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RED CELL DISTRIBUTION WIDTH AT ADMISSION PREDICTS THE FREQUENCY OF ACUTE KIDNEY INJURY AND 28-DAY MORTALITY IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

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ABSTRACT—**Objectives:** To determine the association of red cell distribution width (RDW) at admission with frequency of acute kidney injury (AKI) and 28-day mortality in acute respiratory distress syndrome (ARDS) patients. **Methods:** Two hundred fifty-eight ARDS patients were investigated in retrospective and prospective studies. The primary outcome was frequency of AKI. The secondary outcome was 28-day mortality. **Results:** The retrospective study included 193 ARDS patients, of which 67 (34.7%) were confirmed AKI and 76 (39.4%) died within 28 days. The RDW level in the AKI group was significantly higher than in the non-AKI group ([15.15 ± 2.59]% vs. [13.95 ± 1.89]%). Increased RDW was a significant predictor of frequency of AKI (odds ratio: 1.247, 95% confidence interval [CI]: 1.044, 1.489). The area under the receiver operating characteristic curve of RDW for predicting AKI was 0.687 (95%CI: 0.610, 0.764) and the cut-off value was 14.45 (sensitivity, 56.7%; specificity, 72.8%). In addition, the proportion of patients with RDW ≥ 14.45% in the non-survival group was notably higher compared with the survival group (48.7% vs. 29.1%). Furthermore, cox regression analysis revealed that RDW ≥ 14.45% was associated with 28-day mortality (hazard ratio: 1.817, 95%CI: 1.046, 3.158), while Kaplan–Meier analysis showed patients with RDW ≥ 14.45% had a significantly lower survival rate than those with RDW < 14.45%. The prospective study, on the other hand, included 65 ARDS patients, with frequency of AKI and 28-day mortality in the RDW ≥ 14.45% group significantly higher than in RDW < 14.45%. **Conclusion:** RDW was a significant, independent predictor for frequency of AKI and 28-day mortality in ARDS patients.

KEYWORDS—Acute kidney injury, acute respiratory distress syndrome, mortality, red cell distribution width

ABBREVIATIONS—AKI—acute kidney injury; APACHE II—acute physiology and chronic health evaluation II; ARDS—acute respiratory distress syndrome; AUC—area under curve; BUN—blood urea nitrogen; CI—confidence interval; COPD—chronic obstructive pulmonary disease; CRP—C-reactive protein; CRRT—continuous renal replacement therapy; eGFR—estimated glomerular filtration rate; EICU—emergency intensive care unit; HRs—hazard ratios; ICU—intensive care units; IMV—invasive mechanical ventilation; IQR—interquartile ranges; KDIGO—kidney disease improving global outcomes; LR—likelihood ratio; NLR—neutrophil to lymphocyte ratio; OR—odds ratio; PaO_2/FiO_2—partial pressure of arterial oxygen to the fraction of inspired oxygen; PCT—procalcitonin; RDW—red cell volume distribution width; ROC—receiver operating characteristic curve; SCr—serum creatinine; SD—standard deviation; SOFA—sequential organ failure assessment; UA—uric acid; WBC—white blood cell

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is characterized by pulmonary non-cardiogenic edema and refractory hypoxemia, following a variety of pulmonary or systemic insults (1). It is a common and serious complication in critically ill patients, with an incidence of 10% and a mortality as high as 30% to 40% (2). Classically, local or systemic inflammatory insults have been recognized as an essential feature in the pathogenesis of ARDS. This condition only causes lung tissue damage, but also significantly affects the cardiovascular, renal, and neurological system. Kidney function injury is the most frequent extra-pulmonary organ dysfunction associated with ARDS and this secondary injury is associated with short and long-term mortality in ARDS patients (3). Therefore, exploration of possible predictors is helpful for identifying patients at risk of acute kidney injury (AKI) in ARDS patients and for guiding early management strategies to reduce mortality.

Red blood cell distribution width (RDW) is an index of the degree of circulating erythrocytes' size heterogeneity,

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This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (EC 2021-174). Informed consent was obtained from the enrolled participants after an investigator explained the content of the study.

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traditionally used together with other standard complete blood count parameters to determine prevalence of haematological system diseases, such as anemia (4). Over the years, RDW has been proposed as a strong, independent prognostic marker for many related conditions, with an association between increased RDW and disease severity and mortality established in a plethora of inflammatory disease, including sepsis (5), acute pancreatitis (6), COVID-19 (7), and ARDS (8). More recently, emerging evidence has demonstrated that increased RDW may be associated with the development of AKI in patients with acute medical conditions. Hu et al. reported a significant increase in risk of AKI and short and long-term mortality in patients with increased RDW at time of admission in the coronary care unit (9). Similarly, a trial conducted by Wang et al. showed elevated levels of RDW to be an independent predictor for frequency of AKI and mortality in patients with traumatic brain injuries, using a cut-off of 14.25% (10). Nevertheless, there exists very little information about the relationship between RDW and frequency of AKI and mortality in ARDS patients.

Seeking to expand on this, in this study, we aimed firstly to investigate the relationship between RDW and frequency of AKI in ARDS patients. Furthermore, we speculated that higher RDW levels could be associated with 28-day mortality. Finally, we sought to verify the prediction value of higher RDW level for frequency of AKI and 28-day mortality in ARDS patients.

METHODS

Patient selection criteria

The subjects recruited in our study fell into two key groups (Fig. 1). One group was retrospectively studied (Fig. 1A). In the retrospective study, 193 consecutive ARDS patients hospitalized in the emergency intensive care unit (EICU) at Nanjing Drum Tower Hospital were identified from January 2015 to December 2018. The inclusion criteria included all adult patients who met all the diagnostic criteria from the Berlin definition of ARDS (11), who had been hospitalized in the EICU for longer than 24 h, and for whom there existed complete clinical data. Patients were excluded if the following criteria were met:

(1) they were younger than the age of 18;
(2) they had pre-existing chronic kidney disease (defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 (12)) or receiving renal replacement therapy before admission;
(3) they had suffered AKI prior to ARDS onset;
(4) they displayed evidence of renal transplantation;
(5) they had a history of long-term use of nephrotoxic drugs;
(6) they had a history of malignancy and haematologic disorder.

Another group was investigated prospectively (Fig. 1B). In this case, 65 consecutive ARDS patients hospitalized in the EICU were enrolled into the prospective study between January 2019 and December 2020. The inclusion and exclusion criteria were the same as in the retrospective study. Blood samples were obtained from each patient on admission to the EICU for hematology and biochemistry detection purposes.

Data collection

The demographic characteristics and clinical data were extracted from the Electronic Medical Record System at our institution:

(1) the baseline demographic and clinical characteristics were: age, gender, coexisting conditions (hypertension, diabetes mellitus, congestive heart failure, chronic liver disease, and chronic obstructive pulmonary disease). Mean arterial pressure after admission to the EICU was calculated immediately using the following formula: MAP = systolic blood pressure + 1/3 (systolic blood pressure − diastolic blood pressure) (13).
(2) Laboratory data measured at admission to EICU included white blood cell count (WBC count, normal reference range: $3.5–9.5 \times 10^9$/L), neutrophil to lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, RDW (normal reference range: 0–14%), procalcitonin (PCT, normal reference range: 0–0.05ng/mL), C-reactive protein (normal reference range:0–6 mg/L), serum creatinine (SCr, normal reference range: 58–110 μmmol/L), estimated glomerular filtration rate (normal reference range: >90 mL/min/1.73 m^2), uric acid (UA, normal reference range: 208–506 ummol/L), blood urea nitrogen (BUN, normal reference range: 3.2–7.1 mmol/L), ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, serum lactate (normal reference range: 0.7–2.1mmol/L) were also measured. Measured physiological variables were then used to calculate the acute physiology and chronic health evaluation II (APACHE II) score (14) and the sequential organ failure assessment (SOFA) score (15).
(3) Interventions including invasive mechanical ventilation, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) were record during hospital admission.
(4) Durations of stay in both EICU and hospital were also noted.

The primary outcome was the frequency of AKI. The secondary outcome was 28-day mortality. However, if the patients were discharged within 28 days, we followed up with a telephone interview both in the retrospective and prospective studies. To avoid bias, at the end of the study, the data was analyzed by disinterested doctors.

Definitions

ARDS was defined and its severity stratified according to the Berlin definition (11). AKI was defined using both SCr and output criteria for kidney disease improving global outcomes guidelines (16). The baseline SCr values were assessed using the mean value within 1 year before admission. If baseline SCr values were not available, the lowest SCr on admission was used (17). Severity of AKI was stratified based on kidney disease improving global outcomes criteria. Sepsis shock was defined according to the third international consensus definitions for septic shock (18).

Statistical analysis

All data in the present study were analyzed using SPSS19.0 for Windows (SPSS Inc., Chicago, IL). Normally distributed continuous variables were presented as means ± standard deviation and compared using Student's t test. Non-normally distributed continuous data were presented as median with interquartile ranges and compared using Mann–Whitney U test. Categorical data were presented as frequencies and percentages, and compared using Fisher's exact test, or chi-square test where appropriate. Predictor variables associated with the frequency of AKI in ARDS patients were determined by univariate and forward stepwise multivariate logistic regression analysis. Variables with $P < 0.05$ in univariate analysis were considered potential predictors, and then entered into the multivariate regression model. The receiver operating characteristic curve test was then applied to analyze the predictive value of RDW for the frequency of AKI, while the optimal cut-off value of RDW was determined based on the maximum Youden Index. Prognostic variables for 28-day mortality in ARDS patients that were $P < 0.05$ in univariate analysis were included in multivariate analysis. Cox proportional hazards analysis was performed to determine predictors of mortality presented as hazard ratios (HRs), with a 95% confidence interval (CI). Survival curves were estimated using the Kaplan–Meier method and the mortality of each group was compared with the log-rank test. A P-value of <0.05 was considered statistically significant.

RESULTS

Demographics and characteristics of study population

In the retrospective study, 305 patients diagnosed with ARDS were screened for eligibility, of which 193 patients met the inclusion criteria (Fig. 1A and Table 1). The main cause of ARDS in this study was pneumonia (182/193, 94.3%). Of 193 patients included, the severity of ARDS based on the Berlin definition (11) was mild in 71 patients (36.8%), moderate in

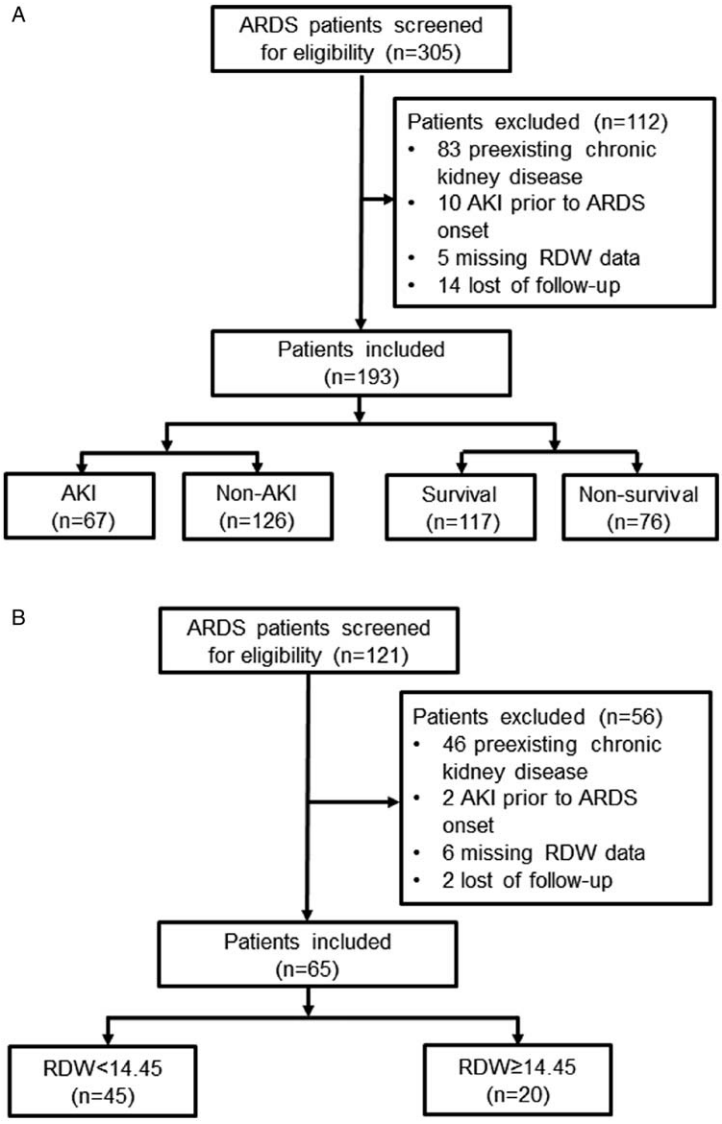

Fig. 1. **Flow chart for study participants.** A, retrospective cohort; B, prospective cohort.

106 patients (54.9%), and severe in 16 patients (8.3%). Frequency of AKI was 34.7% (67/193): 14 patients (20.9%) developed stage I AKI, 15 patients (22.4%) developed stage II AKI, and 38 patients (54.9%) developed stage III AKI. Comparison of baseline characteristics and laboratory findings between patients with and without AKI is shown in Table 1. In the AKI group, patients showed significantly higher values in baseline of physiology and laboratory parameters including APACHE II score, SOFA score, RDW, PCT, SCr, BUN, and UA than those in the non-AKI group. Moreover, the proportion of sepsis shock, CRRT, and the 28-day mortality in AKI group were notably higher than those in the non-AKI group.

In the prospective study, 121 patients with a diagnosis of ARDS were screened for validation, with 65 meeting the inclusion criteria (Fig. 1B, Supplemental File 1: Table S1, http://links.lww.com/SHK/B356). The main cause of ARDS was pneumonia (64/65, 98.5%). Out of 65 patients, the severity of ARDS was mild in 10 patients (15.4%), moderate in 24 patients (36.9%), and severe in 31 patients (47.7%). Frequency of AKI was 27.7% (18/65) with 3 patients (16.7%) developing stage I AKI, 2 patients (11.1%) developing stage II AKI, and 13 patients (72.2%) developing stage III AKI. As shown in Supplemental File 1: Table S1, http://links.lww.com/SHK/B356, in the validation group, patients showed significantly higher values in the baseline of physiology and laboratory parameters including APACHE II score, SOFA score, WBC count, and NLR than those in the retrospective study group. However, the values of SCr, UA, and partial pressure of arterial oxygen to the fraction of inspired oxygen in the validation group were notably lower than those in the retrospective study group. Additionally, the proportion of sepsis shock, invasive mechanical ventilation, and ECMO in the validation group was significantly higher than in the retrospective study group. Length of EICU stay in the validation group was also notably longer than in the retrospective study group.

RDW as a predictor for the frequency of AKI in ARDS patients

Independent factors that predict the frequency of AKI in ARDS patients were further investigated via univariate and

Table 1. **Baseline characteristics and laboratory findings by AKI and Non-AKI groups**

Variable	AKI (n = 67)	Non-AKI (n = 126)	*P* Value
Demographics			
Age, mean ± SD, years	62.52 ± 19.71	60.83 ± 19.14	0.562
Male, sex, n (%)	46 (68.7)	84 (66.7)	0.779
Chronic comorbidities			
Hypertension, n (%)	28 (41.8)	44 (34.9)	0.347
Diabetes mellitus, n (%)	15 (22.4)	22 (17.4)	0.331
Congestive heart failure, n (%)	0 (0)	2 (1.6)	0.772
COPD, n (%)	7 (10.4)	7 (5.6)	0.212
Chronic liver disease, n (%)	0 (0)	2 (1.6)	0.772
Physiology and laboratory parameters			
MAP, mean ± SD, mm Hg	86.37 ± 16.68	91.53 ± 16.58	0.042
APACHE II score, mean ± SD, points	20.96 ± 7.51	17.86 ± 7.26	0.006
SOFA score, mean ± SD, points	6.85 ± 4.81	5.10 ± 3.05	0.008
WBC count, mean ± SD, $\times 10^9$/L	10.01 ± 6.28	9.99 ± 6.71	0.980
NLR, median (IQR)	8.69 (4.00, 17.00)	10.64 (6.65, 18.06)	0.092
RDW, mean ± SD, %	15.15 ± 2.59	13.95 ± 1.89	0.001
PCT, median (IQR), ng/mL	3.00 (0.50, 14.70)	0.40 (0.40, 1.98)	0.001
CRP, median (IQR), mg/L	75.40 (1,935,161.55)	90.20 (90.20,155.32)	0.229
SCr, mean ± SD, μmol/L	81.81 ± 25.91	64.68 ± 20.79	0.001
eGFR, mean ± SD, mL min^{-1} (1.73 m^2)$^{-1}$	115.55 ± 50.61	149.19 ± 71.44	0.002
UA, mean ± SD, μmol/L	319.35 ± 155.29	250.85 ± 108.63	0.002
BUN, median (IQR), μmol/L	7.95 (6.00, 11.34)	7.20 (5.10, 9.50)	0.045
PaO_2/FiO_2, mean ± SD	187.16 ± 56.98	182.93 ± 62.58	0.645
Serum lactate, median (IQR), mmol/L complication	1.65 (0.90, 2.98)	1.10 (0.90, 2.15)	0.206
Sepsis shock, n (%)	38 (56.7)	27 (21.4)	0.001
Intervention			
CRRT, n (%)	32 (47.8)	9 (7.1)*	0.001
IMV, n (%)	27 (40.3)	57 (45.2)	0.510
Outcomes			
The 28-day mortality, n (%)	38 (56.7)	38 (29.9)	0.001
Length of EICU stay, median (IQR), days	12.00 (7.00, 20.00)	13.00 (6.75, 24.00)	0.720
Length of hospital stay, median (IQR), days	15.00 (8.00, 30.50)	17.00 (7.75, 27.00)	0.877

AKI, acute kidney injury; APACHE II, acute physiology and chronic health evaluation II; BUN, blood urea nitrogen; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; EICU, emergency intensive care units; IMV, invasive mechanical ventilation; IQR, interquartile ranges; NLR, neutrophil to lymphocyte ratio; PCT, procalcitonin; PaO_2/FiO_2, partial pressure of arterial oxygen to the fraction of inspired oxygen; RDW, red cell volume distribution width; SCr, serum creatinine; SD, standard deviation; SOFA, sequential organ failure assessment; UA, uric acid; WBC, white blood cell.
*Indications for CRRT in non-AKI group are volume overload (n = 8) and metabolic acidosis (n = 1).

multivariable logistic regression analysis. As shown in Table 2, our results revealed that SOFA (odds ratio [OR]: 1.133, 95%CI: 1.007, 1.274, $P = 0.038$), RDW (OR: 1.247, 95%CI: 1.044, 1.489, $P = 0.015$), and PCT (OR: 1.023, 95%CI: 1.001,1.046, $P = 0.039$) were potential predictors independently associated with AKI. Receiver operating characteristic curves of frequency of AKI in ARDS patients generated using the independent predictors (RDW, PCT, and SOFA) are plotted in Figure 2. The area under curve (AUC) of RDW, PCT, and SOFA was 0.687 (95%CI: 0.610, 0.764, $P = 0.001$), 0.728 (95%CI: 0.642, 0.813, $P = 0.001$), and 0.599 (95%CI: 0.511, 0.686, $P = 0.001$), respectively. When the optimal cut-off value (Maximum Youden index) was 14.45, the sensitivity and specificity of RDW for frequency of AKI in ARDS patients was 0.567 and 0.728, respectively. Meanwhile, the positive likelihood ratio (LR+) was 2.085 and negative likelihood ratio (LR−) was 0.595.

RDW as associated with 28-day mortality in ARDS patients

To determine the predictive value of RDW in 28-day mortality for ARDS patients, we divided the study population into two groups (survival and non-survival) based on the 28-day outcome. As shown in Table 3, in the non-survival group, patients showed significantly higher values in terms of age, APACHE II score, SOFA score, NLR, SCr, BUN, serum lactate and ratio of RDW $\geq$ 14.45% than those in the survival group. Moreover, the rate of use of CRRT in non-survival group was notably higher than that in the survival group. However, the length of EICU and hospital stay in the non-survival group was markedly shorter than those in the survival group.

Independent factors that predicted 28-day mortality in ARDS patients were further investigated via univariate and multivariable Cox regression analysis. As shown in Table 4, age (HR: 1.032, 95%CI: 1.105, 1.049, $P = 0.001$), APACHEII score (HR: 1.078, 95%CI: 1.038, 1.120, $P = 0.001$), RDW $\geq$ 14.45% 14.45% (HR: 1.817, 95%CI: 1.046, 3.158, $P = 0.034$), and SCr (HR: 1.012, 95%CI: 1.002, 1.022, $P = 0.020$) were potential predictors for 28-day mortality. Patients with a RDW $\geq$ 14.45% had a 1.817-fold increased risk of 28-day mortality than patients with an RDW < 14.45% during the follow-up period. Similarly, Kaplan–Meier analysis showed that patients with RDW $\geq$ 14.45% had a significantly lower chance of survival than patients with RDW < 14.45% (log rank $P = 0.001$, Fig. 3).

Table 2. **Independent predictors associated with the incidence of AKI in ARDS patients by univariate and multivariable logistic regression analysis**

	Univariate		Multivariable	
Independent variable	OR (95%CI)	*P* value	OR (95%CI)	*P* value
MAP	0.981 (0.963, 0.999)	0.044		
APACHEII score	1.058 (1.016, 1.102)	0.007		
SOFA score	1.128 (1.039, 1.224)	0.004	1.133 (1.007, 1.274)	0.038
RDW	1.291 (1.107, 1.506)	0.001	1.247 (1.044, 1.489)	0.015
PCT	1.032 (1.008, 1.056)	0.008	1.023 (1.001, 1.046)	0.039
SCr	1.032 (1.018, 1.047)	0.001		
eGFR	0.988 (0.982, 0.995)	0.001		
BUN	1.002 (0.991, 1.014)	0.712		
UA	1.004 (1.002, 1.007)	0.001		

APACHE II, acute physiology and chronic health evaluation II; ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; PCT, procalcitonin; RDW, red cell volume distribution width; SCr, serum creatinine; SOFA, sequential organ failure assessment; UA, uric acid.

Validation of the predict value of RDW for frequency of AKI and 28-day mortality in ARDS patients

To further verify the use of RDW in predicting frequency of AKI and 28-day mortality in ARDS patients, 65 consecutive patients with ARDS hospitalized in our institution from January 2019 to December 2020 were taken and divided into two groups (RDW < 14.45 and RDW ≥ 14.45) based on the optimal cut-off value of RDW previously described. As shown in Table 5, significant differences appeared in the MAP and APACHE II score between the two groups. Moreover, frequency of AKI and 28-day mortality in the RDW ≥ 14.45 group were notably higher than those in RDW < 14.45 group.

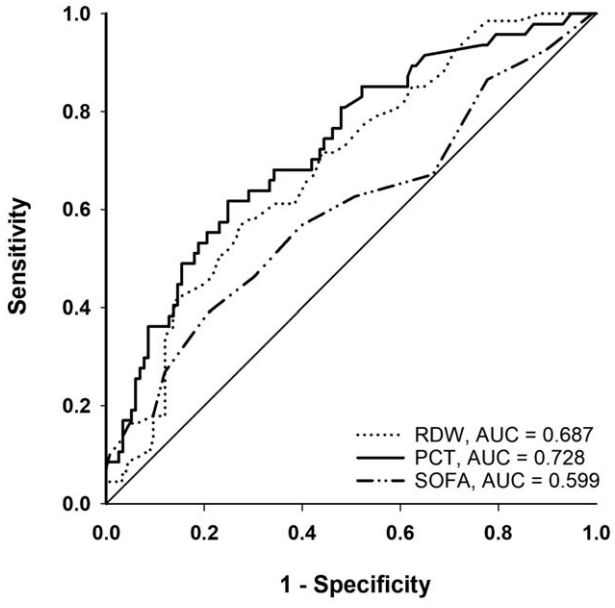

Fig. 2. **ROC curves analyze of RDW, PCT, and SOFA for the frequency of AKI in ARDS patients.** The AUC of RDW, PCT, and SOFA were 0.687 (95%CI: 0.610, 0.764, $P = 0.001$), 0.728 (95%CI: 0.642, 0.813, $P = 0.001$), and 0.599 (95%CI: 0.511, 0.686, $P = 0.001$). AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AUC, area under curve; PCT, procalcitonin; ROC, receiver operating characteristic curve; SOFA, sequential organ failure assessment.

DISCUSSION

In the present study, the results showed that

(1) increased RDW measured at admission was a significant, independent predictor of the frequency of AKI in ARDS patients;
(2) increased RDW level at a prespecified cut-off of RDW $\geq 14.45\%$ would also be associated with 28-day mortality in ARDS patients, moreover, the prognosis of patients in two groups divided according to the cut-off point of 14.45% to be significantly divergent;
(3) ARDS patients with increased RDW showed significantly higher frequency of AKI and 28-day mortality in the prospective validation study.

Thus, physicians should strengthen the attention to this group of vulnerable patients presented with increased RDW at admission, and management strategies are required timely and effectively to prevent the occurrence of AKI and improve the outcomes in ARDS patients, such as avoidance of nephrotoxins, regular monitoring of serum creatinine (within 48 h), and urine output (within 6 h), consideration of hemodynamic monitoring to ensure volume status and perfusion pressure, and the application of lung-protective ventilation (low tidal volume ventilation) (19, 20).

AKI is a common complication in ARDS patients and dramatically increases overall mortality of ARDS patients (19). Previous studies have shown that initial severity of illness, history of diabetes, acidosis at the time of ARDS diagnosis, positive pressure ventilation, as well as driving pressure are associated with frequency of AKI and mortality in ARDS patients (3, 21, 22). However, it is difficult to obtain and evaluate such markers freely during clinical practice. A growing body of evidence suggests that RDW, as a routine and inexpensive laboratory biomarker, is associated with frequency of AKI and mortality in many medical conditions. Akin et al. (23), for example, investigated a total of 630 patients with myocardial infarction who underwent coronary angiography for the detection of risk factors for AKI, indicating that increased RDW is independently associated with frequency

Table 3. **Baseline characteristics and laboratory findings by survival and non-survival groups**

Variable	Survival (n = 117)	Non-survival (n = 76)	*P* value
Age, mean ± SD, years	56.08 ± 19.56	69.63 ± 15.79	0.001
Male, sex, n (%)	77 (65.8)	53 (69.7)	0.570
Chronic comorbidities			
Hypertension, n (%)	39 (33.3)	33 (43.4)	0.157
Diabetes mellitus, n (%)	19 (16.2)	18 (23.7)	0.199
Congestive heart failure, n (%)	2 (1.7)	0 (0)	0.676
COPD, n (%)	9 (7.7)	5 (6.6)	0.771
Chronic liver disease, n (%)	2 (1.7)	0 (0)	0.676
Physiology and laboratory parameters			
MAP, mean ± SD, mm Hg	90.08 ± 15.78	89.52 ± 17.30	0.822
APACHE II score, mean ± SD, points	16.27 ± 6.73	23.02 ± 6.72	0.001
SOFA score, mean ± SD, points	4.91 ± 3.22	6.93 ± 4.37	0.001
WBC count, mean ± SD, $\times 10^9$/L	9.64 ± 7.00	10.55 ± 5.78	0.343
NLR, median (IQR)	9.30 (5.36, 15.09)	12.34 (6.44, 24.25)	0.045
RDW ≥ 14.45%, n (%)	34 (29.1)	37 (48.7)	0.006
PCT, median (IQR), ng/mL	0.40 (0.17, 2.12)	0.61 (0.10, 4.53)	0.553
CRP, median (IQR), mg/L	83.30 (28.75, 144.05)	83.60 (40.40, 173.15)	0.551
SCr, mean ± SD, μmol/L	66.09 ± 25.11	73.97 ± 26.46	0.038
eGFR, mean ± SD, mL min^{-1} (1.73 m^2)$^{-1}$	141.63 ± 75.07	123.77 ± 56.95	0.079
UA, mean ± SD, μmol/L	253.60 ± 121.03	288.71 ± 154.64	0.080
BUN, median (IQR), μmol/L	6.80 (4.75, 8.40)	9.05 (6.73, 12.08)	0.001
PaO_2/FiO_2, mean ± SD	188.94 ± 55.47	177.41 ± 67.49	0.216
Serum lactate, median (IQR), mmol/L complications	1.10 (0.80, 2.33)	1.65 (0.90, 2.70)	0.024
AKI, n (%)	29 (24.8)	38 (50)	0.001
Sepsis shock, n (%)	26 (22.2)	39 (51.3)	0.001
Intervention			
CRRT, n (%)	16 (13.7)	25 (32.9)	0.001
Invasive mechanical ventilation, n (%)	46 (39.3)	38 (50.0)	0.144
Outcomes			
Length of EICU stay, median (IQR), days	19.00 (9.00, 31.00)	7.50 (4.00, 14.00)	0.001
Length of hospital stay, median (IQR), days	22.00 (11.50, 37.00)	8.50 (5.00, 16.75)	0.001

AKI, acute kidney injury; APACHE II, acute physiology and chronic health evaluation II; BUN, blood urea nitrogen; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; IMV, invasive mechanical ventilation; IQR, interquartile ranges; EICU, emergency intensive care units; NLR, neutrophil to lymphocyte ratio; PCT, procalcitonin; PaO_2/FiO_2, partial pressure of arterial oxygen to the fraction of inspired oxygen; RDW, red cell volume distribution width; SCr, serum creatinine; SOFA, sequential organ failure assessment; SD, standard deviation; UA, uric acid; WBC, white blood cell.

of contrast-induced AKI. Zou and colleagues also revealed an association of elevated RDW with AKI development and hospital mortality in patients after cardiac surgery (24). To the best of our knowledge, ours is the first study to investigate the relationship between increased RDW at admission and frequency of AKI in ARDS patients. The results demonstrate that RDW measured at admission is independently associated with an increased risk of AKI in ARDS patients, and for each 1% increase in RDW, frequency of AKI increases by 24.7%. Of note, our study also shows that PCT, as an important inflammatory biomarker, is a potential predictor for frequency of AKI after ARDS. Although the AUC for PCT is higher than for

Table 4. **Independent predictors associated with the 28-day mortality in ARDS patients by univariate and multivariable Cox regression analysis**

	Univariate		Multivariable	
Independent variable	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.029 (1.016, 1.043)	0.001	1.032 (1.105, 1.049)	0.001
APACHEII score	1.086 (1.056, 1.117)	0.001	1.078 (1.038, 1.120)	0.001
SOFA score	1.078 (1.027, 1.132)	0.003		
NLR	1.016 (1.003, 1.030)	0.019		
RDW ≥ 14.45%	1.757 (1.120, 2.754)	0.014	1.817 (1.046, 3.158)	0.034
BUN	1.003 (0.996, 1.010)	0.457		
SCr	1.010 (1.002, 1.019)	0.020	1.012 (1.002, 1.022)	0.020
Serum lactate	1.088 (0.978, 1.209)	0.120		

APACHE II, acute physiology and chronic health evaluation II; ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NLR, neutrophil to lymphocyte ratio; RDW, red cell volume distribution width; SCr, serum creatinine; SOFA, sequential organ failure assessment.

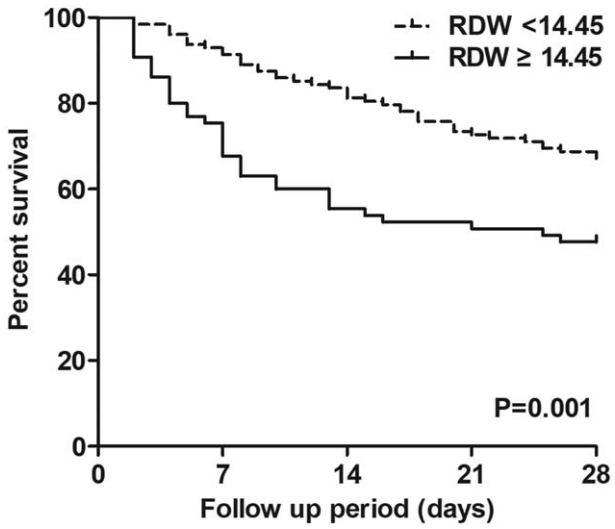

Fig. 3. **Kaplan–Meier survival curve of 28-day mortality according to the optimal cut-off of RDW = 14.45%.**

RDW, the difference between them is not statistically significant. Moreover, PCT is a relatively expensive biomarker, limiting its use for clinical applications (25).

Additionally, we found that patients with an RDW $\geq$ 14.45% had a 1.817-fold increased risk of 28-day mortality than patients with an RDW $<$ 14.45% during the follow-up period, consistent with other findings (8, 26). Therefore, the results of our study further extend the evidence for RDW as a prognostic predictor in ARDS patients, demonstrating an increased risk of short-term mortality in hospitalized patients suffering ARDS. Recently, a prospective observational study performed by Ozrazgat-Baslanti et al. revealed that both rapidly reversible AKI and no AKI patients with sepsis had the same inflammation biomarker levels and survival; however, persistent AKI patients had a significant increase in biomarker levels and higher mortality compared with no AKI patients (27). It indicated that the predict value of RDW might be more powerful by using persistent status of AKI as endpoint. In the present study, we just used the frequency of AKI but not persistent AKI as endpoint. Therefore, further research is

Table 5. **Baseline characteristics and laboratory findings by RDW $<$ 14.45 and RDW $\geq$ 14.45 groups**

Variable	RDW $<$ 14.45 (n = 45)	RDW $\geq$ 14.45 (n = 20)	*P* value
Age, mean ± SD, years	60.91 ± 14.61	60.75 ± 13.00	0.966
Male, sex, n (%)	31 (68.9)	9 (45)	0.068
Chronic comorbidities			
Hypertension, n (%)	17 (37.8)	10 (50.0)	0.356
Diabetes mellitus, n (%)	7 (15.6)	4 (20.0)	0.934
Congestive heart failure, n (%)	2 (4.4)	1 (5.0)	1.000
COPD, n (%)	0 (0)	1 (2.2)	0.675
Chronic liver disease, n (%)	1 (2.2)	0 (0)	1.000
Physiology and laboratory parameters			
MAP, mean ± SD, mmHg	95.19 ± 13.79	85.25 ± 16.97	0.015
APACHE II score, mean ± SD, points	20.27 ± 7.22	25.05 ± 8.85	0.025
SOFA score, mean ± SD, points	6.71 ± 3.05	7.70 ± 3.74	0.265
WBC count, mean ± SD, $\times 10^9$/L	12.89 ± 9.54	14.32 ± 8.73	0.569
NLR, median (IQR)	15.52 (6.75, 26.44)	17.74 (10.25, 47.15)	0.398
PCT, median (IQR), ng/mL	0.59 (0.16, 2.25)	0.87 (0.27, 3.28)	0.348
CRP, mean ± SD, mg/L	116.74 ± 77.55	104.13 ± 74.40	0.542
SCr, mean ± SD, μmol/L	63.17 ± 21.95	57.30 ± 23.49	0.334
eGFR, mean ± SD, mL min^{-1} (1.73 m^2)$^{-1}$	128.25 ± 46.66	135.17 ± 84.39	0.672
UA, mean ± SD, μmol/L	236.10 ± 100.76	241.95 ± 132.68	0.846
BUN, mean ± SD, μmol/L	7.73 ± 3.53	9.16 ± 4.36	0.168
PaO_2/FiO_2, mean ± SD	133.50 ± 62.90	122.40 ± 58.37	0.505
Serum lactate, mean ± SD, mmol/L complications	1.41 ± 0.74	1.61 ± 0.91	0.357
AKI, n (%)	9 (20.0)	9 (45.0)	0.038
Sepsis shock, n (%)	18 (40)	13 (65)	0.063
Intervention			
CRRT, n (%)	3 (6.7)	3 (15.0)	0.544
Invasive mechanical ventilation, n (%)	35 (77.8)	17 (85.0)	0.502
ECMO, n (%)	4 (8.9)	0 (0)	0.414
Outcomes			
The 28-day mortality, n (%)	14 (31.1)	12 (60)	0.028
Length of EICU stay, mean ± SD, days	20.00 ± 13.61	19.20 ± 11.13	0.818
Length of hospital stay, mean ± SD, days	20.51 ± 13.61	18.95 ± 12.31	0.662

AKI, acute kidney injury; APACHE II, acute physiology and chronic health evaluation II; BUN, blood urea nitrogen; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IMV, invasive mechanical ventilation; IQR, interquartile ranges; EICU, emergency intensive care units; NLR, neutrophil to lymphocyte ratio; PCT, procalcitonin; PaO_2/FiO_2, partial pressure of arterial oxygen to the fraction of inspired oxygen; RDW, red cell volume distribution width; SCr, serum creatinine; SOFA, sequential organ failure assessment; SD, standard deviation; UA, uric acid; WBC, white blood cell.

needed to confirm the predict value of RDW by using persistent AKI as endpoint.

Currently, the underlying mechanism between increased RDW level and frequency of AKI and mortality remains unclear. However, it has been suggested that inflammation seems to play an important role (19). In acute and chronic medical conditions, circulating inflammatory mediators and circulating immunology cells not only directly cause the kidney tissue injury, but also increase RDW level through several mechanisms such as affected bone marrow function, reduced erythropoietin production and inhibited erythropoietin maturation, impairment of iron metabolism, promotion of red blood cell membrane deformability, allowing abnormal erythropoietin to spill into systemic circulation, among other effects (28). In this way, instances of increased RDW have been widely studied for use as a valuable biomarker, along with its capability to incidentally predict organ dysfunctions and outcomes in a variety of inflammatory diseases. Interestingly, we did not observe clinical evidence of increased inflammation in patients with higher RDW in our validation study, as values of WBC count, NLR, PCT, and C-reactive protein were comparable between RDW $<14.45\%$ and $\geq 14.45\%$ groups.

The present study has some limitations. First, this is a single-centre study with a relatively small sample size. Therefore, larger-scale, better-designed studies are recommended for validating the findings. Second, pneumonia is the most common cause of ARDS in our study, and this may influence the generalizability of the results as applied to the ARDS population caused by other etiologies, such as severe trauma. Thirdly, we only investigated the association of increased RDW with 28-day mortality in ARDS patients, and the predictive value of RDW should be clarified further through a long-term follow-up study.

CONCLUSIONS

In summary, our study demonstrates that RDW measured at admission is associated with frequency of AKI and 28-day mortality in ARDS patients. This may therefore be used as an easily accessible parameter with which to identify ARDS patients at risk of kidney damage and poor prognosis at time of admission, and to better guide management strategies.

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