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ORIGINAL RESEARCH

# The Red Blood Cell Distribution Width–Albumin Ratio Was a Potential Prognostic Biomarker for Diabetic Ketoacidosis

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**Background:** The red blood cell distribution width (RDW)–albumin ratio (RA) is a new biomarker, which is d-efined as RDW divided by albumin. This study aimed at determining the prognostic values of RA for diabetic ketoacidosis (DKA).

**Methods:** Data were obtained from Medical Information Mart for Intensive Care Database III V1.4 (MIMIC-III) and the RA calculated. Multivariate Cox regression analysis was performed to determine the correlation between RA and 90-day mortality or 365-day mortality. To further investigate the association with RA and mortality, the patients were divided into two groups. The second outcome was the association between the incidence of DKA-related infections and RA.

**Results:** For DKA patients in the ICU, RA was significantly correlated with 90-day mortality (HR: 2.1, 95% CI: 1.5, 3.0, $p < 0.001$) and 365-day mortality (HR: 1.9, 95% CI: 1.5, 2.5, $p < 0.001$). A high RA was independently correlated with increased 90-day mortality (HR: 7.8, 95% CI: 1.8, 34.0, p for trend <0.001) and 365-day mortality (HR: 5.2, 95% CI: 2.4, 11.3, p for trend <0.001). Moreover, RA was found to be an independent predictor for sepsis and septic shock in patients with DKA (HR: 2.9, 95% CI: 2.0, 4.1, $p < 0.001$). After adjusting for confounders, the statistical outcome was the same.

**Conclusion:** A high RA is significantly correlated with increased all-cause mortality of DKA as well as an increased incidence of DKA-related infections. RA is a potential prognostic marker for DKA.

**Keywords:** red blood cell distribution width–albumin ratio, diabetic ketoacidosis, diabetic ketoacidosis–associated infection, all-cause mortality

## Introduction

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes mellitus (DM). The diagnostic criteria of DKA involve hyperglycaemia due to insulin deficiency, positive ketone tests, and metabolic acidosis.[1] While there are about 1–7% of DKA patients with absence of hyperglycemia (blood glucose <250 mg/dl).[2] With the increasing global incidence of DM, the prevalence of DKA in DM patients has also increased.[3,4] Among DM patients, about 4–9% of all acute hospital admissions and 3.5–4.5% of mortalities are associated with DKA.[5] Due to these high rates, it is important to establish an early biomarker for predicting the prognosis of DKA patients.

Even though the mechanisms through which DKA progresses have not been established, several studies suggest that inflammation may be the leading factor

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promoting the progression of DKA.[6–8] Hyperglycemia induces systemic inflammation, enhances cytokine secretion, reduces the secretion and action of insulin, and elevates the generation of free fatty acids, which are ketogenic substrates. Meanwhile, ketosis-induced high oxidative stress levels may lead to abnormal glucose uptake, insulin resistance and decreased insulin secretion.[9] Red blood cell distribution width (RDW), which reflects the heterogeneity of red blood cell (RBC) sizes, is calculated using standard deviation volumes and mean corpuscular volumes of erythrocytes. A high RDW is associated with systemic inflammation and is a predictor for the poor prognoses of many diseases, including cardiovascular, kidney, diabetes, liver and respiratory diseases.[10] Albumin is a major substance maintaining plasma osmolarity before researchers find the association between it and inflammation.[11,12] A low albumin level has been shown to be a marker for poor outcomes in patients with malignancies, critical illnesses, and thrombotic diseases.[11]

Although the roles of RDW or albumin in DKA patients have been reported,[13,14] it is important to establish the prognostic value of RA in these patients. The association between RA and DKA has not been documented. Therefore, we aimed at investigating the association between RA and clinical outcomes of DKA and DKA-related infections.

# Methods

## Data Source

The relevant patient data was downloaded from the Medical Information Mart for Intensive Care Database III V1.4 (MIMIC-III). The database contains private medical records for 53,423 patients who were in the intensive care units (ICU) of Beth Israel Deaconess Medical Center (Boston, USA) from 2001 to 2012. Beth Israel Deaconess Medical Center is a public tertiary care hospital. The data in this database include that of hourly vital signs, laboratory results, procedures, prescriptions, and diagnostic codes. To get access to the database, we completed the course "Protecting Human Research Participants" at the website of the National Institutes of Health and obtained the certification. This study was approved by the Massachusetts Institute of Technology and the Institutional Review Boards. All data accessed complies with relevant data protection and privacy regulations.

## Participant Selection Criteria

DKA patients were selected according to the international classification of disease codes-9 (ICD-9). The inclusion criteria were as follows: 1) age <18 years; 2) Stay time in ICU >48 hours; 3) Those without hematologic diseases; 4) those with comprehensive RDW and serum albumin data; and 5) those whose missing data <5%.

## Data Extraction and Outcomes

The data of DKA patients from MIMIC-III (V1.4) were extracted by structure query language. All the data we collected included age, grand, heart rate, respiratory rate, temperature, percutaneous oxygen saturation (SPO2) systolic blood pressure (SBP), diastolic blood pressure (DBP), serum albumin, lactate, white blood cell (WBC), congestive heart failure (CHF), valvular disease, renal failure, chronic pulmonary disease, hypothyroidism, liver disease, sepsis, sequential organ failure assessment score (SOFA), simplified acute physiology score II (SAPS II).

We enrolled 375 DKA patients from MIMIC-III (V1.4). All the patients were divided into two groups according to the value of RA: RA < 3.88 was regarded as low group, while the others were regarded as high group. All-cause mortality was the primary outcome. Since DKA patients were the most susceptible for infection, we chose sepsis as the secondary outcome.

## Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or interquartile range (IQR), and statistical differences between two groups were accessed by Kruskal–Wallis test. While categorical data were expressed as frequencies, and the $\chi 2$ test or Fisher's exact test (expected frequency <10) was used to compare the differences between groups.

Multivariate Cox regression models were performed to estimate the association between RA and all-cause mortality in DKA. The relationship between RA and DKA-related sepsis was assessed by the Cox proportional hazard regressions. To further accurate the relationships, the patients were divided into seconde according to value of RA. The outcomes of Cox regression were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Model I was adjusted for the confounders age, gender. Model II was adjusted for age, gender, anion gap, CHF, liver disease.

A $p < 0.05$ was considered statistically significant and $p < 0.01$ highly statistically significant. R software

(Version 3.6.2, http://www.r-project.org) was used to conduct analyses.

# Results

## Characteristics of DKA Patients

We enrolled a total of 375 participants and grouped them into two groups: RA < 3.88 was regarded as the low group, while RA > 3.88 was considered as the high group (Table 1). DKA patients with high RA tended to be older, had low levels of heart rates, respiratory rates and DBP. They were more likely to exhibit high levels of SAPSII, SOFA, and had comorbidities of CHF, valvular disease, renal failure, and sepsis.

## The Association Between RA and All-Cause Mortality of DKA Patients in the ICU

Patients in the high RA group exhibited a higher mortality rate than those in the low RA group (Table 1). To investigate the association between RA and mortality, we performed the Cox regression analysis and the results are shown in Table 2. RA was found to be an independent predictor for 90-day mortality (HR: 2.1, 95% CI: 1.5, 3.0, p < 0.001) and 365-day mortality (HR: 1.9, 95% CI: 1.5, 2.5, p < 0.001) in DKA patients. After adjusting for age and gender, RA was independently associated with 90-day (HR: 1.8, 95% CI: 1.3, 2.6, p < 0.001) and 365-day mortality (HR: 1.6, 95% CI: 1.3, 2.1, p < 0.001). After adjusting for multiple confounders, RA was still found to exhibit a statistical significance for 90-day (HR: 2.2, 95% CI: 1.4, 3.6, p < 0.001) and 365-day mortality (HR: 1.6, 95% CI: 1.2, 2.1, p < 0.001). Moreover, second-order analysis also revealed that high RA levels are associated with increased mortality rates among DKA patients. Compared to the reference, the HRs and 95% CIs of RA for the 90-day mortality rate were 7.8 (1.8, 34.0) in the non-adjusted model, 4.9 (1.1, 22.1) in model 1 and 5.5 (1.2, 26.4) in model 2. For the 365-day mortality, a high RA was also associated with increased mortality (HR: 5.2, 95% CI: 2.4, 11.3, p for trend <0.001). After adjusting for confounders, the association remained significant in model 1 (HR: 3.4, 95% CI: 1.5, 7.6, p for trend = 0.003) and model 2 (HR: 3.4, 95% CI: 1.5, 7.7, p for trend = 0.003).

## Association Between RA and DKA-Related Infections

Infections increase morbidity and mortality rates for ICU patients. Therefore, we investigated the association between RA and DKA-related sepsis and septic shock (Table 3). RA was independently associated with sepsis (HR: 2.9, 95% CI: 2.0, 4.1, p < 0.001) and septic shock (HR: 2.8, 95% CI: 1.9, 4.2, p < 0.001) in DKA patients. In model 1, RA was still a significant predictor for sepsis (HR: 2.8, 95% CI: 1.9, 4.1, p < 0.001) and septic shock (HR: 2.9, 95% CI: 1.9, 4.3, p <

**Table 1** Characteristics of Enrolled Patients

| Characteristics | Low Group[a] | High Group[b] | P-value |
|---|---|---|---|
| N | 187 | 188 | |
| Age | 42.7 ± 15.6 | 51.8 ± 17.3 | <0.001 |
| Gender, n (%) | | | 0.491 |
| Male | 112 (59.9) | 106 (56.4) | |
| Female | 75 (40.1) | 82 (43.6) | |
| Vital signs | | | |
| Heart rate, beats/minute | 95.1 ± 14.4 | 91.9 ± 16.4 | 0.046 |
| Respiratory rate, breaths/minute | 18.8 ± 3.5 | 19.9 ± 4.4 | 0.008 |
| SBP, mmHg | 123.7 ± 18.8 | 123.7 ± 18.2 | 0.999 |
| DBP, mmHg | 65.3 ± 12.6 | 62.1 ± 11.1 | 0.009 |
| $SPO_2$, % | 98.2 ± 1.4 | 97.9 ± 1.7 | 0.158 |
| Temperature, °C | 36.9 ± 0.4 | 36.8 ± 0.7 | 0.082 |
| Comorbidities, n (%) | | | |
| Congestive heart failure | 16 (8.6) | 40 (21.3) | <0.001 |
| Valvular disease | 1 (0.5) | 9 (4.8) | 0.011 |
| Renal failure | 21 (11.2) | 59 (31.4) | <0.001 |
| Chronic pulmonary disease | 22 (11.8) | 29 (15.4) | 0.301 |
| Hypothyroidism | 90 (48.1) | 109 (58.0) | 0.056 |
| Liver disease | 15 (8.0) | 16 (8.5) | 0.863 |
| Sepsis | 3 (1.6) | 21 (11.2) | <0.001 |
| Septic shock | 3 (1.6) | 15 (8.0) | 0.004 |
| Laboratory parameters | | | |
| Lactate, mmol/L | 2.0 ± 1.2 | 1.8 ± 1.0 | 0.193 |
| White blood cell, $\times 10^9$/L | 14.2 ± 6.7 | 14.0 ± 7.7 | 0.808 |
| Albumin, g/L | 4.2 ± 0.6 | 3.1 ± 0.4 | <0.001 |
| 90-Day all-cause mortality, n (%) | 2 (1.1) | 15 (8.0) | 0.001 |
| 365-Day all-cause mortality, n (%) | 5 (2.7) | 33 (17.6) | <0.001 |
| SAPSII | 27.8 ± 10.7 | 35.3 ± 13.3 | <0.001 |
| SOFA | 2.8 ± 1.9 | 4.5 ± 3.1 | <0.001 |

**Notes**: [a, b]RA < 3.89 was regarded as the low group, RA > 3.89 was considered as the high group.

**Abbreviations**: RA, red blood cell distribution width–albumin ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; $SPO_2$, oxygen saturation; SAPSII, The Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

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**Table 2** Association Between RA and Mortality of DKA

| | Non-Adjusted[a] | | | Model 1[b] | | | Model 2[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CIs) | P value | P for Trend | HR (95% CIs) | P value | P for Trend | HR (95% CIs) | P value | P for Trend |
| 90-Day all-cause mortality | 2.1 (1.5, 3.0) | <0.001 | | 1.8 (1.3, 2.6) | <0.001 | | 2.2 (1.4, 3.6) | <0.001 | |
| Seconde | | | | | | | | | |
| 2.28–3.88 | Reference | | | Reference | | | Reference | | |
| 3.89–10.25 | 7.8 (1.8, 34.0) | 0.006 | | 4.9 (1.1, 22.1) | 0.038 | | 5.5 (1.2, 26.4) | 0.032 | |
| Group trend | 5.5 (1.6, 19.0) | | 0.006 | 3.8 (1.1, 13.2) | | 0.038 | 4.2 (1.1, 15.3) | | 0.032 |
| 365-Day all-cause mortality | 1.9 (1.5, 2.5) | <0.001 | | 1.6 (1.3, 2.1) | <0.001 | | 1.6 (1.2, 2.1) | <0.001 | |
| Seconde | | | | | | | | | |
| 2.28–3.88 | Reference | | | Reference | | | Reference | | |
| 3.89–10.25 | 7.2 (2.8, 18.4) | <0.001 | | 4.4 (1.7, 11.4) | 0.003 | | 4.3 (1.6, 11.5) | 0.003 | |
| Group trend | 5.2 (2.4, 11.3) | | <0.001 | 3.4 (1.5, 7.6) | | 0.003 | 3.4 (1.5, 7.7) | | 0.003 |

**Notes**: [a]Non-adjusted model adjust for: none; [b]model 1 adjust for: age; gender; [c]model 2 adjust for: age; gender; anion gap; CHF; liver disease.
**Abbreviations**: RA, red blood cell distribution width–albumin ratio; DKA, diabetic ketoacidosis; HR, hazard ratio; CI, confidence interval.

**Table 3** Association Between RA and Sepsis

| | Non-Adjusted[a] | | | Model 1[b] | | | Model 2[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CIs) | P value | P for Trend | HR (95% CIs) | P value | P for Trend | HR (95% CIs) | P value | P for Trend |
| Sepsis | 2.9 (2.0, 4.1) | <0.001 | | 2.8 (1.9, 4.1) | <0.001 | | 3.0 (1.9, 4.6) | <0.001 | |
| Seconde | | | | | | | | | |
| 2.28–3.88 | Reference | | | Reference | | | Reference | | |
| 3.89–10.25 | 7.7 (2.3, 26.3) | 0.001 | | 6.6 (1.9, 23.2) | 0.003 | | 5.8 (1.6, 20.7) | 0.007 | |
| Group trend | 5.5 (2.0, 15.3) | | 0.001 | 4.9 (1.7, 13.8) | | 0.003 | 4.3 (1.5, 12.5) | | 0.007 |
| Sepsis shock | 2.8 (1.9, 4.2) | <0.001 | | 2.9 (1.9, 4.3) | <0.001 | | 3.0 (1.9, 4.8) | <0.001 | |
| Seconde | | | | | | | | | |
| 2.28–3.88 | Reference | | | Reference | | | Reference | | |
| 3.89–10.25 | 5.3 (1.5, 18.7) | 0.009 | | 4.9 (1.4, 17.7) | 0.015 | | 4.2 (1.1, 15.8) | 0.033 | |
| Group trend | 4.0 (1.4, 11.5) | | 0.009 | 3.8 (1.3, 11.0) | | 0.015 | 3.3 (1.1, 10.0) | | 0.033 |

**Notes**: [a]Non-adjusted model adjust for: none; [b]model 1 adjust for: age; gender; [c]model 2 adjust for: age; gender; anion gap; CHF; liver disease.
**Abbreviations**: RA, red blood cell distribution width–albumin ratio; HR, hazard ratio; CI, confidence interval.

0.001). Model 2 revealed a similar result for sepsis (HR: 3.0, 95% CI: 1.9, 4.6, p < 0.001) and septic shock (HR: 3.0, 95% CI: 1.9, 4.8, p < 0.001). Moreover, in the non-adjusted model, a high RA was still found to be a predictor for an increased risk of sepsis (HR: 5.5, 95% CI: 2.0, 15.3, p for trend = 0.001), model 1 (HR: 4.9, 95% CI: 1.7, 13.8, p for trend = 0.003), and model 2 (HR: 4.3, 95% CI: 1.5, 12.5, p for trend = 0.007). An increased RA indicated increased risk of septic shock in the non-adjusted model (HR: 4.0, 95% CI: 1.4, 11.5, p for trend = 0.001), model 1 (HR: 3.8, 95% CI: 1.3, 11.0, p for trend = 0.015), and model 2 (HR: 3.3, 95% CI: 1.1, 10.0, p for trend = 0.033).

## Discussion

In this study, we found that RA was a predictor for all-cause mortality in DKA patients, while an increased RA suggested an elevated risk of mortality. In addition, elevated RA was significantly associated with an increased risk of sepsis and septic shock in DKA patients.

RDW had the prognosis value for DKA. Dai et al reported that high RDW was related to an increased risk of all-cause mortality in DKA patients.[14] While it was reported albumin could predict the occurrence of DKA, Karthikeyan et al had found that lower serum albumin level was associated with a high occurrence of DKA.[15] They found that hypoalbuminemic DKA patients had higher level ketones in urine than normoalbuminemic DKA patients. This result was similar to our article. Although HR of RDW in DKA patients was increased in the above-cited article, the changes in variables were lower than those in our research. Yoo et al also reported that RA is better than RDW for predicting the mortality in acute respiratory distress syndrome. All results supported that RA might have more predict value than using RDW alone.

Zhang et al found RDW was useful predictor for sepsis. Sepsis patients with high value of RDW had higher all-cause mortality.[16] The same trend was found in neonatal sepsis.[17] Albumin also plays a predictive role in sepsis. Kendall et al found that low trend of serum albumin levels over time was associated with poor outcomes in patients with sepsis.[18] It was also a strong predictor for sepsis in the elderly.[19] All these results might partly explain the predicted role of RA in sepsis DKA patients.

The pathogenic mechanisms of DKA have not been clearly elucidated; however, it has been suggested that inflammation may play an important role in the process.[6,7,20] High RDW levels and low albumin levels are strongly correlated with enhanced inflammation.[10,21–25] Inflammatory cytokines lead to iron dysregulation, decreased erythropoietin production, damaged erythrocyte maturation, decreased RBC survival, enhanced immature erythrocyte circulation, and ultimately, increased anisocytosis. Albumin has the capacity for binding pro-inflammatory substances and decreasing inflammatory responses. In summary, a high RA, which represents elevated RDW and suppressed albumin levels, is a predictor for severe inflammation.

There are some limitations associated with this study. All data were obtained from the MIMIC III (v1.4) database; therefore, there may be a potential bias. Moreover, dynamic changes in RA, which may have elucidated on the predictive value of RA for DKA patients, were not evaluated in this study.

## Conclusions

RA is a potential prognostic marker for DKA patients. A high RA is significantly correlated with increased all-cause mortality of DKA and an increased incidence of DKA-related infections.

## Data Sharing Statement

The raw data were available in figshare (dx.doi.org/10.6084/m9.figshare.15105195).

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## Disclosure

The authors declare no conflicts of interest for this research.

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