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RESEARCH ARTICLE

Elevated red cell distribution width opon ICU admission independently predicts mortality in young patients with sepsis-associated encephalopathy: A propensity score-matched retrospective cohort study using MIMIC-IV database

Yalin Zhu[1,2,*], Zhengyu Jiang[2,*], Wangzheqi Zhang[2,3,*], Jie Huang[2], Haoling Zhang[4], Haiwen Wang[1], Jiafeng Wang[2,#], Wen Xu[1,#]

[1]Department of Anesthesiology, Naval Hospital of Eastern Theater, Zhoushan 316004, Zhejiang, China.
[2]Faculty of Anesthesiology, Changhai Hospital, Naval Medical University, Shanghai 200433, China.
[3]School of Anesthesiology, Naval Medical University, Shanghai 200433, China.
[4]Department of Biomedical Sciences, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, Penang, Malaysia.
[*]The authors contribute equally.
[#]The authors are co-corresponding authors.

Corresponding authors: Wen Xu and Jiafeng Wang.

Address correspondence to: Wen Xu, Department of Anesthesiology, Naval Hospital of Eastern Theater, No. 98, Wenhua Road, Dinghai District, Zhoushan 316004, Zhejiang, China.
E-mail: xuwennhet@163.com.
Jiafeng Wang, Faculty of Anesthesiology, Changhai Hospital, Naval Medical University, No. 168, Changhai Road, Yangpu District, Shanghai 200433, China.
E-mail: jfwang@smmu.edu.cn.

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Abstract

Background: Current prognostic research on sepsis-associated encephalopathy (SAE) predominantly focuses on elderly populations, while independent risk markers for young patients remain unclear. **Objective:** To investigate the prognostic value of red cell distribution width (RDW) for 30-day mortality in young SAE patients admitted to the intensive care unit (ICU). **Methods:** This retrospective cohort study analyzed 1,594 SAE patients (18-65 years) from the MIMIC-IV database. Using propensity score matching (1:1 nearest-neighbor matching), 352 matched pairs were generated. RDW-mortality association was assessed through restricted cubic splines, multivariable Cox regression, and Kaplan-Meier analysis. **Results:** Among the 1,594 young patients with SAE analyzed, 144 subjects (9.0%) passed away within 30 days following their ICU admission. Non-survivors exhibited significantly higher baseline RDW than survivors (17.5±3.1 versus 14.9±2.4, P<0.001). Patients exhibiting elevated RDW showed higher rates of hepatic disorders, clotting dysfunction, and impaired kidney function (all P<0.001). RDW and 30-day post-ICU admission mortality were nonlinearly related. After matching (standardized mean difference <0.1 for all covariates), higher RDW values showed a notable association with greater mortality risk over a 30-day period (hazard ratio [HR]=2.7, 95% confidence interval [CI]: 1.4-5.3, P=0.003). Also, after comprehensive adjustment for covariates, each 1-unit increase in RDW was still associated with a 20% rise in the risk of death (HR=1.2, 95% CI: 1.1-1.4, P<0.001). Kaplan-Meier curves confirmed reduced 30-day survival in high-RDW group (log-rank test, P=0.002). **Conclusions:** Elevated RDW at ICU admission independently predicts 30-day mortality in young SAE patients.

Keywords: Sepsis-associated encephalopathy, 30-day mortality in intensive care unit, Red cell distribution width, Predictor, Young patients, MIMIC-IV database

Highlights

- Elevated red cell distribution width (RDW) (>14.65%) at intensive care unit admission independently predicts 30-day mortality in young patients with sepsis-associated encephalopathy (SAE) (hazard ratio =2.7, 95% confidence interval [CI]: 1.4-5.3; P=0.003), persisting after rigorous propensity score matching (352 pairs) and multivariable adjustment.
- RDW achieved an area under the curve of 0.760 (95% CI: 0.720-0.800), outperforming prior reports in elderly sepsis cohorts and underscoring its specificity for young SAE.
- RDW is a low-cost, routinely available biomarker. Its integration into risk stratification could enable early intervention in resource-limited settings, challenging the paradigm of youth conferring low risk in SAE.

1 INTRODUCTION

Sepsis-associated encephalopathy (SAE) represents a major medical complication. The occurrence rate ranges between 8% and over 70%, with variations based on how severe the sepsis condition is in patients requiring critical care [1]. The clinical manifestation of SAE is an acute disorder of consciousness with delirium, hallucinations and agitation [2]. Sepsis is often accompanied by inflammation and coagulation problems. Consequently, systemic inflammation induces SAE by activating endothelial cells and microglial cells, leading to increased blood-brain barrier penetrability and subsequent damage to brain tissue [1, 3, 4]. SAE has been demonstrated to be closely associated with increased short-term mortality and with impairment of cognitive function, anxiety and stress-related disorders; therefore, accurate and convenient assessment of outcomes is particularly crucial [2, 5]. For the clinical front line, a biomarker that is both simple and reliable and can be repeatedly measured at the bedside can help to identify high-risk patients early and guide subsequent treatment decisions. Most existing studies have focused on elderly patients with SAE, whereas younger patients, whose physiological reserve is greater and who are often regarded as a "low-risk population", are instead easily overlooked in research and in clinical alertness [6, 7]. In this population, once SAE occurs, the 30-day mortality rate can still be as high as 9% (data from the present study), and this figure in itself suggests that it is necessary to establish as soon as possible a dedicated early warning tool for young patients.

Red cell distribution width (RDW) is used to quantify the variation in red blood cell (RBC) volume; it reflects the balance between production and clearance of RBCs and can also serve as a simple indicator of acute and chronic systemic inflammatory burden [8]. When RBC homoeostasis is severely disrupted, RDW is usually increased, a phenomenon that is very common in patients with severe infection and can also be seen in various metabolic disorders such as inflammatory diseases, malnutrition and lipid metabolic disturbances [9-11]. An increasing number of studies have found that among populations at intensive care unit (ICU), RDW levels are closely related to patients' survival outcomes and can be used to assess the risk of death in various diseases such as sepsis, diabetes, and hepatic and renal failure [9, 10, 12-15]. It is noteworthy that RDW has also gradually shown potential to reflect the prognosis of encephalopathy and brain injury; the studies by Peng et al. and Yang et al. support the view that RDW can serve as a predictive factor for septic encephalopathy [16, 17]. Additionally, a recent study has proposed a correlation between heightened RDW levels in individuals with traumatic brain injury and increased mortality rates, as well as unfavorable neurological outcomes [18]. Kenangil et al. discovered that Parkinson's disease patients with neuroinflammation as a pathological feature had significantly higher RDW than healthy subjects [19].

While these initial findings propose a plausible association between RDW and brain disorders, further extensive investigations are warranted to authenticate and expand upon these preliminary observations. The predictive value of initial RDW measurements at ICU admission for SAE patient outcomes remains unclear. The goal is to find out how initial RDW relates to ICU prognosis in young patients with SAE, which could facilitate risk stratification.

2 METHODS

2.1 Data sources

The complete collection of patient health states and diseases was constructed utilizing information derived from the openly available Medical Information Mart for Intensive Care, version 4 (MIMIC-IV) database, which contains the Beth Israel Deaconess Medical Center's medical records from 2008 to 2019 [20, 21]. The MIMIC-IV database, a comprehensive healthcare repository featuring anonymized, high-quality clinical data, includes approximately 10,000 recorded ICU stays. The author, JH, was permitted to retrieve and analyze database information. The utilization of these data was endorsed by Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center's Institutional Ethics Board, who also waived informed consent requirements (credential ID: 55826703).

2.2 Cohort selection

In this retrospective study, we examined SAE patients younger than 65 using MIMIC-IV database entries. SAE was defined by the occurrence of sepsis plus either reduced consciousness (Glasgow Coma Scale scores <15) or delirium symptoms. The

identification of sepsis followed Sepsis-3 criteria, requiring suspected infection with an increase in sequential organ failure assessment (SOFA) score to 2 or above. Patient selection was conducted according to the following eligibility standards: (1) first entry into the ICU; (2) length of ICU admission greater than 24 hours. Patients were not eligible if they met any of the following exclusion criteria: (1) primary cerebral trauma; (2) pre-existing mental health conditions or neurologic disorders; (3) development of metabolic, hepatic, or hypertensive encephalopathy, or any hepatic/renal conditions affecting mental status; (4) presence of severe electrolyte or glucose abnormalities, specifically sodium levels below 120 mmol/L, blood glucose above 180 mg/dL, or below 54 mg/dL; (5) documented delirium related to dementia, alcohol withdrawal, or medication use; (6) age ≥65 years; (7) missing RDW data. The process diagram is illustrated in Supplementary Figure 1.

2.3 Data exaction

The original data was obtained from the MIMIC-IV dataset through Structured Query Language executed using Navicat Premium 15.0.12. Data integration was performed using Stata MP 17. The gathered data included: (1) population-related and hospitalization statistics: patient's age, sex, racial background, hospital length of stay (LOS), and LOS in ICU; (2) physical signs and measurements: heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), respiratory rate, and temperature; (3) existing health conditions: myocardial infarction, congestive heart failure, chronic pulmonary disease, renal disease, liver disease, diabetes, and peripheral vascular disease; (4) patient assessment metrics: SOFA score, logistic organ dysfunction system score , and simplified acute physiology score II; (5) treatment procedures: use of vasoactive drugs and invasive mechanical ventilation; (6) laboratory tests: white blood cell count, hemoglobin concentration, mean corpuscular volume, platelet count, RBC count, anion gap, bicarbonate levels, electrolyte levels including sodium, potassium, calcium, and chloride, renal function indices including blood urea nitrogen (BUN) and creatinine, glucose, and blood clotting markers including international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), and RDW [20-22]. It was within the first 24 hours post-ICU admission that these baseline demographic data and assay findings were obtained. For parameters with multiple measurements within this initial 24-hour window, average values were computed, specifically for heart rate, SBP, DBP, MBP, respiratory rate, and body temperature.

2.4 Outcomes

In our research, the main outcome measure was mortality within 30 days following ICU admission. Secondary endpoints encompassed overall in-hospital death rate, duration of hospitalization, and time spent in intensive care.

2.5 Management of missing data

To reduce potential bias, we excluded from our examination any variables containing over 15% missing values. The small number of remaining missing data points was imputed using mean values.

2.6 Statistical analysis

According to the distribution characteristics of the data, continuous variables were expressed as mean ± standard deviation or median (interquartile range), and comparisons between groups were performed using the Mann–Whitney test or Student's t test; categorical variables were expressed as percentages, and Fisher's exact test was used to assess differences. We plotted receiver operating characteristic (ROC) curves to evaluate the ability of RDW to predict 30-day mortality risk in the included patients, and, by means of a generalized additive model with restricted cubic splines, explored whether there was a non-linear association between continuous RDW and the primary outcome. The optimal cut-off value of RDW was determined on the basis of the ROC curve, after first including RDW as a continuous variable in the analysis; subsequently, survival curves were plotted by the Kaplan–Meier method, and survival differences between groups were compared using the log-rank test.

To minimize selection bias and balance baseline characteristics as far as possible, we conducted a one-to-one nearest-neighbour propensity score matching (PSM) analysis with a caliper width of 0.02. Each patient's propensity score was calculated by logistic regression, in which the baseline variables listed in **Table 1** were included. After completing PSM, we compared the standardized mean differences between the two groups, taking 0.15 as the upper limit for acceptable balance.

In order to further evaluate the relationship between RDW and clinical outcomes, we constructed univariable and multivariable Cox regression models respectively. Variables with a P value less than 0.1 in the univariable analysis after PSM were included in the multivariable model to control potential confounders. After matching was completed, we tested the proportional hazards assumption of the Cox model to confirm that there were no time-varying covariates in the adjusted model. All statistical analyses were performed in the R 4.2.0 environment, and a difference was considered statistically significant when $P<0.05$.

3 RESULTS

3.1 Clinical characteristics

A total of 1,594 subjects were included in this study, with a mean age of 49.8±12.1 years, of whom 63.0% were male. Within 30 days after ICU admission, a total of 144 patients (9.0%)

Table 1. Clinical characteristics stratified by preoperative RDW before and after PSM

Variables	Unmatched groups			Matched groups		
	RDW≤14.65 (n=859)	RDW>14.65 (n=735)	P-value	RDW≤14.65 (n=352)	RDW>14.65 (n=352)	P-value
Demographics						
Age, y	47.8±13.1	52.2±10.2	<0.001	51.0±12.2	51.5±10.7	0.597
Male	595 (69.3%)	410 (55.8%)	<0.001	205 (58.2%)	216 (61.4%)	0.398
Race			0.007			0.754
White	485 (56.5%)	428 (58.2%)		211 (59.9%)	202 (57.4%)	
Black	61 (7.1%)	78 (10.6%)		35 (9.9%)	41 (11.6%)	
Others	96 (11.2%)	87 (11.8%)		36 (10.2%)	42 (11.9%)	
Unknown	217 (25.3%)	142 (19.3%)		70 (19.9%)	67 (19.0%)	
Comorbidities						
Myocardial infarction	76 (8.8%)	58 (7.9%)	0.493	32 (9.1%)	33 (9.4%)	0.896
Congestive heart failure	130 (15.1%)	138 (18.8%)	0.053	70 (19.9%)	68 (19.3%)	0.849
Chronic pulmonary disease	160 (18.6%)	195 (26.5%)	<0.001	90 (25.6%)	82 (23.3%)	0.483
Renal disease	59 (6.9%)	107 (14.6%)	<0.001	41 (11.6%)	39 (11.1%)	0.812
Liver disease	133 (15.5%)	342 (46.5%)	<0.001	95 (27.0%)	93 (26.4%)	0.865
Diabetes	109 (12.7%)	128 (17.4%)	0.008	52 (14.8%)	53 (15.1%)	0.916
Peripheral vascular disease	61 (7.1%)	41 (5.6%)	0.216	25 (7.1%)	26 (7.4%)	0.884
Vital signs						
HR, (beats/min)	90.4±17.3	92.6±16.6	0.009	91.8±17.7	92.2±17.0	0.765
SBP, mmHg	115.5±14.8	112.6±14.5	<0.001	114.0±14.7	112.9±14.2	0.318
DBP, mmHg	66.4±10.5	64.0±10.0	<0.001	66.1±9.9	65.1±10.2	0.217
MBP, mmHg	80.0±10.5	77.3±10.4	<0.001	79.4±9.8	78.4±10.5	0.185
RR, (breaths/min)	19.9±4.3	20.0±4.7	0.517	20.2±4.3	20.1±4.7	0.664
Temperature, ℃	37.2±0.6	37.1±0.5	<0.001	37.1±0.6	37.2±0.5	0.678
SpO_2, %	97.2±2.2	96.9±2.1	0.013	97.1±2.1	97.1±2.0	0.864
Scores						
SOFA	6.6±3.5	9.0±4.3	<0.001	7.5±3.6	7.7±3.9	0.457
LODS	5.7±3.0	7.2±3.5	<0.001	6.2±3.2	6.4±3.1	0.474
SAPS II	33.1±11.9	39.6±13.8	<0.001	35.4±12.8	36.3±11.8	0.326
Treatment						
Vasoactive agent	432 (50.3%)	412 (56.1%)	0.022	188 (53.4%)	192 (54.5%)	0.762
Invasive Ventilation	616 (71.7%)	488 (66.4%)	0.022	243 (69.0%)	242 (68.8%)	0.935
Laboratory parameters						
WBC, 10^9/L	13.0±6.4	12.9±11.6	0.004	12.6±7.1	12.8±8.0	0.695
Hemoglobin, g/dl	11.8±2.2	9.7±2.2	<0.001	10.8±2.2	10.6±2.3	0.188
MCV, fl	92.6±6.2	92.5±10.1	0.788	92.7±7.0	93.0±8.8	0.637
PLT, 10^9/L	194.1±85.6	168.4±125.4	<0.001	183.6±93.6	189.2±131.7	0.512
RBC, 10^{12}/L	3.8±0.7	3.3±0.8	<0.001	3.6±0.8	3.5±0.8	0.190
Anion gap, mmol/L	14.8±4.3	15.8±4.9	<0.001	15.0±5.0	15.1±4.7	0.825
Bicarbonate, mmol/L	22.5±4.6	21.7±5.1	<0.001	22.5±5.1	22.2±4.9	0.369
BUN, mg/dl	20.1±19.4	31.5±29.3	<0.001	24.1±25.5	25.1±22.2	0.584
Calcium, mg/dl	8.1±0.8	8.1±1.0	0.502	8.0±0.9	8.0±0.9	0.618
Chloride, mmol/L	104.7±6.5	103.5±7.6	0.001	104.2±7.0	104.6±7.3	0.395
Creatinine, mg/dl	1.3±1.6	1.8±2.0	<0.001	1.4±1.7	1.5±1.8	0.564
Glucose, mg/dl	122.8±25.7	119.6±27.4	0.015	122.4±25.9	120.6±27.3	0.371
Sodium, mmol/L	138.9±4.8	138.1±5.7	0.001	138.7±5.2	138.9±5.5	0.511

Potassium, mmol/L	4.1±0.7	4.2±0.9	0.109	4.1±0.7	4.1±0.8	0.918
INR	1.4±0.5	1.7±0.8	<0.001	1.5±0.7	1.5±0.6	0.613
PT, s	15.0±5.6	18.6±11.3	<0.001	16.2±7.2	16.5±6.6	0.605
APTT, s	34.9±18.8	40.3±22.5	<0.001	37.3±22.2	38.1±20.9	0.614

Note: Values are expressed as number (percentage), mean ± standard deviation, or median (25^{th}-75^{th} percentile). Categorical variables are presented as number (percentage). HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RR, respiratory rate; SOFA, sequential organ failure assessment; LODS, logistic organ dysfunction system; SAPS II, simplified acute physiology score II; WBC, white blood cells; MCV, mean corpuscular volume; PLT, platelet; RBC, red blood cells; BUN, blood urea nitrogen; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; RDW, red blood cell distribution width; PSM, propensity score matching.

Table 2. Clinical outcomes in the SAE patients

Variables	Unmatched groups			Matched groups		
	RDW≤14.65 (n=859)	RDW>14.65 (n=735)	P-value	RDW≤14.65 (n=352)	RDW>14.65 (n=352)	P-value
30-day in-ICU mortality	26 (3.0%)	118 (16.1%)	<0.001	12 (3.4%)	35 (9.9%)	<0.001
Hospital mortality, day	13 (1.5%)	81 (11.0%)	<0.001	6 (1.7%)	24 (6.8%)	<0.001
LOS ICU, day	7.5±7.6	7.6±7.5	0.673	7.5±7.2	7.3±6.6	0.742
LOS hospital, day	17.2±17.7	20.3±17.7	<0.001	17.8±16.5	18.5±14.4	0.558

Note: Values are expressed as mean ± standard deviation or number (percentage). SAE, sepsis-associated encephalopathy; RDW, red blood cell distribution width; ICU, intensive care unit; LOS, length of stay.

died, indicating that even in a relatively young population, short-term mortality risk cannot be ignored. As shown in Supplementary Figure 2, there were obvious differences in RDW levels between groups, and the RDW of patients who died was significantly higher than that of survivors (17.5±3.1 vs 14.9±2.4, P<0.001).

Based on ROC curve analysis, the optimal RDW cut-off value was 14.65, with a corresponding area under the curve (AUC) of 0.760 (95% confidence interval [CI]: 0.720-0.800) (Supplementary Figure 3), according to which the study population was divided into a low-RDW group (n=859) and a high-RDW group (n=735). Comparison of the clinical characteristics of young SAE patients (**Table 1**) showed that, compared with the low-RDW group, patients in the high-RDW group were older, had comorbidities more frequently (except for myocardial infarction and peripheral vascular disease), had higher heart rates and higher disease severity scores, while their blood pressure, body temperature and SpO_2 were relatively lower. Furthermore, the elevated RDW category showed higher anion gap, BUN, creatinine, INR, PT, and APTT values (all P<0.05). In contrast, mean corpuscular volume, calcium, and potassium showed no significant difference between groups, while other parameters were significantly lower in the high-RDW group (all P<0.05).

3.2 PSM procedure

We conducted a 1:1 PSM analysis to equalize covariate distribution between subjects categorized by RDW thresholds, resulting in 352 matched pairs. **Table 1** presents the clinical features of young SAE patients post-matching. Both groups showed comparable distributions of demographics, comorbidities, signs, scores, and laboratory values. The matching quality was evaluated through standardized mean difference calculations pre- and post-PSM (Supplementary Figure 4).

3.3 RDW levels and primary outcomes

The mortality rate at 30 days showed a significant elevation among matched subjects with elevated RDW values (9.9% compared to 3.4%, P<0.001) (**Table 2**). Increased RDW demonstrates an independent correlation with elevated 30-day mortality among young ICU patients experiencing SAE (Supplementary Tables 1 and 2).

Through multivariable Cox proportional hazards analysis evaluating RDW as a continuous parameter, this biomarker demonstrated significant predictive capacity for 30-day ICU mortality in the matched cohort (HR, 1.3 [95% CI, 1.2-1.4], P<0.001). In comparison to individuals with low RDW levels (≤14.65), young ICU patients diagnosed with SAE demonstrated an increased hazard ratio (95% CI) of 2.7 (1.4-5.3) for overall mortality. Other parameters emerged as independent predictors including patient age, liver disease, and body temperature (Supplementary Tables 1 and 2). As a continuous variable, RDW maintained status as an independent predictor of elevated hospital mortality risk (HR, 1.2 [95% CI, 1.1-1.4], P<0.001) (**Table 3**). Following sequential adjustments for demographic factors, comorbid conditions, vital signs, clinical scores, therapeutic measures and pharmacological treatments, and laboratory indicators, the observed correlations in matched patients

Table 3. Association of RDW with outcomes after PSM

Clinical outcome	Unadjusted	Model I	Model II	Model III	Model IV	Model V
30-day in-ICU mortality						
RDW continuous	1.3 (1.2, 1.4) <0.001	1.3 (1.2, 1.4) <0.001	1.2 (1.1, 1.4) <0.001	1.2 (1.1, 1.4) <0.001	1.2 (1.1, 1.4) <0.001	1.2 (1.1, 1.4) <0.001
RDW categorical						
≤14.65	1	1	1	1	1	1
>14.65	2.7 (1.4, 5.3) 0.003	2.8 (1.4, 5.4) 0.002	3.0 (1.6, 5.9) 0.001	2.8 (1.4, 5.8) 0.005	3.0 (1.4, 6.2) 0.004	3.4 (1.5, 7.5) 0.003
Hospital mortality						
RDW continuous	1.2 (1.1, 1.4) <0.001	1.2 (1.1, 1.4) <0.001	1.2 (1.1, 1.4) 0.001	1.2 (1.0, 1.4) 0.016	1.2 (1.0, 1.4) 0.018	1.2 (1.0, 1.4) 0.099
RDW categorical						
≤14.65	1	1	1	1	1	1
>14.65	3.7 (1.5, 9.2) 0.004	4.0 (1.6, 9.8) 0.003	4.0 (1.6, 9.8) 0.003	3.5 (1.3, 9.6) 0.017	3.3 (1.2, 9.5) 0.023	3.2 (1.0, 10.1) 0.052

Note: Values are expressed as HR (95% CI). Model I adjusted for demographics including gender, age, race. Model II adjusted for adjust I model plus comorbidities including myocardial infarction, congestive heart failure, chronic pulmonary disease, renal disease, liver disease, diabetes, peripheral vascular disease. Model III adjusted for adjust II model plus vital signs and scores including HR, SBP, DBP, MBP, RR, temperature, SpO_2, SOFA, LODS, and SAPS II. Model IV adjusted for adjust III model plus treatment including vasoactive agent, and invasive ventilation. Model V adjusted for adjust IV model plus laboratory parameters including WBC, hemoglobin, MCV, PLT, RBC, anion gap, bicarbonate, BUN, calcium, chloride, creatinine, glucose, sodium, potassium, INR, PT, and APTT. HR, hazard ratio; CI, confidence interval; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RR, respiratory rate; SOFA, sequential organ failure assessment; LODS, logistic organ dysfunction system; SAPS II, simplified acute physiology score II; WBC, white blood cells; MCV, mean corpuscular volume; PLT, platelet; RBC, red blood cells; BUN, blood urea nitrogen; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; RDW, red blood cell distribution width; PSM, propensity score matching; ICU, intensive care unit.

maintained statistical significance, as demonstrated in **Table 3**. Nevertheless, upon implementing adjustments in Model V, the association between RDW and hospital mortality risk lost statistical significance (all P>0.05).

Survival analysis indicated significantly poorer 30-day ICU survival in young SAE patients with RDW>14.64% (log-rank test, P=0.002; **Figure 1**).

It was through restricted cubic spline modeling that the nonlinear correlation between RDW and 30-day ICU mortality was shown, where incremental RDW elevations predicted worsening survival probabilities (Likelihood ratio test, P<0.001) (**Figure 2**).

4 DISCUSSION

This study shows that among young patients with SAE, an elevated RDW level (>14.65%) is an independent predictor of 30-day ICU mortality risk, and this association remains stable even after full adjustment for multiple covariates. It is worth emphasizing that we focused on a group that is often overlooked yet very crucial, namely young SAE patients aged 18-65 years with relatively good physiological reserve, whereas previous studies on SAE prognosis and RDW have mostly been based on elderly or mixed-age cohorts. Young patients usually have fewer comorbidities and stronger organ reserve, and the driving factors of their adverse outcomes may be essentially different from those in elderly populations; even so, this study still observed a 30-day mortality rate close to 9%, and RDW was consistently a robust independent predictor, a result that strongly challenges the ingrained notion that "being young equals low risk". At the same time, in young patients, an elevated RDW is more likely to reflect the acute blow to RBC homoeostasis caused by the current acute infectious event such as an intense inflammatory storm or microcirculatory dysfunction, rather than being driven mainly by long-term chronic diseases or confounding factors such as malnutrition; this relationship still exists after adjustment for multidimensional covariates, including comorbidities. Consequently, the RDW threshold (14.65%) and its predictive efficacy (AUC=0.760) identified in this study may be more specific to young SAE patients, and its clinical early-warning value in this population may have been underestimated in previous research.

Previously, studies documented RDW's role in detecting anemia [22, 23]. More recent investigations have demonstrated RDW's connections to numerous infectious and inflammatory conditions [24-27]. In individuals diagnosed with COVID-19, RDW levels were significantly higher among those who developed severe disease or died, as opposed to those who exhibited mild symptoms or recovered from the infection [28-30]. Yeşil et al. revealed that patients with inflammatory bowel disease in the active phase showed higher RDW levels than those in

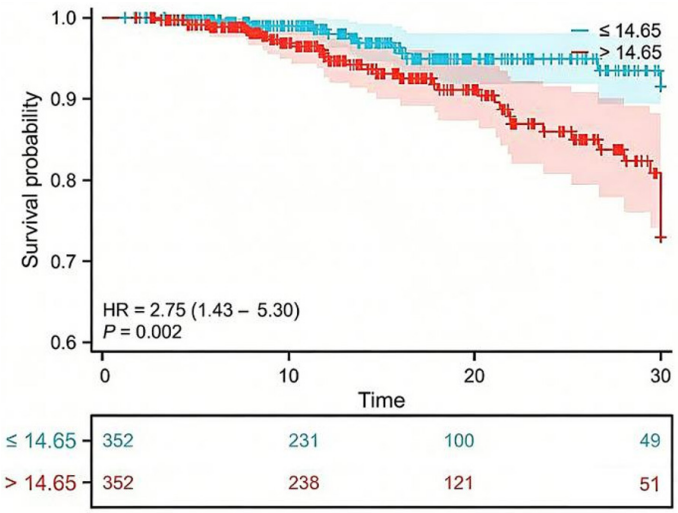

Figure 1. The KaplanMeier curves of 30-day outcomes after PSM. PSM, propensity score matching; HR, hazard ratio.

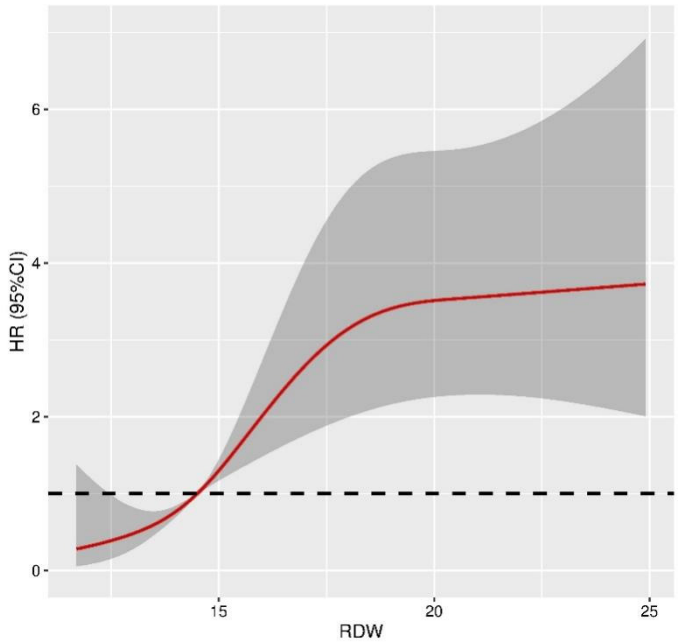

Figure 2. The association between RDW and the probability of 30-day outcomes. The red line represents the HR for each RDW value, while the gray bars represent the 95% confidence interval. RDW, red blood cell distribution width; HR, hazard ratio.

remission, indicating its possible role as a precise and responsive biomarker for identifying active Crohn's disease [24]. Additionally, findings from a retrospective analysis indicated that elevated RDW correlated with increased hospitalization rates and higher 30-day mortality among younger patients suffering from community-acquired pneumonia [25]. To our knowledge, this research represents the first investigation exploring RDW's correlation with short-term clinical outcomes in young SAE patients through analysis of population-level real-world evidence.

Alterations in blood coagulation mechanisms could account for the RDW-prognosis correlation among younger individuals with SAE. During septic conditions, substantial disruptions in coagulation processes occur. Under normal physiological conditions, the activation of blood clotting is regulated by intrinsic anticoagulation systems, differing from normal homeostasis maintained through tissue factor inhibition, protein C activation, and antithrombotic regulation [3]. Sepsis interferes with all three coagulation regulatory mechanisms. Research demonstrated that RDW showed positive associations with various prognostic indicators in multiple hepatic disorders, including serum bilirubin and creatinine concentrations, as well as PT measurements [31]. Elevated RDW is strongly associated with venous thrombosis and early death from acute pulmonary embolism [26, 32]. It is also possible for renal insufficiency to affect RBC production and platelet dysfunction [33, 34]. **Table 1** data revealed a correlation between rising RDW levels and increased incidence of liver-related conditions in this study, which was associated with elevated values of INR, PT, APTT, as well as increased BUN and creatinine levels. This, to some extent, reflects coagulation disorder, hepatic and renal dysfunction in these patients. Coagulation disorders in young SAE patients may be one of the potential mechanisms by which high level of RDW leads to poor outcomes.

An elevated RDW may indicate ineffective erythropoiesis or delayed clearance of erythrocytes, which may be influenced by disease, as it is an early indication of physiological stress [30, 35, 36]. Anisocytosis may indicate the presence of an underlying inflammatory condition, with cytokine release potentially influencing bone marrow functionality [37]. The RDW showed a robust and autonomous positive correlation with traditional markers of inflammation [38]. Inflammatory biomarkers have been used to diagnose, treat, and prognosticate sepsis patients [39, 40]. In septic encephalopathy, infection is accompanied by inflammation and stress. Reduced blood pressure and an elevated heart rate indicate the cardiac stress condition in individuals with high RDW, while the increased heart rate serves as a compensatory mechanism in response to sympathetic nervous system activation. Additionally, patients with high RDW had more extreme differences in white blood cell count.

Previous studies have already suggested that RDW is closely related to systemic inflammation and the prognosis of sepsis, and on this basis the present study approached the topic from a new angle, focusing on the early warning needs of young SAE populations. Most previous work on RDW and sepsis has included elderly or all-age cohorts, whereas young patients, who have stronger physiological reserve and are often labelled as low risk, are often neglected; however, we found that in this population the mortality rate still reached as high as 9%, and

the predictive performance of RDW (AUC=0.760) even exceeded previously reported values in elderly sepsis cohorts (AUC=0.710) [6, 7, 41]. This means that, in young SAE patients, RDW may capture acute injury signals that are more difficult for traditional risk models to identify, such as a more intense coagulation–inflammation cascade manifested as elevated INR, prolonged PT and impaired hepatic and renal function or microcirculatory dysfunction, rather than merely chronic organ failure, which is more common in older populations. At the same time, the independent value of RDW observed in this study challenges the traditional view that RDW is only a surrogate marker of inflammation. Even after strict PSM and comprehensive adjustment for covariates, RDW still maintained a significant predictive role (HR=1.2, P<0.001; **Table 3**), suggesting that the information it integrates also includes microcirculatory damage caused by abnormal RBC morphology, among which anisocytosis, that is, abnormal variation in RBC size, may disturb passage through cerebral capillaries and aggravate SAE-related ischemic and hypoxic injury.

On this basis, we further propose a more exploratory hypothesis: an elevated RDW may not only be a bystander of disease severity, but may also directly participate, through specific pathways, in neurological injury and adverse outcomes in SAE. Anisocytosis reduces the deformability of RBCs and their ability to pass through microvessels, particularly affecting cerebral microcirculation; against the background of sepsis, in which there is already uneven perfusion, stagnant blood flow and tissue hypoxia, an elevated RDW may further limit the delivery of oxygen and nutrients, thereby aggravating ischemic and hypoxic brain injury. The oxygen-carrying and oxygen-releasing functions of morphologically abnormal RBCs may also be impaired, and, in the context of increased metabolic demands of brain tissue during SAE, such functional defects may contribute to relative tissue hypoxia and drive the continuous progression of neurological dysfunction. It is also noteworthy that there is a bidirectional interaction between neuroinflammation in the brain and systemic inflammation and the RBC system: the core mechanisms of SAE include activation of microglia and the release of pro-inflammatory cytokines such as IL-6 and TNF-α, which can inhibit bone marrow hematopoiesis or shorten RBC lifespan; conversely, the intense systemic inflammation and potential oxidative stress reflected by elevated RDW may in turn, by disrupting the blood–brain barrier or through humoral signaling pathways, aggravate neuroinflammation within the brain and form a self-reinforcing vicious cycle [42, 43]. The characteristics and significance of this central–peripheral interaction in young patients with SAE still need to be elucidated systematically.

Compared with many complex or expensive tests, measurement of RDW is simple, rapid and easy to repeat; several studies have linked it with inflammatory diseases and thrombosis, suggesting that RDW may be closely related to the occurrence and prognosis of SAE [24-27]. Because it is affected by the lifespan of RBCs of about 3-4 months, RDW can integrate disease progression information over a relatively long time scale; this characteristic gives it a certain irreplaceability and also makes it promising in improving the accuracy of existing prognostic models for sepsis and SAE. The present study adopted a strict one-to-one PSM design, effectively balancing baseline differences, so that the significant association observed in the matched cohort between elevated RDW and 30-day mortality (HR=2.7, 95% CI: 1.4-5.3, P=0.003), as well as the obvious differences in survival rate between the high- and low-RDW groups (9.9% vs 3.4%, P<0.001), can more reasonably be attributed to RDW itself or to the pathophysiological states that it represents but have not yet been fully quantified, rather than to confounding factors. Relying on the large-scale, high-quality real-world database MIMIC-IV, the results of this study appropriately reflect the predictive performance of RDW in actual clinical settings, suggesting that this easily obtainable, low-cost routine test index has high potential for clinical translation, especially in settings with limited resources or without advanced bedside monitoring methods, where it can be used for rapid risk stratification and optimization of resource allocation.

Although in young SAE cases we observed a robust association between RDW levels and outcomes, this study still inevitably has limitations. The retrospective design based on the MIMIC-IV database may have introduced selection bias; even though PSM was used to reduce baseline differences as far as possible, residual confounding is still difficult to eliminate completely. Some variables in the database were missing, and even though appropriate handling has been carried out, their potential impact on the results still cannot be completely ruled out; at the same time, this study relied on a single database and lacked external cohort validation, so that the generalizability and applicability of the conclusions still need further testing. In addition, this study only evaluated the relationship between RDW and 30-day mortality, and the impact on more long-term outcomes such as long-term survival and quality of life has not yet been systematically assessed. The enrollment of SAE patients in our center is inherently challenging, primarily due to the limited number of eligible cases encountered in routine clinical practice. Therefore, we chose to use a public database for our initial SAE research.

Future research can build on the findings and limitations of this study and continue to expand. On the one hand, it is necessary to carry out large-scale prospective cohort studies covering multiple regions and multiple medical centers, in order to externally validate the results of this study and to compare the predictive performance of RDW for outcomes in young SAE patients under different clinical environments and treatment strategies; on the other hand, the intrinsic links between RDW, coagulopathy and inflammatory responses should be explored in depth, to clarify the specific biological pathways by which high RDW affects SAE prognosis and to provide clues for

potential therapeutic targets. Combining RDW with other novel biomarkers and clinical indicators is expected to construct a more comprehensive prognostic evaluation model for SAE and improve predictive accuracy; for young SAE patients with elevated RDW, strengthening follow-up and dynamic monitoring, particularly the assessment of cognitive function, mental health and overall quality of life, will also help to optimize clinical care and rehabilitation strategies.

On the basis of the new perspective proposed in this study, subsequent work can also focus on several directions with greater application prospects. At the clinical level, multicenter external validation studies are needed to systematically assess the generalizability, sensitivity and specificity of the RDW cut-off value (14.65%) determined in this study in independent and diverse cohorts of young SAE, and to further explore whether this threshold needs to be modified according to the source of infection such as Gram-positive or Gram-negative bacteria or fungi, pathogen virulence or the host genetic background. At the same time, the value of dynamic RDW trajectories should be a focus, for example changes at 24 h, 48 h, 72 h and even later time points after ICU admission, in order to observe whether they have earlier and more precise predictive ability than a single measurement and whether they can indicate disease progression trends, treatment responses such as the effects of anti-infective or anti-inflammatory therapies and the potential for neurological recovery. Another important goal is to construct integrated predictive models that combine RDW especially dynamic RDW with existing organ function scores such as SOFA and APACHE II, novel biomarkers such as the aforementioned markers of neuronal injury and specific inflammatory cytokines and feasible bedside microcirculatory or physiological function assessments, so as to promote the real implementation of precision medicine in critically ill young patients. To verify whether intensified treatment or refined monitoring strategies based on RDW risk stratification can improve short-term survival, neurological recovery and long-term outcomes, rigorously designed prospective randomized controlled trials are still needed, with comprehensive assessment of their risk–benefit ratio, cost-effectiveness and impact on medical resource allocation; this will be one of the key steps in elevating RDW from a simple prognostic marker to a tool for guiding treatment decisions.

5 CONCLUSION

Taken together, using a strict PSM method and large-scale real-world data, this study clearly delineated the level of short-term mortality in young patients with SAE and confirmed that elevated RDW at ICU admission is independently associated with 30-day mortality risk in this population. In doing so, it not only undermines the ingrained perception that young patients are naturally at lower risk, but also highlights the unique value of RDW in prognostic assessment among young SAE patients. Young SAE patients with high RDW levels should therefore receive special attention and more active management in clinical practice.

DECLARATIONS

Author contributions

Yalin Zhu, Zhengyu Jiang and Wangzheqi Zhang wrote the manuscript and performed the data analysis. Jie Huang, Haoling Zhang, Haiwen Wang and Wen Xu checked the data and the results. Yalin Zhu provided the funding of this study. Jiafeng Wang designed the study. Jiafeng Wang and Wen Xu revised the manuscript and supervised research. All authors have reviewed and approved the final version.

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Data availability

The complete dataset referenced throughout our publications is accessible via the public MIMIC-IV database at https://mimic.mit.edu/iv/.

Ethics approval and consent to participate

This investigation adhered to the ethical standards of the Helsinki Declaration in 1964 and its subsequent amendments, or equivalent ethical guidelines, utilizing de-identified data obtained from the publicly accessible MIMIC-IV database. Access authorization was secured through certification ID 55826703 by researcher JH. Ethics approval was granted under a consent waiver protocol by the IRBs of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Supplementary Information

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