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Original Article

Elevated red cell distribution width is associated with poor clinical outcomes in non-ischemic dilated cardiomyopathy

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Abstract: Object: Elevated red cell distribution width (RDW) is associated with adverse outcomes in patients with heart failure. However, the prognostic value of RDW in non-ischemic dilated cardiomyopathy (NIDCM) remains to be further explored. A total of 124 consecutive patients with NIDCM were enrolled in this study. The association between RDW and the prognosis of NIDCM patients, including re-hospitalization risk and death risk, was assessed using Cox's proportional hazards analysis. Results: RDW was elevated in 63 (50.8%) patients. During follow-up, the re-hospitalization rate and all-cause mortality were 58.9% and 28.2%, respectively. Kaplan-Meier survival curve showed that the incidence of both end points was significantly higher in the RDW elevated group than in the RDW normal group (P<0.001). Multiple Cox proportional hazard analysis indicated that RDW (1% higher) remained as independent predictor for all-cause death in patients with NIDCM (hazard ratio, 1.51; 95% confidence interval, 1.21~1.87; P<0.001) and re-hospitalization (hazard ratio, 1.19; 95% confidence interval, 1.06~1.34; P=0.005) after adjustment for other covariates. Conclusion: When RDW was increased by 1%, re-hospitalization of heart failure and all-cause mortality increased by 19% and 51%, respectively. Our study further investigated the independently predicting role of RDW for patients with NIDCM, elevation of RDW could provide useful information for the long-term prognosis of NIDCM.

Keywords: Red cell distribution width, non-ischemic dilated cardiomyopathy, prognosis, re-hospitalization rate

Introduction

Heart failure (HF) is a chronic and progressive disease with high mortality overall world. It could be induced by various causes (i.e. ischemia, viral infection, etc.) and presents as the final stage of all heart diseases. In clinical practice, ischemic cardiomyopathy and non-ischemic cardiomyopathy are two major pathogenesis of HF. Non-Ischemic Dilated cardiomyopathy (NIDCM) is the primary non-ischemic heart muscle disease, as well as one of the major cause for heart failure [1].

Red blood cell distribution width (RDW) is a simple parameter of the standard full blood count and a measure of heterogeneity in the size of circulating erythrocytes, which has traditionally played a role in the differential diagnosis of anaemia.

It has been reported that elevated RDW is deeply related with adverse outcomes of HF patients [2, 3]. However, this association was dependent of other hematological variables such as mean corpuscular volume (MCV) and even hemoglobin or hematocrit levels [2]. The etiology of heart failure is also complex and may be caused by coronary artery disease, endocrine disease, heart valve disease, hypertension, acute pulmonary embolism, emphysema or other chronic lung diseases. NIDCM occupies relatively certain proportion of HF, and the pathogenesis and prognosis of NIDCM are completely different from those of heart failure caused by ischemia or other reasons. However, the prognostic impact of RDW in patients with NIDCM has not been fully elucidated. In the present study, we investigated the association between RDW level and long-term prognosis in patients with NIDCM.

Materials and methods

Study participants

This study complied with the Declaration of Helsinki, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Informed consent was obtained from every enrolled patient. 124 consecutive cases of inpatient with NIDCM (91 men; mean age: 51.6±14.7 years; range, 16-80) were selected from the Department of Cardiology in the First Affiliated Hospital of Zhengzhou University.

NIDCM is defined as a primary heart muscle disease characterized by systolic dysfunction and dilatation of the left or both ventricles in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment, usually leading to heart failure, ventricular/supraventricular arrhythmias, thromboembolism and sudden cardiac death (SCD) [1]. Reduced ejection fraction (EF) (EF<40%) or borderline preserved EF (ranged from 41% to 49%), are both defined as heart failure clinically.

Patients were included if the left ventricular end-diastolic diameter (LVEDD) >55 mm (male)/50 mm (female) with left ventricular ejection fraction (LVEF) <50%, admission to echocardiography. The exclusion criteria of the study was patients with acute myocarditis, specific heart muscle disease, general systemic disease, significant coronary artery stenosis (defined as diameter narrowing of >50% in any of the major coronary arteries or their branches), hypertension (>160/100 mmHg), valvular disease, and sensitivity/toxic reactions [2, 3]. All the patients were given standard medication according to the guideline recommendations during the period of hospitalization and after discharge.

Clinical data collection

Trained research assistants, who retrospectively reviewed all individual medical records, undertook the data collection. Basic information including age, sex, medical histories, course of NIDCM, NYHA heart function classification, history of smoking and alcohol, medical history of diabetes, COPD and atrial fibrillation, and data regarding treatment (oral medications and whether with pacemaker therapy) were collected. Blood samples were taken from the enrolled patients for measurements at baseline. Laboratory measurements were conducted by the clinical laboratory of the First Affiliated Hospital of Zhengzhou University, including RDW, hemoglobin, serum N-terminal pro-brain natriuretic peptide (NT-pro BNP), serum sodium, renal function and total serum protein. LVEF and the size of cardiac chambers (left atrial and both ventricles) were calculated by 2-dimensional echocardiography using a digital imaging system (Vivid-7; GE Medical System, Willoughby, OH). All the data above were collected in the first three days of hospitalization. During the following-up period, adverse events after discharge, were recorded. We set all-cause death and re-hospitalization due to heart failure as the primary clinical outcomes. All patients were followed-up in telephone after discharge until April 2017 or the incidence of the two primary outcomes.

Statistical analysis

The data was analyzed with SPSS version 22.0 (IBM SPSS Inc, Chicago, IL). Continuous variables were presented as medians (inter-quartile) ranges or the mean ± standard deviations (SD). The Shapiro-Wilk's test was performed to evaluate normality. Categorical variables were presented as absolute and relative frequencies. Mean values in groups were compared using parametric statistics (Student's *t* test and analysis of variance) or nonparametric statistics (Mann-Whitney and Kruskal-Wallis' tests), depending on the distribution of the variable of interest. The categorical variables were compared using general X^2 test or Fisher's exact test. If distribution of variables was normal, we selected the Pearson's correlation analysis for univariate correlation analysis; and if not normal, Spearman's correlation analysis was chosen. To identify independent predictors of RDW, multivariate linear regression analysis was performed following univariate correlations, with variables which have a retention of *P*-value less than 0.01 entering into the model. A multivariate Cox proportional hazards model was used to calculate risk ratios for independent predictors of mortality and re-hospitalization in continuous variables. To investigate the difference of survival rate and re-hospitalization rate of patients between the two groups, Kaplan-Meier

Table 1. Baseline characteristics of study patients stratified by RDW below or above the upper limit of normal

Clinical variables	Total patients N=124	RDW≤14.5% N=61	RDW>14.5% N=63	*P*-value
Age (years)	51.6±14.7	53.9±14.2	49.4±14.9	0.092
Gender (% male)	91 (73.4)	45 (73.8)	46 (73.0)	0.924
NYHA functional class (%)				<0.001
II-III	62 (50.0)	41 (67.2)	21 (33.3)	
IV	62 (50.0)	20 (32.8)	42 (66.7)	
Disease duration (years)	2 (0.5)	2 (0.5)	3 (1.5)	0.088
Smoking history (%)	32 (25.8)	17 (27.9)	15 (23.8)	0.606
Alcohol history (%)	22 (17.7)	14 (23.0)	8 (12.7)	0.135
Diabetes (%)	25 (25.1)	15 (24.6)	10 (15.9)	0.226
COPD (%)	7 (5.6)	4 (6.6)	3 (4.8)	0.715
Atrial fibrillation (%)	36 (29)	17 (27.9)	19 (30.2)	0.779
β receptor blocker (%)	90 (72.6)	46 (75.4)	44 (69.8)	0.487
ACEI/ARB (%)	107 (86.3)	53 (86.9)	54 (85.7)	0.850
Spirolactone (%)	111 (89.5)	50 (82.0)	61 (96.8)	0.007
Pacemaker (%)	13 (10.5)	5 (8.2)	8 (12.7)	0.413
RVEDD (mm)	20.0 (17.0, 22.8)	18.0 (17.0, 20.5)	21 (18.0, 27.0)	<0.001
LAD (mm)	47 (40, 52)	44 (39, 49)	50 (42, 55)	0.001
LVEDD (mm)	69 (61, 77)	69.0 (61.5, 76.0)	70.0 (60.0, 78.0)	0.830
LVEF (%)	32 (28, 36)	33 (29, 37)	30 (28, 35)	0.116
SBP (mmHg)	117.0±16.6	121.5±16.4	112.3±15.8	0.003
DBP (mmHg)	72.4±11.8	75.3±12.5	69.6±10.4	0.007
Serum sodium (mmol/L)	139.5 (135.3, 142.3)	141.2 (137.5, 143.0)	138.0 (135.0, 141.0)	0.001
Uric acid (μmol/L)	470.0 (342, 657.5)	415 (316, 592)	510 (405, 670)	0.010
Scr (mL/min)	80.0 (71.0, 100.8)	77.0 (65.0, 92.5)	83.0 (76.0, 108.0)	0.014
Urea nitrogen (mmol/L)	7.6 (6.1, 10.0)	7.2 (5.7, 9.6)	8.5 (6.3, 10.1)	0.083
GFR (ml/min)	87.9 (68.0, 100.6)	91.5 (73.7, 101.2)	82.6 (66.2, 98.2)	0.122
N-Pro BNP (pg/mL)	3570 (1572, 10780)	2320 (1082, 7150)	5580 (3000, 12333)	0.001
Total serum protein (g/L)	65.5 (60.6, 69.6)	64.8 (60.2, 70.2)	65.5 (60.9, 69.1)	0.859
Hemoglobin (g/L)	138.0 (126.0, 146.8)	142.0 (129.0, 147.5)	136.0 (124.0, 145.0)	0.168
RDW (%)	14.6 (13.4, 16.2)	13.4 (13.1, 13.9)	16.2 (15.1, 16.7)	<0.001

Data are expressed as mean ± SD or median (interquartile range). RDW, red cell distribution width; COPD, chronic obstructive pulmonary disease; RVEDD, right ventricular end-diastolic diameter; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; GFR, glomerular filtration rate; BNP, brain natriuretic peptide.

and Log-rank tests were applied. Restricted cubic splines transformation and High-Low charts were completed by R-project version 3.4.2 and SPSS, respectively. The difference was statistically significant when *P*-value <0.05.

Results

Baseline characteristics of subjects

RDW of enrolled patients ranged from 12.1% to 21.4%, the median was [14.6 (13.5, 16.2)]%, and expression of RDW in 63 patients (50.8%) was above the upper limit. With RDW>14.5% as the threshold, the enrolled patients were classified into RDW normal group and RDW elevated group. According to the expression of RDW, patients were divided into two groups (i.e. RDW≤14.5% group [Normal group] and RDW>14.5% group [Elevated group]), and comparison of baseline characteristics between the two groups is listed in **Table 1**.

Between the 2 groups, there were no significant differences in comparison of age, gender, disease duration, smoking history, alcohol history,

Table 2. Univariate and multivariable correlations of RDW with other clinical indicators

Clinical variables	Univariate		Multivariable	
	r	*P*-value	r	*P*-value
Smoking history (%)	-0.172	0.056	-	-
Disease duration (years)	0.199	0.027	-	-
NYHA functional class (%)	0.295	0.001	-	-
Spirolactone (%)	0.315	<0.001	0.456	0.015
RVEDD (mm)	0.400	<0.001	0.399	<0.001
LAD (mm)	0.246	0.006	-	-
Serum sodium (mmol/L)	-0.325	<0.001	-	-
Uric acid (μmol/L)	0.210	0.019	-	-
Creatinine clearance (mL/min)	0.246	0.006	-	-
Urea nitrogen (mmol/L)	0.241	0.007	-	-
N-Pro BNP (pg/mL)	0.288	0.001	0.490	0.027

RVEDD, right ventricular end-diastolic diameter; LAD, left descending artery; BNP, brain natriuretic peptide.

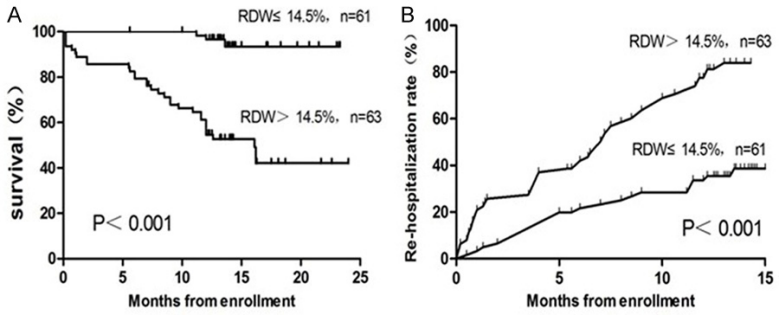

Figure 1. Kaplan-Meier survival analysis depicting the rates of survival (A) and re-hospitalization (B) in relation to RDW.

medical history in diabetes, COPD, or atrial fibrillation, the rate of utilization in β receptor blocker or ACEI/ARB, cardiac pacemaker implantation, LAD, LVEF, urea nitrogen, GFR, total serum protein or hemoglobin (P>0.05). A greater number of patients with elevated RDW had a higher rate of utilization in spirolactone, higher levels of NYHA heart functional class, right ventricular end diastolic diameter (RVEDD), LVEDD, uric acid, Scr, and N-Pro BNP (P<0.05). In addition, subjects with elevated RDW had significantly lower levels of SBP, DBP and serum sodium (P<0.05).

Correlation analysis between RDW and other clinical factors

To determine association of other clinical factors with RDW, we first performed a single related analysis to screen the significant independent variables and then followed with a multiple linear regression analysis. Smoking history, disease duration, NYHA heart functional class, spirolactone, RVEDD, LAD, serum sodium, uric acid, creatinine clearance, urea nitrogen and N-Pro BNP were set up as covariates and RDW was set as dependent variable. Results of analysis indicated that the levels of RDW was positively correlated with RVEDD (r=0.399, P<0.001), NT-pro BNP (r=0.490, P=0.027) and the rate of utilization in spironolactone (r=0.456, P= 0.015) (**Table 2**).

Prognostic value of RDW in patients with NIDCM

During the follow-up period, 35 patients (35/124, 28.2%) died, the mean follow-up period was (13.0±5.3) months. The mortality rate in the RDW normal group and the elevated group was 4.9% and 50.8%, respectively. A total of 73 patients went into hospital due to exacerbations (58.9%) with follow-up period (8.7±4.9) months, including 37.7% of patients in RDW normal group and 79.4% of patients in RDW elevated group.

Kaplan-Meier survival analysis was used to evaluate the predictive ability of RDW on cumulative survival and re-hospitalization for patients with NIDCM. Results showed that patients with an elevated RDW on admission had significantly higher mortality and re-hospitalization rate compared with RDW normal group (**Figure 1**; P<0.001).

In the univariate analysis and multivariable analysis, RDW remained a predictor of mortality (**Table 3**) and re-hospitalization (**Table 4**) in patients with NIDCM. Unadjusted and adjusted results were reported as odds ratios (ORs) with 95% confidence interval (CIs) (**Figure 2**). Especially, RDW (1% higher) was the prognostic factor for re-hospitalization (hazard ratio, 1.19; 95% confidence interval, 1.06~1.34; P=0.005) and

Table 3. Cox proportional Hazard Analysis for mortality in patients with NIDCM (n=124)

Clinical variables	Univariate			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
NYHA functional class (%)	3.32	1.50~6.54	0.002	4.55	1.81~11.49	0.001
Disease duration (years)	1.10	1.01~1.20	0.038	1.06	0.95~1.18	0.278
SBP (mmHg)	0.97	0.95~0.99	0.001	0.97	0.95~1.00	0.072
LAD (mm)	1.05	1.01~1.08	0.011	1.02	0.97~1.06	0.530
RVEDD (mm)	1.13	1.08~1.18	<0.001	1.00	0.93~1.07	0.935
β receptor blocker (%)	0.36	0.18~0.70	0.003	0.20	0.07~0.55	0.002
Serum sodium (mmol/L)	0.85	0.81~0.91	<0.001	0.91	0.83~0.99	0.029
Uric acid (μmol/L)	1.00	1.00~1.01	<0.001	1.00	1.00~1.01	0.057
Scr (mL/min)	1.01	1.00~1.01	0.001	1.01	1.00~1.02	0.190
Urea nitrogen (mmol/L)	1.07	1.02~1.11	0.002	0.91	0.80~1.04	0.176
RDW (%)	1.39	1.21~1.61	<0.001	1.51	1.21~1.87	<0.001

RDW, red cell distribution width; LAD, left atrial diameter; SBP, systolic blood pressure; Scr, serum creatinine.

Table 4. Cox proportional Hazard Analysis for re-hospitalization in patients with NIDCM (n=124)

Clinical variables	Univariate			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
NYHA functional class (%)	2.66	1.64~4.31	<0.001	1.82	1.11~2.99	0.019
Disease duration (years)	1.15	1.08~1.22	<0.001	1.14	1.07~1.22	<0.001
SBP (mmHg)	0.97	0.96~0.99	<0.001	0.97	0.96~0.99	0.001
LAD (mm)	1.05	1.02~1.07	<0.001	1.03	1.00~1.06	0.077
ACEI/ARB (%)	0.31	0.17~0.57	<0.001	0.43	0.21~0.89	0.023
Serum sodium (mmol/L)	0.90	0.86~0.94	<0.001	0.94	0.89~0.99	0.028
Uric acid (μmol/L)	1.00	1.00~1.00	0.002	1.00	1.00~1.00	0.259
Scr (mL/min)	1.01	1.01~1.01	<0.001	1.01	1.00~1.01	0.015
RDW (%)	1.21	1.09~1.34	<0.001	1.19	1.01~1.34	0.005

RDW, red cell distribution width; SBP, systolic blood pressure; LAD, left atrial diameter; Scr, serum creatinine.

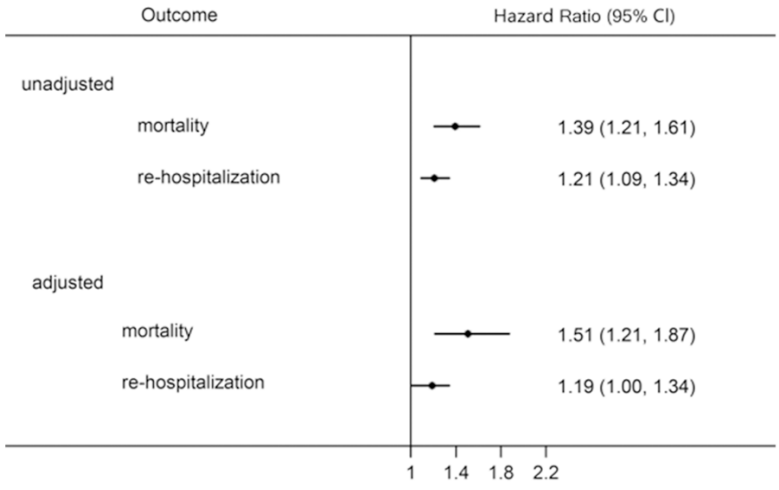

Figure 2. Unadjusted and adjusted analysis for progression of survival and re-hospitalization.

all-cause mortality (hazard ratio, 1.51; 95% confidence interval, 1.21~1.87; P<0.001) after adjustment for other covariates in the Cox regression model.

Restricted cubic splines transformation of RDW was performed after Cox regression analysis (**Figure 3**). The relationship between RDW and all-cause death was shown in **Figure 3A**. The plot of the log-relative hazard vs. RDW indicated a clear cutoff value at the point of 14%. Below the value of 14%, RDW is a protective factor for patients with NIDCM (P<0.05). When the expression of RDW was higher than value of 14%, the risk of mortality was significantly increased (**Figure 3A**, P<0.05).

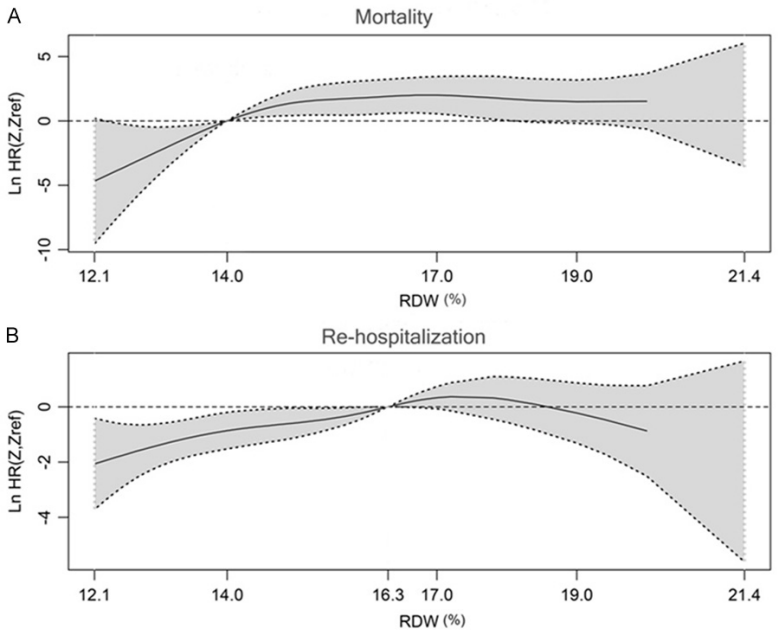

Figure 3. Restricted cubic splines transformation indicating the cut-off point of RDW for indicating the occurrence of mortality (A) and re-hospitalization (B).

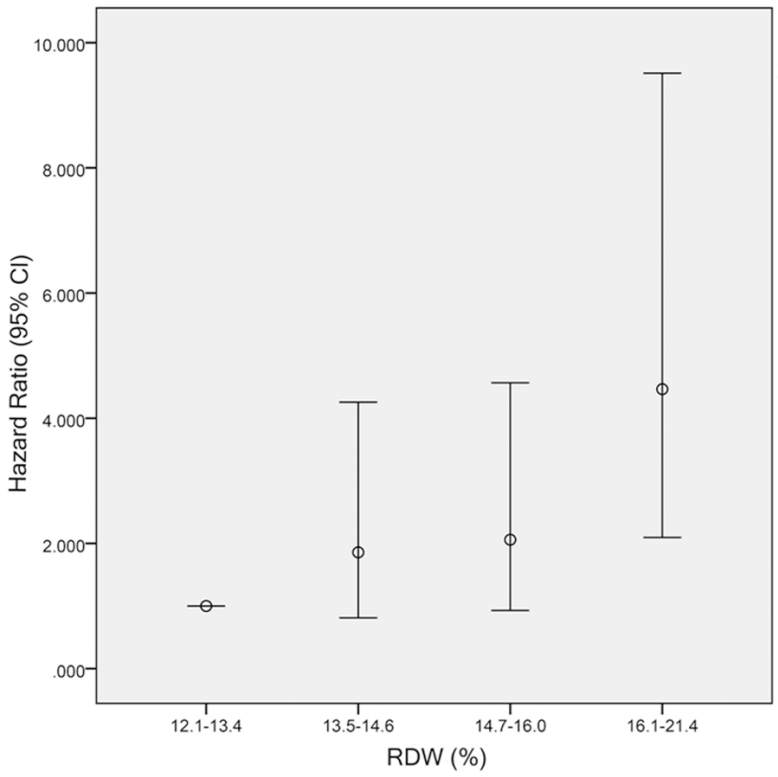

Figure 4. High-Low charts revealing the HR of re-hospitalization with quartiles of RDW.

When coming to the event of re-hospitalization, no significance was observed (**Figure 3B**). Following, the predictive ability of RDW on the risk of re-hospitalization was further analyzed according to the quartiles of RDW. It was found that the risk of re-hospitalization increased steadily with the higher quartiles of RDW after adjustment for age, sex, and study (**Figure 4**), HR was increased greatly when the expression of RDW was higher than 16% (adjusted HR=4.46; 95% CI: 2.10-9.51; P<0.05) when compared to those with the expression of RDW less than 13.4%.

Discussion

RDW is measured during routine complete blood count testing by an automated cell counter, which could reflect the variability in size of circulating red blood cells and aid in diagnosis of differential anaemia together with MCV [4]. Conditions that cause more immature cells to be released into the bloodstream (severe blood loss), abnormal hemoglobins (eg, sickle cell anemia), hemolysis, or hemolytic anemias can modify the shape of RBCs, resulting to an increased RDW.

Increased RDW is associated with poor clinical outcomes of many other diseases, such as coronary heart disease [5], stroke [6], pulmonary embolism [7], pulmonary hypertension [8], respiratory and sleep pause [9], chronic pneumonia [10], cancer [11, 12], pancreatitis [13], sepsis, or septic shock [14]. Also, it has been investigated that RDW, as one indicator to be tested simply and easily test, presents strong prognostic information for pre-

dicting mortality and cardiovascular events in patients with HF when combined with other blood indicators (such as MCV and hemoglobins) [2].

NIDCM is one of the major causes for the progression of heart failure. It is essential to find out one predictor to indicate the progress of NIDCM, which may promote reducing mortality of patients with NIDCM. However, limited studies regarding the predictive role of RDW on the prognosis role of NIDCM were explored.

In this study, we enrolled patients with NIDCM as the single cause of HF, and investigated the predicted role of RDW on the prognosis of NIDCM patients. With RDW>14.5% as the threshold, the enrolled patients were classified into the RDW normal group and the RDW elevated group. In our present study, expression of RDW was positively correlated with the levels of BNP, indicating RDW reflected the degree of HF in some extent (**Table 2**). In the Cox proportional Hazard model for mortality in patients with NIDCM, RDW was correlated with the mortality ($P<0.001$) and re-hospitalization in patients with NIDCM ($P=0.005$). Especially, the incidence of mortality and re-hospitalization rate increased by 51% and 19%, respectively, for each 1% increase in RDW (**Tables 3**, **4** & **Figure 2**). All these findings indicated a strong association between the levels of RDW and the mortality and re-hospitalization rate of patients with NIDCM.

RDW could reflect an underlying inflammatory state, which is associated with adverse clinical outcomes and leads to impaired erythrocyte maturation [15]. Increased pro-inflammatory cytokines (such as IL-1, IL-6, TNF-α, etc.) can inhibit the production of erythropoietin (EPO) [16] and decrease sensitivity of bone marrow erythroid progenitor cells to EPO, resulting in damage of red blood cell, reduction of maturity, and elevation of RDW [17]. Elevated RDW is also associated with high expression of hsCRP and ESR [15]. Additionally, changes of RDW related with oxidative stress. Oxygen radicals inhibit red blood cell maturation, which results in more immature red blood cells released into the peripheral circulation and thus increased the level of blood RDW increased. Also, oxygen radicals can increase red blood cell fragility, reduce red cell deformability, increase erythrocyte damage in peripheral blood, and finally increased levels of RDW [18]. RAAS system activation is an important pathophysiological mechanism in the development of heart failure, and study has shown that RDW elevation was associated with activation of RAAS system, which could aggregate the progress of HF [19]. Furthermore, other possible pathophysiological mechanisms including iron mobilization damage [20], liver and kidney dysfunction [21], nutritional deficiencies, complications, etc. that could also affect expression of RDW.

This study has some limitations. First, it was a single-center study with limited number of enrolled patients. Data was collected according to records when patients were in-patient and followed up. Observational research always could not distinguish causality. In addition, we also lack data on nutritional status, such as vitamin B12, folic acid and iron content, erythrocyte parameters, erythropoietin, and bone marrow conditions, which may have slight effect on the expression of RDW. Further larger-scale studies to obtain more comprehensive data are essential.

Conclusion

In summary, RDW was elevated in more than half of NIDCM patients (50.8%). When RDW increased by 1%, re-hospitalization of heart failure and all-cause mortality increased by 19% and 51%, respectively. Our study further investigated the independently predicting role of RDW for patients with NIDCM and found that elevation of RDW could provide useful information for the long-term prognosis of NIDCM.

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Disclosure of conflict of interest

None.

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References

[1] Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D. Contemporary definitions

and classification of the cardiomyopathies: an American heart association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. Circulation 2006; 113: 1807-16.

[2] van Kimmenade RR, Mohammed AA, Uthamalingam S, van der Meer P, Felker GM, Januzzi JL Jr. Red blood cell distribution width and 1-year mortality in acute heart failure. Eur J Heart Fai 2010; 12: 129-36.

[3] Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM program and the Duke databank. J Am Coll Cardiol 2007; 50: 40-7.

[4] Bessman JD, Gilmer PR Jr, Gardner FH. Improved classification of anemias by MCV and RDW. Am J Clin Pathol 1983; 80: 322-6.

[5] Uyarel H, Ergelen M, Cicek G, Kaya MG, Ayhan E, Turkkan C. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. Coron Artery Dis 2011; 22: 138-44.

[6] Kim J, Kim YD, Song TJ, Park JH, Lee HS, Nam CM. Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. Thromb Haemost 2012; 108: 349-56.

[7] Ozsu S, Abul Y, Gunaydin S, Orem A, Ozlu T. Prognostic value of red cell distribution width in patients with pulmonary embolism. Clin Appl Thromb Hemost 2014; 20: 365-70.

[8] Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol 2009; 104: 868-72.

[9] León Subías E, Gómara de la Cal S, Marin Trigo JM. Red cell distribution width in obstructive sleep apnea. Arch Bronconeumol 2017; 53: 114-119.

[10] Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med 2009; 169: 588-94.

[11] Wei TT, Wang LL, Yin JR, Liu YT, Qin BD, Li JY. Relationship between red blood cell distribution width, bilirubin, and clinical characteristics of patients with gastric cancer. Int J Lab Hematol 2017; 39: 497-501.

[12] Qin Y, Wang P, Huang Z, Huang G, Tang J, Guo Y. The value of red cell distribution width in patients with ovarian cancer. Medicine (Baltimore) 2017; 96: e6752.

[13] Yao J, Lv G. Association between red cell distribution width and acute pancreatitis: a cross-sectional study. BMJ Open 2014; 4: e004721.

[14] Kim CH, Park JT, Kim EJ, Han JH, Han JS, Choi JY. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care 2013; 17: R282.

[15] Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009; 133: 628-32.

[16] Jelkmann WE, Fandrey J, Frede S, Pagel H. Inhibition of erythropoietin production by cytokines. Implications for the anemia involved in inflammatory states. Ann N Y Acad Sci 1994; 718: 300-9; discussion 309-11.

[17] Lacombe C, Mayeux P. The molecular biology of erythropoietin. Nephrol Dial Transplant 1999; 14 Suppl 2: 22-8.

[18] Marinkovic D, Zhang X, Yalcin S, Luciano JP, Brugnara C, Huber T. Foxo3 is required for the regulation of oxidative stress in erythropoiesis. J Clin Invest 2007; 117: 2133-44.

[19] Kato H, Ishida J, Imagawa S, Saito T, Suzuki N, Matsuoka T. Enhanced erythropoiesis mediated by activation of the renin-angiotensin system via angiotensin II type 1a receptor. FASEB J 2005; 19: 2023-5.

[20] Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail 2010; 16: 230-8.

[21] Forhecz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohaszka Z, Janoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009; 158: 659-66.