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# Red Blood Cell Distribution Width Is Associated with All-Cause Mortality in Critically Ill Patients with Cardiogenic Shock

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** There is no previously published epidemiological study exploring the association between red blood cell distribution width (RDW) and mortality in patients with cardiogenic shock (CS). The aim of this study was to examine the association between RDW and the risk of all-cause mortality in these patients.

**Material/Methods:** We analyzed clinical data from the MIMIC-III V1.4 database. We collected data on each patient's demographic parameters, vital signs, laboratory parameters, vital signs, comorbidities, and scoring systems on ICU admission. Cox proportional hazards models were used to assess the association between RDW levels and the 30-day, 90-day, and 365-day mortality in patients with CS.

**Results:** There were 1131 patients meeting inclusion criteria in our study. In multivariate analysis, following adjustment for age, sex, and ethnicity, higher RDW in tertiles and quintiles were all associated with increased risk of 30-day, 90-day, and 365-day all-cause mortality. Furthermore, after adjusting for more relevant confounders, RDW remained a significant predictor of risk of 30-day, 90-day, and 365-day mortality (tertile 3 versus tertile 1: HR, 95% CI: 1.66, 1.19–2.31; 1.73, 1.28–2.33; 1.80, 1.38–2.34). Similarly significant robust associations were found in RDW levels stratified by quintiles.

**Conclusions:** Higher RDW is associated with increased risk of all-cause mortality in critically ill patients with CS.

**MeSH Keywords:** Erythrocyte Indices • Intensive Care Units • Mortality • Shock, Cardiogenic

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## Background

Cardiogenic shock (CS) is defined as a state of critical macro- and microcirculatory dysfunction caused by heart pump failure [1]. There are numerous causes of CS, including acute myocardial infarction (AMI), severe myocarditis, and end-stage dilated cardiomyopathy. Of these, AMI is the most frequent cause [2]. Despite advances in treatment, CS carries a high mortality rate, approaching 50% [3–6]. Considering the poor prognosis of CS in critical illness, several risk factors have been found to be associated with mortality in CS, such as age, systolic blood pressure (SBP), creatinine clearance, and number of vasopressors used [7-9]. Nevertheless, these risk factors are not widely used in clinical practice.

Red blood cell distribution width (RDW) is an indicator of change in erythrocyte volume, and it is generally used for differential diagnosis of anemia. However, recent studies indicated that RDW is a powerful independent predictor of adverse outcomes. It has been found to be related to mortality in patients with coronary artery disease [10], heart failure [11,12], pulmonary hypertension [13], ischemic stroke [14], cancer [15], and acute kidney injury [16]. Previous research has shown that inflammatory cytokines, including Interleukin-6, -7, -8, and -10, are predictors of prognosis in acute myocardial infarction complicated by CS [17]. Proinflammatory cytokines have been shown to inhibit erythrocyte maturation, partly reflecting an increase in RDW [18,19]. Thus, this may be a potential pathophysiological connection between high RDW and CS. However, to the best of our knowledge, there is no previously published epidemiological study exploring the association between RDW and mortality in patients with CS. Therefore, the aim of the present study was to examine the relationship between RDW and risk of all-cause mortality in these patients.

## Material and Methods

### Data source

Similar to our previous studies, we followed the methods of Wang et al. in this study [20–22]. The clinical database we extracted is Multiparameter Intelligent Monitoring in Intensive Care III version 1.4 (MIMIC-III v1.4), which is an freely available critical care database, including de-identified health data associated with ~40 000 critical care patients at Beth Israel Deaconess Medical Center (Boston, USA) from 2001 to 2012 [23]. This database contains demographics such as patient age, sex, ethnicity, and laboratory values such as bicarbonate, creatinine, and platelet; physiological data such as height, weight, temperature and respiratory rate; microbiology data; and survival to and after hospital discharge. We obtained survival data from the Social Security database. The project was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA) and was granted a waiver of informed consent.

### Population selection criteria

Adult patients (≥18 years) with CS using International Classification of Diseases (ICD)-9 code (code=785.51) were included, and these patients had to be hospitalized in the intensive care unit (ICU) at first admission for more than 2 days. Patients with hematologic diseases such as leukemia and myelodysplastic syndrome were excluded from our study.

### Data extraction

We collected ICU admission data such as demographic parameters, vital signs, laboratory parameters, vital signs, comorbidities, scoring systems. The comorbidities included coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation (AFIB), stroke, renal disease, liver disease, malignancy, pneumonia, respiratory failure, and chronic obstructive pulmonary disease (COPD) [24]. We extracted laboratory parameters, including RDW, bicarbonate, anion gap, creatinine, blood urea nitrogen (BUN), chloride, white blood cell (WBC), hematocrit, hemoglobin, platelet, glucose, sodium, potassium, lactate, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT).

Sequential organ failure assessment (SOFA) scores [25] and simplified acute physiology scores II (SAPSII) [26] were obtained at the time of ICU admission. The physiological measurements and clinical information used an equation established in recommendations and accepted formulae. The other extracted data included demographic parameters (age, sex, and ethnicity), vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), respiratory rate, temperature, heart rate, and SPO2), renal replacement therapy, vasopressor use, and length of stay in the ICU. Survival information on vital status was obtained from Social Security Death Index records. The endpoints of our study were 30-day, 90-day, and 365-day all-cause mortality from the date of ICU admission.

### Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or medians and interquartile range (IQR). Categorical data are summarized as number or percentage. We used the chi-square test or one-way ANOVA to test for differences in categorical or continuous factors between different categories of RDW. We used Cox proportional hazards models to assess the association between RDW levels and the 30-day, 90-day,





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and 365-day mortality, and the results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

To determine whether the RDW was independently associated with endpoints, we used 2 multivariate models. In model I, covariates were only adjusted for age, sex, and ethnicity. In model II, we further adjusted for age, sex, ethnicity, respiratory rate, heart rate, temperature, SPO2, SBP, DBP, glucose, anion gap, hemoglobin, ethnicity, bicarbonate, creatinine, chloride, glucose, potassium, APTT, INR, PT, BUN, WBC, CHF, renal disease, liver disease, malignancy, respiratory failure, pneumonia, stroke, vasopressor use, renal replacement therapy, SOFA, and SAPSII. We selected these confounders based on a change in effect estimate of more than 10% [27]. Subgroup analysis of the associations between RDW and 90-day all-cause mortality was performed. All probability values are 2-sided, and values below 0.05 were considered statistically significant. EmpowerStats (*http://www.empowerstats.cn/*, X&Y solutions, Inc, Boston, MA) and R (*http://www.R-project.org*) were used for all statistical analysis.

## Results

### Subject characteristics

There were 1131 ICU admissions meeting inclusion criteria, and 311 patients were excluded in our study. The demographic characteristics of these patients stratified by RDW tertiles are displayed in Table 1. A total of 365 patients were in the low-RDW group (RDW <13.8%), 385 patients were in the mid-RDW group (13.8% to 15.2%), and 381 patients were in the high-RDW group (RDW ≥15.2%). Of these patients, there were 662 (58.5%) men and 771 (68.2%) were white. Patients with high-RDW levels were more likely to be elderly and to report comorbidities of CHF, AFIB, renal disease, liver disease, malignancy, and respiratory failure, and had higher values of anion gap, creatinine, BUN, PT, INR, SOFA, SAPSII, and mortality.

### Association between RDW and mortality

In multivariate analysis, we stratified RDW levels by tertiles and quintiles to assess whether RDW was associated with 30-day, 90-day, and 365-day all-cause mortality in patients with CS (Table 2). In model I, higher RDW in tertiles and quintiles all were associated with increased risk of all-cause mortality after adjustments for age, sex and ethnicity. In model II, after adjusting for age, sex, ethnicity, heart rate, respiratory rate, SPO2, temperature, SBP, DBP, glucose, anion gap, hemoglobin, ethnicity, bicarbonate, creatinine, chloride, glucose, potassium, APTT, INR, PT, BUN, WBC, CHF, renal disease, stroke, malignancy, liver disease, respiratory failure, pneumonia, vasopressor use, renal replacement therapy, SOFA, and SAPSII, high-RDW levels remained a significant predictor of these clinical endpoints compared with the low-RDW levels (tertile 3 versus tertile 1: HR, 95% CI: 1.66, 1.19–2.31; 1.73, 1.28–2.33; 1.80, 1.38–2.34). A similar trend was observed in RDW levels stratified by quintiles; the HRs and 95% CIs (quintile 5 versus quintile 1) were 1.93, 1.25–2.97; 2.04, 1.38–3.03; 2.09, 1.48–2.94, respectively.

### Subgroup analyses

The association between RDW levels and 90-day all-cause mortality was similar in most strata (Table 3), and there were no interactions ($P$=0.0966–0.9514). Significant interactions were observed only for glucose ($P$=0.0287) and hematocrit ($P$=0.0409). Patients with a higher RDW exhibited significantly higher mortality at glucose <149 mg/dl (HR 3.22, 95% CI 2.16–4.81) than at ≥149 mg/dl (HR 1.52, 95% CI 1.11–2.09). A similar trend was observed in patients with hematocrit ≥30% (HR 2.59, 95% CI 1.84–3.65).

## Discussion

The results of our study indicate that higher RDW levels are associated with increased risk of 30-day, 90-day, and 365-day all-cause mortality in critically ill patients with CS. Furthermore, after adjusting for age, sex, ethnicity, and other confounding factors, higher RDW remained a significant predictor of all-cause mortality. To the best of our knowledge, there has been no previous study on the relation between RDW and mortality of CS.

Previous studies have demonstrated a strong relationship between RDW and the severity and prognosis of patients with cardiovascular diseases, including heart failure [28], myocardial infarction [29], coronary atherosclerosis [30], atrial fibrillation [31], and primary hypertension [32]. Although several risk factors appear to contribute to poor outcomes in critical illness [33], the correlation between RDW and these diseases is even stronger than those of traditional risk factors. We previously analyzed the MIMIC-III to study the biomarkers related to the prognosis of a variety of diseases [20,22]. In the present study, we also found that RDW was a significant predictor of poor prognosis in CS patients after adjusting for clinical and laboratory confounding factors. In subgroup analysis, there was no interaction in most strata, and the stratified analysis of interactions indicated that high RDW remained a predictor of mortality. Consequently, the result of our study was a crucial discovery that supplements the findings of previous studies.

CS is a complex pathophysiological process that has been summarized in previous studies [34,35]. In brief, ischemia causes a severe decline in myocardial contractility, inducing a vicious





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**Table 1.** Characteristics of the study patients according to RDW levels.

| Characteristics | RDW (%) | | | P value |
|---|---|---|---|---|
| | <13.8 (n=365) | ≥13.8, <15.2 (n=385) | ≥15.2 (n=381) | |
| Age, years | 68.2±14.5 | 71.3±14.4 | 72.0±12.7 | <0.001 |
| Sex, n (%) | | | | 0.656 |
| Female | 157 (43.0) | 153 (39.7) | 159 (41.7) | |
| Male | 208 (57.0) | 232 (60.3) | 222 (58.3) | |
| Ethnicity, n (%) | | | | 0.029 |
| White | 235 (64.4) | 274 (71.2) | 262 (68.8) | |
| Black | 26 (7.1) | 16 (4.2) | 34 (8.9) | |
| Other | 104 (28.5) | 95 (24.7) | 85 (22.3) | |
| SBP, mmHg | 106.0±14.8 | 107.7±16.3 | 106.4±15.5 | 0.319 |
| DBP, mmHg | 58.0±9.7 | 57.8±11.2 | 56.9±9.7 | 0.287 |
| MBP, mmHg | 75.8±9.6 | 74.9±10.7 | 72.9±10.1 | <0.001 |
| Heart rate, beats/minute | 87.6±16.0 | 88.2±17.6 | 87.9±17.0 | 0.901 |
| Respiratory rate, beats/minute | 19.4±3.9 | 19.7±4.1 | 20.3±4.0 | 0.010 |
| Temperature, °C | 36.8±0.9 | 36.8±0.8 | 36.6±0.9 | <0.001 |
| SPO2,% | 96.9±3.6 | 96.5±4.3 | 95.8±6.6 | 0.012 |
| Comorbidities, n (%) | | | | |
| Congestive heart failure | 99 (27.1) | 138 (35.8) | 160 (42.0) | <0.001 |
| Coronary artery disease | 235 (64.4) | 215 (55.8) | 189 (49.6) | <0.001 |
| Atrial fibrillation | 134 (36.7) | 158 (41.0) | 190 (49.9) | 0.001 |
| Hypertension | 161 (44.1) | 183 (47.5) | 226 (59.3) | <0.001 |
| Stroke | 21 (5.8) | 24 (6.2) | 13 (3.4) | 0.168 |
| Renal disease | 27 (7.4) | 62 (16.1) | 113 (29.7) | <0.001 |
| Liver disease | 4 (1.1) | 11 (2.9) | 19 (5.0) | 0.008 |
| Pneumonia | 103 (28.2) | 119 (30.9) | 109 (28.6) | 0.679 |
| Malignancy | 22 (6.0) | 26 (6.8) | 58 (15.2) | <0.001 |
| Respiratory failure | 136 (37.3) | 168 (43.6) | 172 (45.1) | 0.070 |
| COPD | 17 (4.7) | 24 (6.2) | 45 (11.8) | 0.022 |
| Laboratory parameters | | | | |
| Bicarbonate, mg/dl | 19.9±4.8 | 20.2±5.0 | 19.9±5.9 | 0.689 |
| Anion gap, mmol/l | 14.2±3.5 | 14.3±3.7 | 15.4±4.6 | <0.001 |
| Creatinine, mEq/l | 1.2±1.6 | 1.5±1.3 | 2.2±1.9 | <0.001 |
| Chloride, mmol/l | 101.7±5.9 | 102.3±6.5 | 100.9±6.0 | 0.006 |
| Glucose, mg/dl | 171.3±60.1 | 159.1±53.0 | 155.5±53.4 | <0.001 |
| Hematocrit, % | 31.1±6.9 | 30.3±6.8 | 28.9±6.3 | <0.001 |





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**Table 1 continued.** Characteristics of the study patients according to RDW levels.

| Characteristics | RDW (%) | | | P value |
|---|---|---|---|---|
| | <13.8 (n=365) | ≥13.8, <15.2 (n=385) | ≥15.2 (n=381) | |
| Hemoglobin, g/dl | 10.7±2.4 | 10.3±2.3 | 9.5±2.0 | <0.001 |
| Platelet, $10^9$/l | 198.6±85.7 | 195.9±93.4 | 197.8±109.8 | 0.925 |
| Sodium, mmol/l | 135.3±5.1 | 135.5±4.8 | 135.2±5.1 | 0.764 |
| Potassium, mmol/l | 3.6±0.6 | 3.8±0.6 | 3.9±0.6 | <0.001 |
| BUN, mg/dl | 24.0±15.8 | 29.5±19.2 | 41.1±25.4 | <0.001 |
| WBC, $10^9$/l | 11.8±4.4 | 11.5±5.3 | 11.0±6.1 | 0.134 |
| Lactate, mmol/l | 2.4±2.0 | 1.9±1.7 | 2.0±1.6 | <0.001 |
| PT, second | 14.3±3.2 | 15.3±5.2 | 17.6±8.2 | <0.001 |
| APTT, second | 38.9±22.0 | 39.9±23.7 | 38.6±20.4 | 0.684 |
| INR | 1.3±0.4 | 1.5±0.8 | 1.8±1.6 | <0.001 |
| Scoring systems | | | | |
| SOFA | 5.7±3.5 | 6.6±3.7 | 7.3±3.8 | <0.001 |
| SAPSII | 41.9±15.1 | 45.9±15.8 | 48.3±15.7 | <0.001 |
| Renal replacement therapy, n (%) | 29 (7.9) | 48 (12.5) | 67 (17.6) | <0.001 |
| Vasopressor use, n (%) | 274 (75.1) | 288 (74.8) | 270 (70.9) | 0.340 |
| ICU LOS, day | 8.2±13.6 | 7.6±9.1 | 7.2±8.6 | 0.412 |
| 30-day mortality, n (%) | 88 (24.1) | 125 (32.5) | 155 (40.7) | <0.001 |
| 90-day mortality, n (%) | 104 (28.5) | 152 (39.5) | 195 (51.2) | <0.001 |
| 365-day mortality, n (%) | 131 (35.9) | 182 (47.3) | 239 (62.7) | <0.001 |

SBP – systolic blood pressure; DBP – diastolic blood pressure; MBP – mean blood pressure; COPD – chronic obstructive pulmonary disease; BUN – blood urea nitrogen; WBC – white blood cell; PT – prothrombin time; APTT – activated partial thromboplastin time; INR – international normalized ratio; SOFA – sequential organ failure assessment; SAPSII – simplified acute physiology score II; ICU – Intensive Care Unit; LOS – length of stay.

cycle of decreased cardiac index and decreased blood pressure, thereby impairing cardiac dysfunction and further promoting coronary ischemia [1]. CS entails not just the loss of left ventricular function, it is also a disorder of the entire circulatory system [36]. Systemic inflammation with capillary leakage and microcirculatory disorder lead to the vicious cycle of CS [17]. Pierce et al. [18] found that inflammatory cytokines affected iron metabolism and inhibited bone marrow, which caused an increase of RDW. Additionally, CS can cause activation of the renin-angiotensin system, which leads to an increase in RDW with erythropoiesis [37]. Furthermore, a study showed that when the RDW level was more than 14%, the deformability of red blood cells in microvessels decreased [38]. This results in a decrease in microvascular perfusion, leading to microcirculatory disorders [39,40]. Therefore, it appears that excessively high RDW levels can predict poor outcomes in CS patients.

Our study has some limitations. First, this was a single-center, retrospective study, and was therefore subject to selection bias. Second, we extracted RDW in patients only upon admission to the ICU; we could not obtain it before ICU stay, and it was also unclear whether they were measured by multiple detection machines. These factors can influence the reliability of the results. Third, we did not know patients' iron metabolism status or whether erythropoietin use affected RDW values. Furthermore, the database contains a few inaccurate data elements; therefore, multi-center prospective studies are needed to confirm these findings.





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**Table 2.** HRs (95% CIs) for all-cause mortality across groups of RDW levels.

| RDW,% | Non-adjusted | | Model I | | Model II | |
|---|---|---|---|---|---|---|
| | HR (95%CIs) | P value | HR (95%CIs) | P value | HR (95%CIs) | P value |
| **30-day all-cause mortality** | | | | | | |
| Tertiles | | | | | | |
| <13.8 | 1.0 (ref) | | 1.0 (ref) | | 1.0 (ref) | |
| ≥13.8, <15.2 | 1.42 (1.08, 1.87) | 0.0117 | 1.35 (1.02, 1.77) | 0.0330 | 1.37 (1.01, 1.87) | 0.0457 |
| ≥15.2 | 1.87 (1.44, 2.43) | <0.0001 | 1.81 (1.39, 2.35) | <0.0001 | 1.66 (1.19, 2.31) | 0.0026 |
| *P* trend | <0.0001 | | <0.0001 | | 0.0049 | |
| Quintiles | | | | | | |
| <13.3 | 1.0 (ref) | | 1.0 (ref) | | 1.0 (ref) | |
| ≥13.3, <14.0 | 1.38 (0.94, 2.04) | 0.1017 | 1.40 (0.95, 2.07) | 0.0891 | 1.38 (0.91, 2.08) | 0.1246 |
| ≥14.0, <14.8 | 1.68 (1.16, 2.44) | 0.0064 | 1.58 (1.08, 2.30) | 0.0170 | 1.77 (1.17, 2.68) | 0.0068 |
| ≥14.8, <16.3 | 1.92 (1.33, 2.78) | 0.0005 | 1.82 (1.26, 2.64) | 0.0015 | 1.54 (1.00, 2.37) | 0.0485 |
| ≥16.3 | 2.36 (1.65, 3.37) | <0.0001 | 2.34 (1.64, 3.34) | <0.0001 | 1.93 (1.25, 2.97) | 0.0028 |
| *P* trend | <0.0001 | | <0.0001 | | 0.0120 | |
| **90-day all-cause mortality** | | | | | | |
| Tertiles | | | | | | |
| <13.8 | 1.0 (ref) | | 1.0 (ref) | | 1.0 (ref) | |
| ≥13.8, <15.2 | 1.49 (1.16, 1.91) | 0.0018 | 1.41 (1.10, 1.81) | 0.0074 | 1.41 (1.07, 1.88) | 0.0162 |
| ≥15.2 | 2.07 (1.63, 2.62) | <0.0001 | 2.00 (1.58, 2.55) | <0.0001 | 1.73 (1.28, 2.33) | 0.0003 |
| *P* trend | <0.0001 | | <0.0001 | | 0.0008 | |
| Quintiles | | | | | | |
| <13.3 | 1.0 (ref) | | 1.0 (ref) | | 1.0 (ref) | |
| ≥13.3, <14.0 | 1.56 (1.09, 2.23) | 0.0158 | 1.56 (1.09, 2.24) | 0.0149 | 1.48 (1.01, 2.17) | 0.0420 |
| ≥14.0, <14.8 | 1.91 (1.35, 2.70) | 0.0003 | 1.78 (1.25, 2.52) | 0.0012 | 1.81 (1.23, 2.65) | 0.0025 |
| ≥14.8, <16.3 | 2.25 (1.60, 3.17) | <0.0001 | 2.13 (1.51, 3.00) | <0.0001 | 1.72 (1.16, 2.54) | 0.0064 |
| ≥16.3 | 2.72 (1.95, 3.80) | <0.0001 | 2.71 (1.94, 3.78) | <0.0001 | 2.04 (1.38, 3.03) | 0.0004 |
| *P* trend | <0.0001 | | <0.0001 | | 0.0032 | |
| **365-day all-cause mortality** | | | | | | |
| Tertiles | | | | | | |
| <13.8 | 1.0 (ref) | | 1.0 (ref) | | 1.0 (ref) | |
| ≥13.8, <15.2 | 1.44 (1.15, 1.81) | 0.0013 | 1.37 (1.09, 1.71) | 0.0067 | 1.37 (1.07, 1.77) | 0.0138 |
| ≥15.2 | 2.13 (1.72, 2.64) | <0.0001 | 2.06 (1.66, 2.55) | <0.0001 | 1.80 (1.38, 2.34) | <0.0001 |
| *P* trend | <0.0001 | | <0.0001 | | <0.0001 | |
| Quintiles | | | | | | |
| <13.3 | 1.0 (ref) | | 1.0 (ref) | | 1.0 (ref) | |





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**Table 2 continued.** HRs (95% CIs) for all-cause mortality across groups of RDW levels.

| RDW,% | Non-adjusted | | Model I | | Model II | |
|---|---|---|---|---|---|---|
| | HR (95%CIs) | P value | HR (95%CIs) | P value | HR (95%CIs) | P value |
| ≥13.3, <14.0 | 1.45 (1.05, 2.00) | 0.0236 | 1.45 (1.05, 2.00) | 0.0236 | 1.35 (0.96, 1.89) | 0.0847 |
| ≥14.0, <14.8 | 1.81 (1.33, 2.47) | 0.0002 | 1.69 (1.24, 2.31) | 0.0009 | 1.68 (1.20, 2.36) | 0.0024 |
| ≥14.8, <16.3 | 2.28 (1.69, 3.09) | <0.0001 | 2.12 (1.56, 2.88) | <0.0001 | 1.77 (1.26, 2.49) | 0.0010 |
| ≥16.3 | 2.82 (2.10, 3.78) | <0.0001 | 2.80 (2.08, 3.76) | <0.0001 | 2.09 (1.48, 2.94) | <0.0001 |
| *P* trend | <0.0001 | | <0.0001 | | <0.0001 | |

HR – hazard ratio; CI – confidence interval. Models were derived from Cox proportional hazards regression models. Non-adjusted model adjusted for: none. Adjust I model adjusted for: age, ethnicity and sex. Adjust II model adjusted for: age, sex, ethnicity, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, SPO2, glucose, anion gap, hemoglobin, ethnicity, bicarbonate, creatinine, chloride, glucose, potassium, APTT, INR, PT, BUN, WBC, congestive heart failure, renal disease, liver disease, stroke, malignancy, respiratory failure, pneumonia, vasopressor use, renal replacement therapy, SOFA, SAPSII.

**Table 3.** Subgroup analysis of the associations between RDW and 90-day all-cause mortality.

| | No. of patients | RDW (%) | | | *P* for interaction |
|---|---|---|---|---|---|
| | | <13.8 | ≥13.8, <15.2 | ≥15.2 | |
| CHF | | | | | 0.4534 |
| No | 734 | 1.0 (ref) | 1.36 (1.02, 1.83) | 1.84 (1.38, 2.45) | |
| Yes | 397 | 1.0 (ref) | 1.68 (1.01, 2.79) | 2.70 (1.68, 4.34) | |
| AFIB | | | | | 0.3746 |
| No | 649 | 1.0 (ref) | 1.70 (1.22, 2.37) | 2.16 (1.56, 3.01) | |
| Yes | 482 | 1.0 (ref) | 1.09 (0.74, 1.59) | 1.82 (1.28, 2.58) | |
| CAD | | | | | 0.8231 |
| No | 492 | 1.0 (ref) | 1.30 (0.87, 1.94) | 1.88 (1.29, 2.74) | |
| Yes | 639 | 1.0 (ref) | 1.41 (1.01, 1.95) | 1.96 (1.42, 2.70) | |
| Stroke | | | | | 0.7774 |
| No | 1073 | 1.0 (ref) | 1.40 (1.09, 1.81) | 1.94 (1.52, 2.48) | |
| Yes | 58 | 1.0 (ref) | 1.46 (0.33, 6.47) | 3.31 (0.78, 14.14) | |
| Malignancy | | | | | 0.3202 |
| No | 1025 | 1.0 (ref) | 1.35 (1.04, 1.76) | 1.89 (1.47, 2.44) | |
| Yes | 106 | 1.0 (ref) | 2.44 (0.92, 6.48) | 3.06 (1.27, 7.41) | |
| Liver disease | | | | | 0.5414 |
| No | 1097 | 1.0 (ref) | 1.42 (1.10, 1.83) | 2.01 (1.57, 2.56) | |
| Yes | 34 | 1.0 (ref) | 0.51 (0.09, 2.92) | 0.84 (0.18, 3.95) | |
| Renal disease | | | | | 0.8962 |
| No | 929 | 1.0 (ref) | 1.41 (1.07, 1.84) | 2.04 (1.57, 2.66) | |
| Yes | 202 | 1.0 (ref) | 1.19 (0.59, 2.38) | 1.50 (0.78, 2.88) | |
| Respiratory failure | | | | | 0.3841 |
| No | 655 | 1.0 (ref) | 1.49 (1.05, 2.10) | 2.07 (1.48, 2.88) | |
| Yes | 476 | 1.0 (ref) | 1.23 (0.85, 1.78) | 1.83 (1.29, 2.59) | |





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**Table 3 continued.** Subgroup analysis of the associations between RDW and 90-day all-cause mortality.

| | No. of patients | RDW (%) | | | *P* for interaction |
|---|---|---|---|---|---|
| | | <13.8 | ≥13.8, <15.2 | ≥15.2 | |
| Pneumonia | | | | | 0.8373 |
| No | 800 | 1.0 (ref) | 1.29 (0.95, 1.75) | 1.86 (1.40, 2.47) | |
| Yes | 331 | 1.0 (ref) | 1.74 (1.10, 2.74) | 2.50 (1.60, 3.90) | |
| COPD | | | | | 0.3124 |
| No | 1045 | 1.0 (ref) | 1.32 (1.07, 1.88) | 1.95 (1.48, 2.50) | |
| Yes | 86 | 1.0 (ref) | 0.53 (0.09, 15.37) | 0.41 (0.11, 3.26) | |
| Vasopressor use | | | | | 0.6860 |
| No | 299 | 1.0 (ref) | 0.99 (0.50, 1.95) | 2.01 (1.11, 3.64) | |
| Yes | 832 | 1.0 (ref) | 1.52 (1.16, 1.99) | 2.07 (1.59, 2.69) | |
| Sodium, mmol/l | | | | | 0.5786 |
| <136 | 540 | 1.0 (ref) | 1.21 (0.85, 1.71) | 1.97 (1.43, 2.73) | |
| ≥136 | 591 | 1.0 (ref) | 1.63 (1.13, 2.36) | 2.04 (1.42, 2.93) | |
| Potassium, mmol/l | | | | | 0.7154 |
| <3.7 | 506 | 1.0 (ref) | 1.36 (0.93, 1.97) | 2.00 (1.39, 2.87) | |
| ≥3.7 | 625 | 1.0 (ref) | 1.36 (0.96, 1.92) | 1.90 (1.36, 2.64) | |
| Chloride, mmol/l | | | | | 0.2137 |
| <102 | 513 | 1.0 (ref) | 1.47 (1.00, 2.14) | 2.26 (1.59, 3.21) | |
| ≥102 | 618 | 1.0 (ref) | 1.38 (0.99, 1.94) | 1.85 (1.33, 2.57) | |
| WBC, $10^9$/l | | | | | 0.3119 |
| <10.6 | 556 | 1.0 (ref) | 1.54 (1.00, 2.37) | 2.26 (1.50, 3.38) | |
| ≥10.6 | 575 | 1.0 (ref) | 1.42 (1.04, 1.94) | 2.12 (1.57, 2.87) | |
| Platelet, $10^9$/l | | | | | 0.6210 |
| <184 | 560 | 1.0 (ref) | 1.19 (0.83, 1.70) | 1.81 (1.30, 2.52) | |
| ≥184 | 571 | 1.0 (ref) | 1.67 (1.17, 2.39) | 2.33 (1.64, 3.29) | |
| Hematocrit,% | | | | | 0.0409 |
| <30 | 563 | 1.0 (ref) | 1.20 (0.84, 1.73) | 1.55 (1.10, 2.18) | |
| ≥30 | 568 | 1.0 (ref) | 1.58 (1.12, 2.24) | 2.59 (1.84, 3.65) | |
| Hemoglobin, g/dl | | | | | 0.1139 |
| <10.1 | 547 | 1.0 (ref) | 1.21 (0.83, 1.77) | 1.58 (1.12, 2.25) | |
| ≥10.1 | 584 | 1.0 (ref) | 1.53 (1.09, 2.14) | 2.54 (1.82, 3.55) | |
| Creatinine, mEq/l | | | | | 0.1649 |
| <1.2 | 563 | 1.0 (ref) | 1.46 (0.98, 2.18) | 2.46 (1.66, 3.66) | |
| ≥1.2 | 567 | 1.0 (ref) | 1.10 (0.80, 1.53) | 1.26 (0.92, 1.71) | |
| BUN, mg/dl | | | | | 0.4479 |
| <25 | 562 | 1.0 (ref) | 1.29 (0.88, 1.89) | 2.31 (1.58, 3.37) | |
| ≥25 | 568 | 1.0 (ref) | 1.31 (0.93, 1.85) | 1.51 (1.09, 2.09) | |
| Anion gap, mmol/l | | | | | 0.2410 |
| <14 | 493 | 1.0 (ref) | 1.22 (0.80, 1.88) | 2.00 (1.31, 3.04) | |
| ≥14 | 628 | 1.0 (ref) | 1.63 (1.19, 2.22) | 1.92 (1.43, 2.58) | |





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**Table 3 continued.** Subgroup analysis of the associations between RDW and 90-day all-cause mortality.

| | No. of patients | RDW (%) | | | *P* for interaction |
|---|---|---|---|---|---|
| | | <13.8 | ≥13.8, <15.2 | ≥15.2 | |
| Bicarbonate, mg/dl | | | | | 0.0966 |
| <20 | 496 | 1.0 (ref) | 1.49 (1.08, 2.06) | 1.68 (1.23, 2.32) | |
| ≥20 | 632 | 1.0 (ref) | 1.26 (0.85, 1.89) | 2.40 (1.66, 3.47) | |
| Glucose, mg/dl | | | | | 0.0287 |
| <149 | 560 | 1.0 (ref) | 1.53 (0.99, 2.37) | 3.22 (2.16, 4.81) | |
| ≥149 | 561 | 1.0 (ref) | 1.41 (1.03, 1.93) | 1.52 (1.11, 2.09) | |
| PT, second | | | | | 0.8402 |
| <14.1 | 532 | 1.0 (ref) | 1.36 (0.94, 1.95) | 1.76 (1.19, 2.59) | |
| ≥14.1 | 549 | 1.0 (ref) | 1.29 (0.90, 1.86) | 1.72 (1.23, 2.41) | |
| APTT, second | | | | | 0.8565 |
| <32.1 | 535 | 1.0 (ref) | 1.55 (1.04, 2.30) | 1.86 (1.25, 2.77) | |
| ≥32.1 | 550 | 1.0 (ref) | 1.36 (0.98, 1.90) | 2.10 (1.54, 2.86) | |
| INR | | | | | 0.4453 |
| <1.3 | 496 | 1.0 (ref) | 1.21 (0.81, 1.79) | 1.55 (1.02, 2.35) | |
| ≥1.3 | 585 | 1.0 (ref) | 1.42 (1.01, 2.00) | 1.85 (1.35, 2.54) | |
| SBP, mmHg | | | | | 0.7549 |
| <105 | 562 | 1.0 (ref) | 1.54 (1.11, 2.14) | 2.14 (1.57, 2.91) | |
| ≥105 | 563 | 1.0 (ref) | 1.31 (0.88, 1.94) | 1.83 (1.25, 2.69) | |
| DBP, mmHg | | | | | 0.7295 |
| <57 | 562 | 1.0 (ref) | 1.52 (1.08, 2.12) | 2.07 (1.51, 2.84) | |
| ≥57 | 563 | 1.0 (ref) | 1.32 (0.90, 1.94) | 1.93 (1.32, 2.81) | |
| MBP, mmHg | | | | | 0.9514 |
| <74 | 563 | 1.0 (ref) | 1.60 (1.13, 2.25) | 1.96 (1.42, 2.71) | |
| ≥74 | 563 | 1.0 (ref) | 1.15 (0.79, 1.68) | 1.84 (1.27, 2.66) | |
| Heart rate, beats/minute | | | | | 0.7064 |
| <87 | 563 | 1.0 (ref) | 1.18 (0.81, 1.71) | 1.78 (1.24, 2.54) | |
| ≥87 | 563 | 1.0 (ref) | 1.65 (1.17, 2.32) | 2.18 (1.57, 3.03) | |
| Respiratory rate, beats/minute | | | | | 0.4364 |
| <19 | 563 | 1.0 (ref) | 0.99 (0.68, 1.44) | 1.56 (1.10, 2.23) | |
| ≥19 | 564 | 1.0 (ref) | 1.86 (1.32, 2.62) | 2.34 (1.68, 3.26) | |
| Temperature, °C | | | | | 0.7102 |
| <36.8 | 541 | 1.0 (ref) | 1.34 (0.94, 1.92) | 1.85 (1.32, 2.59) | |
| ≥36.8 | 542 | 1.0 (ref) | 1.46 (1.00, 2.13) | 2.27 (1.57, 3.29) | |
| SPO2,% | | | | | 0.6700 |
| <97.5 | 562 | 1.0 (ref) | 1.19 (0.85, 1.68) | 1.92 (1.40, 2.65) | |
| ≥97.5 | 562 | 1.0 (ref) | 1.67 (1.15, 2.43) | 1.99 (1.38, 2.87) | |
| RRT | | | | | 0.2700 |
| No | 987 | 1.0 (ref) | 1.37 (1.04, 1.80) | 2.10 (1.62, 2.72) | |
| Yes | 144 | 1.0 (ref) | 1.31 (0.70, 2.44) | 1.11 (0.60, 2.06) | |





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**Table 3 continued.** Subgroup analysis of the associations between RDW and 90-day all-cause mortality.

| | No. of patients | RDW (%) | | | *P* for interaction |
|---|---|---|---|---|---|
| | | <13.8 | ≥13.8, <15.2 | ≥15.2 | |
| SOFA scores | | | | | 0.5581 |
| <6 | 493 | 1.0 (ref) | 1.22 (0.77, 1.93) | 1.87 (1.22, 2.87) | |
| ≥6 | 638 | 1.0 (ref) | 1.30 (0.96, 1.76) | 1.75 (1.31, 2.34) | |
| SAPSII scores | | | | | 0.6148 |
| <44 | 545 | 1.0 (ref) | 1.18 (0.74, 1.87) | 1.94 (1.26, 2.97) | |
| ≥44 | 586 | 1.0 (ref) | 1.43 (1.06, 1.93) | 1.93 (1.44, 2.59) | |

CHF – congestive heart failure; AFIB – atrial fibrillation; CAD – coronary artery disease; COPD – chronic obstructive pulmonary disease; WBC – white blood cell; BUN – blood urea nitrogen; PT – prothrombin time; APTT – activated partial thromboplastin time; INR – international normalized ratio; SBP – systolic blood pressure; DBP – diastolic blood pressure; MBP – mean blood pressure; RRT – renal replacement therapy; SOFA – sequential organ failure assessment; SAPSII – simplified acute physiology score II.

## Conclusions

Higher RDW was associated with increased risk of 30-day, 90-day, and 365-day all-cause mortality in critically ill patients with CS.

### Data availability

The clinical data used to support the findings of this study were supplied by Monitoring in Intensive Care Database III version 1.4 (MIMIC-III v.1.4). Although the database is publicly and freely available, researchers must complete the National Institutes of Health's web-based course known as Protecting Human Research Participants to apply for permission to access the database.

### Conflict of interests

None.

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