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Original Article

An analysis of the 28-day mortality risk factors in acute respiratory distress syndrome patients and the establishment of prediction models

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Abstract: Objective: To explore the risk factors and prediction models of 28-day mortality in acute respiratory distress syndrome (ARDS) patients. Methods: A total of 215 ARDS patients treated in our hospital were enrolled in this prospective observational study, including 70 patients who died within 28 days and were placed in the death group, and the remaining 145 patients who survived and were placed in the survival group. The laboratory examination indexes and critical scoring system scores were compared between the two groups. A Cox regression analysis was used to analyze the factors associated with 28-day mortality, and a receiver operating characteristic (ROC) curve was used to analyze the performance of the prediction models. Results: The ROC curve analysis showed that the erythrocyte distribution width (RDW), the neutrophil to lymphocyte ratio (NLR), the procalcitonin to albumin ratio (PAR), and the Murray lung injury score (MLIS) were effective at diagnosing the 28-day mortality, each with an area under the curve (AUC) of >0.5 (P<0.001). A multivariate Cox analysis showed that the RDW, NLR, PAR, and MLIS were independent predictors of 28-day mortality. The results of the multi-index joint prediction showed that the AUC of RDW+NLR+PAR+MLIS was 0.945 (95% CI: 0.910-0.979), and the sensitivity was as high as 94.25%. Conclusion: NLR, PAR, RDW, and MLIS are independent predictors of 28-day mortality, and their combined prediction can significantly improve the predictive ability of the 28-day mortality in ARDS patients.

Keywords: Acute respiratory distress syndrome, 28-day mortality, risk factors, neutrophil to lymphocyte ratio, procalcitonin to albumin ratio

Introduction

Acute respiratory distress syndrome (ARDS) is an inflammatory lung disease which progresses rapidly and is highly destructive. Patients present with severe respiratory failure and require mechanical ventilation and have a fatality rate of 30% to 40% [1, 2]. There are many pathogenic factors for ARDS, and the common ones include septicemia, pneumonia and severe burns, but the factors vary from region to region. For example, sepsis and pneumonia are common causes of ARDS in China [3].

There is still a lack of accurate clinical diagnostic and prognostic prediction methods for ARDS, making its treatment challenging. The current scoring systems for critically ill patients are widely used clinically, such as the acute acute physiology chronic health evaluation II (APACHE II) and the Murray lung injury score (MLIS), which have been proved to be closely related to patient outcomes [2]. However, these scoring systems are often subjective, and they cannot effectively predict the prognoses or death risks of patients with specific diseases [4]. For example, APACHE II is not specific at distinguishing sepsis, ARDS, or acute kidney injury. Another study revealed that there was no difference in the APACHE II scores between ARDS survivors and non-survivors [5]. In addition, the APACHE II score is not designed with pathophysiological indicators, so it is difficult to achieve personalized treatment guidance for clinical patients [6]. Therefore, the further development of the ARDS mortality predictors will have a great clinical value for clinical treatment optimization and patient prognosis.

In recent years, biomarkers have been extensively explored and applied in many clinical dis-

eases, such as in the diagnosis, efficacy and prognostic evaluation of tumors, due to the rapidity and accuracy of measurement [7, 8]. In this study, we attempted to construct prediction models of short-term mortality in ARDS patients using blood biomarkers, including novel inflammatory markers such as the neutrophil-lymphocyte ratio (NLR) [9] and the procalcitonin to albumin ratio (PAR) [10]. Of them, NLR, a prognostic inflammatory biomarker for various diseases such as pneumonia and tumors, can be used to evaluate the efficacy and prognosis of patients with severe pneumonia using dynamic monitoring [11, 12]. A recent study shows that PAR, a sensitive predictor, is significantly related to the prognoses of patients with critical diseases and is negatively associated with the degree of lung injury in ARDS patients [13]. Hence, apart from the scales for critically ill patients, we also analyzed the prediction models of blood biomarkers in order to comprehensively evaluate the performance of different prediction models and provide a reference for the clinical treatment of ARDS.

Materials and methods

Patients

This prospective study included 215 ARDS patients treated in our hospital from March 2018 to June 2020. Among them, 70 patients who died within 28 days of admission were included in the death group, and the remaining 145 patients were included in the survival group. Inclusion criteria: (1) Patients who were diagnosed with ARDS [14]. (2) Patients who had complete clinical data such as their medical history and treatment data. (3) Patients over 18 years old. Exclusion criteria: (1) Patients with malignancies or with severe hematologic system or immune system diseases. (2) Patients whose laboratory examination data, acute physiology chronic health evaluation II (APACHE II) scores, and MLIS could not be obtained within 24 hours of admission.

Ethics statement

This research followed the purpose of the Declaration of Helsinki and was approved by the ethics committee of our hospital. All the patients and their families were informed of this study and signed the informed consent.

Treatment

All the ARDS patients underwent routine treatment after their diagnosis, including ventilator-assisted ventilation to correct hypoxia, antibiotic therapy, anti-shock therapy, the correction of hypoproteinemia, the correction of acid-base imbalance and electrolyte disorders, sedation, as well as the treatment of primary diseases.

Laboratory examination

Upon admission, all the patients had peripheral venous blood drawn for laboratory examinations, including their blood routine, blood biochemical indexes, serum procalcitonin (PCT), and albumin (ALB) levels. Their neutrophils to lymphocytes (NLR) and procalcitonin to albumin (PAR) ratios were also calculated.

Scale evaluation

After their admission, patients were promptly assessed to determine their acute physiology chronic health evaluation II (APACHE II) and Murray lung injury scores (MLIS) [2, 5].

Follow-up

The number of patients who died during their hospitalization was recorded, and the survival of the discharged patients was followed up for 28 days after their disease onset.

Outcome measures

Primary outcome measures: (1) The factors associated with 28-day mortality in ARDS patients. (2) The predictive efficacy of RDW, NLR, PAR, and MLIS, alone or in combination for determining ARDS patients' 28-day mortality. Secondary outcome measures: The laboratory examination indexes and the APACHE II and MLIS scores of the patients in the two groups.

Statistical analysis

SPSS Version 25.0 (SPSS, Inc., Chicago, IL, USA) software was used for the statistical analysis. The count data were expressed as cases (percentage; n, %) and analyzed using chi-square tests. The measurement data that did not follow a normal distribution were represented as the median (interquartile range) (M (QR)), and compared using Mann-Whitney U

Table 1. The baseline data of the two groups of patients ($\bar{x} \pm sd$)

Project	Survival group (n=145)	Death group (n=70)	P
Gender (male/female)	88/57	43/27	0.917
Age (years)	53.2±5.5	54.8±6.0	0.062
Causes of disease (n, %)			
Lung disease	35 (24.14)	36 (51.43)	<0.001
Sepsis	26 (17.93)	12 (17.14)	0.887
Trauma	32 (22.07)	6 (8.57)	0.015
Severe burns	15 (10.34)	7 (10.00)	0.938
Pancreatitis	20 (13.79)	5 (7.14)	0.154
Other	17 (11.72)	4 (5.71)	0.164
History (n, %)			
Diabetes	57 (39.31)	30 (42.86)	0.247
Hypertension	40 (27.59)	28 (40.00)	0.067
Other	48 (33.10)	12 (17.14)	0.014
Mechanical ventilation (n, %)			0.657
Pure invasive mechanical ventilation	50 (34.48)	22 (31.43)	
Invasive-noninvasive sequential mechanical ventilation	95 (65.52)	48 (68.57)	
Other treatments (n, %)			
Resistance to shock	78 (53.79)	37 (52.86)	0.897
Fight infection	128 (88.28)	63 (90.00)	0.708
Glucocorticoid therapy	75 (51.72)	32 (45.71)	0.409
Sedation analgesia	64 (44.14)	26 (37.14)	0.330
Other	55 (37.93)	30 (42.86)	0.449

tests between groups; those conforming to a normal distribution were expressed as ($\bar{x} \pm sd$) and compared using paired sample t tests within groups. Univariate and multivariate Cox regression analyses were used to analyze the related factors of the patients' 28-day mortality, with a patient's death within 28 days as a dependent variable, and a patient's age, sex, disease inducement, treatment method, and laboratory indexes as the independent variables. Receiver operating characteristic (ROC) curves were used to analyze the predictive efficacy of RDW, NLR, PAR, and MLIS. In the joint diagnosis, the probability of the combined indicators was calculated using a binary logistic regression, and the diagnostic efficiency was analyzed using ROC curves. The binary logistic regression equation of RDW+NLR+PAR was $P=1/(1+e^{-(-4.107+0.051\times X1+0.829\times X2+2.477\times X3)})$, and the binary logistic regression equation of RDW+NLR+PAR+MLIS was $P=1/(1+e^{-(-4.034+0.048\times X1+0.783\times X2+2.229\times X3+0.697\times X4)})$. A significant level of $\alpha=0.05$ was used for the two-sided test. $P<0.05$ meant that a difference was statistically significant.

Results

Baseline patient data

The patients' baseline characteristics, such as gender, age, and pathogenic factors are presented in **Table 1**. There were no significant differences in terms of gender or age between the two groups ($P>0.05$). However, compared with the survival group, the proportion of lung diseases was significantly higher ($P<0.001$) and the proportion of trauma was lower in the death group ($P<0.05$). There was a certain difference in the medical histories between the two groups due to the difference in the number of patients included in each group ($P<0.05$). There were no significant differences in the mechanical ventilation or the other treatment courses between the two groups ($P>0.05$).

Comparison of the laboratory examination indexes, The APACHE II and MLIS scores in the two groups

We compared the differences in the laboratory examination indexes and the APACHE II and

Table 2. The two groups' laboratory examination indexes and APACHE and MLIS scores ($\bar{x}$ ± sd)

Indicators	Survival group (n=145)	Death group (n=70)	P
WBC (×10^9/L)	19.56±5.25	21.34±4.22	0.008
NEU (×10^9/L)	8.35±5.60	11.38±6.47	<0.001
LYM (×10^9/L)	1.32±0.24	0.96±0.45	<0.001
GR (%)	79.56±9.63	82.06±10.23	0.090
PCT (μg/L, M (Q))	0.68 (0.31-1.46)	2.62 (0.89-8.78)	<0.001
ALB (g/L, M (Q))	32.04 (28.67-33.78)	27.80 (23.23-30.90)	<0.001
PLT (×10^9/L)	113.75±26.45	105.38±29.73	0.047
EOS (×10^9/L)	0.05±0.07	0.04±0.05	0.232
RDW (%, M (Q))	12.75 (7.38-19.56)	16.38 (8.85-29.36)	<0.001
NLR	12.29±5.10	16.05±6.34	<0.001
PAR	0.033±0.015	0.045±0.022	<0.001
APACHE II (scores)	24.35±4.54	26.22±5.56	0.016
MLIS (scores)	2.18±0.42	2.65±0.67	<0.001

Note: WBC: white blood cell count; NEU: neutrophil count; LYM: lymphocyte count; GR: percentage of neutrophils; PCT: procalcitonin; Alb: albumin; PLT: platelet count; EOS: eosinophil count; RDW: red blood cell distribution width; NLR: ratio of neutrophils to lymphocytes; PAR: procalcitonin to albumin ratio; APACHE II: acute physiology and chronic health II score; MLIS: Murray lung injury score.

Table 3. The predictive efficacy of RDW, NLR, PAR, and MLIS for ARDS patients at 28 days

Indicators	AUC	95% CI	P	Sensitivity (%)	Specificity (%)	Cut-off
RDW	0.782	0.698-0.866	<0.001	78.45	84.58	14.26
NLR	0.852	0.786-0.914	<0.001	87.34	80.89	13.96
PAR	0.899	0.848-0.949	<0.001	91.50	77.45	0.037
MLIS	0.843	0.783-0.908	<0.001	84.26	82.35	2.030

Note: RDW: red blood cell distribution width; NLR: ratio of neutrophils to lymphocytes; PAR: procalcitonin to albumin ratio; MLIS: Murray lung injury score.

MLIS scores between the two groups before the treatment. The results showed that, compared with the survival group, the WBC, NEU, LYM, PCT, ALB, RDW, NLR, and PAR levels were significantly increased in the death group (all P<0.01), the PLT level was significantly decreased (P<0.05), and the APACHE II and MLIS scores were also evidently higher (P<0.05). There were no significant differences in the GR or EOS levels between the two groups (both P>0.05; **Table 2**).

ROC curve analysis

The ROC curve analysis of the four independent predictors in the multivariate Cox regression analysis showed that the AUCs of RDW, NLR, PAR, and MLIS were 0.782, 0.852, 0.899, and 0.843 (all P<0.001), indicating that they all had a predictive value for the 28-day mortality in ARDS patients (**Table 3**; **Figure 1**). When the optimal cut-off value was taken, the sensitivity of PAR was the highest (91.50%), followed by NLR (87.34%), and the sensitivity of RDW was the lowest (78.45%). See **Table 3**.

A Cox regression analysis of the 28-day mortality in ARDS patients

A Cox regression analysis was used to analyze the related factors of the 28-day mortality in ARDS patients. In our univariate analysis, a total of 18 variables that differed between the groups or were of interest (variables of interest referred to factors previously reported to be prognostic, such as a history of hypertension), including age, gender, and laboratory indicators were included. The Cox regression results showed that age, pathogenic factors, surgical history, invasive and noninvasive sequential mechanical ventilation, RDW, NLR, PAR, and the APACHE II and MLIS scores were all related to the patients' 28-day mortality (all P<0.05, **Table 4**). The above significant variables were further included in a multivariate Cox regression analysis, and the results showed that age (HR=1.113, 95% CI: 1.022-1.367), RDW (HR=2.126, 95% CI: 1.233-3.589), NLR (HR=2.803, 95% CI: 1.817-4.849), PAR (HR=3.593, 95% CI: 1.702-6.482), and MLIS (HR=1.832, 95% CI: 1.083-2.839) remained statistically significant and were independent predictors of patients' 28-day mortality, with PAR contributing the most. See **Table 4**.

Performance of the joint prediction models

Further, we drew the ROC of the joint prediction of RDW, NLR, PAR, and MLIS and analyzed the

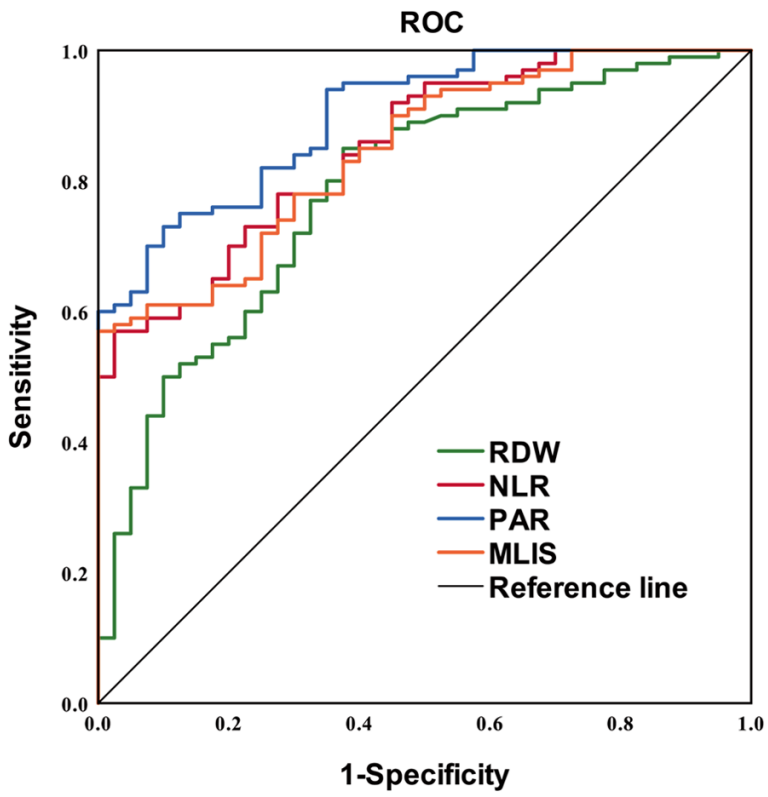

Figure 1. An ROC curve of RDW, NLR, PAR, and MLIS predicting the 28-day mortality in ARDS patients. RDW: red blood cell distribution width; NLR: ratio of neutrophils to lymphocytes; PAR: procalcitonin to albumin ratio; MLIS: Murray lung injury score.

performance of the joint prediction models. The results showed that the AUC of RDW+NLR+PAR was 0.930 (95% CI: 0.890-0.970), which was significantly higher than the AUC of the three predicted separately, and the sensitivity was increased to 93.48% (**Figure 2**). When MLIS was combined (RDW+NLR+PAR+MLIS), the AUC reached 0.945 (95% CI: 0.910-0.979), and the sensitivity was 94.25% (**Figure 2**); however, no statistical difference was observed when compared with RDW+NLR+PAR (Z=0.823, P=0.345).

Discussion

The pathogenesis of ARDS includes a combination of endothelial injury, epithelial injury, intense inflammatory cascade, coagulation disorder, fibrosis, and apoptosis [15, 16]. Related studies have shown that the by-products of the acute dysregulation of various cellular pathways are closely related to the development of disease [17-19]. Therefore, this implies that it is feasible to study the circulating markers related to the prognosis of ARDS. In this study, we retrospectively analyzed the predictive effects of the laboratory examination indexes (mainly WBC, NEU, LYM, PCT, and ALB) of 215 ARDS patients (70 of whom died within 28 days) and their associations with the patient outcomes. These above laboratory examination indexes are those most widely used in clinical practice, and the measurement methods are advanced and quick, so they help speed up the treatment time. Studies have shown that the RDW, NLR, and PAR levels can independently predict the 28-day mortality of ARDS patients, and the combination of the three can further improve the prediction performance, and this is especially true when MLIS is further combined.

In our multivariate Cox regression analysis, RDW, NLR, and PAR were all found to be related to the 28-day mortality of ARDS patients. RDW, a parameter reflecting the heterogeneity of the peripheral blood erythrocyte volume, has been recently found to be abnormally increased in pneumonia, and in liver and kidney failure and other acute or chronic diseases and is considered to be a sensitive predictor of organ dysfunction [20]. It is thought that RDW may play an important role in ARDS inflammation [21]. A previous study by Alkhatib et al. showed that RDW can improve the performance of the mortality prediction models for ARDS patients, and this is consistent with our results [22]. NLR is a novel inflammatory marker, which itself is not a molecule in the human body, but the ratio of neutrophils to lymphocytes [23]. NLR can better reflect the degree of systemic inflammatory response than NEU or LYM alone. A recent retrospective study by Li et al. also shows that high NLR levels are related to poor prognosis in patients with severe ARDS, with a significant difference at the second quartile of 13.06 (11.35-14.89; HR=1.674) [24]. In our study, the

Table 4. A Cox regression analysis of ARDS patient death at 28 days (n=215)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age	1.125	1.038-1.402	0.022	1.113	1.022-1.367	0.032
Gender (male vs. female)	1.085	0.809-1.303	0.088			
Risk factors (lung disease vs. others)	1.953	1.792-3.228	0.018	1.246	0.932-1.875	0.079
History of surgery (yes vs. no)	1.680	1.267-2.904	0.010	1.365	0.974-2.189	0.082
Diabetes (yes vs. no)	1.025	0.595-1.230	0.352			
High blood pressure (Yes vs. No)	1.225	0.982-1.502	0.092			
Invasive-noninvasive sequential mechanical ventilation (yes vs. no)	0.896	0.586-0.995	0.043	0.906	0.669-1.105	0.108
Anti-shock (yes vs. no)	0.938	0.638-1.182	0.084			
Anti-infection (yes vs. no)	0.955	0.775-1.097	0.283			
Glucocorticoid therapy (yes vs. no)	1.092	0.799-1.493	0.064			
Sedation and Analgesia (yes vs. no)	0.907	0.767-1.372	0.192			
WBC	1.056	0.978-1.202	0.075			
PLT	1.106	0.986-1.423	0.095			
RDW	2.303	1.756-4.935	<0.001	2.126	1.233-3.589	0.036
NLR (≥13.96 vs. <13.96)	2.574	1.792-5.523	<0.001	2.803	1.817-4.849	<0.001
PAR (≥0.037 vs. <13.96)	3.394	1.692-6.192	<0.001	3.593	1.702-6.482	<0.001
APACHE II	1.223	1.083-1.735	0.025	1.092	0.834-1.638	0.102
MLIS (≥2.03 scores vs. <2.03 scores)	1.834	1.054-3.017	<0.001	1.832	1.083-2.839	0.036

Note: Note: WBC: white blood cell count; PLT: platelet count; RDW: red blood cell distribution width; NLR: ratio of neutrophils to lymphocytes; PAR: procalcitonin to albumin ratio; APACHE II: acute physiology and chronic health II score; MLIS: Murray lung injury score.

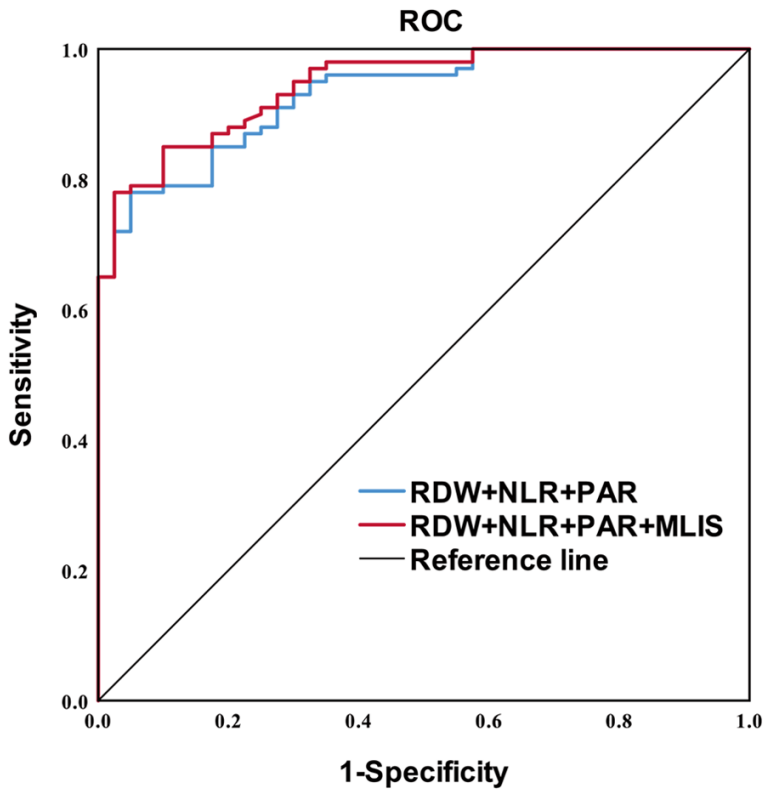

Figure 2. An ROC curve of the joint prediction. The AUC of RDW+NLR+PAR was 0.930 (95% CI: 0.890-0.970). The AUC of RDW+NLR+PAR+MLIS was 0.945 (95% CI: 0.910-0.979). RDW: red blood cell distribution width; NLR: ratio of neutrophils to lymphocytes; PAR: procalcitonin to albumin ratio; MLIS: Murray lung injury score.

cut-off value of NLR was 13.96, which is almost the same as the above results. As to PAR, it is the ratio of PCT to ALB, which can reflect patients' inflammatory and nutritional states [10]. We found that the AUC (0.899) and sensitivity (91.50%) of PAR in predicting the 28-day mortality of ARDS patients were the highest among the four independent predictors (the other three were RDW, NLR, and MLIS). In addition, PAR has the advantages of a quick examination and easy access, indicating that PAR has a great potential for evaluating the prognoses of ARDS patients.

Further, we analyzed the joint prediction efficiency of RDW+NLR+PAR, and the results were encouraging, with an AUC of 0.930 (95% CI: 0.890-0.970) and a sensitivity of 93.48%. The AUC and sensitivity were further improved

after the combination with MLIS, but there was no significant increase compared with RDW+NLR+PAR, and this may be related to the lack of specificity of MLIS [25]. Given that RDW+NLR+PAR has a good predictive performance without increasing the MLIS score, it is suggested that the use of an appropriate combination of circulating markers is highly feasible for predicting the prognosis of ARDS, which may help to avoid the lack of objectivity and the unquantification of the scoring system for critically ill patients, and to win precious time and opportunities for ARDS treatment.

This study also has some limitations. First of all, other specific inflammatory markers that may help improve the performance of prediction models, such as angiopoietin-2 and cytokine-chemokine were not measured in this study; on the other hand, we believe that these markers may not be easily obtained in general medical institutions, and the measurement time and accuracy may also be limited. In addition, this study used an independent cohort and lacks the external verification of risk models based on the ARDS biomarkers. The above limitations are what we need to clarify in our follow-up research.

In conclusion, our research argues that the use of easily available laboratory examination indicators has a great potential in building ARDS mortality prediction models. RDW+NLR+PAR can effectively predict the 28-day mortality risk of ARDS patients, thereby providing patients with a more optimized treatment plan; moreover, the combination of scales for critically ill patients or other potential biomarkers may further improve the ability of the prediction models.

Disclosure of conflict of interest

None.

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