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Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients

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Aims To study the long-term prognostic value of red blood cell distribution width (RDW) in patients hospitalized with acute heart failure (AHF) and to compare the value of this measurement with haemoglobin levels and anaemia status.

Methods and results During a 2-year period, we studied 628 consecutive patients (aged 71 years [interquartile range, IQR: 61–77], 68% male) hospitalized with AHF. Demographic, clinical, echocardiographic, and laboratory characteristics were registered at discharge and patients were closely followed-up for 38.1 months [16.5–49.1]. Median RDW was 14.4% [13.5–15.5] and was higher among decedents (15.0% [13.8–16.1] vs. 14.2 [13.3–15.3], $P < 0.001$). After adjustment for other prognostic factors in a multivariable Cox proportional-hazards model, RDW remained a significant predictor ($P = 0.004$, HR 1.072, 95% CI 1.023–1.124); whereas, haemoglobin or anaemia status did not add prognostic information. RDW levels above the median were associated with a significantly lower survival rate on long-term follow-up (log rank <0.001). These levels were predictive of death in anaemic patients ($n = 263$, $P = 0.029$) and especially in non-anaemic patients ($n = 365$) ($P < 0.001$, HR 1.287, 95% CI 1.147–1.445), even after adjustment in the multivariable model.

Conclusion Higher RDW levels at discharge were associated with a worse long-term outcome, regardless of haemoglobin levels and anaemia status.

Keywords Anaemia • Acute heart failure • Prognosis • Red cell

Introduction

Anaemia is common in patients with heart failure (HF) and has important implications for the prognosis and treatment of this disabling disease.[1] Anaemia in HF is a complex process and its pathophysiology is poorly understood. It typically involves numerous features such as iron and vitamin deficiency, insidious blood loss, haemodilution, renal impairment, bone marrow depression, resistance to erythropoietin, and angiotensin system blockade.[2–4] Anaemia defined by haemoglobin levels has consistently been associated with worse functional status and a higher risk of death in patients with HF, although a cause–effect relationship has not been proved.[5–7]

Red blood cell distribution width (RDW) is a numerical measure of the variability in the size of circulating erythrocytes, recorded during a standard complete blood count.[8,9] Usually, red blood cells are in a standard size, but disorders related to ineffective erythropoiesis or increased destruction cause greater heterogeneity in size and a higher RDW.[9,10] RDW may reflect nutritional deficiencies, bone marrow dysfunction, or systemic inflammation, or may represent an integrative measure of the pathological processes occurring in HF patients.

Recently, a subanalysis of the CHARM study programme has suggested RDW as a new prognostic marker in chronic HF.[11] In patients with coronary disease but without symptomatic HF, higher values of RDW were associated with an increased risk of

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death and new symptomatic HF during long-term follow-up.[12] No other studies have investigated the value of RDW as a prognostic marker in HF patients, and its role in the risk stratification of patients with acute HF (AHF) has not been tested. Moreover, it has not been clarified whether RDW could add prognostic information to haemoglobin levels and anaemia status. More recently, RDW has been found to be predictive of all-cause death in two community-based cohorts and an interrelation between RDW and inflammation has been proposed.[13–15]

We therefore aimed to study whether RDW is useful for risk stratification in a population hospitalized with AHF, and to analyse the prognostic value of RDW compared with that of haemoglobin levels and anaemia status.

Methods

Population studied

During a 2-year period (from January 2002 until December 2003), we studied all patients with AHF admitted to the Cardiology Department of Virgen de la Arrixaca Hospital, Murcia, Spain, which is a tertiary university hospital. Acute HF was diagnosed according to the European Society of Cardiology criteria, defined as a rapid or gradual onset of signs and symptoms of HF, resulting in unplanned hospitalization and including new onset acute HF, without previously known cardiac dysfunction, and acute decompensation of chronic HF.[16] An echocardiographic study was performed on all patients during the index hospitalization (Sonos 5500, Philips, MA, USA). Standardized projections and measurements were performed for the evaluation of cardiac anatomy, ventricular function, and valve competence; left ventricular ejection fraction (LVEF) was measured by Simpson's method, using second harmonic imaging.[17] All demographic, clinical, biochemical, and echocardiographic variables were recorded at the time of hospital discharge. All patients received standard management as recommended by contemporary guidelines, which included the following medication: beta-blockers (56%); angiotensin-converting enzyme-inhibitors and/or angiotensin receptor blockers (84%); loop diuretics (70%); digoxin (30%); oral anticoagulants (32%); and aldosterone antagonists (26%). The local ethics committee approved the study, and all patients gave informed consent. Patient follow-up was performed by means of telephone calls, personal interviews, review of clinical reports, and review of National Death Records. The studied endpoint was all-cause mortality.

Biochemical measurements

Blood samples were obtained prior to hospital discharge, a median of 10 days [interquartile range (IQR): 7–16 days] after admission, following an overnight fast and 10 min of supine rest. Samples were processed immediately for the determination of all biochemical parameters. RDW, haemoglobin, and mean corpuscular volume were determined using the XE-2100 (Sysmex, Kobe, Japan) automated haematology analyser. Anaemia was defined according to World Health Organization criteria: haemoglobin <13 g/dL for men and <12 g/dL for women.[18] A PE modular analyser (Roche Diagnostics, Manheim, Germany) was used for all biochemical measurements. Renal function was determined from the estimated glomerular filtration rate (GFR, mL/min/1.73 m^2) using the abbreviated MDRD formula.[19]

Statistical analysis

All variables were tested for normal distribution by the Kolmogorov–Smirnov test. Continuous variables with normal distribution are expressed as mean $\pm$ standard deviation (SD). Continuous variables with non-normal distribution are summarized as median (IQR). Categorical variables are expressed as number (percentage). RDW had a non-normal distribution, and comparisons between independent groups were made using the Mann–Whitney *U* test. Correlations between RDW and other continuous variables were studied using Spearman's correlation. Kaplan–Meier accumulated survival curves were drawn and Log-Rank values were calculated to assess their statistical significance. Cox proportional hazards models were used to evaluate the association between each baseline variable (*Table 1* and medication at discharge) and all-cause death. A stepwise multivariable Cox proportional hazards analysis was applied to determine the independent prognostic value of RDW. Variables entered into the multivariable model were those predictors with $P < 0.10$ in the univariable analysis, those variables with a significant association with RDW levels, and established predictors of mortality (ischaemic aetiology and LVEF). Hazard ratios (HR) are expressed, as well as their 95% CI. Log-cumulative hazard plots, time-dependent covariates, and Schoenfeld residuals were used to evaluate adherence of the proportional hazard assumptions of the Cox model, and these assumptions were verified by the representation of $\mathrm{Ln}(-\mathrm{Ln}\ S(t))$ for every variable after its categorization. Two-sided tests were used and

Table 1 Population characteristics at time of discharge

Variable	*n* = 628
Age, years	71 [61–77]
Male	427 (68%)
Diabetes mellitus	243 (39%)
Hypertension	356 (57%)
Body mass index, kg/m^2	27.9 $\pm$ 4.0
COPD	121 (19%)
Prior stroke	77 (12%)
NYHA class	2.2 $\pm$ 1.0
I/II/III/IV (%)	26/36/27/11
Prior HF	164 (26%)
Ischaemic aetiology	343 (55%)
Atrial fibrillation	159 (26%)
Bundle branch block	214 (34%)
Haemoglobin, g/dL	12.7 $\pm$ 1.78
Anaemia	263 (42%)
Creatinine, mg/dL	1,2 [1.0–1.44]
GFR, mL/min/1.73 m^2	59 (47–73)
Uric acid, mg/dL	7.3 (6.1–8.9)
Cholesterol, mg/dL	167 (142–196)
C-reactive protein, mg/dL	1.25 (0.50–2.65)
LVEF, %	37 (30–45)
LV end-diastolic diameter, mm	56 $\pm$ 13
Left atrial diameter, mm	46 $\pm$ 9

Data are shown as *n* (%), mean $\pm$ SD, and median [interquartile range].
COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.

a *P*-value of <0.05 was considered statistically significant. SPSS v.15.0 software (SPSS Inc., Chicago, IL, USA) was used.

Results

RDW and study population

The study population consisted of 628 patients, whose characteristics at time of discharge are given in *Table 1*. In the overall population, RDW had a median value of 14.4% (IQR: 13.5–15.5) and was positively correlated with age ($P < 0.001$, $r_s = 0.187$) and NYHA class ($P < 0.001$, $r_s = 0.269$); being higher in patients with NYHA class III–IV (14.8% [13.9–16.1] vs. 14.1% [13.3–15.3], $P < 0.001$), atrial fibrillation (15.0% [13.3–15.4] vs. 14.3% [13.9–15.9], $P < 0.001$) and non-ischaemic aetiology (14.7% [13.8–16.0] vs. 14.2% [13.2–15.2], $P < 0.001$). Among echocardiographic parameters, RDW correlated positively with left atrial diameter ($P = 0.006$, $r_s = 0.163$), but not with LVEF ($P = 0.920$) nor LV end-diastolic diameter ($P = 0.474$). Among biochemical parameters, RDW correlated positively with C-reactive protein ($P = 0.018$, $r_s = 0.185$) and creatinine concentration ($P = 0.01$, $r_s = -0.109$) and inversely with GFR ($P < 0.001$, $r_s = -0.175$) and total cholesterol levels ($P = 0.002$, $r_s = -0.151$).

Among other haematological variables, RDW showed an inverse correlation with haemoglobin levels ($P = 0.001$, $r_s = -0.136$) and mean corpuscular volume (89.9 fL [86.3–92.7]) ($P < 0.001$, $r_s = -0.304$). RDW was significantly higher among anaemic patients (14.9% [13.8–16.1] vs. 14.2% [13.2–15.3], $P < 0.001$), and correlated with haemoglobin and mean corpuscular volume in both anaemic ($P < 0.05$ and $P < 0.001$, respectively) and non-anaemic patients ($P < 0.05$ and $P < 0.001$, respectively).

RDW and survival

A total of 209 (33.3%) patients died during the follow-up period (38.1 months [IQR: 16.5–49.1]). At discharge, patients who died had significantly higher RDW levels (15.0% [13.8–16.1] vs. 14.2% [13.3–15.3], $P < 0.001$) and lower haemoglobin levels (12.3 ± 1.77 vs. 12.8 ± 1.76, $P = 0.001$). In the univariable Cox regression analysis (*Table 2*), RDW was associated with a higher risk of death (per %, HR 1.10, 95% CI 1.06–1.14, $P < 0.001$), as was the haemoglobin level. After adjustment in a multivariable Cox proportional-hazards model (*Table 2*), RDW at discharge remained a significant risk factor (per %, $P = 0.004$, HR 1.072, IC95% 1.023–1.124); whereas, haemoglobin did not add prognostic information. After entering anaemia instead of haemoglobin into the model, the result did not change; RDW remained significant ($P < 0.001$) whereas anaemia did not reach significance ($P = 0.106$) in the multivariable model. As shown in *Figure 1*, patients with RDW levels above the median of 14.4% had a significantly lower survival time (log-rank <0.001) and a higher risk of death in the long-term follow-up ($P < 0.001$, HR 1.89, 95% CI 1.40–2.55).

RDW and anaemia

Taking into account the presence or absence of anaemia, higher RDW values at discharge were associated with a higher risk of death in patients with anaemia ($n = 263$) ($P = 0.029$, per %: HR

Table 2 All patients ($n = 628$): Cox proportional hazards analysis for predictors of death

	Univariable		Multivariable	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
RDW, %	1.100 (1.060–1.142)	<0.001	1.074 (1.021–1.127)	0.004
Haemoglobin, mg/dL	0.833 (0.777–0.893)	<0.001	—	0.524
Age, years	1.046 (1.033–1.060)	<0.001	1.037 (1.022–1.053)	<0.001
NYHA class III/IV	2.135 (1.625–2.807)	<0.001	1.369 (1.155–1.617)	<0.001
Prior HF	1.936 (1.480–2.532)	<0.001	1.481 (1.081–2.029)	0.010
β-Blockers	0.539 (0.410–0.709)	<0.001	—	0.185
GFR, mL/min/1.73 m^2	0.981 (0.975–0.988)	<0.001	0.992 (0.985–1.000)	0.039
Prior stroke	1.817 (1.263–2–615)	0.001	1.481 (1.028–2.255)	0.036
Bundle branch block	1.518 (1.121–2.055)	0.007	—	0.059
Male	0.737 (0.557–0.976)	0.033	—	0.544
Hypertension	1.364 (1.030–1.806)	0.030	—	0.769
COPD	1.375 (1.005–1.882)	0.047	—	0.105
Atrial fibrillation	1.334 (0.993–1.790)	0.055	—	0.585
Ischaemic aetiology	1.058 (0.806–1.390)	0.683	—	0.105
LVEF	0.996 (0.986–1.087)	0.519	—	0.157
LV end-diastolic diameter	1.016 (0.998–1.034)	0.165	—	0.176
Left atrial diameter	1.011 (0.992–1.029)	0.261	—	0.802
C-reactive protein	1.032 (0.997–1.058)	0.120	—	0.620
Cholesterol	0.998 (0.994–1.002)	0.278	—	0.261

COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LEVF, left ventricular ejection fraction; NYHA, New York Heart Association; RDW, red blood cell distribution width.

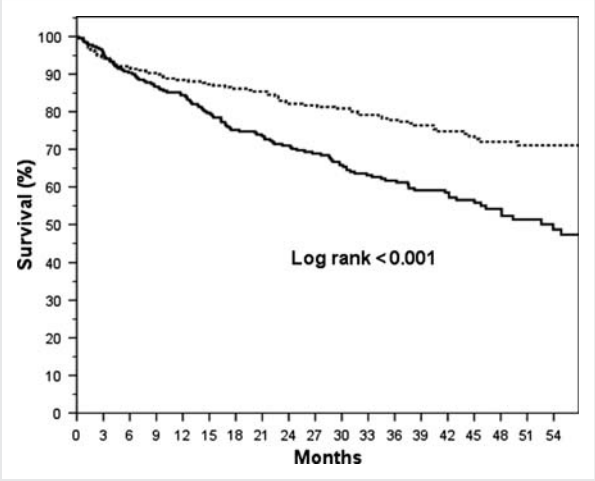

Figure 1 All patients ($n = 628$): Kaplan–Meier survival curves according to red blood cell distribution width values above (continuous line) or below (dotted line) the median (14.4%).

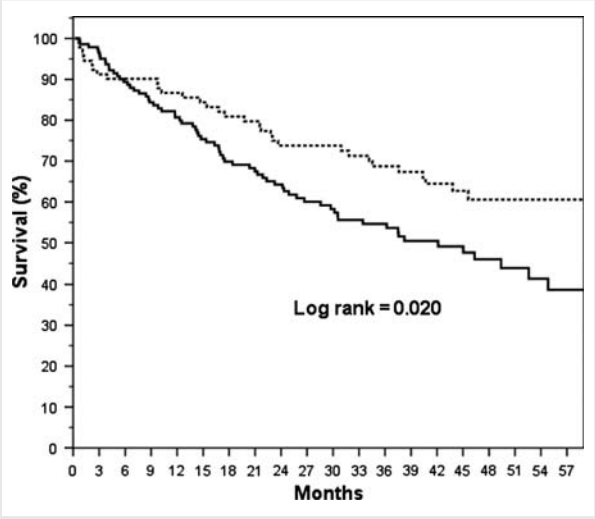

Figure 2 Anaemic patients ($n = 263$): Kaplan–Meier survival curves according to red blood cell distribution width values above (continuous line) or below (dotted line) the median (14.4%).

1.057, 95% CI 1.006–1.112) and especially in those patients without anaemia ($n = 365$) ($P < 0.001$, per %, HR 1.287, 95% CI 1.147–1.445). As shown in the Kaplan–Meier survival curves (*Figures 2* and *3*), the presence of RDW levels above the median value was associated with a lower survival rate regardless of the presence of anaemia. After adjustment in the multivariable Cox proportional hazards analysis, RDW remained a significant risk predictor among non-anaemic patients ($P = 0.009$, *Table 3*), but did not reach significance among anaemic patients ($P = 0.111$); however, the interaction term of anaemia and RDW did not show significance in the entire population ($P > 0.1$).

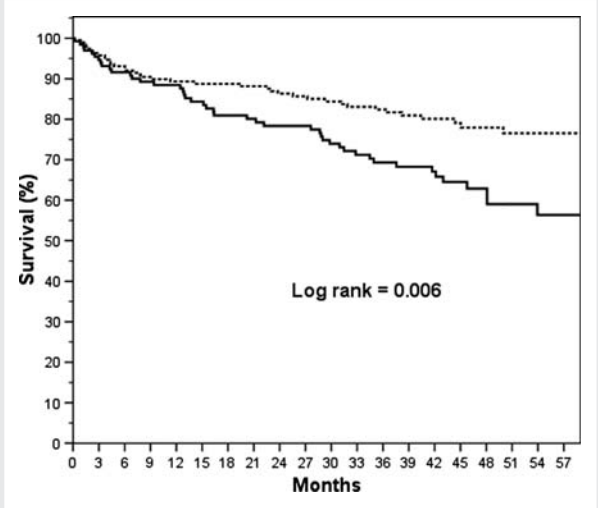

Figure 3 Non-anaemic patients ($n = 365$): Kaplan–Meier survival curves according to red blood cell distribution width values above (continuous line) or below (dotted line) the median (14.4%).

Discussion

This study has shown that a higher RDW level at discharge is associated with a worse long-term outcome in patients hospitalized with AHF, regardless of anaemia status. RDW had greater prognostic value when compared with haemoglobin levels, especially in those patients in the non-anaemic range.

We found a strong independent association between baseline RDW level and the risk of all-cause death in the long-term follow-up of patients admitted for AHF. This prognostic value was significant even after being adjusted for known prognostic factors, treatments, and comorbid conditions, such as cerebrovascular or pulmonary disease. Only one study has previously shown an association between higher RDW and greater mortality in patients with chronic HF: Felker *et al.*[11] found RDW to be a strong independent predictor of greater morbidity and mortality in patients with chronic HF included in the CHARM programme, and replicated this finding in the Duke Databank. In a cohort of patients with coronary artery disease but without symptomatic HF, Tonelli *et al.*[12] also found RDW to be a consistent marker of long-term risk of all-cause death and new symptomatic HF. Our study has confirmed the predictive value of RDW in HF patients and has extended its use to the long-term follow-up of a cohort hospitalized with acute HF. The final model was consistent with previously published models of risk in HF, and supports the validity of RDW as a long-term prognostic marker at discharge.

The mechanism underlying the association between RDW and death in patients with HF is unclear. RDW is elevated when there is increased red cell destruction or, more commonly, ineffective red cell production. RDW may represent a nutritional deficiency (iron, vitamin B12, or folic acid), bone marrow depression, or chronic inflammation. These conditions are often present in patients with heart failure, correlate with the severity of the disease, and are associated with a worse prognosis.[20]

Table 3 Non-anaemic patients (n = 365): Cox proportional hazards analysis for predictors of death

	Univariable		Multivariable	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
RDW, %	1.287 (1.147–1.445)	<0.001	1.180 (1.041–1.338)	0.009
Haemoglobin, mg/dL	0.988 (0.848–1.152)	0.881	—	0.304
Age, years	1.044 (1.025–1.064)	<0.001	1.034 (1.012–1.056)	0.002
NYHA class III/IV	1.662 (1.361–2.029)	<0.001	1.606 (1.238–2.080)	0.001
Prior HF	2.385 (1.572–3.610)	<0.001	1.838 (1.075–3.141)	0.026
β-Blockers	0.445 (0.295–0.669)	<0.001	0.530 (0.330–0.851)	0.010
GFR, mL/min/1.73 m^2	0.986 (0.976–0.997)	0.009	—	0.505
Prior stroke	2.270 (1.341–3.844)	0.002	2.642 (1.505–4.639)	0.001
Bundle branch block	1.493 (0.945–2.357)	0.086	—	0.456
Male	0.829 (0.543–1.265)	0.385	—	0.374
Hypertension	1.100 (0.731–1.655)	0.647	—	0.368
COPD	1.510 (0.962–2.372)	0.073	—	0.915
Atrial fibrillation	1.267 (0.818–1.963)	0.289	—	0.376
Ischaemic aetiology	1.017 (0.679–1.524)	0.935	2.252 (1.332–3.806)	0.002
LVEF	0.994 (0.977–1.010)	0.467	—	0.322
LV end-diastolic diameter	1.021 (0.996–1.048)	0.196	—	0.105
Left atrial diameter	1.019 (0.988–1.051)	0.244	—	0.492
C-reactive protein	1.038 (0.095–1.083)	0.114	—	0.883
Cholesterol	0.997 (0.992–1.002)	0.199	—	0.691

COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LEVF, left ventricular ejection fraction; NYHA, New York Heart Association; RDW, red blood cell distribution width.

In our population, we found an association between RDW and the severity of HF, according to NYHA class. We also found an association with older age and measures of renal insufficiency, both associated with bone marrow depression and erythropoietin deficiency.[20,21] Moreover, absolute or functional iron deficiency and nutritional impairment are common during the course of HF.[22,23] Recently, in a large unselected cohort of patients, RDW showed a strong and graded association with inflammatory markers, which was independent of ferritin, age, sex, and other haematological variables.[15] HF is associated with a chronic inflammatory state; increased levels of inflammatory cytokines are predictors of prognosis and also impact on bone marrow function and iron metabolism.[24,25] In this regard, we found only a weak correlation between RDW and C-reactive protein levels. In addition, RDW may integrate information from the multiple pathological processes that occur during HF progression, such as cellular nutritional deficiencies, renal dysfunction, organ congestion, and inflammatory stress.

The most interesting finding from our study is that RDW was a better prognostic marker than haemoglobin regardless of anaemia status. After multivariable adjustment in the entire population, RDW, but not haemoglobin (or anaemia), was predictive; and after stratifying by anaemia status, RDW was especially predictive in non-anaemic patients. RDW may be an earlier marker of prognosis than haemoglobin, as it may reflect early steps in the complex processes of anaemia, when ineffective production and increased destruction of red cells is occurring, but haemoglobin is still within the normal range. This hypothesis is supported by the fact that the survival curves in our study separated at a later stage in the non-anaemic patients, separation occurred after 6 months in the entire population (*Figure 1*) and after 12 months in the non-anaemic population (*Figure 3*); and diverged progressively during the long-term follow-up period (up to 5 years). However, the anaemic and non-anaemic populations were not identical and the relative velocity of the survival curve separations may be due to other unmeasured variables or co-morbid conditions. Anaemia has been consistently shown to be an independent risk factor for mortality, but to date anaemia correction has not been shown to affect prognosis.[26,27] If the mechanisms that lead to anaemia also affect RDW at an earlier stage, RDW may have an impact upon treatment in non-anaemic patients by identifying an earlier stage in the development of anaemia linked to HF. Consequently, these patients could respond to earlier therapeutic interventions aimed at preventing the development of anaemia.

It is possible that RDW may impact on mortality through mechanisms apart from anaemia. RDW levels have been shown to be associated with other chronic conditions,[28–30] and recently RDW has been found to be a strong predictor of all-cause mortality in two large population cohorts.[13,14] This association was not specific to cardiovascular disease, as RDW also predicted mortality from cancer and chronic lower respiratory tract disease.[13,14] Moreover, the prognostic value of RDW did not seem to be confounded by anaemia. As in our study, RDW predicted mortality among non-anaemic patients.[13,14,31] These findings indicate that

the pathophysiology that leads to increased RDW could affect outcomes in chronically ill patients, irrespective of anaemia status. As discussed above, several authors have suggested that this mechanism might be inflammatory and not directly linked to haemoglobin levels. This hypothesis is supported by the fact that RDW was only modestly correlated with serum haemoglobin, in our population and others.[11,31] If this hypothesis is proved, treatments to prevent anaemia are unlikely to affect prognosis in these patients. Further studies are necessary to elucidate the mechanism linking RDW and prognosis in HF patients.

Limitations

This study was limited mainly by its observational design and the lack of repeated measures of RDW and other anaemia-related measures during the follow-up. Nevertheless, the strengths of this study are the population size and the prolonged follow-up period, together with a consistent multivariable adjustment.

Conclusions

Our findings confirm those of the CHARM subanalysis in a population with AHF, but are particularly notable, given that RDW was found to be a risk factor for mortality regardless of haemoglobin levels and anaemia status. RDW may therefore have potential as an early marker of risk in non-anaemic patients. If confirmed, this finding could have important consequences for the design of future studies focused on the pathophysiology of anaemia and novel therapeutic interventions for treating this condition in HF patients. In addition, RDW is a measurement that is widely available to clinicians as part of the full blood count, which increases its applicability to clinical practice.

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Conflict of interest: none declared.

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