

Influence of Red Blood Cell Distribution Width on All-Cause Death in Critical Diabetic Patients with Acute Kidney Injury

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Objective: To explore the relationship between red blood cell distribution width (RDW) and all-cause death in critical diabetic patients with acute kidney injury (AKI).

Methods: The clinical data of critical diabetic patients with AKI in MIMIC-III database were analyzed retrospectively. According to the survival status of 28-day after AKI and levels of RDW, patients were divided into survival and death groups, high RDW (RDW > 15.3%) and low RDW groups (RDW ≤ 15.3%). Kaplan–Meier curves were used to compare the survival rates of diabetic patients with AKI in different RDW and AKI stages, and Cox regression analysis was used to evaluate the risk factors of 28-day all-cause death in critical diabetic patients with AKI.

Results: A total of 5200 patients with critical diabetic patients with AKI were included in this study with the male to female ratio of 1.53:1. The mean follow-up time was 24.97 ± 7.14 days, and the 28-day all-cause mortality was 17.9% (931/5200). Age, RDW, blood urea nitrogen, serum creatinine, lactic acid, proportion of AKI stage, sepsis and respiratory failure in the death group were higher than those in the survival group, while mean arterial pressure (MAP) and red blood cell count were lower than those in the survival group. Kaplan–Meier analysis showed that the 28-day survival rate of the high RDW group was significantly lower than that of the low RDW group (log-rank $\chi^2 = 9.970$, $P = 0.002$). Multivariate Cox regression analysis showed that advanced age (HR = 1.042, 95% CI = 1.021–1.063), decreased MAP (HR = 0.984, 95% CI = 0.969–0.998), stage 3 AKI (HR = 3.318, 95% CI = 1.598–6.890) and increased RDW (HR = 1.255, 95% CI = 1.123–1.403) were independent risk factors of 28-day all-cause death in critical diabetic patients with AKI ($P < 0.05$).

Conclusion: High level of RDW is an important risk factor of all-cause death in critical diabetic patients with AKI, and it may be used as a valuable index to classify the mortality.

Keywords: diabetes, acute kidney injury, all-cause death, red cell distribution width, critical

Background

Diabetes is one of the most common chronic diseases in the world, which seriously threatens the life and health of human. In recent years, the incidence and prevalence of diabetes have grown significantly throughout the world.¹ According to the International Diabetes Federation Atlas, 10th edition, 537 million adults aged 20–79 are currently living with diabetes, which is expected to rise to 643 million (accounting for 11.3%) by 2030 and 783 million (accounting for 12.2%) by 2045.²

Acute kidney injury (AKI) has a very high incidence and fatality rate in intensive care unit (ICU), and occurs in approximately 50% of critically ill patients.^{3,4} A prospective study showed that about 11.0% of patients with AKI died in ICU, and AKI was an independent risk factor of the increased 28-day mortality (OR = 1.77, 95% CI = 1.17–2.68).⁵ In

addition, AKI is also considered to be one of the common renal complications of diabetes.⁶ A retrospective cohort study showed that the incidence of AKI in patients with diabetes was approximately 48.6%, significantly higher than that in non-diabetic patients (accounting for 17.2%).⁷ Diabetic patients with AKI have poor clinical outcomes, which seriously affect the quality of life of patients. Without timely treatment, critical diabetic patients with AKI are more likely to develop into chronic renal failure or end-stage renal disease, severe infection, heart failure, and even death.^{8,9}

Red blood cell distribution Width (RDW) is a convenient and inexpensive biochemical parameter. As one of the complete blood routine test indexes, RDW is calculated from the ratio of mean red blood cell (RBC) volume to its standard deviation, and mainly reflects the variability of RBC volume.¹⁰ Both diabetes and AKI cause high inflammatory burden. Increased RDW has been reported other inflammatory conditions such as functional bowel conditions,¹¹ rheumatoid arthritis,¹² degenerative vertebral conditions,¹³ malignancy,¹⁴ and autoimmune hepatitis.¹⁵ However, the relationship between RDW levels and prognosis in diabetic patients with AKI is still unclear. This present study retrospectively analyzed the clinical data of Medical Information Mart for Intensive Care III (MIMIC-III) to explore the relationship between RDW and 28-day all-cause death in critical diabetic patients with AKI, providing some reference for evaluation of short-term prognosis and treatment of diabetic patients with AKI.

Materials and Methods

Database

As a free and open public database, MIMIC-III database collected clinical information from more than 50,000 patients who were admitted to the ICU of Beth Israel Deacon Medical Center from 2001 to 2012. The establishment of this database was approved by the institutional review boards of Massachusetts Institute of Technology (MIT, Cambridge, MA, USA) and Beth Israel Deaconess Medical Center. All included patients signed (or commissioned to sign) informed consent forms and were de-identified to protect their privacy. In order to gain access to the database, we completed the National Institutes of Health online course, passed the Protecting Human Study Participants Exam, and received a certificate (No. 30165505). This study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University [approval number: 2019 (KY-E-028)].

Inclusion and Exclusion Criteria

Inclusion criteria: (1) diabetic patients with AKI; (2) ICU length of stay (LOS) ≥ 48 h; (3) serum creatinine (Scr) levels were measured at least twice within 7 days. Exclusion criteria: (1) age < 18 years old; (2) stage 5 chronic kidney disease (CKD) or regular renal replacement therapy (RRT); (3) pregnant women, combined with blood diseases (such as leukemia or myelodysplastic syndrome); (4) patients with missing important baseline data (like RDW); (5) patients who discharged or died within 48h after ICU admission.

Data Collection

Baseline data of patients (including basic characteristics, vital signs, scoring system, laboratory parameters and comorbidities) were recorded. The scoring systems include the Simplified Acute Physiology Score II (SAPSII), Oxford Acute Severity of Illness Score (OASIS) and Sequential Organ Failure Assessment (SOFA) score. Laboratory parameters included white blood cell (WBC) count, hemoglobin (Hb), red blood cell(RBC) count, RDW, platelet (PLT) count, blood urea nitrogen (BUN), Scr, random blood glucose (RBG), and lactic acid (Lac). Complications include acute respiratory distress syndrome (ARDS), congestive heart failure (CHF), sepsis, and renal failure. Vital signs, score system data and laboratory parameters were recorded within 24 hours after admission. For patients admitted to ICU multiple times, the clinical data of the first admission to ICU were selected.

Diagnostic Criteria

AKI and stage were defined according to the diagnostic criteria of KDIGO guidelines:¹⁶ (1) diagnostic criteria of AKI: Scr increase ≥ 0.3 mg/dL within 48h, or increase $> 50\%$ of baseline within 7 days. (2) The criteria of AKI stage: stage 1: Scr increase to 1.5–1.9 times of baseline value or increased ≥ 0.3 mg/dL, stage 2: Scr increase to 2.0–2.9 times of base value, stage

3: Scr increase to 3 times or $\geq 4.0\text{mg/dL}$ or begin RRT. The diagnosis of diabetes was in line with the standards of the World Health Organization:¹⁷ diabetes symptoms plus (1) RBG $\geq 200\text{mg/dL}$, or (2) fasting blood glucose $\geq 126\text{mg/dL}$, or (3) postprandial blood glucose $\geq 200\text{mg/dL}$; patients who had been diagnosed with diabetes and were taking antidiabetic therapy.

Study Grouping and Clinical Outcome

The retrospective cohort study was follow up at 28-day after AKI diagnosis or death (death within 28-day), and the clinical outcome was all-cause death. According to whether they died within 28 days, patients were divided into death group and survival group. Patients were also divided into high RDW group ($\text{RDW} > 15.3\%$) and low RDW group ($\text{RDW} \leq 15.3\%$) according to the median of RDW levels.

Statistical Methods

SPSS22.0 statistical software was used for statistical analysis. Data were tested for normality using the histogram and Shapiro–Wilk tests. Measurement data conforming to normal distribution are expressed as mean \pm standard deviation, and independent sample *t*-tests were used for comparison between groups; data with non-normal distribution are presented as the median and quartiles, and Wilcoxon rank-sum tests were used for comparison between groups. Counting data are expressed as frequency (percentage), and χ^2 tests were used for comparison between groups. Kaplan–Meier survival curves (Log-rank χ^2 method) were used to compare the survival rate of critical diabetic patients with AKI with different levels of RDW and AKI stages. Cox regression analysis was used to explore the independent risk factors of 28-day all-cause death in patients with critical diabetic patients with AKI. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics and Clinical Outcomes

A total of 5200 critical diabetic patients with AKI were included in the analysis, including 3141 (accounting for 60.4%) males and 2059 (accounting for 39.6%) females, with a male to female ratio of 1.53:1. The average follow-up time was 24.97 ± 7.14 days. Among them, 1440 patients (accounting for 27.7%) had AKI stage 1, 1732 (accounting for 33.3%) had AKI stage 2, and 2028 (accounting for 39.0%) had AKI stage 2. Using 15.3% (median of RDW) as truncation value, there were 2070 (accounting for 39.8%) patients in the high RDW group ($\text{RDW} > 15.3\%$) and 3130 (accounting for 60.2%) patients in the low RDW group ($\text{RDW} \leq 15.3\%$). The 28-day all-cause mortality was 17.9% (930/5200). The main causes of death were 361 cases (accounting for 38.8%) of infection, 337 cases (accounting for 36.2%) of cardiovascular and cerebrovascular diseases, and 232 cases (accounting for 25.0%) of other or unknown causes.

Comparison of Clinical Data Between the Death and Survival Groups

As shown in Table 1, age, proportion of stage 3 AKI, SOFA, SAPSII, OASIS, RDW, BUN, Scr, Lac, proportion of sepsis and respiratory failure in the death group were higher than those in the survival group, and mean arterial pressure (MAP) and RBC were lower than those in the survival group ($P < 0.05$). There were no significant differences in the ratio of male to female, ICU LOS, body mass index, temperature, heart rate, respiration, central venous pressure, WBC, Hb, PLT, proportion of CHF, ARDS, hypertension and renal failure between the death group and the survival group ($P > 0.05$).

Risk Factors of All-Cause Death in Critical Diabetic Patients with AKI

According to the clinical data comparison between the death group and the survival group in Table 1, the variables with $P < 0.05$ were included in the multivariate Cox regression analysis, and the results showed that advanced age ($\text{HR} = 1.042$, 95% CI = 1.021–1.063), MAP decreased ($\text{HR} = 0.984$, 95% CI = 0.969–0.998), stage 3 AKI ($\text{HR} = 3.318$, 95% CI = 1.598–6.890) and high RDW ($\text{HR} = 1.255$, 95% CI = 1.123–1.403) were independent risk factors of 28-day all-cause death in critical diabetic patients with AKI ($P < 0.05$, as shown in Table 2).

Table 1 Comparison of Data Between the Death Group and the Survival Group in Critical Diabetic Patients with AKI

Parameters	Death Group	Survival Group	t/ χ^2	P value
Basic characteristics				
Male/female	560/370	2580/1690	0.014	0.907
Age (year)	73.56±10.80	67.07±13.86	4.974	0.001
ICU LOS (day)	8.90±5.56	9.58±9.20	-0.931	0.353
BMI (kg/m ²)	30.14±6.77	31.79±8.28	-1.499	0.135
Vital signs				
Temperature (°C)	37.56±1.13	37.61±0.97	-0.466	0.641
Heart rate (beats/min)	109.52±21.06	107.55±20.73	0.826	0.409
Respiratory (beats/min)	29.79±6.28	28.74±6.70	1.378	0.169
MAP (mmHg)	46.05±13.51	51.61±14.50	-3.392	0.001
CVP (mmHg)	6.89±5.52	6.12±4.04	1.274	0.205
AKI stage			322.565	<0.001
Stage 1	110 (11.8)	1328 (31.1)		
Stage 2	220 (23.7)	1512 (35.4)		
Stage 3	600 (64.5)	1430 (33.5)		
Scoring system				
SOFA	9.27±3.94	7.49±3.47	4.358	<0.001
SAPSII	57.18±14.10	46.84±14.19	6.374	<0.001
OASIS	43.19±7.70	37.84±8.86	5.399	<0.001
Selected laboratory test				
WBC (×10 ⁹ /L)	11.88±6.97	10.77±6.08	1.425	0.157
RBC (×10 ¹² /L)	3.14±0.70	3.35±0.69	-2.557	0.011
Hb (g/dL)	8.62±1.85	8.86±2.11	-1.531	0.126
Platelet (×10 ⁹ /L)	188.51±130.70	175.53±94.25	0.907	0.366
RDW (%)	16.10±2.14	15.16±1.88	3.897	<0.001
BUN (mg/dL)	44.72±28.71	31.67±21.90	4.130	<0.001
Scr (mg/dL)	2.08±1.39	1.66±1.37	2.676	0.008
RBG (mg/dL)	125.46±49.26	115.35±46.27	1.887	0.060
Lactic acid (mmol/L)	2.06±1.31	1.59±0.96	3.154	0.002
Complications				
Sepsis[n (%)]	740 (79.6)	2430 (56.9)	164.778	<0.001
CHF[n (%)]	365 (39.2)	1631 (38.2)	1.457	0.227
ARDS[n (%)]	60 (6.5)	260 (6.1)	0.174	0.677
Respiratory failure[n (%)]	680 (73.1)	2404 (56.3)	89.507	<0.001
Hypertension[n (%)]	700 (75.3)	3181 (74.5)	0.241	0.624
Renal failure[n (%)]	307 (33.0)	1311 (30.7)	1.898	0.168

Note: The bold numbers represent the P values with significant differences.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BMI, body mass index; BUN, blood urea nitrogen; CHF, congestive heart failure; CVP, central venous pressure; Hb, hemoglobin; ICU LOS, intensive care unit length of stay; MAP, mean arterial pressure; OASIS, oxford acute severity of illness score; RBC, red blood cell; RBG, random blood glucose; RDW, red blood cell distribution width; SAPSII, simplified acute physiology score II; Scr, serum creatinine; SOFA, sequential organ failure assessment; WBC, white blood cell.

Influence of RDW on All-Cause Death and Other Adverse Outcomes

As shown in Table 3, patients were divided into high and low RDW groups using the median of RDW as truncation value. The 28-day all-cause mortality, proportion of stage 3 AKI, peak Scr levels, and proportion of RRT were higher in the high RDW group than in the low RDW group ($P < 0.001$).

Table 2 Risk Factors of All-Cause Death in Critical Diabetic Patients with AKI (Multivariate Cox Regression Analysis)

Parameters	B	SE	Wald	HR	95% CI	P value
Age	0.041	0.010	16.387	1.042	1.021–1.063	<0.001
MAP	−0.017	0.008	4.695	0.984	0.969–0.998	0.030
AKI stage			15.241		–	<0.001
Stage 1						
Stage 2	0.176	0.395	0.199	1.193	0.550–2.589	0.656
Stage 3	1.199	0.373	10.355	3.318	1.598–6.890	0.001
SOFA	−0.003	0.048	0.003	0.997	0.907–1.096	0.953
SAPSII	0.023	0.013	2.930	1.023	0.997–1.050	0.087
OASIS	−0.027	0.018	2.221	0.973	0.938–1.009	0.136
Respiratory failure	0.453	0.278	2.666	1.574	0.913–2.712	0.103
Sepsis	0.247	0.300	0.677	1.280	0.711–2.303	0.411
RBC	−0.186	0.291	0.409	0.830	0.470–1.468	0.523
RDW	0.227	0.057	16.068	1.255	1.123–1.403	<0.001
BUN	0.004	0.006	0.532	1.004	0.993–1.015	0.466
Scr	−0.155	0.131	1.390	0.857	0.663–1.108	0.238
Lactic acid	0.181	0.095	3.620	1.198	0.995–1.443	0.057

Note: The bold numbers represent the *P* values with significant differences.

Abbreviations: 95% CI, 95% confidence interval; AKI, acute kidney injury; B, regression coefficient; BE, standard error; BUN, blood urea nitrogen; HR, hazard rate; MAP, mean arterial pressure; OASIS, oxford acute severity of illness score; RBC, red blood cell; RDW, red blood cell distribution width; SAPSII, simplified acute physiology score II; Scr, serum creatinine; SOFA, sequential organ failure assessment.

Table 3 Differences of All Cause Deaths and Other Adverse Outcomes at Different Levels of RDW

Parameters	RDW>15.3%	RDW≤15.3%	t/χ^2	P value
28-day death[n (%)]	501 (24.2)	429 (13.7)	93.481	<0.001
AKI stage			116.396	<0.001
Stage 1[n (%)]	460 (22.2)	980 (31.3)		
Stage 2[n (%)]	621 (30.0)	1111 (35.5)		
Stage 3[n (%)]	989 (47.8)	1039 (33.2)		
Peak Scr (mg/dL)	2.68±1.89	1.91±1.52	4.940	<0.001
RRT[n (%)]	660 (31.9)	470 (15.0)	208.438	<0.001

Note: The bold numbers represent the *P* values with significant differences.

Abbreviations: AKI, acute kidney injury; RDW, red blood cell distribution width; RRT, renal replacement therapy; Scr, serum creatinine.

Influence of Different RDW and AKI Stages on the Survival Rate

As shown in [Figure 1](#), Kaplan-Meier survival analysis showed that the mean survival time of the high RDW group and the low RDW group were [23.68 days (95% CI = 22.55–24.81)] and [25.81 days (95% CI = 25.14–26.49)], respectively. The 28-day cumulative survival rate in the high RDW group was significantly lower than that in the low RDW group (75.7% vs 86.3%; Log-rank $\chi^2 = 9.970$, $P = 0.002$). As shown in [Figure 2](#), the mean survival time of patients with AKI stage 1, 2 and 3 were [27.06 days (95% CI = 26.45–27.67)], [25.95 days (95% CI = 25.04–26.86)], [24.97 days (95% CI = 24.36–25.59)], respectively. The difference in 28-day cumulative survival were statistically significant among the three groups (92.4% vs 87.3% vs 70.4%; Log-rank $\chi^2 = 34.353$, $P < 0.001$).

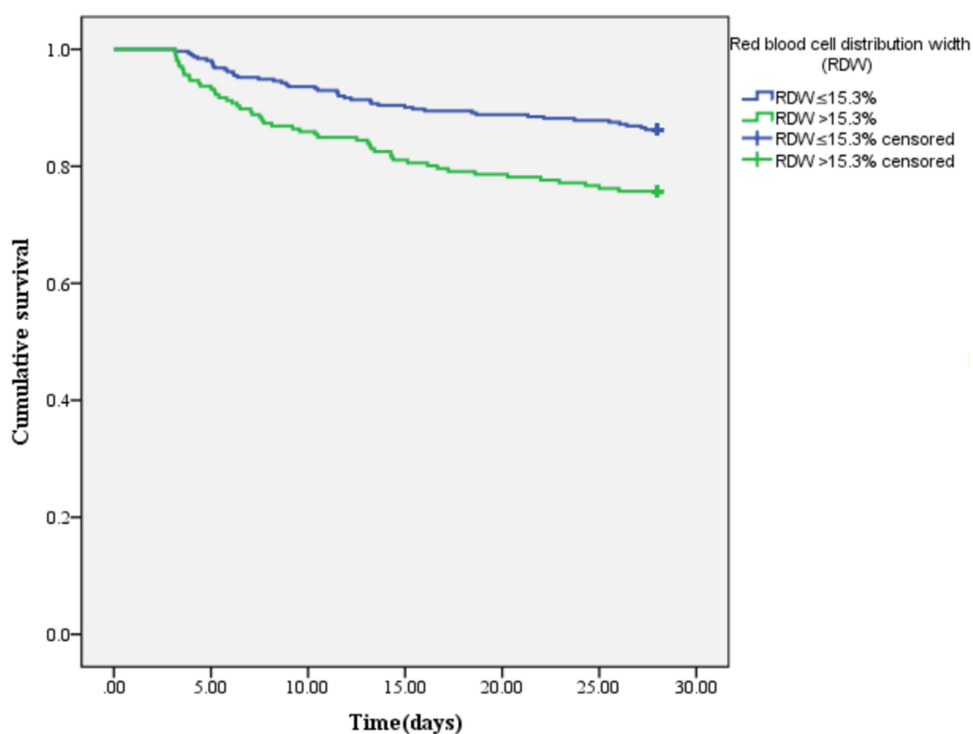


Figure 1 Comparison of survival curves of critical diabetic patients with AKI in different RDW groups (Kaplan–Meier survival curve).

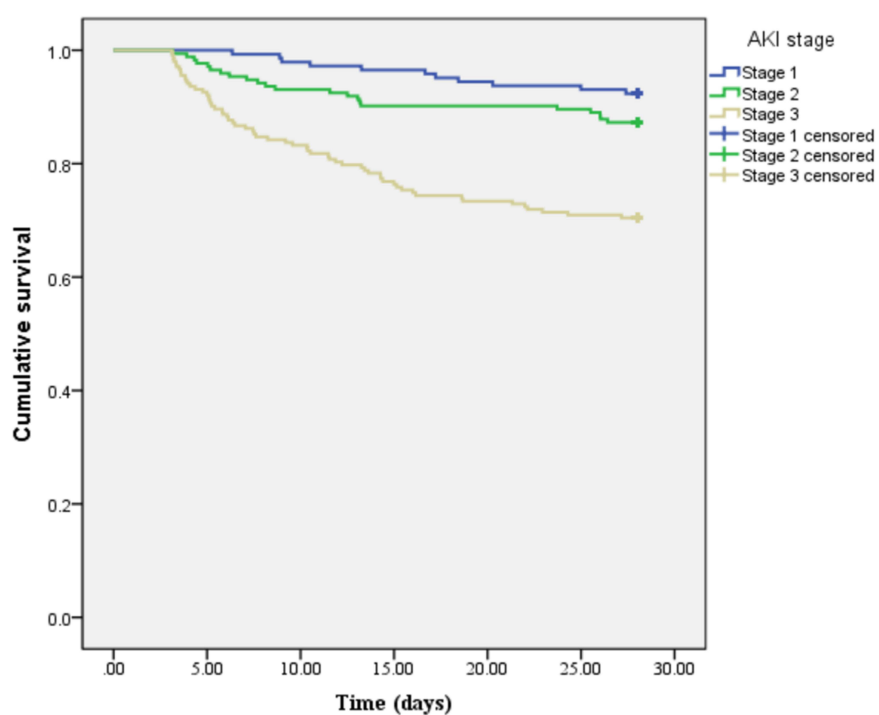


Figure 2 Comparison of survival curves of critical diabetic patients with AKI in different stages (Kaplan–Meier survival curve).

Discussion

In the present retrospective study of 5200 critical diabetic patients with AKI, the relationship between baseline RDW and short-term survival was investigated. After adjusting for confounders, high RDW was an independent risk factor of 28-day all-cause death in critical diabetic patients with AKI. RDW is a parameter reflecting the heterogeneity of RBC volume in peripheral blood. Increased RDW is not only associated with increased RBC destruction and ineffective production, but also indicates iron deficiency anemia, inflammation and malnutrition.¹⁸ A prospective observational study showed that RDW was an independent predictor of AKI (OR = 1.059, 95% CI = 1.024–1.095) and in-hospital mortality (HR = 1.129, 95% CI = 1.005–1.268) in coronary care units.¹⁹ Nanjarapalle et al²⁰ also showed that RDW was a better predictor of mortality in critically ill AKI patients requiring RRT than other disease severity scoring systems (area under the subject working curve was 0.904). In addition, previous studies have investigated the association between RDW and mortality and poor prognosis in patients with renal diseases such as AKI, hemodialysis and peritoneal dialysis.^{21–23} However, the prognoses of patients with diabetic AKI are worse than that of patients with simple diabetes or AKI, and there are little studies on RDW and prognosis of patients with diabetic AKI. In this study, based on MIMIC-III database, the relationship between RDW levels and short-term prognosis of patients with diabetic AKI was confirmed, which may help to stratify the risk of poor prognosis.

Our study showed that the incidence of high RDW in diabetic patients with AKI was 39.8%, which was similar to the results of Jia et al (34.5%)²⁴ and Hu et al (30.8%).¹⁹ It can be seen that the incidence of high RDW in diabetic patients with AKI is high. The mechanisms of high RDW in diabetic patients with AKI are as follows: (1) renal ischemia during AKI might promote erythropoietin production and stimulate RBC proliferation,²⁵ leading to increased RDW. (2) In diabetic patients with AKI, the inflammatory response of body was severe, iron metabolism and bone marrow function were inhibited, and the proliferation and maturation of RBC were inhibited, leading to the increase of RDW value.²⁶ (3) Diabetic patients with AKI were often complicated by oxidative stress, including metabolic disorders, sepsis and hemodynamic disorders, which could lead to increased changes of RBC size, and thus increased the levels of RDW.²⁷ Some reports suggested an association between inflammation and RDW, such as autoimmune diseases²⁸ and COVID-19 infections.²⁹ In addition, inflammation plays an important role both in the pathogenesis of diabetes and AKI, and our study also showed that RDW was associated with AKI in patients with diabetes. On the other hand, other reports found no diagnostic or prognostic value of RDW,^{30,31} which might be due to differences in the observation time of follow-up, variability in the degree of disease, and diversity of the intervention time and therapy in different studies. Our results also showed that patients in the high RDW group had higher AKI stage, peak Scr levels, and proportion of RRT than those in the low RDW group. Previous studies also showed that the glomerular filtration rate could decrease with the increase of RDW, and the increase of RDW was closely related to renal function injury.^{32,33} Thus, high RDW might be closely associated with the increased risk of renal function progression in diabetic patients with AKI. While the progression of renal function was an independent predictor of cardiovascular events and all-cause mortality.³⁴ The effect of RDW on all-cause mortality might also be realized by increasing the risk of renal function progression. In addition, RDW is one of the parameters in blood routine and is easy to detect and obtain in clinic. Therefore, when increased RDW levels were detected clinically in diabetic patients with AKI, the occurrence of short-term renal function progression and poor prognosis should be warned. Clinicians can predict the risk of death by early assessment of RDW and improve the outcome of critical diabetic patients with AKI by actively managing and intervening risk factors.

Our study also showed that stage 3 AKI was an independent risk factor for 28-day all-cause death in critical diabetic patients with AKI. Mo et al³⁵ established a clinical prediction model for short-term mortality in diabetic patients with AKI, and the results showed that AKI stage was also an independent risk factor for 90-day all-cause mortality in diabetic patients with AKI (HR = 4.803, 95% CI = 1.678–13.750), which was consistent with our study. Another prospective study showed that increased AKI severity was associated with in-hospital mortality in ICU patients after adjustment for other variables (OR = 6.884, 95% CI = 3.876–12.228).³⁶ The mechanism of increased mortality in patients with higher stage of AKI might be related to these factors as follows: when diabetes was complicated with severe AKI, oliguria and volume recovery could lead to adverse consequences such as volume overload, metabolic acidosis and electrolyte disorder.³⁷ Inflammation might also lead to dysfunction of multiple organs in the body.³⁸ Uremia toxin might impair the immune function of patients and increase the probability of infection.³⁹ In critical AKI, the complex dosage of

various drugs would lead to treatment failure and adverse drug events, which ultimately could lead to increased mortality.^{40,41} Therefore, the short-term prognosis of critical diabetic patients with AKI might also be predicted according to AKI stage in clinical practice.

However, there were still some limitations in this study: (1) this study was a single-center retrospective study with a small sample size, and the study period was only 28 days. Some potential influencing factors of RDW and death might not be included in the analysis. (2) The diagnosis of AKI was only based on the degree of change in Scr, not including urine volume. (3) Only RDW might underestimate the true cause of poor prognosis. Therefore, multi-center cohort studies with large sample sizes are needed to further explore the specific pathophysiological mechanism of RDW in critical diabetic patients with AKI.

Conclusion

In conclusion, increased RDW is an important risk factor for increased all-cause mortality in critical diabetic patients with AKI, and may be used as a valuable indicator of mortality risk. RDW level may be a potential predictor of short-term renal poor outcome and all-cause mortality in critical diabetic patients with AKI.

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Disclosure

All authors declare that there is no conflict of interest.

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