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The Prognostic Value of Red Cell Distribution Width in Critically Ill Cerebral Infarction Patients: A Retrospective Cohort Study

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Abstract: *Objective:* Red blood cell distribution width (RDW) has been utilized as a prognostic indicator for mortality risk assessment in cardiovascular and cerebrovascular patients. Nevertheless, the prognostic significance of RDW in critically ill patients with cerebral infarction is yet to be investigated. The objective of this study is to examine the association between RDW and the risk of all-cause mortality in cerebral infarction patients admitted to the intensive care unit (ICU). *Method:* A retrospective cohort study was conducted using the Medical Information Mart for Intensive Care IV 2.2 (MIMIC-IV) intensive care dataset for data analysis. The main results were the all-cause mortality rates at 3 and 12 months of follow-up. Cumulative curves were plotted using the Kaplan-Meier method, and Cox proportional hazards analysis was used to examine the relationship between RDW and mortality rates in critically ill cerebral infarction patients. *Results:* The findings indicate that RDW serves as a significant prognostic factor for mortality risk in critically ill stroke patients, specifically at the 3 and 12-month follow-up periods. The observed correlation between increasing RDW levels and higher mortality rates among cerebral infarction patients further supports the potential utility of RDW as a predictive indicator. *Conclusion:* RDW emerges as an independent predictor of mortality risk during the 3 and 12-month follow-up periods for critically ill patients with cerebral infarction.

Keywords: Red blood cell distribution width; Cerebral infarction; Intensive care unit; All-cause mortality rate; MIMIC-IV database

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1. Introduction

Based on the findings of the Global Burden of Disease (GBD) study in 2016, the projected global lifetime risk of stroke among individuals aged 25 and older was 24.9%, representing a notable rise from 1990, which was 22.8%. Moreover, ischemic stroke constituted the majority, accounting for 87% of all cases. Over time, the mortality rate of stroke patients escalated [1,2]. Consequently, ischemic stroke (AIS) persists as the primary cause

of permanent disability and the third leading cause of mortality worldwide [3], imposing significant societal and economic burdens. The provision of suitable and prompt care is widely acknowledged as the cornerstone of managing and nursing patients with cerebral infarction [4]. Timely and efficient care substantially diminishes patient mortality rates [5]. Therefore, there is a need to explore non-invasive serum biomarkers capable of predicting the mortality risk in early-stage critically ill cerebral infarction patients.

The red blood cell volume distribution width (RDW) serves as an indicator of the heterogeneity of red blood cell volume in peripheral blood. Within clinical practice, the standard deviation of RDW not only signifies alterations in red blood cell volume but also serves as an indicator of red blood cell homeostasis [6]. Recent research has demonstrated that RDW may serve as a novel prognostic indicator, potentially reflecting inflammation, oxidative stress, and cellular senescence [7,8]. Numerous studies have demonstrated that elevated RDW constitutes an autonomous risk factor for numerous critically ill individuals, particularly those afflicted with cardiovascular and cerebrovascular ailments [9-12]. Furthermore, heightened RDW levels exhibit some correlation with cerebral infarction and can act as an indicator of the presence of the disease and the mortality risk of patients suffering from this disease [13-15].

RDW holds potential as a pragmatic indicator for prognosticating all-cause mortality in critically ill cerebral infarction patients. The clinical data of patients afflicted with cerebral infarction in the American Intensive Care Medicine Information Market IV (MIMIC-IV version) database were meticulously analyzed to ascertain the correlation between RDW levels and the occurrence of all-cause mortality in cerebral infarction patients. The primary objective of this investigation was to ascertain the clinical significance of RDW in predicting the risk of mortality in critically ill patients with cerebral infarction, thereby facilitating clinical interventions.

2. Methods

2.1. Database

This study employed a restricted observational study utilizing data from the MIMIC-IV database spanning the years 2008 to 2019. The MIMIC-IV database, established and maintained by the Computational Physiology Laboratory at the Massachusetts Institute of Technology (https://physionet.org/content/mimiciv/2.2/), is a large and publicly accessible resource. Access to the database was granted to the first author of this study upon completion of the Collaborative Institution Training Program (CITI) course. To ensure patient privacy, all identifiable personal information within the data has been anonymized, thereby obviating the need to seek individual patient consent.

2.2. Subjects

The inclusion criteria encompass the following: (1) The diagnostic criteria for cerebral infarction among subjects hospitalized for this condition were determined based on the International Classification of Diseases 10th Revision (ICD-10) code 163 and the International Classification of Diseases 9th Revision (ICD-9) code (433.01, 433.11, 433.81, 433.91, 434.01, 434.11, 434.91); (2) the subjects selected were > 18 years old; (3) the assessment of RDW was conducted within 24 hours after admission to the intensive care unit (ICU); (4) this analysis is limited to the initial ICU hospitalization period of patients who have experienced multiple ICU stays.

2.3. Data collection

Structured Query Language (SQL) was utilized in conjunction with PostgreSQL (version 9.6) to extract the basic information of the subjects, such as gender, age, body weight, and severity on admission (measured by

sequential organ failure assessment [SOFA] score, simplified acute physiological score II [SAPS II] score, Glasgow Coma Scale [GCS] score), as well as comorbidities and laboratory variables within the initial 24 hours of ICU admission from the MIMIC-IV database. The presence of hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, heart failure, atrial fibrillation, sepsis, malignant tumors, and renal failure was determined based on ICD codes, specifically ICD-10 and ICD-9. The follow-up period spanned from the date of admission to the date of death.

Most of the variables included in the analysis had missing values. In instances where less than 10% of the required values were missing, multiple interpolation techniques were employed to estimate the missing values. However, variables with a missing rate surpassing 10% were transformed into dummy variables within the model to mitigate potential biases stemming from direct missing values. All screening variables included in the analysis exhibit missing values below 20%.

2.4. Primary outcome

The primary outcome for this study was all-cause mortality at 3 months and 12 months of follow-up. The mortality rate of the discharged patients was acquired from the US Social Security Death Index.

2.5. Data analysis

The variables in our study were categorized into two types: continuous variables and categorical variables. Continuous variables were presented as either mean ± standard deviation or median interquartile range, and their normality was assessed using the Kolmogorov-Smirnov test. To compare continuous variables, the Wilcoxon Mann-Whitney test and Student t-test were employed. On the other hand, categorical variables were described in terms of frequency and percentage, and the distinctions between groups were examined using either Pearson's chi-square test or Fisher's exact test.

We transformed the continuous variables of age and weight into categorical variables, specifically age groups (≤ 70 years, > 70 years) and weight groups (≤ 80kg, > 80kg). The survival rate was assessed using Kaplan Meier analysis, and the differences between RDW groups were evaluated using the logarithmic rank test. The association between RDW and outcomes was examined using the Cox proportional hazards model, with hazard ratios (HR) and 95% confidence intervals (CI) representing the strength of the association. Additionally, we calculated the variance inflation factor (VIF) to assess multicollinearity between variables, excluding univariate factors with a VIF greater than 5. The *P-value* for the trend was determined by treating the quartile level as an ordinal variable. RDW was included in the model as a categorical variable and divided into four groups based on the interquartile range of RDW on the first day of ICU hospitalization: Q1 (RDW ≤ 13.1), Q2 (13.1< RDW ≤ 13.8), Q3 (13.8 < RDW ≤ 15.1), Q4 (15.1 > RDW), with Q1 serving as the reference group. Three models were created: Model 1, which was unadjusted; Model 2, in which age, weight, and SOFA score were adjusted; and Model 3, in which age, weight, race, SOFA score, tumor, renal failure, and sepsis were adjusted.

Furthermore, we conducted additional stratification in our analysis based on age (< 70 years and ≥ 70 years), weight (< 80 kg and ≥ 80 kg), renal failure, and sepsis to assess the reliability of RDW as a prognostic indicator for the primary outcomes. The likelihood ratio tests were employed to examine the interaction between the variables used for stratification in RDW. The statistical analysis was performed using Stata and R software, and a *P-value* of less than 0.05 for bilateral detection was considered statistically significant.

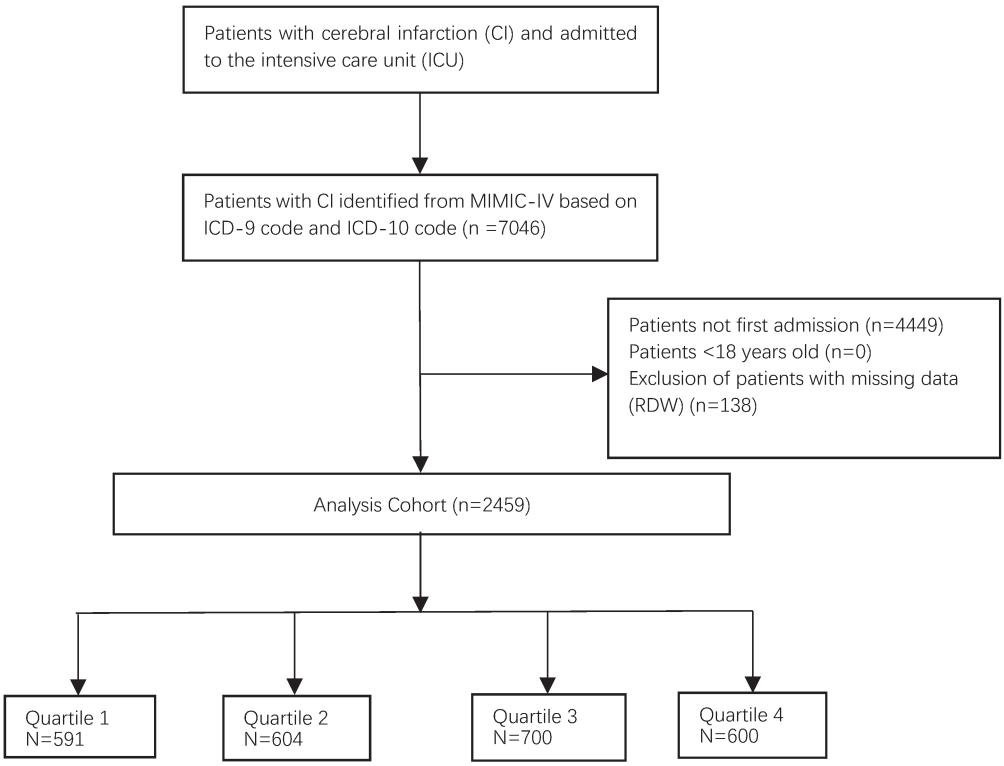

Figure 1. Flow chart of patient selection and division

3. Results

The study cohort comprised a total of 2495 patients who were categorized into four groups based on the interquartile range of RDW on the first day of ICU hospitalization: Q1 (RDW ≤ 13.1), Q2 (13.1 < RDW ≤ 13.8), Q3 (13.8 < RDW ≤ 15.1), and Q4 (15.1 > RDW). The patient screening process diagram is depicted in **Figure 1**. The mean age of the included patients was 69.44 years, with 1224 males (49.06%) and 1271 females (50.94%). The average RDW value for all the selected patients was 14.42.

3.1. Baseline characteristics

The baseline data, categorized based on the RDW quartile spacing, are presented in **Table 1**. Higher RDW values are associated with increased severity of disease score at admission, higher prevalence of sepsis, heart failure, malignant tumor, diabetes, COPD, atrial fibrillation, and renal failure. Elevated levels of sodium, potassium, chlorine, creatinine, and prothrombin were observed, while levels of red blood cells, platelets, and hemoglobin decreased. Furthermore, as RDW values increase, the hospitalization time of patients gradually lengthens, as demonstrated in **Table 1**.

Table 1. Baseline characteristics of stroke patients based on the interquartile distribution of RDW

Characteristic	**Overall (*n* = 2495)**	**Q1 (*n* = 591)**	**Q2 (*n* = 604)**	**Q3 (*n* = 700)**	**Q4 (*n* = 600)**	***P-value***
Age (years)	69.44 (59.07, 82.17)	64.91 (53.87,77.55)	69.47 (59.84,81.67)	72.22 (62.77,84.41)	70.64 (61.40,82.88)	< 0.001
Weight (kg)	79.71 (64.3,91)	81.39 (66.7,94.4)	80 (65.7,91)	79.83 (64.05,91.45)	77.60 (62.3,88.5)	0.001

Table 1 (Continue)

Characteristic	Overall (*n* = 2495)	Q1 (*n* = 591)	Q2 (*n* = 604)	Q3 (*n* = 700)	Q4 (*n* = 600)	*P-value*
Male, *n* (%)	1224 (49.06)	326 (55.16)	298 (49.34)	351 (50.14)	249 (41.5)	< 0.001
Race, *n* (%)					0.011	
Others	955 (38.28)	222 (37.56)	223 (36.92)	247 (35.29)	263 (43.83)	
White	1540 (61.72)	369 (62.44)	381 (63.08)	453 (64.71)	337 (56.17)	
SAPSII score	35.02 (26,42)	29.7 (21,36)	32.63 (25,39)	36.5 (27,43)	40.94 (31,50)	< 0.001
SOFA score	3.93 (2,5)	2.81 (1,4)	3.49 (1.5,5)	4.03 (2,5)	5.34 (3,7)	< 0.001
GCS score	12.68 (11,15)	13.08 (12,15)	12.74 (11,15)	12.49 (11.15)	12.46 (11,14)	0.017
Laboratory tests						
sodium (Eq/L)	144.72 (141,147)	144.22 (140,146)	144.3 (141,147)	144.85 (141,148)	145.5 (141,149)	< 0.001
Potassium (Eq/L)	4.78 (4.2,5.1)	4.6 (4.2,4.8)	4.67 (4.2,4.9)	4.84 (4.3,5.15)	4.98 (4.3,5.4)	< 0.001
Chloride (mEq/L)	109.76 (105,113)	109.15 (105,112)	109.19 (105,112)	110.06 (105,114)	110.58 (106,115)	< 0.001
Creatinine (mg/dL)	1.19 (0.7,1.2)	0.92 (0.7,1)	1.03 (0.7,1.1)	1.2 (0.7,1.3)	1.58 (0.8,1.1)	< 0.001
BUN (mg/dL)	21.76 (13,25)	16.26 (11,19)	18.86 (12,22)	16.48 (13,26.5)	28.69 (15,35)	< 0.001
Hemoglobin (g/dL)	11.73 (10.2,13.3)	12.77 (11.7,14)	12.35 (11.1,13.7)	11.72 (10.3,13.3)	10.11 (8.6,11.4)	< 0.001
WBC (K/uL)	7.87 (5.8,9.3)	7.6 (5.8,8.8)	8.04 (6.1,9.2)	7.89 (5.75,9.4)	7.93 (5.5,9.8)	0.055
RBC (K/uL)	4.13 (3.66,4.6)	4.30 (3.9,4.71)	4.25 (3.81,4.67)	4.16 (3.69,4.62)	3.83 (3.31,4.27)	< 0.001
PLT (tK/uL)	176.95 (126,223)	183.10 (142,221)	180.97 (135,214)	173.06 (118,222)	170.96 (101.5,233)	0.001
Glucose, mg/dL	99.14 (83,108)	98.86 (86,107)	101.53 (86,108)	100.84 (84,111.5)	95 (78,104)	< 0.001
PT	12.58 (11.3,13.2)	12.05 (11.1,12.58)	12.31 (11.2,13)	12.77 (11.55,13.3)	13.13 (11.5,13.9)	< 0.001
Comorbidities, *n* (%)						
Sepsis	1035 (41.48)	178 (30.12)	221 (36.59)	311 (44.43)	325 (54.17)	< 0.001
Hypertension	1358 (54.43)	338 (57.19)	369 (61.09)	392 (56)	259 (43.17)	< 0.001
Heart failure	559 (22.4)	61 (10.32)	104 (17.22)	168 (24)	226 (37.67)	< 0.001
Malignant neoplasms	167 (6.79)	24 (4.06)	35 (5.79)	43 (6.14)	65 (10.83)	< 0.001

Table 1 (Continue)

Characteristic	Overall (n = 2495)	Q1 (n = 591)	Q2 (n = 604)	Q3 (n = 700)	Q4 (n = 600)	*P-value*
Diabetes	712 (28.54)	124 (20.98)	165 (27.32)	220 (31.43)	203 (33.83)	< 0.001
CHD	274 (10.98)	53 (8.97)	67 (11.09)	75 (10.71)	79 (13.17)	0.142
COPD	114 (4.57)	19 (3.21)	21 (3.48)	32 (4.57)	42 (7)	0.007
AF	947 (39.04)	160 (27.07)	219 (36.26)	297 (42.43)	271 (45.17)	< 0.001
RF	594 (23.81)	84 (14.21)	93 (15.4)	189 (27)	228 (38)	< 0.001
Event, *n* (%)						
los_icu	5.60 (1.67,6.82)	5.42 (1.63,6.62)	5.24 (1.67,6)	5.87 (1.66,7.23)	5.81 (1.71,7.04)	0.2567
los_hospital	12.36 (4.6,15.87)	10.45 (3.88,13.26)	10.72 (4.22,13.68)	12.73 (4.87,17.12)	15.46 (5.18,19.68)	< 0.001

Abbreviation: sequential organ failure assessment, SOFA; simplified acute physiological score II, SAPS II; Glasgow Coma Scale, GCS; blood urea nitrogen, BUN; white blood cell, WBC; red blood cell, RBC; prothrombin time, PT; Platelet count, PLT; coronary heart disease, CHD; Chronic obstructive pulmonary disease, COPD; atrial fibrillation, AF; renal failure, RF; length of stay in ICU, los_icu; length of stay in hospital, los_hospital.

3.2. Incidence rate of all-cause mortality among different groups

The Kaplan-Meier survival analysis curve was utilized to evaluate the incidence of all-cause mortality in each group, based on RDW interquartile grouping, as depicted in **Figure 2**. The groups were categorized as follows: Q1 (RDW ≤ 13.1), Q2 (13.1 < RDW ≤ 13.8), Q3 (13.8 < RDW ≤ 15.1), and Q4 (RDW > 15.1). **Figure 2** displays the Kaplan-Meier survival analysis curves for the primary outcome rates of each group. Notably, significant disparities in mortality rates were observed among the groups during the 3-month follow-up (log-rank $P < 0.001$, **Figure 2[a]**). Furthermore, significant findings were also noted during the 12-month follow-up (log-rank $P < 0.001$, **Figure 2[b]**).

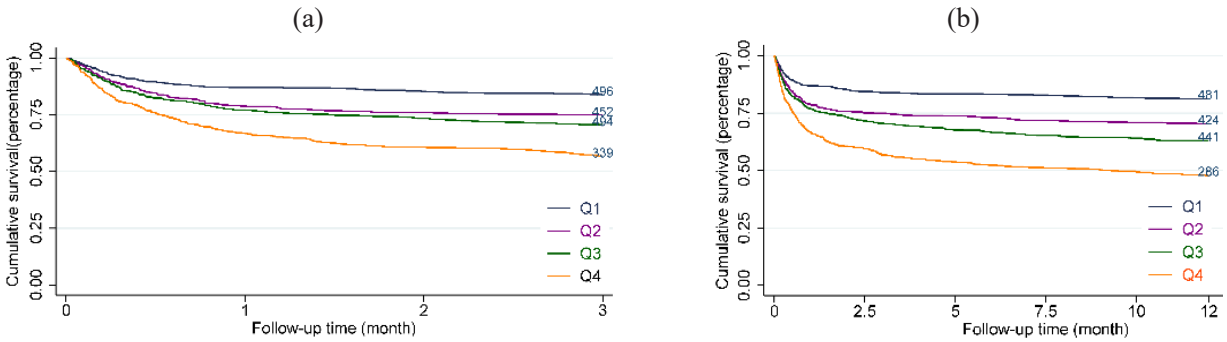

Figure 2. Kaplan-Meier curves showing the cumulative probability of all-cause mortality at (a) 3 months and (b) 12 months

3.3. All-cause mortality rate of RDW and cerebral infarction patients

During the 12-month follow-up period of patients diagnosed with cerebral infarction, a total of 863 individuals passed away, with 714 of them passing away within the initial 3 months of follow-up. Utilizing

Cox proportional hazards analysis, it was determined that a higher level of RDW correlated with an elevated mortality rate among patients afflicted with cerebral infarction within the 3-month follow-up. Employing RDW interquartile spacing for grouping purposes, with the lowest RDW interquartile level serving as the reference group, Model 1 (Q1 vs. Q2: HR 1.64 [95%CI 1.27–2.12], $P < 0.001$; Q3: HR 1.97 [95%CI 1.54–2.51], $P < 0.001$; Q4: HR 3.14 [95%CI 2.48–3.98], $P < 0.001$; P for trend < 0.001) demonstrated a significant upward trend in the mortality rate of stroke patients as the RDW value increased. After adjusting age, weight, and SOFA score in Model 2, the results indicated a significant association between increasing RDW values and mortality in cerebral infarction patients (Q1 vs. Q2: HR 1.39 [95% CI 1.08–1.80], $P = 0.011$; Q3: HR 1.46 [95% CI 1.14–1.87], $P = 0.002$; Q4: HR 1.91 [95% CI 1.50–2.45], $P < 0.001$; P for trend < 0.001). This association remains significant even after further adjusting for important confounding factors in Model 3 (Q1 vs. Q2: HR 1.35 [95% CI 1.04–1.74], $P = 0.023$; Q3: HR 1.37 [95% CI 1.07–1.75], $P = 0.014$; Q4: HR 1.65 [95% CI 1.29–2.12], $P < 0.001$; P for trend < 0.001). Similar findings were also observed in the Cox proportional risk model (**Table 2**) for the 12-month mortality rate among patients with cerebral infarction. Notably, there was a significant positive correlation between the mortality rate and the RDW value, indicating an upward trend.

Table 2. Cox proportional hazard ratios (HR) for all-cause mortality

Categories	Model 1			Model 2			Model 3		
	HR (95%)	*P-value*	*P* for trend	HR (95%)	*P-value*	*P* for trend	HR (95%)	*P-value*	*P* for trend
3-month mortality									
Q1 ($N = 591$)			< 0.001			<0.001			< 0.001
Q2 ($N = 604$)	1.64 (1.27–2.12)	< 0.001		1.39 (1.08–1.80)	0.011		1.35 (1.04-1.74)	0.023	
Q3 ($N = 700$)	1.97 (1.54–2.51)	< 0.001		1.46 (1.14–1.87)	0.002		1.37 (1.07-1.75)	0.014	
Q4 ($N = 600$)	3.14 (2.48–3.98)	< 0.001		1.91 (1.50–2.45)	< 0.001		1.65 (1.29-2.12)	<0.001	
12-month mortality									
Q1 ($N = 591$)			< 0.001			< 0.001			< 0.001
Q2 ($N = 604$)	1.71 (1.35–2.17)	< 0.001		1.46 (1.15–1.86)	0.002		1.41 (1.11-1.79)	0.005	
Q3 ($N = 700$)	2.20 (1.78–2.75)	< 0.001		1.66 (1.32–2.07)	< 0.001		1.55 (1.23-1.94)	<0.001	
Q4 ($N = 600$)	3.45 (2.78–4.29)	< 0.001		2.18 (1.74–2.73)	< 0.001		1.88 (1.50-2.36)	<0.001	

Note: RDW quartiles were used to categorize patients into four groups: Q1 (RDW $\leqslant$ 13.1), Q2 (13.1 $<$ RDW $\leqslant$ 13.8), Q3 (13.8 $<$ RDW $\leqslant$ 15.1), and Q4 (RDW $>$ 15.1). Model 1 was unadjusted; Model 2, in which age, weight, and SOFA score were adjusted; and Model 3, in which age, weight, race, SOFA score, tumor, renal failure, and sepsis were adjusted.

3.4. Subgroup analyses

The consistency of conclusions across various patient subgroups was analyzed, including age, weight, sepsis, and renal failure. During the 3-month follow-up period assessing mortality risk, the results indicated a significant interaction between sepsis and renal failure ($P > 0.05$). Subgroup analysis revealed a significant association between RDW and increased mortality rates in cerebral infarction patients, considering age ($\leq$ 70 years, > 70 years), body weight ($\leq$ 80kg, > 80kg), and patients without sepsis or renal failure (all $P < 0.05$). Additionally, consistent findings were observed in the assessment of mortality risk at the 12-month follow-

up period. Notably, in the subgroup analysis of sepsis patients, a significant correlation was identified between elevated RDW levels and increased mortality rates among cerebral infarction patients, as illustrated in **Table 3**.

Table 3. Subgroup analyses

Subgroups	*N*	Model 1	Model 2			Model 3		
			HR	*P-value*	*P* for trend	HR	*P-value*	*P* for trend
3-month mortality								
Age (years)					0.172			0.123
≥ 70	1303	ref	1.18 (1.07–1.29)	< 0.001		1.12 (1.03–1.23)		
< 70	1192	ref	1.28 (1.13–1.46)	< 0.001		1.21 (1.06–1.37)		
Weight (kg)					0.46			0.87
≥ 80	1078	ref	1.22 (1.07–1.38)	0.002		1.18 (1.04–1.34)		
< 80	1417	ref	1.20 (1.10–1.32)	< 0.001		1.14 (1.04–1.25)		
Sepsis					< 0.001			<0.001
Yes	1035	ref		0.002		1.05 (0.95,1.15)		
No	1460	ref		< 0.001		1.29 (1.15,1.44)		
RF					0.01			0.021
Yes	594	ref	1.07 (0.95–1.21)	0.262		1.06 (0.94–1.20)		
No	1901	ref	1.25 (1.14–1.37)	< 0.001		1.21 (1.10–1.33)		
12-month mortality								
Age (years)					0.055			0.033
≥ 70	1303	ref	1.22 (1.12–1.32)	< 0.001		1.16 (1.07–1.26)		
< 70	1192	ref	1.37 (1.22–1.53)	< 0.001		1.29 (1.15–1.44)		
Weight (kg)					0.39			0.585
≥ 80	1078	ref	1.25(1.11–1.40)	< 0.001		1.19 (1.06–1.35)		
< 80	1417	ref	1.27 (1.17–1.38)	< 0.001		1.21 (1.12–1.32)		
Sepsis					< 0.001			< 0.001
Yes	1035	ref	1.12 (1.03–1.23)	0.01		1.09 (1.0–1.20)		
No	1460	ref	1.39 (1.26–1.55)	< 0.001		1.33 (1.20–1.48)		
RF					0.008			0.013
Yes	594	ref	1.11 (0.99–1.25)	0.136		1.10 (0.98–1.24)		
No	1901	ref	1.31 (1.21–1.43)	< 0.001		1.26 (1.16–1.37)		

4. Discussion

To the best of our knowledge, our study has provided the first evidence of a correlation between RDW and the risk of critical cerebral infarction death in patients admitted to the ICU. Our findings indicate that, even after adjusting for potential confounding factors, higher levels of RDW (upper quartile) are significantly associated with an increased risk of mortality in patients with cerebral infarction, as evidenced by a 3-month mortality rate (HR 1.65 [95%CI 1.29–2.12], $P < 0.001$) and a 12-month mortality rate (HR 1.88 [95%CI 1.50–2.36], $P < 0.001$).

Heterologous erythrocytosis is recognized as an autonomous risk factor for ischemic stroke. Tonelli *et al.*'s investigation in 2008 elucidated the plausible correlation between RDW and cardiovascular and cerebrovascular ailments, including stroke. Their findings demonstrated a significant association between elevated RDW levels and an augmented risk of stroke [13]. Similarly, Jostein et al. identified a positive correlation between increased RDW and the likelihood of stroke in the general populace, with a mere 1% rise in RDW resulting in a 13% escalation in stroke risk [14]. In their study, Gianni *et al.* discovered that elevated levels of RDW can offer valuable prognostic insights for patients with acute cerebral infarction following thrombolysis. Specifically, patients with RDW levels of 14.5% exhibited a heightened risk of 1-year mortality and reduced survival [15]. Similar research demonstrated that RDW serves as a promising independent biomarker for short-term and long-term prognosis in ICU patients [16,17]ÿÿÿþ, thereby enhancing the risk stratification of Simplified Acute Physiology Score (SAPS) and improving the accuracy of mortality predictions within the ICU setting [17]. In contrast to prior investigations concerning the significance of RDW in individuals afflicted with cerebral infarction, this particular study possesses distinct merits. Foremost among these is its substantial sample size (n = 2459), rendering it the largest-sample study hitherto published pertaining to the correlation between RDW and the peril of fatality in critically ill cerebral infarction patients. Additionally, the prognostic value of RDW in predicting long-term mortality risk among critically ill patients with cerebral infarction admitted to the ICU was investigated in this study. Lastly, our findings indicate that the assessment of varying RDW levels upon admission to the ICU exhibits noteworthy disparities in prognosticating the long-term mortality risk.

RDW serves as an indicator for assessing the variability and heterogeneity of red blood cell size in the peripheral blood [18]. The primary causative factors contributing to the augmentation of heterozygous red blood cells are oxidative stress and the aging process of red blood cell progenitors [6,19,20]. Extensive research has demonstrated that oxidative stress intensifies the fragility of red blood cells, diminishes their maturation rate, curtails their lifespan [21], and consequently leads to an elevation in RDW generation [22]. The alterations observed in the morphology and distribution of red blood cells are plausibly attributable to the influence of oxidative stress. The insufficient intrinsic antioxidant potential of reactive oxygen species (ROS) and the inability to maintain endogenous redox balance are key factors in the fundamental pathological progression of cerebral infarction injury [23,24]. Oxidative stress in cerebral infarction can result in neuronal apoptosis, activation of inflammatory signaling pathways, and impairment of the blood-brain barrier, all of which contribute to neurodegeneration and cell death [25-28]. This phenomenon may serve as the underlying pathological mechanism for the potential of RDW to predict the risk of mortality in stroke cases.

In the subgroup analyses, it was found that an increased RDW was significantly associated with the risk of cerebral infarction in patients of certain age (≤ 70 years, > 70 years), weight (≤ 80kg, > 80kg), non-renal failure, and non-sepsis. Furthermore, there was an interaction observed between RDW and renal failure as well as sepsis (P < 0.05). In the context of subgroup analysis, it has been observed that elevated RDW levels are significantly linked to an increased risk of all-cause mortality in individuals without renal failure or sepsis. Conversely, in patients with renal failure or sepsis, there appears to be no association between RDW levels and the risk of all-cause mortality. This phenomenon appears to be in contradiction with prior scholarly investigations. Earlier research has demonstrated a strong correlation between elevated levels of RWD and the likelihood of mortality in adult patients with sepsis, thus indicating its potential as a biomarker for sepsis prediction [29,30]. Furthermore, increased levels of RDW have been found to be independently linked to a worsened prognosis in individuals suffering from acute kidney failure [31,32]. This outcome can be elucidated by a reverse causation: individuals previously diagnosed with these ailments are likely to be undergoing treatment or may have adopted healthier behaviors; Consequently, despite their elevated all-cause mortality rate, their analytical parameters may have

been effectively managed.

The primary strength of our study lies in its ability to demonstrate the significant prognostic value of elevated RDW in predicting mortality among critically ill stroke patients admitted to the ICU within the US cohort. Nevertheless, it is important to acknowledge the limitations of our research. Firstly, our study is limited by its retrospective design and the inherent presence of data bias associated with a single center analysis. Furthermore, our findings only establish an association between RDW and the risk of death in stroke patients instead of a causal relationship. Ultimately, the investigation solely concentrated on the influence of initial RDW on the risk of mortality. Nevertheless, given the dynamic nature of patients' RDW levels throughout their hospital stay, additional research is imperative to substantiate the potential of RDW fluctuations in prognosticating mortality.

5. Conclusion

The findings of our study suggest that RDW serves as a prognostic marker for mortality in ICU patients with cerebral infarction at both 12 and 3 months of follow-up. In this particular population characterized by a heightened risk of mortality, RDW exhibits potential as a valuable tool for risk stratification and management. However, additional research is needed to validate these outcomes and elucidate the underlying mechanism linking RDW to mortality in cerebral infarction patients.

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Disclosure statement

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