Original Article

Neutrophil-to-lymphocyte ratio as a prognostic marker in acute respiratory distress syndrome patients: a retrospective study

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Background: Acute respiratory distress syndrome (ARDS) is the leading cause of high mortality in intensive care units (ICUs) worldwide. An effective marker for prognosis in ARDS is particularly important given the absence of effective treatment strategies aside from small tidal volume ventilation. Previous studies identified an association between the neutrophil-to-lymphocyte ratio (NLR) and prognosis in critical patients. In this study, we explored the prognostic and predictive value of the NLR in ARDS patients.

Methods: We retrospectively included 275 ARDS patients treated at a single institute from 2008 to 2015. After excluding patients with chronic lung disease, acute myocardial infarction and missing data, 247 patients were ultimately included in the analysis. Clinical characteristics and experimental test data, including the NLR, were collected from medical records at 24 hours after the ARDS diagnosis. Independent prognostic factors were determined by multivariate Cox regression analysis. Subgroup stratification was performed according to different factors, and the continuous factors were divided according to the median values.

Results: The NLR in survivors was significantly lower than that in non-survivors (P<0.001). We took the median NLR value as the cut-off point and further divided all patients into a high NLR group (NLR >14) and a low NLR group (NLR ≤14). We found that an NLR >14 was associated with a shorter overall survival (OS) (P=0.005). In the multivariate Cox regression model, we further identified an NLR >14 as an independent prognostic factor for OS [hazard ratio (HR) 1.532, (95% CI, 1.095–2.143), P=0.013]. Subgroup analysis showed that the prognostic value of the NLR was higher in hypertensive patients (P=0.009) and in patients with low red blood cell specific volume (P=0.013), high sodium (P=0.002) and high creatinine levels (P=0.017).

Conclusions: The NLR is potentially a predictive prognostic biomarker in ARDS patients.

Keywords: Acute respiratory distress syndrome (ARDS); neutrophil-to-lymphocyte ratio (NLR); prognostic marker; retrospective study; biomarker

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Introduction

Acute respiratory distress syndrome (ARDS) is the leading cause of high mortality in intensive care units (ICUs) worldwide, affecting millions of people annually (1). Knowledge on epidemiological surveys of ARDS in China has been limited. Epidemiological surveys in Beijing, Shanghai, Chongqing and other regional cities found that the mortality from ARDS among ICU patients in China is variable (22–100%) (2). Although recent advances in intensive care models have been processed (3-4), mortality remains high (1). Therefore, ARDS remains a challenge to critical care medicine.

A prognostic marker for ARDS is particularly important given the absence of effective treatment strategies aside from small tidal volume ventilation. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores and the Simplified Acute Physiology Score (SAPS) have been used to assess the prognosis for critically ill patients (5). However, these scores are not specific to ARDS. Zhang *et al*. (6) established a model to predict risk in ARDS patients. However, the application of this model requires many variables and complex formulas, and obtaining the required information is not convenient. Villar *et al*. (7) created a bedside score for ARDS called APPC, used only in patients with moderate/severe ARDS with protective mechanism ventilation. Moreover, several studies have been conducted to analyze biomarkers in ARDS patients (8-11). However, most current studies of biomarkers require special biological samples of patients, specific group of patients and integration with other clinical data. Thus, the complexity and heterogeneity of the disease makes this assessment very challenging.

Inflammation is known to play a significant role in the development of ARDS and has an impact on its prognosis and symptoms (12). The balance of cytokines and chemokines modulates ARDS pathogenesis. The neutrophil-to-lymphocyte ratio (NLR) is an indicator of systemic inflammation (13). High levels of neutrophil infiltration may be associated with cytotoxicity, vascular stasis and decreased inflammation in response to changes in the balance of pro-inflammatory and anti-inflammatory cytokines (12,14).

Several studies have reported that the NRL could be used in a variety of clinical conditions (15-17). Studies have shown a correlation between the NLR and the severity of the clinical course in ICU patients, and they have suggested that the NLR should be considered a prognostic indicator. Another study reported that the NLR is related to 28-day mortality in severe sepsis or septic shock patients (18). In addition, the NLR has merit due to its simplicity, low cost, and availability compared to other previously proposed biomarkers, making it practical and useful for prognostic indications.

Currently, no simple, routine, and reliable risk factors have been consistently identified to determine the prognosis of ARDS patients. To date, no studies have been reported regarding the relationship between the NLR and outcomes in ARDS patients. We conducted this retrospective study to investigate the potential prognostic value of the NLR in patients with ARDS.

Methods

Patient population

This study was approved by the Clinical Research Ethics Committee of Zhongshan Hospital, Fudan University (Shanghai, China) (B2016-039R). Between January 24, 2008, and July 24, 2015, 3,786 patients were diagnosed with respiratory failure in Zhongshan Hospital, Fudan University. Three medical doctors in the respiratory department at Zhongshan Hospital reviewed the medical records of all patients. A total of 275 patients who met the inclusion criteria were retrospectively enrolled in the study. Ultimately, 28 patients were excluded according to the exclusion criteria, and 247 patients (age 17–93 years) with ARDS were analyzed.

The inclusion criteria are shown in *Figure 1*. American-European Consensus Conference (AECC) criteria (19) were used in this study, and positive end expiratory pressure (PEEP) was not included in the inclusion criteria. The patient exclusion criteria are listed in *Figure 1*. Infiltrates on chest radiographs were evaluated by two independent medical doctors in the imaging department in Zhongshan Hospital.

Data collection and outcome measurements

Baseline data, including age, gender, APACHE II score, risk factors for ARDS, past medical history, ventilation status and experimental examination, were retrospectively collected from medical records and electronic databases. Data on survival were also retrospectively obtained from the medical records. The risk factors studied included pneumonia, non-pulmonary sepsis, aspiration of gastric

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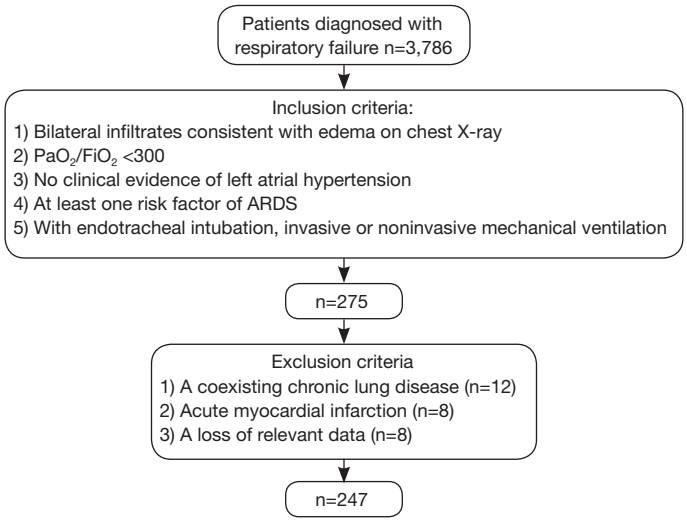

Figure 1 Patient selection. ARDS, acute respiratory distress syndrome.

contents and trauma. The past medical history obtained included surgical history, smoking history, and medical history, including malignant tumors, liver cirrhosis, hypertension and diabetes. The experimental examination included the following: PaO2, hematocrit (HCT), white blood cell (WBC) counts, neutrophil counts, lymphocyte counts, platelets counts, and levels of sodium (Na), potassium (K), blood urea nitrogen (BUN), creatinine (Cr) and albumin. These experimental examinations were recorded at 24 hours after the ARDS diagnosis. The NLR was determined from the blood cytology by dividing the neutrophil count by the lymphocyte count. Patients were categorized into two groups according to the median result of the initial NLR.

Statistical analysis

Data were analyzed using SPSS software version 22.0 (SPSS, Chicago, IL, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). The difference between the two groups was tested using a two-tailed independent Student's *t*-tests for normally distributed variables and the Wilcoxon rank sum test for non-normally distributed data. The associations between the NLR and patient baseline characteristics for non-parametrically distributed variables were assessed using the χ^2 test, Fisher's exact method, or the Cochran-Mantel-Haenszel χ^2 test. Univariate and multivariate analyses were completed with Cox proportional hazards regression tests. The cut-off point for the definition of the NLR was based on the median data. The primary outcome and overall survival (OS) were defined as the time from the diagnosis of ARDS to death from any cause. Kaplan-Meier survival analysis was performed to compare the difference in the survival between higher and lower median NLR values. $P<0.05$ was considered statistically significant.

Results

Baseline patient characteristics

The baseline characteristics of the patients are shown in *Table 1*. The patients in our study consisted of 162 males and 85 females with a median age of 62 years (IQR 48–73 years), and the overall mortality rate was 59.1%. There was a history of smoking in 18.2% of the patients. Invasive mechanical ventilation was available for 133 patients. The most common underlying diagnosis was pulmonary infection (45.3%). Aspiration (20.2%) and non-pulmonary sepsis (20.2%) were the next most common diagnoses. The median value of the initial NLR was 13.8 (IQR, 7.4–24.5) for the overall group. The baseline median APACHE II score was 16 (IQR, 11–21). The baseline characteristics of the surviving and non-surviving patients in the hospital are also shown in *Table 1*. There was a significant difference between the groups in terms of age ($P=0.010$), invasive mechanical ventilation ($P<0.001$), PaO_2/FiO_2 ($P=0.002$), APACHE II score ($P=0.021$), smoking

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Table 1 Comparison of baseline characteristics of patients according to the survival status

Factors	Total (n=247)	Survivors (n=101)	Non-survivors (n=146)	P value
Age (years)	62 [48–73]	60 [42–69]	64 [53–76]	0.010
Gender				0.837
Male	162	67	95	
Female	85	34	51	
Invasive mechanical ventilation				<0.001
No	114	65	49	
Yes	133	36	97	
PaO_2/FIO_2	126 [95–156]	136 [105–164]	116 [85–148]	0.002
APACHE II score	16 [11–21]	11 [8–15]	19 [16–23]	0.021
Surgical history				0.081
No	130	48	82	
Yes	117	53	64	
Smoking				0.011
No	202	75	127	
Yes	45	26	19	
Hypertension				0.929
No	150	61	89	
Yes	97	40	57	
Malignant tumor				0.083
No	211	91	120	
Yes	36	10	26	
Liver cirrhosis				0.044
No	240	101	139	
Yes	7	0	7	
Pneumonia				0.405
No	135	52	83	
Yes	112	49	63	
Non-pulmonary sepsis				0.055
No	197	87	110	
Yes	50	14	36	
Aspiration				0.806
No	197	79	118	
Yes	50	22	28	

Table 1 (*continued*)

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Table 1 (*continued*)

Factors	Total (n=247)	Survivors (n=101)	Non-survivors (n=146)	P value
Trauma				0.531
No	212	85	127	
Yes	35	16	19	
HCT (%)	31.8 (19.4–37.6)	33.9 (25.8–37.5)	31.0 (18.8–37.6)	0.084
WBC (10^9/L)	10.6 (7.0–14.2)	10.9 (6.5–19.1)	15.1 (8.1–34.1)	0.667
Neutrophils (10^9/L)	9.1 (5.9–12.9)	8.7 (6.1–12.0)	9.7 (5.8–13.7)	0.090
Lymphocyte (10^9/L)	0.67 (0.36–1.03)	0.78 (0.49–1.16)	0.58 (0.31–0.96)	0.894
NLR	13.8 (7.4–24.5)	11.0 (7.0–20.3)	15.1 (7.8–30.1)	<0.001
Platelets (10^9/L)	152 [93–250]	187 (133.5–272)	156 (104.5–204.5)	0.016
Na (mmol/L)	141 [138–146]	140 [137–144]	141 [138–146]	0.004
K (mmol/L)	4.1 (3.7–4.7)	4.0 (3.6–4.4)	4.2 (3.8–5.0)	0.004
BUN (mmol/L)	10 (6.4–20)	9 [6–13]	8 [5–11]	<0.001
Cr (μmol/L)	75 [56–143]	66 (51.5–91.5)	91 [61–245]	<0.001
Album (g/L)	28 [24–31]	28 [26–31]	27 (21.8–31)	0.020

Data are shown as median with interquartile range or n; all experimental data were collected within 24 h after ARDS was diagnosed. HCT, hematocrit; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; Na, sodium; K, potassium; BUN, blood urea nitrogen; Cr, creatinine; ARDS, acute respiratory distress syndrome.

history (P=0.011) and liver cirrhosis (P=0.044). There were also significant differences in laboratory values, including the NLR (P<0.001), platelet count (P=0.016), and levels of Na (P=0.004), K (P=0.004), BUN (P<0.001), Cr (P<0.001) and albumin (P=0.020).

Independent risk factors of mortality in ARDS

In the multivariate Cox proportional hazard regression survival model, the factors with a P value less than 0.20 in *Table 1* were added into the final model. In the multivariate proportional hazard Cox regression analysis, survival, age, liver cirrhosis, NLR, Cr and PaO_2/FIO_2 were statistically significant (*Table 2*). We concluded that the risk factors were age, liver cirrhosis and Cr. Meanwhile, only the PaO_2/FIO_2 was a protective factor. We also found that the NLR was an independent risk factor for each 1% increase in the ratio [hazard ratio (HR) 1.011; 95% CI, 1.004–1.017; P=0.03].

Characteristics of patients with an NLR >14

As the NLR was an independent risk factor for mortality in ARDS patients, we used the median value as the cut-off value to divide the patients into two groups (NLR >14 and ≤14). The influence of the NLR on mortality in ARDS patients was analyzed using the hospital mortality, 28-, 90-day mortality and invasive mechanical ventilation as outcomes (*Table 3*). The analysis showed that an NLR >14 was significantly associated with the outcomes for each variable. The Kaplan-Meier curve also demonstrated that an NLR >14 influenced the survival time of ARDS patients (*Figure 2*).

Stratified analysis of the NLR

Figure 3 shows the comparison of clinical parameters for patients with an NLR >14. There was a significant difference between patients with a high NLR (NLR >14) and patients with a low NLR (NLR ≤14) in several subgroups. These subgroups were divided according to their median values. Multivariate Cox analysis identified an NLR >14 as an independent predictive factor for ARDS mortality (HR 1.532, 95% CI, 1.095–2.143, P=0.013) (*Table 2*). Upon stratified analysis, this trend was still observed in

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Table 2 Multivariate cox regression analysis for the risk factors

Variables	HR	95% CI		P value
		Upper	Lower	
Continuously variable of NLR				
Age	1.011	1.001	1.022	0.031
Liver cirrhosis	4.181	1.873	9.333	<0.001
NLR	1.011	1.004	1.017	0.001
Cr	1.001	1	1.002	0.01
PaO_2/FIO_2	0.993	0.989	0.996	<0.001
Categorical variable of NLR				
Age	1.012	1.001	1.022	0.028
Liver cirrhosis	5.317	2.411	11.725	<0.001
NLR >14	1.532	1.095	2.143	0.013
Cr	1.001	1	1.002	0.005
PaO_2/FIO_2	0.993	0.989	0.997	<0.001

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; Cr, creatinine.

Table 3 Comparison between NLR >14 and ≤14

Comparison content	Overall, n=247	NLR >14, n=124	NLR ≤14, n=123	P value
In-hospital mortality	146 (59.1)	83 (56.8)	63 (43.2)	0.012
28-day mortality	124 (50.2)	73 (58.9)	51 (41.1)	0.006
90-day mortality	143 (57.9)	83 (58.0)	60 (42.0)	0.004
Invasive mechanical ventilation	133 (53.8)	78 (58.6)	55 (41.4)	0.004

Data are shown as n (%). NLR, neutrophil-to-lymphocyte ratio.

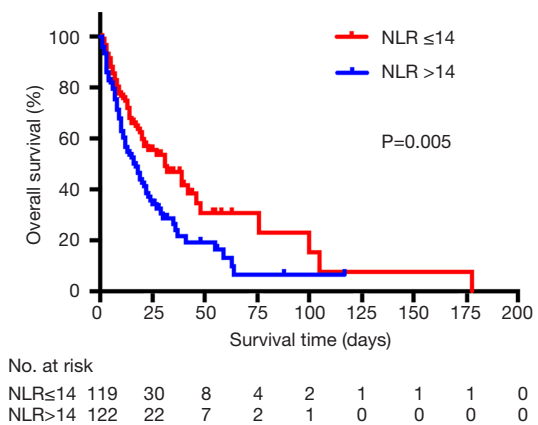

Figure 2 Kaplan-Meier analyses of overall survival according to a neutrophil-to-lymphocyte ratio (NLR) >14 in patients with acute respiratory distress syndrome (ARDS).

certain subgroups, such as the low PaO_2/FIO_2 (PaO_2/FIO_2 <126) (P=0.008), hypertension (P=0.007), malignant tumor (P=0.003), non-pulmonary sepsis (P=0.005), trauma (P=0.031), low HCT (HCT <31.8%) (P=0.006), high sodium (Na ≥141 mmol/L) (P=0.022) and high creatinine (Cr ≥75 μmol/L) (P=0.016) groups (*Figure 3*). Kaplan-Meier analyses also showed the predictive value of an NLR >14 in patients with hypertension (P=0.009), low HCT (P=0.013), high sodium (P=0.002) and high creatinine (P=0.017) (*Figure 4*).

Discussion

Our retrospective study revealed that an NLR measured at 24 hours after ARDS diagnosis was an independent risk factor of mortality in patients with ARDS. The NLR

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Subgroup	NLR >14 (*vs.* NLR ≤14) Hazard ratio (95% CI)	P value
PaO_2/FiO_2*		
≥126	1.283 (0.761-2.163)	0.350
<126	2.065 (1.213-3.517)	0.008
Hypertension		
Yes	2.305 (1.263-4.208)	0.007
No	1.073 (0.646-1.782)	0.785
Malignant tumor		
Yes	8.082 (2.081-31.390)	0.003
No	1.389 (0.973-2.060)	0.102
Non-pulmonary sepsis		
Yes	3.622 (1.490-8.807)	0.005
No	1.345 (0.904-2.001)	0.144
Trauma		
Yes	6.453 (1.188-35.041)	0.031
No	1.405 (0.961-2.053)	0.079
HCT (%)*		
≥31.8	1.115 (0.600-2.672)	0.732
<31.8	2.048 (1.224-3.426)	0.006
Na (mmol/L)*		
≥141	1.707 (1.080-2.700)	0.022
<141	1.592 (0.851-2.979)	0.146
Cr (μmol/L)*		
≥75	1.771 (1.113-2.818)	0.016
<75	1.279 (0.688-2.375)	0.436

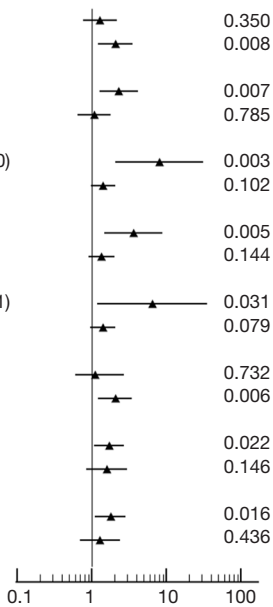

Figure 3 Hazard ratios for overall survival probabilities based on an NLR >14 in patient subgroups stratified by PaO_2/FiO_2, hypertension, malignant tumor, non-pulmonary sepsis, trauma, hematocrit (HCT), and sodium (Na) and creatinine (Cr) levels; P values were calculated by univariate Cox regression analysis, and P<0.05 was regarded as statistically significant. *, divided at the median; CI, confidence interval.

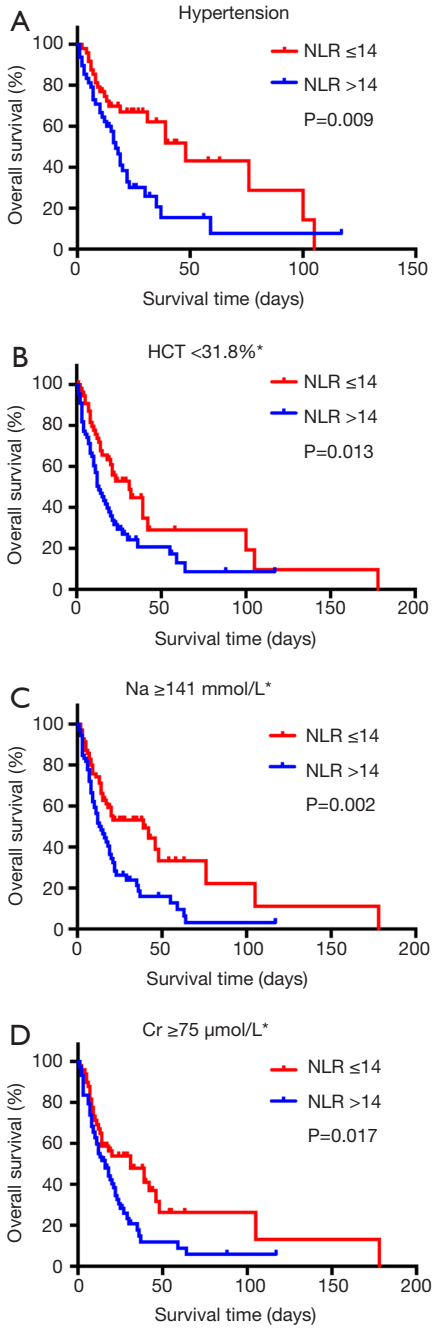

Figure 4 Kaplan-Meier analyses of overall survival in ARDS patients stratified according to subgroups stratified by hypertension, hematocrit (HCT), and sodium (Na) and creatinine (Cr) levels. (A) Overall survival analysis in patients with hypertension; (B) overall survival analysis in patients with HCT <31.8%; (C) overall survival analysis in patients with Na ≥141 mmol/L; (D) overall survival analysis in patients with Cr ≥75 μmol/L. P values were calculated by the log-rank test. *, divided at the median. ARDS, acute respiratory distress syndrome.

was higher in the group of non-survivors than in the survivors. The baseline NLR value could predict mortality independent of age, liver cirrhosis, NLR, Cr and PaO_2/FiO_2. In addition, NLR >14 was used as the cut-off threshold for predicting the mortality of ARDS. Prior to our study, data on ARDS in Chinese patients had not been well described, and the present study is the first to examine the prognostic role of the NLR in patients with ARDS.

Recent studies showed the role of the NLR as an independent predictor of mortality in various diseases, including in critical care medicine. In a prospective study of critically ill patients, a high NLR measured in the emergency department (ED) was independently associated with in-hospital mortality (20). In addition, a high NLR was also related to risk of multi-organ failure and the development of sepsis (18). More recently, Riché *et al.* also identified an association between NLR and risk of death in patients with septic shock (17). In a study conducted by Salciccioli *et al.* (20), NLR measured at the time of

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ICU admission was associated with 28-day mortality in unselected critically ill patients. Hwang *et al*. (18) also found that the initial NLR measured at ED admission was independently associated with 28-day mortality in patients with severe sepsis or septic shock in the ED. However, no study has explored the association between NLR and mortality in ARDS patients.

An increase in the NLR is due to an increase in the neutrophil count and a decrease in the lymphocyte count. The NLR represents the balance between the neutrophil and lymphocyte levels in the body, and it is an indicator of systemic inflammation (13). In this case, a high NLR may indicate that a patient has severe inflammatory progression. Studies have shown that extensive activation of the immune system and immune dysfunction can explain the changes in the neutrophil and lymphocyte counts (17,18). On the other hand, the release of various anti-inflammatory cytokines induces immunosuppression and apoptosis in many lymphocytes (21,22). In this case, neutrophils are continuously released from the bone marrow, resulting in many immature neutrophils recruited into the cycle. Lymphopenia has been found to be an indication of immunosuppression in sepsis (23) and may be a predictor of mortality in ARDS patients.

ARDS is the out-of-control progression of the innate immune-mediated inflammatory response in the context of various risk factors. A variety of inflammatory factors promote the permeability of the alveolar epithelium and vascular endothelial boundary (24). New mechanisms of the innate immune response have been found, such as neutrophils forming extracellular traps (25) in response to endothelial injury and the release of histones, which may cause alveolar damage. The recruitment of neutrophils is mediated by a step-by-step response to inflammatory factors released from endothelial cells, which is further enhanced in ARDS (25). The innate immune recognition process is considered a potential driver of acute lung injury. Neutrophil-dependent lung injury is the key pathway. Neutrophils respond rapidly to inflammation, resulting in a dramatic increase in the number of neutrophils migrating to the lungs (12). Severe and uncontrolled activation of the immune system can lead to lung injury, which is followed by multiple organ failure or death.

Our study revealed the relationship between the NLR and prognosis in ARDS patients. We observed that there were significant differences in the NLR between the survival and non-survival groups (P<0.001). As a high NLR was more likely to indicate a higher mortality, we used a median value as the cut-off value to divide the patients into two groups: NLR >14 and ≤14. The influence of an NLR >14 on the mortality of ARDS patients was analyzed using hospital mortality, 28-, 90-day mortality and mechanical ventilation as outcomes. The Kaplan-Meier curve also demonstrated that an NLR >14 was associated with a reduced OS (P=0.005). These results might imply that an NLR >14 could be associated with a more effective relative prognosis in ARDS. Multivariate analysis identified an NLR >14 as an independent prognostic factor of OS (P=0.029). Subgroup analysis confirmed that the NLR was a prognostic factor of OS in patients with hypertension (P=0.009), HCT <31.8% (P=0.013), Na ≥141 mmol/L (P=0.002) and Cr ≥75 μmol/L (P=0.017). Therefore, we advocate for the use of the NLR in the risk stratification of ARDS patients.

Although many studies have evaluated the prognosis of ARDS (10), no biomarker is considered perfect. The NLR is an extremely common laboratory test, and the initial NLR values can be used to identify high-risk patients with adverse outcomes. These values may also help to assess the host immune response. However, further clinical studies are needed to evaluate the benefit of the NLR in ARDS.

The major limitations of our study are its retrospective design and relatively small sample size. This is a single institution study with a single ethnicity study population, and it remains to be seen whether these results are generalizable to other ethnicities. Future studies on this consideration as well as prospective external validation are required. Additionally, we separated the patients into two groups based on the percentage of the initial NLR. However, the baseline characteristics of the patients were heterogeneous and unbalanced. Moreover, the new definition of ARDS in the context of the Berlin definition was not implemented in this study (26).

Conclusions

Our study showed that a high NLR (>14) at 24 hours after an ARDS diagnosis independently predicted a poor prognosis in ARDS patients. This marker could potentially be used in clinical practice due to its convenience. However, further studies in different ethnicities and larger populations of ARDS patients are required to confirm the current findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Clinical Research Ethics Committee of Zhongshan Hospital, Fudan University (Shanghai, China) (B2016-039R).

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