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Progressive Rise in Red Cell Distribution Width Is Associated with Disease Progression in Ambulatory Patients with Chronic Heart Failure

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Abstract

Background—Single RDW assessment is a consistent prognostic marker of poor outcomes in heart failure as well as in other patient cohorts. The objective of this study is to determine the prognostic value of sequential red cell distribution width (RDW) assessment in ambulatory patients with chronic heart failure.

Methods and Results—We reviewed 6,159 consecutive ambulatory patients with chronic heart failure between 2001–2006, and examined changes in RDW values from baseline to 1-year follow-up. Clinical, demographic, laboratory, and ICD-9 coding data were extracted from electronic health records, and all-cause mortality was followed over a mean follow-up of 4.4 ± 2.4 years. In our study cohort, median baseline RDW was 14.9%. Subjects with RDW $>16\%$ at baseline (18.5% of cohort) was associated with a higher mortality rates than those $\leq 16\%$. For each +1% increment of baseline RDW, the risk ratio for all-cause mortality was 1.17 (95% confidence interval 1.15–1.19, $p < 0.0001$). At 12-month follow-up ($n = 1,601$), a large majority of subjects (68% in 1st tertile, 56% in 2nd tertile of baseline RDW) showed rising RDW, and correspondingly higher risk for all-cause mortality (risk ratio for +1% increase in changes in RDW was 1.08 [95% CI: 1.03–1.13, $p = 0.001$]). This effect was independent of anemia status or other baseline cardiac or renal indices, and particularly strong in those with lower baseline RDW.

Conclusion—In our ambulatory cohort of patients with chronic heart failure, baseline and serial increase in RDW was associated with poor long-term outcomes independent of standard cardiac, hematologic, and renal indices.

Keywords

Red cell distribution width; heart failure; prognosis

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INTRODUCTION

Red cell distribution width (RDW) represents the variability of sizes of circulating erythrocytes, and has been explored in several large clinical databases to be a robust marker of adverse clinical outcomes in patients with chronic heart failure, coronary artery disease, myocardial infarction, or stroke[1–6]. The exact pathophysiologic basis of this association is still not precisely known, but several postulates have been proposed including aging and malnutrition[7], co-existing renal insufficiency[8], relative inadequacy of erythropoietin[9] (but not erythropoietin resistance[10]), underlying inflammatory processes[11], and impaired iron mobilization[12]. Although these findings have been replicated even independent of cardiovascular diseases[13, 14], they all have been limited by associating long-term adverse outcomes with a single time-point assessment, hence unable to determine the influence of changes in RDW over time on long-term outcomes.

We have previously reported the prevalence and pattern of anemia and long-term follow-up data regarding a large, well-characterized, unselected cohort of ambulatory patients seen at our institution with available complete blood count assessment[15]. Utilizing data directly derived from electronic health record, our objective is to validate prior observations regarding the prognostic value of RDW in long-term outcomes in patients with heart failure, while examining the influence of rising RDW over time on long-term adverse outcomes in ambulatory patients with chronic heart failure.

METHODS

Study Population

We identified 6,052 consecutive ambulatory outpatients seen at the Cleveland Clinic Foundation internal medicine or cardiology clinics with documented clinical diagnosis of heart failure with a complete blood count test that included RDW assessment between January 2001 and April 2006. The clinical diagnosis of heart failure was documented in an electronic health record system (*EpicCare*TM, Epic Systems Corp, Madison WI) that was linked to the following *International Classification of Diseases, Ninth Revision* (ICD-9) codes: 242.9, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03–4, 404.13, 404.91, 404.93, 425.1, 425.4–5, 425.7–9, 428.0–1, and 428.9 as previously described[15]. Patients must also have documented LV ejection fraction (LVEF) data within ± 100 days of the first complete blood count analysis (“baseline”) to be included in the study. We excluded patients with a history of congenital heart disease, malignancies, chronic inflammatory diseases, or previously diagnosed inherited or acquired anemia (ICD-9 code 282.x – 285.x), or documented active gastrointestinal bleeding at the time of blood draw. This study has been approved by the Cleveland Clinic Institutional Review Board.

Red Cell Distribution Width

Complete blood count was performed at the Cleveland Clinic Clinical Laboratory utilizing a Sysmex XE-2100 automated hematology analyzer and leukocyte differential counter (Sysmex America, Inc., Mundelein IL). Red cell distribution width (RDW) was calculated as (standard deviation of mean corpuscular volume $\div$ mean corpuscular volume) $\times$ 100. The cut-off of 16% was identified as the upper limit of normal reported.

Baseline Data Synthesis

Clinical, demographic, laboratory, and ICD-9 coding data for primary and secondary diagnoses were extracted from the electronic health record. All clinical data were matched to within ± 100 days of baseline complete blood count analysis. Estimated glomerular filtration rate (eGFR) was calculated through the Modification of Diet in Renal Disease equation[16].

Anemia was defined as hemoglobin (Hb) <12 g/dL for men and <11 g/dL for women as previously described[15]. Based on our criteria, only a subset of patients had B- type natriuretic peptide (BNP) levels available at baseline (n =2,145 or 35%).

All echocardiographic data were derived from the echocardiography reports signed off by Board-certified cardiologist at our institution. As per standard protocol, left ventricular end-diastolic diameter (LVEDD) was measured in the parasternal long-axis view, while left atrial area (LAA) was determined by tracings by the interpreting physician at the 4-chamber view. Left ventricular ejection fraction (LVEF) was determined by visual estimation and confirmed by Simpson's rule. Standard LV diastolic filling pattern was graded on a scale from I to IV based on transmitral inflow profiles. Mitral and tricuspid regurgitation (MR and TR) severity was evaluated on a semi-quantitative scale from 0 to 4+.

Follow-up Data Synthesis

Patients must have consecutive CBC measurements including RDW within ± 100 days of 1-year follow up to be included. Changes in RDW were determined by absolute difference from baseline values. Long-term, all-cause mortality data were collected from the Social Security Death Index and data from electronic health records. Death and cardiac transplant dates were used in survival analysis, censoring cardiac transplantation.

Statistical Analysis

Results are presented in percentages (for dichotomous variable), mean $\pm$ standard deviations (for parametric continuous variable), or median [interquartile range] (for non-parametric continuous variable). Univariable analyses were performed using 2-tailed chi-square test, Student's t-test, and Wilcoxon test, respectively. Spearman's rank correlation coefficient assessed univariate relations between changes in RDW and other clinical measures. Multivariate correlation to changes in RDW used a stepwise model followed by standard least squares fit. The Cochran-Armitage test was used to assess trends across tertiles of baseline RDW. Survival was analyzed using Kaplan-Meier analysis. Multivariate Cox proportional hazards model was used to calculate risk ratios for independent predictors of mortality with incremental increases in continuous variables, and stratified according to tertiles of baseline RDW in subset analyses. Additional Proc HAZARD and proc HAZPRED macros were used to calculate mortality across baseline RDW values as previously described[17]. These procedures had stepwise entry of baseline hemoglobin as the covariate with RDW, where hemoglobin was plotted in quartiles up to projected 5 year follow-up. A p -value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.1 and JMP version 9.0 (SAS Institute, Cary, North Carolina). All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

Study Population

Table 1 demonstrates the baseline characteristics of our study cohort, stratified according to quartiles of RDW. Tertiles of baseline RDW were 1st tertile: RDW $\leq 13.5\%$, 2nd tertile: RDW $>13.5\%$ and RDW $\leq 14.9\%$, 3rd tertile: RDW $>14.9\%$. At baseline, the median RDW was 14.3%, and 18.5% of subjects demonstrated RDW $\geq 16\%$ at baseline ("upper normal limit," Figure 1). Subjects with higher RDW were more likely to have diabetes mellitus, lower hemoglobin levels, higher plasma BNP levels, lower eGFR, lower cholesterol profile, and more impaired LV systolic and diastolic dysfunction (Table 1). As expected, subjects with underlying anemia (RDW $16.0 \pm 2.3\%$ versus $14.3 \pm 1.6\%$, $p < 0.0001$) or renal

insufficiency (RDW $15.1 \pm 1.9\%$ versus $14.3 \pm 1.8\%$, $p < 0.0001$) had overall higher levels of RDW than those with no anemia or renal insufficiency, respectively.

Clinical Determinants of RDW

Among the 6,052 baseline subjects in our cohort, 1,601 (26%) had documented follow-up data at 12 months based on our criteria (mean of 12.8 ± 1.9 months of follow-up). At follow-up, predictors of change in RDW included age, baseline RDW, baseline hemoglobin, as well as change in hemoglobin in univariate analysis (Table 2). Baseline RDW, baseline hemoglobin, and 1-year change in hemoglobin were significant predictors of change in RDW, with baseline RDW as the strongest predictor of change in RDW at 1-year follow-up. As expected, with increasing tertiles of baseline RDW, there were lower percentages of patients who had rising RDW after 1 year (1st tertile: 68%, 2nd tertile: 56%, 3rd tertile: 34%, $p < 0.0001$ for trend).

Baseline RDW and Long-term Mortality

Over a mean follow-up of 4.4 ± 2.4 years, there were 1,963 deaths and 201 cardiac transplants in the overall cohort (annualized mortality 8.1%). In univariate analysis, each +1% increment of baseline RDW had risk ratio 1.17 (95% CI: 1.15 – 1.19, $p < 0.0001$). In multivariate Cox proportional hazards analysis, baseline RDW was a significant predictor of all-cause mortality, although in this model age was the strongest predictor at baseline (Table 3A). Kaplan-Meier analysis showed that baseline RDW $\geq 16\%$ was predictive of higher mortality (Figure 2). Calculated mortality in our model also showed a relatively linear relationship between baseline hemoglobin and baseline RDW, with increasing quartiles of Hb associated with higher long-term mortality (Figure 3).

Changes in RDW and Long-term Mortality

Univariate risk ratios for +1% increase in changes in RDW were 1.08 (95% CI: 1.03 – 1.13, $p = 0.001$) at 1 year follow-up (Figure 4). After 1 year follow-up, change in RDW remained an independent predictor of mortality; other independent predictors include age and BNP (Table 3B). Because baseline RDW was a confounder in the change in RDW, risk ratio analysis of change in RDW was further determined across tertiles of baseline RDW. In univariate analysis, risk ratios for 1-year change in RDW became weaker with increasing tertiles of baseline RDW (1st tertile: RR 1.32 (95% CI: 1.22 – 1.42), $p < 0.0001$, 2nd tertile: RR 1.19 (95% CI: 1.11 – 1.26), $p < 0.0001$, 3rd tertile: RR 1.06 (95% CI: 1.02 – 1.11), $p = 0.007$). Similarly, multivariate risk ratios for 1 year change in RDW became weaker with increasing tertiles of baseline RDW after adjusting for age and BNP (Table 4). This suggests that 1-year change in RDW was a better predictor of mortality in patients with low baseline RDW that increased over time. After dividing into tertiles of baseline RDW, there was a trend towards lower mortality associated with lowering of RDW at follow-up for subjects with the highest baseline RDW (data not shown). Looking at changes in RDW stratified by baseline RDW levels, we observed that those with elevated RDW had similar long-term outcomes when compared with those with lower baseline RDW while those with rising RDW beyond already raised baseline had the poorest outcomes (Figure 4).

DISCUSSION

Apart from confirming the ability for RDW to provide robust risk prediction, our findings present several new insights regarding the prognostic value of RDW in an outpatient population with chronic heart failure that is particularly relevant to clinical practice. First, we demonstrated the ability of RDW to predict long-term outcomes independent of standard cardiac or renal indices, including our subset with BNP levels. Second, we observed that there is progressive rise in RDW in a large majority of patients over time, and particularly in

those with relatively low RDW at baseline a rising RDW may portend poor prognosis. Meanwhile, a reduction in RDW was observed over time in some patients, albeit in a relatively small subset and with more favorable outcomes. Taken together, these findings suggest that monitoring changes in RDW may serve as a robust longitudinal indicator for poor outcomes in the management of heart failure, particularly when an otherwise normal baseline RDW becomes abnormal over time as disease progresses.

The quest to identify a clinically useful biomarker of long-term risk has embarked on many important discoveries of potential biological characteristics that can help clinicians to better gauge underlying disease severity. While cardiovascular specific novel biomarkers have attractive characteristics, many of them remained in the research domain and few have the appeal of standard chemistry or hematology assay panels that are familiar to any healthcare provider. There have even been recent challenges regarding the incremental benefit of novel biomarkers over standard population-based risk assessments[18, 19]. It is in this context that launched the interest in using RDW as a prognostic marker in heart failure, since it is readily available as part of CBC in every standard clinical laboratory and likely already a part of patient profile. Previous studies have demonstrated that high RDW was related to inflammation and impaired iron mobilization[12] but not to erythropoietin resistance[10], whichs may contribute to its prognostic value. This is particularly relevant when anemia and iron deficiency have been recognized as a treatable co-morbid condition.

While a direct link between the evolution of rising RDW with disease progression of heart failure has been proposed, to the best of our knowledge almost all the data published have been derived from blood drawn from a single time-point rather than correlating the natural history of heart failure with changes in RDW. It is clear that incident rise in RDW at any baseline RDW or hemoglobin level conferred poorer outcomes, even though this analysis may also be biased towards those only survived long enough for serial measurements. From our analysis it is clear that other parameters of the hematologic system (baseline or changes in hemoglobin) independently contributed to changes in RDW over time. Hence, RDW may serve as an integrated barometer of longevity based on one of the largest regenerative organs in the body (i.e. a “hematologic age”). In fact, the prognostic value of RDW has also been observed in other conditions with end-organ dysfunction such as renal failure or liver cirrhosis, implying that such observations may not be unique to the cardiovascular system[2, 8, 13, 14, 20], even though cardiac-specific outcomes have been reported to be increased with higher RDW[3, 4].

The novelty of our findings is the apparently strong prognostic role for those with otherwise lowest RDW tertile ($\leq 13.5\%$) to rise over time. This implies that for the large majority of subjects with relatively normal RDW that rising RDW may indicate disease progression. While the clinical utility of RDW maybe limited if RDW itself is a potentially non-modifiable risk marker, two observations maybe worth discussing. First, it is obvious that higher baseline RDW will have less likelihood for RDW to increase over time. This is likely a “regression-to-the-mean” phenomenon, since we defined changes as absolute differences between baseline and follow-up, and therefore the weight of the analysis was largely focused on those with rising RDW. The fact that rising RDW in the lowest baseline RDW tertile over-rides the prognostic significance of age and plasma BNP levels demonstrates the strength of this marker over baseline clinical characteristics. Second, although we did not observe any direct impact of a reduction in RDW with long-term survival in the overall cohort, there appeared to be a trend towards lower total mortality rates in those with lower RDW from baseline to follow-up within the highest tertile of baseline RDW. The quest now is to recognize what specific therapies may directly or indirectly lower RDW, and whether such interventions may alter the natural history of heart failure. We believe that our longitudinal insights have established the prognostic importance of rising RDW, and

highlight the importance of future investigations to determine the role of RDW assessment in clinical decision making in the management of patients with heart failure.

Study limitations

Follow-up RDW was not available in all of the patients under the criteria of 100-day window despite a relatively large sample size remained in the cohort. This is due to the dependence of physicians to order CBC testing within the time period of follow-up. As mentioned, the requirement for follow-up RDW may bias towards those that at least survive the time period of serial blood draws. Baseline measure is arbitrarily defined as the first available complete blood count measure with RDW information, hence may capture patients at different stages of their disease progression.

CONCLUSION

In our ambulatory cohort of patients with chronic heart failure, baseline and serial increase in RDW was associated with poor long-term outcomes independent of standard cardiac, hematologic, and renal indices.

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Figure 1.
Distribution of Red Cell Distribution Width (RDW) at Baseline

Figure 2.
Kaplan-Meier Analysis of Survival Stratified According to RDW $\geq 16\%$ versus RDW $< 16\%$ at Baseline

Figure 3. Prognostic Influence of Anemia and RDW: (A) All-cause mortality across subgroups of patients at baseline RDW according to the presence or absence of anemia; (B) Calculated all-cause 5-year mortality at baseline RDW across hemoglobin quartiles based on the HAZARDS model.

Figure 4.
Kaplan Meier Analysis of Survival Stratified According to Increased versus Decreased/
Unchanged RDW at 1-year follow-up.

Table 1

Baseline characteristics

Baseline Variable	Baseline RDW <16 (n=4,934)	Baseline RDW ≥ 16 (n=1,118)	p-value
Clinical Data			
Age (years)	65 ± 14	67 ± 14	0.009
Gender (% male)	65	63	0.13
Race (% Caucasian)	82	78	0.0002
Heart rate (bpm)	73 ± 13	77 ± 14	<0.0001
Body mass index (kg/m ²)	30 ± 7	29 ± 8	0.66
Systolic blood pressure (mm Hg)	120 ± 23	114 ± 23	<0.0001
Diabetes mellitus (%)	25	31	<0.0001
Hypertension (%)	43	39	0.038
Ischemic etiology (%)	11	12	0.28
Laboratory Data			
Hemoglobin (g/dL)	13.6 ± 2	12.1 ± 2	<0.0001
Mean corpuscular volume (fL)	90.4 ± 5	87.1 ± 8	<0.0001
BNP (pg/mL)	481 ± 644	1,041 ± 1014	<0.0001
BUN (mg/dL)	24 ± 14	36 ± 23	<0.0001
LDL cholesterol (mg/dL)	105 ± 40	87 ± 36	<0.0001
Triglycerides (mg/dL)	172 ± 141	133 ± 117	<0.0001
Serum creatinine (mg/dL)	1.22 ± 0.8	1.69 ± 1.5	<0.0001
eGFR (mL/min/1.73m ²)	72 ± 29	60 ± 34	<0.0001
Medications			
ACE inhibitor (%)/ARB (%)	72/21	65/23	<0.0001
Beta-blocker (%)	78	67	<0.0001
Calcium channel blocker (%)	22	20	0.08
Digitalis (%)	38	37	0.37
Nitrates (%)	38	42	0.010
Statin (%)	56	46	<0.0001
Loop diuretic (%)	80	87	<0.0001
Thiazide diuretic (%)	17	29	<0.0001
Echocardiographic Data			
LV ejection fraction (%-units)	35 ± 17	31 ± 17	<0.0001
LVED diameter (cm)	5.6 ± 1.2	5.6 ± 1.2	0.68
LA area (cm ²)	27 ± 9	29 ± 9	<0.0001
Diastolic stage ≥ II (%)	44	72	<0.0001
MR severity ≥ 3+ (%)	15	26	<0.0001
TR severity ≥ 3+ (%)	8	27	<0.0001

Table 2

Predictors of change in RDW at 1 year follow-up

	Univariate ρ	p-value	Multivariate β	p-value
Baseline RDW	-0.34	<0.0001	-0.51	<0.0001
Age (years)	0.08	0.002	-	-
Heart rate (bpm)	-0.01	0.80	-	-
Systolic BP (mm Hg)	0.13	0.0002	-	-
BNP (pg/mL)	-0.03	0.58	-	-
Creatinine (mg/dL)	0.05	0.05	-	-
HbA1c (%)	0.07	0.15	-	-
MCV (fL)	0.07	0.003	-	-
Baseline Hb (mg/dL)	0.07	0.006	0.10	0.0004
1 year change in Hb (mg/dL)	-0.19	<0.0001	-0.36	<0.0001
LVEF (%)	0.12	<0.0001	-	-
Diastolic stage	-0.07	0.034	-	-
MR severity	-0.02	0.47	-	-
TR severity	-0.06	0.024	-	-

Table 3

Cox multivariate risk ratios for mortality at (A) baseline and (B) 1-year followup.

(A)			
Variable	Increment	Multivariate Risk Ratio (95% CI)	p-value
Baseline RDW (%)	+1	1.09 (1.01 – 1.17)	0.029
Baseline hemoglobin (g/dL)	+1	0.95 (0.88 – 1.04)	0.26
Age (years)	+10	1.34 (1.18 – 1.53)	<0.0001
BNP (pg/mL)	+100	1.02 (1.01 – 1.04)	0.010
LDL cholesterol (mg/dL)	+10	0.95 (0.90 – 0.99)	0.018
eGFR (mL/min/1.73 m ²)	+10	0.99 (0.94 – 1.06)	0.99
LV ejection fraction (%)	+10	1.00 (0.90 – 1.11)	0.90
Diastolic stage	+1	1.00 (0.84 – 1.20)	0.96
LA area (cm ²)	+1	1.02 (0.99 – 1.04)	0.084

(B)			
Variable	Increment	Multivariate Risk Ratio (95% CI)	p-value
1 year change in RDW (%)	+1	1.21 (1.08 – 1.34)	0.002
1 year change in hemoglobin (g/dL)	+1	0.96 (0.84 – 1.09)	0.51
Age (years)	+10	1.42 (1.16 – 1.76)	0.0005
BNP (pg/mL)	+100	1.04 (1.01 – 1.07)	0.006
eGFR (mL/min/1.73 m ²)	+10	0.96 (0.90 – 1.03)	0.26
LV ejection fraction (%)	+10	0.96 (0.83 – 1.12)	0.63

Table 4

Multivariate risk ratios for mortality within different tertiles of baseline RDW.

		Multivariate Risk Ratio (95% CI)		
Variable	Increment	1 st tertile	2 nd tertile	3 rd tertile
1 year change in RDW (%)	+1	1.99 (1.50 – 2.61)***	1.23 (1.04 – 1.39)*	1.16 (1.02 – 1.31)*
Age (years)	+10	1.60 (0.98 – 2.72)	1.14 (0.83 – 1.60)	1.39 (1.09 – 1.80)**
BNP (pg/mL)	+100	1.02 (0.88 – 1.12)	1.04 (0.98 – 1.09)	1.03 (0.99 – 1.06)

*
p<0.05,

**
p<0.01,

p<0.001