Prognostic Value of Change in Red Cell Distribution Width 1 Month After Discharge in Acute Decompensated Heart Failure Patients

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Background: Red cell distribution width (RDW) is a novel prognostic marker independently associated with adverse outcomes in acute decompensated heart failure (ADHF) patients. The aim of the present study was to assess whether the change in RDW after discharge had prognostic value in patients with ADHF.

Methods and Results: RDW was measured in 261 patients admitted with ADHF, at admission and at discharge and 1 month after discharge. Cardiovascular (CV) events were defined as CV mortality and heart failure rehospitalization. Kaplan–Meier analysis showed that patients with positive RDW change between admission and 1 month after discharge (RDW∆1Mdis-adm; n=136) had a significantly higher number of CV events compared with patients with no positive RDW∆1Mdis-adm (n=125; 60.3% vs. 47.2%, log-rank: P=0.007). On Cox hazards analysis, a positive RDW∆1Mdis-adm was an independent predictor of CV events after adjusting for other CV risk factors (hazard ratio, 1.740; 95% confidence interval: 1.149–2.633, P=0.009).

Conclusions: A novel relationship was noted between positive RDW∆1Mdis-adm and CV events in ADHF patients. Measurement of RDW at 1 month after ADHF assists in the prediction of adverse CV outcomes. Therefore, repeated measurement of RDW is a simple and inexpensive method that may facilitate assessment of CV risk stratification in patients with ADHF. (Circ J 2012; 76: 109–116)

Key Words: Acute decompensated heart failure; Prognosis; Red cell distribution width

The risk stratification of patients admitted with acute decompensated heart failure (ADHF) is determined by measuring prognostically significant biomarkers. Red cell distribution width (RDW) is a measurement of size variability of the red blood cells, easily measured using modern cell counters. Generally, a high RDW may reflect reticulocytosis due to iron deficiency anemia and hemolytic disorders. Recently, RDW has been found to be a prognostic marker in patients with heart failure (HF).1–6 Prior myocardial infarction without HF,7,8 and pulmonary hypertension.9 Two large epidemiologic studies further suggested that RDW was associated with all-cause mortality including cardiovascular (CV) mortality even in a cohort without anemia, or iron, folate and vitamin B deficiency.10,11

ADHF is the most common cause for hospitalization for patients >65 years of age.12 Therefore, accurate prediction of ADHF outcome is needed and many approaches for this have been suggested. To date, B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), cardiac troponins, C-reactive protein, uric acid, soluble interleukin-1 receptor family member ST2 (ST2) and their combinations have been found to be related to the severity and prognosis of patients with ADHF.13,14 Serial monitoring and interval change as well as initial value have also been found to be well associated with prognosis in CV disease patients including HF.15–18 Recent studies have reported that both RDW levels at admission and at discharge are prognostic markers independent of NT-proBNP in ADHF patients.2,3,5 No study, however, has investigated repeated measurements of RDW and its prognostic value in ADHF patients. We investigated the prognostic value of change in RDW via measurements at admission, at discharge, and 1 month after discharge in patients with ADHF.
Table 1. Baseline ADHF Patient Characteristics

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Total (n=261)</th>
<th>CV events</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=120)</td>
<td>Yes (n=141)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>143 (54.8)</td>
<td>70 (58.3)</td>
<td>73 (51.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.6±14.2</td>
<td>60.9±15.0</td>
<td>64.0±13.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0±4.5</td>
<td>23.5±5.2</td>
<td>22.6±3.8</td>
</tr>
<tr>
<td>NYHA III, IV</td>
<td>261 (100)</td>
<td>136 (100)</td>
<td>125 (100)</td>
</tr>
<tr>
<td>Admission history</td>
<td>99 (37.9)</td>
<td>27 (22.5)</td>
<td>72 (51.1)</td>
</tr>
<tr>
<td>Ischemic origin</td>
<td>87 (33.3)</td>
<td>55 (39.0)</td>
<td>32 (26.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>81 (31.0)</td>
<td>47 (33.3)</td>
<td>34 (28.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>131 (50.2)</td>
<td>69 (48.9)</td>
<td>62 (51.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>123 (47.1)</td>
<td>50 (41.7)</td>
<td>73 (51.8)</td>
</tr>
<tr>
<td>Dobutamine infusion</td>
<td>74 (28.4)</td>
<td>32 (26.7)</td>
<td>42 (29.8)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>33.2±15.1</td>
<td>33.7±14.3</td>
<td>32.6±15.8</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119.6±21.9</td>
<td>123.3±22.6</td>
<td>116.3±20.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83.1±17.3</td>
<td>83.7±17.9</td>
<td>82.6±16.9</td>
</tr>
<tr>
<td>Discharge medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>207 (79.3)</td>
<td>100 (83.3)</td>
<td>107 (75.9)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>124 (47.5)</td>
<td>70 (49.6)</td>
<td>54 (45.0)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>221 (84.7)</td>
<td>122 (86.5)</td>
<td>99 (82.5)</td>
</tr>
</tbody>
</table>

Data given as mean-SD or n (%). †T-test or chi-square test or Mann-Whitney U-test.

ADHF, acute decompenated heart failure; CV, cardiovascular; BMI, body mass index; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide at admission; Hbadm, hemoglobin at admission; Hbdis, Hb at discharge; Hbdis-adm, Hb at 1-month after discharge; RDWdis, RDW at discharge; RDWdis-adm, RDW at 1-month after discharge; RDWdis−RDWdis−adm, RDWdis−adm, RDW1Mdis−RDWadm; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Methods

Patients

We retrospectively investigated consecutive patients who visited the emergency department (ED) of Severance Cardiovascular Hospital, Seoul, Korea between January 2005 and June 2009 with clinical diagnosis (rare or generalized edema or pulmonary congestion) of ADHF and left ventricular ejection fraction (LVEF) <50% measured on transthoracic echocardiography using Simpson’s biplane rule within 24 h. Two-dimensional echocardiography and RDW measured at admission, at discharge and 1 month after discharge were available for 261 patients. Patients with known hematologic diseases such as hemolytic anemia, neoplastic metastases to bone marrow, pregnancy, severe arthritis, inflammatory bowel diseases and transfusion, iron replacement therapy, which can increase plasma RDW levels, and other extracellular fluid-increasing diseases (eg, hypothyroidism and liver cirrhosis) were excluded.

Measurements of Blood Chemistry and RDW

Patients had venous blood collected for measurement of routine blood chemistry and NT-proBNP at admission. The blood samples were tested with NT-proBNP, which was kept at 4°C, using an electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics, Basel, Switzerland) within 1 h of ED visit. RDW was measured using the Coulter STK-S analyzer (Coulter, FL, USA) in the Severance Cardiovascular Hospital laboratory. RDWadm was defined as RDW at admission; RDWdis as RDW at discharge; RDWdis−adm as RDW at 1-month after discharge; RDWdis−adm as RDWdis−adm; RDW1Mdis−RDWadm; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Circulation Journal Vol.76, January 2012
RDW Change 1 Month After Discharge in ADHF

Expression of Diet in Renal Disease formula as follows: $170 \times (\text{Scr})^{0.999} \times (\text{age})^{0.176} \times (\text{BUN})^{0.170} \times (\text{albumin})^{0.318} \times 0.762$ (if female), where SCr is serum creatinine in mg/dl. The present study was approved by the internal review board of Severance Hospital.

**Clinical Outcomes**
All patients’ followed up records were reviewed. Median post-discharge follow-up was 636 days (interquartile range [IQR], 228–912). The primary endpoint was the composite of CV mortality and HF rehospitalization due to an exacerbation of HF requiring more than the treatment provided before the hospitalization. There were only 2 cases of non-CV mortality.

**Statistical Analysis**
SPSS version 17.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous variables are given as mean±SD except for NT-proBNP, which is given as median and IQR when skewed. Categorical variables are given as numbers or percentages. We compared differences between groups using Student’s t-test, Mann–Whitney U-test and paired Student’s t-test for RDW change. Correlations of RDW change with changes in other variables were examined using Pearson correlation analysis. Kaplan–Meier survival analysis

![Figure 1. Numbers of patients vs. (A) RDWΔdis-adm and (B) RDWΔ1Mdis-adm. RDW, red cell distribution width; RDWΔdis-adm, RDW at discharge–RDW at admission; RDWΔ1Mdis-adm, RDW at 1 month after discharge–RDW at admission.](image-url)
Figure 2. Kaplan–Meier curves for cardiovascular (CV) events according to (A) RDW\(_{\text{dis-adm}}\) and (B) RDW\(_{1\text{Mdis-adm}}\). RDW, red cell distribution width; RDW\(_{\text{dis-adm}}\), RDW at discharge–RDW at admission; RDW\(_{1\text{Mdis-adm}}\), RDW at 1 month after discharge–RDW at admission.
was used to test the influence of the change in RDW on CV events, with log-rank test. The independent effect of variables on CV events was calculated using Cox multivariate proportional hazards regression analysis, incorporating covariates with \( P<0.10 \) on univariate analysis. Hazard ratio (HR) with 95% confidence interval (CI) demonstrated the risk of CV events. \( P<0.05 \) was considered significant and all reported probability values were 2-tailed.

## Results

### Baseline Characteristics of ADHF Patients and Clinical Outcomes

The baseline characteristics are summarized in Table 1. The etiology of HF was idiopathic dilated cardiomyopathy in 77 patients (29.5%), valvular in 45 (17.2%), ischemic in 87 (33.3%) and hypertensive in 17 (6.5%). No significant differences were observed in dobutamine infusion therapy at admission and discharge medications between patients without CV events and with CV events. As compared with patients without CV events, patients who developed CV events had significantly higher previous admission history, lower ischemic origin, lower systolic blood pressure (SBP), lower eGFR, lower Hba1c, lower Hb, lower HbA1c, higher RDWadm, higher RDWdis and higher RDWdis-adm. During a median follow-up of 636 days (IQR, 228–912 days), CV events occurred in 54.0% of patients (141/261), and CV mortality in 12.6% (33/261). The incidence of positive RDWdis-adm was significantly higher in patients who developed CV events than patients without CV events (\( P=0.023 \)). Moreover, LVEF, NT-proBNP and discharge medications were not significantly different between the two groups.

### Changes in RDW After ADHF

Mean RDW changed from 14.2±2.0% at admission to 14.3±1.7% at discharge (\( P=0.493 \)) to 14.4±1.9% at 1 month after discharge (\( P=0.028 \)). Mean RDWadm was 0.06±1.26% and RDWΔdis-adm was 0.12±1.39%. The distribution of RDWΔdis-adm and RDWΔdis-adm are shown in Figure 1. In correlation analysis, RDWΔdis-adm was significantly correlated with RDWdis-adm (\( r=0.787, P<0.001 \)), Hba1c-adm (\( r=-0.246, P<0.0001 \)) and HbA1c-adm (\( r=-0.246, P<0.0001 \)) but not with BUNA1c-adm (\( r=-0.049, P=0.434 \)) nor with creatinineΔdis-adm (\( r=0.041, P=0.516 \)).

### RDWΔdis-adm as an Independent Predictor of CV Events

The primary composite endpoint of the present study was CV events including CV mortality and rehospitalization for HF. On Kaplan–Meier survival analysis, the positive RDWΔdis-adm group (n=109) tended to have a higher number of CV events compared with the no-positive RDWΔdis-adm group (n=152), but this was not significant (57.6% vs. 49.6%, log-rank \( P=0.115 \); Figure 2A). The positive RDWΔdis-adm group (n=136) had a significantly higher number of CV events compared with the no-positive RDWΔdis-adm group (n=125; 60.3% vs. 47.2%; log-rank \( P=0.007 \); Figure 2B), driven by significant change in HF rehospitalization (46.3% vs. 36.0%, log-rank \( P=0.016 \)). CV mortality was not different between the positive RDWΔdis-adm group and the no-positive RDWΔdis-adm group (14.0% vs. 11.2%, log-rank \( P=0.207 \)). On univariate Cox proportional hazards analysis, only positive RDWΔdis-adm (HR, 1.584; 95%CI: 1.133–2.217; \( P=0.007 \)) was a statistically significant predictor among the various RDW variables (Table 2). RDW and anemia at admission have also been found to be prognostic indicators in patients with AHF.3–5 We therefore used Hbadm, RDWadm and positive

### Table 1. Univariate Cox Proportional Hazards Analysis for CV Events

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95%CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Previous admission history</td>
<td>2.418 (1.731–3.376)</td>
</tr>
<tr>
<td>Ischemic origin</td>
<td>1.522 (1.084–2.138)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.398 (1.005–1.946)</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>0.709 (0.482–1.044)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.010 (1.000–1.024)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.990 (0.982–0.999)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>0.994 (0.989–0.999)</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>1.018 (0.998–1.038)</td>
</tr>
<tr>
<td>eGFR (ml · min⁻¹ · 1.73m⁻²)</td>
<td>0.992 (0.986–0.998)</td>
</tr>
<tr>
<td>Hbadm (g/dl)</td>
<td>0.901 (0.840–0.966)</td>
</tr>
<tr>
<td>RDWadm (%)</td>
<td>1.157 (1.089–1.230)</td>
</tr>
<tr>
<td>Positive RDWΔdis-adm</td>
<td>1.584 (1.133–2.217)</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1, 2.
Figure 3. Kaplan–Meier curves for cardiovascular events vs. low/high RDW$_{adm}$ and positive/no-positive RDW$\Delta_{1\text{Mdis-adm}}$. RDW, red cell distribution width; RDW$_{adm}$, RDW at admission; RDW$\Delta_{1\text{Mdis-adm}}$, RDW at 1 month after discharge–RDW at admission. Low RDW$_{adm}$, <13.8%; high RDW$_{adm}$, ≥13.8%.

Figure 4. Increased prognostic value of the addition of RDW$\Delta_{1\text{Mdis-adm}}$ to RDW$_{adm}$ for predicting cardiovascular events according to a Cox proportional hazards model presented as global chi-square data. Adm Hx, admission history; RDW, red cell distribution width; RDW$_{adm}$, RDW at admission; RDW$\Delta_{1\text{Mdis-adm}}$, RDW at 1 month after discharge–RDW at admission.
RDW change 1 month after discharge in ADHF

RDWΔMdis-adm in a multiple Cox regression model to study the additional prognostic power of serial measurements of RDW compared to a single measurement. Positive RDWΔMdis-adm (HR, 1.740; 95% CI, 1.149–2.633; P=0.009) was an independent predictor for CV events after adjusting for previous admission history, ischemic origin, atrial fibrillation, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers use, age, SBP, uric acid, eGFR, Hbadm, and RDWadm (Table 3).

Addition of RDWΔMdis-adm to RDWadm Increases Prognostic Value

We tested whether the addition of RDWΔMdis-adm has an incremental effect on prognostic value when added to RDWadm by dividing patients into 2 groups according to RDWadm. On Kaplan–Meier survival analysis, a group with both high RDWadm (≥13.8%) and positive RDWΔMdis-adm (n=51) had a significantly higher number of CV events than a group with high RDWadm and no-positive RDWΔMdis-adm (n=75), a group with low RDWadm (<13.8%) and positive RDWΔMdis-adm (n=85) and a group with low RDWadm and no-positive RDWΔMdis-adm (n=50) (72.5% vs. 52.9% vs. 56.0% vs. 34.0%; log-rank P<0.001; Figure 3). In a Cox proportional hazards model, the addition of positive RDWΔMdis-adm to RDWadm significantly increased the likelihood of prediction of CV events (global chi-square 36.2 vs. 43.9, P=0.007; Figure 4).

Discussion

The principal findings of the present study are that positive RDWΔMdis-adm is an independent prognostic factor for CV events in ADHF patients, and that repeated measurements of RDW have an increased prognostic value for predicting CV events to single measurement of RDW in these patients. Herein we report interesting data on the potential relationship between positive RDWΔMdis-adm and CV events after ADHF.

Repeated Measurements of RDW After ADHF

RDW was first found to be a prognostic marker in symptomatic chronic HF patients in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study.1 Further studies showed that higher RDW levels at admission and at discharge were associated with poor long-term outcomes regardless of anemia status, thereby demonstrating increased prognostic power compared to NT-proBNP in patients with ADHF.2–5

Repeated measurements and the change in biomarker over time are known to have additive prognostic value compared to single measurements, because the hemodynamic status changes over time after ADHF. The prognostic value of serial measurements of BNP, NT-proBNP and ST2 has been investigated in patients with HF.18,20–23 Recently, Dabbah et al reported that an increase in RDW during hospital stay was associated with poor clinical outcomes, and demonstrated the prognostic importance of serial measurements of RDW in patients with acute myocardial infarction.8 In the present study we observed that positive RDWΔMdis-adm could significantly predict adverse CV events, but positive RDWΔdis-adm could not, although there was a significant correlation between RDWΔMdis-adm and RDWΔdis-adm. Also, we did not find a significant difference in CV events according to absolute change of RDWΔMdis-adm (data not shown). This discrepancy could be explained by the relatively small size of the present subject cohort. Thus, we expect that significant predictive power of positive RDWΔdis-adm could be demonstrated in a large-scale study in the future. The present results show that CV mortality was not different between the positive RDWΔMdis-adm and the no-positive RDWΔMdis-adm groups. This might be because we did not include in-hospital mortality in the present study. One of the main CV events is in-hospital death in patients with ADHF. In addition to RDWΔMdis-adm, RDWadm was also an independent predictor for CV events in the multiple Cox regression model, which is compatible with previous studies.2,3,5 Moreover, the high RDWadm and the positive RDWΔMdis-adm groups had a significantly higher number of CV events than the other groups. Therefore, positive RDWΔMdis-adm has an increased prognostic value compared to RDWadm for the prediction of CV events in ADHF patients.

RDW as a Surrogate Marker of Multiple Pathophysiologies in HF

It is unclear whether RDW has a pathophysiological role in HF or whether it simply identifies a population with severe LV dysfunction. Several mechanisms, however, have been suggested to explain the increase in RDW and how it works as a prognostic marker in patients with ADHF. First, persistent inflammation is known to be a principal pathophysiologic finding and poor prognostic factor for HF.24 Several studies have shown that increased RDW levels in patients with ADHF are associated with increased inflammatory status.25,26 Second, an increase in RDW is associated with increased oxidative stress that characterizes exacerbation of heart failure.27,28 Because oxidative stress is related to red cell survival, it could explain the increase in RDW in ADHF patients.29 Third, increased RDW may be associated with increased hemodynamic overload, which is important in the mechanism of HF exacerbation. Our previous study demonstrated that high RDW levels were significantly associated with elevated early mitral inflow velocity to early diastolic mitral annular velocity (E/E’) after adjusting NT-proBNP.19 Furthermore, a high RDW was correlated with higher erythropoietin, lower serum iron and total iron binding capacity saturation in patients with chronic HF.26 This means that the ability to mobilize and use iron stores may be impaired. Finally, a recent report showed that increased RDW was associated with troponin T, a marker of myocardial injury.30 All these suggested mechanisms may explain why RDW is an independent predictive and prognostic marker in patients with ADHF, indicating that RDW may be a new surrogate marker of multiple pathophysiologic processes in ADHF.

Study Limitations

First, we did not measure NT-proBNP levels at discharge/1 month after discharge and could not compare the prognostic power of RDW change with that of NT-proBNP change due to limitations of the retrospective study design. Further prospective studies are needed to show whether serial measurements of RDW have increased prognostic value compared to well-known markers such as NT-proBNP and ST2.18,21 Second, we did not analyze the data for in-hospital mortality and CV events within 1 month, indicating that the present study may not be free from selection bias, although it was inevitable according to study design. Third, we could not demonstrate prognostic power of baseline LVEF and NT-proBNP level in the present analysis, despite the general concepts in HF. This might be due to the relatively skewed data measured in acute decompensated status. Fourth, we could not investigate hematologic laboratory parameters (eg, total iron binding capacity, serum ferritin level), which could help to distinguish the origin of increased RDW, even though we excluded the patients with transfusion or iron replacement therapy.31 Finally, the present
study group was characterized by a relatively low proportion of ischemic HF and β-blocker use, which may influence the present results. Therefore, a well-designed larger prospective study should be conducted in order to emphasize the clinical importance and application of repeated measurements of RDW after ADHF.

Conclusions

We have shown that repeated measurements of RDW increase the likelihood of predicting CV events compared to single measurements of RDW in ADHF patients. We found that positive RDW after ADHF is a simple and inexpensive method that may assist in determining CV risk in patients with ADHF.

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Disclosure

No conflict of interest declared.

References