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Original Article

Neutrophil-to-lymphocyte ratio is a powerful predictor of adult patients with acute respiratory distress syndrome who might benefit from corticosteroid therapy

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Abstract: Background: There is no convincing pharmacological treatment for patients withacute respiratory distress syndrome (ARDS). The efficacy of corticosteroids in ARDS patients remains controversial. Neutrophil-to-Lymphocyte Ratio (NLR) has displayed as a good biomarker for inflammation and immune status, and thus a prognostic marker in some critical patients of ARDS. In this study, we hypothesized that NLR could also serve as an indicator for the efficacy of corticosteroid therapy in ARDS patients. Methods: Subjects included in this retrospective cohort study with ARDS patients who were admitted to an academic hospital in Wuhan, China, from May 1st, 2020 to April 20th, 2021. Multivariable logisitic regression model was used to evaluate risk factors of 30-day in-hospital mortality and ventilator-free days. Multi-Cox regression model was used to assess the efficacy of corticosteroid treatment in terms of NLR cutoff value. Results: Among the 357 patients in our study, 89 (24.9%) had NLR≥14.35 and 268 (75.1%) had NLR<14.35. Among them, 53 patients with NLR≥14.35 (58.9%) received corticosteroids and 99 patients with NLR<14.35 (37.1%) received corticosteroids. Post-adjustment analysis (by APACHE II score and age) revealed that corticosteroid treatment was associated with a decreased risk of 30-day mortality in the NLR≥14.35 group but with an increased risk of death in the NLR<14.35 group. Use of corticosteroid in NLR≥14.35 group significantly increased ventilator-free days (7.0 vs. 13.0, P<0.001). Conclusion: NLR may be used to help identify ARDS patients who may benefit from corticosteroid treatment. Large-sized randomized controlled trials are warranted to determine the optimal cutoff value of NLR.

Keywords: Neutrophil-to-lymphocyte ratio, corticosteroid, acute respiratory distress syndrome, efficacy, clinical characteristics

Introduction

Acute respiratory distress syndrome (ARDS) is one of the leading causes of high mechanical ventilation rate and in-hospital mortality in emergency department and intensive care units (ICUs) [1, 2]. Among various risk factors, multiple inflammatory factors cause a sharp increase in the infiltration of alveolar epithelial cells and vascular endothelial cells, and the immune-mediated inflammatory response develops and progresses uncontrollably, thereby leading to ARDS. So far, no proven specific effective pharmacological therapy or immunomodulatory treatment is available for ARDS, especially for patients at the early stages of the disease [3, 4].

The Faculty of Intensive Care Medicine and Intensive Care Society Guideline Development Group made the following recommendations as: in the absence of adequate evidence, the use of corticosteroids and the removal of extracorporeal carbon dioxide were applied for the management of adult patients with ARDS [5]. A meta-analysis, which includes nine randomized clinical trials (RCTs), investigated methylprednisolone or hydrocortisone treatment in early or late process of ARDS, supported the notion that such treatment could result in sig-

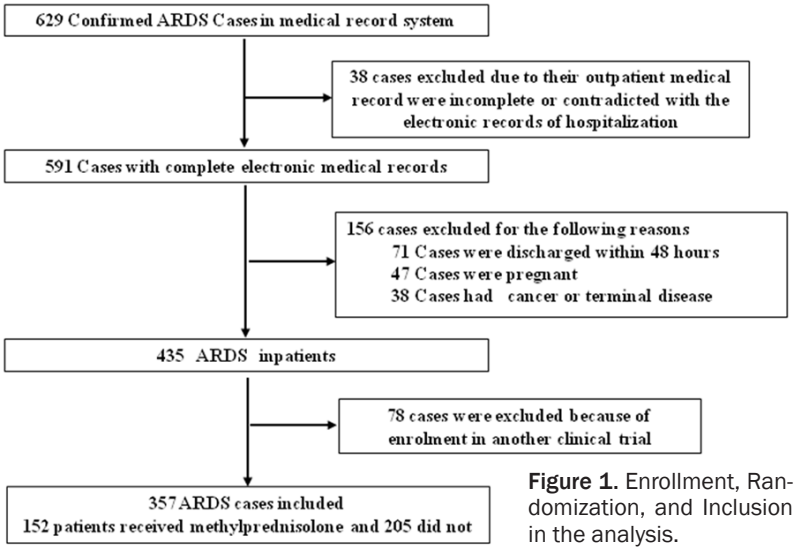

Figure 1. Enrollment, Randomization, and Inclusion in the analysis.

nificant attenuation in systemic inflammation, improvement in gas exchange, reduction of duration of mechanical ventilation and in length of stay in ICU [6, 7]. However, the study failed to provide data on the benefits in terms of mortality [8-10].

On the other hand, some studies showed that glucocorticoids had no beneficial effects on ARDS and, in some cases, may cause more adverse effects, such as secondary infection, elevated blood glucose and increased ventilator dependency, thereby leading to deterioration of the disease [11-14]. Up to now, the efficacy of corticosteroids in ARDS remains controversial. We speculate that such inconsistencies might result from the differences in patient selection, dosages, duration and timing of corticosteroid therapy. The biggest challenge in the quantification or stratification came from the heterogeneity of the enrolled subjects. In addition, more objective, accurate and easily accessible biomarkers for evaluating the effect of corticosteroid on ARDS patients remain unavailable.

Although the serum levels of inflammatory cytokines, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are potentially prognostic biomarkers in ARDS patients, their predictive value for the efficacy of corticosteroid therapy for ARDS patients remain uncertain [15-17]. This retrospective cohort study aimed to evaluate the relationship between the NLR and effects of corticosteroids on mortality, tracheal intubation, and mechanical ventilator-free days from ARDS patients.

Materials and methods

Study participants and definitions

In this retrospective cohort study, our team consecutively included ARDS patients who were admitted to Renmin Hospital of Wuhan University from May 1st, 2020 to April 20th, 2021. The diagnosis of ARDS was based on the American-European Consensus Conference criteria for ARDS, or/and according to the Berlin criteria as moderate-to-severe ARDS [18].

In brief, inclusion criteria were: (1) aged 18 years or older; (2) had acute onset of ARDS at admission, which includes clinical symptoms such as respiratory distress, hypoxemia; (3) bilateral diffuse pulmonary infiltrates of CT scan imaging; (4) as defined by a ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO_2/FiO_2) of 200 mm Hg or less on positive end-expiratory pressure (PEEP) of 10 cm H_2O or more, and FiO_2 of 0.5 or more at 24 h after ARDS onset; (5) One of the following clinical diagnoses (community-acquired pneumonia, sepsis, acute pancreatitis, trauma, multiple organ dysfunction syndrome, chemical inhalation injury, etc.) before or within 1 week of the new occurrence or deterioration of respiratory symptoms.

The clinical data of 629 patients were collected as described in **Figure 1**. Exclusion criteria included (1) pregnancy; (2) having previous medical history of having developed cancer, or severe chronic obstructive pulmonary disease, congestive heart failure, terminal-stage disease; (3) having received receiving corticosteroids or immunosuppressive drugs lasting for 1 month or more; (4) died or was discharged within 48 hours after admission; (5) had no baseline data at the emergency department. In total, 357 patients were included for the final analyses.

This study was approved by the Medical Ethics Committee of Renmin Hospital of Wuhan University and fully complied with the Declaration of Helsinki (Approval Number WDRY20200-K227). The data used in the study were used on anonymous basis, so the requirement for informed consent was waived.

Management of ARDS patients

ARDS patients in the methylprednisolone group received the first dose immediately after acute onset no later than 12 h at emergency department. Treatment with methylprednisolone was maintained for a maximum of 10 days. An intravenous dose of 40 mg was done twice daily from day 1 to day 5, and which was reduced to 40 mg once daily from day 6 to day 10.

All supportive procedure of patients enrolled in the study were not strictly different. In both corticosteroid treatment groups and non-corticosteroid groups, all conventional critical care management were allowed at the discretion of the attending physician, including antibiotic therapy, hemodynamic support, sedation, neuromuscular blocking drugs, prone positioning, aimed at maintaining optimal conditions.

Outcomes and Data collection

The primary outcome was 30-day in-hospital all-cause mortality. The secondary outcome was rate of tracheal intubation and non-invasive positive pressure ventilation (NIPPV), as well as the number of ventilator-free days.

We collected patients' demographic information, coexisting conditions, clinical symptoms, therapeutic intervention, laboratory routine biochemistry and hematological tests, acute physiology and chronic health evaluation II (APCHEII) score; and the sequential organ failure assessment (SOFA) score at admission and during hospitalization from the electronic medical records. All chest CT imaging abnormalities were diagnosed by radiologists and respiratory physicians.

Monitoring data of arterial blood gas analysis and pulmonary parameters (eg, FiO_2, PaO_2, PaO_2/FiO_2, $PaCO_2$, and PH), and hemodynamics parameters (eg, heart rate, respiratory rate, mean blood pressure, and need for inotropy or vasoactive drugs) were collected from nursing record book at admission and during hospitalization.

Statistical analysis

Statistical analysis was performed by employing Stata IC (version 15.1). Continuous variables were presented as median (interquartile ranges) and were compared by using Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and were compared between patients who received corticosteroid and those who did not by utilizing chi-square or Fisher exact test.

Multivariable logistic regression model was used to evaluate risk factors for 30 day in-hospital mortality. Multivariable Cox regression model was employed to assess the efficacy of corticosteroid treatment in ARDS patients stratified by NLR cutoff value. Kaplan-Meier survival curves among ARDS patients stratified by NLR cutoff value were conducted to examine the association between corticosteroid therapy and primary outcomes.

Multi-Cox regression model was utilized for the analysis of survival data. Primary and secondary outcomes were reported with between-group observed differences and 95% confidence intervals. Frequencies of adverse events and complications were compared with the chi-square test. All tests were two-sided and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of ARDS patients at admission

The demographic information and physiological parameters at admission ARDS patients with or without corticosteroid therapy are given in Supplementary Table 1. Compared with non-corticosteroid group, the patients in the corticosteroid group were older, had higher APACHE II score, lung CT score, CRP, Lac, worse PaO_2/FiO_2, lower $CD4^+$ and $CD8^+$ lymphocyte counts, and the higher rate of shock on admission (all $P<0.05$). It is worth noting that the NLR ratio was remarkably higher in the corticosteroid group than in the non-corticosteroid group [NLR 14.82 (7.52-25.25) vs. 8.94 (6.78-16.15), $P<0.001$] (Supplementary Table 1).

The etiology of 357 ARDS patients, in order, were pneumonia (145, 40.61%), sepsis (72, 20.17%), multiple organ dysfunction syndrome (59, 16.52%), acute pancreatitis (45, 12.60%), trauma (28, 7.84%), chemical inhalation injury and acute paraquat poisoning (8, 2.24%).

At admission, 105 of 357 (29.4%) patients received standard oxygenation therapy; 170 of 357 (47.6%) were on high-flow nasal cannula oxygen (HFNC); 53 of 357 (14.8%) were put on noninvasive positive pressure ventilation (NIPPV) and 29 of 357 (8.1%) were on invasive mechanical ventilation. The rates of respiratory support were comparable between corticosteroid and non-corticosteroid (P=0.062).

A total of 152 ARDS patients were intravenously administered 80 mg/daily methylprednisolone from day 1 to day 5 after hospitalization, then reduced to 40 mg/daily from day 6 to day 10. On the other hand, the rest of 205 patients were given non-corticosteroid therapy. The corticosteroid therapy information of patients is detailed in Supplementary Table 2. In the end, 54 patients (35.5%) with corticosteroid therapy and 38 (18.5%) patients without corticosteroid therapy died within 30 days (P<0.01).

NLR is strongly associated with the high risk of 30-day in-hospital mortality

First and foremost, our multivariate Logistic regression revealed that NLR [OR 9.48, 95% CI (3.39-26.52), P<0.001] inherently had the strongest association with 30-day in-hospital mortality among parameters in the blood sample collected at the Emergency department (Supplementary Table 3). Consistent with observations by other researchers [15, 17, 19, 20], our study showed that NLR was an excellent index for patient's inflammation status, immunity status and risk for death.

We selected four candidate threshold values for the prediction of primary clinical outcome of ARDS patients. In our cohort, the median NLR of all patients was 11.68 (IQR 7.67-20.27) at admission. The cutoff value of AUROC (the area under of curve) was 14.35, showing both optimal sensitivity and specificity for the prediction of the risk of 30-day mortality (Supplementary Table 4) since it had the highest Youden index (0.67).

Baseline characteristics of ARDS patients with or without corticosteroid treatment in NLR≥14.35 group and NLR<14.35 group

We examined the effectiveness of corticosteroid treatment by using NLR 14.35 as a cutoff value (**Table 1**). Compared with NLR<14.35 group, the NLR≥14.35 group had higher APACHE II score, Lac, CRP, shock at admission and lower PaO_2/FiO_2 (all P<0.01).

In NLR≥14.35 group, 37 (41.1%) patients received corticosteroid treatment; In corticosteroid subgroup and non-corticosteroid subgroup, NLR was 15.5 (IQR 12.22-22.90) and 17.53 (IQR 10.03-25.31), respectively, and the difference was not statistically significant. Baseline characteristics of corticosteroid subgroup and non-corticosteroid subgroup in NLR≥14.35 group were similar except for alcohol-addiction, past smoking and diabetes. In unadjusted analyses, use of corticosteroid was associated with a decreased mortality (78.4% vs. 59.6%, P=0.063) without statistically significant difference.

In contrast, in the NLR<14.35 group, 100 (37.1%) patients received corticosteroid treatment. NLR [6.38 (IQR 5.68-8.51) vs. 7.23 (IQR 6.16-9.94), P=0.045] was higher in the corticosteroid subgroup. APACHE II score [10 (IQR, 7.5-12.5) vs. 12 (IQR, 8.0-17.0), P<0.001] was greater in the corticosteroid subgroup. The corticosteroid subgroup had higher incidence of shock at admission (10.1% vs. 41.4%, P<0.001, higher CRP, lower PaO_2/FiO_2 level, and lower $CD4^+$ and $CD8^+$ cell counts (**Table 1**). Our unadjusted analyses showed that use of corticosteroid was associated with significantly increased mortality (5.4% vs. 23.0%, P<0.001).

Primary outcome of corticosteroids therapy in ARDS patients stratified by NLR cutoff value ≥14.35

We further explored the possibility to use NLR as an indicator of the efficacy of corticosteroid therapy. We tested the association between corticosteroid therapy and 30-day mortality (primary outcome) in ARDS patients stratified by NLR cutoff value by using the multivariable Cox regression model.

More strikingly, when the study cohort was stratified into two sub-cohorts in terms of

Table 1. Baseline characteristics of ARDS patients with NLR≥14.35 and NLR<14.35 in the corticosteroid and non-corticosteroid groups

Characteristics	Total	No-methylprednisolone NLR≥14.35	Methylprednisolone NLR≥14.35	*P* value	No-methylpredniso-lone NLR<14.35	Methylprednisolone NLR<14.35	*P* value
Patients (no.)	357	37	52		168	100	
Demographics							
Age (year), median (IQR)	58.00 (45.00-69.00)	70.00 (57.00-79.50)	69.00 (61.00-75.00)	0.771	54.0 (39.0-65.0)	56.0 (41.3-67.0)	0.215
Sex, male-no. (%)	184 (51.5)	21 (56.8)	34 (65.4)	0.409	80 (47.6)	49 (49.0)	0.827
Methylprednisolone timing							
Median no. of days since symptom onset (IQR)	10.00 (7.00-13.75)		10.00 (7.25-13.75)			10.00 (7.00-13.75)	
Median no. of days since hospitalization (IQR)	0.50 (0.00-2.00)		0.00 (0.00-1.00)			1.00 (0.00-3.00)	
Coexisting conditions-no (%)							
Cardiovascular disease	101 (28.3)	18 (48.6)	26 (50.0)	0.900	37 (22.0)	20 (20.0)	0.695
Chronic renal disease	8 (2.2)	1 (2.7)	3 (5.8)	0.446	3 (1.8)	1 (1.0)	0.522
Chronic gastrointestinal disease	31 (8.7)	2 (5.4)	4 (7.7)	0.511	20 (11.9)	5 (5.0)	0.060
Stroke	13 (3.6)	2 (5.4)	2 (3.8)	0.554	3 (1.8)	6 (6.0)	0.083
Diabetes	54 (15.1)	12 (32.4)	10 (19.2)	0.155	21 (12.5)	11 (11.1)	0.714
Auto-immune disease	4 (1.1)	1 (2.7)	1 (1.9)	0.661	2 (1.2)	0 (0)	
Smoking history	13 (3.6)	2 (5.4)	0 (0.0)		10 (6.0)	1 (1.0)	0.058
Alcohol-addiction history	12 (3.4)	3 (8.1)	0 (0.0)		8 (4.8)	1 (1.0)	0.160
Severity of illness in ED							
APACHE II score, median (IQR)	12.00 (9.00-18.00)	20.00 (14.50-24.00)	20.50 (13.25-24.00)	1.000	10.00 (7.25-12.75)	12.00 (8.00-16.75)	0.002
Symptoms at admission							
PaO_2/FiO_2 (mmHg), median (IQR)	155.00 (135.00-175.00)	158.00 (145.00-176.50)	156.00 (145.50-180.00)	0.837	186.50 (175.00-202.25)	175.50 (158.50-198.50)	0.036
Temperature (°C), median (IQR)	36.70 (36.40-37.00)	36.80 (36.35-37.00)	36.80 (36.50-37.10)	0.541	36.70 (36.40-37.00)	36.80 (36.40-37.00)	0.523
Heart rate (bpm), median (IQR)	85.00 (78.00-95.00)	88.00 (80.00-107.00)	86.00 (79.00-102.00)	0.516	83.00 (78.00-92.75)	83.00 (77.75-92.00)	0.749
MAP (mmHg), median (IQR)	92.83 (85.67-100.25)	97.00 (85.92-103.33)	100.00 (87.50-113.42)	0.161	92.50 (86.00-98.59)	90.00 (83.67-98.50)	0.152
Physiologic parameters							
PH, median (IQR)	7.42 (7.37-7.46)	7.36 (7.25-7.44)	7.46 (7.42-7.48)	<0.001	7.41 (7.38-7.44)	7.40 (7.37-7.46)	0.698
Lac (mmol/L), median (IQR)	2.73 (1.70-3.83)	2.90 (2.00-5.10)	2.93 (1.80-4.98)	0.572	2.20 (1.63-2.98)	2.20 (1.50-3.40)	0.642
WBC ($\times 10^9$/L), median (IQR)	10.73 (9.36-12.58)	10.80 (7.06-13.34)	11.59 (9.00-13.65)	0.252	9.92 (8.82-11.33)	10.02 (8.88-11.51)	0.432
Neu ($\times 10^9$/L), median (IQR)	9.13 (7.82-12.09)	8.77 (7.41-11.40)	9.48 (8.20-13.29)	0.380	7.91 (7.24-9.35)	8.39 (7.53-9.52)	0.082
Lym ($\times 10^9$/L), median (IQR)	0.79 (0.46-1.04)	0.62 (0.45-0.91)	0.61 (0.48-0.85)	0.920	0.84 (0.73-1.04)	0.91 (0.63-1.15)	0.129
RBC ($\times 10^{12}$/L), median (IQR)	4.20 (3.72-4.60)	4.15 (3.59-4.61)	4.06 (3.83-4.35)	0.808	4.23 (3.72-4.63)	4.24 (3.71-4.74)	0.396
Hb (g/L), median (IQR)	129.00 (117.00-140.00)	128.00 (116.00-143.00)	129.00 (120.25-141.50)	0.542	126.00 (115.00-138.00)	130.00 (119.00-142.50)	0.094
CRP (mg/L), median (IQR)	29.30 (6.45-72.03)	88.25 (46.83-174.88)	62.70 (37.31-135.88)	0.290	11.10 (5.00-40.63)	35.35 (6.93-63.55)	0.003
Na+ (mmol/L), median (IQR)	139.00 (135.00-142.00)	136.00 (134.00-141.00)	136.00 (133.50-139.50)	0.467	140.00 (136.00-143.00)	139.00 (135.00-142.00)	0.103
K+ (mmol/L), median (IQR)	3.73 (3.38-4.19)	3.95 (3.21-4.55)	3.60 (3.05-4.00)	0.192	3.77 (3.40-4.10)	3.70 (3.30-4.20)	0.826
ALT (U/L), median (IQR)	27.00 (18.00-46.00)	27.00 (22.00-47.25)	28.00 (22.00-46.00)	0.894	24.00 (16.00-44.00)	27.50 (18.00-48.75)	0.297
AST (U/L), median (IQR)	30.00 (21.75-45.00)	37.00 (24.75-54.25)	38.00 (25.00-63.00)	0.969	27.00 (20.00-39.00)	30.00 (22.00-42.75)	0.061
Cr (umol/L), median (IQR)	59.00 (50.00-74.00)	68.50 (52.00-128.00)	61.00 (52.00-82.00)	0.155	58.00 (48.00-73.00)	60.50 (50.25-72.00)	0.342
$CD4^+$ (/uL), median (IQR)	363.00 (194.00-567.50)	139.00 (86.00-240.00)	144.00 (102.50-275.50)	0.696	493.50 (315.50-655.75)	383.50 (226.25-537.00)	0.001

$CD8^+$ (/uL), median (IQR)	209.00 (111.50-338.00)	77.00 (52.00-121.00)	68.50 (44.25-116.25)	0.538	303.50 (199.25-426.00)	215.00 (138.25-302.50)	<0.001
$CD4^+/CD8^+$, median (IQR)	1.69 (1.17-2.41)	1.79 (1.13-2.94)	2.25 (1.54-2.96)	0.190	1.59 (1.18-2.06)	1.57 (1.05-2.58)	0.986
Neu/Lym ratio, median (IQR)	11.68 (7.67-20.27)	17.53 (10.03-25.31)	15.50 (12.22-22.90)	0.644	6.38 (5.68-8.51)	7.23 (6.16-9.94)	0.045
Lung CT score, median (IQR)	4.00 (4.00-5.00)	5.0 (4.00-5.00)	5.00 (5.00-5.00)	0.476	4.00 (4.00-4.00)	5.00 (4.00-5.00)	<0.001
Shock at A dmission-no (%)	131 (36.7)	30 (81.1)	43 (82.7)	0.845	17 (10.1)	41 (41.0)	<0.001

Note: IQR: Interquartile range; APACHE II score: Acute Physiology and Chronic Health Evaluation; PO_2: partial pressure of oxygen; Lac: lactic acid; MAP: Mean arterial pressure;WBC: White blood cell; Neu: Neutrophil granulocyte; Lym: Lymphocyte; RBC: Red Blood Cell; Hb: Hemoglobin; CRP: C-reactive protein; Na+: serum natrium; K+: serum kalium; ALT: Alanine transaminase; AST: Aspartate transaminase; Cr: Creatinine; $CD4^+$: $CD4^+$ lymphocyte count; $CD8^+$: $CD8^+$ lymphocyte count. *P* values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or χ^2 test for categorical variable.

Table 2A. Multivariable COX regression models for 30-day mortality of ARDS patients with and without corticosteroid treatment stratified by NLR≥14.35 adjusted by age and APACHE II score

30-day mortality	HR	95% CI	*P* Value
Model 1 NLR≥14.35			
No corticosteroid treatment	reference		
Corticosteroid treatment	0.53	0.32-0.89	0.018
Age (by 10 years)	1.13	0.88-1.44	0.330
APACHE II score (by 10)	2.30	1.58-3.34	<0.001
Model 2 NLR<14.35			
No corticosteroid treatment	reference		
Corticosteroid treatment	2.64	1.7-5.95	0.019
Age (by 10 years)	1.85	1.37-2.51	<0.001
APACHE II score (by 10)	3.98	2.32-6.82	<0.001

Table 2B. Multivariable COX regression models for Ventilator-free days of ARDS patients with and without corticosteroid treatment stratified by NLR≥14.35 adjusted by age and APACHE II score

Ventilator-free days	HR	(95% CI)	*P* value
Model 1 NLR≥14.35			
No corticosteroid treatment	reference		
Corticosteroid treatment	0.67	0.34-1.43	0.023
Age (by 10 years)	1.19	0.80-1.58	0.299
APACHE II score (by 10)	2.29	1.46-3.76	<0.001
Model 2 NLR<14.35			
No corticosteroid treatment			
Corticosteroid treatment	2.98	2.75-5.29	0.039
Age (by 10 years)	2.45	1.90-3.74	<0.001
APACHE II score (by 10)	3.12	2.81-5.53	<0.001

NLR≥14.35 and NLR<14.35, the death risk of NLR≥14.35 patients with corticosteroid therapy was significantly lower than that of without corticosteroid therapy [HR 0.53; 95% CI (0.32-0.89); P=0.018; **Table 2A**; **Figure 2**], especially after they were adjusted in terms of APACHE II score [aHR 2.30; 95% CI (1.58-3.34); P<0.001] and age [aHR 1.13; 95% CI (0.88-1.44); P= 0.331].

Finally, we took NLR≥14.35 as an appropriate threshold values to identify patients who may well benefit from corticosteroid therapy.

Secondary outcomes and adverse effect in ARDS Patients stratified by NLR≥14.35

As to the secondary outcome (**Table 3**), use of corticosteroid in NLR≥14.35 group significantly increased ventilator-free days (7.0 vs. 13.0, P<0.001), In contrast, when the corticosteroid therapy was used in NLR<14.35 group, the ventilator-free days significantly decreased (23.0 vs. 21.5, P= 0.015).

Both crude analysis and post-adjustment analysis in terms of APACHE II score and age revealed that corticosteroid treatment was associated with an increased tendency of ventilator-free days in the NLR≥14.35 group but with a decreased tendency of ventilator-free days in the NLR<14.35 group (**Table 2B**). There was no evidence that weaning in the corticosteroid group was done more quickly than in the no-corticosteroid group. Therefore, it had no effect on the number ventilator-free days.

Furthermore, use of corticosteroid in NLR≥14.35 group significantly decreased the occurrence of shock (56.8% vs. 32.7%, P=0.024) and the incidence of secondary infection (73.0% vs. 46.2%, P<0.012).

The incidence of tracheal intubation (51.4% vs. 40.4%, P=0.378) and noninvasive positive pressure ventilation (NIPPV, 89.2% vs. 73.1%, P=0.062) were also lower in the corticosteroid group but the differences were not statistically significant. The incidence of hyperglycaemia went up marginally but without statistically significant difference (**Table 3**).

Discussion

Multiple clinical studies reported that glucocorticoids were used for treatment of ARDS patients, but the efficacy remain controversial [5-8, 21-23]. While timely administration of corticosteroids could mitigate fever, relieve lung inflammation/fibrosis, and obtain better oxygenation, more studies showed that glucocorticoids had no beneficial effects and potentially caused adverse reactions in patients with ARDS [12-14, 24-26].

These contradictory results might be ascribed to the discrepancies in study designs, which include patients selection, dosage, and duration/timing of glucocorticoid treatment. Presumably, the efficacy of glucocorticoids in ARDS patients depends on right selection of dosage, timing and patients. Firstly, high doses of gluco-

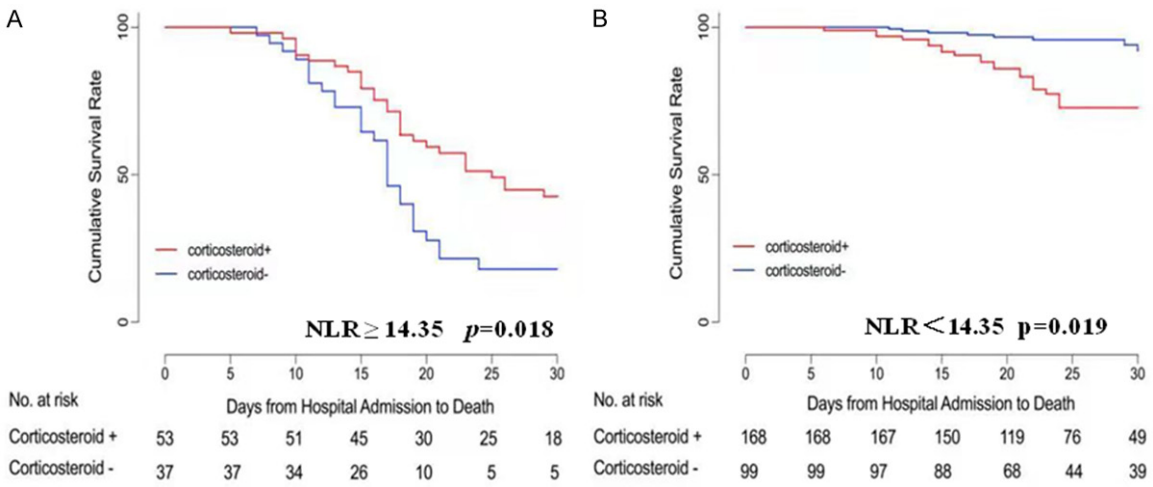

Figure 2. Kaplan-Meier survival curves among ARDS patients receiving corticosteroid (n=221) or not receiving corticosteroid therapy (n=136) stratified by NLR cutoff value. A: Thirty-day survival rate of ARDS patients with NLR≥14.35 [Red line indicates receiving corticosteroid therapy (n=53) and blue line indicates receiving non-corticosteroid therapy (n=37)]; B: Thirty-day survival rate of ARDS patients with NLR<14.35 [Red line indicates receiving corticosteroid therapy (n=168) and blue line indicates receiving non-corticosteroid therapy (n=99)]. *p* value was shown in **Table 3** using Multivariable COX regression models.

Table 3. Outcomes and adverse effects in ARDS patients with NLR≥14.35 and NLR<14.35 in the corticosteroid and non-corticosteroid groups

Outcomes	Total	No-methylprednisolone NLR≥14.35	Methylprednisolone NLR≥14.35	*P* value	No-methylprednisolone NLR<14.35	Methylprednisolone NLR<14.35	*P* value
Patients (no.)	357	37	52		168	100	
Primary Outcome							
30-day Death-no. (%)	92 (25.8)	29 (78.4)	31 (59.6)	0.063	9 (5.9)	23 (23.0)	<0.001
Secondary Outcome							
NIPPV-no. (%)	71 (19.9)	33 (89.2)	38 (73.1)	0.062	56 (33.3)	43 (43.0)	0.113
Tracheal intubation-no. (%)	40 (11.2)	19 (51.4)	21 (40.4)	0.378	6 (3.6)	21 (21.0)	<0.001
Ventilator-free days (IQR)	21.0 (14.0-30.0)	7.0 (3.0-17.0)	13.0 (7.0-31.0)	<0.01	23.0 0 (19.00-33.00)	21.50 (14.00-29.00)	0.015
Adverse Effects							
Shock-no (%)	38 (10.6)	21 (56.8)	17 (32.7)	0.024	10 (6.0)	12 (12.0)	0.081
Hyperglycaemia-no. (%)	55 (15.4)	22 (59.5)	33 (63.5)	0.615	62 (36.9)	44 (44.0)	0.251
Secondary infection during hospitalization-no. (%)	51 (14.3)	27 (73.0)	24 (46.2)	0.012	30 (17.9)	28 (28.0)	0.051
Pulmonary embolism-no. (%)	3 (0.8)	0 (0.0)	3 (5.8)		0 (0.0)	0 (0)	
Vein thrombosis-no. (%)	17 (4.8)	10 (27.0)	7 (13.5)	0.109	4 (2.4)	2 (2.0)	0.838

corticoids undoubtedly do more harm than good [14, 24]. Secondly, timing of initiating glucocorticoids therapy is pivotal [25, 26]. Thirdly, only a fraction of ARDS patients benefits from corticosteroid therapy. Recent researches have suggested that glucocorticoid treatment is better for severe patients (i.e., requiring respiratory support, having septic shock or multiple organ failure, APACHE II score >11) [4, 6-10, 24-26]. A question presents itself: How to identify ARDS patients who can benefit from glucocorticoid therapy?

Among the aforementioned confounding factors, the heterogeneity of the enrolled subjects is the one that renders the quantification or stratification difficulties. NLR is a powerful factor that indicates the prognosis of severe ARDS patients, no matter the community-acquired pneumonia caused by bacterial infection or viral infection [17, 19]. Study performed by Ki-Woong Nam et al. showed a close correlation between the NLR and severity of stroke-associated pneumonia [19]. The multivariate analysis by Zhao et al. demonstrated that the in-hospital

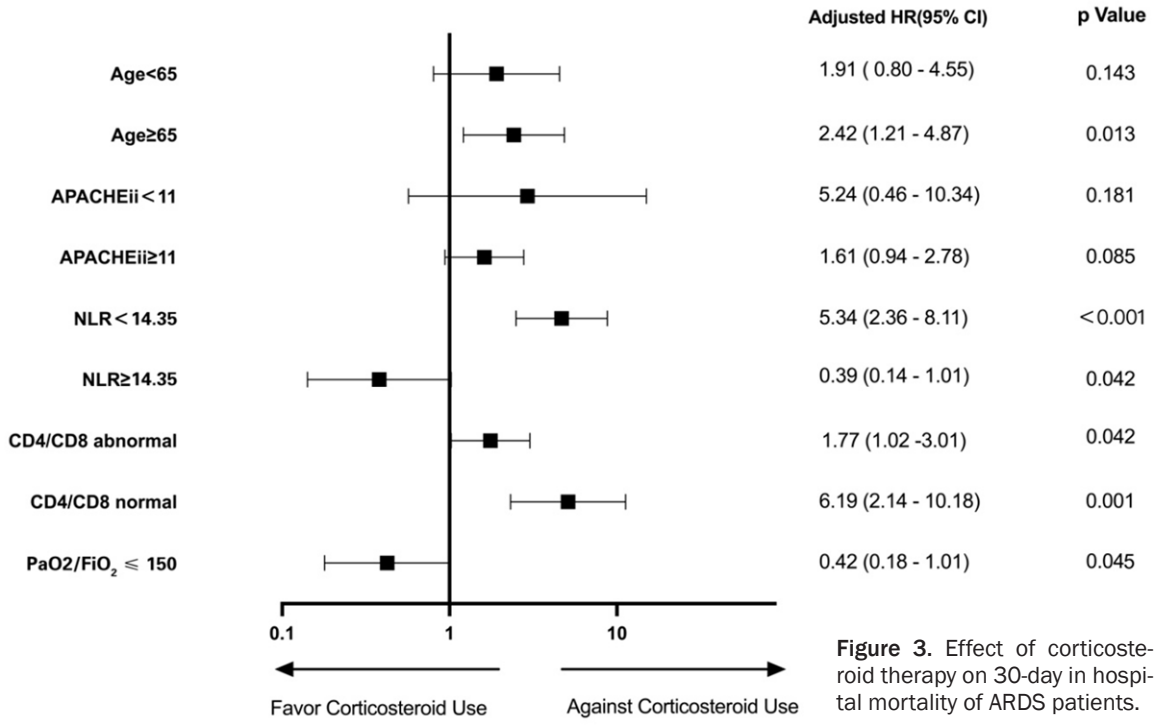

Figure 3. Effect of corticosteroid therapy on 30-day in hospital mortality of ARDS patients.

mortality of ARDS related to COVID-19 pneumonia rose by 8% for each unit increase in NLR [Odds ratio (OR) 1.08; 95% CI (1.01-1.14); P=0.0147] [17].

NLR is an independent risk factor of the in-hospital mortality in ARDS patients [27, 28]. Besides, NLR may help assess the efficacy of corticosteroid therapy in patients with ARDS. In our study, the patients were stratified in light of NLR threshold values of 14.35. We then used the multivariable Cox regression model to evaluate how well each NLR cutoff value worked in identifying patients who could benefit from corticosteroid therapy.

Patients with NLR≥14.35 were found to have a high in-hospital mortality. After costicosteriod treatment, we observed a decrease in hospital mortality. [HR: 0.53, 95% CI (0.32-0.89), P=0.018]. In contrast, the same treatment increases the risk of death of patients with NLR<14.35 by more than three times [HR: 2.64, 95% CI (1.70-5.95), P=0.019]. Such a difference remained after adjustment by APACHE II score and age. We acknowledge that early therapy with methylprednisolon in NLR≥14.35 group could reduce 30-days all cause mortality and increase the duration of ventilator-free days. This also explains the difference between our results and Liu Jiao's conclusions that the use of glucocorticoids in severe ARDS was associated with increased 28-day mortality as shown by log-rank test [12]. In Liu Jiao's study, the team failed to stratify patients into different groups in light of NRL.

Another concern is the serious adverse effects of corticosteroids in the treatment of ARDS. Among the patients with an NLR≥14.35, glucocorticoid therapy significantly reduced the incidence of shock (56.8% vs. 32.7%, P=0.024) and secondary infection (73.0% vs. 46.2%, P=0.012).

On the basis of our findings, we propose that the NLR is efficient in identification of the ARDS patients who would benefit most from corticosteroid therapy. After adjustment by age and APACHE II score, NLR≥14.35 can serve as a strong predictor for the patients who can benefit from corticosteroid therapy. For patients whose NLR<14.35, corticosteroid treatment was found to achieve no conspicuous outcome improvement but associated with significant adverse effects.

Most recently, Li and his colleagues revealed that the clinical benefits of corticosteroid treatment were intimately associated with the NLR

in patients with COVID-19 pneumonia at admission [29]. They believe that, in subjects whose NLR was higher than 6.12 at admission, corticosteroid treatment was significantly correlated with a reduced risk of 60-day all-cause mortality of COVID-19. Among 12862 confirmed COVID-19 patients in their enrollment, 3,254 cases received corticosteroid therapy, of which 97.1% received methylprednisolone. Our study is different from theirs in that the clinical cases in our cohort included not only virus-associated pneumonia, but also ARDS caused by trauma, pancreatitis, aspiration pneumonia, etc.

So far, although there are some substantive clinical evidence to support the use of glucocorticoids, the pathophysiological mechanism still remains unclear [8-10, 24-26, 29-35]. Jesús Villar and his colleagues did a multicentre, randomized controlled trial in 17 intensive care units across Spain. They pointed out that early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with moderate-to-severe ARDS [8]. In RECOVERY clinical practice, glucocorticoids, in many ways, worked on in 60% of critically-ill patients with COVID-19 (e.g., inotropy, vasopressor, irreversible lung injury) [9]. NLR may serve as a prognostic biomarker by indicating neutrophils rising and lymphocytes apoptosis in response of the inflammatory storm. We speculate that the appropriate use of glucocorticoids may be beneficial given that (1) corticosteroids reduce the damage of target organs by inhibiting the storm of pro-inflammatory factors in the initial stage. (2) Glucocorticoid treatment improves alveolar-capillary membrane permeability and alleviated inflammatory-immune response in lung interstitial [32-35]. For patients with less severe inflammatory response at admission, corticosteroid therapy-associated side effects may offset any potential benefits.

In general, our study clearly showed that NLR is a good indicator in identifying those who benefit from corticosteroid treatment. With adjustment by age and APACHE II score using Cox regression model, we stratified patients by NLR cutoff value 14.35. Upon treatment with corticosteroids, ARDS patients with NLR≥14.35 or shock at admission had a decreased risk of 30-days in-hospital mortality. In contrast, ARDS patients who have age ≥65 years or NLR<14.35 (**Figure 3**) showed an increased risk of 30-days in-hospital mortality. Moreover, Cox regression model suggested that the ventilator-free days was remarkably increased in corticosteroid patients with NLR≥14.35. It is worth mentioning that use of corticosteroid in NLR≥14.35 group does not increase secondary nosocomial infections.

In summary, it is reasonable for us to believe that NLR≥14.35 can be used to identify ARDS patients who may benefit most from methylprednisolone therapy. We believe that our finding has great clinical value. In terms of the treatment of ARDS at the Emergency department or ICU, physicians are required to accurately select patients who would be most suitable to receive the glucocorticoids treatment in time. As the NLR is readily obtainable from blood cell counts and can be repeatedly measured and dynamically observed, it may help physicians to identify ARDS patients who are fit for corticosteroid therapy at admission.

Limitations

The study has several limitations. First, the study was a retrospective design in one single setting. Second, inflammatory storm and immunity function has not been deeply investigated in ARDS patients who received corticosteroid therapy or not. Third, we did not go further to investigate how corticosteroids impact diabetes or glycemic fluctuation in ARDS patients. Fourth, since the study was of observational nature, it was difficult to definitively identify the causal relationship between corticosteroid administration and the mortality in ARDS patients who had a high NLR at admission. Fifth, whether the NLR cutoff value 14.35 is applicable to other ARDS patients associated with different etiological classifications or inflammatory morbidities needs further investigation.

Conclusions

NLR was found to be a powerful predictor of the prognosis for ARDS patients. NLR >14.35 could serve as a strong indicator for the ARDS patients who can benefit from corticosteroid therapy. Since the NLR can be rapidly and easily obtained from differential blood cell counts, our research is a pivotal hint in identifying patients to initiate corticosteroid therapy promptly.

The development and implementation of prospective studies and multiple-center randomized controlled clinical trials is needed.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Baseline characteristics and physiological parameters of ARDS patients in the corticosteroid and non-corticosteroid groups at admission

Characteristics	Total	No-methylprednisolone	Methylprednisolone	*P* value
Patients (no.)	357	205	152	
Demographics				
Age (yr), median (IQR)	58.0 (45.0-69.0)	64.0 (49.0-71.0)	68.5 (56.0-77.0)	0.016
Sex, male-no. (%)	184 (51.5)	101 (49.3)	83 (54.6)	0.318
Coexisting conditions-no. (%)				
Cardiovascular disease	101 (28.3)	55 (26.8)	46 (30.3)	0.476
Chronic renal disease	8 (2.2)	4 (2.0)	4 (2.6)	0.727
Chronic gastrointestinal disease	31 (8.7)	22 (10.7)	9 (5.9)	0.110
Stroke	13 (3.6)	5 (2.4)	8 (5.3)	0.159
Diabetes	54 (15.1)	33 (16.1)	21 (13.8)	0.552
Auto-immune disease	4 (1.1)	3 (1.5)	1 (0.7)	0.639
Smoking history	13 (3.6)	12 (5.9)	1 (0.7)	0.009
Alcohol-addiction history	12 (3.4)	11 (5.4)	1 (0.7)	0.016
Severity of illness at admission				
APACHE II score, median (IQR)	12.00 (9.00-18.00)	14.00 (12.00-20.00)	18.50 (12.00-23.00)	<0.001
Symptoms at admission				
PaO_2/FiO_2 (mmHg), median (IQR)	155.00 (135.00-175.00)	155.00 (138.00-171.00)	143.00 (129.50-161.50)	0.020
Temperature (°C), median (IQR)	36.70 (36.40-37.00)	36.80 (36.50-37.10)	36.70 (36.50-37.28)	0.311
Heart rate (bpm), median (IQR)	85.00 (78.00-95.00)	86.00 (80.00-104.00)	88.00 (81.00-98.00)	0.910
MAP (mmHg), median (IQR)	92.83 (85.67-100.25)	93.33 (86.67-101.33)	95.33 (87.00-106.50)	0.978
Physiologic parameters				
PH, median (IQR)	7.42 (7.37-7.46)	7.40 (7.35-7.44)	7.43 (7.38-7.47)	0.001
Lac (mmol/L), median (IQR)	2.93 (1.90-4.03)	2.20 (1.68-3.23)	3.97 (2.90-4.87)	0.040
WBC ($\times10^9$/L), median (IQR)	10.73 (9.36-12.58)	10.63 (9.16-12.73)	11.50 (9.65-13.16)	0.327
Neu ($\times10^9$/L), median (IQR)	9.13 (7.82-12.09)	8.89 (7.59-11.07)	9.62 (7.99-12.89)	0.367
Lym ($\times10^9$/L), median (IQR)	0.79 (0.46-1.04)	0.82 (0.49-1.21)	0.65 (0.38-0.97)	0.089
RBC ($\times10^{12}$/L), median (IQR)	4.20 (3.72-4.60)	4.12 (3.69-4.71)	4.00 (3.68-4.47)	0.691
Hb (g/L), median (IQR)	129.00 (117.00-140.00)	126.00 (116.00-143.00)	125.50 (118.50-138.75)	0.075
CRP (mg/L), median (IQR)	29.30 (6.45-72.03)	48.50 (8.30-91.50)	61.05 (41.40-131.85)	0.001
Na+ (mmol/L), median (IQR)	136.00 (133.00-139.00)	139.00 (135.00-142.00)	136.00 (133.00-140.00)	0.016
K+ (mmol/L), median (IQR)	3.73 (3.38-4.19)	3.60 (3.30-4.20)	3.60 (3.00-4.00)	0.351
ALT (U/L), median (IQR)	27.00 (18.00-46.00)	27.00 (19.00-49.00)	25.00 (18.75-46.00)	0.215
AST (U/L), median (IQR)	30.00 (21.75-45.00)	33.00 (23.00-47.00)	39.00 (25.00-54.00)	0.027
Cr (umol/L), median (IQR)	59.00 (50.00-74.00)	61.00 (49.00-77.00)	60.00 (50.75-80.25)	0.474
$CD4^+$ (/uL), median (IQR)	363.00 (194.00-567.50)	312.00 (168.00-549.00)	230.00 (112.25-413.25)	<0.001
$CD8^+$ (/uL), median (IQR)	209.00 (111.50-338.00)	183.00 (85.00-326.00)	127.50 (59.00-214.50)	<0.001
$CD4^+/CD8^+$, median (IQR)	1.69 (1.16-2.41)	1.63 (1.16-2.14)	1.79 (1.13-2.75)	0.142
Neu/Lym ratio, median (IQR)	11.68 (7.67-20.27)	8.94 (6.78-16.15)	14.82 (7.52-25.25)	<0.001
Lung CT score, median (IQR)	4.0 (4.00-5.00)	4.00 (4.00-5.00)	5.0 (5.00-5.00)	<0.001
Shock on Admission-no. (%)	131 (36.69)	47 (22.93)	84 (55.26)	<0.001

Note: IQR: Interquartile range; APACHE II score: Acute Physiology and Chronic Health Evaluation; PO2: partial pressure of oxygen; Lac: lactic acid; MAP: Mean arterial pressure; WBC: White blood cells; Neu: Neutrophil granulocytes; Lym: Lymphocytes; RBC: Red Blood Cell; Hb: Hemoglobin; CRP: C-reactive protein; Na+: serum natrium; K+: serum kalium; ALT: Alanine transaminase; AST: Aspartate transaminase; Cr: Creatinine; $CD4^+$: $CD4^+$ lymphocyte count; $CD8^+$: $CD8^+$ lymphocyte count. *P* values were calculated by Mann-Whitney U test for non-normally distributed continuous variables and Fisher's exact test or χ^2 test for categorical variables.

Supplementary Table 2. Corticosteroid use in ARDS patients stratified by different NLR cutoff value

Corticosteroid Use	Total (n=357)	NLR≥11.68 (n=178)	NLR<11.68 (n=179)	NLR≥14.35 (n=107)	NLR<4.35 (n=250)	NLR≥20.27 (n=89)	NLR<20.27 (n=268)
Methylprednisolone; n (n%)	152 (42.6)	97 (54.5)	55 (30.7)	64 (59.8)	88 (35.2)	52 (58.4)	100 (37.3)
Duration of corticosteroids use; median (IQR); d	6.00 (3.25-8.00)	6.00 (3.00-8.00)	6.00 (4.00-7.00)	6.00 (3.00-8.75)	6.00 (4.00-7.00)	6.00 (3.25-9.00)	6.00 (3.25-7.00)
Duration of corticosteroids use for survivor; median (IQR); d	6.50 (4.00-8.00)	7.00 (4.00-9.00)	6.00 (4.00-7.00)	8.00 (5.00-14.00)	6.00 (4.00-7.00)	8.00 (5.50-12.00)	6.00 (4.00-7.00)
Duration of corticosteroids use for non-survivor; median (IQR); d	6.00 (3.25-8.00)	6.00 (3.00-8.00)	6.00 (4.00-7.00)	6.00 (3.00-8.75)	6.00 (4.00-7.00)	6.00 (3.25-9.00)	6.00 (3.25-7.00)
Accumulated dose; median (IQR); mg	240.00 (160.00-400.00)	280.00 (120.00-450.00)	220.00 (160.00-300.00)	320.00 (125.00-480.00)	220.00 (160.00-315.00)	360.00 (160.00-480.00)	220.00 (160.00-320.00)
Daily dose; median (IQR); mg	40.00 (40.00-60.00)	40.00 (40.00-65.33)	40.00 (31.11-40.00)	60.00 (40.00-74.05)	40.00 (31.43-40.00)	60.00 (40.00-78.33)	40.00 (31.90-78.10)
Duration between onset of illness and corticosteroid initiation; median (IQR); d	10.00 (7.00-13.75)	10.00 (7.00-14.00)	10.00 (7.00-12.00)	10.00 (7.25-14.00)	10.00 (7.00-12.00)	10.00 (7.25-13.75)	10.00 (7.00-13.75)
Duration between hospital admission and corticosteroid initiation; median (IQR); d	0.50 (0.00-2.00)	0.00 (0.00-2.00)	1.00 (0.00-4.00)	0.00 (0.00-1.00)	1.00 (0.00-3.750	0.00 (0.00-1.000	1.00 (0.00-3.00)

Note: IQR: Interquartile range. The median NLR of all ARDS patients was 11.68 (IQR 7.67-20.27). The cutoff value of AUROC (the area under of curve) was 14.35 for predicting of the risk of 30-day mortality.

Supplementary Table 3. Parameters in the blood sample associated with 30-day in-hospital mortality in ARDS patients

Parameters	Multivariate Logistic Regression		
	OR	95% CI	*P* value
Neutrophil count >9.5; 10^9/L	2.79	0.96-8.16	0.059
Lymphocyte count <0.8; 10^9/L	1.25	0.56-2.81	0.588
NLR increase[a]	9.48	3.39-26.52	<0.001
Platelet count <100.0; 10^9/L	1.61	0.58-4.49	0.363
$CD4^+$ Lymphocyte count <500/mL	7.62	1.90-30.56	0.004
$CD4^+/CD8^+$ ratio abnormal[b]	0.82	0.39-1.75	0.612
CPR >10 mg/L	0.77	0.24-2.48	0.655

Note: OR: odd ratio; CI: confidence interval. a: Neutrophil-to-lymphocyte ratio (NLR) increase was defined as >14.35. The cutoff value was determined according to the median value of NLR of our cohort. b: $CD4^+/CD8^+$ ratio abnormal was defined as $CD4^+/CD8^+$ ratio >2.0 or $CD4^+/CD8^+$ ratio <1.4.

Supplementary Table 4. NLR Cutoff Values for Predicting Mortality in ARDS Patients

Parameters	Cutoff =7.67	Cutoff =11.68	Cutoff =14.35	Cutoff =20.27
Sensitivity	0.98	0.94	0.80	0.66
Specificity	0.35	0.66	0.87	0.89
PPV	0.34	0.48	0.67	0.66
NPV	0.98	0.97	0.93	0.88
Youden Index	0.33	0.60	0.67	0.55

Note: NLR: neutrophil-to-lymphocyte ratio; PPV: positive predict value; NPV: negative predict value. The median NLR of all patients was 11.68 (IQR 7.67-20.27). The cutoff value of AUROC (the area under of curve) was 14.35 for predicting of the risk of 30-day mortality. All patients with ARDS (n=357).