Red blood cell distribution width is an independent predictor of mortality in acute kidney injury patients treated with continuous renal replacement therapy

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Abstract

Background. A potential independent association was recently demonstrated between high red blood cell distribution width (RDW) and the risk of all-cause mortality in patients with cardiovascular disease, although the mechanism remains unclear. However, there have been no reports on the relationship between RDW and mortality in acute kidney injury (AKI) patients treated with continuous renal replacement therapy (CRRT). In this study, we assessed whether RDW was associated with mortality in AKI patients on CRRT treatment in the intensive care unit (ICU).

Methods. We enrolled 470 patients with AKI who were treated with CRRT at the Yonsei University Medical Center ICU from August 2007 to September 2009 in this study. We performed a retrospective analysis of demographic, biochemical parameters and patient outcomes. Following CRRT treatment, 28-day all-cause mortality was evaluated.

Results. At the initiation of CRRT treatment, RDW level was significantly correlated with white blood cell count, hemoglobin (Hb) and total cholesterol. Patients with high RDW levels exhibited significantly higher 28-day mortality rates than patients with low RDW levels (P < 0.01). Baseline RDW level, Sequential Organ Failure Assessment (SOFA) score, low mean arterial pressure (MAP) and low cholesterol levels were independent risk factors for mortality. In multivariate Cox proportional hazard analyses, RDW at CRRT initiation was an independent predictor for 28-day all-cause mortality after adjusting for age, gender, MAP, Hb, albumin, total cholesterol, C-reactive protein and SOFA score.

Conclusion. Our study demonstrates that RDW could be an additive predictor for all-cause mortality in AKI patients on CRRT treatment in the ICU.

Keywords: acute kidney injury; continuous renal replacement therapy; mortality predictor; red blood cell distribution width

Introduction

Red blood cell distribution width (RDW), which expresses variation in size of circulating erythrocytes, is routinely reported as part of a complete blood cell count [1]. Red blood cells (RBCs) have a standard size, but disorders related to ineffective erythropoiesis or increased destruction cause greater heterogeneity in size and a higher RDW [2]. RDW is used to differentiate the causes of anemia and is a predictive marker for mortality in various cohorts as demonstrated in observational studies. Recent studies have reported a strong independent association between increased RDW and the risk of adverse outcomes in patients with heart failure and coronary heart disease [3, 4]. Moreover, RDW has been found to be predictive of all-cause death in two community-based cohorts regardless of hemoglobin (Hb) levels and anemia status [5]. Although a recent study suggested that higher RDW is associated with systemic inflammation and undernutrition and represents an integrative measure of the pathological process [6], the mechanism for the association between RDW and mortality remains unclear.

Acute kidney injury (AKI) is a common and serious problem in critically ill patients and is an independent risk factor for mortality in patients admitted to the intensive care unit (ICU) [7]. Continuous renal replacement therapy (CRRT) is the established treatment modality in critically ill patients with AKI in the ICU [8]. Several predictors of survival in patients on CRRT have been described based on cross-sectional and retrospective studies [9, 10]. However, the relevance of RDW to mortality risk in AKI patients treated with CRRT has rarely been addressed. In this study, we explored whether RDW is associated with mortality in AKI patients receiving CRRT treatment at a single ICU center in Korea.

Materials and methods

Patients

Clinical and laboratory data were retrieved from the Yonsei CRRT Database. We enrolled 632 patients who started CRRT from August 2007 to
September 2009 in the present study. We excluded 162 patients who died within the first 24 h of CRRT treatment, who were <18 years of age, who were on chronic dialysis or were diagnosed with terminal malignancy. A total of 470 patients were included in the study. Demographic, clinical, biochemical data at the time of CRRT initiation and echocardiographic parameters at the time of ICU admission were recorded. For disease severity assessment, Sequential Organ Failure Assessment (SOFA) score was evaluated at the initial time of CRRT treatment.

**ICU setting**

The investigational site was a self-contained, 99-bed medical and surgical ICU in a 2076-bed teaching hospital in Korea, and there are 12 CRRT machines in this ICU. The decision to start CRRT was made by the nephrologist in charge of the patient, and the trained and educated nurses executed and maintained the system.

**CRRT protocol**

Vascular access for CRRT was achieved via either the femoral vein, the internal jugular vein or the subclavian vein. Continuous veno-venous hemofiltration (CVVHDF) was performed in most of the patients using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Gambro, Hechingen, Germany) platform. CRRT was initiated at a blood flow rate of 100 mL/min which was gradually increased to a rate of 150 mL/min. The dose of ultrafiltration was targeted to 40 mL/kg/h and Hemosol (Gambro) was replaced by predilution method.

**Laboratory assessment**

Hb levels, hematocrit and RDW were measured at the initiation of CRRT treatment, using the Advia 2120 Hematology Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). RDW is reported as a coefficient of variation (percentage) of RBC volume. The reference range for RDW in our laboratory is 11.5–14.5%. Glomerular filtration rate was calculated using the simplified Modification of Diet in Renal Disease equation.

**Echocardiography assessment**

Echocardiography was performed at the time of ICU admission with a portable PROSOUND ALPHA10 echocardiograph (ALOKA, Tokyo, Japan) according to our ICU policy.

**Statistical analysis**

Continuous variables are presented as mean ± SD and categorical variables as numbers and percentages. Based on RDW level, we divided patients into a higher RDW group (≥14.6%) and a normal RDW group (<14.6%). Baseline characteristics of the groups were compared using Student’s t-test for continuous variables and using χ²-test for categorical variables. We evaluated 28-day all-cause mortality as study endpoints. Survival curves were designed using the Kaplan–Meier method, and comparisons were made using the log-rank test. Survival analysis was also performed according to SOFA score as an established risk factor. For this analysis, patients were divided into two groups by 11.0 of SOFA score, which was previously reported to have a high discriminated power on mortality in ICU patients [13]. Prognostic variables for mortality were analyzed by using the univariate Cox proportional hazards model, and variables with P-value <0.1 were used in multivariate Cox proportional hazards model. The univariate and multivariate Cox regression analysis are presented as hazard ratios (HRs) and the 95% confidence interval. Additional Cox proportional hazard analysis was performed by using RDW as a continuous variable. We made a plot of cumulative martingale residual and RDW, and we checked the assumption of linearity hold for RDW in the Cox model after Kolmogorov-type supremum test by 1000 simulation based on residual pattern (P = 0.254), using SAS (version 9.1.3, SAS Institute Inc. Cary, NC). We conducted receiver operating characteristic (ROC) analysis to compare the predictive accuracy of RDW and SOFA score and the area under the curve (AUC) was calculated. In addition, we graded by RDW group on a scale of 1–2 (normal RDW group, 1; and higher RDW group, 2) and added to baseline SOFA score. AUC was calculated for RDW levels, SOFA score and SOFA score plus graded RDW score. Differences were considered statistically significant at the two-sided P < 0.05 level. Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL).

**Results**

### Population characteristics

Baseline characteristics of patients divided according to RDW binaries are presented in Table 1. RDW ranged from 11.7 to 28.0% (mean 15.7% ± 2.3 SD), and 317 patients (67.5%) had RDW above the upper limit of normal (≥14.6%). Patients with high RDW values had higher white blood cell (WBC) counts. They had lower Hb and cholesterol levels compared to patients with normal RDW values. However, there were no significant differences in age, sex, mean arterial pressure (MAP), SOFA score, creatinine, estimated glomerular filtration rate (eGFR), albumin, iron profile (iron, total iron-binding capacity, transferrin saturation) and echocardiographic parameters between the two groups.

According to RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) stratum, CRRT was started at ‘Risk’ stage in 140 (29.7%) patients. There was no significant difference in RDW levels and total SOFA score among RIFLE stratum. However, compared with SOFA score except for renal score, the score of the patients in the Risk stage was higher than in the ‘Failure’ stage (9.9 ± 2.4 versus 8.9 ± 2.6) although statistically not significant (P = 0.089).

On the point of anticoagulation, 364 (77.4%) patients received anticoagulation and unfractionated heparin was the most common choice of anticoagulation (49.1%). The remaining patients were treated with various kinds of anticoagulant (e.g. nafamostat mesilate or low-molecular weight heparin). In a while after some time, 106 (22.6%) patients did not receive any drugs for circuit anticoagulation.

### Associations between RDW values and other parameters

There were significant positive correlations between baseline RDW values and WBC (r = 0.12, P < 0.05) and SOFA score (r = 0.18, P < 0.01). In contrast, baseline RDW values were negatively correlated with Hb (r = −0.20, P < 0.01) and cholesterol (r = −0.16, P < 0.01). There were no correlations between RDW level and age, C-reactive protein (CRP), eGFR, albumin, left ventricular ejection fraction and left ventricular end-diastolic dimensions (Table 2).

### Comparisons between the death and survival group during the study period

During the study period, 295 (62.8%) patients had died by Day 28. Based on patient deaths within 28 days, patients were classified as death and survivor groups. In the death group, the RDW value (16.0 ± 2.5 versus 15.3 ± 1.9%, P < 0.01) and SOFA score (12.9 ± 3.1 versus 10.3 ± 2.7, P < 0.01) were significantly higher, while MAP was significantly lower (77.4 ± 15.6 versus 85.4 ± 17.4 mmHg, P < 0.01) compared with those in the survivor group. However, there were no differences in presence of sepsis (68.8 versus 61.1%, P = 0.112), in the history of operation (27.2 versus 30.1%, P = 0.140), in Charlson’s comorbidity indices (5.3 versus 5.1, P = 0.663) and in intervals from ICU admission to CRRT start between death and survivor group (4.0 versus 3.3 days, P = 0.139). All patients reached values of ultrafiltration of at least 80% of prescribed dose, and there was no significant
The 28-day mortality rate was significantly higher in the elevated RDW group (P < 0.05, Figure 1A) and in patients with high SOFA score (P < 0.01, Figure 1B) compared to the normal RDW group and in patients with low SOFA score. Combining these two factors, patient survival was the lowest in patients with both high RDW and SOFA score (P < 0.01, Figure 1C). Furthermore, higher RDW group revealed lower survival rate even in the same SOFA score group (P < 0.05, Figure 1C). Univariate Cox regression analysis revealed increases in mortality risk in the higher RDW group and in patients with increased CRP levels, high SOFA score, hypoalbuminemia, low cholesterol levels and decreased MAP (Table 3). The higher RDW group remained robust as a significant predictor of 28-day mortality even after adjustment for age, gender, CRP, Hb, albumin, total cholesterol, MAP and SOFA score (HR 1.230, P < 0.05 in Table 4). Furthermore, in a multivariate Cox regression analysis using RDW as a continuous variable, high RDW levels (per 1% increase, HR 0.996, P < 0.05) and decreased MAP (per 1 mmHg increase, HR 1.063, P < 0.05) were independent risk factors for 28-day all-cause mortality when adjusted for age, gender, CRP, albumin and Hb levels (Table 3).

The ROC curves using variables (RDW value, SOFA score plus graded RDW score) are plotted in Figure 2. The AUCs of RDW value and SOFA score (92.1% for 28-day mortality) were significantly higher than those of RDW value alone (74.6%) and SOFA score alone (71.1%). Furthermore, the AUC combined with SOFA and graded RDW score was 98.7% for 28-day mortality.

**Discussion**

The results of our study indicate that RDW level is an independent predictor of mortality and is in addition to
other established prognostic variables such as SOFA score in AKI patients treated with CRRT in the ICU. When the patients were divided into two groups according to baseline RDW levels, the survival rate was significantly lower in the higher RDW group compared with the normal RDW group. In addition, for each 1% increase in RDW level as a continuous variable, 28-day mortality rate was increased by 6.3%, when adjustments were made for age, gender, MAP, Hb, albumin, total cholesterol, CRP and SOFA scores by Cox proportional hazards model. Therefore, RDW appears additive to other established prognostic variables such as SOFA score [11, 12].

In patients with chronic heart failure or ischemic heart disease, RDW is regarded as a potential predictor of mortality [3, 4, 13–15]. Epidemiologic cohort studies have also demonstrated that higher RDW level is associated with deaths from cardiovascular disease, cancer and any other cause [16]. Previous studies suggest that the relevance of higher RDW to mortality risk is related to chronic pathological conditions and is not specific to a single organ system or process [17]. Moreover, a recent study carried out in patients with acute heart failure suggests that RDW has prognostic significance in acute conditions [18]. Our study adds to the evidence that baseline RDW is a significant determinant of mortality in AKI patients requiring CRRT. Taken together, we surmise that RDW may be a potent marker of mortality not only in chronic conditions but also in acute phase of diseases.

RDW is a coefficient of variation of RBC size and, when elevated, reflects the state of anisocytosis [1, 2]. RDW is typically elevated in conditions of ineffective red cell production (including iron deficiency, vitamin B12 or folate deficiency and hemoglobinopathies), increased red cell destruction and following blood transfusion [19–22]. The elevation of RDW has been associated with other disease processes including liver disease, malnutrition, occult colon cancer and neoplastic metastases to marrow [23–25]. RDW could also be elevated in patients with renal impairment. Lippi et al. [26] demonstrated that increasing RDW levels were associated with declining residual renal functions independent of age, gender, mean corpuscular volume and Hb values. In the present study, elevation of RDW values was common among AKI patients, occurring in ~60% of patients and was found to have a significant association with patient outcomes.

Although the underlying mechanism for the association between RDW values and mortality is not fully understood, several plausible explanations have been suggested in prior reports. Systemic inflammation has been shown to predict progressive illness, cardiovascular mortality and death in ICU patients. Systemic inflammatory response impacts bone marrow function and iron metabolism [27, 28] and proinflammatory cytokines have been found to inhibit erythropoietin-induced erythrocyte maturation and proliferation and downregulate erythropoietin receptor expression, which is associated with RDW increases [29]. A recent study has been demonstrated that RDW is related to CRP levels, which is known as acute phase reactant, and is significantly associated with worse outcomes in patients with heart failure [30]. In this study, we observed that RDW significantly correlated with WBC count, supporting the notion that increased systemic inflammatory response could partly participate to the increasing RDW levels in AKI patients. The other explanation may be related to malnutrition. Malnutrition is well-known to affect clinical outcomes of

Fig. 1. Kaplan–Meier plots for cumulative 28-day survival. Patients with high RDW levels (A) or high SOFA scores (B) showed significantly lower survival rates than patients with normal RDW levels or low SOFA scores (P < 0.05 and P < 0.01). These two factors combined together (C), patient’s survival was the lowest in patients with both high RDW levels and SOFA scores (P < 0.01).
AKI patients as well as end-stage renal disease patients [31]. Since AKI patients have an increased catabolic state, malnutrition is common in AKI patients, especially those patients requiring CRRT [32]. It is well documented that malnutrition is also significantly related to high RDW levels. A recent report showed that low cholesterol is associated with mortality and is strongly correlated with higher RDW levels [6, 33]. In this study, RDW was significantly correlated with WBC count as a systemic inflammatory marker and low cholesterol level as a malnutrition marker. Taken together, these findings suggest that malnutrition and inflammation could be associated with adverse outcomes in critically ill patients and that RDW may be an integrative marker of this complex malnutrition–inflammation syndrome [6].

However, because RDW was independently associated with all-cause mortality after adjustment for CRP and cholesterol level, these proposed explanations should not be the only reasons for the association between RDW and mortality. Todd et al. [17] also demonstrated that the relation of RDW to mortality risk may not entirely depend on inflammation because the risk associated with RDW was not significantly diminished in participants with a low CRP level compared to those with a high CRP level. Further study is needed to clarify the mechanism for the association between RDW values and mortality afterward.

Our study had several potential limitations that should be noted. Firstly, despite the fact that our results were based on a large sample, this study was a retrospective cohort study without a prespecified hypothesis. The characteristics of the study patients were quite heterogeneous and risk factors for mortality in patients requiring CRRT are frequently interrelated. Given the large numbers of potential predictors evaluated and the initial lack of hypothesis-guided selection of variables, we could not rule out the possibility of residual confounding. Secondly, despite a single measure of RDW levels that could have reflected acute changes in RDW induced by blood loss or hemolysis, we did not evaluate fluctuations in RDW levels and thus could not account for possible variation over time. In addition, we could not evaluate use of erythropoietin or reticulocyte count that might have affected RDW values. Despite these limitations, a major strength of this study is that it is based on a relatively large

### Table 3. Cox proportional hazards analysis for 28-day mortality using RDW as a continuous variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>P-value</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDW (per 1% increase)</td>
<td>1.066 (1.020–1.115)</td>
<td>&lt;0.01</td>
<td>1.063 (1.011–1.17)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.014 (1.004–1.025)</td>
<td>&lt;0.01</td>
<td>1.007 (0.996–1.019)</td>
<td>0.190</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>0.981 (0.920–1.045)</td>
<td>0.553</td>
<td>0.996 (0.925–1.071)</td>
<td>0.905</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>0.769 (0.630–0.938)</td>
<td>&lt;0.05</td>
<td>0.874 (0.695–1.099)</td>
<td>0.249</td>
</tr>
<tr>
<td>T. chol (mg/dL)</td>
<td>0.994 (0.991–0.997)</td>
<td>&lt;0.01</td>
<td>0.996 (0.993–0.999)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.981 (0.974–0.988)</td>
<td>&lt;0.01</td>
<td>0.983 (0.975–0.991)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SOFA score</td>
<td>1.230 (1.172–1.291)</td>
<td>&lt;0.01</td>
<td>1.200 (1.139–1.264)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (per 1 year increase)</td>
<td>0.997 (0.980–1.005)</td>
<td>0.496</td>
<td>1.000 (0.991–1.008)</td>
<td>0.909</td>
</tr>
<tr>
<td>Male (versus female)</td>
<td>1.130 (0.887–1.440)</td>
<td>0.324</td>
<td>0.941 (0.723–1.225)</td>
<td>0.652</td>
</tr>
<tr>
<td>Presence of sepsis (versus non-sepsis)</td>
<td>1.215 (0.950–1.555)</td>
<td>0.120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIFLE (versus risk stage)</td>
<td></td>
<td>0.320</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury stage</td>
<td>1.119 (0.838–1.493)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure stage</td>
<td>1.271 (0.931–1.736)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>1.003 (0.996–1.010)</td>
<td>0.421</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>0.999 (0.981–1.017)</td>
<td>0.879</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA vol index (mL/m²)</td>
<td>0.997 (0.989–1.005)</td>
<td>0.517</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aHR, hazard ratio; T. chol, total cholesterol; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LA vol index, left atrial volume index.*

*bMultivariate model; adjusted for age, gender, CRP, Hb, albumin, total cholesterol, MAP and SOFA score.*

### Table 4. Cox proportional hazards analysis for 28-day mortality according to RDW group

<table>
<thead>
<tr>
<th>RDW Group</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher RDW group (RDW ≥ 14.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.288</td>
<td>1.023–1.620</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.230</td>
<td>1.020–1.593</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.212</td>
<td>1.011–1.712</td>
</tr>
</tbody>
</table>

*CI, confidence interval. Model 1: unadjusted relative risk, Model 2: adjusted for age, gender, CRP, Hb, albumin, total cholesterol, MAP and SOFA score, Model 3: adjusted for Model 2 plus sepsis, dose of ultrafiltration, history of operation and RIFLE stage.*

Fig. 2. The ROC curves using variables (RDW value, SOFA score and SOFA score plus graded RDW score). The AUCs of RDW value and SOFA score for 28-day mortality were 0.586 and 0.694, respectively, (P < 0.01). Moreover, the AUC combined with SOFA and graded RDW score was 0.746 (P < 0.01).
number of patients requiring CRRT. Moreover, because the same ICU policy was applied to the patients in a single center, the patients in our study experienced no differences in ICU care such as decision-making process of CRRT, and there were a few missing data sets. Although our data clearly support an association between RDW and adverse outcomes in critically ill patients requiring CRRT as demonstrated in prior cohort studies, additional prospective studies are required to evaluate these findings.

In conclusion, we found that higher RDW could be independently associated with the risk of all-cause mortality in AKI patients treated with CRRT. This finding suggests that RDW may aid in risk stratification and can represent a less expensive marker to predict adverse outcomes in critically ill patients with AKI.

Acknowledgements. This work was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A084001).

Funding. None declared.

Conflict of interest statement. None declared.

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Received for publication: 4.1.11; Accepted in revised form: 2.5.11