrophage/CD5L,³⁵ adrenomedullin,³⁶ and acetylcarnitine.³⁷ However, these biomarkers can only be used in the laboratory setting. As red cell distribution width is a routine parameter assessed as part of a complete blood cell count, measurement of this parameter does not involve additional cost. As red cell distribution width was found to improve the predictive efficacy of the classical severity scores, its inclusion must be considered in the development of new scoring systems in the future.

As mentioned in the published literature, red cell distribution width can predict poor outcome in several diseases. However, the exact mechanism had not been validated. One hypothesis proposes that red cell

distribution width can indicate other underlying abnormalities. A red cell distribution width higher than the normal range may demonstrate abrupt red blood cell damage or, more generally, ineffective erythropoiesis. Previous studies have shown a strong association of red cell distribution width with erythrocyte sedimentation rate and high-sensitivity C-reactive protein (CRP), independent of abundant confounding factors.³⁸ Inflammatory factors, such as interleukin-6,³⁹ white blood cell count, fibrinogen,⁴⁰ and CRP can alter erythrocyte homeostasis and may help improve red cell distribution width levels by impairing iron metabolism, shortening red blood cell survival, and inhibiting red blood cell production. Thus, these phenomena may explain the findings of the current study. Moreover, underlying metabolic abnormalities, including poor nutritional status, shortening of telomere length, dyslipidemia, oxidative stress, and hypertension, can cause an increase in red cell distribution

width.² Sepsis is a condition that involves organ dysfunction triggered by a dysregulated host response to infection; thus, all the above abnormalities reflecting the severity of sepsis may lead to a poor outcome.

Our study has several strengths, which differ from other previous studies. First, unlike one recent study,⁴¹ we analyzed the data of a large sample ($n=9743$ from 177 hospitals), making this the largest study investigating the relationship between red cell distribution width and outcome of sepsis. Compared with patients from the MIMIC III database, the data of those from the eICU-CRD are more recent (2001–2012 vs. 2014–2015). Second, we revised our inclusion criteria by incorporating the SOFA score based on the latest definition of sepsis, which has rarely been adopted in previous retrospective studies.^{34,42}

The present study also has several limitations, which should be considered when interpreting the findings. First, owing to the retrospective nature of this study, selection bias and misclassification or information bias might have been introduced. Only randomized controlled trials can identify a causal relationship. Second, the red cell distribution width was only assessed in patients upon ICU admission, and the changes in red cell distribution width during the ICU stay were not evaluated. Third, owing to the absence of post-discharge data in the eICU-CRD, we did not assess the relationship between red cell distribution width and long-term prognosis in critically ill patients with sepsis. Fourth, some factors, such as deficiencies of iron, vitamin B12, and folate, were not considered as secondary causes of red cell distribution width elevation owing to limited data available in the eICU-CRD.

Conclusion

This study showed that red cell distribution width can predict hospital mortality in

patients with sepsis and has prognostic importance beyond the use of SOFA and APACHE IV scores. However, further prospective cohort studies must be conducted to validate the findings of this study.

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Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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