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Red cell distribution width predicts mid-term prognosis in patients hospitalized with acute heart failure: the RDW in Acute Heart Failure (RE-AHF) study

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Abstract

The aim of the study was to evaluate the prognostic role of red cell distribution width (RDW) in a broad population of patients hospitalized for acute heart failure (AHF). In a retrospective cohort observational study, 451 consecutive patients discharged for AHF were categorized in patients with low RDW ($\leq 14.8\%$) and high RDW ($> 14.8\%$). The rates of death from all causes or of hospital readmission for worsening heart failure and death were determined after a median follow-up of 18 months. The overall population has a median age of 80 years (IQR 72–85), 235 patients (52%) were males. Patients with a higher RDW have more comorbidities and a higher Charlson Index. At follow-up, 200 patients (44%) had died and 247 (54%) had died or were readmitted for HF: in the cohort with low RDW, 70 patients (36.4%) had died, whereas in the cohort with high RDW, 165 patients (63.7%) had died: the unadjusted risk ratio of patients with high RDW was 2.03 (log-rank test: $p < 0.0001$). In a multivariate Cox regression model, the hazard ratio for death from any cause in the 'high RDW' cohort is 1.73 (95% confidence interval 1.2–2.48; $p = 0.003$); the RDW adds prognostic information beyond that provided by conventional predictors, including age; etiology of HF; anemia; hyponatremia; estimated glomerular filtration rate; NT-proBNP levels; Charlson comorbidity score, atrial fibrillation, functional status, therapy with renin–angiotensin–aldosterone system inhibitors, beta-blockers. RDW is a powerful marker of worse long-term outcomes in patients with AHF, and its prognostic value is maintained beyond that provided by other well-established risk factors or biomarkers.

Keywords Acute heart failure · Red cell distribution width · Prognosis · Comorbidities

Introduction

Risk stratification of patients discharged from the hospital for acute heart failure is critical to assist in the choice of appropriate therapy, to better counsel patients, to define follow-up strategies, and also to propose palliative care [1–3].

Several variables have been shown to predict long-term mortality or readmission to the hospital in acute heart failure, including demographics, clinical history, physical examination, comorbidities and frailty syndrome, laboratory findings (hyponatremia, low eGFR, suppression of tumorigenicity 2 (ST2), high level of natriuretic peptides, anemia and iron deficiency), measures of cardiac function or structure obtained by echocardiography, or the presence of specific therapies [4–8]. Although most of these predictors are easy to obtain in clinical practice, others are more complex or expensive to acquire, limiting their widespread use at the bedside.

Red cells distribution width (RDW), a parameter routinely reported in complete blood cell counts, and therefore nearly always available in all hospitalized patients, has recently been proposed as a prognostic marker in chronic heart failure, acute coronary syndrome, cancer and renal diseases: the mechanism linking all these diseases to increase of RDW is unknown, but seems to be related to a slight reduction in the in vivo rate of RBC turnover, expanding the low-volume tail of the RBC population's volume distribution, and

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thereby increasing RDW [9]. Another hypothesis proposes that RDW might increase via erythropoietin secretion and subsequent erythropoiesis amplification induced by chronic or episodic hypoxia. In this model, RDW can be considered as a biomarker of chronic exposure to hypoxia [10]. Furthermore, RDW increases in iron deficiency, a condition associated with reduced exercise capacity and poor prognosis independently of anemia and left ventricular ejection fraction in patients with heart failure [11–14].

Nowadays the role of RDW in predicting long-term prognosis in unselected patients hospitalized with acute heart failure is not fully elucidated: particularly it is not clear if the prognostic value of RDW is independent from other powerful predictors of long-term mortality or readmission as comorbidities and functional status impairment.

Therefore, we aim to evaluate the long-term prognostic role of RDW and RDW changes during hospitalization aside from comorbidities and other common prognostic factors, in patients admitted to the hospital for acute heart failure.

Methods

The REd Cell Distribution Width in Acute Heart Failure (RE-AHF) study was designed as a retrospective cohort study, as part of a clinical audit program on acute heart failure management, conducted in 2014 at the S. Croce e Carle Hospital, Cuneo, Italy. This is a tertiary teaching-hospital with 824 bed and 25,000 admissions in 2014, sited in the southern Piedmont region and provided with a coronary intensive care unit, cardiac catheterization laboratory and cardiac surgery facility.

Patient selection

All consecutive patients discharged from the hospital from January 1, 2013, through December 31, 2013 with the main diagnosis of 'Heart failure' were considered for follow-up. We selected patients by searching the administrative database of the hospital with the following discharge codes, according to the International Classification of the Diseases (ICD)—9: 428.X, 402.X and 5184. Each retrieved patient record was checked by G.R. and A.G. to verify inclusion and exclusion criteria. Acute heart failure was defined according to the Guidelines of the European Society of Cardiology as a rapid or gradual onset of signs and symptoms of heart failure, resulting in unplanned hospitalization and including new onset acute heart failure, without previously known cardiac dysfunction, and acute decompensation of chronic heart failure [1].

Exclusion criteria were multiple admissions (only first admission in the current year was considered to avoid sample bias), any planned admission (e.g., for ICD or CRT implantation) or a history of blood transfusion in the last 3 months. Overall a cohort of 451 patients was studied (Fig. 1).

This study complied with the Declaration of Helsinki and was approved by the local ethics committee (Prot. no. 15040).

Data extraction

Demographic characteristics (gender and age), underlying diseases and comorbidities, vital parameters (systolic and diastolic blood pressure, heart rate, hemoglobin oxygen saturation) in the Emergency Department (ED), clinical presentation (NYHA class, de novo heart failure or recurrent episode), etiology of the cardiac disease (coronary artery disease, hypertension, valvular disease or other), presence of functional impairment (defined as a need for assistance for at least one activity of daily living, i.e., ADL score < 12), current medications, presence of devices (CRT or ICD), echocardiographic findings, and analytical results (including hemoglobin, hematocrit, RDW, mean corpuscular volume (MCV), electrolytes, serum creatinine and N-terminal pro-brain natriuretic peptide, NT-proBNP (Siemens

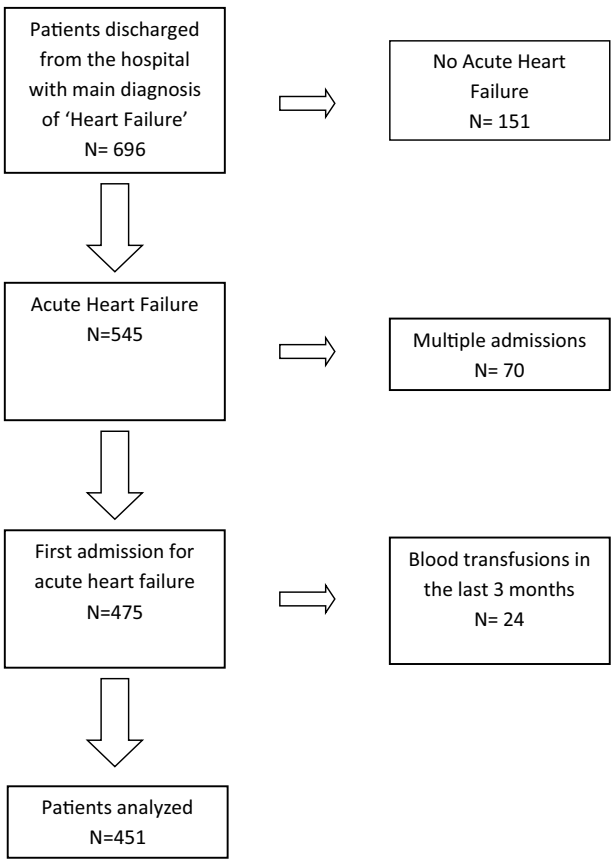

Fig. 1 Flowchart of patient selection process in the RE-AHF study

Immulite) were recorded at admission (i.e., first available data). Values of hemoglobin, RDW, MCV and serum sodium were recorded also at discharge (i.e., the last available data). Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [15]. RDW was measured by Sysmex XE-5000 (Dasit SpA, Cornaredo, Italy), and was reported as the coefficient of variation (in percent) of erythrocyte cell volume. The delta RDW (DRDW) was calculated as the difference between the last and first (at admission) RDW values. A Charlson Comorbidity Score, a weighted measure of comorbidities, was also calculated [16].

According to the European Society of Cardiology Guidelines, an echocardiographic study was performed on all patients with 'the novo' acute HF admission, in patients with hemodynamic instability, in patients suspected of acute life-threatening structural or functional cardiac abnormalities, or in patients with unknown cardiac function. Left ventricular ejection fraction (LVEF) was measured by Simpson biplane method. Overall 57% of patients had an echocardiographic study performed by an experienced cardiologist during the index hospitalization, whereas the remaining 43% had studies dating back 1 year or less.

Finally, patients were categorized into two cohorts, with 'low RDW' ($\leq 14.8\%$) and 'high RDW' ($> 14.8\%$), using as cut-off the median value of the RDW at admission of the whole population.

Outcomes

The rate of death from any causes and the composite endpoint of death from any cause or readmission to the hospital for acute heart failure were determined after a median follow-up of 18 months. The outcomes were determined by hospital records review, or by phone calls to patients or to their relatives or to the referring primary physicians. A further admission to other hospitals was a rare event because of the local organization of the health system; however, when it occurred, it was intercepted by phone calls follow-up and recorded in the database. Moreover, to assess the quality of follow-up we calculate the simplified person-time follow-up rate [17], that was 93%.

Statistical analysis

Data were described as means and standard deviations or median (interquartile range) for quantitative variables as appropriate; percentages were used for categorical variables. The normal distribution of the variables was evaluated by the skewness–kurtosis test. Differences between groups were analyzed using the *T* test for quantitative variables and the Chi-square contingency test or Fisher's exact test for the categorical ones. Survival was estimated with the Kaplan–Meier method, and comparisons were made using the log-rank test. Univariate and multivariate Cox proportional hazard model was used to identify variables associated with survival. Only variables that reached a statistical significance ($p < 0.05$) at univariate analysis were included in the multivariate Cox models. Since the Charlson comorbidity index includes different weighted variables, we tested both a model with the Charlson Index and a model with the single variables of the score that reached a statistical significance at univariate analysis (dementia, COPD, chronic kidney disease and metastatic cancer). In all analyses, $p < 0.05$ was considered statistically significant. All statistical analysis was conducted using STATA/IC 14.0 Software (StataCorp LP, USA).

Results

The demographic, clinical and biochemical characteristics of the studied population

The overall population had a median age of 80 years (IQR 72–85), 235 patients (52%) were males. The baseline characteristics of the population and of two cohorts are described in Tables 1 and 2. Patients with a high RDW are more likely than patients with a low RDW to have atrial fibrillation (57% vs 40% $p < 0.0001$) or history of COPD (29% vs 19%, $p = 0.02$) and less likely to have 'de novo' HF (37% vs 49%, $p = 0.009$); moreover, the high RDW cohort has a higher Charlson Comorbidity Score (median: 5, 25°–75° percentile: 3–7 vs 4, 2–6, $p < 0.001$) and NT-proBNP levels (6228 pg/mL, IQR 2513–15,282, vs 5094 pg/mL, IQR 1937–10,616, $p = 0.02$) and lower hemoglobin (12.0 ± 2 g/dL vs 13.3 ± 1.8 g/dL $p < 0.0001$), mean corpuscular volume (88.1 ± 9 fL vs 91.8 ± 5 fL $p < 0.0001$) and eGFR (52.7 ± 24 mL/min vs 61.2 ± 22 mL/min, $p = 0.0001$) levels than the low RDW cohort.

Setting of admission

With respect to the setting of admission to the hospital, 129 patients (29.5%) were admitted to the Cardiology Unit, whereas 307 (70.4%) were admitted to a general ward (Internal Medicine or Geriatric ward). Patients with a high RDW were more likely to be admitted to a general ward (74.9% versus 64.5%, $p < 0.02$).

Outcomes: death for all causes

At follow-up, 185 patients (42%) had died: in the cohort with a low RDW ($N = 189$) 52 patients had died (27%) whereas in the cohort with a high RDW ($N = 247$), 133 patients (53%) had died. The unadjusted risk ratio for all-cause death in

Table 1 Baseline characteristics of the study population overall and according to RDW values

	Overall ($N=451$)	RDW ≤ 14.8 ($N=231$)	RDW > 14.8 ($N=220$)	p value
Age (years)	80 (72–85)	80 (72–85)	79 (72–85)	0.84
Gender (male)	235 (52)	125 (54)	110 (50)	0.40
Etiology of HF				
Hypertension	237 (53)	129 (55)	108 (51)	0.40
Coronary artery disease	135 (30)	67 (30)	68 (30)	0.96
Valvular disease	107 (24)	52 (23)	55 (26)	0.47
Other	61 (13)	26 (11)	35 (16)	0.16
'De novo' HF	194 (43)	113 (49)	81 (37)	0.009
Ejection fraction (%)	38 ± 13	37 ± 13	39 ± 12	0.41
Systolic dysfunction	293 (65)	143 (62)	147 (67)	0.242
Mild	45 (10)	18 (8)	28 (13)	
Moderate	85 (19)	39 (17)	48 (22)	
Severe	149 (33)	69 (30)	70 (32)	
NYHA Class III or IV	383 (85)	196 (85)	187 (85)	0.97
Activity of daily living comorbidities	126 (28)	64 (28)	62 (28)	0.90
Atrial fibrillation	218 (49)	92 (40)	126 (57)	0.0001
Diabetes mellitus	131 (29)	60 (26)	71 (33)	0.11
Cerebrovascular disease	80 (18)	31 (16)	49 (19)	0.49
Dementia	63 (14)	28 (12)	35 (16)	0.28
COPD	108 (24)	44 (19)	64 (29)	0.02
Cancer	81 (18)	35 (15)	46 (20)	0.38
Charlson Comorbidity Score	4 (3–6)	4 (2–6)	5 (3–7)	0.0001
Vital parameters				
SBP/DBP (mmHg)	143/81 ± 30/16	148/83 ± 30/17	142/80 ± 28/15	0.05/0.08
HR (bpm)	92.6 ± 25.3	93.0 ± 25.5	91.8 ± 25.3	0.6
SpO_2 (%)	95 (91–97)	95 (91–97)	95 (91–97)	0.8
Therapies				
CRT and/or AICD, %	54 (12)	24 (11)	30 (14)	0.31
ACE inhibitors/ARB, %	270 (60)	155 (67)	115 (52)	0.002
Beta-blockers, %	221 (49)	127 (55)	94 (43)	0.02
Ivabradine, %	32 (7)	16 (7)	16 (7)	0.97
Aldosterone antagonists, %	243 (54)	122 (53)	121 (55)	0.52
Oral anticoagulant, %	163 (36)	69 (30)	94 (43)	0.005
Loop diuretics, %	405 (90)	203 (88)	202 (92)	0.16
Erythropoietin, %	8 (2)	1 (0.5)	7 (3)	0.02
Length of hospital stay (days)	8 (6–12)	7 (5–10)	9 (6–13)	0.002
All causes death	200 (44,3)	74 (32)	125 (57)	< 0.0001
Death or readmission for HF	247 (54)	98 (42)	149 (67)	< 0.0001

Data are expressed as number (percentage), mean ± standard deviation or median (25–75% percentiles) as appropriate

COPD chronic obstructive pulmonary disease, *SBP and DBP* systolic and diastolic blood pressure, *SpO_2* hemoglobin saturation in oxygen, *eGFR* glomerular filtration rate estimated with CKD-EPI formula, *CRTD* cardiac resynchronization therapy, *AICD* automated implantable cardioverter defibrillator, *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blockers

patients with high RDW is 2.03 (1.50–2.74 95% confidence interval (CI), log-rank test $p < 0.0001$, Fig. 2).

Variables showing univariate association with the endpoint (Table 3) were entered in multivariate analysis. In the multivariate Cox regression model, the hazard ratio for death from any cause for the patients with high RDW as compared with those with a low RDW is 1.73 (95% CI 1.20–2.48; $p = 0.003$); the RDW adds prognostic information beyond that provided by conventional risk factors, including the patient's age; hypertensive etiology of heart failure; dependency in activity of daily living; comorbidities, assessed by the Charlson Comorbidities Score;

Table 2 Baseline laboratory variables overall and according to RDW values

	Total ($N=451$)	RDW ≤ 14.8 ($N=192$)	RDW > 14.8 ($N=259$)	p value
NT-proBNP (pg/mL)	5530 (2332–13,386)	5254 (1996–10,646)	6228 (2557–15,453)	0.03
Log NT-proBNP (pg/mL)	3.71 ± 0.52	3.65 ± 0.52	3.77 ± 0.51	0.01
eGFR (mL/min)	57.4 ± 23.5	61.2 ± 22	52.7 ± 24	< 0.0001
RCP (mg/dL)	18.6 (9–38)	16 (8–38)	22 (11–39)	0.12
Hb (g/dL)	12.7 ± 2.0	13.3 ± 1.8	12.0 ± 2.0	< 0.0001
MCV (fL)	90 ± 8	91.8 ± 5.1	88.1 ± 9.4	< 0.0001
RDW (%) at admission	14.8 (14–16.1)	14 (13.5–14.4)	16.1 (15.4–18)	< 0.0001
RDW (%) at discharge	14.7 (13.8–16.1)	13.9 (13.3–14.4)	16.1 (15.2–17.9)	< 0.0001
Delta RDW	− 0.06 ± 1.0	− 0.04 ± 0.5	− 0.07 ± 1.3	0.77

Data are expressed as number (percentage). Mean ± standard deviation or median (25–75% percentiles) as appropriate. Delta RDW was calculated as the difference between the last and first (at admission) RDW values

NT-proBNP N-terminal of pro-brain natriuretic peptide, *Hb* hemoglobin, *MCV* mean corpuscular volume, *RCP* reactive C-protein

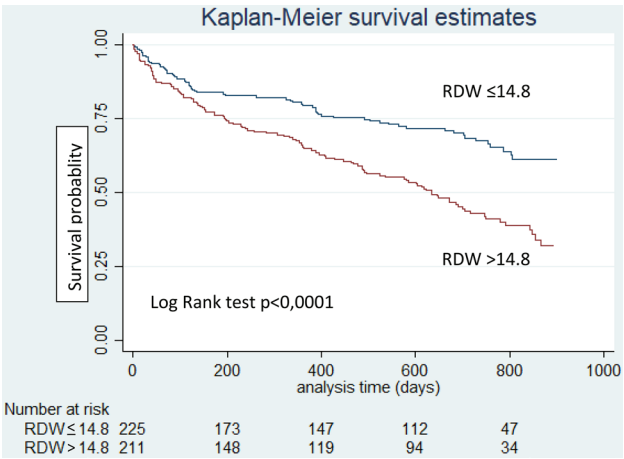

Fig. 2 Kaplan–Meier survival curve showing cumulative survival probability according to RDW values

diastolic blood pressure; eGFR (mL/min); hemoglobin level; serum sodium; log NT-proBNP; therapy with ACE-I or ARB, beta-blockers or loop diuretics (Table 4).

Oral anticoagulation was likely underused in our patients with atrial fibrillation both in the cohort with a high RDW (patients anticoagulated: 83/147, 57%) and in the cohort with a low RDW (48/71, 65%, Pearson Chi-squared 0.6, $p=0.43$). At univariate analysis, anticoagulation therapy is not associated with outcome, however, if we limit the analysis to the atrial fibrillation patients, the result is significant (HR 0.6, 95% CI 0.40–0.89, $p=0.03$). Thus, we performed a multivariate analysis on our patients with atrial fibrillation, including RDW, Delta RDW, age, ADL impairment, Charlson's Score and oral anticoagulation in the model (see Table 7 ESM): oral anticoagulation is not significantly associated with the outcome (HR 0.97, 95% CI 0.59–1.59, $p=0.91$).

Outcomes: death for all causes or heart failure hospitalization

At follow-up, 247 (54%) patients had died or were hospitalized for acute heart failure: in the cohort with a low RDW 98 (42%) patients had died or were readmitted whereas in the cohort with a high RDW, 149 (67%) patients had died or were readmitted. Considering only the readmissions for heart failure decompensation, overall 94 patients (21%) were readmitted to the hospital in the follow-up period, 36 (16%) in the cohort with a low RDW and 58 (27%) in the cohort with a high RDW ($p=0.004$). The median (25°–75° percentiles) length of hospital stay for patients readmitted is 7 (5–10) days. The unadjusted risk ratio for the composite outcome in patients with a high RDW is 1.89 (log-rank test $p<0.0001$, Fig. 4 and Table 5 ESM).

In the multivariate Cox regression models, the hazard ratio for death from any cause or heart failure readmission for the patients with a high RDW as compared with those with a low RDW is 1.55 (95% confidence interval, 1.08–2.22; $p<0.01$); the RDW adds prognostic information beyond that provided by patient's age; hypertensive etiology of heart failure; dependency in activity of daily living; comorbidities assessed by the Charlson Comorbidities Score; 'de novo' heart failure; systolic dysfunction; NYHA class; eGFR (mL/min); hemoglobin levels; serum sodium; log NT-proBNP; therapy with ACE-I or ARB or loop diuretics.

RDW variations during hospitalization and RDW at discharge

During the hospital stay, the mean RDW difference between admission and discharge (Delta RDW) is − 0.06 ± 1.03%: RDW worsened in 150 patients (34.4%), 54 patients (28%) belonging to the 'low RDW' cohort and 96 patients (38%) to

Table 3 Univariate analysis for death for all causes

	HR	95% CI	*p* value
Demography			
Age (by 10 years)	1.64	1.40–1.93	0.000
Gender (male)	0.58	0.64–1.14	0.323
Etiology of HF			
Hypertension	0.69	0.52–0.93	0.01
Coronary artery disease	1.16	0.86–1.59	0.31
Valvular disease	1.53	1.12–2.10	0.008
Other	1.12	0.74–1.70	0.58
'De novo' HF	0.66	0.49–0.90	0.008
Systolic dysfunction	1.20	0.86–1.68	0.28
NYHA Class III or IV	1.15	0.72–1.83	0.53
Comorbidities			
Atrial fibrillation	1.22	0.91–1.63	0.18
Diabetes mellitus	0.97	0.75–1.25	0.78
Cerebrovascular disease	1.18	0.82–1.69	0.38
Dementia	2.53	1.80–3.57	0.000
COPD	1.70	1.25–2.32	0.001
Chronic kidney disease	1.35	0.99–1.84	0.05
Cancer	1.07	0.89–1.29	0.48
Metastatic cancer	1.26	1.13–1.40	0.000
Charlson Comorbidity Score	1.19	1.12–1.27	0.000
Activity of daily living	3.39	2.52–4.56	0.000
Vital parameters			
SBP (mmHg)	0.99	0.99–0.99	0.04
DBP (mmHg)	0.98	0.97–0.99	0.001
HR (bpm)	1.00	0.99–1.01	0.56
SpO_2 (%)	0.97	0.95–0.99	0.01
Therapies			
CRTD and/or AICD, %	1.43	0.96–2.14	0.08
ACE inhibitors/ARB, %	0.37	0.28–0.50	0.000
Beta-blockers, %	0.65	0.48–0.87	0.004
Ivabradine, %	1.12	0.66–1.90	0.7
Aldosterone antagonists, %	0.97	0.72–1.30	0.83
Oral anticoagulant, %	0.79	0.58–1.07	0.14
Loop diuretics, %	2.22	1.18–4.21	0.01
Erythropoietin, %	1.76	0.77–0.97	0.14
Laboratory (at admission)			
Na	0.96	0.92–0.99	0.013
Hb	0.90	0.84–0.95	0.002
MCV	1.01	0.99–1.03	0.390
RDW	1.18	1.11–1.25	< 0.0001
RDW > 14.8	2.03	1.50–2.74	< 0.0001
Creatinine	1.22	1.12–1.34	< 0.0001
eGFR	0.99	0.98–0.99	< 0.0001
Log NT-proBNP	2.24	1.60–3.13	< 0.0001
RCP	1.00	0.99–1.01	0.113
Laboratory (at discharge)			
Na	0.97	0.93–1.01	0.146
Hb	0.85	0.79–0.92	< 0.0001
MCV	1.01	0.99–1.03	0.429
RDW	1.14	1.08–1.20	< 0.0001
RDW > 14.8	2.45	1.81–3.31	< 0.0001
Delta RDW	1.10	0.98–1.23	0.109
Delta RDW > 0	2.09	1.56–2.78	< 0.0001

COPD chronic obstructive pulmonary disease, *SBP and DBP* systolic and diastolic blood pressure, *SpO_2* hemoglobin saturation in oxygen, *eGFR* glomerular filtration rate estimated with CKD-EPI formula, *CRTD* cardiac resynchronization therapy, *AICD* automated implantable cardioverter defibrillator, *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blockers, *NT-proBNP* N-terminal of pro-brain natriuretic peptide, *Hb* hemoglobin, *MCV* mean corpuscular volume, *RCP* reactive C-protein

Table 4 Cox proportional hazards estimates of the determinants of death for all causes

	HR	95% CI	*p* value
RDW > 14.8 at admission[a]	1.73	1.20–2.48	0.003
Increase RDW in hospital[a]	1.54	1.08–2.18	0.01
RDW at discharge	1.15	1.06–1.24	0.001
Age (by 10 years)	1.35	1.10–1.65	0.003
ADL (at least one impaired)[a]	2.01	1.37–2.93	< 0.0001
Charlson Comorbidity Score	1.10	1.02–1.18	0.01
'De novo' heart failure[a]	0.78	0.54–1.13	0.19
History of hypertension[a]	0.67	0.49–0.92	0.02
Atrial fibrillation	1.07	0.75–1.52	0.39
DBP (mmHg)	0.99	0.98–1.00	0.26
Hb (g/L)	1.02	0.93–1.12	0.60
eGFR < 30 mL/min[a]	0.96	0.63–1.46	0.85
Na at admission (mEq/L)	0.96	0.92–1.00	0.07
log NT-proBNP (pg/mL)	1.64	1.15–2.32	0.005
RAS inhibitors[a]	0.58	0.40–0.82	0.003
Beta blockers[a]	1.06	0.73–1.55	0.72
Loop diuretics[a]	1.32	0.62–2.81	0.46

The estimate gives the outcome increment associated with any category or one unit increase in the predictor (10 years for age)

[a]Yes/no

the 'high RDW' cohort ($p = 0.024$). The worsening of RDW during hospitalization is associated with an increased risk of death at follow-up (HR 2.09, 95% CI 1.56–2.78 $p < 0.0001$), and this finding is also maintained when the Delta RDW is included in the multivariate Cox model (HR 1.45, 95% CI 1.01–2.08, $p < 0.05$, Table 4 and Fig. 3).

As expected, the RDW at discharge is higher in the group at a higher baseline RDW (16.8 ± 2.2 vs 13.9 ± 0.6 $p < 0.0001$). RDW at discharge is associated with a 14% increase in mortality risk at follow-up (for each 1% increase in RDW, unadjusted HR 1.14, 95% CI 1.08–1.23 $p < 0.0001$, Table 3); the unadjusted HR for mortality for an RDW > 14.8

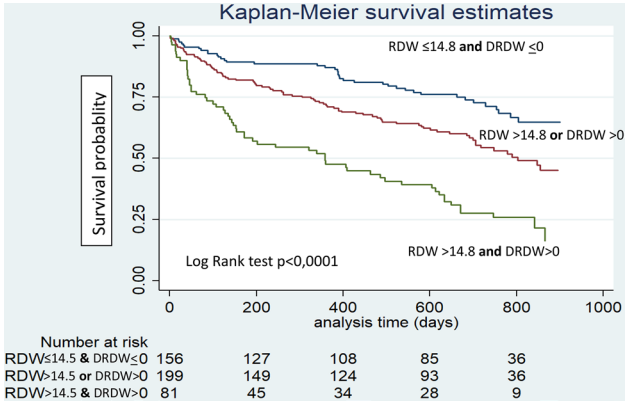

Fig. 3 Survival curve according to RDW values and Delta RDW. Negative (≤0) DRDW means a reduced RDW value at discharge; DRDW > 0 was an increased RDW at the end of hospitalization

at discharge is 2.45 (95% CI 1.81–3.31, $p < 0.0001$, Table 3). At multivariate analysis, the RDW at discharge is found to be a significant independent predictor of all-cause mortality (adjusted HR 1.15 per 1% increase in RDW, 95% CI 1.06–1.24, $p = 0.001$, Table 4).

Discussion

The present study shows that unselected patients admitted to the hospital with AHF and high RDW values measured at admission, have a two time higher risk of death and 55% higher risk of death and heart failure hospitalization at a 18-months follow-up compared to patients with a low RDW, and that this prognostic value is maintained beyond that provided by hemoglobin levels, NT-proBNP, or other well-established risk factors or biomarkers, including comorbidities and dependency in activity of daily living. Moreover, our data also confirms that RDW increase during the hospital course and RDW obtained at discharge are powerful independent prognostic indicators.

In 2007, RDW was for the first time, associated with prognosis in chronic heart failure: among 36 laboratory values considered in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, higher Red Cell Distribution Width (RDW) shows the greatest association with morbidity and mortality [18].

Pascual-Figal evaluated the prognostic role of RDW measured at discharge in a selected population of acute HF patients admitted to a Cardiology Department [19]: as expected, their patients were in median 10 years younger, had lower prevalence of atrial fibrillation and more ischemic etiology of HF compared to our unselected population. As in our study, higher RDW levels at discharge are associated with a worse long-term outcome, regardless of hemoglobin levels and anemia status.

Moreover, our data are in agreement with the study of Makoul et al. who demonstrate a marked increase in mortality and rehospitalizations among patients in whom RDW became elevated during hospital course [20]. Also Ferreira et al. show that an enlarging RDW from admission to discharge and elevated RDW values at discharge are independently associated with mid-term adverse events over and above hemoconcentration (as measured by a change in hemoglobin during hospitalization) [21]. Huang in 2014 performed a systematic review and meta-analysis of 17 cohort studies that evaluated the prognostic value of RDW for patients with either acute or chronic HF, with a total of 18,288 patients: the results indicated that an increased baseline RDW, as well as the change in RDW during treatment are associated with a poor prognosis in patients with HF. In this review, the pooled HR shows that each 1% increase in RDW on admission is associated with a 10% higher risk of future mortality events [22]. However, only one of the studies included in the meta-analysis was adjusted for comorbidities, and none were adjusted for functional status. Similar results were obtained by a more recent meta-analysis of 17 studies with a total of 41,311 patients: the authors acknowledge the possibility that residual confounding not included in the analysis could limit their conclusions [23].

Several studies demonstrate that multimorbidity is very common in acutely hospitalized older patients and that among this population the dependency in ADL, frailty and comorbidities are strongly associated with in-hospital and long-term mortality [8, 24–26]. Moreover, previous studies document an independent adverse effect of comorbidities and impaired functional status on mortality in older patients with AHF, in keeping with our results [27]. Among comorbidities, chronic obstructive pulmonary disease is suspected to induce a proinflammatory state with increase of interleukin-6 and consecutive increase of RDW [28].

Therefore, the question whether RDW also maintains its prognostic power after controlling for such potential confounders is not negligible, if we consider the aging of the acute heart failure patients and the prevalence of comorbidities in this population, where RDW might routinely be applied: in our study we assess this question, also showing for the first time the independent prognostic role of RDW after controlling for these potential confounding factors, included functional status, COPD and other comorbidities.

In a prospective local registry including 402 consecutive hospitalized AHF patients, Sotiropoulos et al. show that a high RDW measured at admission is associated with an increased mortality in AHF patients with LVEF ≥ 50% while there is no interaction between a high RDW and mortality in AHF patients with LVEF < 50% [29]: in our study there are no significant associations between RDW and the presence

or the degree of systolic dysfunction, the NYHA class at admission or the etiology of heart failure, whereas atrial fibrillation and decompensated chronic heart failure are most likely to be present in patients with a high RDW; moreover, the NYHA class and the presence of systolic dysfunction or atrial fibrillation are not associated with outcomes at univariate analysis: these findings may be accounted for by the older age and higher prevalence of comorbidities that characterize our 'real world' population.

Furthermore, our data confirm the independent prognostic role of RDW from hemoglobin values in this population: even if hemoglobin either measured at admission or at discharge were strongly associated with both outcomes in our study, however its prognostic value is not maintained when tested with RDW in bivariate and multivariate analysis. Although the prognostic role of anemia and iron depletion in AHF is well established [8, 30], our data suggest that RDW might be better predictive than hemoglobin in the acute heart failure population, probably reflecting and integrating multiple pathophysiological mechanisms, including not only anemia but also hypoxemia, inflammation and nutritional status.

Lastly, our data also show a strong association between RDW and the composite outcome of death and rehospitalization, suggesting a role of anisocytosis, not only in predicting mortality, but also in identifying a group at higher risk of readmission to the hospital.

Limitations

We acknowledge that our study presents several limitations. First, the design is that of a single hospital, retrospective study, with potential selection bias; however, RDW and Delta RDW were available for all patients included in the study, avoiding the potential selection bias due to incomplete collection of data typical of a retrospective design. Second, we cannot control for laboratory parameters likely associated with RDW variability such as ferritin or transferrin. Third, we are not able to report about iron therapy in our population: however, iron therapy is recommended by the 2016 European Society of Cardiology guidelines in chronic HF patients with iron deficiency in order to alleviate HF symptoms, and improve exercise capacity and quality of life, but inpatient iron deficiency correction after stabilizing hospitalization for AHF is thus far an intervention not supported by the available evidence [31, 32]. Moreover, Craenenbroeck show that treatment with intravenous ferric carboxymaltose in patients with chronic heart failure leads to a RDW increased within 4 weeks (+0.54% absolute change from baseline) [33]. The median length of stay in our patients was 8 days: thus even if a possible oral or i.v. iron supplementation in patients with iron deficiency was started early in the hospital course, it is likely that its impact on RDW increase would have been negligible, and in any case, would act towards improving the prognosis of the patients treated, decreasing rather than amplifying the results of our study.

Conclusions

The present study shows that the RDW is a powerful marker of long-term mortality in patients admitted to the hospital with AHF, and its prognostic value is maintained beyond that provided by hemoglobin levels, comorbidities, functional dependency or other well-established risk factors or biomarkers.

Its wide availability and its independent prognostic value make RDW an intriguing candidate for a risk stratification of hospitalized patients with AHF, based on admission variables and aimed at choosing a better path for in-hospital decision-making and out-of-hospital follow-up, targeting for example iron deficiency or functional status impairment. Clearly, further studies are warranted to understand if RDW alone or in a multiple-variables approach could not only identify a high-risk population of AHF patients, but also assist the physicians in selecting a personalized management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions.

Informed consent Because of the retrospective design, informed consent was not obtained from individual patients, but permission for data analysis and to perform the study was granted by the Institutional Research Ethics Committee, in accord with national and international recommendations and Helsinki declaration.

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