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# Predictive Values of Red Blood Cell Distribution Width in Assessing Severity of Chronic Heart Failure

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**Background:** This retrospective study was performed to evaluate the value of baseline red blood cell distribution width (RDW) for predicting the severity of chronic heart failure (CHF) compared with N-terminal prohormone brain natriuretic peptide (NT-ProBNP) and other hematological and biochemical parameters.

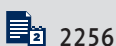
**Material/Methods:** Hematological and biochemical parameters were obtained from 179 patients with New York Heart Association (NYHA) CHF class I (n=44), II (n=39), III (n=41), and IV (n=55). Receiver operator characteristic (ROC) curves were used for assessing predictive values.

**Results:** RDW increased significantly in class III and IV compared with class I ( $14.3 \pm 2.3\%$  and  $14.3 \pm 1.7\%$  vs.  $12.9 \pm 0.8\%$ ,  $P < 0.01$ ). Areas under ROCs (AUCs) of RDW and NT-ProBNP for class IV HF were 0.817 and 0.840, respectively. RDW was markedly elevated in the mortality group compared with the survival group ( $13.7 \pm 1.7$  vs.  $15.8 \pm 1.8$ ,  $P < 0.01$ ). The predictive value of RDW was lower than that of NT-ProBNP but was comparable to white blood cell (WBC), neutrophil (NEU), lymphocyte (L), and neutrophil/lymphocyte ratio (N/L) for mortality during hospitalization, with AUCs of 0.837, 0.939, 0.858, 0.891, 0.885, and 0.885, respectively. RDW and NT-proBNP showed low predictive values for repeated admission ( $\geq 3$ ). RDW was an independent risk factor for mortality (OR=2.531, 95% CI: 1.371–4.671).

**Conclusions:** RDW increased significantly in class III and IV patients and in the mortality group. The predictive value of RDW is comparable to NT-proBNP for class IV and lower than that of NT-proBNP for mortality. Elevated RDW is an independent risk factor for mortality.

**MeSH Keywords:** **Erythrocyte Indices • Heart Failure • Predictive Value of Tests**

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## Background

Chronic heart failure (CHF) is accompanied by high co-morbidity and mortality. Red blood cell distribution width (RDW) represents the variability of sizes of circulating erythrocytes. Increased RDW is associated with increased morbidity and mortality in patients with CHF [1]. CHF is regarded as a systemic disease based on the chronic inflammation status. In the setting of long-standing CHF, other organ systems are also involved [2]. A recent study showed that RDW is a prognostic factor for adverse outcomes in patients with advanced stage HF and is superior to more traditionally used indices [3]. In patients with HF, N-terminal prohormone brain natriuretic peptide (NT-ProBNP) is a proven standard prognostic indicator [4]. NT-proBNP levels have been independently linked with elevated RDW in suspected HF patients [5]. RDW and NT-proBNP are strong independent predictors of 90-day cardiovascular events in patients hospitalized with acute heart failure (AHF) [6]. However, the comparison of the 2 indices for the prediction of CHF degree and mortality during hospitalization has not been investigated. Furthermore, increased plasma levels of BNP and NT-proBNP are not specific to HF and may be influenced by a variety of cardiac and non-cardiac conditions, including myocardial ischemia, cardiac arrhythmias, sepsis, shock, and anemia [7]. The predictive value of NT-proBNP is insufficient, especially when levels are moderately elevated [8]. Many types of inflammatory biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), have been found to be consistent predictors of coronary heart disease (CHD) events [9]. Uric acid (UA) was recently established as a prognostic marker for poor outcomes in CHF [10]. An elevated white blood cell (WBC) count is a well-recognized indicator of inflammation [11], but the mechanism of the association between HF and hematological parameters is not well understood.

In this study we aimed to evaluate the predictive value of RDW for the severity of HF and mortality during hospitalization and compared it with NT-ProBNP and other hematological and biochemical parameters. We also sought to determine the association between RDW and serum NT-proBNP as well as other inflammatory parameters, such as UA and hs-CRP, to elucidate the mechanism of the association between RDW and CHF preliminarily.

## Material and Methods

A total of 179 consecutive patients admitted to the Department of Cardiology in our hospital with a diagnosis of CHF during the period of January 2012 to April 2015 were analyzed retrospectively. Severity of HF was assessed by New York Heart Association (NYHA) functional class. NYHA class II, III, and IV were the test groups and class I was the control group. Diagnosis of HF was mainly based on the clinical judgment

of 2 experienced cardiac clinicians using clinical, biochemical, echocardiography, and radiology evaluations. Exclusion criteria included acute coronary syndrome, active hepatobiliary disease, or myocarditis. Patients with dysfunctional renal parameters without renal disease history (considered as having cardiorenal syndrome) were included (serum creatinine <4 mg/dL). Echocardiography was performed by an experienced cardiac sonographer using the Philips IE33 ultrasound system (Andover, MD) with 2.5–3.5 MHz transducer measurements. The procedure was performed following international recommendations [7]. Hematological parameters were detected using an XT1800I blood cell analyzer, and RDW was calculated as (standard deviation of mean corpuscular volume ÷ mean corpuscular volume) × 100. The cutoff of 16% was identified as the upper limit of normal reported. Anemia was defined as hemoglobin (Hb) <12 g/dL for men and <11 g/dL for women. Other hematological parameters include WBCs, neutrophils (NEU), and lymphocytes (L). Biochemical parameters were assayed using a CI16200 blood biochemical automatic analyzer. The serum NT-proBNP level was measured by automated electrochemiluminescence immunoassay (ECLIA) (proBNP kit, Roche Diagnostics, Mannheim, Germany) on a Roche Cobas E601 analyzer (Roche Diagnostics). The survival group included patients whose HF was stable or relieved during hospitalization or who had been discharged from the hospital before the data were collected. The mortality group consisted of patients who died during hospitalization. The readmission group was composed of patients who were hospitalized more than twice.

The study was performed in accordance to the principles of the Declaration of Helsinki and its appendices as well as local and national laws. Written informed consent was obtained from each patient.

## Statistical analysis

All analyses were conducted using SPSS version 16 (SPSS, Chicago, IL). Continuous variables are presented as mean ± SD and were compared using the *t* test or one-way analysis of variance (ANOVA) for values with normal distributions. The non-parametric Mann-Whitney *U* test was used for variables with abnormal distribution. The correlations were evaluated by Spearman rank correlation test. We constructed receiver operating characteristic (ROC) curves and areas under the curve (AUCs) and calculated the 95% confidence interval (CI) for the parameters to determine the diagnostic accuracy in predicting severity of HF. Optimal cutoffs, sensitivity, and specificity were defined as maximum Youden index. Logistic regression analysis was used to calculate independent risk factors of mortality during hospitalization. Parameters used for logistic regression include age, sex, and those with *P* < 0.1 in correlation with mortality using univariate analysis. *P*-value < 0.05 was considered significant.

**Table 1.** Baseline characteristics of patients with different classes of HF ( $\bar{x}\pm SD$ ).

Variables	Heart failure class			
	I	II	III	IV
N	44	39	41	55
M/F	24/20	24/15	19/22	29/18
Age (year)	61.2±13.2	67.5±13.5*	67.1±13.3*	72.8±10.5**
WBC ( $\times 10^9$ /mL)	7.2±2.3	7.9±2.9	6.4±2.4	8.3±3.4
NEU (%)	61±14	65.3±16.3	61.7±11.2	70.7±11.4**
L (%)	30.6±13.2	26.2±14.3	27.9±9.4	20.1±9.7**
N/L ratio	2.7±1.9	5.9±9.2**	3.02±2.98	5.3±4.8*
RBC ( $\times 10^{12}$ /mL)	4.56±0.5	4.42±0.6	4.39±0.6*	4.35±0.5
HB (g/L)	135.8±19.2	128.2±27.0	126.2±18.7*	127.3±18.9*
HCT (%)	40.9±4.8	38.1±10.2	37.8±7.0*	39.2±6.0
RDW (%)	12.9 ±0.8	13.0±0.8	14.3±2.3**	14.3±1.7**
MPV	10.5±0.9	11.0±1.4	10.6±1.2	11.2±2.4*
UA ( $\mu$ mol/L)	375.1±129.9	368.1±119.2	413.9±159.0	459.7±188.5**
hs-CRP (mg/L)	12.6±34.4	9.0±20.6	11.7±18.7	40.1±80.0**
NT-proBNP (pg/ml)	1418.9±4550.1	1364.2±2292.9**	3154.2±5281.6**	6833.2±7506.1**
ALB (g/L)	42.3±4.	41.4±4.6	39.5±4.8**	37.9±5.2**
BUN (mmol/L)	6.8±5.1	7.9±3.9	7.9±4.1	9.3±4.5**
sCr ( $\mu$ mol/L)	74.7±7.3	70.1±21.7	77.8±47.3	120.6±137.6*

Compared with class I \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; WBC – white blood cell; NEU – neutrophil; RBC – red blood cell; HB – hemoglobin; HCT – hematocrit; RDW – red cell distribution width; UA – uric acid; NT-ProBNP – N-terminal prohormone brain natriuretic peptide; hs-CRP – high-sensitivity C-reactive protein; BUN – blood urea nitrogen; sCr – serum creatinine.

## Results

### Demographic and baseline clinical characteristics

Of 179 cases, 44 (24.6%) were NYHA class I, 39 (21.8%) were class II, 41 (22.9%) were class III, and 55 (30.7%) were class IV. Mean ages in class II (67.5±13.5 years,  $P=0.003$ ), III (67.1±13.3 years,  $P=0.021$ ), and IV (72.8±10.5 years,  $P=0.000$ ) were higher than in class I (61.2±13.2 years). Overall, 133 (70.3%) patients were hospitalized less than 3 times and 46 (29.7%) were hospitalized more than twice. There were 10 mortalities in the class IV group during hospitalization.

### Hematological and biochemical parameters in different classes of HF

Among the hematological parameters, the percentage of neutrophils (NEU) (70.7±11.4% vs. 61.0±14.0%,  $P < 0.01$ ), RDW (14.3±1.7 vs. 12.9±0.8,  $P < 0.01$ ) was significantly increased, lymphocyte (L) decreased markedly (20.1±9.7 vs. 30.6±13.2%,  $P < 0.01$ ), and N/L (5.3±4.8 vs. 2.7±1.9,  $P < 0.05$ ) were notably elevated in class IV compared with those in class I. RDW was also elevated in class III compared with class I. RBC counts and Hb

levels were decreased markedly in class III and IV compared with class I. Table 1 shows the data.

Among the biochemical parameters, serum UA and hs-CRP level were significantly elevated in class IV compared with class I (459.7±188.5 vs. 375.1±129.9  $\mu$ mol/L,  $P < 0.01$ , and 40.1±80.0 mg/L vs. 12.6±34.4,  $P < 0.01$ , respectively). NT-proBNP levels were elevated remarkably in class II (1364.2±2292.9 pg/mL), III (3154.2±5281.6 pg/mL), and IV (6833.2±7506.1 pg/mL) compared with class I (1418.9±4550.1 pg/mL) ( $P < 0.01$ ). The blood urea nitrogen (BUN) (9.3±4.5 vs. 6.8±5.1 mmol/L,  $P < 0.01$ ) and serum creatinine (sCr) levels (120.6±137.6 vs. 74.7±7.3  $\mu$ mol/L,  $P < 0.01$ ) were profoundly increased in class IV compared with class I. The serum albumin (ALB) levels decreased markedly in class III and IV ( $P < 0.01$ ) (Table 1).

In patients with class I, WBC ( $r=0.389$ ,  $P=0.001$ ), NEU ( $r=0.344$ ,  $P=0.003$ ) RBCs ( $r=-0.354$ ,  $P=0.002$ ), RDW ( $r=0.231$ ,  $P=0.047$ ), Hb ( $r=-0.307$ ,  $P=0.008$ ), and hs-CRP ( $r=0.37$ ,  $P=0.001$ ) had strong correlations with serum NT-proBNP level. Only RBC count ( $r=-0.221$ ,  $P=0.045$ ) had a clear negative correlation with RDW. In patients with evident HF (class II–IV), the associations of RDW ( $r=0.43$ ,  $P=0.000$ ), NEU ( $r=0.573$ ,  $P=0.000$ ) and hs-CRP ( $r=0.415$ ,  $P=0.000$ )

**Table 2.** Cut-off values, sensitivity and specificity of hematological and other biochemical parameters for the prediction of HF class IV.

	Cutoff values	AUC (95%CI)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	LR+	LR-
RDW (%)	13.2	0.817 (0.753, 0.871)	85.7	65.4	52.7	90.9	2.45	0.22
NEU (%)	58.9	0.682 (0.609, 0.750)	92.7	43.6	42.1	90.9	1.64	0.17
N/L ratio	2.18	0.701 (0.628, 0.767)	87.3	52.4	44.9	90.3	1.83	0.24
L (%)	27.4	0.709 (0.637, 0.775)	83.6	58.9	47.4	89.0	6.58	0.00
NT-proBNP (pg/ml)	751.6	0.84 (0.781, 0.899)	96.2	64.0	55.4	97.0	2.68	0.059
hs-CRP (mg/L)	8.1	0.704 (0.630, 0.771)	56.6	78.7	53.6	80.7	2.60	0.55

HF – heart failure; AUC – area under ROC curve; SEN – sensitivity; SPE – specificity; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio.

**Table 3.** Comparison of hematological and other biochemical parameters ( $\bar{x}\pm SD$ ) in patients of first hospitalization and repeated admission.

Variables	Times of hospitalization	
	1-2	≥3
N	133	46
M/F	71/62	29/17
Age (year)	65.1±12.9	74.2±10.6**
WBC (×10 <sup>9</sup> /mL)	7.5±2.9	7.4±2.9
NEU (%)	64.0±13.7	68.4±13.4
L (%)	26.7±12.4	23.1±11.6
N/L ratio	4.1±5.7	4.8±4.6
RBC (×10 <sup>12</sup> /mL)	4.5±0.5	4.3±0.6
HB (g/L)	130.6±21.7	125.5±19.0
RDW (%)	13.4±1.6	14.0±1.3
UA (μmol/L)	392.0±144.5	454.1±185.3*
NT-proBNP (pg/ml)	2675.6±4506.9	8264.6±1245.9
BUN (mmol/L)	7.4±4.3	9.6±4.8**

Comparison between two groups \*  $P<0.05$ ; \*\*  $P<0.01$ .

with serum NT-proBNP level were more profound than those in class I, and RDW was positively correlated with NEU ( $r=0.225$ ,  $P=0.027$ ) and negatively with Hb ( $r=-0.418$ ,  $P=0.000$ ). The relationship between NEU and RDW was stronger in class III ( $r=0.200$ ,  $P=0.044$ ) and class IV ( $r=0.331$ ,  $P=0.001$ ). In all patients, RDW was positively correlated with NT-proBNP ( $r=0.509$ ,  $P<0.001$ ), hs-CRP ( $r=0.243$ ,  $P=0.001$ ), NEU ( $r=0.191$ ,  $P=0.01$ ), and UA ( $r=0.29$ ,  $P<0.001$ ), and was negatively with Hb ( $r=-0.327$ ,  $P<0.01$ ). No association was observed between RDW and RBC counts.

**Predictive value of hematological parameters for severity of HF**

Table 2 shows the ROC analysis, cutoff values, AUCs (95% CI), sensitivity (SEN), specificity (SPE) of RDW, NEU, N/L, NT-proBNP,

and CRP for the prediction of class IV. RDW and NT-proBNP showed a moderate predictive value, and other parameters showed a low predictive value for class IV. All parameters indicated a low predictive value for class I-III (data not shown).

**Hematological and biochemical parameters in patients with different lengths of hospitalization**

Patients who underwent hospitalization more than twice were older than those hospitalized less than 3 times ( $74.2\pm 10.6$  vs.  $65.1\pm 12.9$  years,  $P<0.01$ ). Hematological parameters had no remarkable difference between the 2 groups. Only the increase of NEU ( $68.4\pm 13.4$  vs.  $64.0\pm 13.7\%$ ,  $P=0.051$ ) nearly reached a significant difference.

**Table 4.** Hematological and biochemical parameters of patients in survival group and death group ( $\bar{x}\pm SD$ ).

Variables	Survival group	Death group
N	169	10
M/F	92/57	4-6
Age (year)	67.1±13.0	74.2±10.5
WBC ( $\times 10^9$ /mL)	7.2±2.6	11.8±4.5**
NEU (%)	64.1±13.3	81.9±9.1**
L (%)	26.7±12.0	10.8±5.5**
N/L ratio	3.9±5.2	10.2±6.2*
RBC ( $\times 10^{12}$ /mL)	4.4±0.5	4.2±0.8
HB (g/L)	130.0±21.0	120.1±22.4
HCT (%)	39.2±7.2	37.5±7.1
RDW (%)	13.7±1.7	15.8±1.8**
UA ( $\mu$ mol/L)	402.6±154.1	521.6±201.8*
hs-CRP (mg/L)	14.9±39.0	123.8±120.2*
NT-proBNP (pg/ml)	2914.0±5094.6	4544.0±9000.6**
BUN (mmol/L)	7.6±4.2	14.3±5.3**
sCr ( $\mu$ mol/L)	77.8±47.3	120.6±137.6**

Compared with class I \*  $P < 0.05$ ; \*\*  $P < 0.01$ .

**Table 5.** Predictive value of hematological and other biochemical parameters for mortality during hospitalization.

	Cutoff values	AUC (95%CI)	SEN (%)	SPE (%)	PPV (%)	NPV (%)	LR+	LR-
RDW (%)	14.7	0.837 (0.767, 0.888)	70	87	24.1	98	5.38	0.34
WBC ( $\times 10^9$ /mL)	8.08	0.858 (0.741, 0.977)	90	72.8	16.4	99.2	3.31	0.14
NEU (%)	76	0.891 (0.809, 0.974)	80	81.7	20.5	98.6	4.36	0.21
L (%)	16.2	0.885 (0.829, 0.927)	90	81.7	22.5	99.3	4.91	0.21
N/L ratio	3.317	0.885 (0.799, 0.971)	100	68.1	15.6	100	3.13	0
NT-proBNP (pg/mL)	4884	0.939 (0.896, 0.982)	100	84.8	27.3	100	6.58	0
hs-CRP (mg/L)	20.9	0.839 (0.653, 1.024)	87.5	86.2	22.3	99.3	6.35	0.14
Age (years)	60	0.687 (0.494, 0.880)	100	33.1	8.1	100	1.5	0

AUC – area under ROC curve; SEN – sensitivity; SPE – specificity; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio.

Among the biochemical parameters, NT-proBNP (8264.6±1245.9 vs. 2675.6±4506.9 pg/mL,  $P < 0.05$ ) and UA (454.1±185.3 vs. 392.0±144.5  $\mu$ mol/L,  $P < 0.05$ ) were significantly elevated in patients who were hospitalized more than twice compared with those who were hospitalized less than 3 times (Table 3).

#### Hematological and biochemical parameters in patients who survived and those who died

Among hematological parameters, RDW (15.8±1.8 vs. 13.7±1.7,  $P < 0.01$ ), WBC (11.8±4.5 vs. 7.2±2.6,  $P < 0.01$ ), NEU (81.9±9.1 vs. 64.1±13.3%,  $P < 0.01$ ), and N/L (10.2±6.2 vs. 3.9±5.2,  $P < 0.05$ ) indicated a marked elevation, and lymphocytes (L) (10.8±5.5

vs.  $26.7 \pm 12.0$ ,  $P < 0.01$ ) were notably decreased. Among the biochemical parameters, NT-proBNP ( $14544.0 \pm 9000.6$  vs.  $2914.0 \pm 5094.6$  pg/ml,  $P < 0.01$ ), BUN ( $14.3 \pm 5.3$  vs.  $7.6 \pm 4.2$  mmol/L,  $P < 0.01$ ), sCr ( $120.6 \pm 137.6$  vs.  $77.8 \pm 47.3$   $\mu$ mol/L,  $P < 0.01$ ), UA ( $521.6 \pm 201.8$  vs.  $402.6 \pm 154.1$   $\mu$ mol/L,  $P < 0.05$ ), and hs-CRP ( $123.8 \pm 120.2$  vs.  $14.9 \pm 39.0$  mg/L,  $P < 0.05$ ) were profoundly increased in the mortality group compared to the survival group (Table 4).

### Predictive value of hematological and biochemical parameters for mortality

NT-proBNP at a cutoff of 4884 pg/mL showed a high predictive value for mortality during hospitalization; AUROC (95% CI), SEN, SPE, PPV, and NPV were 0.939 (0.896, 0.982), 100%, 84.8%, 27.3%, and 100%, respectively. WBC, NEU, N/L ratio, L, RDW, and hs-CRP showed a moderate predictive value for mortality. Data are shown in Table 5.

### Independent risk factors for mortality

Logistic regression analysis showed RDW ( $OR = 2.531$ , 95%CI: 1.371–4.671,  $P = 0.003$ ) and WBC ( $OR = 1.832$ , 95%CI: 1.202–2.793,  $P = 0.005$ ) as the independent risk factors for mortality during hospitalization. Hs-CRP was a near risk factor ( $OR = 1.009$ , 95%CI: 0.009–1.019,  $P = 0.06$ ). Age and sex were not independent risk factors for mortality.

## Discussion

Increased RDW has emerged as a predictor of poor outcome in CHF [12], in agreement with our results. We observed that RDW is significantly increased in class III and IV patients compared with the class I group and the mortality group in comparison with the survival group. In addition, we demonstrated that although RDW is a predictor of mortality during hospitalization, the predictive value is lower than NT-ProBNP and similar to other hematological parameters, including WBC, NEU, lymphocyte, and N/L. The predictive values of RDW and NT-ProBNP were comparably moderate for advanced HF. RDW is an independent risk factor for mortality, but the mechanisms of the relation between HF and RDW elevation is not well understood.

RBCs perform essential functions in the human body, such as gas exchange between blood and tissues, due to the ability to deform and flow in the microvascular network [13]. Changes in osmolality lead to either swelling or shrinkage of RBCs under pathophysiological conditions and markedly decrease the deformability of RBCs [14], which ultimately reduce microvascular perfusion and tissue hypoxia, aggravating HF. This may be one of the mechanisms by which CHF is associated with elevated RDW. In addition, RDW is an index of anisocytosis that

reflects mean corpuscular volume heterogeneity. It is a predictor of early anemia associated with deficiency of iron, vitamin B12, or folic acid [13], which reflects the presence of immature RBCs in the periphery caused by increased red blood cell destruction, pathologic iron homeostasis, and ineffective erythropoiesis [15]. It has been established that iron deficiency increases with the severity of HF and is a prognostic factor of CHF [12,16]. Our results suggest that RDW has a strong negative correlation with Hb in severe HF patients. CHF occurring in a state of chronic systemic inflammation and inflammation is known to block iron metabolism and erythropoietin response. RDW has been shown to be a link between ineffective erythropoiesis and chronic inflammation of CHF [17]. Thus, RDW can be regarded as an inflammatory indicator. A previous study indicated that elevated inflammatory markers, including WBC count, are associated with increased adverse cardiac events and death [18]. Our data also indicated that RDW is positively correlated with NEU and hs-CRP, especially in advanced-stage CHF. This may be another reason for the association between increased RDW and severity of CHF.

On the other hand, raised RDW may be the result of reduced tissue perfusion. Recent research showed that RDW is positively correlated with central venous pressure (CVP) and negatively with mixed venous oxygen saturation (SvO<sub>2</sub>), but serum BNP level does not have any significant relation with these parameters [19].

Other factors, such as malnutrition [20] and renal function impairment [21] in CHF, can lead to decreased erythropoietin (EPO) secretion and development of anemia, which is involved in the association of hematological parameters and CHF. We also found that serum albumin (ALB) decreased significantly and blood urea nitrogen (BUN) and serum creatinine (sCr) increased markedly in class IV patients (Table 1).

### Limitations

First, this was a nonrandomized, retrospective study and only in-hospital baseline data were collected; therefore, the influence of changes in RDW over time on long-term outcomes could not be determined. Second, healthy controls were not recruited, and the small number of patients studied may have affected the results.

## Conclusions

The association of RDW and CHF involves several factors. RDW is significantly increased in advanced HF patients and is an independent risk factor for mortality during hospitalization. Therefore, decreased RDW during or after treatment may be used in clinical practice as an indicator of reduced risk of

death. RDW is a part of complete blood count, is inexpensive, and is widely available as a tool for the prediction of prognosis and guidance of treatment of CHF.

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## Conflicts of interest

The authors declare that they have no conflict of interest.