Original Paper

Red Blood Cell Distribution Width is an Independent Predictor of AKI and Mortality in Patients in the Coronary Care Unit

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Key Words

Red blood cell distribution width • Acute kidney injury • Mortality • Coronary care unit

Abstract

Background/Aims: We investigated the hypothesis that RDW is an independent predictor of acute kidney injury (AKI) and mortality in patients in the coronary care unit (CCU). **Methods:** In this prospective, observational study, we screened 412 adults admitted to the CCU at Zhongnan Hospital of Wuhan University from January 1, 2014 to June 1, 2015. AKI was defined based on the KDIGO-AKI criteria. The survivors were followed up for up to 2 years after hospital discharge. The primary endpoint of the study was the incidence of AKI, while the secondary endpoints of the study were in-hospital mortality and 2-year mortality. **Results:** RDW was significantly correlated with the acute physiology and chronic health evaluation II (APACHEII) score, hemoglobin, mean corpuscular volume, inflammatory marker levels, nutrition and renal function at the time of CCU admission. The incidence of AKI was much higher in the high RDW group (RDW $\geq 14.0\%$) than in the low RDW group, a finding that was confirmed by multivariable logistic regression, which showed that RDW was independently associated with the incidence of AKI (odds ratio (OR), 1.059, 95% coincidence interval (95% CI), 1.024-1.095, $P=0.001$). A total of 61 patients died during their hospital stay, and baseline RDW was also an independent predictor of in-hospital mortality (hazard ratio (HR), 1.129, 95% CI 1.005-1.268, $P=0.041$). Patients with a high RDW exhibited significantly higher 2-year mortality than patients with a low RDW during a median follow-up period of 19.8 months ($P<0.001$), and RDW independently predicted the risk of 2-year mortality (HR, 1.189, 95% CI 1.045 to 1.354, $P=0.009$) in the multivariate Cox proportional hazard analysis after adjustments for other clinical and laboratory variables. **Conclusion:** RDW is an independent predictor of AKI and mortality in patients in the CCU.

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Introduction

As a parameter routinely reported as form of the complete blood count, red cell distribution width (RDW), is a numerical measure of the variability in size of circulating erythrocytes, which is virtually limited to the differential diagnosis of anemia even until now. An increased RDW, even an RDW within the normal reference range, was recently demonstrated to be a strong independent predictor of adverse outcomes not only in chronic conditions, such as heart failure, coronary artery disease [1], pulmonary hypertension [2] and cancer [3], but also in acute illnesses, such as acute coronary syndrome [4], acute heart failure [5] and ischemic stroke [6]; however, the mechanism underlying this phenomenon is incompletely elucidated.

Acute kidney injury (AKI) is characterized by intrarenal and systemic inflammation and is associated with high morbidity and mortality, particularly in critically ill patients [7, 8]. Clinical trials have demonstrated that RDW has prognostic value in patients with chronic kidney disease [9], patients receiving hemodialysis or peritoneal dialysis [10-14] and patients with AKI who are being treated with continuous renal replacement therapy [15]. Moreover, a limited study found a connection between RDW and contrast-induced AKI (CI-AKI) in patients with ST-segment-elevation myocardial infarction who underwent primary percutaneous coronary intervention [16, 17]. In addition, to our knowledge, no study has investigated the association between RDW and the risk of AKI in critically ill patients. In this prospective observational study, we aimed to explore the hypothesis that RDW is an independent predictor of AKI and mortality in patients in the coronary care unit (CCU).

Materials and Methods

Study design

We performed a prospective observational study involving 445 adult patients (23 to 97 years) who were admitted to the CCU at Zhongnan Hospital of Wuhan University from January 1, 2014 to June 1, 2015. The following participants were eligible for the study: (1) patients who had been hospitalized in the CCU for more than 48 hours and (2) patients with at least one serum creatinine measurement within the 6-month period before their CCU admission. The exclusion criteria included pre-existing peritoneal dialysis or maintenance hemodialysis, urinary tract infection or obstruction, cancers, and a history of renal transplantation. A total of 412 [135 (32.8%) males and 277 (67.2%) females] adult patients were ultimately enrolled in our study. The primary diagnoses for these patients included acute coronary syndrome (268 patients, 65.0%), chronic coronary artery disease (81 patients, 19.7%), acute decompensated heart failure (16 patients, 3.9%), arrhythmia (32 patients, 7.8%) and other diseases (15 patients, 3.6%).

Demographic, clinical and biochemical data were collected for all the patients enrolled in the study immediately after they were admitted to the CCU and before they received any in-hospital treatments. Acute physiology and chronic health evaluation II (APACHEII) scores were determined for all eligible participants to evaluate the severity of their diseases. This method of risk stratification is a generally accepted tool for assessing the prognoses of adult patients in ICUs [18]. The survivors were followed up via record reviews or telephone interviews as needed for up to 2 years after hospital discharge.

The primary outcome of the study was the incidence of AKI, which was stratified based on its severity, according to the KDIGO Clinical Practice Guidelines for AKI. The guidelines are based on criteria pertaining to serum creatinine concentrations [19]. Preexisting chronic kidney disease (CKD) was diagnosed in patients who were diagnosed with CKD or patients with an estimated glomerular filtration rate (eGFR) of less than 60 ml/min per 1.73 m² before hospital admission. The eGFR was calculated with the serum creatinine measurement obtained during the 6-month period before admission and was estimated by the Cockcroft-Gault equation [20], as this equation has the best prognostic value in patients with acute coronary syndrome [21, 22].

The secondary outcomes of the study included in-hospital mortality and 2-year mortality from admission to the end of the 2-year follow-up period (each patient's death status and date of death were determined through reviews of hospital records and telephone calls to each patient's home).

This study was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University.

Laboratory measurements

Blood samples were obtained immediately after each patient was admitted to the CCU and before each patient received any in-hospital treatments. Hematologic testing was performed with a Sysmex (Sysmex Corporation, Kobe, Japan) automated hematology analyzer. RDW was calculated using standardized methods and was routinely reported as a percentage in the complete blood cell count. The reference range for RDW in our laboratory is 10.1-16.0%.

Statistical analyses

SPSS 22.0 software was used for all analyses. Descriptive analysis results are reported as the mean $\pm$ SD or as medians (interquartile ranges) for continuous variables and as proportions for categorical variables. We divided our cohort into groups according to their RDWs and outcomes using classification and regression tree (CART) and chi-square automatic interaction detection (CHAID). These methods choose the best continuous variable cutoff for determining the most accurate prognoses using repeated automated CHI tests [23]. We used two-sample t tests or the Mann-Whitney U test to compare continuous variables across groups and Pearson's chi-squared test (χ^2) to compare categorical variables across groups. We also calculated Spearman correlation coefficients for the relationships between RDW and other biochemical factors. We calculated adjusted odds ratios (ORs) for AKI with multivariable logistic regression. The prognostic factors for mortality were determined by a univariate Cox proportional hazards model, and the variables with a P -value <0.1 were included in the multivariate Cox proportional hazards model. Cumulative survival curves as a function of time were generated by Kaplan-Meier analysis and were compared by log-rank tests. To measure the sensitivity and specificity of RDW at different cutoff values, we generated a conventional ROC curve. We also calculated the area under the curve (AUC) to ascertain the quality of RDW as a predictor of AKI and mortality. In these analyses, RDW was modeled both as a categorical variable and as a continuous variable. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Subject characteristics

All the patients in the CCU were divided into separate groups according to their RDWs (Table 1), which ranged from 11.0% to 25.3% ($13.7 \pm 1.5\%$). We compared patients with an elevated RDW with patients without an elevated RDW. Patients with a high RDW were older and had higher serum creatinine and APACHEII scores and lower mean arterial pressure, hemoglobin, serum albumin, prealbumin, and serum triglyceride than patients with a low RDW (RDW $<14.0\%$). Patients with a high RDW also had lower mean corpuscular volumes and eGFRs than patients with a low RDW. Higher RDWs were more frequent in patients with preexisting CKD and male patients than in patients without preexisting CKD and female patients. However, there was no difference in comorbidities or drug usage before CCU admission between the two groups.

Association between RDW and other parameters

The Spearman correlation coefficients showed that RDW was significantly positively correlated with leucocyte counts ($r=0.139$, $P=0.005$), hs-CRP ($r=0.129$, $P=0.009$), serum creatinine ($r=0.126$, $P=0.01$) and APACHEII scores ($r=0.319$, $P<0.001$). Moreover, baseline RDW was negatively correlated with hemoglobin levels ($r=-0.391$, $P<0.001$), MCV ($r=-0.296$, $P<0.001$), eGFR ($r=-0.270$, $P<0.001$) serum albumin ($r=-0.403$, $P<0.001$), prealbumin ($r=-0.292$, $P<0.001$) and serum triglyceride ($r=-0.174$, $P<0.001$). However, we noted no correlations between RDW and age or total cholesterol in the current study (Table 2).

Table 1. Characteristics of the CCU patients on admission. BMI, body mass index; MAP, mean arterial pressure; MCV, mean corpuscular hemoglobin; RDW, red cell distribution width; hs-CRP, hypersensitive c reactive protein; eGFR, estimate glomerular filtration rate; APACHEII, acute physiology and chronic health evaluation II; LOS, length of hospital stay. ^aDefined as a preadmission eGFR <60 ml•min⁻¹•1.73 m⁻²; ^bPreadmission eGFR were calculated by the Cockcroft-Gault equation

Characteristic	RDW ≥ 14.0% (n=127)	RDW<14.0% (n=285)	P-value
Age, year	74.0±11.0	65.3±13.2	<0.001
Gender, male, n (%)	72 (56.7)	205 (71.9)	0.007
BMI, kg/m ²	23.8±3.5	23.7±3.4	0.841
Preexisting clinical conditions			
CKD ^a , n (%)	30 (23.6)	29 (10.2)	0.002
Hypertension, n (%)	88 (69.3)	178 (62.5)	0.174
Diabetes, n (%)	36 (28.3)	80 (28.1)	0.858
Preadmission medication			
Aspirin, n (%)	110 (86.6)	256 (89.8)	0.341
ACEI/ARB, n (%)	57 (44.9)	140 (49.1)	0.427
β-blockers, n (%)	71 (55.9)	185 (64.9)	0.088
Loop diuretics, n (%)	46 (36.2)	76 (26.7)	0.091
Characteristics on admission			
Mean arterial pressure, mmHg	89.8±19.7	93.6±16.0	0.042
Leucocyte, ×10 ⁹ /L	9.2±1.7	8.5±2.1	0.092
Hemoglobin, g/L	108.8±24.0	129.9±18.3	<0.001
MCV, fL	88.4±9.4	91.8±4.2	0.001
RDW, %	15.3±1.7	13.0±0.6	<0.001
Serum creatinine, umol/L	97.6±16.5	77.1±12.6	0.020
eGFR ^b , ml/min per 1.73 m ²	76.0±10.1	89.6±10.4	<0.001
Serum albumin, g/L	35.1±4.9	38.3±4.0	<0.001
Total cholesterol, mg/dl	4.0±0.9	4.1±0.9	0.055
Serum triglycerides, mg/dl	1.4±0.2	1.7±0.3	0.005
hs-CRP, mg/L	5.7 (2.4, 19.3)	4.1 (1.5, 16.4)	0.610
Prealbumin, mg/L	176.9±47.5	218.0±32.7	<0.001
APACHEII score, points	9.7±2.0	7.2±1.3	<0.001
Length of hospital stay, days	12.8±2.2	12.3±2.6	0.556
Outcomes			
AKI	63 (49.6)	67 (23.5)	<0.001
Stage 1	27	45	
Stage 2	22	15	
Stage 3	14	7	
In-hospital mortality, n (%)	28 (22.0)	33 (11.6)	0.013
2-year mortality, n (%)	33 (33.3)	18 (7.1)	<0.001

RDW as a predictor of the primary end point

AKI occurred in 130 (31.6%) patients in this study. The incidence of AKI was much higher in the high RDW group than in the low RDW group (49.6% versus 23.5%, $P<0.001$, Table 1). RDW values were associated with AKI in the univariate logistic regression analysis (unadjusted OR, 1.157, 95% CI 1.081 to 1.463, $P=0.003$), a finding that was supported by the results of the multivariate analyses. RDW was also an independent predictor of AKI (OR, 1.059, 95% CI 1.024 to 1.095, $P=0.001$) after adjustments for age, gender, preexisting CKD, body mass index (BMI), APACHEII scores, hemoglobin, MAP levels, serum albumin, total cholesterol, eGFR and hs-CRP (Table 3). A higher RDW was still associated with AKI development when RDW was analyzed as a categorical variable (adjusted OR, 1.853, 95% CI 1.086-3.162, $P=0.024$) (Table 4).

RDW value as a predictor of secondary outcomes

Both in-hospital mortality (22.0% versus 11.6%, $P=0.013$) and 2-year mortality (33.3% versus 7.1%, $P<0.001$) were significantly higher in the high RDW group than in the low RDW group (Table 1). Fig. 1 shows that RDW and the presence of AKI had additive effects on the risks of in-hospital and 2-year mortality in all participants. Patients who developed AKI while

Table 2. Correlations between baseline RDW and selected clinical parameters

Variables	RDW (%)	
	r	P-value
Age (years)	0.067	0.178
Complete blood count parameters		
Hemoglobin, g/L	-0.391	<0.001
Mean corpuscular hemoglobin, fl	-0.296	<0.001
Markers of inflammation		
hs-CRP, mg/L	0.129	0.009
Leucocyte, $\times 10^9/L$	0.139	0.005
Markers of nutrition		
Serum albumin, g/L	-0.403	<0.001
Total cholesterol, mg/dl	-0.081	0.100
Serum triglycerides, mg/dl	-0.174	<0.001
Prealbumin, mg/L	-0.292	<0.001
Markers of renal function		
eGFR, ml/min per 1.73 m ²	-0.270	<0.001
Serum creatinine, umol/L	0.126	0.010
APACHEII score, points	0.319	<0.001

Table 3. Univariate and multivariate logistic regression analysis of the ability of RDW to predict AKI when used as a continuous variable (n=412). OR, odds ratio; 95% CI, 95% confidence interval; ^aMultivariate model: adjusted for age, gender, preexisting CKD, BMI, APACHEII scores, hemoglobin, MAP, serum albumin, total cholesterol, eGFR and hs-CRP

	Univariate OR (95% CI)	P-value	Multivariate ^a OR (95% CI)	P-value
RDW, %	1.157 (1.081-1.463)	0.003	1.059 (1.024-1.095)	0.001
APACHEII score	1.376 (1.274-1.486)	<0.001	1.267 (1.143-1.405)	<0.001
Hemoglobin, g/L	0.954 (0.943-0.965)	<0.001	0.937 (0.903-1.032)	0.290
MAP, mmHg	0.977 (0.964-0.989)	<0.001	0.993 (0.977-1.009)	0.402
Male (versus female)	1.031 (0.662-1.607)	0.893	0.983 (0.495-1.954)	0.961
Age, year	1.060 (1.040-1.080)	<0.001	1.025 (1.002-1.048)	0.033
BMI, kg/m ²	0.995 (0.936-1.057)	0.870	0.980 (0.900-1.068)	0.652
Serum albumin, g/L	0.886 (0.842-0.932)	<0.001	0.980 (0.895-1.073)	0.664
Total cholesterol, mg/dl	0.804 (0.635-1.019)	0.072	0.705 (0.493-1.008)	0.056
eGFR, ml/min per 1.73 m ²	0.974 (0.965-0.982)	<0.001	0.994 (0.967-1.023)	0.696
hs-CRP, mg/L	1.005 (1.000-1.011)	0.069	1.007 (1.000-1.014)	0.054
preexisting CKD	6.757 (3.693-12.361)	<0.001	2.256 (1.001-5.084)	0.050
MCV, fl	0.909 (0.651-1.268)	0.573		
Serum triglycerides, mg/dl	0.873 (0.716-1.065)	0.180		
Hypertension	1.355 (0.870-2.112)	0.179		
Diabetes	1.034 (0.651-1.643)	0.887		

Table 4. Logistic regression analysis of the incidence of AKI according to RDW. Model 1 for AKI: adjusted for age, gender and BMI; Model 2 for AKI: adjusted for Model 1 plus preexisting CKD, APACHEII, hemoglobin, MAP, albumin, total cholesterol, eGFR, and hs-CRP. Model 3 for AKI: adjusted for Model 2 plus treatment with aspirin, ACEIs/ARBs, β -blockers or loop diuretics

	High RDW group (RDW $\geq$ 14.0%)		P-value
	OR	95% CI	
Model 1	2.576	1.602-4.141	<0.001
Model 2	1.928	1.137-3.269	0.015
Model 3	1.853	1.086-3.162	0.024

having an RDW $\geq$ 14.0% had the highest overall mortality, while patients with AKI alone or AKI with only an increased RDW displayed a better cumulative survival rate. Moreover, univariate Cox regression analysis revealed that the risk of in-hospital mortality was increased in the high RDW group and in older patients with preexisting CKD; high APACHEII scores;

increased hs-CRP; lower hemoglobin, serum albumin, MAP; and eGFR. In addition, RDW was still a significant predictor of mortality after adjustments for age, gender, BMI, preexisting CKD, APACHEII, hs-CRP, hemoglobin, serum albumin, eGFR and MAP (adjusted HR, 1.129, 95% CI 1.005 to 1.268, $P=0.041$) (Table 5). Furthermore, a higher RDW was also an independent risk factor for in-hospital mortality in the multivariate Cox regression analysis when used as a categorical variable (adjusted HR, 1.777, 95% CI 1.069 to 3.799, $P=0.037$).

After hospital discharge, the survivors were followed up for a median of 19.8 months (interquartile range, IQR=17.0 to 21.5). A total of 51 patients died during follow-up, and the crude 2-year mortality rate in the study population was 14.5% (Table 1). RDW also remained a crucial robust predictor of 2-year mortality, both as a continuous variable (HR, 1.189, 95% CI 1.045 to 1.354, $P=0.009$, Table 5) and as a categorical variable (HR, 1.924, 95% CI 1.220 to 3.033, $P=0.005$, Table 6), even after adjustments for age, gender, BMI, preexisting CKD, APACHEII, hemoglobin, MCV, serum albumin, eGFR, hs-CRP, serum triglyceride and MAP.

Performance of RDW as a predictor of outcomes, as determined by ROC curve analysis

ROC curves generated using the indicated variables (RDW, APACHEII scores and RDW plus APACHEII scores) are plotted in Fig. 2A-B. The AUCs for the relationships between RDW and AKI, in-hospital mortality and 2-year mortality were 0.630, 0.632 and 0.634, respectively, while those for the relationships between APACHEII scores and AKI, in-hospital mortality and 2-year mortality were 0.762, 0.768 and 0.724, respectively. Furthermore, the AUCs for the relationships between the combination of APACHEII scores and RDW and AKI, in-hospital mortality and 2-year mortality were 0.771, 0.777 and 0.739, respectively.

Discussion

The results of our study indicate that RDW is an independent predictor of AKI and mortality in patients in the CCU. When the patients were divided into two groups based on

Fig. 1. Kaplan-Meier survival curves for in-hospital mortality (A) and 2-year mortality (B) according to the presence of AKI and the RDW category.

Table 5. Cox proportional hazards analysis of the ability of RDW to predict in-hospital and 2-year mortality when used as a continuous variable. Multivariate model for in-hospital mortality: adjusted for age, gender, BMI, APACHEII, hemoglobin, MAP, albumin, eGFR, preexisting CKD and hs-CRP. Multivariate model for 2-year mortality: adjusted for age, gender, BMI, APACHEII, hemoglobin, MCVs, albumin, eGFR, hs-CRP, preexisting CKD, serum triglyceride and MAP

	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
For in-hospital mortality (n=412)				
RDW, %	1.154 (1.037-1.285)	0.009	1.129 (1.005-1.268)	0.041
APACHEII score	1.179 (1.121-1.241)	<0.001	1.168 (1.080-1.263)	<0.001
Hemoglobin, g/L	0.983 (0.974-0.993)	0.001	1.005 (0.993-1.019)	0.453
MAP, mmHg	0.972 (0.958-0.986)	<0.001	0.980 (0.966-0.994)	0.006
Male (versus female)	0.931 (0.551-1.573)	0.790	1.110 (0.608-2.026)	0.734
Age, year	1.031 (1.010-1.052)	0.004	1.004 (0.977-1.033)	0.766
BMI, kg/m ²	0.949 (0.884-1.020)	0.158	0.933 (0.852-1.023)	0.139
eGFR, ml/min per 1.73 m ²	0.984 (0.976-0.993)	0.001	0.982 (0.955-1.010)	0.210
hs-CRP, mg/L	1.006 (1.002-1.011)	0.008	1.008 (1.002-1.013)	0.005
Preexisting CKD	2.110 (1.205-3.697)	0.009	1.269 (0.535-3.010)	0.589
Serum albumin, g/L	0.968 (0.915-1.023)	0.247		
Total cholesterol, mg/dl	0.966 (0.733-1.274)	0.808		
Serum triglycerides, mg/dl	0.820 (0.596-1.130)	0.226		
MCV, fL	1.016 (0.976-1.058)	0.444		
Hypertension	1.390 (0.834-2.138)	0.207		
Diabetes	1.023 (0.594-1.762)	0.935		
For 2-year mortality (n=351)				
RDW, %	1.235 (1.141-1.336)	<0.001	1.189 (1.045-1.354)	0.009
APACHEII score	1.192 (1.143-1.243)	<0.001	1.146 (1.075-1.222)	<0.001
Hemoglobin, g/L	0.979 (0.967-0.990)	<0.001	0.999 (0.987-1.010)	0.836
Male (versus female)	0.847 (0.575-1.245)	0.397	0.875 (0.545-1.404)	0.580
Age, year	1.038 (1.021-1.055)	<0.001	1.002 (0.980-1.025)	0.857
BMI, kg/m ²	0.968 (0.916-1.024)	0.258	0.956 (0.893-1.022)	0.187
eGFR, ml/min per 1.73 m ²	0.967 (0.951-0.983)	<0.001	1.001 (0.988-1.014)	0.855
Serum albumin, g/L	0.933 (0.896-0.971)	0.001	1.014 (0.963-1.066)	0.602
hs-CRP, mg/L	1.005 (1.002-1.009)	0.003	1.006 (1.002-1.010)	0.005
Preexisting CKD	1.922 (1.230-3.004)	0.004	1.008 (0.548-1.856)	0.979
MAP, mmHg	0.978 (0.966-0.990)	<0.001	0.982 (0.971-0.993)	0.002
Triglycerides, mg/dl	0.806 (0.648-1.002)	0.053	0.934 (0.740-1.178)	0.564
MCV, fL	0.992 (0.965-1.020)	0.577	0.961 (0.869-1.062)	0.434
Total cholesterol, mg/dl	0.922 (0.752-1.129)	0.431		
Hypertension	1.262 (0.863-1.847)	0.230		
Diabetes	1.116 (0.734-1.696)	0.608		

Table 6. Cox proportional hazards analysis of in-hospital mortality and 2-year mortality according to the RDW group. Model 1 for in-hospital mortality: unadjusted relative risk; Model 2 for in-hospital mortality: adjusted for age, gender, APACHEII, hemoglobin, MAP, albumin, eGFR and hs-CRP. Model 3 for in-hospital mortality: adjusted for Model 2 plus treatment with aspirin, ACEIs/ARBs, β -blockers or loop diuretics. Model 1 for 2-year mortality: unadjusted relative risk; Model 2 for 2-year mortality: adjusted for age, gender, APACHEII, hemoglobin, MCVs, albumin, eGFR and hs-CRP; Model 3 for 2-year mortality: adjusted for Model 2 plus treatment with aspirin, ACEIs/ARBs, β -blockers or loop diuretics

	Higher RDW group (RDW $\geq$ 14.0%)		P-value
	HR	95% CI	
For in-hospital mortality (n=412)			
Model 1	1.835	1.137-3.346	0.002
Model 2	1.820	1.098-3.018	0.020
Model 3	1.777	1.069-3.799	0.037
For 2-year mortality (n=351)			
Model 1	2.117	1.218-3.681	0.008
Model 2	1.951	1.161-3.861	0.014
Model 3	1.924	1.220-3.033	0.005

the baseline RDW, the incidence of AKI and both the in-hospital mortality and the 2-year mortality were much higher in the high RDW group than in the low RDW group. Moreover, for each 1% increase in RDW as a continuous variable, the incidences of AKI, in-hospital mortality and 2-year mortality increased by 5.9%, 12.9%, 18.9%, respectively, after adjustments for a variety of other clinical and laboratory variables.

Only two studies investigated the value of RDW for predicting the risk of CI-AKI. Akin *et al.* performed a cross-sectional study of 630 patients with ST-segment-elevation myocardial infarction who underwent primary percutaneous coronary intervention and

concluded that RDW was an independent predictor of CI-AKI (OR=1.406, 95% CI 1.120 to 1.792), based on the multivariate logistic regression results [16]. A similar conclusion was reached in another study [17]. Nevertheless, to the best of our knowledge, this is the first study to investigate the relationship between RDW and AKI in patients in the CCU. We found that for each 1% increase in RDW, the incidence of AKI increased by 5.9%.

The association between RDW and renal function has been discussed in several studies. Ujaszasi *et al.* noted an association between increased RDW (>14.0%) and a decrease in the eGFR (OR=1.267, 95% CI 1.121-1.431) after multivariate adjustments for comorbidities, iron deficiency, inflammation and nutritional status in a cross-sectional study of 723 kidney transplant recipients [24]. Similarly, the Spearman correlation coefficient data collected in this study showed that RDW was negatively correlated with the eGFR ($r=-0.270$, $P<0.001$). In addition to being linked to renal function, an elevated RDW has also been associated with higher mortality in patients with CKD[9], kidney transplant recipients [25] and patients with AKI who are receiving continuous renal replacement therapy [15]. Moreover, a recent study investigated the impact of RDW on mortality in patients receiving hemodialysis and concluded that RDW may be a better predictor of mortality than hemoglobin, ferritin, and iron saturation values [12]. A similar association was noted in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Hsieh *et al.* retrospectively observed 313 patients undergoing CAPD and found that a higher RDW ($RDW \geq 15.3\%$) was consistently associated with overall and cardiovascular disease-related mortality independent of other common risk factors (HR, 3.48, 95% CI 1.44-8.34, HR, 2.58, 95% CI 1.31-5.09, respectively)[10]. Our study has added to the evidence showing that baseline RDW is a significant and hemoglobin- and MCV-independent determinant of mortality, whether in-hospital mortality or 2-year mortality, in

Fig. 2. ROC analyses of predictors of AKI and mortality in CCU patients. (A-C) The ability of RDW, APACHEII scores and RDW plus APACHEII scores to predict AKI (A), in-hospital mortality (B), and 2-year mortality (C) in all CCU patients.

patients in the CCU.

Although the mechanisms linking RDW to AKI and mortality are still unclear, several feasible explanations for these links have been suggested in previous studies. First, inflammation inhibits bone marrow function and iron metabolism [26, 27], and proinflammatory cytokines have been shown to inhibit erythropoietin-induced erythrocyte maturation and proliferation and to downregulate erythropoietin receptor expression, changes associated with increases in RDW [28]. In addition, AKI is known to be associated with intrarenal and systemic inflammation [29]. Forhecz *et al.* found that multiple inflammatory markers, including interleukin-6, soluble tumor necrosis factor (TNF) receptor I, soluble TNF receptor II, and C-reactive protein, and prealbumin concentrations and RDW were correlated with AKI in a study of 195 patients with systolic heart failure [30]. In the current study, leucocyte counts, hs-CRP levels and decreased prealbumin levels were significantly correlated with a higher RDW. Second, red blood cells transport oxygen to tissues, such as peripheral muscle. An increased RDW is associated with a significant increase in the number of red blood cells whose hemoglobin is incompletely saturated with oxygen. Nishiyama *et al.* demonstrated that RDW was significantly related to peak oxygen uptake in 78 patients with coronary artery disease and speculated that RDW reflects oxygen transport capacity and that a reduction in oxygen transport capacity may be one of the mechanisms responsible for the relationship between an increased RDW and a poor prognosis in cardiovascular disease [31]. Third, oxidative stress leads to increases in variations in the size of red blood cells, which are reflected by an increase in RDW. Semba *et al.* demonstrated that serum levels of selenium, a maker of antioxidant levels, were an independent predictor of RDW in 786 disabled community-dwelling women [32]. Using the data from NHANES III, Patel *et al.* verified that serum levels of antioxidants, including carotenoids, selenium and vitamin E, were strongly associated with RDW and that the association between RDW and all-cause mortality did not weaken even after adjustments for these variables [33]. Finally, RDW levels have been demonstrated to reflect malnutrition [30], which has been shown to be associated with an increased risk of mortality in patients with CKD [34]. Peng *et al.* noted a positive correlation between malnutrition and RDW in a cohort of 1293 patients receiving peritoneal dialysis and observed that RDW emerged as an independent predictor of cardiovascular mortality [35]. Similar associations were also observed in patients receiving hemodialysis and kidney transplant recipients [12, 13, 25]. In this study, we found that RDW was negatively correlated with the levels of malnutrition parameters (albumin, prealbumin and serum triglyceride), showing that undernutrition may be associated with increases in RDW.

This study had several strengths. First, to our knowledge, this is the first study to investigate the relationship between baseline RDW and the risk of AKI. Second, we employed a prospective observational design and a rigorous protocol for screening the patients in the CCU and performed the abovementioned hematologic parameter measurements in a blinded manner. Finally, we assessed the usefulness of baseline RDW as a predictor of short-term prognoses during a 2-year follow-up of patients hospitalized in the CCU, thereby broadening the clinical importance of RDW in disease diagnosis and prognosis determination.

This study also had some limitations. First, it was a single-center study of 412 patients in the CCU. Second, we measured RDW on the first day of the admission but did not assess changes in RDW in any patients during their hospital stay or their 2-year follow-up. Third, the diagnosis of AKI was based only on an increased serum creatinine level. We did not use urine output to diagnose AKI because an indwelling urinary catheter was not placed in most of the patients enrolled in this study [36]. Furthermore, we did not evaluate patients' iron metabolism status and thus could not determine if erythropoietin use or reticulocyte counts affected RDW.

Conclusion

In summary, the current study showed that baseline RDW can serve as an early predictor of AKI development and mortality in patients in the CCU and that for each 1% increase in RDW, the incidences of AKI, in-hospital mortality and 2-year mortality increased by 5.9%, 12.9%, 18.9%, respectively. Given that RDW is a readily available hematological parameter that can be assessed without an additional cost, we propose that in addition to being useful for diagnosing anemia, RDW is also useful for stratifying the risks of AKI and mortality. Additional studies are needed to investigate the mechanisms underlying the relationships between RDW and other clinical parameters.

Disclosure Statement

The authors of this manuscript state that they do not have any Disclosure Statements and nothing to disclose.

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