Relationship between Red Cell Distribution Width and Short-term Outcomes in Acute Coronary Syndrome in a Chinese Population

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Abstract

Objective This study was undertaken to determine the relationship between red cell distribution width (RDW) and short-term outcomes in acute coronary syndrome (ACS) in a Chinese population.

Methods and Patients A total of 1,654 patients with ACS on admission were divided into four groups according to quartiles of baseline RDW. The relationships between RDW and one-month cardiac mortality as well as heart failure and recurrent infarction were assessed.

Results Higher RDW values were associated with increased one-month cardiac mortality (quartile 1: 0.2%; quartile 2: 0.6%; quartile 3: 3.3%; quartile 4: 8.1%; $p < 0.001$) and one-month heart failure and recurrent infarction (quartile 1: 2.1%; quartile 2: 2.7%; quartile 3: 3.6%; quartile 4: 15.2%; $p < 0.001$). Logistic regression analysis revealed that RDW independently predicted for cardiac mortality (OR: 2.116, 95% CI: 1.427-3.137, $p < 0.001$) and heart failure and recurrent infarction (OR: 2.134, 95% CI: 1.602-2.844, $p < 0.001$) during a one-month follow-up in patients with ACS.

Conclusion The present study indicates that elevated RDW could predict an increased risk of short-term adverse outcomes in patients with ACS.

Key words: red cell distribution width, acute coronary syndrome, cardiac mortality, heart failure

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Introduction

Red cell distribution width (RDW), a measure of red blood cell size heterogeneity, is reported as part of the routine blood cell count. Recent studies have reported that higher RDW is associated with long-term mortality in patients with heart failure, stable coronary disease, and also in the general population (1-3). However, there is no information regarding the short-term prognostic significance of RDW in Chinese patients with acute coronary syndrome (ACS). In this study, we investigated the association between RDW and the risk of short-term mortality and adverse cardiovascular outcomes in patients with ACS in a Chinese population.

Materials and Methods

Patients

From January 2006 to May 2010, 1,654 consecutive patients (961 men and 693 women) with ACS who were admitted to our institute were enrolled; these included ST-segment elevation myocardial infarction [(STEMI) 374 patients], non-ST-segment elevation myocardial infarction (NSTEMI) 323 patients], and unstable angina pectoris [(UA) 957 patients]. Diagnostic criteria of STEMI is 1) typical, prolonged chest pain at rest (>30 minutes); 2) ST-segment elevation ≥ 0.2 mV at the J point in 2 or more contiguous, precordial leads, or ≥ 0.2 mV in 2 or more adjacent limb leads on the standard 12-lead electrocardiogram (ECG); and

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3) increased serial serum markers of myocardial damage [>2 -fold increase over the upper normal range required for creatine kinase (CK) and troponin-I (TnI)] (4). UA/NSTEMI is defined by electrocardiographic (ECG) ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent) (5). Patients with equivocal or uninterpretable ECGs (i.e., left bundle branch block, paced rhythm, or persistent ST-segment elevation after a previous MI) were not included in the study. Basic drug treatment for ACS included antiplatelet agents, Beta-blockers, angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) and statins. Qualifying patients received thrombolytic therapy (tissue-type plasminogen activator or streptokinase) or underwent percutaneous coronary intervention (PCI) according to the discretion of the attending cardiologist. Each patient underwent PCI using standard techniques performed by experienced interventional cardiologists. Bleeding of PCI was small.

Furthermore, this study did not include patients with a history of anemia and blood transfusions, chronic heart failure, neoplastic, renal, liver, or thyroid disease, or patients receiving treatment with anti-inflammatory drugs. Patients with acute or chronic infections and autoimmune disease were also excluded from the study. The study protocol was approved by the ethics committee of our institution, and written informed consent was obtained from all participating subjects.

Clinical data collection

A special questionnaire was used to collect information on lifestyle, environmental factors, and medical history of the study population. Patients who reported smoking at least 1 cigarette per day for at least 1 year were defined as current smokers. Diabetes mellitus was defined as a previous diagnosis, use of diet or antidiabetic medicines, or fasting venous blood glucose level ≥ 126 mg/dL on 2 occasions in previously untreated patients. Patients who received medications for hypertension, or those with seated systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least 3 separate clinic visits were also identified. Height, weight, and body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Left ventricular ejection fractions (LVEF) were measured with Doppler echocardiography during the 3 days after admission.

Blood collection and assays

On admission, venous blood was obtained from all patients enrolled in the study. RDW, brain natriuretic peptide (BNP), high-sensitivity C-reactive protein (hs-CRP) and other biochemistry measurements were carried out by our biochemistry department using standard methods. Within 24 hours after admission, creatine phosphokinase (CPK) was measured for 6 hours and the maximum was recorded. The

normal reference range for RDW in this laboratory is 0.0% to 15.0%.

Study endpoints

All patients were followed-up for up to 1 month after discharge using a standardized protocol that included outpatient visits, telephone contacts, and the recording of recurrent cardiac events. The primary end point was cardiac death and the second outcomes were readmission for management of heart failure and recurrent infarction. A death was classified as cardiac if the predominant and immediate cause was related to myocardial infarction (MI) or ischemia, arrhythmia, refractory congestive heart failure, or sudden death. Heart failure was defined by the presence of new symptoms of dyspnea with pulmonary venous congestion on x-ray with interstitial or alveolar edema requiring hospitalization.

Statistical analysis

The study population was divided into 4 groups according to quartiles of baseline RDW. The lowest quartile served as the reference group. Data are expressed as means $\pm$ standard deviation (SD) for normally distributed variables. Non-normally distributed values are expressed as median and interquartile ranges. Qualitative data are presented as numbers (percentages). The comparison of the data among the four groups was performed by a one-way ANOVA or Kruskal-Wallis test for continuous variables and by a chi-square test for categorical variables. Correlations between RDW and other biochemistry measurements were assessed using Spearman's rank correlations test for these continuous variables with non-normal distribution, and logistic regression was used to analyze the relationship between RDW and short-term adverse outcomes of ACS. Logistic regression was adjusted for RDW categorized according to quartiles of distribution, BNP >100 ng/mL, LVEF $<40\%$, age >65 years, gender, history of hypertension and diabetes, smoking status, BMI, AMI on presentation, serum creatinine, peak CPK, number of diseased vessels ≥ 2 , Troponin-I (TNI), hs-CRP, white blood cell (WBC), hemoglobin and medical therapy (antiplatelet agents, beta-blockers, ACE-inhibitor/ARB, statins, thiazide diuretic and reperfusion therapy). A value of $p<0.05$ was considered statistically significant. All calculations were performed using SPSS statistical software for windows V11.5 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics

Compared with the control subjects, patients with higher RDW values were significantly older ($p<0.001$) and were observed with a significantly higher incidence in men than women ($p<0.001$). They were more likely to have history of hypertension ($p<0.001$) and diabetes mellitus ($p=0.007$) and to be current smoker ($p<0.001$). Meanwhile, there were significant higher levels of BMI ($p=0.005$), creatinine ($p<$

Table 1. Baseline Characteristics of the Study Population, Mean±SD, Number (%), or Median (Interquartile Range)

Characteristic	RDW quartiles				p value
	≤12.1 (n=419)	12.2-12.8 (n=364)	12.9-13.2 (n=463)	≥13.3 (n=408)	
Age (y)	62.62±11.90	63.02±11.90	66.30±10.78	67.06±12.92	<0.001
Gender (male)	257(61.3%)	118(32.4%)	321(69.3%)	265(65.0%)	<0.001
Hypertension (history)	241(72.8%)	242(79.6%)	348(85.1%)	307(80.4%)	<0.001
Diabetes mellitus	83(19.7%)	82(22.4%)	128(27.7%)	113(27.7%)	0.007
Current smoker	137(32.7%)	114(31.3%)	207(44.7%)	195(47.8%)	<0.001
BMI (kg/m ²)	24.68±3.43	24.64±3.32	25.37±3.09	25.50±3.54	0.005
AMI on presentation	171(41.2%)	153(42.3%)	194(42.6%)	179(44.3%)	0.810
Scr (μmol/L)	69.83±24.66	70.44±24.74	76.48±29.21	84.94±41.17	<0.001
Peak CPK (IU/L)	97.0(59.0-657.0)	108.0(60.0-1037.0)	117.0(61.0-949.0)	113.0(54.0-1230.0)	0.429
TNI (ng/mL)	0.21(0.01-2.36)	0.12(0.05-2.27)	2.84(0.05-9.19)	2.70(0.05-17.9)	<0.001
hs-CRP (mg/L)	1.38(0.03-4.02)	1.52(0.12-6.50)	1.68(0.01-5.29)	2.31(0.18-12.80)	<0.001
BNP (ng/mL)	79.7(0.98-294)	54.7(5.20-175)	51.6(0.1-123)	280.0(0.17-774)	<0.001
WBC (×10 ⁹ /L)	7.86±3.75	7.95±3.19	7.89±2.78	8.10±3.20	0.718
HGB (g/L)	139.11±49.93	133.57±13.72	133.11±38.49	127.96±20.77	0.016
LVEF (%)	62.60±11.67	61.74±9.71	60.92±9.08	58.19±12.30	<0.001
Number of diseased vessels ≥2 (stenosis ≥50%)	136(32.5%)	115(31.6%)	157(33.9%)	142(34.8%)	0.776
Medication	-	-	-	-	-
Antiplatelet agents	356(85.6%)	306(84.3%)	389(84.1%)	318(78.6%)	<0.001
Beta-blockers	360(86.3%)	302(83.1%)	370(80.5%)	330(81.2%)	<0.001
ACE-inhibitor/ARB	348(83.4%)	288(79.6%)	384(83.2%)	339(83.1%)	0.360
Statins	369(88.2%)	324(89.3%)	403(87.7%)	359(88.9%)	<0.001
Thiazide diuretic	8(2.3%)	15(3.5%)	14(3.4%)	16(4.3%)	0.194
Reperfusion therapy	235(56.1%)	200(55.7%)	259(56.2%)	220(54.4%)	0.926

Abbreviations: BMI, body mass index; AMI, Acute myocardial infarction; Scr, serum creatinine; CPK, creatine phosphokinase; TNI, Troponin-I; hs-CRP, high-sensitivity C-reactive protein; BNP, brain natriuretic peptide; WBC, white blood cell; HGB, hemoglobin; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2. Spearman's Correlations Analysis between RDW and Other Biochemistry Markers (n=1654)

Variable	RDW	
	r value	p value
BNP	0.211	<0.001
hs-CRP	0.070	0.018
TNI	0.110	0.003
Scr	0.118	<0.001
WBC	-0.003	0.913
HGB	-0.111	0.001

Abbreviations: BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; TNI, Troponin-I; Scr, serum creatinine; WBC, white blood cell; HGB, hemoglobin.

Correlations between RDW and other biochemistry markers

In the whole study population, using RDW as a continuous variable, there was a slight correlation between RDW and BNP ($r=0.211$, $p<0.001$). The correlation coefficient between RDW and hs-CRP was 0.070 ($p=0.018$). Correlations between RDW and other biochemistry markers are presented in Table 2.

Relationship between RDW and cardiac mortality at 1 month

Follow-up information was available for 1,604 patients (97.0%) from the 1,654 ACS patients at 1 month. There were a total of 50 deaths (3.1%) classified as cardiac in etiology. Cardiac death was more likely to occur in patients with higher RDW values (quartile 1: 0.2%; quartile 2: 0.6%; quartile 3: 3.3%; quartile 4: 8.1%; $p<0.001$). After multivariable adjustment for other important covariates mentioned above, the variables remaining in the equation were RDW (quartiles), BNP>100 ng/mL and LVEF<40% (Table 3). Using baseline RDW as a categorical variable according to quartiles, the adjusted Odds Ratio for cardiac mortality in-

0.001), troponin-I ($p<0.001$), hs-CRP ($p<0.001$) and BNP ($p<0.001$) in patients with higher RDW values. They had a lower level of hemoglobin ($p=0.016$) and LVEF ($p<0.001$). However, there was no significant difference in AMI on presentation, peak CPK, WBC, medication of ACE-I/ARB and thiazide diuretic, number of diseased vessels ≥ 2 or reperfusion therapy among the four groups. Clinical characteristics of patients according to quartiles of baseline RDW are presented in Table 1.

Table 3. Logistic Regression Analysis for Predictors of Cardiac Mortality

Variable	Odds Ratio	95% Confidence Interval	p value
BNP>100	3.510	1.221-10.093	0.020
RDW(quarters)	2.116	1.427-3.137	<0.001
LVEF<40%	4.149	2.001-8.602	<0.001

Abbreviations: BNP, brain natriuretic peptide; RDW, Red cell distribution width; LVEF, left ventricular ejection fraction.

crease was 2.116 (95% CI: 1.427-3.137, $p<0.001$). Meanwhile, BNP>100 ng/mL (OR: 3.510, 95% CI: 1.221-10.093, $p=0.020$) and LVEF<40% (OR: 4.149, 95% CI: 2.001-8.602, $p<0.001$) were identified as significant independent predictors of cardiac mortality by logistic regression analysis.

Relationship between RDW and heart failure and recurrent infarction at 1 month

During one-month follow-up, 95 patients (5.9%) were re-admitted for management of heart failure and recurrent infarction. Higher RDW values were associated with increased prevalence of heart failure and recurrent infarction: (quartile 1: 2.1%; quartile 2: 2.7%; quartile 3: 3.6%; quartile 4: 15.2%; $p<0.001$). Based on multivariable logistic regression analysis, RDW (quarters) was found to be an independent predictor of heart failure and recurrent infarction at 1 month (OR: 2.134, 95% CI: 1.602-2.844, $p<0.001$). In addition, logistic regression analysis also identified age>65 years (OR: 2.010, 95% CI: 1.135-3.560, $p=0.017$) and diabetes mellitus (OR: 2.279, 95% CI: 1.345-3.862, $p=0.002$) and LVEF<40% (OR: 5.009, 95% CI: 2.694-9.316, $p<0.001$), as significant independent predictors of heart failure and recurrent infarction at 1 month (Table 4).

Discussion

The present study showed that adverse events were more likely to occur in patients with ACS during short-term follow up if they had higher RDW values. Furthermore, RDW was positively correlated with BNP and hs-CRP. Logistic regression analysis revealed that RDW was an independent predictor for cardiac mortality and the onset of heart failure and recurrent infarction during a one-month follow-up in patients with ACS. The results suggest that measuring the RDW level may provide valuable information for short-term risk stratification of ACS. These findings are also notable given that RDW is widely available to clinicians as part of the complete blood count and therefore incurs no additional costs, in contrast to other novel markers of cardiovascular risk.

RDW reflects the variability in circulating red blood cell size. It is based on the width of red blood cell volume distribution curve, with larger values indicating greater variability (6, 7), RDW is typically increased in conditions of ineffective red cell production (such as iron deficiency, B12 or folate deficiency, and hemoglobinopathies), increased red cell destruction (such as hemolysis), and with blood transfusion (8, 9). However, all of these conditions were not pre-

Table 4. Logistic Regression Analysis for Predictors of Heart Failure and Recurrent Infarction

Variable	Odds Ratio	95% Confidence Interval	p value
Age>65 years	2.010	1.135-3.560	0.017
Diabetes mellitus	2.279	1.345-3.862	0.002
RDW (quarters)	2.134	1.602-2.844	<0.001
LVEF<40%	5.009	2.694-9.316	<0.001

Abbreviations: RDW, Red cell distribution width; LVEF, left ventricular ejection fraction.

sent in our study population and adjustment for multiple potential confounders attenuated but did not eliminate the strong association between higher RDW levels and the adverse clinical outcomes.

The mechanism by which elevated values of RDW are associated with adverse outcomes is unknown. It has been suggested that RDW may reflect other known markers of prognosis in heart failure, such as inflammatory cytokines, which may affect bone marrow function and iron metabolism (10, 11). Inflammatory cytokines have been found to suppress the maturation of erythrocytes, allowing juvenile erythrocytes to enter into circulation and thereby leading to an increase in heterogeneity of the size (12, 13). Furthermore, higher RDW may reflect enhanced erythropoiesis resulting from elevated circulating levels of neurohumoral mediators (14, 15). There is increasing evidence that a chronic inflammatory state and neurohumoral activation each contribute to adverse clinical outcomes in patients with ACS (16, 17).

In the present study, RDW was positively correlated with BNP ($r=0.211$, $p<0.001$) and hs-CRP ($r=0.070$, $p=0.018$). Although BNP is produced mainly by the ventricle, a variety of vasoconstrictive neurohormones including angiotensin II and norepinephrine have been found to directly enhance BNP secretion (18, 19). These aspects may explain RDW was positively correlated with BNP in our study. However, we can see that the correlation coefficients between RDW and BNP, hs-CRP were both low; the time of blood collection might affect the values. Thus, in this study we could not reveal the exact mechanism of the association of higher RDW and increased adverse outcomes in patients with ACS. Additional studies should be performed to determine the underlying factors that affect RDW.

The present study had several limitations. First, this was a post hoc observational analysis, and therefore we cannot rule out the possibility of residual confounding. However, the hypothesis that RDW levels would be associated with adverse outcomes was formulated before analyses were started, reducing the risk of spurious conclusions. Second, although we speculate that neurohumoral activation may be a mechanistic link between increased RDW and adverse outcomes in this population, we did not measure the plasma level of angiotensin II or norepinephrine in our patients. Third, we did not have data on the changes in RDW during the hospital course. Changes in RDW during the hospital course for ACS may predict short-term clinical outcomes better (20).

In conclusion, in patients with ACS, elevated RDW could predict an increased risk of short-term adverse outcomes. More studies are needed to address the mechanism and treatment.

The authors state that they have no Conflict of Interest (COI).

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