ORIGINAL ARTICLE

Red blood cell distribution width as a prognostic factor of mortality in elderly patients firstly hospitalized due to heart failure

Marta Salvatori[1,2,3], Francesc Formiga[4], Rafael Moreno-Gónzalez[4], David Chivite[4],
Margherita Migone De Amicis[1,2,3], Maria Domenica Cappellini[1,2,3], Xavier Corbella[4,5]

1   Università degli Studi di Milano, Scuola di Specializzazione in Medicina Interna, Milano, Italy
2   Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
3   Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italy
4   Servicio de Medicina Interna, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
5   Facultad de Medicina y Ciencias de la Salud, Universitat Internacional de Catalunya, Barcelona, Spain

ABSTRACT

BACKGROUND   Red blood cell distribution width (RDW) is a risk factor related to adverse outcome in patients with heart failure (HF). Less is known about its role in patients in their first hospitalization for HF.

AIMS   Our objective was to investigate the prognostic role of RDW in elderly patients hospitalized for acute HF for the first time.

METHODS   We reviewed all patients aged 65 years or older admitted to a tertiary-care university hospital with a main diagnosis of acute HF during a 2-year period (January 2013 to December 2014). Patients were divided into 2 groups according to admission RDW values (<15% or ≥15%).

RESULTS   A total of 897 patients were included in the study. Mean (SD) age was 80.25 (7.6) years. Admission RDW was 15% or higher in 474 patients (52.8%), with a mean (SD) RDW of 15.5% (2.3%). Multivariable analysis confirmed the relationship between a higher RDW on admission and a previous diagnostic history of diabetes and higher serum sodium concentrations on admission. All-cause mortality was higher among patients with RDW of 15% or more at 1 year follow-up (29.6% vs 23.2%, *P* = 0.03). Multivariate analysis confirmed the association between RDW and higher risk of 1-year mortality, as well as with older age, higher Charlson comorbidity index, higher potassium serum concentrations, and no hypertension as a previous diagnosis.

CONCLUSIONS   In elderly patients experiencing their first admission due to acute HF, a higher RDW at baseline might help identify those at higher risk for 1-year all-cause mortality.

INTRODUCTION   Red blood cell distribution width (RDW) is a numerical measure of the variability in the size of circulating erythrocytes. This parameter is routinely reported as part of the complete blood count, but its use is generally restricted to narrowing the differential diagnosis of anemia and hematologic disorders.[1]

Recent studies have linked an elevated RDW with poor cardiovascular outcome in several distinct populations[2] such as patients with stable coronary artery disease,[3] acute coronary syndrome,[4] acute myocardial infarction (MI),[5] stroke,[6] and acute or chronic heart failure (HF).[7-15] Notably, the relationship between RDW and outcome in HF was found to be independent of hemoglobin (Hb), hematocrit, mean corpuscular volume, or mean corpuscular Hb concentrations.[16,17]

Since HF is a widely spread condition among patients aged 65 or more, characterized by high hospitalization and mortality rates even when receiving the best available treatment, there is a need for assessing prognostic factors immediately upon the first episodes of decompensation,

WHAT'S NEW?
Red blood cell distribution width (RDW) is a numerical measure of the variability in the size of circulating erythrocytes and its use is generally restricted to narrowing the differential diagnosis of anemia and hematologic disorders. An elevated RDW has been reported to be associated with poor cardiovascular outcomes. Therefore, we attempted to investigate the value of RDW as a predictor of 1-year all-cause mortality in a population of patients aged 65 or older, who were previously not evaluated and were hospitalized for acute decompensated heart failure for the first time. We confirmed that after the 1-year follow-up, the mortality rate was higher in patients with an RDW of 15% or more as compared with those with an RDW of less than 15%. These results suggest that a simple laboratory measurement can be very useful in evaluating the prognosis of elderly patients admitted for the first time for acute heart failure.

in order to promptly implement preventive and treatment measures in such population according with HF risk stratification.

The aim of our study was to investigate the value of RDW as a predictor of 1-year all-cause mortality in a previously nonevaluated population aged 65 or more in their first hospitalization for acute decompensated HF.

METHODS This retrospective study was performed at the Bellvitge University Hospital, a 750-bed tertiary-care public hospital in Barcelona, Spain. The study design was described previously.[18] In brief, within a 24-month period (January 2013 – December 2014), we retrieved administrative data regarding all consecutive patients aged 65 or more with HF as the main discharge diagnosis. We chose 65 years as the cutoff age because most of the patients admitted during that period where 65 years of age or older, thus eliminating the small percentage of younger patients to create a more uniform study sample. We decided to focus on patients during their first hospitalization to standardize the sample, and to put our attention to elderly HF patients because this issue has been poorly explored so far.[18]

All medical records were reviewed in order to select only those patients who fulfilled clinical criteria for acute HF and were admitted for the first time. We excluded those who had been previously hospitalized with a primary or secondary diagnosis of HF prior to the index admission. We also excluded patients younger than 65 years and those who, besides experiencing a first-ever acute HF admission, were also diagnosed with advanced comorbidity such as cancer, severe dementia (Global Deterioration Scale, 6–7), or other organ-specific diseases (chronic obstructive pulmonary disease, chronic kidney disease, or liver diseases considered to have short life expentancy. Patients presenting with HF secondary to an acute coronary syndrome, and those emergency patients who were

discharged directly home within 24 hours after emergency department admission or transferred to other acute care hospitals were also excluded. All doubts regarding inclusion in the study were discussed by the investigators' revision panel. The ethics committee of Bellvitge University Hospital approved the overall protocol (PR2016/16).

Heart failure was clinically confirmed according to the Framingham criteria. Collected data included demographics, medical history, and all clinical information related to HF signs and symptoms recorded on admission. Moreover, we collected data on chronic therapies used by patients on a long-term basis. In cases where echocardiographic data were available, we recorded ejection fraction (EF) values and we classified HF as preserved EF type when the EF value was 50% or more. A complete blood cell count and basic blood chemistry panel were obtained, including renal function (plasma creatinine values plus the estimated glomerular filtration rate calculated according to the abbreviated Modification of Diet in Renal Disease equation),[19] as well as ionic, lipid, and glycemic profiles. Unfortunately, the plasma concentration of N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) was not available at our hospital at the time of the study, so this parameter could not be evaluated in a proportion of patients on admission, and it was excluded from the data collection procedures. Anemia was defined according to the World Health Organization criteria as a Hb value of less than 13 g/dl for men and of less than 12 g/dl for women. We also assessed the length of hospital stay, comorbidity, and medications prescribed on discharge.

Procedure The study population was divided into 2 groups depending on the RDW cutoff value of 15%, chosen on the basis of a recently published model for early risk stratification in patients with acute HF. Patients with HF with an RDW of 15% or more had approximately 3-fold higher odds of experiencing a new HF-related event during the 1-year follow-up, compared with those with an RDW lower than 15%.[16]

Follow-up During the follow-up, only the data on the patients' vital status were collected. The main outcome of the present study was 1-year all-cause mortality, measured as time-to-event data after discharge. The 30-day mortality rate was also measured as a secondary outcome. The mortality status was determined by trained physician adjudicators on the basis of medical records from hospitalizations, emergency room visits, death certificates, and autopsy and coroner's reports, when available. No patients were lost to follow-up.

TABLE 1 Baseline characteristics of patients hospitalized for acute heart failure for the first time, according to red blood cell distribution width on admission

Parameter	RDW ≥15% (n = 474; 52.8%)	RDW <15% (n = 423; 47.2%)	P value
Age, y, mean (SD)	79.96 (7.7)	80.5 (7.5)	0.22
Sex, female, n (%)	270 (57)	237 (56)	0.83
HFpEF, n (%) (n = 377)	155 (69.8)	110 (71)	0.81
Charlson index, mean (SD)	2.44 (1.85)	2.04 (1.6)	0.001
Length of stay, days, median (range)	6 (4–10)	4 (3–7)	0.001
Chronic therapies, n, mean (SD)	8.9 (3.5)	8.1 (3.3)	<0.001
Medical history, n (%)			
Coronary artery disease (n = 213)	109 (23)	104 (24.6)	0.58
Dyslipidemia (n = 495)	271 (57.2)	224 (53)	0.23
Diabetes mellitus (n = 340)	202 (42.6)	138 (32.6)	0.003
Hypertension (n = 772)	418 (88.2)	354 (83.7)	0.05
COPD (n = 195)	92 (19.4)	103 (24.3)	0.07
CKD (n = 234)	131 (27.6)	103 (24.3)	0.26
Atrial fibrillation (n = 340)	185 (39)	155 (36.6)	0.51
Dementia (n = 37)	34 (7.2)	33 (7.8)	0.72
Known anemia (n = 185)	126 (26.6%)	59 (13.9%)	<0.001
Laboratory tests			
Hemoglobin, g/dl, mean (SD)	11.23 (2.0)	12.71 (6.4)	<0.001
Platelets, 10^3/ μl, median (range)	183.35 (13.90–258.25)	174.00 (13.60–241.00)	0.19
Lymphocytes, 10^3/ml, median (range)	901 (169–1400)	900 (250–1500)	0.96
Creatinine, μmol/l, mean (SD)	124.5 (6528.2)	109.3 (60.6)	0.01
eGFR, ml/min, mean (SD)	57.9 (28.2)	61 (25.6)	0.08
Sodium, mmol/l, mean (SD)	138.7 (4.5)	138.1 (4.34)	0.04
Potassium, mmol/l, mean (SD)	4.2 (0.6)	4.2 (0.5)	0.89

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease equation); HFpEF, heart failure with preserved ejection fraction; RDW, red blood cell distribution width

Statistical analysis Normally distributed continuous variables were reported as mean (SD) and categorical variables as proportions. The t test was used to compare continuous variables, with a previous Levene test for equality of variances, while either the χ^2 test or Fisher exact test was used to compare categorical or dichotomous variables. A logistic regression analysis was performed to determine, at the multivariate level, the baseline factors associated with the presence of an RDW of less than 15% or 15% or higher on admission. This procedure was used to estimate the unadjusted and adjusted odds ratio (OR) with 95% CI. Variables used in this logistic regression were those associated in the bivariate analysis. The final adjusted model was obtained using the backward stepwise method. We used the Cox regression model to evaluate the relationship (estimated as hazard ratios [HRs]) between the presence of an RDW of 15% or higher and all-cause mortality over time. Covariates used for the adjustment of baseline variables were also evaluated in a stepwise Cox multivariable regression analysis, incorporating all of them with P value of less than 0.05 in the univariate analysis. Finally, Kaplan–Meier survival curves and the log-rank test as a function of patients' RDW category were calculated from baseline to the time of censoring. These analyses were conducted with the SPSS program (version 21.0, SPSS Inc., Chicago, Illinois, United States). The tests were 2-sided and P values of less than 0.05 were considered significant.

RESULTS A total of 897 patients were included in the study; their mean (SD) age was 80.25 (7.6) years and 507 (56.5%) of them were women. Echocardiography was available during the index admission for 377 patients (42%). Out of those, 42% had HF with preserved EF and the remaining patients had reduced or intermediate EF. The mean (SD) Hb value was 11.9 (4.7) g/dl, and the mean (SD) RDW value was 15.5 (2.3). RDW was 15% or higher in 474 patients (52.8%). Of them, 204 were men (43%) and 270 were women (57%). A total of 126 patients (26.6%) had a previous diagnosis of anemia before index admission, and 330 (69.6%) fulfilled the World Health Organization criteria for anemia on admission.

Baseline differences between patients with an RDW of less than 15% and 15% or higher are reported in TABLE 1. Patients with an RDW of 15% or higher had a higher prevalence of diabetes, had been more often diagnosed with anemia, and showed a higher χ^2 score. Furthermore, patients with an RDW of 15% or higher were using a higher number of chronic therapies at the time of the first hospitalization for acute HF. Regarding admission laboratory tests, patients with an RDW of 15% or higher presented higher creatinine concentrations, lower Hb values, and higher serum sodium concentrations on admission. Finally, these patients had a longer length of hospital stay during index admission.

The multivariate analysis confirmed a significant and independent relationship between the RDW of 15% or higher and a prior diagnosis of diabetes (OR, 1.48; 95% CI, 1.11–1.97) as well as higher serum sodium concentrations (OR, 1.05; 95% CI, 1.02–1.08), but the association with Hb concentrations, creatinine value, a previous diagnosis of anemia, and higher χ^2 scores lost the association found in the baseline data comparison.

TABLE 2 Thirty-day mortality and 1-year all-cause mortality after the first hospitalization for acute heart failure, according to baseline red blood-cell distribution width value

Mortality	All patients	RDW ≥15% (n = 474)	RDW <15% (n = 423)	P value
In-hospital mortality	48 (5.4)	32 (6.8)	16 (3.8)	0.049
All-cause 30-day mortality	86 (9.6)	56 (11.8)	30 (7.1)	0.02
All-cause 1-year mortality	239 (26.6)	141 (29.7)	98 (23.2)	0.03

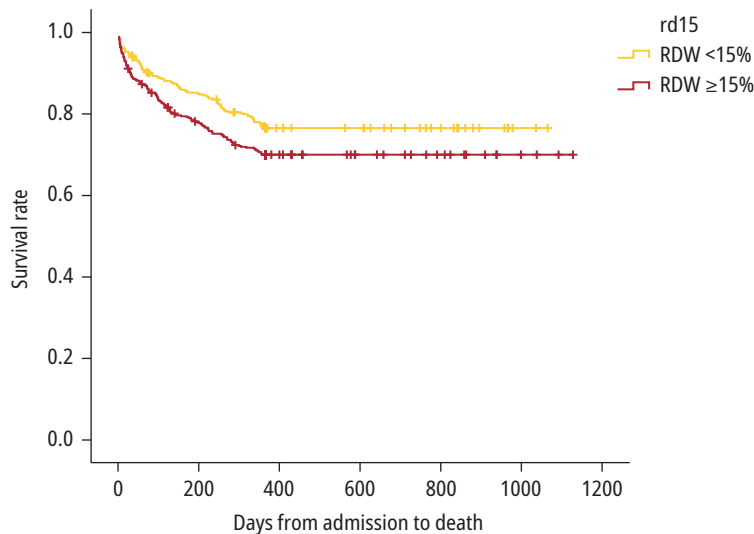Data are shown as number (percentage) of patients.

Abbreviations: see TABLE 1

FIGURE 1 Proof of equality of survival distributions for red blood cell distribution width of 15% or higher and less than 15%

All-cause mortality All-cause mortality was higher in patients with an RDW of 15% or higher during the index admission (6.8 vs 3.8%, P = 0.049), within the first 30 days after discharge (11.8% vs 7.1%, P = 0.02), and after 1 year follow-up (29.6% vs 23.2%, P = 0.03) (TABLE 2). Baseline and discharge data between patients alive and deceased after the 1-year follow-up are compared in TABLE 3. The 1-year survival curves for both RDW groups are shown in FIGURE 1. The multivariate analysis confirmed that the presence of an RDW of 15% or higher at the time of the first admission due to acute decompensated HF in patients aged 65 or older was independently associated with a higher risk of 1-year all-cause mortality (HR, 1.41; 95% CI, 1.05–1.90). Other independent factors associated with a higher 1-year mortality risk were older age (HR, 1.08; 95% CI, 1.06–1.10), higher comorbidity measured by the χ^2 (HR, 1.13; 95% CI, 1.05–1.22), and higher blood potassium concentrations on admission (HR, 1.424; 95% CI, 1.12–1.81). Prior hypertension appeared to be an independent factor associated with a better prognosis (HR, 0.50; 95% CI, 0.34–0.70).

DISCUSSION Interestingly, our study showed that an abnormally increased RDW was not only a common finding (52.8%) among elderly patients at the first admission for acute HF, but also an independent predictor of a higher risk of 1-year all-cause mortality.

An abnormal RDW has been previously reported to be a common finding in the overall population of patients with HF,[20] although important differences in its prevalence have been found, depending on the cutoff values used. Nonetheless, the prevalence reported in our study was slightly higher than that previously described by Allen et al,[20] using a similar RDW cutoff value. In a cohort of 1016 ambulatory patients from the STAMINA-HFP registry, 31% of patients had RDW higher than 15%. Percentages more similar to the ones showed in the present study were also reported by Bonaque et al[10] in a population of 698 consecutive outpatients with chronic HF (48%), who used a slightly lower RDW cutoff of 14.8%. On the contrary, a significantly lower percentage of an altered RDW (18.5%) was reported by Cauthen et al[21] in 6159 consecutive ambulatory patients with chronic HF, using an RDW cutoff of 16%.

Our patient population with an RDW of 15% or higher more often showed a concomitant previous diagnosis of diabetes when compared with patients with normal RDW. The significant relationship between RDW increase and coexisting diabetes found in our study has been also described in some recent studies, suggesting an interesting interaction between diabetic status and RDW.[22,23] Furthermore, these patients also had higher sodium levels on admission. To our knowledge, although the detection of hypernatremia in such patients with HF seems to have an uncertain clinical significance, this association has never been previously described in literature.

Similarly, no investigations have been published to date reporting the other association found in our study between an abnormal RDW and higher plasma creatinine levels on admission. Although this association lost significance in the multivariate analysis in our elderly patients, recent reports have validated the role of RDW as a prognostic marker in patients with chronic kidney disease.[24]

Patients with an RDW of 15% or higher also had a higher number of long-term therapies prior to the index hospitalization, showed a higher number of comorbidities, more often presented anemia prior to HF hospitalization, and had lower Hb levels and higher creatinine levels on admission than patients with an RDW of less than 15%. Furthermore, these patients showed a longer hospital stay during the index admission. However, none of the above conditions were found to be significant in the multivariate analysis.

Regarding prognosis, our results confirmed that the 1-year mortality rate was higher among elderly patients with an RDW of 15% or higher

TABLE 3 Clinical differences between patients deceased and alive after 1 year of follow-up after the first hospitalization for acute heart failure

Parameter	Mortality		P value
	Yes (n = 239; 26.6%)	No (n = 658; 73.4%)	
Age, y, mean (SD)	83.4 (7.89)	79.11 (7.2)	<0.001
Sex, female, n (%)	141 (59)	366 (55.6)	0.37
HFpEF, n (%) (n = 377)	51 (63.8)	214 (72)	0.15
Charlson index, mean (SD)	2.6 (1.99)	2.12 (1.66)	0.001
Length of stay, d, median (range)	5 (3–8)	6 (4–11)	0.001
Chronic therapies, n, mean (SD)	8.6 (3.5)	8.5 (3.45)	0.77
Medical history, n (%)			
Coronary artery disease	52 (21.8)	161 (24.5)	0.4
Dyslipidemia	122 (51)	373 (56.7)	0.13
Diabetes mellitus	82 (34.3)	258 (39.2)	0.18
Hypertension	190 (79.5)	582 (88.4)	0.001
COPD	57 (23.8)	138 (21)	0.36
CKD	71 (29.7)	163 (24.8)	0.14
Atrial fibrillation	86 (36)	254 (38.6)	0.48
Dementia	26 (10.9)	41 (6.2)	0.02
Known anemia	63 (26.4)	122 (18.5)	0.01
Laboratory tests			
Hemoglobin, g/dl, mean (SD)	11.29 (2.13)	12.16 (5.37)	0.02
RDW, %, mean (SD)	15.7 (2.31)	15.4 (2.33)	0.12
Platelets, 10^3/ml, median (range)	176.50 (133.00–250.00)	180.00 (81.50–245.00)	0.55
Lymphocytes, 10^3/ml, median (range)	1000 (170–1500)	900 (275–1300)	0.07
Creatinine, µmol/l, mean (SD)	124.5 (65.6)	111.5 (61)	0.01
eGFR, ml/min, mean (SD)	55.5 (29.7)	60.8 (25.9)	0.01
Sodium, mmol/l, mean (SD)	137.98 (5.18)	138.6 (4.17)	0.11
Potassium, mmol/l, mean (SD)	4.4 (0.64)	4.2 (0.54)	<0.001
Medication at discharge, n (%)			
ACEIs / ARBs	101 (52.9)	430 (65.3)	0.002
β-Blockers	83 (43.5)	356 (54.1)	0.01
MRAs	22 (11.5)	77 (11.7)	0.94
Loop diuretics	181 (94.8)	629 (95.6)	0.63
Thiazide	8 (4.2)	45 (6.8)	0.18

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; others, see TABLE 1

identified RDW as a novel independent marker of adverse outcome and mortality rates in chronic and acute HF.[7] However, these studies mostly evaluated patients with chronic HF and a history of repeated episodes of HF decomposition, for which RDW anomalies could be a marker of a more advanced disease. Interestingly, in our cohort of elderly patients admitted because of the first episode of acute decompensated HF, an RDW of 15% or higher predicted not only 1-year mortality but also in-hospital and 30-day mortality after discharge.

Older age, a higher number of comorbidities measured by the χ^2 test, and a higher blood potassium concentration documented on admission were the other factors, in addition to RDW, independently associated with a higher risk of 1-year mortality in the multivariate analysis. Regarding plasma potassium concentrations in patients admitted for worsening HF, although hypokalemia is a common feature after aggressive diuresis, a considerable increase in serum potassium levels is also observed in elderly patients with HF and impaired renal function or as an adverse effect related to some medications used in HF.[25] Thus, because of its associated risk for life-threatening arrhythmias and conduction system abnormalities, the potential role of hyperkalemia in predicting mortality in our study population is not surprising.[26]

Previous data showing the role of abnormal RDW as a predictor of readmissions or prognostic factor for all-cause mortality have been mainly reported in patients with chronic HF in the outpatient setting.[10] Some of these studies found RDW and NT-proBNP to be independent predictors of adverse clinical events in chronic HF.[11] RDW showed a similar prognostic power for predicting all-cause mortality to that of NT-proBNP in a study by Al-Najjar et al[12] in a population of 1087 ambulatory patients with HF with reduced ejection fraction. Moreover, in a cohort of 205 patients with acute HF, von Kimmenade et al[13] reaffirmed the clinical value of RDW as a predictor of 1-year mortality in addition to other well-established prognostic markers such as NT-proBNP.

Concerning the specific group of patients admitted due to HF for the first time, some previous scattered studies already highlighted a higher prevalence of increased RDW in such population.[8] Furthermore, Makhoul et al[9] found that an abnormal RDW is a strong independent predictor of higher morbidity and mortality, as much as an increase in RDW during hospitalization also portends a worse clinical outcome.

On the other hand, a higher prevalence of anemia among HF patients with a higher RDW is a well-reported association in literature. Although anemia is also a well-known prognostic factor for predicting mortality in HF,[18] RDW generally appears to be an independent prognostic

compared with the other subgroup (29.6% vs 23.2%, P = 0.03). Similarly to other cardiovascular diseases, some previous studies have

factor beyond its clinical association with other hematologic laboratory parameters such as Hb or mean corpuscular volume.[17] This independent prognostic role of RDW was confirmed in a study conducted over a 2-year period in a cohort of 628 consecutive patients hospitalized for acute HF, for whom higher RDW levels were associated with a worse long-term outcome after discharge, regardless of Hb levels and anemia status.[26]

The analysis of data collected from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Program and the Duke Databank suggested that RDW has higher statistical association with poor outcome than other widely accepted risk factors such as ejection fraction, New York Heart Association functional class, or renal function.[14] Of note, RDW has been recently included as a determinant for an early risk stratification of the HF population, showing that patients with an RDW of 15% or higher had approximately 3-fold higher odds of experiencing a HF-related episode of readmission or death, during a 1-year follow-up, when compared with those with a lower RDW value.[16] However, the specific mechanistic links between RDW and poor prognosis in cardiovascular disease and HF have not yet been fully understood, although it has been proposed that a higher RDW might be a consequence of the impaired erythrocyte maturation secondary to the overall deleterious effects of the underlying HF-related inflammatory state.[15]

Our study has some limitations. It was a retrospective analysis and data were collected from electronic medical records. Data on NT-proBNP, iron status, or anemia-related blood parameters were scarce, and only a half of the population had an echocardiography performed during the index admission. Data on antiplatelet and anticoagulant drug use were not collected. A recent study reported that RDW increases in HF within 96 hours of hospitalization; nevertheless, we did not collect data regarding RDW dynamic changes during hospitalization.[27] Another limitation is the lack of control blood tests, neither at the first month nor after the 1-year follow-up. Although it has been reported that an elevated RDW was associated with poorer LV deformation assessed by speckle tracking echocardiography in HF patients with similar ejection fraction, we were unable to assess this.[28] Finally, the study did not include the possible precipitating factors. Actually, for many patients the first hospitalization coincided with the diagnosis of the disease.

On the other hand, we would like to highlight some of the strengths of the study, such as the relatively high number of patients, all carefully selected as presenting with their first-time ever clinical episode of acute HF (confirmed by an accurate medical record review), and the fact that there were no dropouts during the 1-year follow-up.

In conclusion, an RDW value of 15% or higher was present on admission in more than half of our elderly patients firstly hospitalized due to acute HF. Importantly, when compared with the group of patients with normal RDW, those with an RDW of 15% or higher showed higher all-cause mortality rates, either during the index admission, or within the first 30 days and 1 year after discharge. The RDW value of 15% or or higher on admission might help identify patients at higher risk for 1-year all-cause mortality. Whether a direct pathogenic mechanism explains this association (RDW anomalies and higher risk of mortality in the elderly HF population) remains to be confirmed in future studies.

REFERENCES

1 Bessman JD, Gilmer PR Jr, Gardner FH. Improved classification of anemias by MCV and RDW. Am J Clin Pathol. 1983; 80: 322-326.

2 Uyarel H, Isik T, Ayhan E, et al. Red cell distribution width (RDW): a novel risk factor for cardiovascular disease. Int J Cardiol. 2012; 154: 351-352.

3 Tonelli M, Sacks F, Arnold M, et al; for the Cholesterol and Recurrent Events (CARE) Trial Investigators. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation. 2008; 117: 163-168.

4 Sharma R, Agrawal VV. The relationship between red blood cell distribution width (RDW CV) and C reactive protein (CRP) with the clinical outcomes in non-St elevation myocardial infarction and unstable angina pectoris: a 6 months follow up study. Int Cardiovasc Forum J. 2015; 2: 5.

5 Uyarel H, Ergelen M, Cicek G, et al. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. Coron Artery Dis. 2011; 22: 138-144.

6 Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci. 2009; 277: 103-108.

7 Huang YL, Hu ZD, Liu SJ, et al. Prognostic value of red blood cell distribution width for patients with heart failure: a systematic review and meta-analysis of cohort studies. PLoS One. 2014; 9: e104861.

8 Borné Y, Smith JG, Melander O, et al. Red cell distribution width and risk for first hospitalization due to heart failure: a population-based cohort study. Eur J Heart Fail. 2011; 13: 1355-1361.

9 Makhoul BF, Khourieh A, Kaplan M, et al. Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure. Int J Cardiol. 2013; 167: 1412-1416.

10 Bonaque JC, Pascual-Figal DA, Manzano-Fernandez S, et al. Red blood cell distribution width adds prognostic value for outpatients with chronic heart failure. Rev Esp Cardiol. 2012; 65: 606-612.

11 Forhecz Z, Gombos T, Borgulya G, et al. Red cell distribution width: a powerful prognostic marker in heart failure. Eur J Heart Fail. 2010; 12: 415.

12 Al-Najjar Y, Goode KM, Zhang J, et al. Red cell distribution width: an inexpensive and powerful prognostic marker in heart failure. Eur J Heart Fail. 2009; 11: 1155-1162.

13 van Kimmenade RR, Mohammed AA, Uthamalingam S, et al. Red blood cell distribution width and 1-year mortality in acute heart failure. Eur J Heart Fail. 2010; 12: 129-136.

14 Felker GM, Allen LA, Pocock SJ, et al; CHARM Investigators. 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: 40-47.

15 Uyarel H, Isik T, Ayhan E, Ergelen M. Red cell distribution width (RDW): a novel risk factor for cardiovascular disease. Int J Cardiol. 2012; 154: 351-352.

16 Xanthopoulos A, Giamouzis G, Tryposkiadis K, et al. A simple score for early risk stratification in acute heart failure. Int J Cardiol.2017; 230: 248-254.

17 Wołowiec Ł, Rogowicz D, Banach J, et al. Prognostic significance of red cell distribution width and other red cell parameters in patients with chronic heart failure during two years of follow-up. Kardiol Pol. 2016; 74: 657-664.

18 Migone de Amicis M, Chivite D, Corbella X, et al. Anemia is a mortality prognostic factor in patients initially hospitalized for acute heart failure. Intern Emerg Med. 2017; 12: 749-756.

19 Levey AS, Coresh J, Greene T et al; Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem. 2007; 53: 766-772.

20 Allen LA, Felker GM, Mehra MR, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail. 2010; 16: 230-238.

21 Cauthen CA, Tong W, Jain A, et al. Progressive rise in red cell distribution width is associated with disease progression in ambulatory patients with chronic heart failure. J Card Fail. 2012; 18: 146-152.

22 Nada AM. Red cell distribution width in type 2 diabetic patients. Diabetes Metab Syndr Obes. 2015; 8: 525-533.

23 Engström G, Smith JG, Persson M, et al. Red cell distribution width, haemoglobin A1c and incidence of diabetes mellitus. J Intern Med. 2014; 276: 174-183.

24 Hsieh YP, Chang CC, Kor CT, et al. The predictive role of red cell distribution width in mortality among chronic kidney disease patients. PLoS One. 2016; 11: e0162025.

25 Khan SS, Campia U, Chioncel O, et al. Changes in serum potassium levels during hospitalization in patients with worsening heart failure and reduced ejection fraction (from the EVEREST trial). Am J Cardiol. 2015; 115: 790-796.

26 Pascual-Figal DA, Bonaque JC, Redondo B, et al. Red blood cell distribution width predicts long term outcome of anemia status in acute heart failure patients. Eur J Heart Fail. 2009; 11: 840-846.

27 Turcato G, Zorzi E, Prati D, et al. Early in-hospital variation of red blood cell distribution width predicts mortality in patients with acute heart failure. Int J Cardiol. 2017; 243: 306-310.

28 Eroglu E, Kilicgedik A, Kahveci G, et al. Red cell distribution width and its relationship with global longitudinal strain in patients with heart failure with reduced ejection fraction: a study using two-dimensional speckle tracking echocardiography. Kardiol Pol. 2018; 76: 580-585.