Red cell distribution width is associated with all-cause mortality in patients with acute stroke: a retrospective analysis of a large clinical database

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Abstract

Objectives: This study aimed to evaluate the association between the red blood cell distribution width (RDW) and mortality in patients with stroke.

Methods: We conducted a retrospective cohort study on patients with stroke in the Medical Information Mart for Intensive Care Database III. Cox proportional hazards regression models were used to estimate hazard ratios of 30-day, 90-day, and 1-year mortality in relation to the RDW level.

Results: A total of 4134 patients were enrolled, including 2646 patients with ischemic stroke and 1668 with hemorrhagic stroke. After adjustment for potential confounders, the hazard ratio (95% confidence interval) of 30-day mortality for the second (RDW: 13.4%–14.3%) and third (>14.3%) tertiles was 1.15 (0.96, 1.37) and 1.40 (1.17, 1.68), respectively, compared with the reference group (<13.4%). A two-piecewise linear regression model was established and the inflection point of RDW was 16.7%. When RDW was >16.7%, an increase in RDW did not increase stroke mortality.

Conclusions: The RDW is a prognostic factor of patients with stroke. This finding needs to be confirmed in future prospective studies.

Keywords

Red blood cell distribution width, acute stroke, all-cause mortality, Medical Information Mart for Intensive Care Database III, coronary heart disease, diabetes mellitus

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Introduction

Globally, stroke affects more than 9 million people every year. Stroke is the second most common cause of death.\(^1\)\(^2\) Although rates of stroke mortality have declined in recent decades, the absolute number of people who die from stroke is increasing.\(^3\)\(^4\) The outcome of stroke is strongly affected by many variables, and a variety of indices related to the immune reaction,\(^5\) inflammatory response,\(^6\)\(^7\) and metabolic homeostasis\(^8\)\(^9\) are helpful for predicting prognosis. This evidence suggests that multidimensional evaluation of patients with stroke is required and that some reliable prognostic indicators need to be found. Furthermore, future research is warranted to develop a reliable tool for early prediction of stroke outcome in everyday clinical practice.

Red blood cell distribution width (RDW) is a simple and cost-effective marker. RDW is the ratio of the standard deviation of erythrocyte volume to the mean corpuscular volume. Traditionally, RDW has been recognized as a differential diagnostic biomarker for anemia. RDW is elevated in patients with thalassemia, post-transfusion, and iron deficiency. Recent evidence has shown that RDW is closely associated with many clinical outcomes of cardiovascular events,\(^10\)\(^11\)\(^12\) including heart failure,\(^13\) acute coronary syndrome,\(^14\) atrial fibrillation,\(^15\) and ischemic cerebrovascular disease.\(^16\) Several cohort studies have reported that the RDW level is associated with prognosis of ischemic stroke.\(^16\)\(^17\)\(^18\) However, several important confounding factors, including sex, severity of disease, and cardiovascular disease, were not considered in these studies.

To the best of our knowledge, no study has assessed the association between RDW and short-term and long-term mortality in patients with stroke. Therefore, we aimed to investigate the relationship between RDW and outcomes in patients with stroke.

Methods

Study population

We conducted a retrospective cohort study using the Medical Information Mart for Intensive Care Database III (MIMIC-III database).\(^19\) The MIMIC-III database includes more than 50,000 patients who were admitted to the intensive care unit at Beth Israel Deaconess Medical Center from 2001 to 2012.\(^19\)\(^20\) A detailed description of this database has been published elsewhere.\(^5\) This study was approved by the Institutional Review Boards of the Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Requirement for individual patient consent was waived because the project did not affect clinical care and all protected health information was de-identified (https://www.nature.com/articles/sdata201635/).

Patients were included if (i) admission was for diagnosis of stroke, (ii) a blood count was acquired on the first day of admission, and (iii) the hospital stay was >2 days. Exclusion criteria were as follows: neoplastic hematological disorder; chronic inflammatory or malignant disease; recent blood transfusion; and missing data >5%. We used the International Classification of Diseases, Ninth Revision (ICD-9) codes and identified patients with a primary discharge diagnosis of ischemic stroke (ICD-9 433.\(^\times1\), 434.\(^\times1\), 436) and hemorrhagic stroke (ICD-9 431, ICD-9 430).

Data extraction and management

We collected the patients’ demographic data (age, sex, and race), clinical characteristics, comorbidities, laboratory parameters, and scoring systems. Clinical characteristics included body mass index (BMI), heart rate, oxygen saturation (SpO₂), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Comorbidities included hypertension,
diabetes mellitus (DM), chronic liver disease, chronic renal disease, coronary heart disease (CHD), chronic heart failure, atrial fibrillation (AF), alcohol abuse, and drug abuse. Laboratory parameters included RDW, hemoglobin, white blood cell count, glucose, hematocrit, blood urea nitrogen (BUN), serum creatinine, and serum albumin. Baseline characteristics and laboratory parameters were obtained within the first 24 hours after admission of patients. The Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Scale (GCS) score were recorded.20

Outcomes
The primary outcome was 30-day mortality, and the secondary outcomes were 90-day mortality and 1-year mortality. The date of admission of patients was the start date for follow-up and all participants were followed for at least 1 year. The date of mortality was obtained from Social Security Death Index records.

Statistical analyses
The statistical analysis process was divided into four steps. First, the patients were divided into tertiles on the basis of baseline RDW. Continuous data are expressed as means with standard deviations and were compared using analysis of variance or the Kruskal–Wallis H test. Categorical data are expressed as frequency or percentage and were compared using the $\chi^2$ test and Fisher’s exact test. Second, Cox proportional hazards regression models were used to estimate the hazard ratio (HR) with 95% confidence interval (CI) for the association between RDW and mortality. The lowest level of each RDW was considered as a reference group. In model 1, no covariates were adjusted. Model 2 was adjusted for age, sex, and race. Model 3 was adjusted for the following confounders: age, sex, race, BMI, SBP, heart rate, SpO$_2$, respiratory rate, hematocrit, hemoglobin, BUN, prothrombin time (PT), international normalized ratio (INR), CHD, AF, DM, alcohol abuse, GCS score, SAPS II, and SOFA score. The confounders were selected on the basis of changing the effect estimate >10%.21,22 Third, smooth curve fitting was used to create non-linear correlations of RDW with 30-day mortality. A two-piecewise linear regression model was applied to determine the threshold effect of RDW on 30-day mortality. The inflection point of RDW, at which the correlation of RDW with 30-day mortality began to reverse, was determined using the recursive method. Finally, we performed subgroup analyses to determine whether the associations differed for the classified stratifications. Likelihood ratio tests were used to evaluate the interactions of subgroups. We used R statistical software (www.r-project.org) for statistical analysis. $P$ values <0.05 were considered statistically significant.

Results
Patients’ characteristics
The baseline characteristics of 4134 eligible patients with new stroke are shown in Table 1. There were 2646 patients with ischemic stroke and 1668 with hemorrhagic stroke. The patients included 1913 women and 2221 men with a mean age of 68.1 ± 15.4 years and mean RDW of 14.2% ± 1.41%. The patients were divided into tertiles by using a RDW <13.4% (n = 1313), 13.4%–14.3% (n = 1423), and >14.3% (n = 1398). Patients with a higher calibrated RDW (>14.3%) were significantly more likely to be older, female sex, and black, to have a reported a history of CHD, AF, chronic heart failure, DM, and hypertension, and to have a higher heart rate, SAPS II, SOFA score, BMI, and C-reactive protein.
Table 1. Characteristics of the study patients in relation to RDW levels.

| Characteristics            | RDW (%) | P value |
|----------------------------|---------|---------|
|                            | <13.4   | 13.4–14.3 | >14.3    |
| RDW (S)                    | 12.8 ± 0.4 | 13.8 ± 0.3 | 15.7 ± 1.2 | <0.001   |
| Number                     | 1313   | 1423 | 1398 |
| Age, years                 | 63.8 ± 16.7 | 69.3 ± 14.2 | 70.9 ± 14.4 | <0.001   |
| Sex, n (%)                 |        |       |       |
| Female                     | 610 (46.5) | 602 (42.3) | 701 (50.1) | <0.001   |
| Male                       | 703 (53.5) | 821 (57.7) | 697 (49.9) |
| Race, n (%)                |        |       | <0.001 |
| White                      | 987 (75.2) | 1043 (73.3) | 1018 (72.8) |
| Black                      | 57 (4.3) | 90 (6.3) | 120 (8.6) |
| Other                      | 269 (20.5) | 290 (20.4) | 260 (18.6) |
| BMI, kg/m²                 | 23.1 ± 2.2 | 22.5 ± 2.5 | 22.0 ± 2.4 | <0.001   |
| SBP, mmHg                  | 129.3 ± 16.3 | 129.6 ± 17.5 | 128.0 ± 19.0 | 0.037   |
| DBP, mmHg                  | 63.6 ± 10.6 | 63.0 ± 10.9 | 61.8 ± 11.6 | <0.001   |
| SpO₂, %                    | 97.5 ± 2.1 | 97.5 ± 2.2 | 97.4 ± 2.8 | 0.238   |
| Heart rate, beats/minute   | 78.2 ± 14.2 | 79.8 ± 14.8 | 82.0 ± 15.3 | <0.001   |
| Comorbidities              |        |       | <0.001 |
| CHD, n (%)                 |        |       | <0.001 |
| No                         | 1092 (83.2) | 1061 (74.6) | 1026 (73.4) |
| Yes                        | 221 (16.8) | 362 (25.4) | 372 (26.6) |
| AF, n (%)                  |        | <0.001 |
| No                         | 1071 (81.6) | 1007 (70.8) | 887 (63.4) |
| Yes                        | 242 (18.4) | 416 (29.2) | 511 (36.6) |
| CHF, n (%)                 |        | <0.001 |
| No                         | 1271 (96.8) | 1316 (92.5) | 1204 (86.1) |
| Yes                        | 42 (3.2) | 107 (7.5) | 194 (13.9) |
| DM                         |        | <0.001 |
| No                         | 1101 (83.9) | 1113 (78.2) | 1048 (75.0) |
| Yes                        | 212 (16.1) | 310 (21.8) | 350 (25.0) |
| Hypertension               |        | <0.001 |
| No                         | 1059 (80.7) | 1088 (76.5) | 939 (67.2) |
| Yes                        | 254 (19.3) | 335 (23.5) | 459 (32.8) |
| Alcohol abuse              |        | 0.083 |
| No                         | 1301 (99.1) | 1403 (98.6) | 1371 (98.1) |
| Yes                        | 12 (0.9) | 20 (1.4) | 27 (1.9) |
| Drug abuse                 |        | 0.003 |
| No                         | 1310 (99.8) | 1411 (99.2) | 1378 (98.6) |
| Yes                        | 3 (0.2) | 12 (0.8) | 20 (1.4) |
| Elixhauser-30              | 15.4 ± 13.3 | 16.8 ± 13.4 | 18.2 ± 13.1 | <0.001 |
| C-reactive protein, nmol/L | 31.4 ± 53.3 | 40.9 ± 79.0 | 48.5 ± 83.8 | <0.001 |
| Hemoglobin, g/L            | 133.2 ± 16.4 | 128.1 ± 19.3 | 117.3 ± 19.3 | <0.001 |
| Hematocrit, %              | 38.8 ± 4.6 | 37.8 ± 5.4 | 35.0 ± 5.7 | <0.001 |
| WBC count, 10⁹/L           | 12.9 ± 5.1 | 13.1 ± 5.7 | 13.3 ± 11.2 | 0.372 |

(continued)
levels than those with a lower RDW (all $P < 0.001$).

**Association between RDW and outcome of stroke**

Table 2 shows effect sizes of the associations between RDW and stroke outcome. For 30-day mortality, a total of 1005 deaths occurred during the follow-up period. In the unadjusted model 1, the HR (95% CI) of 30-day mortality for the second (13.4%–14.3%) and third (≥14.3%) tertiles was 1.18 (1.00, 1.39) and 1.64 (1.40, 1.91), respectively, compared with the reference group ($P$ for trend <0.0001). For 90-day and 1-year mortality, similar trends were also observed, and the risk was more evident with a higher RDW (all $P$ for trend <0.0001).

To determine nonlinearity of RDW and 30-day mortality, we performed smooth curve fitting (Figure 1). After adjusting for age, sex, race, BMI, SBP, heart rate, SpO2, respiratory rate, hematocrit, hemoglobin, BUN, PT, INR, CHD, AF, DM, alcohol abuse, GCS score, SAPS II, and SOFA score, non-linear relationships were observed. Because of limitations of classification analysis, the two-piecewise linear regression model was established, and the inflection point of RDW was 16.7 (Table 3). To the left of the inflection point (RDW ≤16.7%), the HR (95% CI) was 1.14 (1.07, 1.21) ($P < 0.0001$). A relationship between RDW and 30-day mortality was not detected for a RDW >16.7% (HR 0.96 [95% CI 0.88, 1.04]).
Subgroup analysis

In subgroup analysis, the associations between RDW and 30-day mortality in patients with stroke were similar for most covariates (Table 4). Significant interactions were observed for age ($P = 0.0104$), a history of CHD ($P = 0.0238$), and a history of DM ($P = 0.0145$). The HR (95% CI) of 30-day mortality for the second and third tertiles was 1.25 (1.01, 1.56) and 1.81 (1.46, 2.25), respectively, compared with the reference group in patients with ischemic stroke. Increased RDW in patients who were younger than 70.1 years of age predicted a poorer prognosis of stroke, whereas RDW did not predict prognosis of stroke in elderly patients ($\geq 70.1$ years).

Discussion

To the best of our knowledge, this is the first study to investigate the associations between RDW and short-term and long-term mortality in patients with stroke. The main findings of this study were that a higher RDW was associated with increased all-cause mortality in patients with stroke in the short-term and long-term. We also

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Table 2. HRs and 95% CIs for mortality across groups of RDW.

| RDW | Model 1 | Model 2 | Model 3 |
|-----|---------|---------|---------|
|     | HR (95% CI) | $P$ value | HR (95% CI) | $P$ value | HR (95% CI) | $P$ value |
| Thirty-day all-cause mortality | | | |
| RDW (per 0.1 change) | 1.16 (1.12, 1.21) $< 0.0001$ | 1.17 (1.12, 1.21) $< 0.0001$ | 1.12 (1.06, 1.17) $< 0.0001$ |
| Tertiles (%) | | | |
| $< 13.4$ | Reference | Reference | Reference |
| 13.4–14.3 | 1.18 (1.00, 1.39) 0.0547 | 1.20 (1.01, 1.41) 0.0351 | 1.15 (0.96, 1.37) 0.1231 |
| $> 14.3$ | 1.64 (1.40, 1.91) $< 0.0001$ | 1.67 (1.43, 1.95) $< 0.0001$ | 1.40 (1.17, 1.68) 0.0003 |
| $P$ for trend | $< 0.0001$ | $< 0.0001$ | $< 0.0001$ |
| Ninety-day all-cause mortality | | | |
| RDW (per 0.1 change) | 1.20 (1.15, 1.24) $< 0.0001$ | 1.20 (1.16, 1.25) $< 0.0001$ | 1.13 (1.08, 1.18) $< 0.0001$ |
| Tertiles (%) | | | |
| $< 13.4$ | Reference | Reference | Reference |
| 13.4–14.3 | 1.26 (1.08, 1.46) 0.0034 | 1.28 (1.09, 1.49) 0.0018 | 1.17 (1.00, 1.38) 0.0495 |
| $> 14.3$ | 1.90 (1.64, 2.18) $< 0.0001$ | 1.94 (1.68, 2.24) $< 0.0001$ | 1.51 (1.28, 1.78) $< 0.0001$ |
| $P$ for trend | $< 0.0001$ | $< 0.0001$ | $< 0.0001$ |
| One-year all-cause mortality | | | |
| RDW (per 0.1 change) | 1.21 (1.17, 1.25) $< 0.0001$ | 1.22 (1.18, 1.25) $< 0.0001$ | 1.13 (1.08, 1.17) $< 0.0001$ |
| Tertiles (%) | | | |
| $< 13.4$ | Reference | Reference | Reference |
| 13.4–14.3 | 1.32 (1.15, 1.52) $< 0.0001$ | 1.34 (1.17, 1.54) $< 0.0001$ | 1.21 (1.05, 1.40) 0.0107 |
| $> 14.3$ | 2.03 (1.79, 2.32) $< 0.0001$ | 2.07 (1.82, 2.36) $< 0.0001$ | 1.55 (1.33, 1.80) $< 0.0001$ |
| $P$ for trend | $< 0.0001$ | $< 0.0001$ | $< 0.0001$ |

Model 1: no covariates were adjusted.
Model 2: covariates were adjusted for age, sex, and race.
Model 3: covariates were adjusted for age, sex, race, body mass index, systolic blood pressure, heart rate, oxygen saturation, respiratory rate, hematocrit, hemoglobin, blood urea nitrogen, prothrombin time, international normalized ratio, coronary heart disease, atrial fibrillation, diabetes mellitus, alcohol abuse, Glasgow Coma Scale score, Simplified Acute Physiology Score II, and Sequential Organ Failure Assessment score.

HR, hazard ratio; CI, confidence interval; RDW, red blood cell distribution width.
found nonlinearity of the relationship between RDW and 30-day mortality.

Several cohort studies have reported that the RDW level was associated with prognosis of patients with ischemic stroke. Among these studies, the number of enrolled participants ranged from 316 to 602, and the number of patients with incident stroke ranged from 40 to 117. All of these studies showed that RDW was an independent risk factor for mortality. These studies were all limited by the relatively small sample size. Some studies included patients who underwent thrombolysis for ischemic stroke. In these studies, a non-linear relationship and subgroup analysis of the relationship between RDW and mortality were not performed.

The precise mechanism by which elevated RDW values are associated with increased mortality in acute stroke is unclear. Low-grade chronic inflammation plays an important role in the mechanism of developing stroke. Elevation in plasma pro-inflammatory cytokine levels may inhibit erythropoietin-induced maturation and proliferation of erythrocytes, and may downregulate erythropoietin receptor expression, resulting in an increased RDW. However, the possibility that the association of RDW with mortality is based on the premise of low-grade chronic inflammation is unlikely. Furthermore, oxidative stress disrupts erythropoiesis and alters blood cell membrane deformability and the half-life of red blood cells in the circulation, causing increased heterogeneity of erythrocyte size. Additionally, cells are affected by factors, such as hyperglycemia and inflammatory factors, all of which lead to decreased cell deformation ability, increased osmotic

![Figure 1. Relationship between RDW and logit-transformed mortality by using the Lowess smoothing technique.](image)

RDW, red blood cell distribution width.

**Table 3. Fitting model by two-piecewise linear regression.**

| Model Type                              | HR (95% CI) | P value |
|----------------------------------------|-------------|---------|
| Fitting model by standard linear regression | 1.12 (1.06, 1.17) | < 0.0001 |
| Fitting model by two-piecewise linear regression | 1.14 (1.07, 1.21) | 0.0001 |
| Inflection point of RDW (%)            | 16.7        |         |
| ≤16.7                                  | 0.96 (0.88, 1.04) | 0.3385 |
| >16.7                                  | 0.96 (0.88, 1.04) | 0.3385 |
| P for log likelihood ratio test        | 0.004       |         |

The model was adjusted for age, sex, race, body mass index, systolic blood pressure, heart rate, oxygen saturation, respiratory rate, hematocrit, hemoglobin, blood urea nitrogen, prothrombin time, international normalized ratio, coronary heart disease, atrial fibrillation, diabetes mellitus, alcohol abuse, Glasgow Coma Scale score, Simplified Acute Physiology Score II, and Sequential Organ Failure Assessment score.

HR, hazard ratio; CI, confidence interval; RDW, red blood cell distribution width.
brittleness, enhanced aggregation, and impaired Na\(^+/K^+\)-ATPase activity. These processes can cause an elevation in RDW and lead to vascular complications.\(^{29}\) This is the first cohort study to assess RDW and the risk of mortality in patients who were admitted to the intensive care unit with acute stroke. Nevertheless,
limitations of this study should be acknowledged as follows. First, this was a retrospective cohort study and it could not prove a causal relationship between mortality and stroke. Second, as with any cohort study, we attempted to adjust for possible risk factors, such as BMI, smoking status, comorbidities, and others. However, residual confounders cannot be completely ruled out, including pro-inflammatory factors, and other known or unknown confounders. Third, for RDW, only data from the first 24 hours of admission were selected. Therefore, the relationship between subsequent changes in RDW and prognosis was not evaluated. We used baseline assessment only, which increased the risk of misclassification bias.

Conclusions

The RDW is a prognostic factor of patients with stroke. This finding needs to be confirmed in future prospective studies.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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