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Prognostic value of red blood cell distribution width in patients with left ventricular systolic dysfunction: Insights from the COMMIT-HF registry

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Abstract

Background: *Previous studies have reported that in patients with heart failure, an increased value of red cell distribution width (RDW) is associated with adverse outcomes. Nonetheless, data regarding the association between RDW values and long-term mortality in patients with left ventricular systolic dysfunction (LVSD) are lacking.* The aim *of this investigation was to examine the relationship between mortality and RDW in patients with ischemic and non-ischemic LVSD.*

Methods: *Under analysis was 1734 patients with a left ventricular ejection fraction (LVEF) ≤ 35% of whom were hospitalized between 2009 and 2013. Patients were divided into three groups based on RDW tertiles. Low, medium and high tertiles were defined as RDW ≤ 13.4%, 13.4% < RDW ≤ 14.6% and RDW > 14.6%, respectively.*

Results: *There was a stepwise relationship between RDW intervals and comorbidities. Patients with the highest RDW values were older and more often diagnosed with anemia, diabetes, atrial fibrillation and chronic kidney disease. The main finding of our analysis was the presence of an 8-fold increase in all-cause mortality in the entire cohort between high and low RDW tertile. Cox hazard analysis identified RDW as an independent predictive factor of mortality in all patients (HR 2.8; 95% CI 2.1–3.8; p < 0.0001) and in subgroups of patients with ischemic (HR 2.8; 95% CI 2.0–3.9; p < 0.0001) and non-ischemic (HR 3.3; 95% CI 2.01–5.5; p < 0.0001) LVSD.*

Conclusions: *The highest RDW tertile was independently associated with higher long-term mortality compared with low and medium tertiles, both in all patients with a LVEF ≤ 35% and in subgroups of patients with ischemic and non-ischemic LVSD.* (Cardiol J 2018; 25, 3: 377–385)

Key words: red cell distribution width, heart failure, mortality, iron metabolism disorders, ventricular ejection fraction

Introduction

Red blood cell distribution width (RDW) reflects variability in the size of circulating erythrocytes and is a marker of anisocytosis [1]. In recent years, anisocytosis has emerged as a prognostic biomarker in cardiovascular disease. Numerous studies have noted the relationship between RDW values and adverse clinical outcomes in the setting of coronary artery disease (CAD), including patients undergoing percutaneous coronary interventions in the course of stable coronary

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artery disease and patients with acute coronary syndromes (ACS) [2, 6–8].

The pioneering work assessing the role of RDW in heart failure (HF) was published by Felker et al. [9]. The authors noted that increased RDW was a novel, strong independent predictor of higher morbidity and mortality among patients with chronic HF included in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study. The authors confirmed this finding in the Duke Databank for Cardiovascular Disease. In both analyses RDW exhibited a higher statistical association with outcome than conventional risk scores such as left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) functional class. Subsequent studies (including a meta-analysis) have confirmed the predictive role of RDW as a risk factor of short- and long-term mortality among patients with chronic and acute decompensated HF. However, patients in those studies were selected according to HF symptoms, Framingham criteria and NYHA class, irrespective of HF origin and LVEF values [9–14].

This study aimed to explore the relationship between RDW at admission and all-cause, long-term mortality in a wide spectrum of patients hospitalized with a LVEF of ≤ 35% in the COnteMporary Modalities In Treatment of Heart Failure (COMMIT-HF) registry maintained by the 3rd Chair and Department of Cardiology of the Silesian Center for Heart Diseases, Poland (ClinicalTrials.gov Identifier: NCT01471522). It was also sought to establish whether RDW has the same prognostic value in patients with ischemic and non-ischemic left ventricular systolic dysfunction (LVSD).

Methods

Patient selection

The analyzed cohort consisted of a subset of patients in the COMMIT-HF registry, an ongoing project at this institution (the Silesian Center for Heart Diseases). The COMMIT-HF registry included patients with LVEF of ≤ 35% without ACS [15, 16]. Baseline characteristics and in-hospital data were recorded on case report forms. Demographic data, concomitant diseases and laboratory parameters such as RDW are stored in this database. All patients underwent LVEF assessment during the initial 24 h of the index hospitalization. The exclusion criterion was ACS. Additionally, we have excluded patients with serious concurrent systemic disease resulting in reduced life expectancy (n = 64). A total of 1734 patients admitted to our institution were analyzed between January 2009 and December 2013. Patients were divided into three groups according to baseline tertiles of RDW. Low, medium and high tertiles were defined as RDW ≤ 13.4% (n = 569), 13.4% < RDW ≤ 14.6% (n = 585) and RDW > 14.6% (n = 580), respectively. Survival analysis, stratified by RDW tertile, was used to evaluate the usefulness of RDW in predicting all-cause long-term mortality in the whole cohort and separately for patients with ischemic and non-ischemic LVSD. This investigation conforms to the principles outlined in the Declaration of Helsinki and has been approved by the Ethics Committee at the District Chamber of Physicians.

Blood sampling

Blood samples were obtained on admission and processed immediately. Complete blood counts were performed using the Sysmex XS1000i and XE2100 apparatus (Sysmex Corporation, Kobe, Japan). RDW was defined as the quotient of standard deviation (SD) of red blood cell volume and its mean volume and is expressed as a percentage according to the following formula: RDW = (SD of red blood cell volume / mean cell volume) × 100. Higher RDW values reflect greater variations in red blood cell volume.

Follow-up data

The primary endpoint was death from any cause. Information on survival was based on the National Health Fund insurance status, which can be electronically verified as the National Health Fund insurance policy is compulsory for all Polish citizens. Insured patients were marked as alive. Complete follow-up data were available for the whole cohort.

Statistical analysis

Continuous variables were presented as the mean and SD or median with interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. The assumption of normality for continuous variables was verified via the Shapiro-Wilk test. Continuous variables were compared across RDW tertiles using analysis of variance or Kruskal-Wallis tests. Categorical variables were compared using χ^2 test.

Associations between RDW tertiles and mortality were analyzed using the Kaplan-Meier method with log-rank testing. Univariate and multivariate Cox regression models were utilized to evaluate the association between RDW tertiles and

mortality. The stepwise selection method of model building was used, with p-value set to 0.2 to allow a confounder into the model and *P*-value set to 0.1 for a confounder to stay in the model. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and blood urea nitrogen were not included in multivariable analysis because data on these parameters were available for only a minority of patients. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) were presented. Receiver-operating characteristic (ROC) curves were estimated for models with and without RDW. Areas under ROC curves (AUC) for these models were compared using logistic regression method. The interpretation of statistical significance was based on a value of $\alpha = 0.05$. Statistical analyses were performed using the SAS statistical software package, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and the STATISTICA 10 software (StatSoft Inc., Tulsa, Oklahoma, USA).

Results

Baseline characteristics of the patient population

The study cohort consisted of 1734 patients with LVSD (1387 males), with a median age of 61.0 years (IQR: 53.0÷71.0 years). Baseline clinical characteristics of the patients across RDW tertiles are presented in Table 1. Ischemic etiology was diagnosed in 370 (65.2%), 378 (65.6%) and 376 (63.8%) subjects in low, medium and high RDW tertiles, respectively. A stepwise relationship was observed between RDW tertiles and co-morbidities in the whole group. Subjects in the highest RDW tertile were significantly older, had a higher prevalence of anemia, atrial fibrillation and stage III or higher chronic kidney disease compared with patients in other tertiles. The patients in the highest RDW tertile also had a worse clinical status defined as higher NYHA functional class on admission. Echocardiographic parameters were unanimously inferior in the highest RDW tertile, with significantly lower LVEF, higher end-systolic and end-diastolic volumes as well as diameters, with a significantly higher occurrence of both mitral and aortic severe valve disease compared with patients in low and medium tertiles. Analysis of these findings revealed a stepwise relationship between RDW tertiles and lower hemoglobin concentration, higher bilirubin, blood urea nitrogen, creatinine, uric acid and N-proBNP titers. Total cholesterol levels were significantly lower across higher RDW tertiles. Significant differences were observed between some of the groups with regard to prescribed medical treatment. Patients in the highest tertile were less frequently treated with angiotensin-converting-enzyme inhibitors (ACEI), statins, β-blockers and received antiplatelet treatment. In contrast, they presented more frequently with loop and thiazide diuretics, digoxin and oral anticoagulation treatments.

Survival analysis

Follow-up data were available for the whole cohort. Median follow-up was 660 days (IQR 331÷1074 days). The primary endpoint was all-cause mortality. During the observation period, 443 (25.5%) deaths were reported. The comparison of baseline characteristics between patients who survived and those who died during follow-up period is presented in **Supplementary Table 1**. In the whole cohort there was an almost 8-fold increase in all-cause 12-month mortality in high RDW tertile compared with low tertile (3.2% vs. 24.0%, $p < 0.01$).

The analysis of crude HR revealed significantly higher mortality for both medium (HR 1.9; 95% CI 1.4–2.5; $p < 0.0001$) and high RDW tertiles (HR 4.3; 95% CI 3.3–5.7; $p < 0.0001$) in comparison to the lowest tertile. In Cox regression analysis, the highest RDW tertile was an independent factor related to higher long-term mortality (HR 2.8; 95% CI 2.1–3.8; $p < 0.0001$), along with older age, diabetes and severe mitral insufficiency. Using RDW as a continuous variable, the adjusted HR for 12-month mortality was 1.26 (95% CI 1.21–1.3). Higher LVEF and hemoglobin levels, and administration of ACEI and β-blockers, were shown to independently improve survival (Fig. 1). RDW > 14.6% (high teritle cut-off) had sensitivity of 0.55 (95% CI 0.51–0.59) and specificity of 0.74 (95% CI 0.72–0.76) in predicting all-cause mortality in the whole patient cohort. AUC for model with RDW was significantly higher than for model without RDW (**Suppl. Fig. 1 and Table 2**). Kaplan-Meier survival curves across RDW tertiles are presented in Figure 2.

Kaplan-Meier curves in the ischemic LVSD etiology subgroup reveal significant differences in mortality across RDW tertiles (Fig. 2). This was confirmed by the Cox regression analysis, where high RDW tertile was an independent factor related to higher long-term mortality (HR 2.8; 95% CI 2.0–3.9; $p < 0.0001$) (Fig. 3). Results of the analysis were similar in the whole population, with anemia, prior stroke and higher heart rate were also identified as factors impairing prognosis.

Table 1. Baseline clinical characteristics of the studied population grouped according to red blood cell distribution width (RDW) tertiles.

Clinical characteristics	RDW tertile			P
	Low (n = 569) RDW ≤ 13.4%	Medium (n = 585) 13.4% < RDW ≤ 14.6%	High (n = 580) RDW > 14.6%	
Age [years][a]	58.9 ± 12.7	61.9 ± 12.8	61.7 ± 12.5	< 0.001
Women[a]	19.5%	21.9%	18.7%	0.4
Body mass index [kg/m^2][a]	27.9 ± 4.3	27.8 ± 5.2	27.2 ± 5.0	0.05
Diabetes mellitus[a]	37.6%	38.1%	47.9%	< 0.01
Hypertension[a]	53.5%	51.3%	49.5%	0.4
Anemia[a]	26.4%	31.6%	50.3%	< 0.01
Previous myocardial infarction[a]	50.1%	45.8%	46.6%	0.3
Previous PCI[a]	23.9%	21.0%	14.8%	< 0.01
Previous stroke[a]	4.9%	6.5%	8.3%	0.1
Chronic kidney disease stage III+[a]	20.6%	25.6%	40.5%	< 0.01
eGFR [mL/min/1.73 m^2][a]	80.8 (63.8–97.4)	75.4 (59.4–94.5)	67.5 (49.5–89.0)	< 0.001
Atrial fibrillation[a]	20.2%	35.2%	44.1%	< 0.01
NYHA class on admission[a]				< 0.001
I	17.6%	11.5%	8.3%	
II	42.2%	37.1%	25.3%	
III	35.3%	41.5%	48.5%	
IV	4.9%	9.9%	17.9%	
Hospitalization due to symptoms of acute heart failure[a]	11.6%	17.0%	16.6%	0.018
Systolic BP [mmHg][a]	127.4 ± 21.3	124.3 ± 21.6	119.5 ± 22.4	< 0.001
Diastolic BP [mmHg][a]	78.1 ± 13	76.6 ± 13.1	74 ± 13.7	< 0.001
Heart rate [bpm][a]	76.5 ± 16.3	79.6 ± 20.1	80.6 ± 18.9	< 0.001
RDW [%][a]	12.9 ± 0.4	14.0 ± 0.3	16.5 ± 2	< 0.001
Hemoglobin [mmol/L][a]	8.9 ± 1	8.7 ± 1.1	8.1 ± 1.2	< 0.001
MCHC [mmol/L][a]	21.26 ± 0.61	21.03 ± 0.62	20.71 ± 0.75	< 0.001
White blood cell count [× 10^3/μL][a]	7.6 ± 2.3	7.9 ± 2.7	7.8 ± 2.7	0.2
Bilirubin [μmol/L][b]	13.3 ± 9.1	15.9 ± 17.2	19 ± 13.3	< 0.001
Blood urea nitrogen [mmol/L][c]	8.4 ± 4.5	8.9 ± 4.6	11.9 ± 7.9	< 0.001
Creatinine [μmol/L][a]	93.4 ± 36.5	95.7 ± 38.2	117.3 ± 86.6	< 0.001
NT-proBNP [pg/mL][d]	699 (274.7–1855.0)	1891 (942.3–3861.0)	3260 (1420–6476)	< 0.001
Cholesterol [mmol/L][e]	4.7 ± 1.3	4.8 ± 3	4.2 ± 1.3	< 0.001
Uric acid [μmol/L][f]	411.5 ± 115	436.2 ± 125.1	463.4 ± 149.9	< 0.001
ACEI[a]	78.2%	73.3%	69.0%	< 0.01
ARB[a]	7.9%	7.1%	7.1%	0.8
Beta-blockers[a]	97.5%	94.9%	93.9%	0.01
Diuretics (loop and thiazide)[a]	80.7%	84.1%	88.3%	< 0.01
MRA[a]	85.9%	84.3%	81.6%	0.1
Statins[a]	79.8%	76.6%	67.7%	< 0.01
Digoxin[a]	15.5%	22.9%	31.9%	< 0.01
Calcium-blockers[a]	8.8%	8.0%	7.7%	0.8
Antiplatelet treatment[a]	73.1%	71.8%	65.4%	< 0.01
Oral anticoagulation[a]	23.4%	36.6%	43.0%	< 0.01

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Table 1 (cont.). Baseline clinical characteristics of the studied population grouped according to red blood cell distribution width (RDW) tertiles.

Clinical characteristics	RDW tertile			P
	Low (n = 569) RDW ≤ 13.4%	Medium (n = 585) 13.4% < RDW ≤ 14.6%	High (n = 580) RDW > 14.6%	
Insulin[a]	14.5%	12.7%	18.1%	0.04
Ischemic etiology[a]	65.2%	65.6%	63.8%	0.8
Valvular etiology[a]	4.9%	8.9%	12.9%	< 0.01
Other etiology[a]	30.3%	23.7%	24.5%	0.04
LV ejection fraction [%][a]	27.4 ± 5.5	26.4 ± 5.9	24.3 ± 6.5	< 0.001
LV end systolic diameter [mm][a]	51.5 ± 9.8	52.2 ± 10.4	54.8 ± 11.6	< 0.001
LV end diastolic diameter [mm][a]	64.2 ± 8.3	64.6 ± 9.3	66.3 ± 10.3	< 0.001
LV end systolic volume [mL][a]	144.4 ± 66.3	152.9 ± 68.7	162.8 ± 83.2	0.003
LV end diastolic volume [mL][a]	195.1 ± 75.4	204.5 ± 82.3	213.6 ± 98.6	0.01
Severe mitral insufficiency[a]	7.6%	11.6%	20.9%	< 0.01
Severe aortic valve insufficiency/stenosis[a]	2.3%	5.3%	9.1%	< 0.01
All-cause 12-month mortality[a]	3.2%	10.1%	24.0%	< 0.01

Continuous variables are presented as median (interquartile range) or mean ± standard deviation. Dichotomic variables are presented as percentage. Data available for: [a]100% of patients; [b]97.9% of patients; [c]39.6% of patients; [d]18.1% of patients; [e]87.3% of patients; [f]88.5% of patients; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; BP — blood pressure; eGFR — estimated glomerular filtration rate; LV — left ventricular; MRA — mineralocorticoid receptor antagonists; MCHC — mean corpuscular hemoglobin concentration; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; PCI — percutaneous coronary intervention

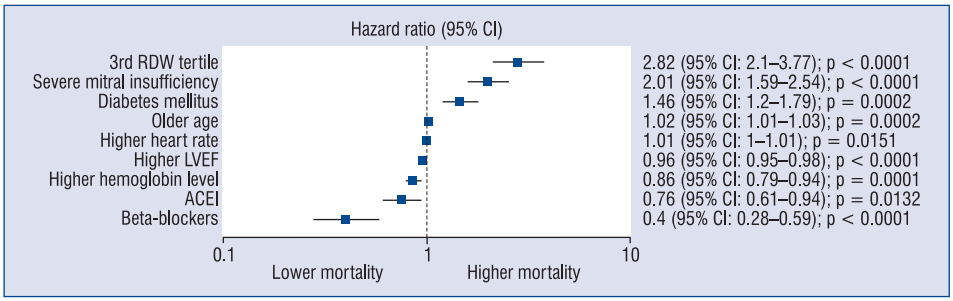

Figure 1. Predictors of mortality. Adjusted hazard ratio for the following parameters: older age (per 1 year increase), heart rate (per 1 bpm increase), hemoglobin on admission (per 1 mmol/L increase), left ventricular ejection fraction (LVEF) (per 1% increase); ACEI — angiotensin-converting enzyme inhibitors; CI — confidence interval; RDW — red cell distribution width.

In the non-ischemic etiology group, Kaplan-Meier analysis revealed significant differences in survival between subsequent RDW tertiles (Fig. 2). The influence of RDW was again confirmed in this subpopulation by Cox regression analysis (HR 3.3; 95% CI 2.0–5.5; p < 0.0001) (Fig. 4).

Discussion

The primary finding of this study was that baseline RDW appeared to be a strong, positive risk factor for all-cause mortality in long-term follow-up of patients with a LVEF of 35% or less. An increased RDW was significantly associated with worse long-term outcome in subgroups of both ischemic and non-ischemic LVSD. The prognostic value of RDW was significant after adjusting for known confounders including comorbid conditions and treatments. To our knowledge, this analysis represents the first report of elevated RDW as a robust prognostic marker of all-cause mortality in patients hospitalized with a LVEF of 35% or less.

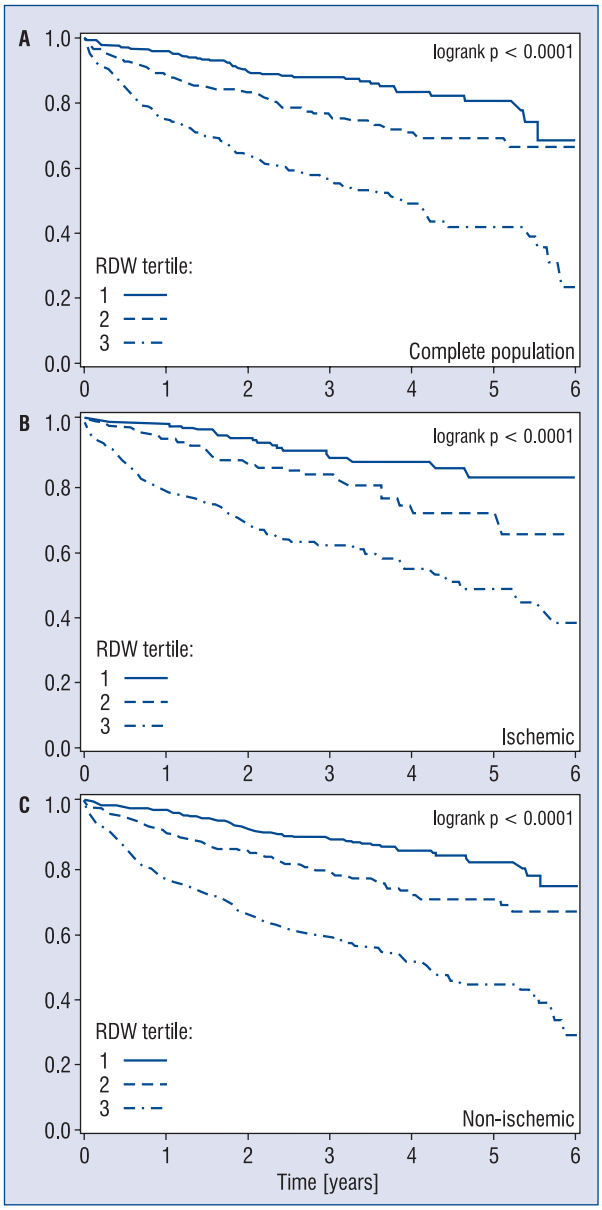

Figure 2. Kaplan-Meier plot showing crude cumulative incidence of all-cause death depending on tertiles of admission red cell distribution width (RDW) in the entire group (**A**), the ischemic (**B**) and the non-ischemic (**C**) subpopulation.

Elevated RDW had been shown to predict poor outcomes in the normal population [17, 18], in patients with CAD [2–6], and in patients with HF [10–14]. The present analysis is the first to demonstrate the predictive value of RDW both in patients with ischemic and non-ischemic LVSD. The results of this analysis are in line with results of recently published studies. Sargento [19] showed that high RDW is associated with worse outcomes in optimally medicated HF outpatients with reduced LVEF. Furthermore Bozorgi et al. [20] demonstrated that RDW predicts the presence of severe LVSD in post myocardial infarction patients. In contrast, Sotiropoulos et al. [21] reported that high RDW is associated with long-term mortality in patients with preserved, but not reduced ejection fraction. The results of prospective studies with long-term follow-up (Tromsø and National Health and Nutrition Examination Survey) demonstrate that high RDW values are associated with increased risk of myocardial infarction and mortality due to CAD in the general population [17, 18], and in elderly patients without age-associated diseases [22]. Tonelli et al. [4] have shown that RDW is a risk factor for myocardial infarction, stroke and symptomatic HF in patients with stable CAD. A meta-analysis performed by Patel et al. [22] in older adults revealed that RDW was a powerful predictor of mortality in community-dwelling older adults. In this analysis, a distinct gradient in mortality risk associated with increasing RDW was reported: for every 1% increase in RDW, the risk of death increased by 14% [22]. Additionally, a meta-analysis by Huang et al. [11] confirmed that in patients with HF, increased RDW either at baseline or at discharge, as well as changes in RDW during treatment, were associated with poor prognosis. In this analysis, all-cause mortality increased by 10% with each 1% increase in baseline RDW [11]. In our study, every 1% increment in RDW increased all-cause mortality by 18.3% (95% CI 12.3–24.7%) in the group of patients with ischemic LVSD and 25.1% (95% CI 17.3–33.4%) in non-ischemic LVSD patients.

Mechanisms underlying the relationship between RDW and poor outcome are not fully understood. A variety of mechanisms have been proposed for the associations among cardiovascular disease, HF, RDW and outcomes. It is difficult to determine whether RDW is only an epiphenomenon of various concomitant disorders or if it is directly responsible for poor prognosis. It is possible that RDW may impact mortality through mechanisms unrelated to anemia and iron status. A high RDW is associated with increased mortality in patients with HF regardless of baseline hemoglobin level [10, 12]. RDW has also been shown to possess prognostic value in non-anemic patients [23]. However, Pascual-Figal et al. [24] have identified RDW as a predictor of the development of new-onset anemia over a 6-month follow-up period in non-anemic patients with decompensated HF. Not surprisingly, RDW is affected by iron metabolism status [25]. Jankowska et al. [26] have indicated that disturbances in iron metabolism are associated with mortality in patients with HF.

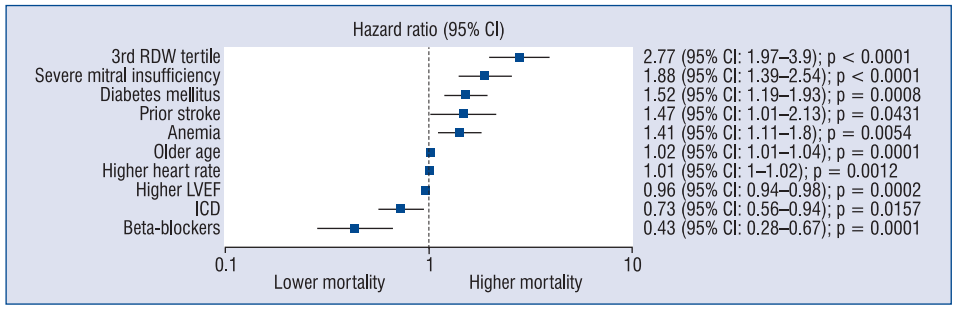

Figure 3. Predictors of mortality in the subpopulation of patients with ischemic left ventricular systolic dysfunction. Adjusted hazard ratio for the following parameters: older age (per 1 year increase), heart rate (per 1 bpm increase), left ventricular ejection fraction (LVEF) (per 1% increase); CI — confidence interval; RDW — red cell distribution width; ICD — implantable cardioverter-defibrillator

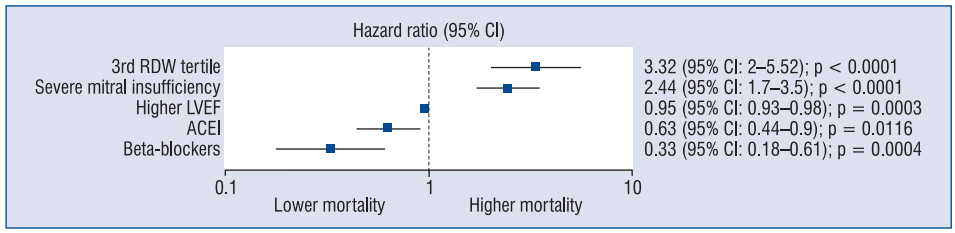

Figure 4. Predictors of mortality in patients with non-ischemic left ventricular systolic dysfunction. Adjusted hazard ratio for left ventricular ejection fraction (LVEF) (per 1% increase); ACE — angiotensin-converting enzyme inhibitors; CI — confidence interval; RDW — red cell distribution width.

Another explanation for the relationship between RDW and outcomes may be chronic inflammation. Inflammation, even of low intensity, may play a crucial role in atherogenesis and HF [27]. Previous studies have demonstrated a relationship between RDW and indicators of inflammation such as erythrocyte sedimentation rate, high sensitivity C-reactive protein, fibrinogen, interleukin-6, soluble tumor necrosis factor (TNF) receptor I and soluble TNF receptor II [25, 28, 29]. Additionally, chronic inflammation leads to disturbances in iron metabolism and an impaired bone marrow response to erythropoietin, increasing the RDW value [29, 30]. Chronic inflammation is often observed in patients with chronic kidney disease [27, 31]. Lippi et al. [32] have demonstrated a significant association between high RDW and impaired renal function.

It has been shown that oxidative stress is responsible for shortening the lifespan of RBC, thus increasing the production and release of young cells into circulation, which is reflected in an increased RDW [33]. Oxidative stress also generates oxidized low density lipoprotein, which plays an important role in atherogenesis [34].

The above-mentioned mechanisms indicate a correlation between RDW and other known risk factors, although it is impossible to clearly identify the exact mechanism by which high erythrocyte anisocytosis is a negative prognostic marker in patients with CAD and HF. In our opinion, the prognostic value of RDW derives mainly from the negative impact of inflammation, oxidative stress, and iron deficiency on bone marrow erythropoiesis in patients with LVSD. Nonetheless, RDW routinely measured as a part of whole blood count, could be an inexpensive and robust biomarker, that would be useful in risk stratification in patients with LVSD.

Limitations of the study

A limitation of the current study is that it was a single-center observational study with inherent weakness related to retrospective analysis. A single blood sample was used at admission to calculate RDW and this study included all-cause mortality as the endpoint. Data regarding nutritional status,

such as iron plasma concentration, deficits of folic acid, vitamin B12, erythropoietin, ferritin and reticulocyte levels were not included. Moreover, current NT-proBNP titers were available only for a limited subset of patients (18.1%). Strengths of this study include a large patient cohort, detailed data on clinical, echocardiography and laboratory parameters, a long follow-up period and no patients lost to follow-up.

Conclusions

In this study RDW was a robust predictor of long-term mortality in patients hospitalized with a LVEF of ≤ 35%, independently of LVSD etiology. Further investigations are needed to outline the exact underlying pathophysiology of poor outcomes in patients with LVSD and high erythrocyte anisocytosis.

Acknowledgements

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Conflict of interest: None declared

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