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*Original Article*

# Predictive value of red blood cell distribution width for the long-term prognosis of patients with acute ST elevation myocardial infarction after percutaneous coronary intervention

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**Abstract:** Objective: To study the predictive value of red blood cell distribution width (RDW) for the long-term prognosis of patients with acute ST elevation myocardial infarction (STEMI) after percutaneous coronary intervention (PCI). Methods: A total of 309 patients with acute ST elevation myocardial infarction (STEMI) who underwent PCI in our hospital from Nov. 2009 to Aug. 2013 were selected as the subjects. According to the upper limit of the normal range of RDW (14%), patients were divided into the high RDW group and the low RDW group. Death was considered as the primary endpoint of the study, and major adverse cardiovascular events (MACE) as the secondary endpoint. Kaplan-Meier survival analysis was used to determine the difference in the cumulative survival rate between the two RDW groups. Multivariate Cox regression analysis was used to study the independent influencing factors in STEMI patients after PCI. Results: The longest follow-up time was 40 months; the median follow-up time was 10 (3-24) months. The mortality rate of patients in the high RDW group was higher than that of patients in the low RDW group ($P$=0.018). The incidence of MACE ($P$=0.003) and mortality rate ($P$=0.029) of patients in the high RDW group was significantly higher than those of the patients in the low RDW group. However, there was no significant difference in the incidence of recurrent myocardial infarction event, target vessel revascularization, and stroke between the high and low RDW groups. Multivariate Cox regression analysis showed that age (hazard ratio [HR]: 1.06; 95% confidence interval [95% CI]: 1.02-1.08; $P$=0.004), white blood cells (HR: 1.16; 95% CI: 1.07-1.25; $P$<0.001), high RDW (HR: 2.21, 95% CI: 1.23-4.67, $P$=0.023), creatinine (HR: 1.007, 95% CI: 1.003-1.011, $P$=0.001), and left ventricular ejection fraction (HR: 0.93; 95% CI: 0.89-0.98; $P$=0.002) were independent factors influencing the mortality rate of STEMI patients. Kaplan-Meier survival analysis showed that the cumulative survival rate of the patients in the high RDW group was significantly lower than that of the patients in the low RDW group (Log Rank =8.00, $P$=0.005). The cumulative mortality rate was 19.5% in the high RDW group and 8.1% in the low RDW group. The difference in the cumulative mortality rate between the two groups was significant ($\chi^2$=8.80, $P$=0.003). Conclusion: Our results suggest that high RDW is an independent risk factor for long-term mortality of STEMI patients after PCI and it can be used for risk stratification in patients after admission.

**Keywords:** Red blood cell distribution width, ST elevation myocardial infarction, percutaneous coronary intervention, mortality, major adverse cardiovascular events

## Introduction

The main pathogenesis of ST segment elevation myocardial infarction (STEMI) is the occlusion of the coronary lumen in whole or in part caused by coronary atherosclerotic plaque rupture and thrombosis [1]. Although the treatment for STEMI has been improved, STEMI patients still have a high mortality rate, and their long-term prognosis is poor [1, 2]. The red blood cell distribution width (RDW), which quantitatively reflects the outside red blood cell volume, is a commonly used indicator of heterogeneity [3]. The degree of variation in the volume

of red blood cells in the peripheral blood increases as the RDW increases. The reasons for an increase in RDW values include incapability to produce red blood cells due to the lack of iron, vitamin B2, or folic acid; hemolysis, which leads to increased red blood cell destruction; and blood transfusion [4]. RDW is often used in clinical settings as a diagnostic parameter for anemia [5]. Recent studies have shown that an increased RDW may be a predictive factor for heart failure and coronary heart disease mortality and that it can be regarded as a dependent indicator of cardiovascular mortality; however, some have shown that a high RDW cannot identify patients at high risk for cardiovascular disease [6]. This prospective research aimed to explore the relationship between high RDW and adverse events in STEMI patients after percutaneous coronary intervention (PCI) and to provide a theoretical basis for RDW as a prognostic indicator of STEMI after PCI.

## Methods

### *Research subjects*

Patients who were diagnosed with STEMI and admitted to our hospital from Nov 2009 to Aug 2013 were considered as subjects. Inclusion criteria were as follows: 1) sustained chest pain within 12 hours (cardiogenic shock within 18 hours); 2) ST-segment elevation of at least 1 mm in two or more contiguous leads (2 mm for V1-V3); and 3) appearance of new-onset left bundle branch block. The exclusion criteria were as follows: 1) severe liver and kidney dysfunction; 2) autoimmune diseases; 3) cancer, chemotherapy, or organ transplant; 4) blood diseases such as anemia and leukemia; 5) blood transfusion within the past 1 month; and 6) acute and chronic infections.

### *RDW measurement*

Blood samples were collected, from all patients at the time of admission, from the cubital vein using a vacuum tube. RDW and related indicators (e.g., RBC, white blood cell count, and mean platelet volume) were examined using the Sysmex XS-800 automatic blood cell analyzer (Sysmex, Japan). The normal reference value for RDW is in the range of 11%-14% according to the analyzer. In this study, 14% was set as the threshold; those with RDW>14% were included in the high RDW group and those with RDW≤14% were included in the RDW group.

### *Follow up*

Case collection table was used to collect basic information of patients such as data regarding laboratory examination results, coronary angiography results, process after PCI, and in-house mortality rates. Regular clinic or telephone interviews were adopted to obtain follow up data after patients were discharged from the hospital.

Follow-up data included data regarding adverse cardiovascular events (death, recurrent myocardial infarction, target vessel revascularization, and stroke), follow-up time, and drug use. The follow-up ended when patients experienced a cardiovascular event or on August 31, 2014; the average follow-up duration was 20 months.

### *Definitions*

Essential hypertension was diagnosed mainly based on the 2010 Chinese guidelines for the management of hypertension: three times extraordinary day brachial blood pressure measurement, SBP≥140 mmHg and/or DBP≥90 mmHg, while not taking antihypertensive drugs. Even if the blood pressure was below 140/90 mmHg, hypertension was diagnosed if the patient had a history of hypertension and the patient was receiving antihypertensive drug treatment [7]. Diabetes was diagnosed according to the standards of diabetes set by the World Health Organization in 1999. Patients with random blood glucose ≥11.1 mmol/l or fasting venous plasma glucose ≥7.0 mmol/l or 2-h OGTT blood glucose ≥11.1 mmol/l, along with typical clinical symptoms of diabetes were also diagnosed with diabetes. Moreover, patients taking insulin or oral hypoglycemic drugs were considered to have diabetes as well [8]. Dyslipidemia was diagnosed, according to the 2007 China Adult Dyslipidemia Prevention Guide [9], if any one of the following was noted: TC≥5.18 mmol/l, TG≥1.70 mmol l, HDL-C<1.04 mmol/l, LDL-C≥3.37 mmol/l, or routine use of lipid-lowering drugs. Smoking status was determined based on the WHO smoking recommendations: subjects were considered to have a smoking history if they smoked ≥5 cigarettes per day and had been smoking for ≥3 years, if

**Table 1.** Clinical baseline data of the two groups of patients

| Variable | Low RDW group (n=186) | High RDW group (n=123) | $\chi^2$/t | *P* |
|---|---|---|---|---|
| Age (years old) | 56±12 | 62±11 | -4.18 | <0.001 |
| Male [n (%)] | 129 (82.2) | 121 (79.6) | 0.33 | 0.567 |
| Diabetes history [n (%)] | 37 (23.6) | 40 (26.3) | 0.31 | 0.577 |
| Hypertension history [n (%)] | 79 (50.3) | 74 (48.7) | 0.08 | 0.774 |
| Smoking history [n (%)] | 94 (59.9) | 89 (58.6) | 0.39 | 0.820 |
| Systolic pressure (mmHg) | 123±17 | 124±21 | -0.21 | 0.831 |
| Diastolic pressure (mmHg) | 76±14 | 75±13 | 0.55 | 0.585 |
| Heart rate (b/min) | 79±14 | 79±13 | -0.13 | 0.895 |
| White blood cell count ($10^9$/L) | 10.9±3.6 | 10.9±3.8 | -0.14 | 0.892 |
| Red blood cell count ($10^9$/L) | 4.73±0.54 | 4.53±0.68 | 2.74 | 0.007 |
| Hemoglobin (g/L) | 144±18 | 137±20 | 3.45 | 0.001 |
| Serum creatinine (umol/L) | 80±41 | 90±53 | -1.89 | 0.059 |
| Left ventricular ejection fraction (%) | 59±6 | 56±7 | 3.41 | 0.001 |
| After discharge of drug therapy [n (%)] | | | | |
| Aspirin | 180 (96.7) | 118 (95.9) | 0.15 | 0.697 |
| Clopidogrel | 185 (99.5) | 122 (99.2) | 0.10 | 0.749 |
| Statins | 179 (96.2) | 120 (97.6) | 0.42 | 0.520 |
| Beta blockers | 166 (89.2) | 108 (87.8) | 0.15 | 0.695 |
| ACEI/ARB | 151 (81.2) | 102 (82.9) | 0.15 | 0.697 |
| Left main disease [n (%)] | 8 (4.3) | 10 (8.1) | 1.99 | 0.160 |
| Genisi integral | 45 (32-82) | 59 (38-84) | -1.966 | 0.045 |

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Adrenergic receptor blocker.

had a >10-year history of smoking, or if they had quit smoking less than 1 year ago. Subjects were considered to be alcohol consumers if they consumed any kind of alcohol once a week on an average. Gensini integral method was used to assess every branch of coronary artery stenosis quantitative. Coronary artery diameter stenosis ≤25% as 1 point, 26% to 50% as 2 points, 51% to 75% as 4 points, 76% to 90% as 8 points, 91% to 99% as 16 points, 100% as 32 points, multiplied by different coefficients of vascular lesions segment. The total integral was the sum of each of the segment points [10].

*Statistical analysis*

SPSS17.0 statistical software was used for statistical analysis. Data that followed a normal distribution were expressed as mean ± standard deviation. Data that did not follow a normal distribution were shown as the median and interquartile range. The independent sample t test was used for comparisons between the two groups, and the F test was used for testing among three or more groups when data were consistent with a normal distribution; the rank sum test was used when the data did not follow a normal distribution. Count data was represented by using frequency and percentage. Group comparison was tested by using the $\chi^2$ test. Kaplan-Meier survival analysis was adopted to determine the difference in mortality rates between the high and low RDW patients. Multivariate Cox regression analysis was applied to determine the relationship between high RDW and mortality in patients with STEMI. If the two-sided *P* value was <0.05, the difference was considered as statistically significant.

## Results

*Research subjects*

In total, 309 patients with STEMI were selected. Of these, 80.9% were men. The patients were aged 45-81 years. The median age was 63 years, and the average age was 65.6±12.8 years.

**Table 2.** Comparison of adverse events in the two groups

| Variable | Low RDW group (n=186) | High RDW group (n=123) | $\chi^2$/t | *P* |
|---|---|---|---|---|
| Died during hospitalization [n (%)] | 9 (4.8) | 15 (12.2) | 5.59 | 0.018 |
| MACE occurred after discharge [n (%)] | 25 (13.4) | 33 (26.8) | 8.70 | 0.003 |
| Death [n (%)] | 5 (2.7) | 10 (8.1) | 4.75 | 0.029 |
| Recurrent myocardial infarction [n (%)] | 2 (1.1) | 1(0.8) | 0.05 | 0.818 |
| Target vessel revascularization [n (%)] | 2 (1.1) | 4 (3.3) | 1.84 | 0.175 |
| Stroke [n (%)] | 1 (0.5) | 2 (1.6) | 0.91 | 0.340 |

MACE: Major adverse cardiovascular events, RDW: Red cell distribution width.

**Table 3.** Results of the multivariate cox regression analysis of the mortality of STEMI patients after discharge

| Variable | Univariate cox regression analysis | | | Multiariable cox regression analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | 1.07 | 1.03-1.10 | <0.001 | 1.06 | 1.02-1.08 | 0.004 |
| Systolic pressure | 0.98 | 0.96-0.94 | 0.006 | - | - | - |
| Diastolic pressure | 0.96 | 0.94-0.99 | 0.002 | - | - | - |
| Heart rate | 1.03 | 1.01-1.05 | 0.007 | - | - | - |
| White blood cells | 1.15 | 1.07-1.24 | <0.001 | 1.16 | 1.07-1.25 | <0.001 |
| Red blood cells | 0.45 | 0.28-0.72 | 0.001 | - | - | - |
| Hemoglobin concentration | 0.98 | 0.97-0.99 | 0.004 | - | - | - |
| Higher RDW group | 2.30 | 1.20-4.39 | 0.012 | 2.21 | 1.23-4.67 | 0.023 |
| Creatinine | 1.005 | 1.002-1.008 | <0.001 | 1.007 | 1.003-1.011 | 0.001 |
| Triglycerides | 0.69 | 0.50-0.96 | 0.028 | - | - | - |
| Total cholesterol | 0.71 | 0.51-0.99 | 0.041 | - | - | - |
| Left ventricular ejection fraction | 0.92 | 0.88-0.95 | <0.001 | 0.93 | 0.89-0.98 | 0.002 |

RDW: Red cell distribution width.

*Characteristics of patients in the two groups*

The High RDW group had a higher average age (*P*<0.001), higher Gensini integral (*P*<0.05), lower red blood cell count (*P*=0.007), lower hemoglobin (*P*=0.001) levels, and lower left ventricular ejection scores (*P*=0.001) than the low RDW group. These differences were statistically significant (**Table 1**).

*Adverse cardiovascular events in the two groups*

The mortality rate of the high RDW group was significantly higher than that of the low RDW group (*P*=0.018) during the time in the hospital. Meanwhile, the incidence of MACE (*P*=0.003) and mortality rate (*P*=0.029) in the high RDW group were both significantly higher than those in the low RDW group in the follow up period. However, the incidence of recurrent myocardial infarction event, target vessel revascularization, and stroke events were not significantly different between the two groups (**Table 2**).

*Multivariate cox regression analysis of the mortality of STEMI patients after discharge*

Univariate Cox regression analysis showed that age, systolic blood pressure, diastolic blood pressure, heart rate, white blood cells, red blood cells, hemoglobin concentration, high RDW, creatinine, triglycerides, total cholesterol, and left ventricular ejection fraction were related to the mortality rates of STEMI patients after discharge from the hospital. Multivariate Cox regression analysis showed that age (HR: 1.06; 95% CI: 1.02-1.08; *P*=0.004), leukocytes (HR: 1.16; 95% CI: 1.07-1.25; *P*<0.001), high RDW (HR: 2.21; 95% CI: 1.23-4.67; *P*=0.023), creatinine (HR: 1.007; 95% CI: 1.003-1.011; *P*=0.001), and left ventricular ejection fraction (HR: 0.93; 95% CI: 0.89-0.98; *P*=0.002) were all independent factors that predicted mortality

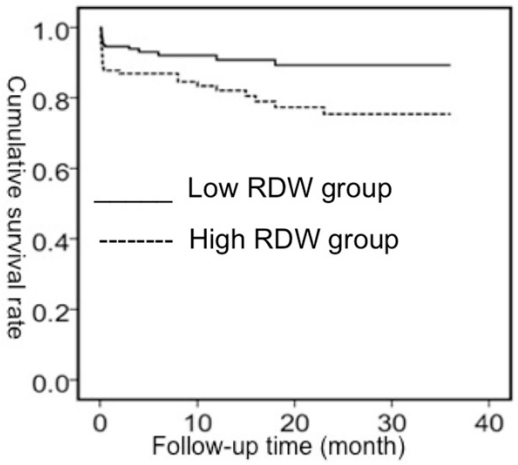


**Figure 1.** Survival analysis between the two groups after discharge.

of STEMI patients after their discharge from the hospital (**Table 3**).

*Survival analysis between the two groups after discharge from the hospital*

As shown in the Kaplan-Meier survival analysis, the cumulative survival rate of the high RDW group was significantly lower than that of the low RDW group (Log Rank =8.00, $P$=0.005). The high RDW group had a cumulative mortality rate of 19.5% while the low RDW group had a cumulative mortality of 8.1%; the difference was statistically significant ($\chi^2$=8.80, $P$=0.003) (**Figure 1**).

## Discussion

This research showed that STEMI patients with a high RDW had relatively higher mortality and long-term mortality rates after leaving the hospital and a lower cumulative survival rate than patients with a low RDW. Also, high RDW was found to be an independent risk factor of death in STEMI patients. Thus, data regarding high RDW obtained during admission can be used for risk stratification in STEMI patients after PCI.

Fukuta *et al*. studied 206 cases of coronary heart disease for the first time in 2009 [11] and reported that RDW and atrial natriuretic peptide (B-type natriuretic peptide) are significantly correlated. In the same year, Lippi *et al.* [12] reported that RDW has a diagnostic value for emergency acute coronary syndrome (acute coronary syndrome [ACS]); the area under the ROC was 0.71, the sensitivity was 0.79, the specificity was 0.50, and the optimal clinical cut-off point was 14%. The RDW value for ACS patients was higher than that of non-cardiac chest pain patients. Nabais [13] followed-up 1,796 ACS patients for 6 months and found that a high RDW at admission is an independent influential factor for short-term all-cause mortality and cardiac death in ACS patients.

After following-up 619 cases of non-ST-segment elevation myocardial infarction (non-ST-segment elevation myocardial infarction) for 4 years, Azab *et al.* [14] found that when the RDW increases by 1 unit, the risk of death increases by 10%. Lappe *et al.* [15] followed up 1489 cases of coronary heart disease for 8.4-15.2 years and found that higher RDW is an independent predictor of coronary heart disease in patients with all-cause mortality. Poludasu *et al.* [16] studied 859 patients who had undergone PCI and after adjusting for confounding factors, found that RDW and long-term mortality have no significant relationship. Currently, there are no consistent findings on the long-term prognostic value of RDW for acute myocardial infarction [17]. This study is a prospective study with a follow-up time of 40 months. This study further validates that high RDW is an independent predictor of short-term and long-term prognosis for patients with STEMI after PCI and shows that high RDW has an important clinical value for assessing the severity of STEMI patients after PCI.

Oxidative stress and inflammation are both assumed to be the key factors influencing the RDW [18]. Semba *et al.* [19] followed up women aged ≥65 years in the community with moderate to severe disability for 12 months and 24 months. They discovered that selenium influences RDW independently. They also confirmed that oxidative stress is effective in reducing the life span of red blood cells by making them more susceptible to hemolysis [20, 21].

Inflammation and ineffective erythropoiesis have a strong correlation. Inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, and IL-6 desensitize the production of red blood cells from bone marrow hematopoietic progenitor cells and inhibit red blood cell maturation, resulting in anisocytosis [22].

Tonelli *et al.* [23], in a prospective study, found that high RDW and adverse outcomes were significantly related, after several adjustments for confounding variables including estimated glomerular filtration rate (EGFR) were made. However, other studies showed a significant relation between increased RDW and impaired renal function and complications. This relationship may be partly due to the fact that chronic inflammatory conditions such as chronic kidney disease cause RBC abnormalities.

The technology for RDW determination is advanced; moreover, the test is easy to perform and has low costs and hence, it can be one of the most basic routine clinical blood examinations; accordingly, it has been widely used in our medical institution at all levels. Therefore, use of RDW values for the preliminary assessment of the prognosis of patients with STEMI can be easily implemented. Although it is not clear how cardiovascular disease results in an increase in RDW, RDW can be used in clinical settings as a marker for cardiovascular disease, which can help in early detection and diagnosis.

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## Disclosure of conflict of interest

None.

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