

Original Research

Red Blood Cell Distribution Width Is a Significant Prognostic Marker in Advanced Heart Failure, Independent of Hemoglobin Levels

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Introduction: Advanced heart failure (HF) is associated with increased morbidity and mortality; traditionally used prognostic factors often fail to predict the outcome. Increased red blood cell distribution width (RDW) has recently been recognized as an important unfavorable prognostic factor in HF, independent of anemia; however, the role of RDW in patients with advanced HF has not yet been investigated.

Methods: Eighty consecutive patients with stage D heart failure, recently hospitalized for HF decompensation, were enrolled. A Cox proportional-hazard model was used to determine whether RDW was independently associated with outcome.

Results: At study entry, ejection fraction (EF), pulmonary capillary wedge pressure (PCWP), hemoglobin (Hb) and RDW were $25 \pm 8.6\%$, 27.5 ± 8 mmHg, 12.5 ± 1.9 mg/dL and $18 \pm 3.5\%$ (normal $<14.5\%$) respectively. At 6 months, 44 patients (55%) had died. In this patient population, EF ($p=0.45$), PCWP ($p=0.106$), age ($p=0.54$), albumin (0.678), iron ($p=0.37$), creatinine ($p=0.432$), iron deficiency defined by bone marrow aspiration ($p=0.37$), bilirubin ($p=0.422$), peak VO_2 ($p=0.057$) and Hb ($p=0.95$) were not significant predictors of a worse outcome. However, RDW was a significant marker for adverse prognosis ($p=0.007$, HR: 1.14, CI: 1.04-1.24) and retained its prognostic significance even when corrected for Hb values (HR: 1.15, CI: 1.05-1.27, $p=0.003$).

Conclusions: RDW is a significant prognostic factor for an adverse outcome in patients with advanced stage heart failure who have experienced recent decompensation, independent of the presence of anemia or malnutrition, and is superior to more traditionally used indices. RDW may be associated with severe disease by reflecting subtle metabolic and proinflammatory abnormalities in HF.

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The syndrome of heart failure (HF) develops as a result of the advanced stage of many cardiac diseases and represents a major cause of morbidity and mortality. Its prevalence has increased in recent decades because of population aging, as well as therapeutic advances in the management of patients in the earlier stages of heart disease, allowing them to survive until they develop heart failure.

Anemia is one of the most important comorbidities associated with HF,¹ initially recognized in 2000 by Silverberg et al, who published the first reports describing a decrease in blood hemoglobin content with increasing severity of congestive HF.¹ Several studies that followed have documented both a greater mortality associated with anemia and a higher prevalence of anemia in patients with advanced

congestive HF.^{2,3} In addition, previous studies have shown that the correction of anemia significantly improved cardiac and renal function, exercise capacity, and quality of life in HF patients.⁴⁻⁷

Red cell distribution width (RDW) is routinely reported by the automated laboratory equipment used to perform complete blood counts and reflects variability in the size of circulating red cells (anisocytosis). It is calculated as the percentage of the standard deviation of RBC size/mean corpuscular volume. Recently, higher RDW levels have been correlated with deaths and cardiovascular events in patients with previous myocardial infarction but no symptomatic HF.⁸ In a retrospective analysis, Felker et al reported that a higher RDW is one of the most powerful predictors of morbidity and mortality in patients with HF, showing a stronger association with outcome than traditional risk factors such as New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF).⁹ However, until now the prognostic significance of RDW has not been investigated in advanced stage HF. It is known that, in end-stage disease, many of the parameters traditionally used for predicting outcome perform less satisfactorily. Our aim was to assess, in a population of patients hospitalized with acute decompensated HF, whether RDW retains its prognostic significance, and whether values at admission could independently predict mortality at 6 months more accurately than other prognostic factors.

Methods

Study population

Eighty consecutive patients with severe systolic HF, who were receiving maximum standard treatment and required hospitalization for acute decompensation, were enrolled in the study. Clinical variables of the studied group recorded at baseline were: age, sex, NYHA functional class, etiology of cardiomyopathy, date of HF onset, and underlying heart rhythm. All patients underwent echocardiographic evaluation of left ventricular function and right heart catheterization for the measurement of right and left filling pressures at admission. Patients who were able to exercise underwent a cardiopulmonary exercise stress test and peak VO_2 was measured, while in patients who were not able to perform a stress test, the peak VO_2 measured within the past six months was used for risk assessment. Anemic patients ($n=8$) underwent bone

marrow aspiration for determination of anemia etiology as previously described.¹⁰ Patients were excluded if they had severe valvular dysfunction, a history of valve replacement or heart transplantation, primary pulmonary hypertension, end-stage renal disease requiring hemodialysis, or an active malignancy, or if they had received a blood transfusion within the previous 6 months—conditions that could interfere with the RDW value because of hemolysis or secondary anemia.

Laboratory parameters

At admission, blood samples were collected and immediately processed. Hemoglobin and hematocrit as well as RDW values were determined using the automated blood analyzer XE-2100 (Sysmex, Kobe, Japan). Anemia was defined according to World Health Organization criteria (hemoglobin <12 g/dL in men and <11.5 g/dL in women). In all patients, serum iron measurements were obtained and bone marrow aspiration was performed in those with anemia. Renal function was assessed by creatinine concentration.¹¹ Total bilirubin (mg/dL), total protein and albumin (g/dL) levels were also measured. The primary endpoint was death from any cause or implantation of a left ventricular assist device. Mean follow up was 286 ± 355 days.

Statistical analysis

Values are reported as mean \pm standard deviation. Univariate and multivariate Cox regression proportional-hazard models were used to assess the prognostic significance of the various parameters. Results are reported as hazard ratio (HR) with 95% confidence intervals (CI).

Results

Baseline characteristics

Patients' clinical characteristics at admission are shown in Table 1. Mean age was 57.8 ± 12.4 years and 2.4% were women. All patients were in NYHA functional class IV, mean LVEF was $25 \pm 8.5\%$, mean central venous pressure (CVP) was 13.6 ± 7 mmHg and mean pulmonary capillary wedge pressure (PCWP) was 27.5 ± 8 mm Hg. The etiology of HF was ischemic in 49%, idiopathic dilated cardiomyopathy in 41%, and other in 4%. Seventy-four (26%) pa-

Table 1. Baseline characteristics of the study population.

Age (yrs)	57.8 ± 12.5
Ejection fraction	25 ± 8.5%
Female	2.5%
NYHA functional class IV	100%
Race (white)	100%
Serum creatinine, mg/dL	1.57 ± 0.7
Hemoglobin, mg/dL	12.5 ± 1.9
Atrial fibrillation/flutter	26%
Albumin g/dL	3.8 ± 0.4
Total bilirubin, mg/dL	4
Iron deficiency by bone marrow aspiration	46% in anemic patients 60% overall
Serum iron (µg/dL)	65 ± 38

NYHA – New York Heart Association.

tients presented with atrial fibrillation on the baseline electrocardiogram. At hospitalization, 87% of the patients were on treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, 61% were on β-blockers, 69% on loop diuretics, 32% on digoxin, and 29% on spironolactone.

Survival analysis

Mean hemoglobin concentration in the patient population was 12.5 ± 2 mg/dL and hematocrit was 39 ± 6%. A total of 60% of the patients had anemia according to World Health Organization (WHO) criteria. RDW ranged from 14.1% to 35.1% (median 18%), and only one patient (1.25%) had an RDW value within the normal range (11.8-14.5%).

Forty-four patients (55%) died within the 6-month follow-up period. In univariate analysis using a Cox regression model, the only significant laboratory predictor of adverse outcome was an increased RDW level (p=0.007, HR: 1.13, CI: 1.04-1.24). The mean values in each group are presented in Table 2. To investigate whether this parameter had prognostic information independent of other anemia indices, multivariate models were generated that included either hematocrit (or hemoglobin), or serum iron (or iron deficiency identified at bone marrow examination) together with RDW. Again, RDW was the only significant predictor of death or left ventricular assist device implantation (p=0.003) (adjusted HR per percent increase in RDW: 1.15; 95% CI, 1.05-1.27).

None of the other known clinical or laboratory risk factors had significant predictive value in this patient cohort (Table 3), with the exception of a trend for VO₂ peak (p=0.057). A limitation of this param-

Table 2. Baseline characteristics in both groups studied.

Parameter	Group 1 (Survival >6 months)	Group 2 (Survival <6 months)
Age (years)	56.4 ± 13.5	58 ± 11.5
Weight (kg)	87.7 ± 25	88.8 ± 20.9
PCWP (mmHg)	26.2 ± 6.7	28 ± 8.8
Creatinine (mg/dL)	1.4 ± 0.55	1.6 ± 0.75
Urea	95 ± 59	97 ± 48

PCWP – pulmonary capillary wedge pressure.

Table 3. Prognostic value of different parameters in Cox regression analysis.

Variable	Hazard ratio	95% CI	p
Age (years)	1.008	0.98-1.03	0.5
Ejection fraction (%)	0.98	0.94-1.02	0.4
PCWP (mmHg)	1.038	0.99-1.08	0.1
RDW (%)	1.13	1.03-1.23	0.007
Hemoglobin (g/dL)	0.974	0.82-1.14	0.8
Iron (µg/dL)	1.006	0.96-1.05	0.4
Iron deficiency	0.67	0.27-1.61	0.4
Albumin (g/dL)	0.86	0.45-1.69	0.7
Creatinine (mg/dL)	1.19	0.76-1.88	0.4
SAP (mmHg)	0.999	0.98-1.01	0.9
Total bilirubin (mg/dL)	1.2	0.76-1.91	0.4
VO ₂ peak (mL/kg/min)	1.16	0.99-1.36	0.06

PCWP – pulmonary capillary wedge pressure; RDW – red cell distribution width; SAP – systolic arterial pressure.

eter in the present study was that it was not available in all patients. The rest of the laboratory and clinical parameters were not significantly associated with the final outcome: hemoglobin (p=0.95), hematocrit (p=0.76), PCWP (p=0.106), LVEF (p=0.45), CVP (p=0.96), age (p=0.54), albumin (p=0.67), creatinine (p=0.43), bilirubin (p=0.422), peak VO₂ (p=0.057), and serum iron (p=0.37).

Discussion

In patients hospitalized with acute decompensated HF, RDW values at admission were a significant prognostic factor for adverse outcome at 6 months. No other clinical or laboratory parameter could predict outcomes in this patient population. Despite the fact that 60% of the patients presented with anemia, RDW remained an independent predictor of outcome after adjusting for hemoglobin or iron deficiency in the bone marrow, indicating that its value is not dependent exclusively on anemia or iron deficiency. RDW had a higher statistical association with outcome than ejection fraction, NYHA functional class,

peak VO_2 , blood urea concentration, or renal function in the population of this study. This is consistent with previous reports where traditionally accepted risk factors were shown to have less predictive value in advanced stage HF.^{12,13}

RDW is an indicator of the degree of variation in RBC size (i.e. anisocytosis) and is routinely reported by automated laboratory equipment used to perform complete blood counts.¹⁴ Clinical conditions where RDW is typically elevated are ineffective red cell production (such as iron deficiency, B12 or folate deficiency, and hemoglobinopathies), increased red cell destruction (such as hemolysis), or after blood transfusion. Elevation of RDW has been associated with other disease processes, including liver disease, malnutrition, occult colon cancer, and neoplastic metastases to bone marrow.^{15,16} Conceivably, RDW may represent an integrative measure of multiple pathologic processes in HF (e.g. nutritional deficiencies, renal dysfunction, hepatic congestion, inflammatory stress), explaining its association with clinical outcomes. In our study, though, RDW level was not associated with either albumin, creatinine, or iron deficiency.

A previous analysis of two large populations of patients with HF found a strong independent association between RDW and clinical outcomes, including all-cause mortality,⁸ similar to the findings in a small single-center study of hemodialysis patients.¹⁷ Our study confirms and extends these results in a population of severely sick patients in need of hospitalization after acute decompensation. One of the most intriguing findings of our study is that the prognostic significance of RDW was independent of anemia, iron deficiency, renal dysfunction or other concomitant clinical conditions. Despite the fact that almost 60% of the patients had anemia, hemoglobin values did not confer any prognostic information in this patient population. Similarly, iron deficiency, confirmed by bone marrow aspiration, was not correlated with outcome. Nor was the duration of HF correlated with the final endpoint. Interestingly, RDW values did not differ between patients with iron deficiency and those without, emphasizing that iron deficiency is not the underlying mechanism of increased RDW in severely sick HF patients.

Higher levels of RDW might reflect an underlying inflammatory state that is associated with adverse clinical outcomes¹⁸⁻²⁰ and leads to impaired erythrocyte maturation.²¹ Inflammatory cytokines have been shown to be predictors of prognosis in HF, and also

may impact bone marrow function and iron metabolism.²² Proinflammatory cytokines have been found to inhibit erythropoietin-induced erythrocyte maturation, which is reflected in part by an increase in RDW.²³ These potential mechanisms were not directly assessed in our study and will require confirmation in future studies.

Conclusions

RDW appears to be a strong predictor of clinical outcomes in advanced stage HF. This is particularly important for this patient population, where traditional risk factors are of limited value and invasive, high risk and costly treatments (left ventricular assist device, ultrafiltration, cardiac resynchronization therapy) are often required. A reliable prognostic indicator of an adverse outcome could prove invaluable for treatment planning and appropriate implementation of the different therapeutic strategies available for advanced stage HF.

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