Red Cell Distribution Width as a Novel Prognostic Marker in Heart Failure

Data From the CHARM Program and the Duke Databank

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Objectives

The goal of this study was to identify potentially novel laboratory markers of risk in chronic heart failure patients.

Background

Although a variety of prognostic markers have been described in heart failure, a systematic assessment of routine laboratory values has not been reported.

Methods

All 2,679 symptomatic chronic heart failure patients from the North American CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program had a wide range of laboratory measures performed at a core facility, enabling us to assess the relationship between routine blood tests and outcomes using a Cox proportional hazards model. We then replicated our findings in a cohort of 2,140 heart failure patients from the Duke Databank.

Results

Among 36 laboratory values considered in the CHARM program, higher red cell distribution width (RDW) showed the greatest association with morbidity and mortality (adjusted hazard ratio 1.17 per 1-SD increase, p < 0.001). Higher RDW was among the most powerful overall predictors, with only age and cardiomegaly showing a better independent association with outcome. This finding was replicated in the Duke Databank, in which higher RDW was strongly associated with all-cause mortality (adjusted hazard ratio 1.29 per 1 SD, p < 0.001), second only to age as a predictor of outcome.

Conclusions

In 2 large contemporary heart failure populations, RDW was found to be a very strong independent predictor of morbidity and mortality. Understanding how and why this marker is associated with outcome may provide novel insights into heart failure pathophysiology. (J Am Coll Cardiol 2007;50:40–7) © 2007 by the American College of Cardiology Foundation

Accurate risk stratification of patients with chronic heart failure is critically important to efficiently target the use of evidence-based therapies and identify high-risk patients who may benefit from advanced treatments. In addition to improving risk stratification, identification of new prognostic markers may provide insight into underlying pathophysiology or suggest avenues for therapeutic development. To date, a wide variety of clinical variables and biological markers have been used to create predictive models for survival in patients with chronic heart failure (1,2).

Routine measurement of panels of laboratory tests is nearly ubiquitous in the management of heart failure (3). Many laboratory findings have been shown to be associated with outcome in heart failure (4,5). Previous analyses from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program have highlighted the prognostic value of anemia across a broad range of ejection fractions in patients with chronic heart failure (6). However, the nature of interaction between the hema-
ological system and the heart failure syndrome remains poorly characterized.

The CHARM program was unique among large prospective heart failure trials in that it analyzed a wide range of laboratory values at a central core laboratory in a large cohort of patients. Thus, the CHARM program provides a distinctive opportunity to broadly characterize routine laboratory values in a contemporary chronic heart failure cohort and assess their relationship to outcome. The purpose of this study was to identify and validate new prognostic markers for chronic heart failure among 36 commonly collected laboratory measures.

First, we analyzed data from the CHARM program to identify laboratory parameters that were associated with clinical outcomes (derivation phase). Subsequently, we sought to replicate our findings in an independent dataset, the Duke Databank for Cardiovascular Disease. We herein report the identification and validation of red cell distribution width (RDW) as a novel independent predictor of adverse outcomes in patients with chronic heart failure.

### Methods

**Patient population for derivation dataset.** Details and key findings of the CHARM program have been published previously (7). Briefly, the CHARM program randomized patients with symptomatic chronic heart failure to candesartan or placebo. The program consisted of 3 separate trials that shared inclusion and exclusion criteria, end point definitions, and follow-up.

| Table 1 Baseline Characteristics for CHARM North American Study Cohort |
|-----------------|-----------------|-----------------|-----------------|
| Variable              | CV Death or HF Hospitalization | Without Event (n = 1,727) | With Event (n = 952) |
|                      | Mean or %       | SD               | Mean or %       | SD               |
| Demographic and clinical       |                 |                 |                 |                 |
| Age (yrs)              | 64.1            | 11.5            | 67.4            | 11.3            |
| Ejection fraction       | 0.40            | 0.15            | 0.36            | 0.16            |
| Heart rate (beats/min)  | 71.2            | 11.8            | 73.0            | 12.2            |
| Systolic blood pressure (mm Hg) | 129.1        | 18.0            | 126.5           | 19.8            |
| Diastolic blood pressure (mm Hg) | 74.7        | 10.6            | 71.8            | 10.6            |
| Body mass index (kg/m²) | 29.8            | 6.4             | 29.3            | 6.5             |
| Female                 | 34.3%           |                 | 31.7%           |                 |
| NYHA functional class II | 42.7%           |                 | 24.5%           |                 |
| NYHA functional class III | 56.1%          |                 | 70.1%           |                 |
| NYHA functional class IV  | 1.3%            |                 | 5.5%            |                 |
| Race (white)           | 84.8%           |                 | 85.8%           |                 |
| Previous hospitalization for HF | 62.4%        |                 | 77.7%           |                 |
| Etiology (ischemic)    | 65.0%           |                 | 71.5%           |                 |
| Medical history         |                 |                 |                 |                 |
| Previous MI            | 51.1%           |                 | 57.1%           |                 |
| Stroke                 | 9.4%            |                 | 12.7%           |                 |
| Hypertension           | 65.8%           |                 | 68.2%           |                 |
| Diabetes mellitus      | 30.8%           |                 | 48.8%           |                 |
| Coronary artery bypass grafting | 30.8%    |                 | 34.9%           |                 |
| Percutaneous coronary revascularization | 20.8%  |                 | 19.7%           |                 |
| Implanted cardioverter-defibrillator | 3.5% |                 | 5.1%            |                 |
| Atrial fibrillation     | 25.3%           |                 | 35.2%           |                 |
| Signs and symptoms      |                 |                 |                 |                 |
| Dyspnea on exertion    | 66.3%           |                 | 76.7%           |                 |
| Venous congestion      | 36.1%           |                 | 47.7%           |                 |
| S3 gallop              | 12.9%           |                 | 22.1%           |                 |
| Cardiomegaly           | 8.4%            |                 | 20.1%           |                 |
| Pulmonary crackles     | 10.5%           |                 | 16.8%           |                 |
| Electrocardiogram       |                 |                 |                 |                 |
| Atrial fibrillation/flutter | 10.2%        |                 | 13.6%           |                 |
| Bundle branch block    | 18.1%           |                 | 27.5%           |                 |
| Pathological Q-wave     | 16.3%           |                 | 13.7%           |                 |
| Left ventricular hypertrophy | 13.8%       |                 | 14.1%           |                 |

**Abbreviations and Acronyms**

- **ACE** = angiotensin-converting enzyme
- **HR** = hazard ratio
- **NYHA** = New York Heart Association
- **RDW** = red cell distribution width

**References**

- Felker et al. 2007:40–7
- CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; **CV** = cardiovascular; **HF** = heart failure; **MI** = myocardial infarction; **NYHA** = New York Heart Association.
methods. The study included: 1) patients with left ventricular ejection fraction >40% (CHARM-preserved); 2) patients with angiotensin-converting enzyme (ACE) inhibitor intolerance and a left ventricular ejection fraction ≤40% (CHARM-alternative); and 3) patients on ACE inhibitors and with a left ventricular ejection fraction ≤40% (CHARM-added). The primary end point of each constituent trial was time to cardiovascular death or hospitalization for the management of worsening heart failure (adjudicated by a blinded events committee), and the primary end point of the overall program was all-cause mortality. All patients enrolled in the CHARM program in North America (n = 2,679) had a panel of routine laboratory tests measured at the time of randomization by a central core laboratory, and this cohort served as the population for this analysis. Follow-up was for a median of 34 months in the study cohort. The CHARM trials were approved by the institutional review boards of participating centers.

**Statistical methods for derivation dataset.** Baseline variables were described using means and standard deviations or percentages, as appropriate. Correlations between variables of interest were determined using correlation coefficients. A Cox proportional hazards model was used to evaluate the relationship between preselected clinical variables and the end point of interest. This modeling was performed separately for time to cardiovascular death.
or heart failure hospitalization (the primary end point of the constituent trials) and for all-cause mortality (the primary end point of the overall program). A “best clinical model” (excluding laboratory data) was created from the overall program dataset (n = 7,599) using standard modeling techniques (2). Briefly, models were built using a forward stepwise variable selection procedure. A value of p < 0.01 was set as the level of significance for including variables in the model because of the large number of candidate variables being considered. Randomization to candesartan or placebo was included in all models. The variables selected for this model were then used to estimate a final model for the study cohort for whom laboratory data were available (n = 2,679). Subsequently, laboratory parameters were added to this model one at a time in a forward stepwise fashion to generate a final model that combined both clinical and laboratory parameters. Adjusted hazard ratios (HRs) for continuous variables were described using standardized HRs, the HR associated with a 1-SD change in the variable. The statistical contribution of each variable to the prediction of outcome was assessed by the chi-square statistic.

To evaluate the potential effects of non-normal distribution of laboratory values on our findings, we repeated the modeling with log transformation on all laboratory values before entering them into the model. To evaluate the possibility of nonlinear relationships between variables and outcome, we repeated the models with a quadratic term included for each laboratory value. Finally, we tested for statistical interactions between variables for which there was a theoretical rationale for interactions.

Replication dataset. To assess the validity of these findings, we investigated the prognostic association of laboratory variables identified in the CHARM program in an independent cohort of patients from the Duke Databank for Cardiovascular Disease. Briefly, the Duke Databank is a clinical database that includes all patients who have undergone cardiac catheterization at Duke University Medical Center since 1969 (8). Mortality follow-up data are complete for over 96% of patients. For the purposes of this analysis, we defined a dataset that would be composed of a contemporary, broadly representative heart failure population similar to that in the CHARM program. This consisted of patients entered into the Duke Databank from 1999 to 2003 who had symptomatic heart failure (New York Heart Association [NYHA] functional class II or greater) regardless of ejection fraction, and who had an RDW value available. Patients were excluded from the analysis if they had primary valvular heart disease or complex congenital heart disease. Because data on cause of subsequent hospitalizations and cause of death were not universally available, time to all-cause mortality was used as the primary end point for the replication phase. The replication study was approved by the Duke University Institutional Review Board.

In the replication dataset, multivariable Cox proportional hazards modeling was used to identify the relationship

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<th>Table 3 Final Multivariable Model for Cardiovascular Death or Heart Failure Hospitalization in the CHARM Cohort (Including Laboratory and Clinical Variables)</th>
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<td>Bilirubin total</td>
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<td>Uric acid</td>
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<td>Glycohemoglobin A1C</td>
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<td>Creatinine</td>
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<td>Clinical variables</td>
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<td>Age (per 10 yrs over age 60)</td>
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<td>Ejection fraction (per 5% decrease below 45)</td>
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<td>Diabetes: insulin treated</td>
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<td>Diabetes: other</td>
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<td>Prior HF hospitalization within 6 months</td>
</tr>
<tr>
<td>Prior HF hospitalization but not within 6 months</td>
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<tr>
<td>Cardiomegaly</td>
</tr>
<tr>
<td>NYHA functional class III</td>
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<tr>
<td>NYHA functional class IV</td>
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<tr>
<td>Diagnosis of HF over 2 yrs ago</td>
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<tr>
<td>Bundle branch block</td>
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<tr>
<td>Randomization to candesartan</td>
</tr>
</tbody>
</table>

*Hazard ratios for continuous variables shown as standardized hazard ratios (HR per 1 SD).
Abbreviations as in Table 1.
between RDW and all-cause mortality after adjustment for other clinical and laboratory predictors of outcome. As in the CHARM database, the relationship between RDW and outcome was expressed as a standardized HR.

Results

The CHARM population characteristics. Baseline clinical characteristics for patients enrolled in the CHARM program in North America (n = 2,679) are shown in Table 1. Thirty-six laboratory parameters obtained as part of standard chemistry and hematology panels were considered as potential laboratory predictors of outcome (listed in Table 2).

Laboratory predictors of outcome in the CHARM program. In the CHARM cohort, 952 patients suffered a primary outcome event (cardiovascular death or heart failure hospitalization). As previously described, a best clinical model was initially constructed using clinical characteristics alone (without laboratory values or medications). In this clinical model, the most powerful predictors of outcome were diabetes mellitus, recent hospitalization for heart failure, age, and ejection fraction (2). The 36 candidate laboratory parameters were then evaluated to identify associations between each individual biochemical variable and outcome. In univariable analysis of laboratory predictors (adjusted for the variables in the final clinical model but not for other laboratory variables), the most powerful (based on the chi-square statistic) laboratory predictors of outcome were increased RDW, increased uric acid, and increased blood urea nitrogen. To evaluate these laboratory parameters in the context of all available clinical information, a final multivariable model was generated that included all significant laboratory and clinical predictors (Table 3). In this final model, the laboratory values most predictive of adverse outcomes were increased RDW (HR 1.17 per 1-SD increase, \( p < 0.0001 \)), higher total bilirubin (HR 1.14 per 1-SD increase, \( p < 0.0001 \)), decreased lymphocyte count (HR 0.86 per 1-SD increase, \( p < 0.0001 \)), and increased uric acid (HR 1.13 per 1-SD increase, \( p = 0.0005 \)). Notably in this final model, increased RDW was among the most significant overall predictors of outcome, showing stronger statistical association than many traditional measures of risk such as NYHA functional class and ejection fraction. Of clinical variables tested, only age and cardiomegaly showed stronger independent association with outcome than RDW. Log-transforming laboratory values did not significantly alter the association of RDW with outcomes (HR 1.85 for 1-SD increase in the log of RDW, \( p < 0.0001 \)), nor was there any evidence for a nonlinear relationship between RDW and outcome (p value for quadratic term of RDW = 0.11). The relationship of RDW to the primary composite outcome is shown in Figure 1A. The effect of candesartan in reducing the primary composite outcome in the CHARM program (Table 3) was not modified by the baseline level of RDW.

Figure 1 Outcomes by RDW Quintiles

Adjusted hazard ratios by quintile of red cell distribution width (RDW) for cardiovascular (CV) death or heart failure (HF) hospitalization in the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program (A), all-cause mortality in CHARM (B), and all-cause mortality in Duke Databank (C).

To further evaluate this association, we repeated the modeling using the end point of all-cause mortality (625 events). In this mortality analysis, the association between RDW and outcome was less marked, but RDW remained a highly significant independent predictor of outcome (adjusted HR 1.12 per 1-SD increase, \( p = 0.006 \)) after
adjustment for other clinical and laboratory measures (Fig. 1B, Table 4).

Replication in Duke Databank. The replication dataset contained 2,140 patients from the Duke Databank who experienced 368 end points (deaths). In univariate analysis, we found RDW to be strongly predictive of all-cause mortality (HR 1.47 per 1-SD increase, \( p < 0.001 \)). After adjustment for a wide range of clinical and laboratory covariates in a multivariable model, RDW remained strongly associated with mortality (adjusted HR 1.29 per 1-SD increase, \( p < 0.001 \)) (Table 4, Fig. 1C). Based on chi-square analysis, RDW was second only to age with regard to the statistical strength of association as a predictor of all-cause mortality.

RDW and hemoglobin. Given the association of hemoglobin with adverse outcomes seen in previous studies, we evaluated the relationship between hemoglobin and RDW in both the CHARM dataset and the Duke Databank. In both datasets, RDW and hemoglobin were moderately negatively correlated with each other (correlation coefficient of \( r = 0.27 \) in the CHARM program and \( r = 0.40 \) in the Duke Databank). In all final multivariable models, both RDW and hemoglobin were significant predictors even after adjustment for all other predictors. There was no evidence for

<p>| Table 4 | Final Multivariable Model for All-Cause Mortality in CHARM Cohort (Including Laboratory and Clinical Variables) |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
<th>Chi-Square</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>0.78</td>
<td>0.71–0.85</td>
<td>31.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bilirubin total</td>
<td>1.19</td>
<td>1.11–1.27</td>
<td>24.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>1.18</td>
<td>1.10–1.26</td>
<td>20.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.85</td>
<td>0.78–0.93</td>
<td>14.24</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.84</td>
<td>0.76–0.92</td>
<td>13.75</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sodium</td>
<td>1.14</td>
<td>1.04–1.25</td>
<td>8.18</td>
<td>0.004</td>
</tr>
<tr>
<td>RDW</td>
<td>1.12</td>
<td>1.03–1.20</td>
<td>7.65</td>
<td>0.006</td>
</tr>
<tr>
<td>Monocytes</td>
<td>1.11</td>
<td>1.02–1.20</td>
<td>6.63</td>
<td>0.0100</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.10</td>
<td>1.01–1.20</td>
<td>4.87</td>
<td>0.03</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 10 yrs over age 60)</td>
<td>1.49</td>
<td>1.33–1.66</td>
<td>49.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction (per 5% decrease below 45)</td>
<td>1.13</td>
<td>1.09–1.18</td>
<td>35.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.63</td>
<td>0.52–0.76</td>
<td>21.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diagnosis of HF over 2 yrs ago</td>
<td>1.48</td>
<td>1.24–1.76</td>
<td>18.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.69</td>
<td>1.32–2.15</td>
<td>17.77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes: insulin treated</td>
<td>1.60</td>
<td>1.26–2.03</td>
<td>14.72</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diabetes: other</td>
<td>1.41</td>
<td>1.16–1.71</td>
<td>12.09</td>
<td>0.0005</td>
</tr>
<tr>
<td>Dependent edema</td>
<td>1.34</td>
<td>1.13–1.60</td>
<td>10.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m² decrease below 27.5)</td>
<td>1.05</td>
<td>1.02–1.09</td>
<td>8.79</td>
<td>0.003</td>
</tr>
<tr>
<td>NYHA functional class III</td>
<td>1.33</td>
<td>1.10–1.62</td>
<td>8.40</td>
<td>0.004</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td>1.29</td>
<td>1.08–1.54</td>
<td>7.87</td>
<td>0.005</td>
</tr>
<tr>
<td>NYHA functional class IV</td>
<td>1.68</td>
<td>1.14–2.48</td>
<td>6.77</td>
<td>0.009</td>
</tr>
<tr>
<td>Diastolic blood pressure (per 10-mm Hg decrease)</td>
<td>1.09</td>
<td>1.01–1.19</td>
<td>4.84</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Hazard ratios for continuous variables shown as standardized hazard ratios (HR per 1 SD). Abbreviations as in Table 1.

<p>| Table 5 | Final Multivariable Analysis for All-Cause Mortality From Duke Databank Cohort |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio*</th>
<th>95% CI</th>
<th>Chi-Square</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.49</td>
<td>1.32–1.69</td>
<td>39.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RDW</td>
<td>1.29</td>
<td>1.16–1.43</td>
<td>21.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.79</td>
<td>0.71–0.88</td>
<td>17.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td>1.19</td>
<td>1.08–1.30</td>
<td>13.31</td>
<td>0.0003</td>
</tr>
<tr>
<td>Noncardiac Charlson index†</td>
<td>1.14</td>
<td>1.05–1.23</td>
<td>11.02</td>
<td>0.0009</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.85</td>
<td>0.76–0.95</td>
<td>8.75</td>
<td>0.003</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.88</td>
<td>0.78–0.98</td>
<td>5.30</td>
<td>0.02</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.78</td>
<td>0.62–0.99</td>
<td>4.33</td>
<td>0.04</td>
</tr>
<tr>
<td>Male</td>
<td>1.27</td>
<td>1.01–1.60</td>
<td>4.10</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Hazard ratios for continuous variables shown as standardized hazard ratios (HR per 1 SD). †Charlson index is a combined measure of noncardiac comorbidity. Abbreviations as in Table 1.
statistical interaction between RDW and hemoglobin (p > 0.05 for interaction term in all models). The RDW was a more powerful predictor (based on chi-square analysis) than hemoglobin in the CHARM composite end point model and the Duke Databank mortality model. Hemoglobin was a stronger predictor than RDW in the CHARM mortality model.

Discussion

The primary finding of this study is that increased RDW was a strong independent predictor of greater morbidity and mortality in patients with chronic heart failure. This finding was observed in a large clinical trial database and subsequently replicated in a large hospital registry database. This association remained after adjustment for a wide variety of clinical and laboratory variables. In both datasets RDW was among the strongest prognostic markers. The RDW had higher statistical association with outcome than widely accepted measures of risk such as ejection fraction, NYHA functional class, and renal function. To our knowledge, this represents the first report of elevated RDW as a potential prognostic marker in chronic heart failure.

Several features support the validity of our findings. The other prognostic markers identified in our analyses are consistent with previously published models in heart failure, with regard to both traditional markers of risk (such as age, ejection fraction, and NYHA functional class) and other prognostic laboratory markers (9,10). The confirmation of our observation in an independent dataset suggests that the association between RDW and outcome is very unlikely to be caused by the play of chance.

Potential mechanisms. Red cell distribution width is a quantitative measure of anisocytosis, the variability in size of the circulating erythrocytes. It is routinely measured by automated hematology analyzers and is reported as a component of the complete blood count. Red cell distribution width is typically elevated in conditions of 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. Conceivably, RDW may represent an integrative measure of multiple pathologic processes in heart failure (e.g., nutritional deficiencies, renal dysfunction, hepatic congestion, inflammatory stress), explaining its association with clinical outcomes. Although not previously correlated with cardiovascular outcomes, elevation of RDW has been associated with other disease processes, including liver disease, malnutrition, occult colon cancer, and neoplastic metastases to marrow (11,12).

A variety of mechanisms have been proposed for the association between anemia and outcomes in heart failure, including inflammatory stress, nutritional deficiencies, inadequate production of erythropoietin, and the impact of comorbidities (13). Any or all of these mechanisms could also impact RDW. It is possible that the relationship of these variables and outcome is more directly reflected through impact on RDW than on hemoglobin. However, in both the CHARM program and the Duke Databank, RDW was only modestly correlated with serum hemoglobin, and remained an independent predictor of outcome after adjusting for hemoglobin.

Red cell distribution width also may be related to other known markers of prognosis in heart failure, such as inflammatory cytokines. Inflammatory cytokines have been shown to be predictors of prognosis in heart failure, and also may impact bone marrow function and iron metabolism (14,15). Proinflammatory cytokines have been found to inhibit erythropoietin-induced erythrocyte maturation, which is reflected in part by an increase in RDW (16). Future studies that carefully evaluate RDW in the context of more complete evaluation of iron metabolism and markers of inflammation in heart failure patients may provide further insight into the mechanisms of the interaction between the hematologic and cardiovascular systems.

Study limitations. Chi-square statistics reflect the statistical significance of relationships, but do not provide a formal evaluation of the contribution of a variable to explained variance, and as such are not a formal measure of predictive validity. We did not focus on model performance because the purpose of this analysis was not to develop a risk model, but rather to explore novel factors that may be prognostically important and thus warrant further investigation.

This study is a retrospective review of clinical datasets without a prespecified hypothesis, and as such is subject to the limitations of this type of analysis. Given the large number of potential predictors evaluated and the initial lack of hypothesis-guided selection of variables, some observed associations in the derivation dataset may be related to chance alone. However, the high level of statistical significance observed for RDW in both the derivation dataset and replication dataset minimizes this possibility.

Conclusions

We identified elevated RDW as a novel and important predictor of morbidity and mortality in patients with chronic heart failure. Red cell distribution width, a largely overlooked variable available to clinicians for most of their patients with heart failure, has greater independent association with outcome than many other clinical and laboratory parameters promoted for use in estimating prognosis. This study should prompt further evaluation of the association between RDW and outcome in heart failure to improve understanding of pathophysiology and to better risk-stratify patients with chronic heart failure.

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