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Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure

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ABSTRACT

Background: Increased red blood cell distribution (RDW) has been associated with adverse outcomes in patients with heart failure. We studied the association between baseline RDW and changes in RDW during hospital course with clinical outcomes in acute decompensated heart failure (ADHF) patients.
Methods and results: We prospectively studied 614 patients with ADHF. Baseline RDW and RDW change during hospital course were determined. The relationship between RDW and clinical outcomes after hospital discharge was tested using Cox regression models, adjusting for clinical characteristics, echocardiographic findings and brain natriuretic peptide levels. During follow up (1 year), 286 patients (46.6%) died and 84 were readmitted for ADHF (13.7%). Median RDW was significantly higher among patients who died compared to patients who survived (15.6% interquartile range [14.5 to 17.1] vs. 14.9% mg/L interquartile range [14.1 to 16.1], $P<0.0001$). Compared with patients in the 1st RDW quartile, the adjusted hazard ratio [HR] for death or rehospitalization was 1.9 [95% CI 1.3–2.6] in patients in the 4th quartile. Changes in RDW during hospitalization were strongly associated with changes in mortality risk. Compared with patients with persistent normal RDW (<14.5%), the adjusted HR for mortality was 1.9 [95% CI 1.1–3.1] for patients in whom RDW increased above 14.5% during hospital course, similar to patients with persistent elevation of RDW (HR was 1.7, 95% CI 1.2–2.3).
Conclusion: In patients hospitalized with ADHF, RDW is a strong independent predictor of greater morbidity and mortality. An increase in RDW during hospitalization also portends adverse clinical outcome.

1. Introduction

Heart failure (HF) is the leading cause for hospitalization among patients older than 65 years of age [1]. Clinical trials and observational studies have identified multiple prognostic factors in patients admitted with acute decompensated heart failure, including renal function, hyponatremia, brain natriuretic peptide (BNP) and cardiac troponins [2]. Red blood cell distribution width (RDW) is a measure of the variability in the size of circulating erythrocytes, that can be used in the classification of anemia and in the detection of early iron and folate deficiency [3].

Recently, RDW has been shown to be among the strongest predictors of both mortality and HF hospitalizations in patients with either stable or decompensated heart failure (HF) [4–8]. Previous studies on the relationship between RDW and clinical outcomes of HF patients have used a single RDW measurement. However, RDW may be a dynamic variable, with rapid changes in acute disease states [9]. In the present study we explore the possibility that changes in RDW during hospital stay for acute decompensated heart failure (ADHF) may provide prognostic information beyond a single RDW value.

2. Methods

Between January 2008 and April 2010, we prospectively studied all patients admitted to the Rambam Medical Center, Haifa, Israel with the primary diagnosis of ADHF and survived the index hospitalization. Eligible patients were those hospitalized as with new-onset or worsening preexisting heart failure as primary cause of admission or those with significant heart failure symptoms that developed during the hospitalization where heart failure was the primary discharge diagnosis [10]. ADHF was diagnosed according to the European Society of Cardiology criteria including a brain natriuretic peptide (BNP) level >400 pg/mL [11]. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review committee on human research.

Hemoglobin levels, mean corpuscular volume (MCV) and RDW were measured on admission and prior to hospital discharge, using the Advia 120 Hematology Analyzer

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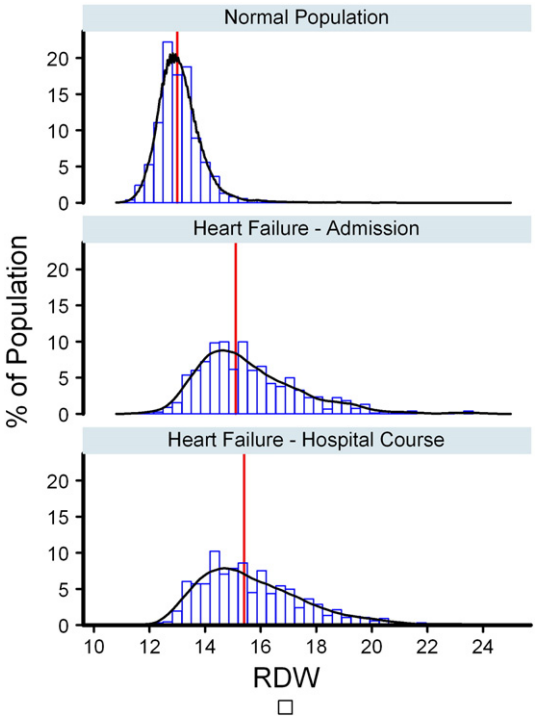

Fig. 1. Frequency distribution (expressed as percentage of the entire population; vertical axis) of RDW in normal subjects and in the study population. The red line shows the median value. $P = 0.003$ for the comparison between admission and hospital course data.

(Siemens Healthcare Diagnostics). When more than 2 RDW measurements were available, the second RDW measurement was taken as the last RDW measurement during hospitalization. Data on RBC transfusions was collected in each patient. Anemia was defined as hemoglobin levels lower than 13 g/dL in men and 12 g/dL in women, in accordance with the World Health Organization (WHO) criteria [12]. RDW is reported as coefficient of variation (in percent) of red blood cell volume. The normal range for RDW in our laboratory is 11.5 to 14.5%. The correctness of this normal range was confirmed by analyzing RDW data in 17293 ambulatory subjects who attended the Rambam Center for Preventive Medicine for a medical examination and health counseling. In this group, mean RDW was 13.1% (median 13.0%) with 95% confidence interval of RDW of 12.0 to 14.4%. Patient BNP levels were measured with the AxSYM BNP microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA).

2.1. Study endpoints

All patients were followed for 12 months after hospital discharge. The primary end point of the study was all-cause mortality [13] or readmission for the management of HF. Readmission for HF was defined if the main reason for a new admission was new symptoms of dyspnea with pulmonary venous congestion on X-ray with interstitial or alveolar edema and BNP > 400 pg/mL. Following hospital discharge, clinical endpoint information was acquired by reviewing the national death registry and by contacting each patient individually and independently reviewing the hospital course for major clinical events if the patient had been re-hospitalized.

2.2. Statistical analysis

Continuous variables are presented as mean (SD) or medians (with interquartile ranges), and categorical variables as numbers and percentages. The baseline characteristics of the groups were compared using analysis of variance for continuous variables and by χ^2 statistic for categorical variables. Changes in RDW at different time points were evaluated by using a nonparametric approach to paired measures (Wilcoxon signed-ranks test).

The distribution of RDW was skewed. Therefore, logarithmically transformed values of RDW (ln RDW) were used. The strength of the association between RDW and clinical and biochemical variables was assessed by univariable linear regression of ln RDW on each variable separately followed by multiple linear regression with backward selection. In addition to age and gender (which were forced into the model) baseline variables considered for inclusion in the multivariable model included: history of hypertension, history of diabetes, atrial fibrillation, estimated GFR, BUN, serum sodium, baseline hemoglobin, MCV, BNP, cardiac troponin I and left ventricular ejection fraction and medications.

To avoid assuming linearity, RDW was categorized according to quartiles of the distribution, with the lowest quartile serving as the reference group. Survival curves were constructed using the Kaplan–Meier method, and comparisons were made using the log–rank test. Stepwise Cox proportional hazards models with backward selection were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for RDW categories. The Cox models were adjusted for age, gender, history of diabetes, hypertension, smoking status, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), serum sodium, atrial fibrillation, elevated cardiac troponin

Table 1
Baseline clinical characteristics according to quartiles of baseline RDW.

Characteristic	RDW quartile				*P* value
	≤14.3 (n = 156)	14.4–15.2 (n = 158)	15.3–16.5 (n = 148)	≥16.6 (n = 152)	
Age (years)	78 ± 12	77 ± 10	77 ± 10	75 ± 13	0.12
Male gender	64 (41)	67 (52)	79 (53)	72 (47)	0.13
Coronary artery disease	96 (62)	103 (65)	90 (61)	94 (62)	0.84
History of hypertension	127 (84)	126 (86)	133 (84)	17 (76)	0.09
Diabetes mellitus	81 (53)	72 (49)	78 (50)	74 (48)	0.78
Creatinine (mg/dL)	1.4 ± 0.6	1.6 ± 1.1	1.7 ± 1.1	1.7 ± 0.9	0.02
eGFR (ml·min^{-1}/1.73 m^{-2})	52 ± 24	50 ± 24	46 ± 21	47 ± 24	0.09
BUN (mg/dl)	30 ± 15	31 ± 17	35 ± 22	38 ± 25	0.001
Serum sodium (mmole/l)	137 ± 5	137 ± 6	137 ± 5	137 ± 5	0.61
Baseline hemoglobin (g/dl)	12.2 ± 1.8	11.9 ± 1.8	11.4 ± 1.6	10.7 ± 2.0	<0.0001
Anemia (WHO)	84 (54)	97 (61)	106 (72)	123 (81)	<0.0001
Mean corpuscular volume (μm^3)	90 ± 5	89 ± 6	86 ± 7	84 ± 8	<0.0001
Intravenous iron	5 (3)	2 (1)	7 (5)	13 (9)	0.02
Erythropoietin	0 (0)	1 (1)	1 (1)	5 (3)	0.03
Blood transfusion	1 (1)	0 (0)	2 (1)	11 (7)	<0.0001
BNP (pg/ml)	1227 ± 930	1343 ± 103	1544 ± 1102	1550 ± 1061	0.01
cTn I elevation (%)	19 (12)	24 (15)	22 (15)	16 (11)	0.57
Left ventricular ejection fraction (%)	47 ± 18	42 ± 18	42 ± 18	42 ± 20	0.30
Medications					
Beta blockers	96 (62)	108 (68)	97 (66)	107 (70)	0.38
ACE inhibitors/ARBs	102 (65)	104 (66)	90 (61)	88 (58)	0.42
Loop diuretics	131 (86)	130 (88)	125 (79)	110 (71)	<0.0001
Spironolactone	25 (16)	26 (18)	24 (15)	21 (14)	0.78
Digoxin	13 (9)	15 (10)	7 (4)	9 (6)	0.20
Days hospitalized	7 [5–11,12,13]	7 [4–11]	7 [4–11,12]	8 [5–11,12,13]	0.33

Values are expressed as number (%) of patients, mean value ± SD, or Median [Interquartile Range].
ACE = angiotensin converting enzyme; ARB = Angiotensin receptor blockers.