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ORIGINAL ARTICLE

Red blood cell distribution width predicts in-hospital mortality in patients with a primary diagnosis of seizures in the ICU: a retrospective database study

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Abstract

Purpose The aim of this study was to determine the predictive value of red blood cell distribution width (RDW) in patients with a primary diagnosis of seizures admitted to the intensive care unit (ICU) in terms of in-hospital mortality.

Methods This was a retrospective study of the eICU Collaborative Research Database of adult patients (aged 18–88 years) with a primary diagnosis of seizures in 2014 and 2015. The prognostic value of RDW was investigated using a receiver operating characteristic (ROC) curve, multiple logistic regression model, and net reclassification index (NRI).

Results We identified 1568 patients who met the inclusion criteria. High RDW was significantly correlated with in-hospital mortality after adjusting for potential confounders with an odds ratio (OR) of 3.513 (95% confidence interval [CI]:1.699–7.266). The area under the ROC curve of RDW for in-hospital mortality was 0.7225. Compared with the prediction of in-hospital mortality using APACHE IV score alone, the continuous NRI with the RDW variable was 0.3507 (95%CI: 0.0584–0.6431, $p < 0.05$). The length of stay in the ICU of patients with an RDW >14.65% was significantly increased compared to those with normal RDW (log-rank test, $p < 0.0001$).

Conclusion RDW width can be useful for prediction of in-hospital mortality in patients with seizures admitted to the ICU, and it provides additional prognostic value beyond the APACHE IV score alone.

Keywords Seizure · Red blood cell distribution width · Intensive care unit · In-hospital mortality · eICU-CRD database

Introduction

Epilepsy is a serious neurological disease requiring costly treatment [1]. The lifetime prevalence of active epilepsy is reported to be 7.60 per 1000 persons [2]. In 2016, epilepsy affected 45 million people worldwide, and the age-standardized mortality rate of idiopathic epilepsy was 126 per 100,000 people [3]. Some patients with epilepsy, including status epilepticus, must be admitted to the intensive care unit (ICU). Early risk stratification is crucial to improve patient outcome.

The red blood cell distribution width (RDW) is a measure of the variability in the size of circulating erythrocytes, which reflects the degree of heterogeneity of erythrocyte volume [4]. It was originally used for differential diagnosis of anemias in laboratory hematology [5]. Recently, RDW was found to be a prognostic marker in patients with chronic obstructive pulmonary disease, gastrointestinal disorders, diabetes mellitus, cardiovascular and cerebrovascular diseases, heart failure, and acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [6–10].

An increase in RDW may be associated with a variety of underlying metabolic abnormalities, such as inflammation and oxidative stress [11]. Seizure induces the production of the inflammatory cytokine IL-6 in the blood and cerebrospinal fluid [12, 13], causing an inflammatory response. Peripheral inflammation can lead to increased susceptibility to epilepsy by inducing neuro-inflammation and oxidative stress in the

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hippocampus [14]. Furthermore, oxidative stress can be the result of seizure activity and may exacerbate the consequences of seizures [15]. Serum levels of antioxidants were significantly lower in patients with epilepsy compared to healthy controls [16]. In a rat model of acquired epilepsy, targeting oxidative stress with clinically used drugs can improve long-term disease outcome [17]. In a general convulsive seizure, the patient experiences hypoxia. Ischemia activates the cell system, for example, by increasing the production of mature red blood cells and releasing them into the peripheral blood. Thus, we hypothesized that the increase of RDW may be associated with mortality in patients with severe epilepsy. The present study aimed to determine the effectiveness of RDW as a predictor of in-hospital mortality in patients admitted to the ICU with epilepsy as the primary diagnosis.

Materials and methods

Data source

The eICU-Collaborative Research Database (CRD) is a large multi-center critical care database made available by the MIT Laboratory for Computational Physiology in partnership with Philips Healthcare, which holds data associated with over 200,000 patient stays across the USA in 2014 and 2015. These data are de-identified, and include vital signs, diagnoses, measures of disease severity, treatment information, and care plan documents. This study used the current version of the database, v 2.0 (17 May 2018), and used PostgreSQL v. 11.2 (The PostgreSQL Global Development Group, https://www.postgresql.org/) for data querying and management.

One of the authors was authorized to access data from eICU-CRD for medical research. Since this study was a retrospective analysis of a de-identified database from a third party that had been approved by its institutional review board (IRB), approval from our IRB was exempted.

Study population

We included patients admitted to the ICU with a primary diagnosis of seizures. The inclusion criteria for participants were as follows:

1. Primary diagnosis of 'seizures (primary—no structural brain disease)' upon admission to the ICU
2. Aged 18–88 years
3. First admission to the ICU in the database
4. ICU stay of more than 4 h
5. Availability of all critical information (RDW within the first 24 h in the ICU, APACHE IV scores, mortality, and sex)

Altogether 1568 incidents of seizure from 219 ICUs in 152 hospitals fulfilled the inclusion criteria (Fig. 1).

Clinical factors

The demographic characteristics, the initial vital signs upon ICU admission, RDW values, other laboratory results, severity-of-disease scores (Acute Physiology and Chronic Health Evaluation IV [APACHE IV]), mortality, cause of admission, and length of ICU stay were collected from the database. APACHE was the score designed to assess the severity of illness as well as the prognosis in the ICU, and APACHE IV is the latest version, which includes physiologic measurements, age, and chronic health status [18]. Furthermore, we calculated the Charlson Comorbidity Index (CCI) based on the ICD diagnostic code of the electronic medical record database to assess the effect of comorbidities on the patient's condition. The CCI is a useful tool to measure comorbid disease status and predict mortality by classifying or weighting 19 comorbid conditions [19], and it has been validated in various large populations [20, 21]. Only the first result was included in the study, when the patient had multiple laboratory result records within 24 h of admission to the ICU.

Statistical analysis

Categorical variables were presented in terms of frequency and percentage, while continuous variables were presented in terms of the median and interquartile range (IQR). All continuous data with non-normal distribution were compared using the Kruskal–Wallis H test. Fisher's exact test was used to compare categorical variables. The optimal cut-off point of RDW grouping was determined by the Youden index of the ROC curve. The Youden index is a frequently used summary measure of the ROC curve that determined the optimal cutoff points, emphasizes both sensitivity and specificity. The values range from 0 to 1.

The percentage of missing data was less than 12.5% in all covariates, and multiple imputations using the chained equations method were used. The net reclassification index (NRI) was used to assess whether red blood cell distribution width offers additional predictive information over classical severity-of-disease scores. Variables that were significant in univariate analyses were included in binary logistic multivariate regression analyses and significance was set at 0.10.

To avoid collinearity among several covariates, only variables which did not contribute to APACHE IV scores were included in the multivariate model. Other significance tests were performed two-sided, and a p-value < 0.05 was considered statistically significant. All analyses were conducted using R 3.6.1 package with the mice, pROC, PredictABEL, and ggplot2 packages (R Core Team, https://www.R-project.org/).

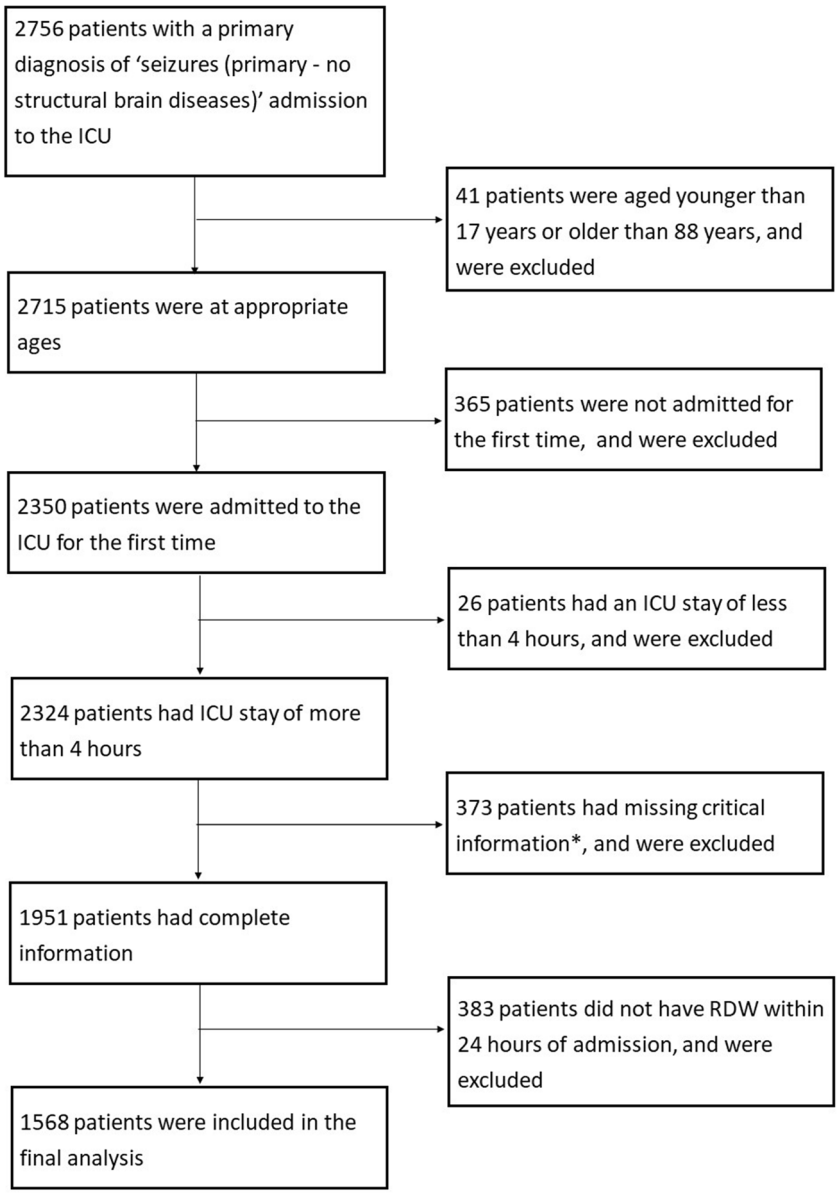

Fig. 1 Data collection flowchart. *ICU*, intensive care unit; *RDW*, red blood cell distribution width. *Critical information = RDW within the first 24 h in the ICU, APACHE IV scores, mortality and sex

Results

We identified 1568 patients treated for seizure in the ICU over 2 years. The demographics and baseline characteristics are shown in Table 1. The participants were categorized into two groups according to the Youden index in the ROC curve (normal: RDW ≤ 14.65%, high: RDW > 14.65%; Fig. 2). The in-hospital mortality rate of ICU patients with a diagnosis of seizure was 46/1568 (2.93%). The group with a higher RDW also had a higher in-hospital mortality rate (6.44% vs 1.15%, $p < 0.05$).

ROC curve analysis showed an RDW cut-off value of 14.65 (73.9% sensitivity and 67.5% specificity) to discriminate the risk of in-hospital mortality (Fig. 2). The area under the curve (AUC) was > 0.6 for both curves. The AUC of RDW was 0.7225 (95% CI: 0.6523–0.7926, $p < 0.05$), which was slightly less than the AUC of APACHE IV scores. The AUC of APACHE IV scores was 0.8109 (95%CI: 0.7525–0.8693, $p < 0.05$). To determine whether the RDW provided extra prognostic value over the APACHE IV score, NRI was used for further data analysis. Compared with the prediction of in-hospital mortality using APACHE IV alone, the continuous NRI with the RDW variable was 0.3507 (95%CI: 0.0584–0.6431, $p < 0.05$).

The univariate analysis revealed that many factors were associated with in-hospital mortality, such as albumin, APACHE IV score, and high RDW. The factors with a p value less than 0.1 were included in the multivariate regression analysis. Some factors which were included as a component in the APACHE IV score were not included in the multivariate regression analysis to avoid the effect of multicollinearity, such as BUN, hemoglobin, and

Table 1 Baseline characteristics of the study population

	Overall	Survivor	Non-survivor	*p*
Number	1568	1522	46	
Age (year), (median [IQR])	54.00 [39.00, 65.00]	54.00 [38.00,65.00]	70.00 [52.50,77.75]	<0.001
Female (%)	732 (46.7)	707 (46.5)	25 (54.3)	0.364
Ethnicity (%) *				0.47
African American	258 (16.6)	253 (16.8)	5 (10.9)	
Asian	21 (1.4)	21 (1.4)	0 (0.0)	
Caucasian	1147 (73.9)	1109 (73.6)	38 (82.6)	
Hispanic	53 (3.4)	53 (3.5)	0 (0.0)	
Native American	14 (0.9)	13 (0.9)	1 (2.2)	
Other/unknown	60 (3.9)	58 (3.8)	2 (4.3)	
APACHE IV score (median [IQR])	49.00 [35.00, 68.00]	48.00 [35.00,67.00]	83.50[59.25,97.00]	<0.001
BMI (kg/m^2), (median [IQR])	25.92 [22.61, 31.13]	25.90 [22.64, 31.12]	26.62 [22.17, 32.34]	0.95
MAP (mmHg), (median [IQR])	93.70 [82.00, 106.70]	94.00 [82.30, 106.70]	83.50 [72.33, 99.35]	0.007
Heart rate (BPM) (median [IQR])	89.00 [77.00, 101.00]	89.00 [76.00, 101.00]	94.00 [82.00, 111.50]	0.132
RDW (%), (median [IQR])	13.90 [13.10, 15.20]	13.90 [13.10, 15.20]	15.15 [14.48, 17.20]	<0.001
MCH (pg), (median [IQR])	30.40 [28.90, 31.85]	30.40 [28.90, 31.90]	30.60 [29.00, 31.70]	0.936
MCHC (g/dL), (median [IQR])	33.40 [32.60, 34.20]	33.40 [32.60, 34.20]	32.90 [31.90, 34.00]	0.013
Albumin (g/dL), (median [IQR])	3.40 [2.90, 3.70]	3.40 [2.98, 3.80]	2.60 [2.30, 2.90]	<0.001
BUN (mg/dL), (median [IQR])	12.00 [8.00, 18.00]	12.00 [8.00, 17.00]	17.00 [13.00, 30.00]	<0.001
Creatinine (mg/dl), (median [IQR])	0.80 [0.64, 1.10]	0.80 [0.63, 1.10]	0.92 [0.78, 1.47]	0.008
Glucose (mg/dL), (median [IQR])	109.00 [94.00, 138.00]	109.00 [94.00,137.00]	109.00 [94.00, 147.00]	0.935
WBC (*10^9/L), (median [IQR])	9.20 [7.00, 12.60]	9.20 [7.00, 12.60]	9.20 [6.92, 13.38]	0.742
Hematocrit (%), (median [IQR])	36.50 [32.80, 40.00]	36.70 [32.90, 40.00]	34.25 [28.75, 38.02]	0.003
Hemoglobin (g/dL), (median [IQR])	12.20 [10.90, 13.40]	12.25 [10.90, 13.40]	11.25 [9.20, 12.47]	0.001
Platelet (*10^9/L), (median [IQR])	199.00 [152.00, 250.00]	199.00 [152.00,250.00]	210.00 [153.00, 255.50]	0.738
Potassium (mmol/L) (median [IQR])	3.80 [3.40, 4.10]	3.80 [3.40, 4.10]	3.85 [3.60, 4.18]	0.331
Sodium (mmol/L) (median [IQR])	139.00 [136.00,141.00]	139.00 [136.00,141.00]	138.00 [135.00, 141.75]	0.757
INR (median [IQR])	1.10 [1.00, 1.30]	1.10 [1.00, 1.30]	1.30 [1.10, 1.63]	0.069
Lactate (mmol/L) (median [IQR])	1.60 [1.00, 2.40]	1.60 [1.00, 2.40]	2.00 [1.50, 2.40]	0.113
GOT (u/L) (median [IQR])	24.00 [16.00, 40.00]	24.00 [16.00, 40.00]	30.00 [17.00, 49.00]	0.509
GPT (u/L) (median [IQR])	28.00 [19.00, 51.00]	27.00 [19.00, 50.00]	32.00 [20.00, 71.00]	0.228
Bilirubin (mg/dl), (median [IQR])	0.50 [0.40, 0.90]	0.50 [0.30, 0.90]	0.60 [0.40, 0.97]	0.331
CCI (median [IQR])	2.00 [0.00, 4.00]	2.00 [0.00, 4.00]	5.00 [2.00, 7.00]	<0.001

ICU, intensive care unit; *APACHE*, Acute Physiology and Chronic Health Evaluation; *BMI*, body mass index; *MAP*, mean arterial pressure; *BPM*, beats per minute; *RDW*, red blood cell distribution width; *MCH*, mean corpuscular hemoglobin; *MCHC*, mean corpuscular hemoglobin concentration; *BUN*, blood urea nitrogen; *WBC*, white blood cell; *INR*, international normalized ratio; *GOT*, glutamic-oxaloacetic transaminase; *GPT*, gamma-glutamyl transferase; *CCI*, Charlson Comorbidity Index. *The discrepancy between the total number of patients and the actual number is due to missing data

albumin. Using the APACHE IV score, high RDW was found to be a predictor of in-hospital mortality. A high RDW was significantly correlated with in-hospital mortality after adjusting for potential confounders with an odds ratio (OR) of 3.999 (95% CI: 2.059–8.258) (Table 2 and Fig. 3).

APACHE, Acute Physiology and Chronic Health Evaluation; *MCHC*, mean corpuscular hemoglobin concentration; *RDW*, red blood cell distribution width; *CI*, confidence interval

Kaplan-Meier survival estimates were used to compare the ICU length of stay between surviving patients with RDW > 14.65% and those with RDW ≤ 14.65%. The results showed that the length of stay in the ICU of patients with RDW > 14.65% was significantly increased compared to that of patients with RDW≤ 14.65% (log-rank test, $p < 0.0001$; Fig. 4).

Hours of ICU stay in surviving patients were compared between patients with RDW ≤ 14.65% and > 14.65% by using the log-rank test.

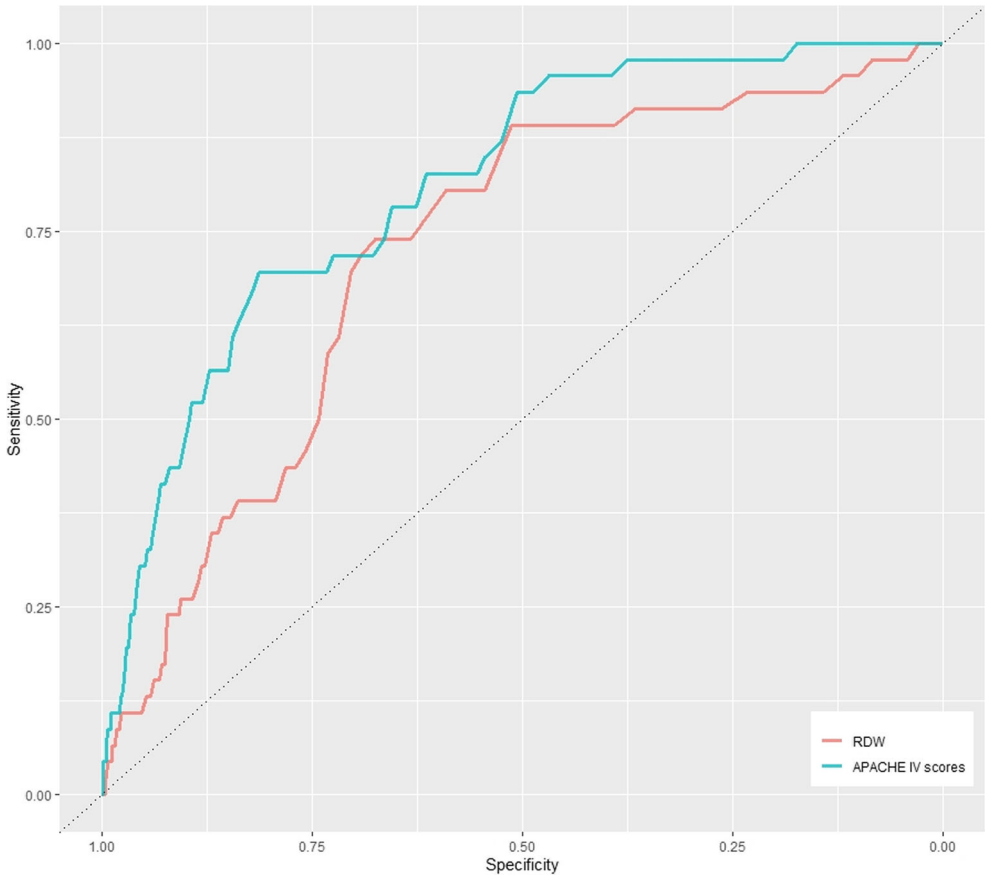

Fig. 2 ROC curves of red cell distribution width and classic severity-of-disease scores for hospital mortality

Discussion

This retrospective study demonstrated that RDW was an independent predictor of in-hospital mortality in patients with seizures admitted to ICU. Patients with RDW > 14.65% had a longer stay in the ICU. RDW played a significant predictive role, although its AUCs were slightly less than that of the APACHE IV score, which is a precisely designed, widely used scoring system.

RDW has been found to be a prognostic factor of mortality for many serious diseases, such as acute ischemic stroke, heart failure, acute respiratory distress syndrome, acute kidney injury, hip fracture, and cancer [22–27], even in a cohort of clinically diverse, multi-condition hospitalized patients [28].

Table 2 Predictors of hospital mortality

Predictor	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p* value	Adjusted OR	95% CI	*p* value
Female	1.372	0.762–2.473	0.292			
APACHE IV score	1.047	1.034–1.059	<0.001	1.041	1.028–1.053	<0.001
MCHC	0.708	0.578–0.866	<0.001	0.914	0.735–1.1352	0.414
Chloride	1.005	0.964–1.048	0.814			
Platelet	1.000	0.997–1.003	0.974			
Potassium	1.542	1.062–2.239	0.023	1.195	0.834–1.713	0.331
RDW group (high)	5.896	3.027–11.486	<0.001	3.513	1.699–7.266	<0.001
BMI	1.002	0.973–1.031	0.913			
CCI	1.281	1.173–1.401	<0.001	1.076	0.964–1.202	0.193

APACHE, Acute Physiology and Chronic Health Evaluation; *MCHC*, mean corpuscular hemoglobin concentration; *RDW*, red blood cell distribution width; *BMI*, body mass index; *CCI*, Charlson Comorbidity Index; *CI*, confidence interval; *OR*, odds ratio

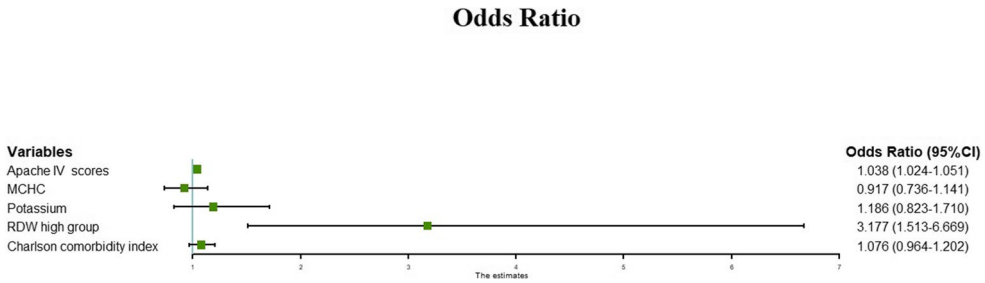

Fig. 3 The odds ratio and 95% CI of various variables in the multivariate analysis

Moreover RDW was associated with mortality risk in hospitalized adults infected with SARS-CoV-2[10]. Some scholars have studied the relationship between RDW and differentiation of febrile seizure types, but their conclusions are inconsistent [29, 30].

To our knowledge, this is the first study to show the relationship between RDW and mortality in patients with seizures. Epilepsy is a serious neurological disease, and early risk stratification of patients with seizures admitted to ICU is crucial to improve their outcomes. At present, the "epidemiology-based mortality score in status epilepticus" (EMSE) is commonly used to predict in-hospital mortality of patients with status epilepticus (SE) [31]. However, EMSE does not apply to all patients with seizures admitted to the ICU, and the mortality rate varies greatly depending on the type of epileptic seizure. This is a challenge for doctors. The stratification of the EMSE score makes the calculation complicated and is not conducive to clinical use. In contrast, RDW is a simple, widely used, inexpensive predictor that is easy to re-administer, and this makes identification of patient trends easy.

It is still unknown why RDW is associated with in-hospital mortality in patients with severe epilepsy, but there are several possible explanations for its underlying biological mechanism. First, and most important, is inflammation [32, 33]. In different studies, RDW has been found to be closely associated with different markers of acute phase inflammation, such as interleukin-6, soluble tumor necrosis factor (TNF) receptor I and soluble TNF receptor II, C-reactive protein (CRP), and prealbumin concentrations. These indicators have correlations with biomarkers of ineffective erythropoiesis, such as serum iron, ferritin, and soluble transferrin receptor levels, which cause a larger RDW [34]. Moreover, the association between RDW and highly-sensitive CRP level and erythrocyte sedimentation rate is independent of numerous confounders [35]. Seizure induces the production of the inflammatory cytokine IL-6 [12, 13], which may cause an increase in RDW through the inflammatory response. Some drugs or interventions which target several inflammatory pathways may display anti-epileptogenesis [36]. Second, oxidative stress is also an important physiological mechanism. Epileptic seizures can induce oxidative stress [37, 38]. In suboptimal responses to oxidative stress, large immature red blood cells are released and this leads to an increase in RDW [39]. Oxidative stress can contribute to status epilepticus-associated mortality, and survival can be improved by pharmacological targeting of oxidative stress [40]. Furthermore, oxidative stress is associated with all causes of mortality among elderly people [41]. Third, patients with high RDW are more likely to have abnormal coagulation, which may lead to more severe brain damage and ultimately to poorer outcomes [42].

This retrospective study had several limitations. It lacked information on the etiology and type of epileptic seizures.

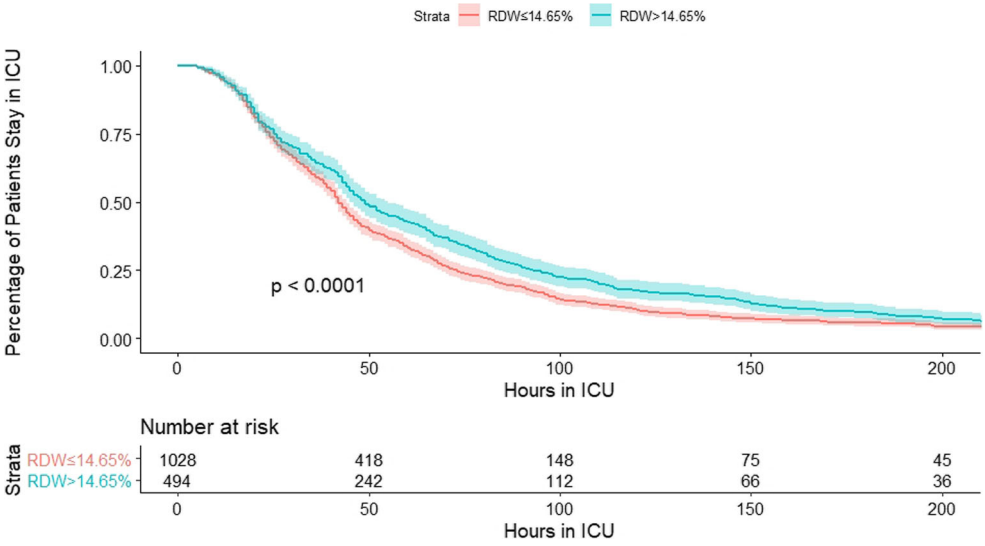

Fig. 4 Kaplan-Meier survival estimates for patient with seizures by RDW

These factors also may have contributed to the poor prognosis. Because all patients included in the database were from the USA, it is uncertain whether our results are applicable to other countries. However, our study population included participants with a variety of ethnic backgrounds. In addition, some factors known to increase RDW, such as the deficiency of iron, vitamin B-12, and folate, were not considered in the reanalysis. However, this study did include a large sample size which reduces the impact of these limitations.

Conclusions

We concluded that RDW can predict in-hospital mortality in patients with seizures admitted to the ICU, and that RDW provides extra prognostic value compared to the APACHE IV score. The RDW is also related to a longer ICU stay. Our conclusions should be confirmed by further prospective cohort studies.

Data availability Due to the license of the eICU-CRD database, we cannot supply the data file directly. Source code for all analyses can be found at https://github.com/shaou77/rdw_seizures upon publication of this paper.

Code availability This study used the current version of the database, v. 2.0 (17 May 2018), and used PostgreSQL v. 11.2 (The PostgreSQL Global Development Group, https://www.postgresql.org/) for data querying and management.

Declarations

Ethical approval None.

Consent for publication All authors read and approved the manuscript.

Conflict of interest None.

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