Red blood cell distribution width at admission predicts outcome in critically ill patients with kidney failure: a retrospective cohort study based on the MIMIC-IV database

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ABSTRACT

Purpose: We aimed to explore whether red blood cell distribution width (RDW) could serve as a biomarker to predict outcomes in critically ill patients with kidney failure in this study.

Materials and methods: This retrospective study was conducted with the Medical Information Mart for Intensive Care IV (MIMIC-IV). A total of 674 patients were divided into three groups based on tertiles of RDW. We used the generalized additive model, Kaplan–Meier curve, and Cox proportional hazards models to evaluate the association between RDW and clinical outcomes. We then performed subgroup analyses to investigate the stability of the associations between RDW and all-cause mortality.

Results: Nonlinear and J-shaped curves were observed in the generalized additive model. Kaplan–Meier analysis showed that patients with elevated RDW had a lower survival rate. The Cox regression model indicated that high levels of RDW were most closely associated with ICU mortality and 30-day mortality (HR = 4.71, 95% CI: 1.69–11.64 and HR = 6.62, 95% CI: 2.84–15.41). Subgroup analyses indicated that the associations between RDW and all-cause mortality were stable.

Conclusions: Elevated levels of RDW were associated with an increased risk of all-cause mortality, and RDW could be an independent prognostic factor for kidney failure.

1. Introduction

Chronic kidney disease (CKD) is a serious public health problem worldwide, placing a huge economic burden on health care systems and dramatically influencing quality of life [1,2]. Diabetes mellitus and hypertension are the most common primary causes of CKD, followed by glomerulonephritis, nephrolithiasis, and polycystic kidney disease [3]. As reported, the prevalence of CKD is approximately 8.6% in men and 9.6% in women among people over age 20 in high-income countries [4]. It is disappointing that the prevalence will continue to increase due to aging of the population and increased prevalence of risk factors that contribute to CKD, such as diabetes mellitus and hypertension [5]. Currently, CKD is classified into five stages based on a decreased estimated glomerular filtration rate (eGFR) and increased urinary albumin-creatinine ratio (ACR) [6]. When the eGFR is less than 15 mL/min/1.73 m², it means that chronic kidney disease enters stage 5.

The progression to kidney failure (also called end-stage kidney disease ESKD) is one of the most important disease-related complications for patients with CKD. There may be no obvious discomfort in the early stage of kidney failure, but with the progressive decline of kidney function, the toxin further accumulates in the body, which can cause various symptoms of uremia, such as nausea, vomiting, poor appetite, skin pruritus, ammonia odor, edema, and anemia [7,8]. Kidney replacement treatment (KRT) such as dialysis or kidney transplant is required for the survival of kidney failure patients [9]. In many high-income countries, kidney failure patients account for approximately 0.1% of the total population, but 1–2% of health care expenditures [4]. Prognostic biomarkers can provide useful information for more elaborate risk classification, effective health care management, and delivery of the best patient care possible.

Red blood cell distribution width (RDW) is a parameter that indicates the size variation of red blood...
cells (RBCs). Increased size variability of RBCs is defined as anisocytosis. It is commonly used to identify different types of anemia in clinical practice. Its normal baseline range varies from 11.5% to 14.5% [10]. Recently, increasing numbers of researchers have focused on the predictive roles of RDW for mortality in critically ill patients. For instance, some studies show that there are correlations between RDW and outcomes of patients admitted to intensive care units (ICUs), such as diabetic ketoacidosis [11], sepsis [12], cardiogenic shock [13], acute respiratory distress syndrome (ARDS) [14], and acute kidney injury (AKI) [15]. Relevant literature had obtained that the increase of RDW predicted the mortality of patients with kidney failure [16,17]. However, the temporal change of its predictive effect was unknown. We aimed to explore whether the baseline of RDW could be used as a biomarker to predict the clinical outcomes of kidney failure patients in the ICU, and its predictive effect over time.

2. Materials and methods

2.1. Database

All data were extracted from the Medical Information Mart for Intensive Care IV database (MIMIC-IV version 1.0), a publicly accessible database updated in March 2021, and maintained by the Department of Medicine at Beth Israel Deaconess Medical Center and the Laboratory for Computational Physiology at Massachusetts Institute of Technology. MIMIC-IV contains comprehensive information for patients admitted to the Beth Israel Deaconess Medical Center from 2008 to 2019 [18]. Any credentialed user of the PhysioNet can freely access the database. A modular approach is adopted when organizing data to highlight the data source. The data were rooted in two in-hospital database systems: a custom hospital-wide electronic health record (EHR) and an ICU-specific clinical information system. The database is comprised of details of over 500,000 hospital admissions and 70,000 ICU admissions. The identities of all patients in this database were eliminated to protect their privacy. One of our coauthors, Xuefang Liu, participated in an online training course to obtain access to the database. She passed two exams termed (“Conflicts of Interest” and ‘Data or Specimens Only Research’) and obtained access to this database (certification number: 43645869).

2.2. Patient selection

A total of 14,807 hospital admitted patients diagnosed with kidney failure were identified from the database using the ICD-9 code. Among the patients, 3914 were admitted to the ICU. We further excluded repeat ICU and hospital admissions, keeping only the first admission to the ICU according to admission time to the ICU. Patients who had accompanying neoplastic disease or acquired immune deficiency syndrome (AIDS) were not within the scope of our study. Patients in the ICU for less than 24 h or without RDW values within 24 h after admission were also excluded. We further excluded those who underwent kidney transplantation or lacked dialysis-related information. Finally, 674 patients were enrolled in this study.

2.3. Data extraction

We conducted our study with the MIMIC-IV database by using Structured Query Language (SQL) and PostgreSQL software (version 9.6.22). These data included RDW, age, sex, laboratory results, the status of kidney replacement therapy, severity scores, comorbidities, admission time, discharge time, ICU-intime, ICU-outtime, and date of death. If RDW were measured for several times within 24 h after admission to the ICU, we used the first measurement value. The severity score, calculated according to the physiological and laboratory parameters for prognosis estimation, including sequential organ failure assessment (SOFA) [19], acute physiology score III (APS III), simplified acute physiology score II (SAPSII) [20], the Oxford acute severity of illness score (OASIS) [21], the systemic inflammatory response syndrome (SIRS) status [22], and the logistic organ dysfunction system (LODS) score [23] was extracted from the MIMIC-IV database. The laboratory results included hemoglobin, platelets, WBC, MCV, anion gap, bicarbonate, BUN, calcium, chloride, creatinine, glucose, sodium, and potassium. The comorbidities included myocardial infarction, chronic heart failure, peripheral vascular disease, chronic pulmonary disease, diabetes, cerebrovascular disease, and severe liver disease. We detected whether multicollinearity existed in regression analyses by a variance inflation factor (VIF) with a reference value of 5 [24,25]. The clinical outcomes in our study included ICU mortality, 30-day mortality, 180-day mortality, and 1-year mortality from the date of ICU admission.

2.4. Statistical analysis

The Kolmogorov–Smirnov test was used to estimate whether continuous variables were normally distributed. Due to the absence of normal distribution for our continuous data, they were presented as medians (first quartile – third quartile). Differences between the
groups were identified using Kruskal–Wallis H tests. Categorical variables are presented as numbers and percentages. The Chi-squared test was applied to determine any significant differences between the groups. p < 0.05 was defined as statistically significant in this analysis. A generalized additive model (GAM) was used to identify the relationship between RDW and ICU mortality and 30-day, 180-day, and 1-year all-cause mortality. We conducted a Kaplan–Meier curve to analyze the potential association between RDW and survival rates according to tertiles of RDW.

The Cox regression model was used to evaluate the relationships between RDW tertiles and all-cause mortality. The results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). We incorporated variables including demographic characteristics, the status of kidney replacement therapy, severity score, and comorbidity as confounders, and they were included in the multivariate logistic regression analysis. Based on previous literature, the first tertile group was chosen as the reference. In Model I, we merely adjusted for age and sex. In model II, we further adjusted for the status of kidney replacement therapy, SOFA, APSIII, OASIS, SAPSII, SIRS, LODS, myocardial infarction, chronic heart failure, peripheral vascular disease, chronic pulmonary disease, diabetes, cerebrovascular disease and severe liver disease. Subgroup analyses were performed to investigate whether the predictive effect of RDW differed across various subgroups, including age, sex, the status of RRT, severity scale score, and comorbidity.

We performed all statistical analyses with R (http://www.R-project.org) and EmpowerStats (http://www.empowerstats.com/en/, X&Y solutions, Inc., Boston, MA).

3. Results

3.1. Subject characteristics

According to the exclusion criteria mentioned above, 674 patients diagnosed with kidney failure were finally enrolled in our study. The selection process is shown in Figure 1. Patients were divided into three groups on the basis of the tertiles of RDW. A total of 223 patients were in the low-RDW group, 221 patients in the middle-RDW group, and 230 patients in the high-RDW group. Their basic characteristics are summarized in Table 1. Patients with high levels of RDW were more likely to have higher values of APSIII and lower levels of hemoglobin and glucose, and to report comorbidities of severe liver disease. All-cause mortality in patients with middle and high levels of RDW was significantly higher compared with those with low levels of RDW.

3.2. RDW levels and clinical outcomes

We found that the relationships between the RDW and the all-cause mortality for each endpoint were nonlinear, as shown by the J-shaped curve in Figure 2. The Kaplan–Meier curve displayed survival rates of subjects with different RDW levels in Figure 3. The results indicated that higher RDW levels were significantly associated with decreased survival rates (p < 0.001).

A Cox proportional hazards regression model was further employed to determine the associations between RDW and all-cause mortality for each endpoint in patients with kidney failure (Table 2). The lower RDW group (RDW < 15.4) was used as the reference. If only adjusting for age and sex, middle levels of RDW associated with an increased risk of ICU and 1-year all-cause mortality compared with low levels of RDW in Model I (ICU mortality: HR = 2.29, 95% CI: 1.09, 4.81, and 1-year mortality: HR = 1.91, 95% CI: 1.11–3.28) (p < 0.05). High levels of RDW were associated with an increased risk of all-cause mortality for each endpoint (ICU mortality: HR = 3.06, 95% CI: 1.50–6.25; 30-day mortality: HR = 4.31, 95% CI: 2.26–8.22; 180-day mortality: HR = 3.56, 95% CI: 2.10–6.03; 1-year mortality: HR = 3.52, 95% CI: 2.11–5.86). In Model II, middle levels of RDW remained independently correlated with
increased risks of ICU mortality and 30-day, 180-day, and 1-year all-cause mortality after adjustment for age, sex, laboratory results, kidney replacement therapy, SOFA, APSII, OASIS, SAPSII, SIRS, LODS, myocardial infarction, chronic heart failure, peripheral vascular disease, chronic pulmonary disease, diabetes, cerebrovascular disease, and severe liver disease. The HRs for 30-day, 90-day, 180-day, and 1-year outcomes were 3.81 (1.48, 9.77), 2.85 (1.22, 6.68), 2.55 (1.28, 4.92), and 2.51 (1.37, 4.77) ($p < 0.05$), respectively, in patients with middle levels of RDW. High levels of RDW were associated with an increased risk of all-cause mortality for each endpoint in model II (ICU mortality: HR = 4.71, 95% CI: 1.69–11.64; 30-day mortality: HR = 6.62, 95% CI: 2.84–15.41; 180-day mortality: HR = 4.43, 95% CI: 2.41–9.21; 1-year mortality: HR = 4.08, 95% CI: 2.19–7.62).

### 3.3. Subgroup analysis

As shown in Table 3, subgroup analyses were performed to investigate the stability of the associations between RDW levels and one-year all-cause mortality. The associations were similar in every strata, and there were no interactions ($p > 0.05$).

### 4. Discussion

Dialysis therapies have been remarkably improved in the 1990s and 2000s. The potential to scale the use of dialysis to treat large numbers of patients with kidney failure is exciting. Regrettably, among populations with access to dialysis, mortality remains unacceptably high, mainly driven by cardiovascular events and infection [26,27]. In our present study, of the 674 enrolled...
patients who received their first dialysis treatment, approximately 20% died within one year after their first admission to the ICU.

Several scoring systems are used to evaluate prognosis and develop personalized treatment plans for patients admitted to the ICU [28,29], but none of them are specific to kidney failure patients. More importantly, the scoring system generally contains many parameters, which does not allow clinicians to quickly determine the prognosis of kidney failure patients. Therefore, easily accessible predictive biomarkers for kidney failure patients are urgently needed for clinical practice. RDW has emerged as a novel prognostic marker for serious adverse events in recent decades. An increasing number of researchers are focusing on the role of RDW in kidney disease [30,31]. Aktepe OH et al. revealed that a high RDW level was significantly associated with worse survival outcomes in patients with metastatic kidney cell carcinoma treated with targeted therapy [32].

Zou et al. showed that elevated levels of RDW might be an independent prognostic factor for severe and poor prognosis of AKI in patients undergoing cardiac surgery [33].

One meta-analysis by Zhang et al. suggested that high levels of RDW were probably associated with increased risks of all-cause mortality in CKD patients [30]. We observed a J-shaped, nonlinear relationship between RDW level and ICU, 30-day, 180-day, and 1-year all-cause mortality. The Kaplan–Meier curve indicated that patients with middle and high levels of RDW had a lower survival rate. After adjusting for potential confounders, middle and high levels of RDW were associated with an increased risk of ICU, 30-day, 180-day, and 1-year all-cause mortality in critically ill patients with kidney failure. High levels of RDW were most closely associated with ICU mortality and 30-day mortality. The predictive effect of RDW on the risk of all-cause mortality gradually declined as follow-up time.

Figure 2. Association between RDW and all-cause mortality. (A) ICU all-cause mortality; (B) 30-day all-cause mortality; (C) 180-day all-cause mortality; (D) 1-year all-cause mortality.
increased. Therefore, the value of RDW could provide useful information for risk classification to clinicians and caregivers and help to identify patients with a high risk of death in the ICU.

In terms of the results of the subgroup analysis, there were no interactions in every strata. RDW was a risk factor in all of these interactive stratifications. This confirmed that the relationship between RDW and all-cause mortality was stable.

Regarding the underlying mechanisms between higher RDW levels and elevated all-cause mortality of patients with kidney failure, malnutrition, systemic inflammation, and oxidative stress (OS) have been proposed as possible etiologies. First, malnutrition is known to increase RDW, which is common in patients on dialysis in terms of dialysis-induced nutrient losses and the implementation of a low protein diet [34,35]. Second, inflammation inhibits iron metabolism and the hematopoietic function of bone marrow. Research has confirmed that proinflammatory cytokines can downregulate the expression of erythropoietin receptor and thereby inhibit erythropoietin-induced RBC maturation and proliferation [36,37], which is related to increased RDW. Finally, increased heterogeneity of RBCs might result from OS [38,39]. OS is present even in the early stages and is further exacerbated by dialysis due to contact with the dialysis membrane via blood, low levels of vitamins C and E, reduced selenium levels, and decreased activity of the glutathione system [40]. Altogether, it is probable that patients with kidney failure would have elevated levels of RDW. In our study, we confirmed that a higher RDW level was associated with all-cause mortality after adjusting for potential confounders.

Several limitations need to be mentioned in the study. First, this study was a single-center observational study, and inherent selection biases were inevitable. To confirm this conclusion, prospective research with a

Figure 3. Kaplan–Meier survival curves for all-cause mortality in critically ill patients with kidney failure. (A) ICU all-cause mortality; (B) 30-days all-cause mortality; (C) 180-days all-cause mortality; (D) 365-days all-cause mortality.
Table 2. HRs (95% CIs) for all-cause mortality across groups of RDW.

| Variable                      | Crude Mode | p value | Adjusted Model I | p value | Adjusted Model II | p value |
|-------------------------------|------------|---------|------------------|---------|------------------|---------|
|                               | HR (95% CIs) |         | HR (95% CIs)     |         | HR (95% CIs)     |         |
| ICU all-cause mortality       |             |         |                  |         |                  |         |
| RDW (%)                       | 1.23 (1.11, 1.35) | <0.0001 | 1.24 (1.12, 1.36) | <0.0001 | 1.27 (1.11, 1.46) | 0.0007  |
| <15.4                         | 1.0 (ref)   |         | 1.0 (ref)        |         | 1.0 (ref)        |         |
| ≥15.5, <17.1                  | 2.35 (1.12, 1.42) | 0.0237 | 2.29 (1.09, 4.81) | 0.0284 | 3.81 (1.48, 9.77) | 0.0055  |
| >17.2                         | 3.11 (1.33, 6.35) | 0.0018 | 3.06 (1.50, 6.25) | <0.0001 | 4.71 (1.69, 11.64) | 0.0025  |
| 30-day all-cause mortality    |             |         |                  |         |                  |         |
| RDW (%)                       | 1.30 (1.18, 1.42) | <0.0001 | 1.30 (1.18, 1.43) | <0.0001 | 1.35 (1.19, 1.54) | <0.0001 |
| <15.4                         | 1.0 (ref)   |         | 1.0 (ref)        |         | 1.0 (ref)        |         |
| ≥15.5, <17.1                  | 1.97 (0.97, 3.97) | 0.0589 | 1.93 (0.95, 3.89) | 0.0681 | 2.85 (1.22, 6.68) | 0.0159  |
| >17.2                         | 4.37 (2.30, 8.32) | <0.0001 | 4.31 (2.26, 8.22) | <0.0001 | 6.62 (2.84, 15.41) | <0.0001 |
| 180-day all-cause mortality   |             |         |                  |         |                  |         |
| RDW (%)                       | 1.26 (1.16, 1.36) | <0.0001 | 1.26 (1.16, 1.37) | <0.0001 | 1.27 (1.14, 1.41) | <0.0001 |
| <15.4                         | 1.0 (ref)   |         | 1.0 (ref)        |         | 1.0 (ref)        |         |
| ≥15.5, <17.1                  | 1.78 (1.01, 3.13) | 0.0466 | 1.74 (0.98, 3.07) | 0.0566 | 2.55 (1.28, 4.92) | 0.0077  |
| >17.2                         | 3.60 (2.13, 6.09) | <0.0001 | 3.56 (2.10, 6.03) | <0.0001 | 4.43 (2.41, 9.21) | <0.0001 |
| 1-year all-cause mortality    |             |         |                  |         |                  |         |
| RDW (%)                       | 1.25 (1.15, 1.35) | <0.0001 | 1.25 (1.15, 1.36) | <0.0001 | 1.24 (1.12, 1.38) | <0.0001 |
| <15.4                         | 1.0 (ref)   |         | 1.0 (ref)        |         | 1.0 (ref)        |         |
| ≥15.5, <17.1                  | 1.95 (1.13, 3.34) | 0.0158 | 1.91 (1.11, 3.28) | 0.0197 | 2.51 (1.37, 4.77) | 0.0032  |
| >17.2                         | 3.55 (2.14, 5.91) | <0.0001 | 3.52 (2.11, 5.86) | <0.0001 | 4.08 (2.19, 7.62) | <0.0001 |

HR: hazard ratio; CI: confidence interval. Models were derived from Cox proportional hazards regression models. Model I adjusted for age, gender; Model II adjusted for age, gender, APSIII, OASIS, SAPSII, SOFA, SIRS, LODS, hemoglobin, platelets, WBC, MCV, anion gap, bicarbonate, BUN, calcium, chloride, creatinine, glucose, sodium, potassium, Myocardial Infarction, Congestive Heart Failure, Peripheral Vascular Disease, Chronic Pulmonary Disease, Diabetes, Cerebrovascular Disease, Severe Liver Disease.

Table 3. Subgroup analyses of the association between RDW and 365-day mortality.

| Subgroups          | N       | <15.2   | ≥15.2, <17 | ≥17 | p for interaction |
|--------------------|---------|---------|------------|-----|------------------|
| Age                |         |         |            |     |                  |
| ≤68                | 337     | 1.0     | 2.3 (1.0, 5.3) | 4.8 (2.2, 10.4) | 0.5098 |
| >68                | 337     | 1.0     | 1.6 (0.8, 3.4) | 2.7 (1.4, 5.3) | 0.6254 |
| Gender             |         |         |            |     |                  |
| Male               | 386     | 1.0     | 2.3 (1.1, 4.7) | 4.3 (2.2, 8.6) | 0.4953 |
| Female             | 288     | 1.0     | 1.5 (0.7, 3.5) | 2.7 (1.3, 5.9) | 0.6801 |
| Kidney replacement therapy |       |         |            |     |                  |
| Hemodialysis       | 643     | 1.0     | 1.9 (1.1, 3.3) | 3.5 (2.1, 6.0) | 0.1580 |
| Peritoneal dialysis| 31      | 1.0     | 2.2 (0.1, 40.8) | 3.2 (0.3, 41.9) | 0.5114 |
| APSIII             | 15–62   | 336     | 1.0     | 1.8 (0.7, 4.7) | 2.4 (0.9, 6.3) | 0.6140 |
| 63–158             | 338     | 1.0     | 2.4 (1.2, 4.7) | 4.1 (2.2, 7.6) | 0.2877 |
| OASIS              | 12–34   | 326     | 1.0     | 1.6 (0.6, 4.3) | 4.4 (1.8, 10.6) | 0.0544 |
| 35–64              | 348     | 1.0     | 2.4 (1.2, 4.6) | 3.2 (1.7, 6.1) | 0.4080 |
| SAPSII             | 15–42   | 328     | 1.0     | 1.8 (0.7, 4.5) | 3.3 (1.4, 7.8) | 0.6921 |
| 43–101             | 346     | 1.0     | 2.1 (1.1, 4.1) | 3.8 (2.0, 7.3) | (continued) |
large multi-center design is still necessary. Second, we only focused on levels of RDW and other parameters at admission to the ICU. Changes in RDW level at different periods might provide additional prognostic information. Third, the RDW value may fluctuate during the early period after dialysis, or affected by bleeding or hemolysis. When facing this situation, it is necessary to combine with other biomarkers to estimate the patient’s state. Finally, although we tried our best to control for confounders, there might still be other unknown factors influencing the results.

5. Conclusion

Our study demonstrated that the RDW level could be a predictive marker for critically ill patients with kidney failure in ICU, and elevated levels of RDW at admission...
were associated with an increased risk of ICU, 30-day, 180-day, and 1-year all-cause mortality.

**Clinical significance**

Several scoring systems are used to evaluate prognosis and develop personalized treatment plans for patients admitted to the ICU, but none of them are specific for kidney failure patients. More importantly, the scoring system generally contains many parameters, which does not allow clinicians to quickly determine the prognosis of kidney failure patients. In this study, we found that RDW, an easily accessible indicator, could serve as a prognostic biomarker for kidney failure patients admitted to the ICU, which might be very helpful for more elaborate risk classification, effective health care management, and delivery of the best patient care possible.

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**Ethics approval and consent to participate**

Ethical approval was received from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA) when organizing the database. All data are anonymous in this database, and the requirement for individual patient consent is exempt.

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