Prognostic value of neutrophils to lymphocytes and platelets ratio for 28-day mortality in patients with acute respiratory distress syndrome：A retrospective study

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Research Article

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Abstract

Background

Acute respiratory distress syndrome (ARDS) is a rapidly progressive and fatal respiratory failure disease that often occurs in critically ill patients. Since ARDS is associated with immune dysregulation and coagulation abnormalities, it is necessary to identify an appropriate predictor that can accurately predict ARDS mortality based on its pathophysiology. Therefore, this study aimed to evaluate the clinical value of neutrophils to lymphocytes and platelets ratio (N/LPR) in predicting 28-day mortality in ARDS patients.

Methods

From July 2018 to October 2021, the medical records of ARDS patients were retrospective reviewed. Neutrophil count, lymphocyte count, and platelet count were collected, and the neutrophil-to-lymphocyte ratio (NLR) and N/LPR were calculated. Multivariate logistic regression analyses were performed to identify independent predictors of 28-day mortality in ARDS. Receiver operating characteristic (ROC) curve with the area under curve (AUC) was used to evaluate optimal cutoff values for 28-day mortality in ARDS. Kaplan-Meier analysis was used to estimate the 28-day survival probabilities stratified by optimal cutoff values of N/LPR and NLR.

Results

A total of 136 ARDS patients were included in this study and were further divided into survivors (n = 69) and non-survivors (n = 67) groups according to their survival status after 28 days. There were no significant differences between the two groups in age, sex, history of smoking and drinking, comorbidities, and reasons of admission ($P > 0.05$). Non-survivors had significantly higher neutrophil counts, NLR and N/LPR and had significantly lower platelet counts than survivors ($P < 0.05$). Multivariate regression analysis revealed that N/LPR, NLR and platelet counts were independent predictors for 28-day mortality in ARDS ($P < 0.05$). The ROC analyses showed that N/LPR with optimal cutoff value of 10.57(sensitivity: 74.6%; specificity:72.5%) is a more reliable predictor for 28-day mortality in ARDS than NLR and platelet count (AUC:0.785 vs. 0.679vs. 0.326). Further subgroup analysis confirmed that ARDS patients with N/LPR < 10.57 had significantly lower 28-day mortality than patients with N/LPR ≥ 10.57($P < 0.001$). Kaplan–Meier analysis also confirmed that ARDS patients with N/LPR < 10.57 had significantly longer survival.

Conclusion

N/LPR is an independent risk factor associated with 28-day mortality in ARDS patients and shows better performance in predicting mortality rate than NLR.

Background

Acute respiratory distress syndrome (ARDS) is a common cause of respiratory failure, especially in life-threating patients in the intensive care unit (ICU)[1, 2].Despite recent advances in medical treatment and understanding of the pathophysiology of ARDS, its high morbidity and mortality continue to severely impact patient health and has become a substantial public health burden[3, 4]. In a large observational study of ICU patients in 50 countries, the prevalence of ARDS in ICU admission was 10.4%, with a very high in-hospital mortality rate of 35–46%[5]. Therefore, it is necessary and important to identify crucial prognostic factors for ARDS patients to provide timely early intervention to improve survival.

The neutrophil-to-lymphocyte ratio (NLR), the number of neutrophils divided by the number of lymphocytes, has been studied extensively as an independent prognostic factor in systemic inflammatory diseases[6]. Although several studies further reported the predictive prognostic value of NLR in ARDS patients [7–9], NLR only reflects the inflammatory and immune status in these patients. In fact, the occurrence and development of ARDS is more complex, which is related to the crosstalk between systemic inflammatory response, abnormal immune regulation, and coagulation dysfunction[10].Therefore, there is an urgent need to identify novel predictive biomarkers that can precisely predict the prognosis of ARDS patients. In the recent years, the neutrophils to lymphocytes and platelets ratio (N/LPR) has received considerable attention. Several recent studies reveal the prognostic value of N/LPR in assessing systemic inflammatory responses and demonstrate that N/LPR can reflect the tight interplay between inflammation, coagulation, and immune response[11, 12].Given the importance of platelets in ARDS pathogenesis[13], we speculate that N/LPR may be a more appropriate prognostic indicator for predicting mortality of ARDS patients. Therefore, this study aimed to investigate whether N/LPR could be used to predict the 28-day mortality in ARDS patients and further compare it with NLR indicator.

Materials And Methods

Patient population

From July 2018 to October 2021, medical records of ARDS patients from Department of Critical Care Medicine of Yongchuan Hospital affiliated to Chongqing Medical University were retrospectively reviewed. The inclusion criteria were as follows: (1) Age 18 or over; (2) Confirmed diagnosis of ARDS according to the guideline for diagnosis and therapy of acute lung injury and acute respiratory distress syndrome [14]; (3) Stable hemodynamics; and (4) Complete medical history. The exclusion criteria were as follows: (1) Pregnant and lactating women; (2) Hematologic disorders; (3) Malignant tumors and/or immune disorder; and (4) Taking drugs within the past week that may affect the number of neutrophils, lymphocytes and platelets. This study was approved by the Institutional Review Board (IRB) of Chongqing Medical University (IRB number: #2020-84) and conducted in accordance with the Declaration of Helsinki. The requirement of written informed consent was waived by the IRB due to the retrospective nature of the study.

Study design

The study endpoint was the 28-day mortality. Clinical data of all eligible patients were collected, including age, sex, a history of smoking and drinking, comorbidities, and reason of admission. Acute physiology and chronic health evaluation II (APACHE-II) score, sequential organ failure assessment (SOFA) score and laboratory test results (PaO_2/FiO_2 ratio, neutrophil counts, lymphocyte counts, and platelet counts) recorded within 24hours after the ARDS diagnosis were also collected. The NLR is calculated as the ratio between the neutrophil and lymphocyte counts measured in peripheral blood, as follows: Neutrophil count / lymphocyte count. The NLPR is calculated as follows: Neutrophil count× 100 / (lymphocyte count× platelet count). If multiple values were evaluated within 24 hours after diagnosis, the worst value was used. All eligible patients were followed up for 28 days to calculate the 28-day mortality.

Statistical analysis

All statistical analyses in this study were performed using SPSS version 28 (IBM Corp, Armonk, NY). Continuous data with normal distributions were presented with mean ± standard deviation (SD), and the difference between groups was analyzed using t-test. Continuous data with probability distributions were presented with medians and quartiles, and the difference between groups was analyzed Mann-Whitney U test. Categories data were presented with frequencies and percentage and compared using Chi-square test. Binary logistic regression analysis was used to identify potential predictors associated with the 28-days mortality in ARDS patients. The predictive prognostic values of each risk factors for mortality were evaluated by the receiver operating characteristic (ROC) curve method and area under the curve (AUC). Stratified analysis of 28-day mortality of ARDS was performed using the optimal cut-off values. Survival curves were estimated by Kaplan-Meier survival analysis, and the differences between groups were determined by log-rank test. A P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of ARDS patients

A total of 225 patients diagnosed with ARDS were screened. Among them, 89 patients were excluded from this study, including 7 patients under the age of 18, 1 patient in the pregnancy, 16 patients with hematologic disorders, 25 patients with malignant tumors, 9 patients with immune disorders, and 31 patients who had taken antiplatelet drugs or leukocyte increasing drugs in the past 1 week. Finally, a total of 136 eligible ARDS patients were included in the analysis (Fig. 1). Among them, 67ARDS patients died within 28 days (non-survivors) and 69 survived (survivors). Table 1 shows the baseline and clinical characteristics of the survivors and non-survivors. There were no significant differences between the two groups with respect to age, sex, smoking history, drinking history, comorbidities, and reason of admission ($P > 0.05$). Compared with non-survivors, survivors had significantly lower APACHE-II scores (22 vs. 27, $P = 0.026$) and SOFA scores (7 vs. 9, $P < 0.001$) and significantly higher PaO_2/FiO_2 ratios (173.55 vs. 147.64, $P = 0.011$) at admission.

Table 1
Baseline characteristics of ARDS patients according to the 28-day survival status

Variables	Survivors (n = 69)		Non-survivors (n = 67)		P value
Age, years	61.8	± 1.711	65.1	± 1.534	0.157
Male, n (%)	42	(60.9%)	49	(79.1%)	0.129
Smoking, n (%)	29	(42. 0%)	38	(56.7%)	0.087
Alcohol, n (%)	27	(40.3%)	34	(50.7%)	0.173
Comorbidities					0.183
Hypertension, n (%)	27	(40.3%)	18	(26.9%)	
Diabetes mellitus, n (%)	7	(10.1%)	4	(6. 0%)	
Coronary artery disease, n (%)	0	(0%)	3	(4.5%)	
Reason of admission					0.228
Cor pulmonale, n (%)	31	(44.9%)	42	(62.7%)	
Sepsis, n (%)	6	(8.6%)	4	(6. 0%)	
Trauma, n (%)	5	(7.2%)	3	(4.5%)	
Others, n (%)	27	(40.3%)	18	(26.9%)	
APACHE-II score, median (IQR)	22	(7)	27	(10)	**0.026**
SOFA score, median (IQR)	7	(4)	9	(4)	**< 0.001**
PaO2/FiO2, mean (mmHg)	173.55	± 7.357	147.64	± 6.740	**0.011**
Data are presented as median (IQR) or n(%), Bold indicates factors that are statistically significant					
Abbreviations: APACHE-II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; IQR, interquartile range; ARDS, acute respiratory distress syndrome; FiO2: Fraction of inspired oxygen; PaO2: Partial pressure of arterial oxygen					

Table 2 shows the laboratory parameters of ARDS patients on admission. There were statistically significant differences between groups in neutrophil count, platelet count, NLR and N/LPR ($P < 0.05$). Non-survivors had significantly higher neutrophil counts, NLR and N/LPR and lower platelet counts than survivors (all $P < 0.05$). Moreover, there was no significant difference between group in the lymphocyte counts ($P > 0.05$).

Table 2
Laboratory parameters of ARDS patients according to the 28-day survival status

Variables	Survivors (n = 69)	Non-survivors (n = 67)	P-value
Neutrophil count (10^9/L)	9.14	11.52	**0.001**
Lymphocyte count (10^9/L)	0.69	0.64	0.519
Platelet count (10^9/L)	167	125	**0.000**
NLR	8.25	15.02	**0.000**
N/LPR	12.48	16.92	**0.000**
Bold indicates factors that are statistically significant			
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; N/LPR, neutrophils to lymphocytes and platelets ratio; ARDS, acute respiratory distress syndrome			

Identification of N/LRP as an independent predictor for 28-day mortality in ARDS patients

Univariate and multivariate logistic regression analyses were performed to identify independent predictor of 28-day mortality in ARDS patients. As shown in Table 3, N/LPR (OR = 8.934, P = 0.003), NLR (OR = 5.218, P = 0.022) and platelet counts (OR = 3.895, P = 0.048) were independent predictors associated with 28-day mortality in ARDS patients. ROC curve analysis was further performed to determine the accuracy of the three predictors and to identify their optimal cutoff values. The results showed that N/LPR had the strongest predictive effect than NLR and platelet count (Fig. 2). The AUCs of the N/LPR, NLR and platelet count were 0.785 (95% CI: 0.708–0.862, P = 0. 000), 0.679 (95% CI: 0.589–0.768, P = 0. 000) and 0.326 (95% CI: 0.235–0.417, P = 0. 000), respectively (Table 4). When the optimal cut-off value of N/LPR was 10.57 to discriminate the 28-day mortality in ARDS patients, the sensitivity and specificity were 74.6% and 72.5%, respectively. The optimal cut-off value for NLR was 14.20, with a sensitivity of74.6%and a specificity of59.4%.

Table 3
Binary logistic regression analysis of 28-day mortality prediction for ARDS patients

Variables	B	Walds	OR	P-value
APACHE-II	0.04	0.047	0.699	0.403
PaO2/FiO2	-0.004	0.004	1.16	0.282
SOFA	0.007	0.121	0.003	0.954
Neutrophil count	0.103	0.053	3.694	0.055
Platelet count	0.018	0.009	3.895	**0.048**
N/LPR	0.475	0.159	8.934	**0.003**
NLR	-0.204	0.089	5.218	**0.022**
Bold indicates factors that are statistically significant				
Abbreviations: APACHE-II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; NLR, neutrophil-to-lymphocyte ratio; N/LPR, neutrophils to lymphocytes and platelets ratio; ARDS, acute respiratory distress syndrome; OR, Odds ratio, FiO2: Fraction of inspired oxygen; PaO2: Partial pressure of arterial oxygen				

Table 4
Predictive value of potential indicators in predicting 28-day mortality in ARDS patients

Indicators	AUC	95% CI	Optimal cutoff value	Sensitivity (%)	Specificity (%)
Platelet count	0.326	0.235–0.417	-	-	-
N/LPR	0.785	0.708–0.862	10.57	74.6	72.5
NLR	0.679	0.589–0.768	14.20	74.6	59.4
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; N/LPR, neutrophils to lymphocytes and platelets ratio;					
ARDS, acute respiratory distress syndrome; AUC, Area under the curve; CI, Confidence interval					

Validation of the efficacy of N/LPR with an optimal cutoff value in predicting 28-day mortality in ARDS patients

To further confirm the predictive values of N/LPR and NLR for 28-day mortality, 136 ARDS patients were divided into two groups according to the optimal cutoff values determined by above ROC analysis. The number of deaths, 28-day mortality and mean survival time in the two groups were subsequently calculated. As shown in Table 5, ARDS patients with N/LPR ≥ 10.57 had higher number of death than ARDS patients with N/LPR < 10.57(50 vs. 17). In addition, ARDS patients with N/LPR ≥ 10.57 had significantly higher 28-day mortality (68.5% vs. 27.0%, P < 0.001) and significantly shorter survival time (5 vs. 8 months, P = 0.002). Regarding NLR, the number of death and 28-day mortality in ARDS patients with NLR ≥ 14.20 were notably higher than that in ARDS patients with NLR < 14.20 (Table 5). ARDS patients

with higher NLR also survived significantly longer than those with lower NLR (P = 0.048). Furthermore, the predictive values of N/LPR and NLR were further validated using the Kaplan-Meier analysis. The results showed that the 28-day mortality of ARDS patients with N/LPR ≥ 10.57 was significantly lower than that of patients with N/LPR < 10.57 (31.51% vs. 73.02%, P < 0.001, Fig. 3A). Meanwhile, patients with an NLR ≥ 14.20 also had significantly worse survival probability than patients with NLR < 14.20 (28-day mortality: 35.06% vs. 71.19%, P < 0.001, Fig. 3B). The results of these analyses suggest that both N/LPR and NLR are good predictors of 28-day mortality in ARDS patients.

Table 5
Comparison of 28-day mortality and survival in ARDS patients with different N/LPR and NLR values

	Patients	Death (n)	28-day mortality (%)	Survival time (mean ± SD, days)	
N/LPR < 10.57	63	17	27.0	8	± 8.14
N/LPR ≥ 10.57	73	50	68.5	5	± 6.20
P-value			**<0.001**	**0.002**	
NLR < 14.20	59	17	28.8	8	± 7.75
NLR ≥ 14.20	77	50	64.9	5	± 6.94
P-value			**<0.001**	**0.048**	
Bold indicates factors that are statistically significant					
Abbreviations: N/LPR, neutrophils to lymphocytes and platelets ratio, NLR, neutrophil-to-lymphocyte ratio, SD, Standard deviation; ARDS, acute respiratory distress syndrome					

Discussion

Previous studies have shown that N/LPR is a good indicator to evaluate systemic inflammatory diseases, because it can comprehensively reflect the aspects of inflammation, coagulation, and immunity[11, 12, 15].The predictive value of N/LPR was first determined by Koo et al. in a retrospective study of 1099 patients who underwent cardiovascular surgeries [11]. The results revealed that N/LPR can be used as an indicator to evaluate inflammatory status of acute kidney injury (AKI) and mortality in patients after high-risk cardiovascular surgeries, and that the predictive accuracy of N/LPR is better than that of NLR or platelet count. A retrospective analysis by Liu et al. [15]also confirmed the clinical value of N/LPR in reflecting inflammatory response, immune function and coagulation dysfunction of sepsis patients. N/LPR not only has better predictive value than NLR, but also can effectively predict 28-day mortality in sepsis patients admitted to ICU. Therefore, after comprehensive consideration of the pathogenesis of ARDS involving a complex interplay of multiple aspects of inflammatory response imbalance, abnormal coagulation function, and uncontrolled immune regulation, we thought to investigate the clinical value of N/LPR in ARDS patients and determine the optimal cutoff value for N/LPR to predict28-day mortality. Our results showed that non-survivors had significantly higher NLR and N/LPR values than survivors (P <

0.05). Although logistic regression analyses revealed that both NLR and N/LPR were independent predictors, ROC curve analysis further indicated that N/LPR was better than NLR for predicting 28-day mortality in ARDS (AUC:0.785 vs. 0.679). Furthermore, survival analyses confirmed that ARDS patients with high N/LPR or NLR values had higher mortality and lower survival months than patients with low N/LPR or NLR values ($P < 0.05$). Our results clearly revealed that ARDS patients with high N/LPR or NLR are associated with a higher risk of death, and that N/LPR has a better clinical value than NLR in predicting the 28-day mortality in ARDS patients.

The pathogenesis of ARDS is very complex, mainly manifested as an imbalance between inflammation and coagulation [16, 17].NLR is known to be a sensitive indicator that can reflect systemic inflammatory response[18], and has been shown to useful in assessing the prognosis of various inflammatory disease, such as sepsis [19], rheumatoid arthritis [20], and coronary artery disease [21], as well as the recent epidemic of coronavirus disease 2019 (COVID-19)[22, 23]. In this study, the elevated NLR value was found to be significantly associated with the prognosis of ARDS. This association may be due to the imbalance of inflammation and immune cell-mediated inflammatory cascades[24]. In ARDS patients, the balance between pro-inflammatory and anti-inflammatory mechanisms is disrupted, leading to an inflammatory waterfall effect and creating a vicious circle[24, 25]. The NLR is ratio between the neutrophil counts and lymphocyte counts measured in peripheral blood. Neutrophils, key immune cells in the ARDS inflammatory microenvironment, increase in number with the intensification of systemic inflammatory response. Lymphocytes, important immune cells in protecting pulmonary microvascular endothelial cells, are negatively associated with increased inflammatory risk. Therefore, changes in NLR values reflect not only aspects of acute and chronic inflammation (neutrophil counts), but also aspects of adaptive immunity (lymphocyte counts)[24, 26, 27]. In this study, non-survivors had significantly higher neutrophil counts than survivors ($P < 0.05$). Furthermore, although not statistically significant, there was a trend which indicated that the lymphocyte counts of non-survivors was lower than that of survivors. Importantly, non-survivors had significantly higher NLR values than survivors ($P < 0.05$), which is consistent with the previous study by Wang et al.[28]. Taken together, these suggest that NLR, an indicator of inflammatory status, can be used as a predictor for evaluating the 28-day mortality in ARDS.

Although our findings reveal the predictive potential of NLR for 28-day mortality, NLR can only reflect aspects of inflammatory response and immune status, ignoring the role of coagulation abnormalities in ARDS patients. In the recent study by Wu et al., coagulation dysfunction was identified as a risk factor associated with the development of ARDS and subsequent progression to death in patients with COVID-19 pneumonia[29]. Coagulation dysfunction in patients with ARDS is mainly due to the exposure of tissue factor (TF) and interaction with neutrophil elastase, resulting in the activation of coagulation cascade[10, 30]. In the prospective study by Ozolina et al.[31], patients who developed ARDS had significantly higher plasma TF concentrations than patients who did not develop ARDS. For COVID-19 patients at a high risk of developing ARDS, neutrophil elastase inhibitors showed promising therapeutic in reducing the development and progression of ARDS[32]. In the pro-inflammatory state, the imbalance between coagulation and anticoagulation and protein C-mediated impairment of endogenous anticoagulation can further exacerbate the inflammatory response[33]. Furthermore, a study investigating the relationship

between protein C and acute lung injury (ALI) showed that ALI patients with low levels of plasma protein C were associated with higher mortality [34].

Platelets and coagulation mutually influence each other, and their close interplay contributes to the balance of hemostasis and bleeding[35]. Therefore, the association between platelets and ARDS may be due to the extensive cross talk between coagulation and inflammation[30, 36, 37]: platelets interact with neutrophils to form platelet–neutrophil complexes, which recruit more neutrophils, trigger endothelial and immune cell activation, and finally the development of ARDS. In our study, non-survivors had significantly lower platelet counts than survivors, suggesting that low platelet counts are associated with poor prognosis in ARDS. This finding is also supported by several studies showing that platelet count is an independent predictor of mortality in ARDS patients[31, 33, 36].Furthermore, our findings are consistent with the study by Wang et al.[38]that thrombocytopenia accelerate the progression of ARDS and increase mortality in critically ill patients.

There were several limitations in this study. First, this study is a single-center study in China, and the conclusion may only applicable to similar populations. Therefore, the applicability of N/LPR to other populations or races need to be further explored. The second limitation is the small sample size. This limits our further exploration of other potential confounding factors that may affect the prognosis of ARDS. Future large-scale prospective studies should be conducted to overcome the current disadvantages of this study and to further confirm the clinical application of N/LPR predictor for 28-day mortality in ARDS patients.

Conclusions

Our study revealed the clinical values of N/LPR in ARDS patients. N/LPR with a cutoff value of 10.57is not only a good predictor of 28-day mortality in ARDS patients, but also shows better predicting accuracy than NLR. Therefore, N/LPR should be considered as one of the routine indicators for monitoring and reporting the health status of ARDS patients in clinical practice, which can provide judgment reference for physicians.

Abbreviations

ARDS
Acute respiratory distress syndrome
N/LPR
Neutrophils to lymphocytes and platelets ratio
NLR
Neutrophil-to-lymphocyte ratio
ROC
Receiver operating characteristic
APACHE-II

Acute Physiology and Chronic Health Evaluation II
SOFA
Sequential Organ Failure Assessment
AUC
Area under the curve
CI
Confidence interval
ICU
Intensive care unit
IRB
Institutional Review Board
SD
Standard deviation
OR
Odds ratio
COVID-19
Coronavirus disease 2019
TF
Tissue factor
ALI
Acute lung injury
FiO2
Fraction of inspired oxygen
PaO2
Partial pressure of arterial oxygen
AKI
acute kidney injury
IQR, interquartile range

Declarations

Authors contributions

All authors participated in the interpretation of the study results and review of the manuscript.SY N designed and conducted all experiments, drafted the manuscript, and performed the statistical analyses. NW planned the study and drafted the manuscript. HJ W and QY L participated in the date collection. WT and ZT contributed to the study design and the revision of the manuscript. All authors read and approved the final manuscript.

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Availability ofdata and materials

The datasets used and analyses during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective comparative study was approved by the Institutional Review Board (IRB) of Chongqing Medical University (IRB number: #2020-84) and conducted in accordance with the Declaration of Helsinki. The requirement of written informed consent was waived by the IRB due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

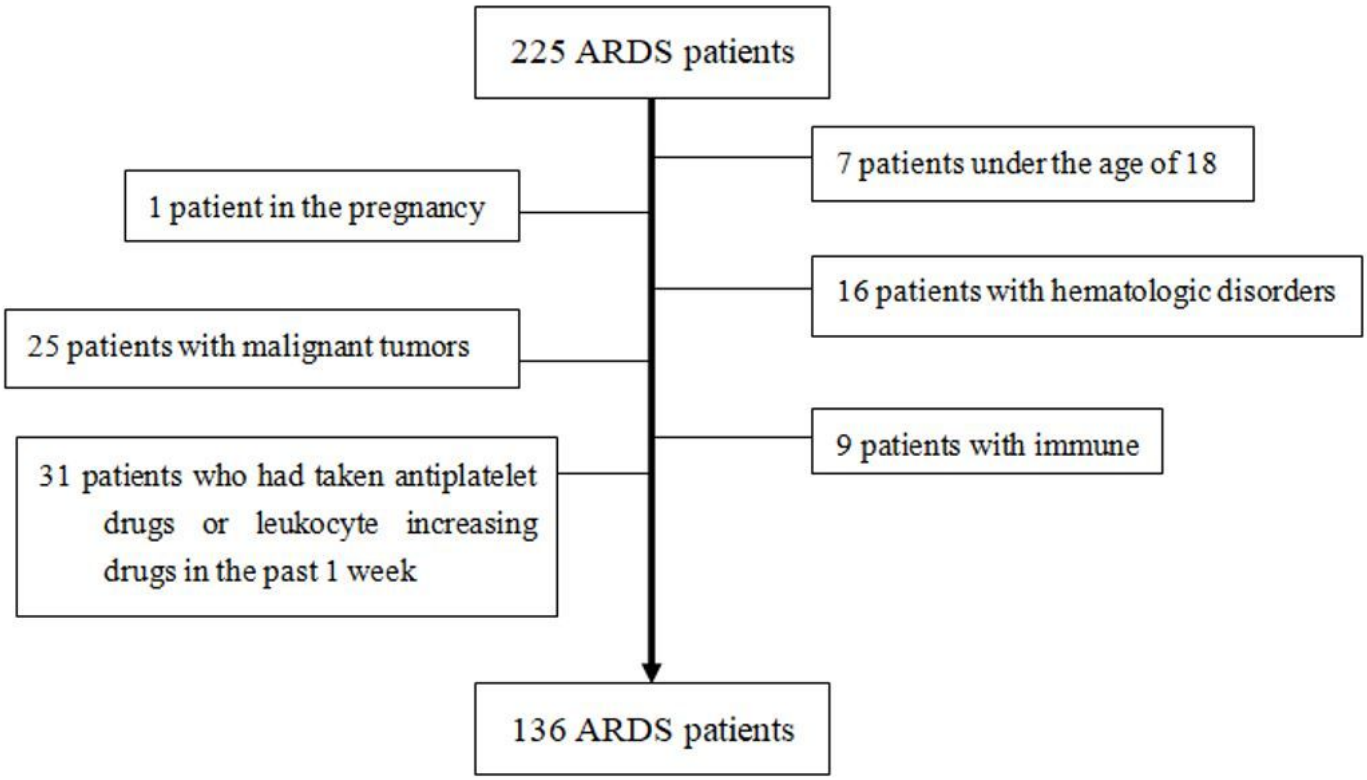

Figure 1

Flow-chart of the patient inclusion process.

Abbreviations: ARDS, acute respiratory distress syndrome

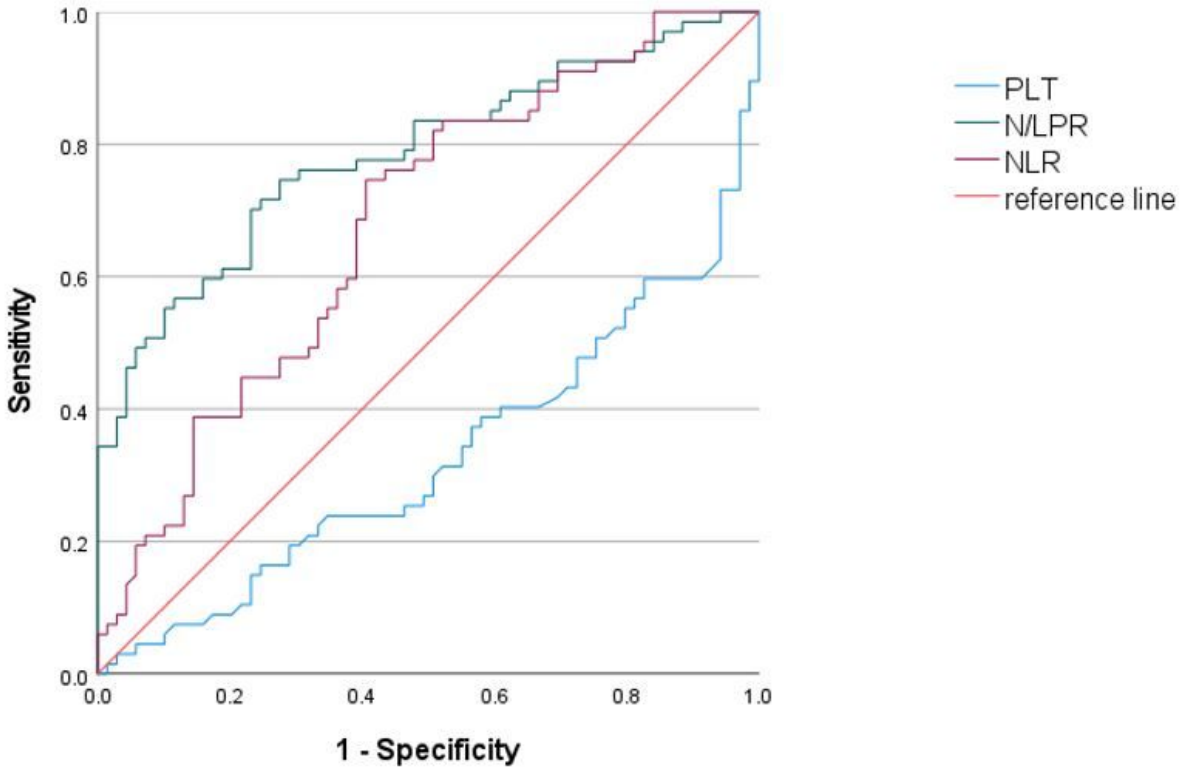

Figure 2

ROC curves for predicting 28-day death in ARDS patients

Abbreviations: N/LPR, neutrophils to lymphocytes and platelets ratio; NLR, neutrophil-to-lymphocyte ratio; PLT, Platelet count; ROC, receiver operating characteristic; ARDS, acute respiratory distress syndrome

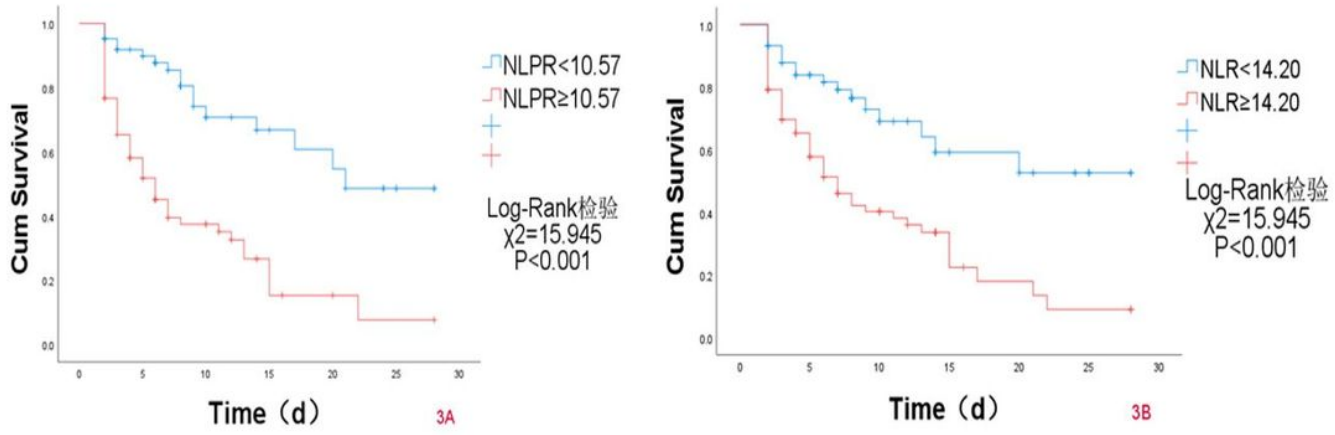

Figure 3

Kaplan-Meier curves for28-day survival mortality of ARDS patients with different peripheral blood N/LPR and NLR

(A) N/LPR with an optimal cutoff value of 10.57. (B) ARDS patients with an optimal cutoff value of 14.20. Abbreviations: N/LPR, neutrophils to lymphocytes and platelets ratio, NLR, neutrophil-to-lymphocyte ratio, ARDS, acute respiratory distress syndrome