ORIGINAL RESEARCH ARTICLE

Red cell distribution width and mortality in acute heart failure patients with preserved and reduced ejection fraction

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Abstract

Background   Elevated red blood cell distribution width (RDW) is a valid predictor of outcome in acute heart failure (AHF). It is unknown whether elevated RDW remains predictive in AHF patients with either preserved left ventricular ejection fraction (LVEF) ≥50% or reduced LVEF (<50%).

Methods and results   Prospective local registry including 402 consecutive hospitalized AHF patients without acute coronary syndrome or need of intensive care. The primary outcome was all-cause mortality (ACM) at 1 year after admission. Demographic and clinical data derive from admission, echocardiographic examinations (n = 269; 67%) from hospitalization. The Cox proportional hazard model including all patients (P < 0.001) was adjusted for age, gender, and RDW quartiles. Independent predictors of 1-year ACM were cardiogenic shock (HR 2.86; CI: 1.3–6.4), male sex (HR 1.9; CI: 1.2–2.9), high RDW quartile (HR 1.66; CI: 1.02–2.8), chronic HF (HR 1.61; CI: 1.05–2.5), valvular heart disease (HR 1.61; CI: 1.09–2.4), increased diastolic blood pressure (HR 1.02 per mmHg; CI: 1.01–1.03), increasing age (HR 1.04 by year; CI: 1.02–1.07), platelet count (HR 1.002 per G/l; CI: 1.0–1.004), systolic blood pressure (HR 0.99 per mmHg; CI: 0.98–0.99), and weight (HR 0.98 per kg; CI: 0.97–0.99). A total of 114 patients (28.4%) died within the first year; ACM of all patients increased with quartiles of rising RDW (χ^2 18; P < 0.001). ACM was not different between RDW quartiles of patients with reduced LVEF (n = 153; χ^2 6.6; P = 0.084). In AHF with LVEF ≥50% the probability of ACM increased with rising RDW (n = 116; χ^2 9.9; P = 0.0195).

Conclusions   High RDW is associated with increased ACM in AHF patients with preserved but not with reduced LVEF in this study population.

Keywords   Red cell distribution width; Prognosis; Acute heart failure; Left ventricular ejection fraction

Background

Acute heart failure (AHF) is associated with an adverse prognosis with an all cause mortality (ACM) of 10–20% at 2–3 months and 17–37% at 1 year.[1–5] Single biomarkers on top of clinical assessment are useful for risk stratification in patients with chronic heart failure (HF).[6,7] However in AHF, the incremental predictive value of a single biomarker is small when added to a clinical score. Results from the Multinational Observational Cohort on Acute Heart Failure (MOCA) study suggest improved risk prediction when miscellaneous biomarkers are assessed simultaneously.[5] This concept accounts for the absence of one single relevant pathomechanism in AHF while accepting that interpretation

of test results is more difficult. Red cell distribution width (RDW) is a readily available biomarker increasing with cytokine activation, impaired iron mobilization, and decreasing haemoglobin level.[8–10] RDW, thus, integrates various pathophysiological mechanisms associated with HF progression, which can explain why elevated RDW is a robust marker of risk for mortality in acute and chronic HF.[11–13] This prospective registry of consecutive patients hospitalized for AHF investigates whether elevated RDW remains predictive in AHF patients when patients are grouped by LVEF ≥50% or LVEF <50%.

Methods

This is a prospective registry of consecutive patients ($n = 408$) hospitalized for AHF at a tertiary centre. Patients presenting with AHF at the Emergency Wards were included when hospitalized for heart failure at our institution and after signing the consentment. Patients with acute coronary syndrome, or cardiogenic shock in need of intensive care were not included. Outcome parameter of this registry was 1-year all cause mortality (ACM). Patients without outcome ($n = 6$) were excluded from final analysis. The local ethical committee approved the study protocol.

Demographic, clinical, and laboratory data were obtained at admission. Echocardiographic data derive from standard transthoracic studies signed by a board-certified cardiologist at our institution; all exams were performed during index hospitalization. Physicians' diagnosis of co-morbidity followed the respective guidelines.[14–16] RDW was measured using the Advia 120 Hematology Analyzer (Siemens Healthcare Diagnostics). RDW was reported as coefficient of variation (in percent) of erythrocyte cell volume.

Statistical analysis

Continuous variables are presented as mean (± SD) or median (± interquartile range; IQR). Categorical variables are presented as numbers and percentages. Analysis of variance compared continuous variables, and χ^2-statistic compared categorical variables.

RDW quartiles were defined in accordance with the literature[13,17,18] with the lowest quartile serving as the reference group. The distribution of RDW was skewed; therefore, logarithmically transformed values of RDW (ln RDW) were used as dependent variable for multiple linear regressions as reported elsewhere.[13] Age, gender, and RDW quartiles were forced into the model predicting ACM; independent explanatory variables were identified by backward elimination of variables associated with RDW at a probability (P) of <0.1 in univariate analysis.

Stepwise Cox proportional hazards models calculated the hazard ratio (HR) selecting covariables on the basis of backward stepwise analysis with removal set at $P < 0.1$. Survival curves were calculated using the Kaplan–Meier method; comparison of survival curves used the log-rank test. All tests were two-sided and used a significance level of $P < 0.05$. Analyses were performed using the R statistical software (version R 3.1.0) (R development core team).

Results

Patients with high RDW were older, had a higher incidence of previous HF-related hospitalizations, and chronic HF was more prevalent by trend ($P = 0.0612$). Patients in the high RDW quartile had lower LVEF, lower systolic and diastolic blood pressure, and lower haemoglobin; creatinine, C-reactive protein, and NT-proBNP levels were higher. Patients with high RDW received more often loop diuretics and oral anticoagulation (*Table 1*).

Table 2 depicts clinical and laboratory parameters independently associated with RDW. The final model explained 37% of the variability in RDW. RDW was independently related with in-hospital mortality ($P = 0.008$). Correlation was poor between RDW and LVEF ($P = 0.21$), eGFR ($P = 0.12$), or length of stay ($P = 0.10$). RDW levels and haemoglobin levels correlated with strength of -0.0021 ± 0.0002 ($P = 0.021$).

Table 3 shows the results of a multivariable Cox model (maximal logistical likelihood -614.37; LR test statistic: 79.74; $P = 1.2 \times 10^{-11}$). The following variables were associated with increased HR (listed in increasing order): platelets, age, diastolic blood pressure, valvular pathology, chronic HF, elevated RDW, male sex, and cardiogenic shock. Variables with a decreased HR are listed in decreasing order: lower RDW, weight, and systolic blood pressure. Haemoglobin level was not retained in the proportional hazards model predicting 1-year ACM.

During follow-up 114 patients (28.4%) died. The Kaplan–Meier analysis including all patients showed a graded increased probability of mortality with increasing quartile of RDW (*Figure 1(A)*; χ^2 18; $P = 0.0004$). In patients with reduced LVEF, mortality was not significantly different between RDW quartiles (*Figure 1(B)*; χ^2 6.6; $P = 0.084$). Study patients with preserved LVEF showed a graded increased probability of mortality with rising RDW quartile (*Figure 1(C)*; χ^2 9.9; $P = 0.0195$).

Table 4 compares characteristics of AHF patients with preserved and reduced LVEF. AHF patients with preserved LVEF were older, the number of previous hospitalizations for HF was lower, and the prevalence of female gender and diagnosis of *de novo* HF was higher. AHF patients with preserved LVEF more often presented with hypertensive

Table 1 Characteristics of RDW quartiles

Quartiles RDW Number (*n*)	[12.2,14.2] 133	[14.3,15.2] 91	[15.3,16.6] 98	[16.7,32.1] 80	*P*-value
Demographics					
Age (y)	76 (64–83)	80 (74–85.5)	78 (71–83)	79 (74–83)	0.0093
Male gender (%)	83 (62.4)	47 (51.6)	58 (59.2)	45 (56.2)	0.4363
Prev. HHF (%)	23 (17.3)	19 (20.9)	23 (23.5)	31 (38.8)	0.0041
CHF (%)	72 (54.1)	57 (62.6)	67 (68.4)	56 (70)	0.0612
In hospital mort (%)	6 (4.5)	5 (5.5)	5 (5.1)	9 (11.2)	0.2055
LoS (days)	9 (4–15)	11 (4–15)	9 (4–16)	11 (5–15)	0.6543
Classification					
CS (%)	3.8	4.4	4.1	5	0.9768
PE (%)	28	25.3	21.4	27.5	0.6535
RHF (%)	4.5	7.7	17.3	16.2	0.0042
HTN crisis (%)	14.3	13.2	7.1	5	0.0873
Decomp HF (%)	48.8	49.4	50	46.3	0.9637
Characteristics					
LVEF (%)	42 (30–60)	50 (40–60)	40 (25–60)	40 (25–60)	0.0259
HR (bpm)	91 (77–105)	87.5 (72–105)	94 (79–107)	90(75–106)	0.6373
SR (%)	73 (54.9%)	49 (53.8%)	50 (51%)	38 (47.5%)	0.7207
SBP (mmHg)	151 (130–168)	144 (126–171)	142(128–166)	129 (114–151)	0.0001
DBP (mmHg)	86 (76–96)	84 (68–97)	82.5 (76–93)	77 (64–88)	0.0008
BMI	26.9 (24–31)	26.1 (23–32)	26 (24–30)	25 (23–29)	0.7347
Comorbidities					
Diabetes (%)	36.8	35.2	37.8	51.2	0.1315
Hypertension (%)	82.7	84.6	87.8	83.8	0.7474
COBP (%)	18	20.9	7.1	11.2	0.0242
Biological test					
Crea (mmol/l)	101 (80–128)	102 (82–137)	106 (88–152)	112 (94–157)	0.0170
CRP (mg/l)	10 (4–61)	16 (9–53)	14.5 (6–30)	20.5 (10–51)	0.0816
NT-proBNPx10^3 (pg/ml)	3.8 (1.9–6.8)	3.0 (1.3–4.4)	6.8 (3.3–10.1)	7.8 (3.5–16.2)	0.0021
Haemoglobin (G/l)	130 (116–146)	127 (114–136)	121 (107–141)	114 (99–125)	0.0000
Platelets (G/l)	219 (173–280)	225 (190–263)	233 (190–300)	225 (169–288)	0.6993
Medication					
Betablocker (%)	36.1	38.5	39.8	43.8	0.7367
ACE-I (%)	37.6	35.2	42.9	48.8	0.2588
ARB (%)	26.3	27.5	31.6	17.5	0.1941
MR-blocker (%)	9.8	12.1	21.4	20	0.0438
Loop diuretic (%)	45.9	48.4	65.3	70	0.0006
Digoxin (%)	11.3	13.2	15.3	18.8	0.4809
ASA (%)	51.1	53.8	52	57.5	0.8375
OAC (%)	24.8	36.3	43.9	53.8	0.0002
Clopidogrel (%)	18.8	23.1	23.5	17.5	0.6319

Prev. HHF, previous hospitalization for heart failure; in hosp mortality, in hospital mortality; LoS, length of stay; CS, cardiogenic shock; PE, pulmonary edema; RHF, right heart failure; HTN, hypertension; decomp HF: decompensated heart failure; LVEF, left ventricular ejection fraction; HR, heart rate; SR, sinus rhythm; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

crisis whereas prevalence of ischemic aetiology and diabetes was lower. The prevalence of valvular pathology was not

Table 2 Strength of the correlation between RDW (ln RDW) and different variables

	Estimate (SD)	*P*-value
Age	0.0016 (0.0005)	0.002
SBP	-0.0005 (0.0002)	0.021
Haemoglobin	−0.0021 (0.0002)	<0.0001
Leucocytes	0.0050 (0.0009)	<0.0001
Oral anticoagulation	−0.0422 (0.0210)	0.0461
Prothrombin time	−0.0015 (0.0003)	<0.0001
Prev HHF	0.02448 (0.0131)	0.0637
Right heart failure	0.0607 (0.0174)	0.000556
Diabetes mellitus	0.0297 (0.0113)	0.0088

See legend *Table 1*.

significantly different between HF patients with preserved and reduced systolic ejection fraction. In AHF patients with preserved LVEF systolic blood pressure was higher while heart rate and NT-proBNP levels were lower.

Overall 19.9% of all patients presented with high RDW, 65% of these patients had a transthoracic echocardiography during hospitalization; 63.4% of these presented a LVEF <50%. Patients with LVEF ≥50% and high RDW were older (80 vs. 75 y; *P* = 0.013), heart rate was lower (80 vs. 90 bpm *P* = 0.04), and history of HF was less frequent (47 vs. 79%, *P* = 0.04). The burden of comorbidities (i.e. diabetes, arterial hypertension, chronic obstructive bronchopulmonary disease, BMI, renal dysfunction by eGFR) was not significantly different between patients with high RDW and LVEF of <50% or ≥50%.

Table 3 Adjusted proportional hazards model for all cause 1-year mortality

Covariate	Mean/(%)	HR (97.5% CI)	P-value
Age (y)	75.2	1.044 (1.02–1.07)	<0.0001
Gender (male)	58%	1.904 (1.24–2.93)	0.030
RDW quartile			
(14.3–15.2)	0.24	0.761 (0.43–1.34)	0.341
(15.2–16.6)	0.25	0.877 (0.51–1.51)	0.638
(16.6–32.1)	0.17	1.686 (1.02–2.79)	0.041
Weight (kg)	79	0.978 (0.97–0.99)	0.001
Syst. BP (mmHg)	147	0.985 (0.98–0.99)	0.002
Diast. BP (mmHg)	85	1.020 (1.01–1.03)	0.011
Card. shock	3.6%	2.864 (1.29–6.35)	0.010
Platelets (G/l)	235	1.002 (1.0–1.004)	0.018
Chronic HF	60.9%	1.611 (1.05–2.48)	0.030
β-blocker	42.5%	0.735 (0.50–1.09)	0.128
Valvular HD	46.4%	1.606 (1.09–2.38)	0.018

Female gender and lowest RDW group were used as reference; valvular HD, valvular heart disease.

Discussion

The results of the present study add to the available data regarding the predictive relevance of elevated RDW in acute HF. First, the results confirm the relevance of high RDW for prediction of mortality in AHF.[11–13] Second, the present study population shows that high RDW is associated with increased mortality in AHF patients with LVEF ≥50% while there is no interaction between high RDW and mortality in AHF patients with LVEF < 50%.

The small size of the present study population raises the concern whether the sample is representative. However, demographic, clinical, and biological characteristics of the present study collectively correspond with respective characteristics reported from larger studies in AHF.[19,20] In addition, the present study replicates associations between

Figure 1 (A) RDW quartiles and 1-year survival of all AHF patients. (B) RDW quartiles and 1-year survival in AHF patients with LVEF <50%. (C) RDW quartiles and 1-year survival in AHF patients with LVEF ≥50%.
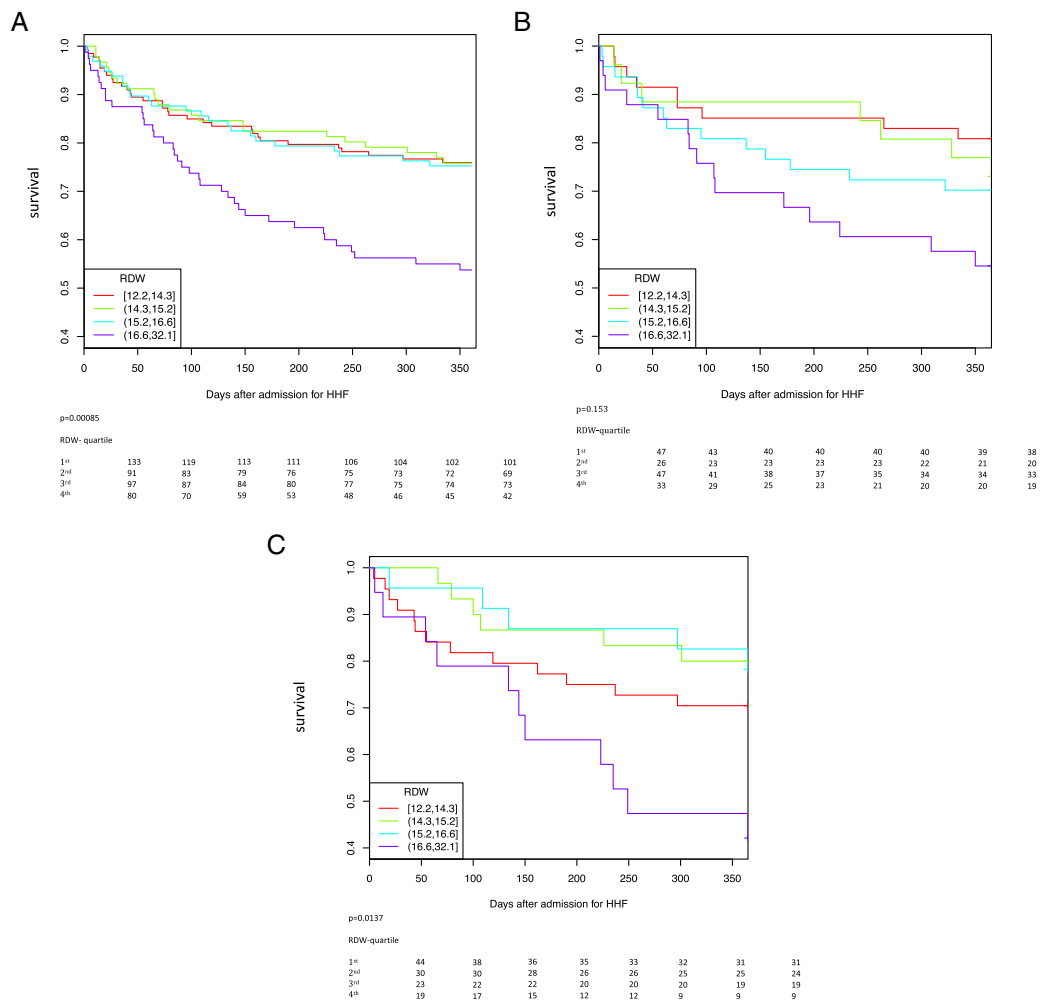
Table 4 Demographics and characteristics of AHF patients with reduced and preserved ejection fraction

Number (*n*)	All 402	LVEF ≥ 50% 117	LVEF < 50% 154	*P*-value
Demographics				
Age (y)	78 (70–84)	79 (74–84)	73 (64–81)	<0.0001
Gender (male, %)	234 (57.4)	48 (41)	110 (71.4)	<0.0001
Previous HHF (%)	96 (23.5)	22 (18.8)	49 (31.8)	0.023
Hx of CHF (%)	252 (61.8)	52 (44.4)	113 (73.4)	<0.0001
LVEF	40 (30–60)	60 (55–65)	30 (25–40)	<0.0001
ICD (%)	19 (4.7)	0 (0)	15 (9.7)	0.001
Pacemaker (%)	49 (12)	10 (8.5)	24 (15.6)	0.12
Phenotype of AHF				
Cardiogenic shock	17 (4.2)	2 (1.7)	11 (7.1)	0.07
Pulmonary oedema	104 (25.5)	30 (25.6)	45 (29.2)	0.61
RH decompensation	44 (10.8)	10 (8.5)	20 (13)	0.34
Hypertensive crisis	42 (10.3)	21 (17.9)	3 (1.9)	<0.0001
Global decompensation	193 (49.2)	54 (46.3)	75 (48.8)	0.12
Cardiac pathology				
CAD (%)	232 (56.9)	53 (45.3)	107 (69.5)	<0.0001
LV dilatation (%)		6 (5.1)	81 (52.6)	<0.0001
Mild MR (%)		88 (75.2)	146 (94.8)	0.16
Moderate MR (%)		9 (7.7)	8 (5.2)	
Mild AR (%)		51 (43.6)	81 (52.3)	0.37
Moderate AR (%)		2 (1.8)	2 (1.3)	
Comorbidity				
Diabetes mellitus (%)	159 (39)	35 (29.9)	73 (47.4)	0.005
Hypertension (%)	341 (83.6)	100 (85.5)	125 (81.2)	0.44
COBP (%)	159 (14.5)	3 (11.1)	23 (14.9)	0.46
BMI	26 (24–31)	26 (24–29)	26 (24–31)	0.56
Biological parameters				
SBP (mmHg)	142 (124–164)	150 (132–170)	133 (120–151)	<0.0001
DBP (mmHg)	84 (72–94)	81 (74–93)	84 (72–92)	0.76
Heart rate (bpm)	90 (75–105)	83 (70–100)	97 (84–117)	<0.0001
Sinus rhythm (%)	211 (51.7)	67 (57)	82 (53)	0.59
Creatinine (mmol/l)	105 (84–141)	97 (81–134)	109 (86–151)	0.054
NT-proBNPx10^3 (pg/ml)	4.5 (2.1–9.5)	3.3 (1.7–7.8)	6.8 (3.9–13.4)	0.002
CRP (mg/l)	15(6–47)	14.5 (6–54)	13 (6–44)	0.54
NIPV (%)	138 (33.8)	39 (33.3)	60 (39%)	0.41
In hosp mortality *n* (%)	26 (6.4)	5 (4.3)	10 (6.5)	0.60
LoS (days)	10 (4–15)	10 (6–17)	11 (7–16)	0.62

See legend *Table 1*, NIPV, non-invasive pulmonary ventilation, for others see *Table 1*. Parenthesis indicates IQR if not indicated otherwise.
P-values refer to comparison of HF patients with reduced or preserved LVEF.
CAD, coronary artery disease; MR, mitral regurgitation; AR, aortic regurgitation.

RDW and outcome as described elsewhere, in particular, the negative correlation of RDW with haemoglobin levels as reported in the Candesartan in Heart Failure: Assessment of the Reduction in Mortality and Morbidity (CHARM),[8] and in the STAMINA-HFP (Study of Anemia in HF Population) or the UNITE-HF (United Investigators to Evaluate Heart Failure) registry.[9] In addition, this study replicates the relation of high RDW with increased mortality already described in other AHF study populations.[11–13] Finally, high RDW was retained in the model for prediction of ACM similar to other studies in acute or chronic HF.[8,13,17]

In the general population, RDW increases with conditions of ineffective red cell production (such as iron deficiency, folate or B12 deficiency, and hemglobinopathy), increased red cell destruction, or after blood transfusion. Anaemia is a strong predictor of mortality in heart failure suggesting that RDW is a strong predictor for mortality and morbidity[8,10,12] because of the high prevalence of anaemia.[8] In fact, some heart failure studies link elevated RDW with inflammation,

malnutrition, and renal dysfunction that may all impact on erythropoiesis.[18,21] However, results from the CHARM North America study cohort (*n* = 2697) indicate a prognostic role of RDW that is independent from haemoglobin level based on the observation that both parameters were retained in the final model for prediction of ACM but without reciprocal interaction.[8] This observation was replicated in the Duke Databank cohort providing supportive evidence.[8] Additional evidence for a distinct role of RDW derives from the European Prospective Investigation into Cancer and Nutrition (EPIC) Norfolk study and the Malmö Cancer and Diet study which show an association of RDW with incident heart failure while RDW was in this middle-aged healthy population without relation to iron metabolism or inflammation.[22,23]

High RDW is associated with increased interleukin-6 levels (IL-6) as shown in the STAMINA-HFP and the UNITE-HF registries.[9] In patients with mild or moderate HF with reduced LVEF, increased IL-6 levels are associated with increased risk of disease progression.[24] Furthermore, IL-6

are likely to be relevant in HF with preserved HF as suggested in a study by Collier *et al.* which showed an increase of IL-6 levels in patients with LVEF ≥50% and heart failure symptoms while IL-6 was low in patients without HF symptoms.[25,26] Complementary evidence of a pathophysiological role of IL-6 in HF derives from the Health, Aging, and Body Composition (ABC) study that showed a correlation between increased IL-6 levels and incident HF with preserved LVEF.[27] Because blood samples were not retained from the present study population, we cannot correlate RDW with IL-6 levels; however, increased CRP levels in patients with high RDW suggest increased IL-6 levels because IL-6 levels correlate with CRP levels patients with AHF and chronic HF.[24,28]

In the present study, high RDW was associated with increased mortality in patients with LVEF ≥50% while mortality was not different between RDW groups of patients with reduced LVEF. Several characteristics of the two subgroups may explain this finding: first, evidence-based pharmacological treatment[6] was increased in the majority of patients with reduced LVEF <50% during hospitalization (inhibitors of the renin–angiotensin system: 70% to 92%; β-blocker treatment: 35 to 58%; antagonists of the mineralocorticoid receptor: 21 to 38%). It is well known that increase of pharmacological HF treatment improves 1-year survival;[6,13] therefore, mortality difference between the RDW quartiles in the present study may have decreased because of improved drug therapy; second, more patients with preserved LVEF and low RDW had developed AHF because of hypertensive crisis. Hypertensive crisis is associated with a low mortality[29] suggesting accentuation of the mortality difference between low and high RDW quartiles; third, recent results from the Swedish Heart failure registry suggest that β-blocker treatment reduces ACM in HF patients with preserved LVEF.[30] Only 42% of the study patients with preserved LVEF ≥50% were on β-blocker treatment suggesting an increased hazard for mortality in patients without β-blocker in accordance with the proportional hazards model of this study. In fact, β-blocker treatment decreased from 52% to 41% in patients with preserved LVEF and high RDW.

Study limitations

The single-centre study design, the sample size, and the outcome parameter of 1-year all-cause mortality without consideration of cardiovascular mortality or rehospitalization rate represent limitations of the study. Furthermore, echocardiograms were not obtained in all patients, which might have introduced a selection bias. However, characteristics of patients with or without echocardiogram were not significantly different.

Conclusions

We have shown for the first time the prognostic relevance of RDW in AHF with preserved ejection suggesting that RDW may help to stratify risk already at admission. In a next step, this observation should be confirmed in a larger AHF population with echocardiographic exams obtained during index hospitalization. In addition, the results of this study merit further work-up of the interaction of RDW and IL-6 in AHF with preserved ejection fraction, and thus, increase our understanding of clinically relevant pathomechanisms in these patients.

Acknowledgement

Conflict of Interest

None declared.

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