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Red blood cell distribution width is an independent risk factor in the prediction of acute respiratory distress syndrome after severe burns

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ABSTRACT

Background: The occurrence of acute respiratory distress syndrome (ARDS) significantly increases the mortality and morbidity of major burns; there are few laboratory markers that predict the development of ARDS in severe burns. This study was to investigate the relationship between complete blood count (CBC) parameters and the incidence of ARDS in severe burn patients.

Methods: An eight-year retrospective study was performed on 610 severe burn patients who were admitted to the First Affiliated Hospital of Anhui Medical University and Rui Jin Hospital of Shanghai Jiao Tong University from January 2008 to December 2015. The patients were divided into two groups based on the development of ARDS. A blood sample was taken at admission and CBC parameters were examined. Univariate logistic regression analysis was used to evaluate the risk factors for the development of ARDS.

Results: Of these 610 patients, 143 developed ARDS giving a rate of 23.44%. The percentage of deep second degree and full thickness burn, inhalation injury and red blood cell distribution width (RDW) were independently associated with the development of ARDS in severe burn patients. Every 1% increase in RDW was associated with a 29% increase in the risk to develop ARDS.

Conclusions: The findings of this study suggest that an elevated RDW is associated with an increased risk of ARDS and RDW is an independent risk factor in the prediction of ARDS after severe burns.

1. Introduction

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Acute respiratory distress syndrome (ARDS) describes the severe respiratory dysfunction by refractory hypoxemia and progressive respiratory distress. ARDS is one of the most common complications in patients with severe burns and is closely related to the prognosis of burns. The incidence of ARDS in severe burn patients was about 20–50% [1], and 33% of mechanically ventilated burn patients developed ARDS [2]. During the early phase of severe burn injury, the cause of ARDS included pneumonia, inhalation lesions, fluid overdose and polytrauma [3,4]. It is well established that the incidence of ARDS is associated with the massive systemic inflammatory response. The damage of endothelial and epithelial layers lead to the development of hyaline membranes in the alveoli, then a large number of acute inflammatory cells and red blood cells penetrate the alveoli, which causes deteriorated gas exchange and the lung parenchyma injury [5].

Despite the fact that mechanic ventilation and fiber bronchoscopy have significantly improved its outcomes, ARDS still remains one of the leading causes of death after severe burn injury, especially those complicated with inhalation lesions [4]. Early diagnosis and effective treatment of ARDS can significantly reduce the mortality and improve recovery. Therefore, it is important that the development of ARDS is predicted at an early stage in severely burnt patients after thermal injury.

Complete blood count (CBC) is the most common available blood test worldwide, even the laboratories with basic equipment can yield more than 10 measurements. Red blood cell distribution width (RDW) is one part of the routine blood parameters and reflects the degree of heterogeneity in erythrocyte volume. A number of studies have well been demonstrated that RDW was an independent prognostic biomarker in patients with coronary disease, severe sepsis, and septic shock, as well as in critically ill patients [6–8]. However, there was little information regarding RDW in the prediction of ARDS in severely burned patients. The objective of this study was to investigate the relationship between RDW and the incidence of ARDS after severe burns.

2. Materials and methods

2.1. Patients

This is a retrospective study of 652 severe burn patients admitted to the First Affiliated Hospital of Anhui Medical University and Rui Jin Hospital of Shanghai Jiao Tong University between January 2008 and December 2015. The personal information, baseline demographic data and injury characteristics of the patients were routinely recorded on the case history upon admission to the burn center. The severe burn patients or their close relatives were informed in detail that their clinical and laboratory data may be used for research via informed consent forms, which include benefits and risks of participating, availability of counseling services and voluntary participation, and acquired their approval. All methods were approved by Humanities Subjects Review Committee of Hefei Anhui Medical University Hospital, Hefei, Anhui, and implemented in accordance with relevant guidelines and regulations. The clinical and laboratory data were reviewed from the paper-based and electric medical records. All data of the two hospitals were collected by the same team under the unified standard.

This study included adult (age of 18 years or older) patients who were diagnosed with severe burn (the total body surface area $\geq$30%), hospitalized within 24 h after injury, accepted standardized fluid resuscitation according to the Chinese formula (1.5 mL/kg body weight $\times$ TBSA% +2000 mL dextrose solution), and length of hospital stay was more than 3 days. Patients with cardiac disease, kidney disease, or other conditions such as hemolytic anemia, bone marrow arrest, or other inflammatory diseases were excluded from the study.

2.2. ARDS definition

Since most incidences of ARDS occurred within 1 week after burn injury, the included patients were divided into two groups: a non-ARDS group, who did not develop ARDS, and an ARDS group, who did develop ARDS based on the Berlin definition [9]. Mechanic ventilation was conventionally performed on the patients that developed ARDS to provide effective gas exchange. All patients were followed-up for up to 90 days after injury. The main endpoint was the development of ARDS.

2.3. Clinical and laboratory parameter

A blood sample was collected on admission and CBC test included white blood cell (WBC), neutrophils (N), lymphocytes (L), red blood cell (RBC), hemoglobin, erythrocyte mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width coefficient of variation (RDW-CV), and platelet (PLT). All parameters were sampled within the first 24 h after burn injury and the normal reference ranges were shown in Table 1.

Table 1 – Normal reference range of CBC test parameters.

Laboratory variables	Reference range
WBC ($\times 10^9$/L)	4.0–10.0
Neutrophils ($\times 10^9$/L)	1.40–6.50
Lymphocytes ($\times 10^9$/L)	1.00–3.30
RBC ($\times 10^{12}$/L)	3.50–5.00
Hemoglobin (g/L)	110.0–150.0
MCV (fL)	80.2–97.7
MCH (pg)	27.3–34.4
MCHC (g/L)	320.0–360.0
RDW (%)	11.00–16.00
PLT ($\times 10^9$/L)	100.0–300.0

Note: WBC, white blood cell count; RBC, red blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; PLT, platelet count.

2.4. Statistical analysis

Continuous numerical variables were presented as the mean ± standard deviation (SD) and compared using student's t-test. Categorical data were presented with frequency (%) and compared by chi-square test. Univariate logistic regression analysis was conducted to evaluate the risk factors for the development of ARDS of severe burn patients. Multivariate logistic regression was used to estimate the clinical and laboratory parameters with the ARDS after major burn after adjustment for potential factors.

3. Results

3.1. Patients

We included 652 patients in the study, among which 610 had severe burns by removing 41 undesirable patients (32 patients with burns area less than 30%, 8 patients with a hospitalization period of less than 48 h and 2 patients with incomplete data record). A total of 184 patients had inhalation injury. One hundred and forty-three patients who met the eligibility criteria and accepted the mechanical ventilation were diagnosed with ARDS during hospitalization. Eighty-eight patients died within 90 days due to burns.

3.2. Baseline characteristic

Table 2 shows their baseline characteristics. Patients were divided into two groups according to ARDS status: The ARDS group and the non-ARDS group. In the ARDS group, a higher proportion with a larger %TBSA and a longer length of hospital stay were found; what's more, the ARDS group had a higher mortality rate. During the first week after injury, 72.4% non-ARDS patients had an operation, while 27.6% of patients for ARDS group underwent an operation. There was no significant difference in age or gender between the two groups. While WBC, neutrophils, lymphocytes, and RDW were significantly higher in ARDS patients than non-ARDS patients (WBC (22.55 ± 11.10) × 10^9/L vs. (18.48 ± 6.93) × 10^9/L, $P < 0.01$; neutrophils (19.43 ± 9.89) × 10^9/L vs. (16.00 ± 6.48) × 10^9/L, $P < 0.01$; lymphocytes (1.74 ± 1.30) × 10^9/L vs. (1.36 ± 0.96) × 10^9/L, $P < 0.01$; RDW (13.63 ± 1.45)% vs. (13.25 ± 0.99)%, $P < 0.01$) (Table 3). No significant difference was found in RBC (5.07 ± 0.85) × 10^{12}/L vs. (5.07 ± 1.17) × 10^{12}/L, $P > 0.05$; hemoglobin (154.82 ± 26.90) g/L vs. (155.37 ± 38.20) g/L, $P > 0.05$; MCV (88.97 ± 5.02) fL vs. (89.03 ± 5.98) fL, $P > 0.05$; MCH (30.60 ± 2.04) pg vs. (30.61 ± 2.50) pg, $P > 0.05$; MCHC (343.47 ± 11.77) g/L vs. (343.52 ± 15.66) g/L, $P > 0.05$; PLT (191.49 ± 70.36) × 10^9/L vs. (188.68 ± 116.05) × 10^9/L, $P > 0.05$ between non-ARDS group and ARDS group.

Table 2 – Baseline characteristics of the patients.

Demographics	Severe burn patients
Age (median)	45 (18-75) years
Male	73.4%
LOS (median)	34 (3-219) days
TBSA % (median)	51.7% (30-100%)
Mortality	88%

Note: LOS, length of hospital stay.

3.3. Regression analysis for the developed of ARDS

Univariate logistic regression analysis revealed that patients with higher %TBSA, % deep second degree, % full thickness burn, WBC, neutrophils, lymphocytes, RDW and inhalation injury had a significant risk in the development of ARDS. Every 1% increase in RDW was associated with a 29% increase in the risk to develop ARDS.

Multivariate logistic regression analysis demonstrated that % deep II degree, % full thickness burn, inhalation injury and RDW were independent predictors of the development of ARDS (Table 4). The association of RDW and the development of ARDS after severe burn injury remained significant after adjusting for TBSA %, % deep second degree, % full thickness burn, inhalation injury, surgery during the first week, WBC, neutrophils, and lymphocytes.

4. Discussion

ARDS is a severe inflammatory disorder of the lung, with the mortality rate of 30-50% [9–11]. And one of the pathological change of ARDS is pulmonary edema,which may affect the value of RDW [12]. The identification of patients at risk of developing ARDS as well as mortality rate after diagnosing of the disease are still remaining challenges and has been widely studied. In recent years, a great deal of clinical and biomarker parameters were found to be related to ARDS, such as the levels of plasma profiles of peptidase inhibitor 3, neutrophil elastase, blood bilirubin level at ICU admission and inhalation lesions [4,13,14]. However, to our knowledge, there are few studies on biomarkers related to the development of ARDS after severe burns. In this study, we found that the RDW is an independent risk factor for the prediction of ARDS after severe burn.

RDW, which is affected by iron content, vitamin B12, folic acid, corpuscular volume, and so on [15], is easily available in patients and has been identified as a potential biomarker to categorize individuals at risk for future adverse events [16,17], especially heart diseases. Allen et al. found that increased RDW was an independent predictor of mortality in patients with heart failure [18]. Further, Zhang et al presented that RDW is a prognostic indicator for patients with heart failure, which were caused by coronary heart disease and dilated cardiomyopathy [19]. One hundred and twenty-eight patients with hypertension, seventy-four patients with prehypertension and 36 healthy controls participated by Tanindi et al., and the study showed that higher RDW values are correlated with higher systolic and diastolic blood pressures [20]. In lung diseases, Koma et al. found that RDW was associated with lung cancer [21] and acute pulmonary embolism, [22] respectively. The study of Hampole and his coworkers indicated that RDW was independently associated with death in patients with pulmonary hypertension [23]. In the study by Alkhatib et al, there was a 58% mortality rate of ARDS patients who had an upward trend in RDW while 33% had a downward trend [24].

Table 3 – Comparison of subjects that did not develop ARDS with subjects that did develop ARDS.

	non-ARDS	ARDS	P value
Demographics			
Number of patients	467	143	
Age (years)	45.15±16.50	44.59±14.29	0.714
Gender (M/F)	341/126	107/36	0.669
Clinical variables			
TBSA %	46.40±15.12	69.10±22.74	0.000
% deep II degree	22.22±13.86	26.48±19.81	0.018
% full thickness burn	14.19±17.20	38.35±28.59	0.000
Inhalation injury, n (%)	85 (46.2)	99 (53.8)	0.000
Surgery during the first week, n (%)	241 (72.4)	92 (27.6)	0.007
LOS, days	31.69±21.66	41.94±36.22	0.002
Mortality (%)	37 (42.0)	51 (58.0)	0.000
Laboratory variables			
WBC ($\times 10^9$/L)	18.48±6.93	22.55±11.10	0.000
Neutrophils ($\times 10^9$/L)	16.00±6.48	19.43±9.89	0.000
Lymphocytes ($\times 10^9$/L)	1.36±0.96	1.74±1.30	0.001
RBC ($\times 10^{12}$/L)	5.07±0.85	5.07±1.17	0.986
Hemoglobin (g/L)	154.82±26.90	155.37±38.20	0.872
MCV (fL)	88.97±5.02	89.03±5.98	0.907
MCH (pg)	30.60±2.04	30.61±2.50	0.942
MCHC (g/L)	343.47±11.77	343.52±15.66	0.968
RDW (%)	13.25±0.99	13.63±1.45	0.005
PLT ($\times 10^9$/L)	191.49±70.36	188.68±116.05	0.784

Note: data are presented as mean±SD, or number (%). LOS, length of hospital stay. WBC, white blood cell count; RBC, red blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; PLT, platelet count.

Table 4 – Risk factors associated with the presence of ARDS after severe burn injury.

	β	SE	Wald	P value	OR	95%CI	
						Lower	Upper
Age (years)	−0.002	0.006	0.134	0.714	0.998	0.986	1.010
Male (n)	0.094	0.219	0.183	0.669	1.098	0.715	1.687
TBSA %	0.060	0.006	113.154	0.000	1.062	1.050	1.074
% deep II degree	0.017	0.006	8.031	0.005	1.017	1.005	1.029
% full thickness burn	0.044	0.005	90.769	0.000	1.045	1.036	1.055
Inhalation injury	−2.314	0.217	113.389	0.000	0.099	0.065	0.151
Surgery during the first week	−0.526	0.198	7.077	0.008	0.591	0.401	0.871
WBC ($\times 10^9$/L)	0.057	0.012	24.373	0.000	1.059	1.035	1.083
Neutrophils ($\times 10^9$/L)	0.058	0.013	21.075	0.000	1.060	1.034	1.086
Lymphocytes ($\times 10^9$/L)	0.295	0.086	11.862	0.001	1.343	1.135	1.588
RBC ($\times 10^{12}$/L)	0.002	0.102	0.000	0.983	1.002	0.821	1.223
Hemoglobin (g/L)	0.001	0.003	0.037	0.847	1.001	0.994	1.007
MCV (fL)	0.002	0.018	0.017	0.898	1.002	0.967	1.039
MCH (pg)	0.004	0.044	0.007	0.935	1.004	0.920	1.095
MCHC (g/L)	0.000	0.007	0.002	0.963	1.000	0.986	1.015
RDW (%)	0.258	0.079	10.798	0.001	1.294	1.110	1.510
PLT ($\times 10^9$/L)	0.000	0.001	0.125	0.724	1.000	0.997	1.002

Note: OR, odds ratio; CI, confidence interval.

Our previous study further demonstrated that the ratio of RDW and PLT was an independent value for burn mortality prediction at the 3rd and 7th day after injury, which is quite important for the prognosis of severe burns [25].

As far as we know, this is the first paper to delve into the relationship between RDW and ARDS after severe burns. These data come from the First Affiliated Hospital of Anhui Medical University and Shanghai Rui Jin Hospital, which contained a relatively large sample size and reliable content. In this large retrospective study, 610 severe burn patients were classified into two groups based on the occurrence of ARDS, and the CBC test was carried out to find its relationship with ARDS. In order to reduce interference with the result, the known risk factors were adjusted into the univariate and multivariate regression

analyses. The risk factors including % TBSA, % deep second degree, % full thickness burn, WBC, neutrophils, lymphocytes, inhalation injury, which are crucial to the development of ARDS after severe burns. The ARDS group of patients had a higher RDW compared with the non-ARDS group of patients after severe burn injury, while there was no correlation of RBC, hemoglobin, MCV, MCH, MCHC, PLT to the development of ARDS. The result of this study that the increase of 1% in RDW corresponded to the increase of 29% in the risk of developing ARDS suggested that RDW was an independent predictor for the development of ARDS after severe burn.

Nevertheless, we acknowledge several limitations of this study. First, the value of RDW is not continuous, which may make the result less convincing. Second, this study did not rule out other risk factors, such as race, geography, economic capacity, and infection. Third, the retrospective nature of the design limited the research. Although the sample size was large, consisting of 610 patients, the participants were not representative of the general population, because the patients are only from a certain area of China.

5. Conclusion

ARDS is a common and serious syndrome after a severe burn, and it is fatal. This study demonstrates the relationship between RDW and ARDS after severe burn. RDW is an independent predictor of the development in severe burns, thus we can adjust the treatment of burn patients according to the value of RDW.

Conflicts of interest

None.

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Disclosure statement

The authors have nothing to disclose.

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