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

Nan Cai,* Min Jiang,† Chao Wu,* and Fei He†

*Department of Infectious Disease, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, Nanjing, 210008, China; and †Department of Emergency Medicine, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, 210008, China

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 outcomes; LR—likelihood ratio; NLR—neutrophil to lymphocyte ratio; OR—odds ratio; PaO2/FiO2—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—urate; 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 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,
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 m² (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 recruitment and exclusion criteria were the same as in the retrospective study. Blood samples were obtained from each patient upon 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 x 10⁹/L), neutrophil to lymphocyte ratio (NLR), serum albumin (normal reference range: 3.6–5.5 g/dL), serum ALT, AST, and creatinine (normal reference range: 0.6–1.3 mg/dL). Serum creatinine (Scr) was measured immediately using the following formula: Scr = C₁ × (dy/dt) / C₀, where Scr is the concentration of creatinine, C₀ is the baseline Scr concentration, C₁ is the Scr concentration at time of admission, and dy/dt is the change in Scr concentration over time (14).

3. Interventions including invasive mechanical ventilation, continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) were recorded during hospital admission.

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 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
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
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 \( \geq 14.45\% \) (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 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, ×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 m²)⁻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        |
| PaO2/FiO2, 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; PaO2/FiO2, 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).
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.

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

| Table 3 |
| --- |
| **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, ×10⁹/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, m mol/L | 66.09 ± 25.11 | 73.97 ± 26.46 | 0.038 |
| eGFR, mean ± SD, mL min⁻¹ (1.73 m²)⁻¹ | 141.63 ± 75.07 | 123.77 ± 56.95 | 0.079 |
| UA, mean ± SD, µmol/L | 250.60 ± 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 |
| PaO₂/FiO₂, 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 (22.6) | 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; PaO₂/ FiO₂, 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.

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

| Table 4 |
| --- |
| **Independent variable** | **Univariate** | **Multivariate** |
| | 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 |
| APACHE II 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 | 1.078 (1.027, 1.132) | 0.003 |
| NLR | 1.016 (1.003, 1.030) | 0.019 | 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 | 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 | 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.
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 needed.

![Kaplan–Meier survival curve of 28-day mortality according to the optimal cut-off of RDW $= 14.45\%$.](image)

**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 $\pm$ SD, years                             | 60.91 $\pm$ 14.61       | 60.75 $\pm$ 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 $\pm$ SD, mmHg                               | 95.19 $\pm$ 13.79       | 85.25 $\pm$ 16.97           | 0.015     |
| APACHE II score, mean $\pm$ SD, points                 | 20.27 $\pm$ 7.22        | 25.05 $\pm$ 8.85            | 0.025     |
| SOFA score, mean $\pm$ SD, points                      | 6.71 $\pm$ 3.05         | 7.70 $\pm$ 3.74             | 0.265     |
| WBC count, mean $\pm$ SD, $\times 10^9$/L             | 12.89 $\pm$ 9.54        | 14.32 $\pm$ 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 $\pm$ SD, mg/L                              | 116.74 $\pm$ 77.55      | 104.13 $\pm$ 74.40          | 0.542     |
| SCr, mean $\pm$ SD, $\mu$mol/L                        | 63.17 $\pm$ 21.95       | 57.30 $\pm$ 23.49           | 0.334     |
| eGFR, mean $\pm$ SD, mL/min$^{-1}$ (1.73 m$^2$)$^{-1}$ | 128.25 $\pm$ 46.66      | 135.17 $\pm$ 84.39          | 0.672     |
| UA, mean $\pm$ SD, $\mu$mol/L                         | 236.10 $\pm$ 100.76     | 241.95 $\pm$ 132.68         | 0.846     |
| BUN, mean $\pm$ SD, $\mu$mol/L                        | 7.73 $\pm$ 3.53         | 9.16 $\pm$ 4.36             | 0.168     |
| PaO$_2$/FiO$_2$, mean SD                               | 133.50 $\pm$ 62.90      | 122.40 $\pm$ 58.37          | 0.505     |
| Serum lactate, mean $\pm$ SD, mmol/L complications     | 1.41 $\pm$ 0.74         | 1.61 $\pm$ 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 $\pm$ SD, days              | 20.00 $\pm$ 13.61       | 19.20 $\pm$ 11.13           | 0.818     |
| Length of hospital stay, mean $\pm$ SD, days          | 20.51 $\pm$ 13.61       | 18.95 $\pm$ 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 >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.

REFERENCES

1. Sweeney RM, McAuley DF: Acute respiratory distress syndrome. *Lancet* 88(10058):2416–2430, 2016.
2. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG, Calfee CS: Acute respiratory distress syndrome. *Nat Rev Dis Primers* 5(1):18, 2019.
3. Panichote A, Mehkri O, Hastings A, Hanane T, Demirjan S, Torbie H, Mireles-Cabodevilla E, Krishnan S, Duggal A: Factors associated with acute kidney injury in acute respiratory distress syndrome. *Ann Intensive Care* 9(1):74, 2019.
4. Parizadeh SM, Jafarzadeh-Esfehani R, Baurayni C, Aghgheh R, Shafee M, Rahmani F, Parizadeh MR, Seifi S, Ghayour-Mobarhan M, Ferns GA, et al.: The diagnostic and prognostic value of red cell distribution width in cardiovascular disease: current status and prospective. *Biofactors* 45(4):507–516, 2019.
5. Uffen JW, Oomen P, de Regt M, Oosterheert JJ, Kaasjager K: The prognostic value of red blood cell distribution width in patients with suspected infection in the emergency department. *BMC Emerg Med* 19(1):76, 2019.
6. Zhao J, Li ZL, Zhang ZD, Ma XC: Prognostic value of red blood cell distribution width for severe acute pancreatitis. *World J Gastroenterol* 25(32):4739–4748, 2019.
7. Karampitsakos T, Akinosoglu K, Papaioannou O, Panou V, Koromilas A, Bakakos P, Loukides S, Bouros D, Gogos C, Tzouvelekis A: Increased red cell distribution width is associated with disease severity in hospitalized adults with SARS-CoV-2 infection: an observational multicentric study. *Front Med (Lausanne)* 7:616292, 2020.
8. Yu XS, Chen ZQ, Hu YF, Chen JX, Xu WW, Shu J, Pan JY: Red blood cell distribution width is associated with mortality risk in patients with acute respiratory distress syndrome based on the Berlin definition: a propensity score matched cohort study. *Heart Lung* 49(5):641–645, 2020.
9. Hu Y, Liu H, Fu S, Wan J, Li X: Red blood cell distribution width is an independent predictor of AKI and mortality in patients in the coronary care unit. *Kidney Blood Press Res* 42(6):1193–1204, 2017.
10. Wang RR, He M, Ou XF, Xie XQ, Kang Y: The predictive value of RDW in AKI and mortality in patients with traumatic brain injury. *J Clin Lab Anal* 34(9):e23373, 2020.
11. ARDS Definition Task Force. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS: Acute respiratory distress syndrome: the Berlin definition. *JAMA* 307(23):2526–2533, 2012.
12. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 63(5):713–735, 2014.
13. DeMers D, Wachs D: Physiology, Mean Arterial Pressure. *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.*
14. Escare J, Kelley MA: Admission source to the medical intensive care unit predicts hospital death independent of APACHE II score. *JAMA* 264(18):2389–2394, 1990.
15. Vincent JL., Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thys LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22(7):707–710, 1996.
16. Khwaja A: KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 120(4):c179–c184, 2012.
17. Bu X, Zhang L, Chen P, Wu X: Relation of neutrophil-to-lymphocyte ratio to acute kidney injury in patients with sepsis and septic shock: a retrospective study. *Int Immunopharmacol* 70:372–377, 2019.
18. Singer M, Deutschschmidt CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Cooperstein CM, et al.: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315(8):801–810, 2016.
19. Seeley EJ: Updates in the management of acute lung injury: a focus on the overlap between AKI and ARDS. *Adv Chronic Kidney Dis* 20(1):14–20, 2013.
20. Ronco C, Bellomo R, Kellum JA: Acute kidney injury. *Lancet* 394(10121):1949–1964, 2019.
21. Karampitsakos T, Akinosoglou K, Papaioannou O, Panou V, Koromilas A, Bakakos P, Loukides S, Bouros D, Gogos C, Tzouvelekis A: Increased red cell distribution width is associated with disease severity in hospitalized adults with SARS-CoV-2 infection: an observational multicentric study. *Front Med (Lausanne)* 7:616292, 2020.
22. Yu XS, Chen ZQ, Hu YF, Chen JX, Xu WW, Shu J, Pan JY: Red blood cell distribution width is associated with mortality risk in patients with acute respiratory distress syndrome based on the Berlin definition: a propensity score matched cohort study. *Heart Lung* 49(5):641–645, 2020.
23. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 63(5):713–735, 2014.
24. DeMers D, Wachs D: Physiology, Mean Arterial Pressure. *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.*
25. Escare J, Kelley MA: Admission source to the medical intensive care unit predicts hospital death independent of APACHE II score. *JAMA* 264(18):2389–2394, 1990.
26. Vincent JL., Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thys LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22(7):707–710, 1996.
27. Khwaja A: KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 120(4):c179–c184, 2012.
28. Bu X, Zhang L, Chen P, Wu X: Relation of neutrophil-to-lymphocyte ratio to acute kidney injury in patients with sepsis and septic shock: a retrospective study. *Int Immunopharmacol* 70:372–377, 2019.
29. Singer M, Deutschschmidt CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Cooperstein CM, et al.: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315(8):801–810, 2016.
30. Seeley EJ: Updates in the management of acute lung injury: a focus on the overlap between AKI and ARDS. *Adv Chronic Kidney Dis* 20(1):14–20, 2013.
31. Ronco C, Bellomo R, Kellum JA: Acute kidney injury. *Lancet* 394(10121):1949–1964, 2019.
32. Karampitsakos T, Akinosoglou K, Papaioannou O, Panou V, Koromilas A, Bakakos P, Loukides S, Bouros D, Gogos C, Tzouvelekis A: Increased red cell distribution width is associated with disease severity in hospitalized adults with SARS-CoV-2 infection: an observational multicentric study. *Front Med (Lausanne)* 7:616292, 2020.