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# Association between red blood cell distribution width and mortality in diabetic ketoacidosis

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**Abstract**

**Background:** No epidemiological studies have assessed the impact of red blood cell distribution width (RDW) on the prognosis of diabetic ketoacidosis (DKA) patients in the intensive care unit (ICU). Thus, we investigated whether RDW was associated with mortality in DKA patients.

**Material and method:** We analyzed data from MIMIC-III. RDW was measured at ICU admission. The relationship between RDW and mortality of DKA was determined using a multivariate Cox regression analysis. The primary outcome of the study was 365-day mortality from the date of ICU admission. We also conducted a subgroup analysis to further confirm the consistency of associations.

**Results:** In total, 495 critically ill DKA patients were eligible for analysis. In the univariable Cox regression model for 365-day all-cause mortality, RDW was a predictor of all-cause mortality in DKA patients (hazard ratio [HR]: 1.30, 95% confidence interval [CI]: 1.19–1.43). After adjusting for confounders, RDW was still a particularly strong predictor (HR: 1.23, 95% CI: 1.05–1.45). The same relationship was also observed for 90-day all-cause mortality (HR: 1.29, 95% CI: 1.02–1.65).

**Conclusions:** High RDW was associated with risk of all-cause mortality in DKA patients in the ICU. RDW was an independent prognostic factor for these patients.

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## Introduction

Over the past decade, the prevalence of diabetes mellitus (DM) in human populations has increased significantly due to increased intake of high-fat foods and reduced physical activity.[1] Diabetic ketoacidosis (DKA) is a life-threatening acute complication of DM that is characterized by a pathological imbalance between severe insulin deficiency and excessive glucagon, resulting in clinical changes such as hyperglycemia, ketosis, electrolyte imbalance, and metabolic acidosis.[2,3] More than 100,000 DKA patients are admitted to American hospitals each year.[3] Despite implementing standardized protocols for maintaining electrolyte balance and insulin replacement, DKA remains a serious and inevitable complication and a leading cause of death in DM patients, which leads to significant treatment costs.[3–5] Sometimes DKA patients will enter the ICU because hospital-specific policies prevent the use of intravenous insulin infusions on general wards, which causes resource shortages for critically ill patients.[6] Therefore, evaluating the risk factors of DKA is crucial for clinicians with regard to patient outcomes and resource use.

RDW is a laboratory index that measures the size variation of circulating red blood cells (RBCs).[7] Previously, the clinical use of RDW was limited to the differential diagnosis of anemia.[8] Recently, several clinical studies have demonstrated that RDW is an independent prognostic marker for mortality,[9] especially in patients with cardiovascular disease (e.g., heart failure,[10] coronary artery diseases,[11] or acute coronary syndrome[12]) and over the long-term in patients with community-acquired pneumonia.[13] Other studies have further demonstrated that RDW is a novel inflammatory marker that plays an important role in the development of inflammation.[14–16] As a systemic metabolic disease, DKA has also been reported to be associated with the inflammatory and immune responses of the hyperglycemic state.[16,17] Inflammation is of vital significance in the generation and development of DKA. Based on the above findings, we hypothesized that RDW might have a relationship with DKA. However, to our knowledge, no study has directly explored the association between RDW and DKA outcomes. Therefore, this study was designed to investigate whether RDW could independently predict the prognosis of DKA patients in the ICU.

## Materials and method

### *Study cohort*

This was a longitudinal, single-center, retrospective cohort study that used multiparameter intelligent monitoring III version 1.3 (MIMIC-III v1.3) in the ICU, which is a public and freely available ICU database software.[18] The database includes more than 38,000 ICU patients admitted to Beth Israel Deaconess Medical Center from 2001 to 2012.[18,19] MIMIC-III also includes demographics, laboratory results, records of care progress, intravenous medications, fluid balance, and other clinical variables.[18] To protect privacy, information regarding the included patients were hidden.

### Population selection criteria

All adult patients (age: ≥18 years) who were initially diagnosed with DKA in the ICU were searched in the database. Cases were defined as adult critically ill patients diagnosed with DKA.[18,20] Patients were excluded according to the following criteria: (1) no RDW measurement during the ICU stay; (2) hematologic disease (e.g., leukemia or myelodysplastic syndrome); (3) ICU stay <48 hours; and (4) missing >5% of individual data. The primary outcome of the study was 365-day mortality from the date of ICU admission; 90-day mortality after ICU admission was the secondary outcome.

### Data sources

The PostgreSQL tool (version 9.6) was used to extract data. All clinical parameters were recorded in the first 24 hours after patient admission.[21] Physiologic information including heart rate, mean blood pressure, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, and respiratory rate were measured by bedside monitors. Laboratory values included bicarbonate, platelet, blood urea nitrogen (BUN), glucose, sodium, creatinine, chloride, hematocrit, hemoglobin, mean corpuscular volume (MCV), mean hemoglobin concentration (MHC), mean corpuscular hemoglobin concentration (MCHC), and white blood cell (WBC). Comorbidities included congestive heart failure (CHF), atrial fibrillation (AF), chronic renal disease (CKD), chronic liver disease, coronary artery disease (CAD), acute respiratory distress syndrome (ARDS), and malignancy. We also calculated Elixhauser Comorbidity Index, acute physiology score III (APSIII), and systemic inflammatory response syndrome (SIRS).

### Statistical analysis

All data were analyzed with R software version 3.42. All statistical analyses were two-sided and $p < 0.05$ was interpreted as statistically significant. Continuous variables were first examined for normality. Normal data are expressed as mean ± standard deviation (SD), while categorical data are summarized as number or percentage. To compare the groups, we used the chi-square test for categorical variables and analysis of variance, and the Kruskal–Wallis test for continuous variables.[22] Factors related to RDW values were determined by multivariate linear regression. We then used Cox proportional hazards models to determine whether RDW was independently associated with all-cause mortality, from which the hazard ratio (HR) and 95% confidence interval (CI) were calculated.

We ran two models for each endpoint. Covariates were adjusted for age, gender, and ethnicity in model I, while in model II, covariates were further adjusted for APSIII, SIRS, CHF, stroke, ARDS, SBP, MCV, MHC, and MCHC. All selected variables were based on associations with the outcomes or a change in effect estimate of more than 10%. Potential multicollinearity between covariates was quantified by calculating the variance inflation factor (VIF),[23] which provided an index of how much the variance of an estimated regression coefficient was increased due to collinearity. A VIF value >5 was considered evidence of multicollinearity.

Stratification analyses were performed to investigate whether the effect of RDW differed across various subgroups, including CHF, AF, CKD, CAD, vasoactive drugs, and RRT.

## Results

### Subject characteristics

Among the 38,597 reviewed patients, 495 were eligible for this analysis. Patient characteristics are summarized in Table 1,

**Table 1.** Characteristics of the study participants according to their 365-day survival outcomes.

| | 365-mortality | | | |
|---|---|---|---|---|
| Clinical variable | Overall | Survival | Mortality | *P value* |
| N | 495 | 440 | 55 | |
| Age, years | 47.5 ± 17.8 | 45.4 ± 16.9 | 64.0 ± 16.3 | <0.001 |
| Gender, n (%) | | | | <0.001 |
| Female | 256 (51.7) | 231 (52.5) | 25 (45.5) | |
| Male | 239 (48.3) | 209 (47.5) | 30 (54.5) | |
| Ethnicity, n (%) | | | | 0.378 |
| White | 306 (61.8) | 271 (61.6) | 35 (63.6) | |
| Black | 103 (20.8) | 95 (21.6) | 8 (14.5) | |
| Other | 86 (17.4) | 74 (16.8) | 12 (21.8) | |
| RDW, % | 13.9 ± 1.6 | 13.8 ± 1.3 | 15.0 ± 2.7 | <0.001 |
| SBP, mmHg | 122.6 ± 17.2 | 122.4 ± 16.6 | 124.1 ± 21.6 | 0.700 |
| DBP, mmHg | 63.2 ± 10.4 | 63.5 ± 10.2 | 60.5 ± 12.0 | 0.095 |
| Respiratory rate, beats/minute | 19.1 ± 4.0 | 18.9 ± 3.8 | 20.6 ± 5.0 | 0.015 |
| Temperature, °C | 36.9 ± 0.5 | 36.9 ± 0.5 | 36.8 ± 0.9 | 0.309 |
| Comorbidities, n (%) | | | | |
| Congestive heart failure | 32 (6.5) | 24 (5.5) | 8 (14.5) | 0.017 |
| Atrial fibrillation | 21 (4.2) | 14 (3.2) | 7 (12.7) | 0.005 |
| Coronary artery disease | 68 (13.7) | 55 (12.5) | 13 (23.6) | 0.035 |
| Chronic kidney disease | 56 (11.3) | 47 (10.7) | 9 (16.4) | 0.255 |
| Chronic liver disease | 23 (4.6) | 20 (4.5) | 3 (5.5) | 0.733 |
| Malignancy | 27 (5.5) | 15 (3.4) | 12 (21.8) | <0.001 |
| Elixhauser Comorbidity Index | 8.9 ± 9.8 | 8.7 ± 9.7 | 14.2 ± 11.1 | 0.042 |
| Laboratory parameters | | | | |
| Bicarbonate, mmol/L | 14.1 ± 5.8 | 14.0 ± 5.8 | 15.9 ± 6.8 | 0.234 |
| Creatinine, mEq/L | 1.3 ± 1.4 | 1.3 ± 1.4 | 2.1 ± 1.7 | <0.001 |
| Chloride, mmol/L | 97.2 ± 9.1 | 97.2 ± 9.1 | 100.4 ± 8.8 | 0.188 |
| Glucose, mg/dL | 122.2 ± 53.4 | 121.0 ± 52.5 | 158.1 ± 67.4 | 0.017 |
| Hematocrit, % | 32.4 ± 5.7 | 32.5 ± 5.6 | 30.5 ± 7.9 | 0.441 |
| Hemoglobin, g/dL 12–16 | 11.1 ± 2.0 | 11.1 ± 1.9 | 10.3 ± 2.7 | 0.282 |
| MCV, fL 80–100 | 85.2 ± 12.2 | 85.5 ± 12.1 | 83.8 ± 18.6 | 0.256 |
| MHC, pg 27–31 | 29.4 ± 2.6 | 29.6 ± 2.4 | 29.5 ± 3.1 | 0.721 |
| MCHC, g/L 320–360 | 346.6 ± 22.4 | 348.6 ± 21.4 | 350.2 ± 25.2 | 0.291 |
| Platelet, $10^9$/L | 245.7 ± 100.1 | 247.9 ± 99.3 | 180.2 ± 104.8 | 0.012 |
| BUN, mg/dL | 21.6 ± 19.7 | 21.0 ± 19.4 | 39.6 ± 21.2 | <0.001 |
| WBC, $10^9$/L | 11.0 ± 5.0 | 11.1 ± 5.0 | 10.9 ± 6.2 | 0.706 |
| RRT, n (%) | 25 (5.1) | 16 (3.6) | 9 (16.4) | <0.001 |

SBP: systolic blood pressure; DBP: diastolic blood pressure; MCV: Mean corpuscular volume; MHC: Mean hemoglobin concentration; MCHC: Mean corpuscular hemoglobin concentration; WBC: white blood cell; BUN: blood urea nitrogen; RRT: Renal replacement therapy.
Significance level $p < 0.05$.

and patients were divided into survival and mortality groups. In total, 440 patients had a survival outcome, while 55 had a fatal outcome. Among the cohort, 239 patients (48.3%) were men, 256 (51.7%) were white, the mean age was 47.5 ± 17.8 years, and the average RDW was 13.9% ± 1.6%. Patients with high mortality were generally

older and had a history of CHF, AF, CAD, and malignancy. Additionally, this group had higher creatinine, glucose, sodium, platelets, and BUN.

### Association between RDW and mortality

In the univariable Cox regression model for 365-day all-cause mortality, RDW was a predictor of all-cause mortality in DKA patients in the ICU (HR: 1.30, 95% CI: 1.19–1.43) (Table 2). For 365-day all-cause mortality adjusted for age gender, and ethnicity (model I), RDW was a particularly strong predictor of all-cause mortality in DKA patients in the ICU (HR: 1.27, 95% CI: 1.14–1.42, $P < 0.001$). When adjusted for age, gender, ethnicity, APSIII, SIRS, CHF, stroke, ARDS, SBP, MCV, MHC, and MCHC (model II), the predictive role of RDW was still statistically significant (HR: 1.23, 95% CI: 1.05–1.45, $P < 0.05$). For 90-day all-cause mortality adjusted for the same confounders (model II), the same relationship was observed (HR: 1.29, 95% CI: 1.02–1.65, $P < 0.05$).

### Subgroup analyses

We conducted subgroup analyses to determine the consistency of associations between RDW and risk of hospital mortality in critically ill DKA patients (Table 3). This analysis showed that CKD patients with higher RDW had a significantly higher risk of hospital mortality (HR: 1.35, 1.05–1.74, $P < 0.05$).

## Discussion

The main finding of this study was that RDW was independently associated with 90-day and 365-day all-cause mortality in DKA patients post ICU admission. The association remained significant after adjusting for age, gender, ethnicity, APSIII, SIRS, CHF, stroke, ARDS, SBP, MCV, MHC, and MCHC. While previous studies have shown that RDW is independently associated with several adverse outcomes,[10,11,24] our study indicated that RDW was an independent predictor of mortality in critically ill DKA patients.

To our knowledge, this is the first study to assess RDW as a long-term prognostic marker of DKA patients admitted to the ICU. The precise mechanism underlying the relationship between RDW and all-cause mortality in DKA is unclear. However, some hypotheses have been proposed, among which inflammatory responses[14,15] and oxidative stress[25–27] are the most popular.

Several observational studies have described an association between elevated

**Table 2.** Hazard ratios and 95% confidence intervals for mortality across groups.

| Outcome | Non-adjusted | | Model I[a] | | Model II[b] | |
|---|---|---|---|---|---|---|
| | HR (95% CIs) | $P_{value}$ | HR (95% CIs) | $P_{value}$ | HR (95% CIs) | $P_{value}$ |
| 90-day all-cause mortality | 1.25 (1.08–1.44) | 0.0027 | 1.19 (1.01–1.41) | 0.0498 | 1.29 (1.02–1.65) | 0.0372 |
| 365-day all-cause mortality | 1.30 (1.19–1.43) | <0.0001 | 1.27 (1.14–1.42) | <0.0001 | 1.23 (1.05–1.45) | 0.0089 |

HR: hazard ratio; CI: confidence interval.

[a]Model I covariates were adjusted for age, gender and ethnicity.

[b]Model II covariates were adjusted for age; gender; ethnicity; APSIII; SIRS, CHF; stroke; ARDS; SBP; MCV; MHC and MCHC.

Significance level $p < 0.05$.

**Table 3.** Subgroup analysis of associations between RDW and hospital mortality.

| | No. of patients | HR (95% CI) | $P_{value}$ |
|---|---|---|---|
| Congestive heart failure | | | |
| No | 463 | 1.11 (0.98–1.25) | 0.1066 |
| Yes | 32 | 1.11 (0.72–1.71) | 0.6286 |
| Atrial fibrillation | | | |
| No | 474 | 1.05 (0.90–1.23) | 0.5128 |
| Yes | 21 | 1.10 (0.83–1.45) | 0.5013 |
| Chronic kidney disease | | | |
| No | 439 | 1.07 (0.93–1.24) | 0.3552 |
| Yes | 56 | 1.35 (1.05–1.74) | 0.0198 |
| Chronic liver disease | | | |
| No | 472 | 1.12 (1.00–1.26) | 0.0504 |
| Yes | 23 | 0.43 (0.07–2.46) | 0.3412 |
| Malignancy | | | |
| No | 468 | 1.25 (1.06–1.47) | 0.0075 |
| Yes | 27 | 1.17 (0.95–1.43) | 0.1363 |
| Coronary artery disease | | | |
| No | 427 | 1.14 (1.02–1.28) | 0.0228 |
| Yes | 68 | 1.06 (0.71–1.58) | 0.7700 |
| Vasoactive drug | | | |
| No | 436 | 1.16 (1.01–1.33) | 0.0371 |
| Yes | 59 | 1.06 (0.89–1.27) | 0.4982 |
| RRT | | | |
| No | 470 | 1.09 (0.94–1.26) | 0.2404 |
| Yes | 25 | 1.01 (0.80–1.28) | 0.9214 |

SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cell; BUN: blood urea nitrogen; RRT: Renal replacement therapy.
Significance level $p < 0.05$.

RDW and changes in inflammatory biomarkers.[14] The proliferation and maturation of erythrocytes were inhibited by proinflammatory cytokines.[14,15] Increased RDW may reflect the extent of inflammation, which negatively impacts patient survival.[9,28,29] There has also been a reported association between higher RDW and increased levels of the inflammatory marker C-reactive protein. It has also been suggested[9,30,31] that RDW reflects the variability in the size of circulating RBCs. The increase in RDW results from the release of reticulocytes into the circulation. The increased number of smaller erythrocytes may reflect an increase in vesicle shedding by RBCs.[32,33] Additionally, RDW is associated with endothelial function, is primarily assessed by flow-mediated dilation and can be used as a measure of potential metabolic disorders.[34]

The relationship between RDW and mortality in this study may also be related to oxidative stress. High oxidative stress may result in increased RDW, which may be due to reduced RBC survival and increased release of large and small premature erythrocytes into peripheral circulation (anisocytosis).[27,35] This is due to the release of heterogeneous RBCs with poor oxygen carrying capacity into the peripheral circulation, which can damage the microcirculation of local tissue *via* hypoxia.[25,26] The increased RDW may promote the formation of

thrombus, which may be released into the circulation through immature reticulocytes, but the role of immature reticulocytes in thrombosis is unclear. The neurohumoral response to arterial underfilling may also contribute to this association.[36–38]

The main advantage of this study is that it is the first comprehensive assessment of the relationship between RDW and mortality in DKA patients in the ICU. RDW appears to be a long-term prognostic indicator for patients admitted to the ICU for DKA. Additionally, RDW is widely available and adds no additional cost to the patient. Moreover, the number of patients participating in our study was large.

We acknowledge that this study also had some limitations. First, our study was a retrospective observational study with inherent biases. For this reason, selection bias cannot be ignored. Second, the study did not investigate potential changes in RDW over time, which may provide additional prognostic information. Third, the groups differed in the number of patients with malignancy, but our study did not assess whether malignancy affected survival differences in the two groups. Finally, the nutritional status of the patient was unknown, and nutritional deficiency, which can lead to elevated RDW, may be a confounding variable.

## Conclusions

This study showed that RDW is a long-term prognostic marker for patients admitted to the ICU for DKA, and that higher RDW is associated with an increased risk of mortality in these patients. However, to confirm the relationship between RDW and poor prognosis in DKA, further studies, especially large-scale prospective studies, are needed.

## Ethics and consent statements

Because this was a retrospective analysis of a large clinical database, ethics and consent statements are inapplicable for our study. All data in our study were extracted from a freely accessible database, the Medical Information Mart for Intensive Care Database III (MIMIC-III). The setting and use of this database were approved by the institutional review boards of the Massachusetts Institute of Technology (Boston, MA) and Beth Israel Deaconess Medical Center (Cambridge, MA). All personal information included in the database have been de-identified to safeguard privacy. Data are available from MIMIC-III for researchers who have completed the National Institutes of Health's online course for Protecting Human Research Participants.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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