Research Article

Differences in the predictive value of red cell distribution width for the mortality of patients with heart failure due to various heart diseases

Yang ZHANG1, Yan WANG1, Jin-Suo KANG1, Jin-Xing YU1, Shi-Jie YIN2, Xiang-Feng CONG1, Xi CHEN1

1Department of Clinical Laboratory Center, Fuwai Hospital & Cardiovascular Institute, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
2Department of Heart Failure Center, Fuwai Hospital & Cardiovascular Institute, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Abstract

Background Increased red blood cell distribution width (RDW) is associated with adverse outcomes in patients with heart failure (HF). The objective of this study was to compare the differences in the predictive value of RDW in patients with HF due to different causes.

Methods We retrospectively investigated 1,021 HF patients from October 2009 to December 2011 at Fuwai Hospital (Beijing, China). HF in these patients was caused by three diseases; coronary heart disease (CHD), dilated cardiomyopathy (DCM) and valvular heart disease (VHD). Patients were followed-up for 21 ± 9 months. Results The RDW, mortality and survival duration were significantly different among the three groups. Kaplan–Meier analysis showed that the cumulative survival decreased significantly with increased RDW in patients with HF caused by CHD and DCM, but not in those with HF patients caused by VHD. In a multivariable model, RDW was identified as an independent predictor for the mortality of HF patients with CHD (P < 0.001, HR 1.315, 95% CI 1.122–1.543). The group with higher N-terminal pro-brain natriuretic peptide (NT-proBNP) and higher RDW than median had the lowest cumulative survival in patients with HF due to CHD, but not in patients with HF due to DCM. Conclusions RDW is a prognostic indicator for patients with HF caused by CHD and DCM; thus, RDW adds important information to NT-proBNP in CHD caused HF patients.

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Keywords: Coronary heart disease; Dilated cardiomyopathy; Heart failure; Red blood cell distribution width; Valvular heart disease

1 Introduction

Heart failure (HF) is a chronic, progressive illness that carries a very poor prognosis and is highly prevalent worldwide.[1,2] HF affects nearly four million Chinese people and is associated with elevated rates of mortality.[3] To target effective therapies for the most appropriate patients, there is a need for a simple but accurate prognostic indicator.

Red cell distribution width (RDW) is readily available from a standard full blood count and is a measure of variation in red blood cell (RBC) size. It is used clinically for morphological classification of anemia and the differential diagnosis of small cell anemia.[4] Furthermore, RDW has been shown to be a powerful predictor of short- and long-term outcomes in a patients with HF.[5–7] However, the etiology of heart failure is a complex and may be caused by myocardial systolic dysfunction, coronary artery disease, endocrine disease, heart valve disease, hypertension, acute pulmonary embolism, emphysema or other chronic lung diseases. Thus, in this study, our primary aim was to investigate differences in the prognostic value of RDW among patients with HF due to various heart diseases in order to expand the application of RDW in such patients.

2 Methods

2.1 Study samples

We identified 1,021 consecutive patients with HF hospitalized in the HF ward in Fuwai Hospital (Beijing, China), from October 2009 to December 2011. The diagnosis of HF
was made by two clinicians with broad experience according to the European Society of Cardiology (ESC) guidelines.\[8\] To reduce the impact of other factors on RDW or the endpoint, the following patients were excluded: those with incomplete medical records, under 18 years old, with diseases such as infectious endocardial inflammation, aortic dissection, constrictive pericarditis, hydropericardium and pulmonary thromboembolism. In addition, patients with thyroid disease, acute cerebral vascular disease, cancer, chronic obstructive pulmonary diseases, end-stage renal disease and other diseases with the potential to change RDW were excluded. All the patients were given standard medication according to the guideline recommendations during the period of hospitalization and after discharge. Furthermore, all patients or their families were followed-up in telephone calls after discharge. The endpoint was defined as all-cause death. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki, and all study participants gave informed consent.

2.2 Clinical data collection

Clinical information on the patients, including age, sex, body mass index (BMI) and complicating diseases, was recorded on admission. Blood samples were taken from the participants for measurements at baseline, including routine blood tests, N-terminal pro-brain natriuretic peptide (NT-proBNP) and biochemical indexes. The blood samples were collected using a standard procedure after a 1-h fast, and were sent to the core laboratory of Fuwai Hospital for immediate testing using standard techniques. The RDW, RBC count, and hemoglobin (Hb) were tested using Sysmex XE-2100 blood cell analyzers and appropriate reagents; alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), blood urea nitrogen (BUN), serum creatinine (CREA), uric acid (URIC) and high-sensitivity C-reactive protein (hs-CRP) were assayed using a Hitachi 7180 biochemistry autoanalyzer; plasma NT-proBNP was measured with a dedicated kit (NT-proBNP assays; Biomedica, Vienna, Austria). Chest X-radiography and echocardiography were performed and the left ventricular ejection fraction (LVEF) was measured according to the biplane Simpson rule. During the follow-up period, adverse events after discharge, such as rehospitalization due to HF or all-cause death, were recorded. If a patient was readmitted several times for HF exacerbation, we recorded the time of the first readmission. If a patient was readmitted to hospital and then died, death was regarded as an adverse event and the time of death was recorded. Following an all-cause death event, the follow-up period for this patient ended.

2.3 Statistical analyses

The results are presented as percentages for dichotomous variables, mean ± SD for parametric continuous variables, and the median (interquartile range) for nonparametric continuous variables. Two groups were compared by t-test or Mann-Whitney U-test or the Kruskal-Wallis H-test; further comparisons were performed by the Bonferroni method. Univariate analysis was used to select clinical variables, which were related to an endpoint with a P-value of < 0.05. A multivariate Cox proportional hazards model was used to calculate risk ratios for independent predictors of mortality with incremental increases in continuous variables. The RDW was non-normally distributed and is represented as the median [first quartile, third quartile: M (Q1, Q3)]. The survival rate of patients, estimated by Kaplan–Meier and log-rank tests, was analyzed to investigate the difference between two groups. Receiver operating characteristic (ROC) curve analysis was used to estimate the predictive value of RDW for death risk in patients with HF; the areas under the curve (AUC) were compared by the Z-test. The data were analyzed statistically using SPSS version 17.0.

3 Results

3.1 Baseline characteristics

In total, 1,021 participants were enrolled consecutively in this study. During the follow-up period (21 ± 9 months), 116 (11.4%) participants were lost to follow-up, and 137 (15.1%) patients died. Effective follow-up was achieved for 905 cases (Figure 1). The mean age of the participants was 59.4 ± 13.6 years. The potential causes of HF were CHD (503, 55.6%), dilated cardiomyopathy (155, 17.1%), and valvular disease (155, 17.1%). Other characteristics of the patients are listed in Table 1.

![Figure 1. Selection of follow-up patients. CHD: coronary heart disease; DCM: dilated cardiomyopathy; HF: heart failure VHD: valvular heart disease.](http://www.jgc301.com)
3.2 RDW is an independent risk factor for death in patients with HF

In the univariate analysis, the significant clinical variables were BMI, NYHA heart function classification, blood pressure, heart rate, LVEF, RDW, NT-proBNP, Hb, TP, ALB, ALT, AST, TBIL, DBIL, BUN, CREA, and URIC. In the multivariate Cox proportional hazard analysis, RDW was identified as a significant variable in predicting mortality (Table 2).

3.3 Differences in the prognostic value of RDW in patients with HF due to various heart diseases

CHD, DCM, and VHD are the main causes of HF. Therefore, we selected patients with these three main causes for this study and stratified the population into three groups accordingly. In the univariate analysis, RDW remained a predictor of mortality in patients with CHD and DCM, but not in those with VHD (Table 3).

Kaplan–Meier analysis was used to evaluate the predictive ability of RDW on cumulative survival by stratification of the patients into four groups according to the quartiles of RDW. It was found that cumulative survival was significantly lower in patients with CHD and DCM in the higher quartiles of RDW, but cumulative survival was not significantly different for those with VHD (Figure 2).

As shown in Table 4, after adjustment for potential confounding factors (NT-proBNP, Hb, LVEF, and age) in a multivariable Cox proportional hazards model, RDW remained an independent predictor for CHD mortality; however, RDW was no longer a predictor for DCM mortality.

We stratified the population into three groups according
Table 3. Univariate analysis of predictors for major causes of heart failure.

|                          | CHD (n = 503) |                  | DCM (n = 155) |                  | VHD (n = 155) |                  |
|--------------------------|---------------|-----------------|---------------|-----------------|---------------|-----------------|
|                          | HR (95% CI)   | P-value         | HR (95% CI)   | P-value         | HR (95% CI)   | P-value         |
| Age, yrs                 | 1.020 (0.995–1.045) | 0.121           | 1.003 (0.980–1.027) | 0.788          | 1.027 (0.995–1.060) | 0.100           |
| Male vs. female          | 1.641 (0.957–2.813) | 0.072           | 0.942 (0.429–2.066) | 0.881          | 0.672 (0.314–1.438) | 0.306           |
| BMI, kg/m²               | 0.835 (0.769–0.906) | 0.000           | 0.909 (0.837–0.987) | 0.024          | 0.902 (0.814–1.001) | 0.052           |
| SBP, mmHg                | 0.981 (0.967–0.995) | 0.007           | 0.971 (0.949–0.994) | 0.015          | 0.988 (0.968–1.009) | 0.254           |
| DBP, mmHg                | 0.988 (0.966–1.011) | 0.300           | 0.954 (0.924–0.985) | 0.004          | 0.986 (0.959–1.014) | 0.312           |
| Heart rate, beats/min    | 1.036 (1.020–1.052) | 0.000           | 0.983 (0.965–1.001) | 0.069          | 0.990 (0.990–1.029) | 0.341           |
| NYHA class               | 1.894 (1.308–2.743) | 0.001           | 1.751 (1.016–3.020) | 0.044          | 2.530 (1.357–4.718) | 0.003           |
| LVEF, %                  | 0.932 (0.913–0.952) | 0.000           | 0.958 (0.915–1.003) | 0.067          | 0.966 (0.942–0.991) | 0.009           |
| RDW, % (IQR)            | 1.464 (1.327–1.616) | 0.000           | 1.355 (1.225–1.499) | 0.000          | 1.086 (0.915–1.289) | 0.344           |
| NT-proBNP, fmol/mL (IQR) | 1.000 (1.000–1.000) | 0.000           | 1.001 (1.000–1.001) | 0.000          | 1.000 (1.000–1.001) | 0.000           |
| Hb, g/L (IQR)           | 0.976 (0.964–0.988) | 0.000           | 0.993 (0.975–1.011) | 0.456          | 0.989 (0.973–1.005) | 0.193           |
| RBC, 1012/L (IQR)       | 0.673 (0.443–1.023) | 0.064           | 0.849 (0.521–1.386) | 0.513          | 0.640 (0.385–0.862) | 0.084           |
| TP, g/L (IQR)           | 0.965 (0.930–1.001) | 0.059           | 0.953 (0.911–0.998) | 0.039          | 0.960 (0.925–0.996) | 0.031           |
| ALB, g/L (IQR)          | 0.844 (0.802–0.887) | 0.000           | 0.884 (0.832–0.939) | 0.000          | 0.915 (0.864–0.970) | 0.003           |
| ALT, IU/L (IQR)         | 1.003 (1.002–1.004) | 0.000           | 1.000 (0.993–1.007) | 0.029          | 1.003 (1.001–1.005) | 0.001           |
| AST, IU/L (IQR)         | 1.001 (1.001–1.002) | 0.000           | 1.000 (0.992–1.008) | 0.959          | 1.004 (1.002–1.006) | 0.000           |
| TBL, µmol/L (IQR)       | 1.011 (1.003–1.020) | 0.006           | 1.017 (1.008–1.026) | 0.000          | 1.005 (0.995–1.016) | 0.330           |
| DBIL, µmol/L (IQR)      | 1.113 (1.075–1.151) | 0.000           | 1.045 (1.030–1.061) | 0.000          | 1.012 (0.990–1.035) | 0.294           |
| BUN, mmol/L (IQR)       | 1.119 (1.087–1.152) | 0.000           | 1.197 (1.094–1.309) | 0.000          | 1.067 (1.008–1.131) | 0.027           |
| URIC, µmol/L (IQR)      | 1.005 (1.003–1.006) | 0.000           | 1.003 (1.001–1.006) | 0.001          | 1.002 (1.000–1.005) | 0.025           |
| CREA, µmol/L (IQR)      | 1.006 (1.003–1.000) | 0.000           | 1.002 (0.990–1.014) | 0.729          | 1.011 (1.005–1.018) | 0.000           |
| hs-CRP, mg/L (IQR)      | 1.093 (1.034–1.154) | 0.002           | 1.104 (1.023–1.192) | 0.011          | 1.158 (1.066–1.258) | 0.001           |

ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; CERA: creatinine; CHD: coronary heart disease; DBIL: direct bilirubin; DBP: diastolic blood pressure; DCM: dilated cardiomyopathy; Hb: hemoglobin; hs-CRP: high sensitive C-reactive protein; HR: hazard ratio; IQR: interquartile range; LVEF: left ventricular ejection fraction; NT-proBNP: amino terminal B-type natriuretic peptide; NYHA class: New York Heart Association functional class; RBC: red blood cell; RDW: red blood cell distribution width; SBP: systolic blood pressure; TBL: total bilirubin; TP: total protein; URIC: uric acid; VHD: valvular heart disease.

3.4 RDW adds important prognostic information to NT-proBNP in HF due to CHD

We then stratified the population into four groups according to the median of RDW (13.4%) and NT-proBNP (1566.0 fmol/mL) with the purpose of exploring the power of RDW to adding prognostic information to NT-proBNP. We found that the group of patients with RDW > 13.4% and NT-proBNP > 1566.0 fmol/mL had the lowest cumulative survival in patients with HF due to CHD (Figure 3A). However, for those patients with the NT-proBNP phase at the same level, the cumulative survival was significantly lower in patients with increased RDW. In patients with HF due to DCM, it was found that cumulative survival of patients with RDW < 13.4% and NT-proBNP > 1566.0 fmol/mL was significantly lower than the group of patients with RDW > 13.4% and NT-proBNP > 1566.0 fmol/mL (Figure 3B).
Figure 2. Survival curves for patients with heart failure of different etiologies. Kaplan–Meier survival curves showing the total HF patients with heart failure (A); HF patients due to coronary heart disease (B); dilated cardiomyopathy (C); and valvular heart disease (D) grouped by RDW quartile. CHD: coronary heart disease; DCM: dilated cardiomyopathy; HF: heart failure; RDW: red cell distribution width; VHD: valvular heart disease.

Table 4. Cox multivariate risk ratio for mortality from CHD and DCM.

| Variable     | Increment | CHD P-value | Multivariate Risk Ratio (95% CI) | CHD P-value | Multivariate Risk Ratio (95% CI) |
|--------------|-----------|-------------|----------------------------------|-------------|----------------------------------|
| RDW, %       | +1        | < 0.001     | 1.347 (1.150, 1.578)             | 0.264       |                                  |
| NT-proBNP, fmol/mL | +100     | 0.029       | 1.016 (1.002, 1.031)             | < 0.001     | 1.057 (1.026, 1.088)             |
| Hb, g/L      | +10       | 0.104       |                                  | -           |                                  |
| LVEF, %      | +10       | 0.003       | 0.636 (0.474, 0.854)             | 0.843       |                                  |
| Age, yrs     | +10       | 0.395       |                                  | 0.767       |                                  |

CHD: coronary heart disease; DCM: dilated cardiomyopathy; Hb: hemoglobin; LVEF: left ventricular ejection fraction; NT-proBNP: amino terminal B-type natriuretic peptide; RDW: red blood cell distribution width.

4 Discussion

RDW reflects the variability in size of circulating RBCs and, when elevated, defines the state of anisocytosis. Felker et al. first reported the increase in mortality and morbidity in patients with CHF and elevated RDW. Subsequent studies
Table 5. RDW, mortality and survival time in the three groups, and ROC curve analysis.

| Cause of heart failure (n) | Mortality (%) | RDW (%) M (Q1, Q3) | Survival time (day) M (Q1, Q3) | ROC curve analysis AUC | P-value | 95% CI |
|---------------------------|---------------|---------------------|-------------------------------|------------------------|---------|-------|
| CHD (503)                 | 11.7          | 13.1 (12.6, 13.8)   | 726.0 (495.0, 882)            | 0.704                  | < 0.001 | 0.609–0.799 |
| VHD (155)                 | 19.4          | 14.0 (13.4, 15.3)** | 657.0 (444.0, 864.0)**        | 0.593                  | 0.168   | 0.462–0.724    |
| DCM (155)                 | 23.2          | 13.9 (13.0, 14.9)** | 628.0 (412.0, 852.0)****      | 0.753                  | < 0.001 | 0.647–0.860 |

*P < 0.05, **P < 0.01; A P-values of AUC are calculated by comparison between CHD and DCM. AUC: area under the curve; CHD: coronary heart disease; DCM: dilated cardiomyopathy; ROC: receiver operator characteristic; VHD: valvular heart disease.

Figure 3. Survival curves for patients with heart failure of different etiologies according to median concentrations of RDW and NT-proBNP. (A): Survival curves of patients with coronary heart disease grouped by median concentrations of RDW and NT-proBNP; (B): survival curves of patients with dilated cardiomyopathy grouped by median concentrations of RDW and NT-proBNP. CHD: coronary heart disease; DCM: dilated cardiomyopathy; NT-proBNP: amino terminal B-type natriuretic peptide; RDW: red cell distribution width.

showed that increased RDW is associated with increased mortality in patients with chronic and acute HF,[10–12] acute myocardial infarction,[13,14] coronary artery disease,[15–17] acute coronary syndromes,[18] and stroke.[19] However, HF is a complex disease, with a variety of causes.[20] Therefore, in this study our primary aim was to investigate differences in the prognostic value of RDW among patients with HF due to various heart diseases and to apply it more effectively in predicting outcomes of HF patients.

4.1 Prognostic value of RDW in patients with HF due to various heart diseases

Kaplan–Meier analysis was used to evaluate the effect of RDW on cumulative survival by stratification of the patients into four groups according to the quartile of RDW.

4.1.1 RDW and CHD-HF

Cumulative survival was significantly lower in patients with CHD in the higher quartiles of RDW. The AUC of RDW for predicting the mortality of HF patients due to CHD was 0.704, showing that that RDW is an effective predictor of mortality in this group.

After adjustment for potential confounding factors (NT-proBNP, Hb, LVEF, and age) in a multivariable Cox proportional hazards model, RDW remained an independent predictor for CHD mortality. Consequently, we considered combining RDW with another biomarker to testify whether RDW could provide additional information for prognosis. On this occasion, NT-proBNP is a good choice as it has relatively authoritative power in the prognosis of HF.[21,22] The lowest cumulative survival for the patients with CHD was observed in the group with both RDW and NT-proBNP above the median values. In addition, with NT-proBNP values of the same level, the cumulative survival of patients with RDW above the median was lower than those with RDW below the median (dark blue line vs. red line and light blue line vs. green line in Figure 3A). These data indicate that the combination of NT-proBNP and RDW provide
more information on the prognosis of patients with HF due to CHD than that provided by NT-proBNP alone.

### 4.1.2 RDW and DCM-HF

Cumulative survival was significantly lower in patients with DCM in the higher quartiles of RDW. The AUC of RDW for predicting the mortality of HF patients due to DCM was 0.753, showing that that RDW is an effective predictor of mortality in this group.

However, after adjustment for potential confounding factors (NT-proBNP, Hb, LVEF, and age) in a multivariable Cox proportional hazards model, RDW was no longer a predictor for DCM mortality. The combination of NT-proBNP and RDW failed to provide additional information for prognosis of patients with HF due to DCM than that provided by NT-proBNP alone. This may be related to the small number of patients in this group.

#### 4.1.3 RDW and VHD-HF

Cumulative survival in every RDW quartile group was similar in patients with VHD. The AUC of RDW for predicting the mortality of HF patients due to VHD was 0.593, indicating that RDW is not an effective predictor of mortality in this group.

These published data and the novel observations of this study provide a further understanding of why measurement of RDW is not an effective predictor of mortality in this group. The AUC of RDW for predicting the mortality of HF patients due to CHD and DCM, but not VHD. In a multivariable Cox proportional hazards model, RDW was no longer found to be an independent predictor of DCM mortality. The combination of NT-proBNP and RDW provide more information on the prognosis of patients with HF due to CHD than that provided by NT-proBNP alone. This study should prompt further evaluation of the association between RDW and outcome in HF due to different to improve our understanding of the pathophysiology and to improve risk-stratification.

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