Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(7) 1–10

DOI: 10.1177/0300060520941317
journals.sagepub.com/home/imr
SAGE

Red cell distribution width is correlated with all-cause mortality of patients in the coronary care unit

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Abstract

Objective: The predictive value of red blood cell distribution width (RDW) in patients in the coronary care unit (CCU) remains unknown. This study aimed to examine the prognostic value of RDW in these patients.

Methods: Clinical data were extracted from the Medical Information Mart for Intensive Care-III database. Baseline data were collected within 24 hours after patients' first admission to the CCU. The outcomes of our study were 30-day and 90-day mortality.

Results: A total of 8254 patients were included and their mean age was 66.9 ± 15.8 years (56% were men). For 30-day all-cause mortality, the hazard ratios (95% confidence interval) of the medium RDW (13.7–15.3) and high-RDW groups > 15.3) were 1.72 (1.55, 1.91) and 2.57 (2.33, 2.85), respectively, compared with the reference group in an unadjusted model. This association remained similar in multivariate models. Similar correlations were observed for 90-day all-cause mortality. The areas under the curve of RDW and the Sequential Organ Failure Assessment (SOFA) score were 0.625 and 0.692, respectively.

Conclusions: RDW is correlated with an increased risk of 30-day and 90-day mortality of patients in the CCU. The predictive value of RDW is not as good as that of the SOFA score.

Keywords

Red cell distribution width, coronary care unit, all-cause mortality, cardiovascular disease, Medical Information Mart for Intensive Care-III database, Sequential Organ Failure Assessment score

Date received: 4 March 2020; accepted: 19 June 2020

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Introduction

Cardiovascular disease (CVD) has become the main cause of death worldwide, accounting for nearly one third of all deaths.[1] This constitutes 17% of overall national health expenditures in the USA. A growing number of patients are dying from ischemic heart disease, with more than 1.6 million deaths in 2017 compared with 10 years earlier.[2] The coronary care unit (CCU) is staffed with specialists and equipped with facilities to treat those who suffer from severe CVD. Outcomes of patients in the CCU need to be improved and prognostic factors need to be examined for these critical patients.[3,4]

Red blood cell distribution width (RDW) is a parameter of the whole blood count.[5,6] Several studies[7,8] have shown that RDW may be a novel prognostic factor reflecting not only chronic illnesses, such as heart failure,[9] coronary heart disease (CHD),[10] and hypertension,[11] but also acute conditions, such as ischemic stroke.[12] To the best of our knowledge, no studies have shown a relationship between the risks of patients in the CCU and RDW. Therefore, we used the Medical Information Mart for Intensive Care (MIMIC)-III database[13] to assess the association between outcomes of CCU patients and RDW.

Materials and methods

Study population

The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[14] MIMIC-III (version 1.4) is a database of a single center recording medical information for more than 50,000 patients who were admitted in Beth Israel Deaconess Medical Center ([BIDMC] a teaching hospital affiliated with Harvard Medical School, Boston, MA) between 2001 and 2012.[13] The database includes basic information of patients, treatment details, and survival data. MIMIC-III has obtained approval from the Institutional Review Boards of the BIDMC and the Massachusetts Institute of Technology. To gain access to this database, we completed online courses required by the National Institutes of Health and completed the tests of Protecting Human Research Participants. Our institutional ethics review committee waived the need for approval of the study protocol and informed consent because our study involved retrospective analysis of a public database.

Of 58,976 distinct patients in the database, patients were included if they met the following criteria: (1) CCU patients; and (2) length of hospital stay > 2 days. The exclusion criteria were as follows: (1) age < 18 years; (2) missing $> 5\%$ medical data; and (3) patients were diagnosed with leukemia or lymphoma. The first intensive care unit admission was included when patients had multiple admissions to the CCU.

Covariates

Data that were extracted from database within the first day after intensive care unit admission included demographic data, physiological variables, comorbidities, basic laboratory parameters before therapy, and scoring systems. Demographic information included age, sex, race, and body mass index. Comorbidities included hypertension, diabetes, atrial fibrillation, and CHD. Laboratory measurements comprised hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, blood urea nitrogen, serum sodium, serum chloride, serum glucose, and the prothrombin time (PT) over the first 24 hours. The Sequential Organ Failure Assessment (SOFA) score,[15] the Simplified Acute

Physiology Score (SAPS),[16] and the Elixhauser Comorbidity Index (ECI) were also included.

Outcomes

The primary and secondary outcomes were set as mortality in 30 days and 90 days, respectively. The period of observation began at the patients' first admission and ended at death. The date of mortality was collected from the records in the Social Security Death Index.

Statistical analyses

The study participants were subdivided into tertiles according to RDW values (<13.7%, 13.7%–15.3%, and > 15.3%). The mean ± standard deviation was used for continuous variables. The Kruskal–Wallis H test or analysis of variance was applied to compare different groups. Categorical variables are expressed as number or percentage and were compared with the chi-square test or Fisher's exact test.

Cox proportional hazards regression was applied to assess the association between all-cause mortality and RDW, and the results are shown as the hazard ratio (HR) with 95% confidence interval (CI).[17] Two models of multivariate analysis were established for each endpoint and the lowest RDW level (<13.7%) was set as the reference group. In model 1, the covariates included age, sex, and race. In model 2, hemoglobin, hematocrit, WBC count, serum chloride, serum glucose, blood urea nitrogen, PT, CHD, atrial fibrillation, diabetes, the SAPS II, the SOFA score, and the ECI score were further adjusted. The confounders were selected on the basis of changing the effect estimate > 10%.[17–19] Stratification analyses were performed to investigate whether the associations differed with the classified stratification. Continuous variables were converted into categorical variables on the basis of the tertile and an interaction test was performed. The tests of effect modification based on subgroups applied interaction terms among subgroup indicators, and then the likelihood ratio test was conducted. To examine the predictive value of RDW, we performed receiver operator characteristic (ROC) curve analysis for 30-day mortality on the basis of RDW and the SOFA score.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for analyses. All of the tests were two-sided and $P < 0.05$ indicated a significant difference.

Results

Features of the patients

A total of 8254 individuals were eligible for this analysis and the mean (standard deviation) age was 66.9 ± 15.8 years, 56% of which were men. The baseline characteristics of all the subjects are listed in Table 1. According to the RDW value, the study participants were subdivided into tertiles (i.e., < 13.7%, 13.7%–15.3%, and > 15.3%). Patients in the group with an RDW > 15.3% were significantly more likely to be older and had a higher SOFA score, SAPS, and ECI score (all $P < 0.001$). Patients with a high RDW value had significantly lower serum sodium levels, serum glucose levels, platelet count, hematocrit, hemoglobin, and WBC count (all $P < 0.001$). The prevalence of AF, hypertension, and diabetes was also significantly higher in those with a high RDW (all $P < 0.01$) (Table 1).

Association between RDW and mortality

Different models were established to evaluate the relationships between RDW and outcomes of patients in the CCU, following adjustment for possible confounders. The results of these relationships are shown in

Table 1. Baseline characteristics of the study population.

Characteristics	RDW			*P* value
	<13.7%	13.7%–15.3%	>15.3%	
RDW	13.1 ± 0.5	14.5 ± 0.4	17.3 ± 1.8	<0.001
n	2614	2871	2769	
Age, years	63.5 ± 17.0	68.4 ± 15.0	68. 5 ± 15.0	<0.001
Sex, n (%)				<0.001
Female	1053 (40.3)	1239 (43.2)	1309 (47.3)	
Male	1561 (59.7)	1632 (56.8)	1460 (52.7)	
Race, n (%)				<0.001
White	1742 (66.6)	2165 (75.4)	1892 (68.3)	
Black	417 (16.0)	250 (8.7)	472 (17.0)	
Other	455 (17.4)	456 (15.9)	405 (14.6)	
BMI, kg/m^2	28.3 ± 8.1	36.9 ± 172.7	31.2 ± 88.6	<0.001
Comorbidities				
CHD, n (%)				<0.001
No	1192 (45.6)	1523 (53.0)	1585 (57.2)	
Yes	1422 (54.4)	1348 (47.0)	1184 (42.8)	
AF, n (%)				<0.001
No	1835 (70.2)	1638 (57.1)	1570 (56.7)	
Yes	779 (29.8)	1233 (42.9)	1199 (43.3)	
DM				<0.001
No	2038 (78.0)	2098 (73.1)	1999 (72.2)	
Yes	576 (22.0)	773 (26.9)	770 (27.8)	
Hypertension				<0.001
No	2274 (87.0)	2232 (77.7)	1885 (68.1)	
Yes	340 (13.0)	639 (22.3)	884 (31.9)	
Laboratory indices				
Hemoglobin, g/L	123 ± 20	117 ± 20	109 ± 18	<0.001
Hematocrit, %	36.9 ± 5.5	35.5 ± 5.7	33.4 ± 5.2	<0.001
WBC count, 10^9/L	13.5 ± 6.0	13.3 ± 6.6	13.0 ± 13.1	0.185
Platelet count, 10^9/L	263.2 ± 105.4	253.5 ± 112.2	247.5 ± 134.2	<0.001
BUN, mmol/L	1.6 ± 1.1	2.2 ± 1.5	2.6 ± 1.7	<0.001
Serum sodium, mmol/L	140.0 ± 4.3	139.7 ± 4.7	139.4 ± 4.7	<0.001
Serum chloride, mmol/L	105.9 ± 6.4	104.9 ± 6.7	104.0 ± 6.6	<0.001
Serum glucose, mmol/L	12.1 ± 8.2	11.0 ± 6.0	9.9 ± 4.9	<0.001
PT, s	16.7 ± 8.5	18.6 ± 12.6	20.8 ± 15.3	<0.001
Scoring systems				
SAPS II	17.4 ± 5.1	19.0 ± 4.9	19.5 ± 5.0	<0.001
SOFA score	3.9 ± 2.8	4.7 ± 3.0	5.3 ± 3.0	<0.001
ECI score	8.2 ± 10.5	12.7 ± 11.6	16.7 ± 12.7	<0.001
Mortality, n (%)				
30-day				<0.001
No	2371 (90.7)	2488 (86.7)	2303 (83.2)	
Yes	243 (9.3)	383 (13.3)	466 (16.8)	

(continued)

Table 1. Continued.

Characteristics	RDW			*P* value
	<13.7%	13.7%–15.3%	>15.3%	
90-day				<0.001
No	2246 (85.9)	2287 (79.7)	1983 (71.6)	
Yes	368 (14.1)	584 (20.3)	786 (28.4)	
One-year				<0.001
No	2070 (79.2)	1914 (66.7)	1494 (54.0)	
Yes	544 (20.8)	957 (33.3)	1275 (46.0)	

Data are presented as the mean ± standard deviation or n (%).
RDW: red cell distribution width, n: number, BMI: body mass index, CHD: coronary heart disease, AF: atrial fibrillation, DM: diabetes mellitus, WBC: white blood cell, BUN: blood urea nitrogen, PT: prothrombin time, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment, ECI: Elixhauser Comorbidity Index.

Table 2. For all-cause mortality in 30 days, the HRs (95% CI) in the groups of mid-RDW (13.7%–15.3%) and high RDW (>15.3%) were 1.72 (1.55, 1.91) and 2.57 (2.33, 2.85) in the unadjusted model, respectively, with a significant difference compared with the reference group (both $P < 0.0001$). After adjusting for age, sex, and race, this association remained and was significant (both $P < 0.0001$). Similar results were observed in model 2. For 90-day all-cause mortality, a similar relationship was also observed between RDW.

Subgroup analyses

In subgroup analyses, the relationship between RDW and the risk of death in 30 days remained similar in most strata (Table 3) and only a few significant interactions were observed. There were significant interactions for age and sex (both P for interaction < 0.001) in the association between RDW and 30-day mortality.

ROC analysis

ROC curve analysis was performed to assess the potential prognostic value of RDW in patients in the CCU (Figure 1). The areas under the curve of RDW and the SOFA score were 0.625 and 0.692, respectively. When RDW was combined with the SOFA score, the area under the curve was 0.701.

Discussion

Several previous studies have investigated the prognostic value of RDW in a given cardiovascular disease, such as acute myocardial infarction,[7] heart failure,[9] and hypertension.[11] However, few studies have discussed the association between RDW and the mortality of patients in the CCU. Hu et al.[20] concluded that RDW is an independent predictor of mortality in patients in the CCU. This finding is consistent with our study where RDW remained strongly associated with all-cause mortality of patients in the CCU after adjusting for prognostic factors. However, we found that the predictive value of RDW was not as good as that of the SOFA score.

CVD is a heavy burden to the healthcare system, especially because of its increasing mortality and morbidity.[21] In the past 50 years, improvement of CCUs has contributed to better outcomes of critical patients. Therefore, investigating useful prognostic biomarkers of mortality in the early stage in the CCU is important. RDW, which is a routine parameter in a routine blood test,

Table 2. Association between RDW and mortality of patients in the CCU.

	Crude model		Model 1		Model 2	
RDW	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
30-day all-cause mortality						
RDW (per 0.1 change)	1.15 (1.13, 1.16)	<0.0001	1.15 (1.14, 1.17)	<0.0001	1.06 (1.03, 1.08)	<0.0001
Fitted groups						
<13.7%	Ref		Ref		Ref	
13.7%–15.3%	1.72 (1.55, 1.91)	<0.0001	1.52 (1.37, 1.69)	<0.0001	1.21 (1.05, 1.40)	0.008
>15.3%	2.57 (2.33, 2.85)	<0.0001	2.33 (2.10, 2.58)	<0.0001	1.48 (1.28, 1.71)	<0.0001
P for trend	<0.0001		<0.0001		<0.0001	
90-day all-cause mortality						
RDW (per 0.1 change)	1.13 (1.11, 1.15)	<0.0001	1.13 (1.11, 1.15)	<0.0001	1.03 (1.00, 1.06)	0.03
Fitted groups						
<13.7%	Ref		Ref		Ref	
13.7%–15.3%	1.50 (1.32, 1.71)	<0.0001	1.32 (1.16, 1.50)	<0.0001	0.99 (0.83, 1.18)	0.89
>15.3%	2.17 (1.91, 2.45)	<0.0001	1.94 (1.71, 2.19)	<0.0001	1.25 (1.05, 1.49)	0.01
P for trend	<0.0001		<0.0001		0.0008	

RDW: red cell distribution width, HR: hazard ratio, CI: confidence interval, Ref: reference.

Cox proportional hazards regression models were used to calculate HRs with 95% CIs. Crude Model: no covariates were adjusted; model 1: covariates were adjusted for age, sex, and race; model 2: covariates were adjusted for age, sex, race, hemoglobin, hematocrit, white blood cell count, serum chloride, serum glucose, blood urea nitrogen, prothrombin time, coronary heart disease, atrial fibrillation diabetes, the Simplified Acute Physiology Score II, the Sequential Organ Failure Assessment score, and the Elixhauser Comorbidity Index score.

Table 3. Subgroup analysis of the associations between RDW and 30-day mortality.

Subgroups	No. of patients	RDW			*P* for interaction
		<13.7%	13.7%–15.3%	>15.3%	
Age (years)					<0.0001
<68.7	4127	1.0	1.87 (1.56, 2.25)	3.28 (2.77, 3.88)	
≥68.7	4127	1.0	1.36 (1.20, 1.55)	1.99 (1.76, 2.26)	
Sex					<0.0001
Female	3601	1.0	1.54 (1.32, 1.81)	2.25 (1.94, 2.62)	
Male	4653	1.0	1.48 (1.28, 1.70)	2.33 (2.03, 2.67)	
Race					0.9723
White	5799	1.0	1.55 (1.37, 1.75)	2.25 (1.99, 2.53)	
Black	1139	1.0	1.73 (1.14, 2.63)	2.88 (2.02, 4.12)	
Others	1316	1.0	1.26 (0.99, 1.61)	2.28 (1.82, 2.86)	
BMI (kg/m^2)					0.4015
<27.3	2348	1.0	1.70 (1.42, 2.03)	2.62 (2.21, 3.12)	
≥27.3	2352	1.0	1.70 (1.36, 2.12)	2.62 (2.11, 3.26)	
CHD					0.5238
No	4300	1.0	1.20 (1.04, 1.39)	2.02 (1.77, 2.32)	
Yes	3954	1.0	1.87 (1.60, 2.18)	2.51 (2.16, 2.93)	
DM					0.3055
No	6135	1.0	1.49 (1.32, 1.69)	2.37 (2.11, 2.67)	
Yes	2119	1.0	1.58 (1.29, 1.95)	2.15 (1.76, 2.64)	
AF					0.1922
No	5043	1.0	1.63 (1.41, 1.88)	2.65 (2.31, 3.04)	
Yes	3211	1.0	1.32 (1.13, 1.54)	1.86 (1.60, 2.16)	
Hypertension					0.8100
No	6391	1.0	1.55 (1.38, 1.75)	2.58 (2.30, 2.89)	
Yes	1863	1.0	1.17 (0.93, 1.48)	1.42 (1.13, 1.77)	

RDW: red cell distribution width, BMI: body mass index, CHD: coronary heart disease, DM: diabetes mellitus, AF: atrial fibrillation.

represents the change in erythrocyte volume. Several studies have indicated the prognostic value of RDW in critical diseases.[7,8]

The precise mechanisms underlying the relationship between mortality of patients in the CCU and RDW remain unknown. Potential hypotheses of involved mechanisms have been proposed, among which inflammation is the most popular. Inflammation is a major factor leading to various diseases, including CVD. Chronic low-level inflammation plays an important part in formation of plaques in atherosclerosis, subsequently contributing to instability of plaques and formation of thrombus. Previous studies have shown that the mechanisms of CVD may be associated with disruption of vascular barriers, accumulation of neutrophils, and an increase in pro-inflammatory cytokines.[22–24] Inflammatory responses can affect the function of bone marrow and some inflammatory cytokines can inhibit maturation of erythrocytes, thus leading to an increase in reticulocytes and an increase of RDW. Furthermore, oxidative stress can induce an increase of RDW via decreasing the life

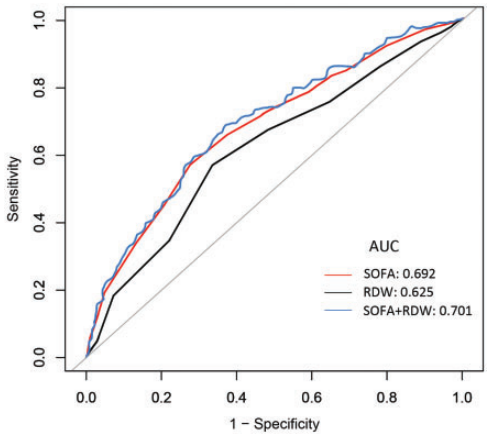

Figure 1. Receiver operator characteristic curve analysis for 30-day mortality of patients in the coronary care unit. AUC: area under the curve, SOFA: Sequential Organ Failure Assessment, RDW: red cell distribution width.

span of erythrocytes and releasing premature erythrocytes into the peripheral circulation.

As an easily-available biomarker, RDW has been used to predict the prognosis of various diseases.[7–12] Although the predictive value of RDW is not as good as that of SOFA score, it can play a role in rapid clinical evaluation. However, the results may be affected by a few factors, such as sepsis, transfusion, and changes in the microcirculation. An increase in RDW, which indicates anisocytosis, occurs with deficiency of folate, vitamin B12, and iron. Additionally, an increased RDW can also occur in hemolysis or after blood transfusion. In patients with sepsis, RDW may also significantly change.[25,26]

There are some limitations in our study. First, a single-center, retrospective study design was applied. Therefore, there was selection bias in our study. Consequently, prospective multicenter research is required in the future to solve this problem. Second, data were extracted from the first measurement at patients' admission. Because blood cells have a short lifespan, serial testing may be much more helpful than a single test. Third, RDW is easy to obtain in clinical practice, but the loss of RDW in the database is still common, which may lead to selection bias.

Conclusion

RDW levels are correlated with an increased risk in 30-day and 90-day mortality of patients in the CCU. However, the predictive value of RDW is not as good as that of the SOFA score.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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