The Combination of APACHE II Score, Neutrophil/lymphocyte Ratio And Expired Tidal Volume Could Better Predict Noninvasive Ventilation Failure In Pneumonia-Induced Mild To Moderate ARDS Patients

Wei Sun
Capital Medical University, Beijing
Zujin Luo
Capital Medical University, Beijing
Zhixin Cao
Capital Medical University, Beijing
Jing Wang
Capital Medical University, Beijing
Liming Zhang
Capital Medical University, Beijing
Yingmin Ma (ma.yingmin@163.com)
Capital Medical University, Beijing

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Abstract

Background: To identify the variables easily obtained at the bedside for prediction of failure of noninvasive ventilation (NIV) among pneumonia-induced mild to moderate acute respiratory distress syndrome (ARDS) patients.

Methods: A total of 131 pneumonia-induced mild to moderate ARDS patients were enrolled in this retrospective observational study. Electronic medical records were reviewed to determine whether NIV succeeded or failed for each patients, and we compared the variables between NIV success and failure patients. Multivariate logistic regression analysis were made to identify the independent factors of NIV failure, and we developed an equation based the results of the analysis. Receiver-operating characteristic (ROC) curves were built to assess the efficacy of variables to predict NIV failure. Kaplan-Meier curves for 28-day survival were built to compare the mortality between different groups.

Results: 64 (48.9%) patients experienced NIV failure. APACHE II score, neutrophil/lymphocyte ratio (NLR) and expired tidal volume (Vte) were independent factors for predicting NIV failure. The combination value of APACHE II score, NLR and Vte had better efficacy of predicting NIV failure (AUC, 0.9; 95% CI 0.845-0.955) than APACHE II score (AUC, 0.818; 95% CI0.745-0.891), NLR (AUC, 0.839; 95% CI 0.765-0.913) and Vte (AUC, 0.805; 95% CI 0.729-0.881) respectively. The cumulative survival probability within 28 days was lower in patients with combination value>59.17 (P<0.001 by log-rank test), APACHE II score>16.5 (P<0.001 by log-rank test), NLR>7.22 (P<0.001 by log-rank test) and Vte>8.96ml/kg (P<0.001 by log-rank test).

Conclusions: The combination of APACHE II score>16.5, NLR>7.22 and Vte>8.96ml/kg may be a useful surrogate for predicting NIV failure among pneumonia-induced ARDS patients, and patients with combination value>59.17 should cautiously monitored during NIV. Further study with a larger sample size is warranted.

Background

The use of noninvasive ventilation (NIV) dramatically increased in patients with acute respiratory failure (1) as it significantly reduces the work of breathing, thereby reducing the need for intubation.(2, 3)Compared to NIV, Intubation for invasive mechanical ventilation (IMV) is associated with many complications, such as diaphragmatic weakness and ventilator-associated pneumonia.(4, 5) However, the NIV failure rate is around 50% in patients with hypoxemic respiratory failure,(6, 7) and patients who experience NIV failure are more likely to die in hospital.(8, 9) Therefore, it is advisable to enhance the accuracy of early identification of ARDS patients who may not benefit from NIV.

ARDS is still associated with high mortality despite the improvement of treatments such as the use of low tidal volume ventilation.(10) A number of studies have attempted to identify possible factors of NIV failure but with conflicting results.(7, 11, 12) One potential mechanism for conflicting results reported by the literatures is that different underlying etiologies of ARDS may have variable clinical phenotypes, with

different risk and prognostic factors.(13, 14) There are significant heterogeneity between pulmonary and extrapulmonary ARDS in terms of pathology, inflammation response and respiratory mechanics.(15, 16)

Pulmonary infections account for the vast majority of ARDS risk factors(17). We performed this study to examine variables easily obtained at the bedside for prediction of NIV failure among pneumonia-induced mild to moderate ARDS patients.

Methods

Subjects and study design

This was a single-center retrospective observational study, including 131 pneumonia-induced ARDS patients, conducted in the department of respiratory and intensive care unit of Beijing Chao-Yang Hospital west campus from 2016 January to 2020 December. Since the current study did not impose any diagnostic and therapeutic influence on patients, the Institutional Review Board for Beijing Chao-Yang Hospital approved the study with a waiver of informed consent (No. 2016-KE-95). The current study was conducted in accordance with the Declaration of Helsinki.

The patients'selection were shown in Figure 1. Berlin definition of ARDS (18) were adopted to evaluate the patients, and 234 patients were diagnosed with ARDS (mild to moderate). A total of 103 patients were excluded since underlying cause of ARDS were not pneumonia, and 8 patients were NIV intolerant.

NIV failure was defined as failure to maintain a PaO_2/FiO_2 of >100mmHg, respiratory rate above 40 breaths/min, inability to protect the airway (coma or seizure disorders), management of thick tracheal secretions, inability to correct dyspnea, lack of improvement of signs of high respiratory muscle workload, respiratory or cardiac arrest, and hemodynamic instability without response to fluids and vasoactive agents.(19)

Bi-level or CPAP mode was applied for patients. The airway pressure and other ventilator parameters were set according to clinical practice and patients' tolerance, and these parameters were adjusted according to arterial blood gas. An oronasal mask was used for all subjects. Supplemental oxygen flow adjusted to maintain oxygen saturation above 90%.

The primary outcome of the current study was the NIV failure, and secondary outcome was the 28-day survival.

Measurements

Patients' baseline characteristics were recorded, including age, gender, length of stay in hospital, APACHE II score, the use of glucocorticoid before admission, and comorbidities (including kidney failure, respiratory diseases, malignancy, heart failure, liver function impairments, gastrointestinal bleeding, diabetes and hypertension). Vital signs (including heart rate, temperature, respiratory rate, systolic pressure, diastolic pressure) were recorded. Arterial blood gas and peripheral venous blood were obtained

at the time of admission. Treatment and the condition of NIV used were obtained by reviewing the medical charts.

Statistical Analyses

To compare continuous variables, the Kolmogorov–Smirnov test was used to test the normality of the data, Levene's test was applied to assess homogeneity of variance. Continuous data were expressed as median with interquartile range or mean±standard deviation as appropriate, and categorical data were expressed number with percentage. Normally distributed continuous variables were analyzed using the unpaired Student's t test. Non-normally distributed continuous variables were analyzed using the Mann–Whitney U-test. Categorical variables were analyzed using the Chi-squared test. Multivariate logistic regression analyses with a conditional forward stepwise regression model were used to determine whether any of factors were independently associated with NIV failure. A equation was built based on the results of multivariate logistic regression analyses and the combination value of each patients was calculated according to the equation. Receiver-operating characteristic (ROC) curves was constructed to evaluate the ability of markers to predict NIV failure. For each ROC curve, the optimal cutoff values, sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, Youden's index, area under curve (AUC), and 95% CI were calculated. Kaplan-Meier 28-day survival curves were constructed and log-rank tests were used to compare the curves. All analyses were two-tailed, and differences were considered as statistically significant at $p<0.05$. The SPSS software package (version 21.0) was utilized for all statistical analysis.

Results

Baseline characteristic and laboratory data at admission between NIV failure and NIV success

Based on Figure 1, NIV failure occurred in 33.3% of mild and 69.9% of moderate ARDS patients respectively. As a whole, the rate of NIV failure was 48.9% in this study. According to table 1, the proportion of males was higher (76.6%) in NIV failure group compared to NIV success subjects (52.2%). Moreover, NIV failure subjects had higher APACHE II score ($P<0.001$), respiratory rates ($P=0.007$) and expired tidal volume (Vte) ($P<0.001$) than NIV success group. As suggested in table 1, patients in NIV failure group presented with worse laboratory data. More specifically, they had lower PaO_2/FiO_2, $PaCO_2$, albumin and higher leukocyte, neutrophil/lymphocyte ratio (NLR) and CRP values than NIV success group. In addition, kidney failure ($P=0.005$) was more commonly observed among patients in NIV failure compared to NIV success patients.

Table 1. Comparisons of baseline characteristic and laboratory data at admission

	NIV failure (n=64)	NIV success (n=67)	P value
Age	65(57-77)	66(59-76)	0.68
Gender, male (n, %)	49(76.6)	35(52.2)	0.006
LOS	17(9-26)	15(10-20)	0.437
APACHE II	20±4.6	14±3.6	<0.001
Heart rate (beats/min)	97(80-111)	88(78-100)	0.032
Systolic Pressure	120(110-131)	128(117-148)	0.004
Temperature	36.8(36.5-37.3)	36.5(36.3-37)	0.083
Respiratory Rate	23(20-30)	21(20-24)	0.007
Expired tidal volume(ml/kg)	10.03±1.07	8.87±0.88	<0.001
pH	7.44±0.062	7.44±0.052	0.789
PaO_2/FiO_2 (mmHg)	194±78	236±53	0.001
$PaCO_2$ (mmHg)	33.9(30.4-36)	35.6(32.7-42.2)	0.004
HCO_3^- (mmol/L)	25.4(22.5-26.4)	24.8(23.6-27.3)	0.624
Leukocyte count ($x10^9$/L)	9.5(7.6-12.2)	7.4(5.3-9.6)	0.001
Neutrophil count ($x10^9$/L)	8.6(6.5-10.9)	5(3.2-7.8)	<0.001
Lymphocyte count ($x10^9$/L)	0.65(0.44-0.92)	1.29(0.90-1.87)	<0.001
NLR	9.93(8.31-11.95)	3.84(2.83-7.16)	<0.001
CRP (mg/L)	99(35-120)	38(8-62)	<0.001
PCT (ng/ml)	0.29(0.05-5.47)	0.1(0.05-5.27)	0.204
BUN(mmol/L)	6.23(4.62-9.75)	6.40(4.02-9.80)	0.411
Cr(umol/L)	77.3(58.5-98)	68.5(56.7-96.4)	0.331
Albumin (g/L)	28.4(23.9-33)	33(29.2-37)	0.001
BNP (ng/ml)	737(196-3517)	461(40-2278)	0.05
Use of glucocorticoid	19(29.7)	10(14.9)	0.058
kidney failure	34(53.1)	19(28.4)	0.005
Respiratory diseases	22(34.4)	24(35.8)	1
Malignancy	12(18.8)	5(7.5)	0.07

Heart failure	13(20.3)	23(34.3)	0.081
Liver function impairments	14(21.9)	14(20.9)	1
Gastrointestinal bleeding	5(7.8)	2(3)	0.267
Diabetes	17(26.6)	23(34.3)	0.35
Hypertension	25(39.1)	31(46.3)	0.156

Abbreviations: LOS, length of stay in hospital; APACHE II, acute physiology and chronic health evaluation II; PaO_2, arterial oxygen tension; FiO_2, fraction of inspired oxygen; $PaCO_2$, arterial carbon dioxide tension; HCO_3^-, bicarbonate; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; BUN, blood urea nitrogen; Cr, Creatinine; BNP, brain natriuretic peptide.

Risk factors of NIV failure

According to multivariate logistic regression analyses (Table 2), APACHE II score (OR, 0.77; 95% CI, 0.654-0.907, P=0.002), Vte (OR, 0.343; 95% CI, 0.153-0.768; P=0.009) and NLR (OR, 0.838; 95% CI, 0.704-0.997; P=0.046) were independent factors for predicting NIV failure. Multivariate logistic regression analyses was made with covariates including gender, heart beats, respiratory rates, PaO_2/FiO_2, $PaCO_2$, Leukocyte, CRP, albumin and kidney failure.

Table 2. Multivariate logistic Regression Analysis of Risk Factors for NIV Failure

	B	OR	95%CI		P value
Gender	1.201	3.323	0.949	11.64	0.06
APACHE II	-0.261	0.77	0.654	0.907	0.002
Heart beats	0.023	1.024	0.988	1.061	0.199
Respiratory rate	-0.074	0.929	0.811	1.064	0.285
PaO_2/FiO_2	-0.002	0.998	0.987	1.008	0.646
$PaCO_2$	-0.013	0.987	0.877	1.111	0.832
Vte	-1.069	0.343	0.153	0.768	0.009
Leukocyte	0.067	1.069	0.883	1.294	0.494
NLR	-0.177	0.838	0.704	0.997	0.046
CRP	-0.013	0.987	0.973	1.002	0.094
Albumin	-0.021	0.979	0.886	1.082	0.68
Kidney failure	0.366	1.442	0.384	5.419	0.588

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; PaO_2, arterial oxygen tension; FiO_2, fraction of inspired oxygen; $PaCO_2$, arterial carbon dioxide tension; Vte. expired tidal volume; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein.

Logistic regression equation was build based on the β-coefficient of APACHE II, Vte and NLR:

$$L = APACHE + \frac{1.069}{0.261} * Vte + \frac{0.177}{0.261} * NLR$$

$$L = APACHE + 4.096 * Vte + 0.678 * NLR$$

(L was the combination value of APACHE II, Vte and NLR)

Predictive ability of APACHE II score, Vte, NLR and Combination value for NIV failure

The ROC curves were displayed in Figure 2. Table 3 showed that the AUC of combination value (0.9; 95%CI, 0.845-0.955) were higher than APACHE II (0.818), NLR (0.839) and Vte (0.805). Combination value had the highest sensitivity (0.922), specificity (0.806), positive predictive value (0.819), negative predictive value (0.915) and diagnostic accuracy (0.863) among all the markers. The cutoff value for predicting NIV failure was combination value>59.17, APACHE II>16.5, NLR>7.22 and Vte>8.96ml/kg.

Table 3. ROC curve data

	APACHE II	NLR	Vte (ml/kg)	Combination value
Cutoff	16.5	7.22	8.96	59.17
Sensitivity, %	0.844	0.922	0.859	0.922
Specificity, %	0.687	0.731	0.657	0.806
Positive predictive value, %	0.72	0.766	0.705	0.819
Negative predictive value, %	0.821	0.907	0.83	0.915
Diagnostic accuracy	0.763	0.824	0.756	0.863
Youden's index	0.531	0.653	0.516	0.728
AUC	0.818	0.839	0.805	0.9
95% CI	0.745-0.891	0.765-0.913	0.729-0.881	0.845-0.955

Abbreviations: ROC, receiver-operating characteristic; AUC, area under the curve; CI, confidence interval; APACHE II, acute physiology and chronic health evaluation II; Vte. expired tidal volume; NLR, neutrophil/lymphocyte ratio.

Patients'28-day survival

As suggest in Figure 3, the cumulative survival probability within 28 days was lower in patients with APACHE II score>16.5 (P<0.001 by log-rank test), NLR>7.22 (P<0.001 by log-rank test), Vte>8.96ml/kg (P<0.001 by log-rank test) and combination value>59.17(P<0.001 by log-rank test).

Discussion

In the current study, we developed a novel equation for predicting NIV failure in pneumonia-induced mild to moderate ARDS patients. This equation takes into account APACHE II score, NLR and Vte, which can be easily obtained by bedsides assessment and laboratory test. Thus, this equation may be a concise and convenient tool to evaluate the patients and predict NIV failure.

Initially, the use of NIV in patients with ARDS focused on immunocompromised patients such

as those with hematologic malignancies. (20, 21) Mounting evidence suggested that subgroup of ARDS patients could benefit from NIV and avoided intubation. (19) Previous literatures reported that 50% NIV failure rate occurred in 50% patients with ALI/ARDS, which was in line with our results.

Our study showed that NLR (>7.22) was the independent contributor of NIV failure among pneumonia-induced ARDS patients. Previous studies have demonstrated that elevated NLR was an independent predictor of mortality of ARDS patients.(22, 23) Current study included pneumonia patients and infection was their original cause of ARDS, and the infection-derived signals activated the release of neutrophil from bone morrow to the circulation and targeted organ.(24) During ARDS, neutrophils are the first leukocytes recruited to sites of inflammation in response to chemotactic factors released by activated macrophages and pulmonary epithelial and endothelial cells.(25) The neutrophil recruited to the lung executed its function by releasing reactive oxygen species (ROS), antimicrobial peptides, and multiple proteinases, also by forming the neutrophil extracellular traps.(26) However, inappropriate or excessive activation of neutrophil can cause by-stander damage to the tissue,(27) including increased alveolar-capillary barrier permeability, lung edema, and ultimately irreversible hypoxemia. Kim Hoenderdos and colleague demonstrated that hypoxia could inhibit the apoptosis of neutrophil and augment neutrophil-mediated injury by upregulates neutrophil degranulation,(28) and this conclusion indicated that hypoxemia and the excessive neutrophil activation perpetuated a vicious cycle. It has been demonstrated that the concentration of neutrophils in the bronchoalveolar lavage fluid (BALF) of patients with ARDS correlates with the severity of disease and with poor outcome.(29) Besides, neutrophils isolated from sepsis patients with a diagnosis of ARDS were also shown to mediate profound loss of endothelial barrier integrity in vitro.(30) In addition, reduced lymphocyte count was the independent predictor of mortality in severe infectious patients.(31) In the current study, NIV failure patients presented with significant higher level of circulating neutrophil count, lower lymphocyte count and lower level of PaO_2/FiO_2, which could mean more neutrophil released from bone marrow and meanwhile more neutrophil apoptosis inhibited by worse hypoxemia in the NIV failure group. More prominent alveolar-

capillary barrier damage and lung edema mediated by neutrophil made it is hard to maintain oxygenation with NIV, and it is reasonable that patients with higher level of NLR tend to require intubation.

The other main finding of our study is that Vte (>8.96ml/kg) was independently associated with NIV failure for pneumonia-induced ARDS patients. Our conclusion was consistent with the previous study, which have showed that in ARDS patients, the expired tidal volume above 9.5mL/kg predicted body weight accurately predicts noninvasive ventilation failure.(32) During NIV, the tidal volume results from both the airway pressure delivered by the ventilator and the respiratory muscle pressure generated by the patient's respiratory drive. The reason of increased respiratory drive included hypoxia due to lung collapse and shunt, raised concentrations of CO_2 due to high dead space and elevated metabolic demand and so forth. Tonelli et al. reported that elevated inspiratory effort (defined as lack of reduction in the swing of esophageal pressure after 2 hours from start of NIV) is an accurate predictor of NIV failure among moderate-to-severe acute hypoxemic respiratory failure patients.(33) We found that NIV failure patients tended to have faster respiratory rate and lower level of $PaCO_2$, which implied these patients had higher respiratory drive than NIV success subjects did. Higher tidal volume can be a potential surrogate of the severity of the ongoing disease process. In the current study, patients with higher Vte had lower PaO_2/FiO_2 and higher inflammatory response (higher CRP and leukocyte). Moreover, a high Vte may also act as a worsening factor during NIV by inducing superimposed ventilator-induced lung injury (VILI). In invasively ventilated ARDS patients, the fundamental ventilation strategy is the small tidal volume.(34) Many previous studies has proved that lower tidal volumes can improve survival in patients with ARDS by reducing the VILI, (35-37) and high tidal volume could increase cytokine released into systemic circulation by activating inflammatory cells within the pulmonary vasculature.(38) Patients with higher Vte were prone to have more severe pneumonia and more prominent inflammation response, which would lead to NIV failure.

APACHE II scores (>16.5) was also the independent factor of NIV failure and mortality, and this conclusion was in line with the previous literatures. (39, 40) In summary, the equation based the logistic regression analysis included three independent contributor to the NIV failure. APACHE II scores could serve as the tool of overall evaluation including multiple organ function and laboratory test, and NLR was the surrogate of systematic inflammation reflected by severity of infection and neutrophil activation, and Vte could act as a marker of pulmonary local inflammation reflected by respiratory drive and lung overdistention. Because the equation consists of variables that are easily acquired at bedside, it can be used to evaluate the efficacy of NIV. Pneumonia-induced ARDS patients with a combination value of >59.17 are the candidate of NIV failure, and high-risk patients should be handled with caution and delayed intubation should be avoided.

Conclusions

This study indicated that the combination of APACHE II score, NLR and Vte may be considered as a preferable marker for predicting NIV failure among pneumonia-induced ARDS patients. We suggested that patients with higher combination value NIV support should be assessed with caution to avoid

delayed intubation. Nevertheless, further studies with a larger sample size are necessary to decide whether the combination of these three markers is able to improve NIV outcomes in pneumonia-induced ARDS patients.

Limitation

This study had certain limitations. Firstly, it is a single center study and relatively small sample size, thus our results ought to be generalized with discreetness to other clinical settings. Secondly, we did not validate our equation due to the small sample size. Thirdly, because of the retrospective nature of the study, respiratory mechanics related parameters were not available.

Abbreviations

NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; ARDS: acute respiratory distress syndrome; LOS: length of stay in hospital; APACHE II: acute physiology and chronic health evaluation II; PaO_2: arterial oxygen tension; FiO_2: fraction of inspired oxygen; $PaCO_2$: arterial carbon dioxide tension; HCO_3^-: bicarbonate; NLR: neutrophil/lymphocyte ratio; CRP: C-reactive protein; PCT: procalcitonin; BUN: blood urea nitrogen; Cr: Creatinine; BNP: brain natriuretic peptide. Vte: expired tidal volume; ROC: receiver-operating characteristic; AUC: area under the curve; CI: confidence interval.

Declarations

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the academic ethics and moral supervision committee of the Bejing Chaoyang hospital. Since the current study did not impose any diagnostic and therapeutic influence on patients, the Institutional Review Board for Beijing Chao-Yang Hospital approved the study with a waiver of informed consent.

Consent for publication

Written informed consent was obtained from all participants prior to inclusion in this study.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figures

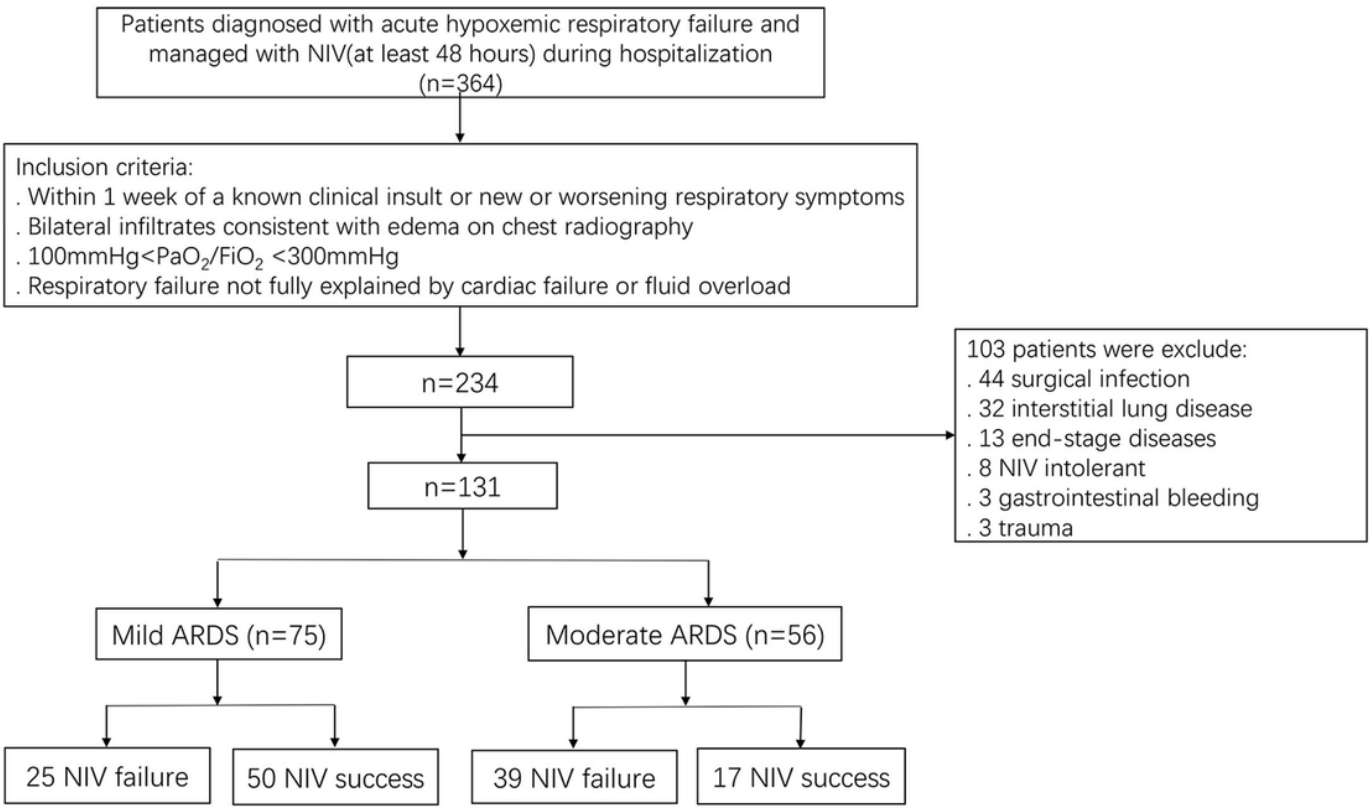

Figure 1

Patients selection chart. NIV, noninvasive ventilation. ARDS, acute respiratory distress syndrome.

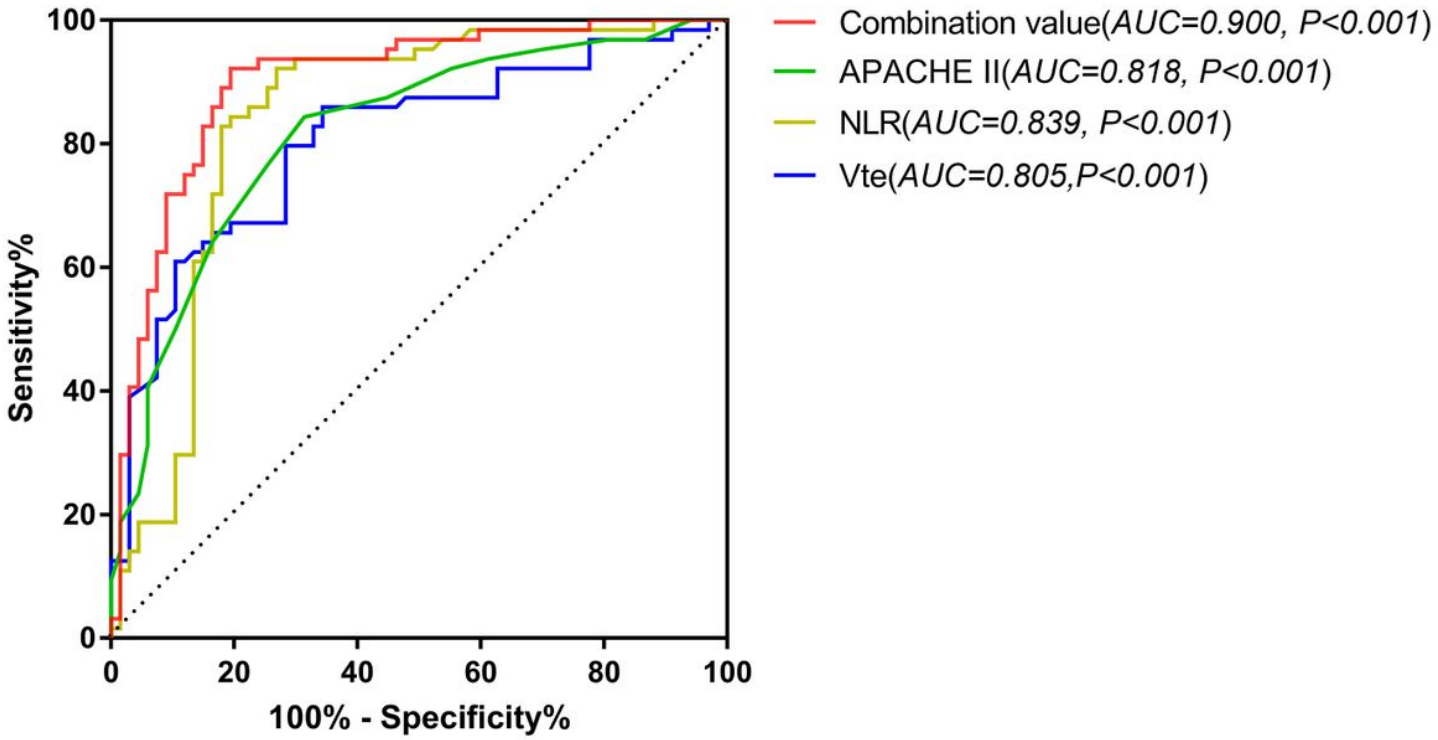

Figure 2

Receiver-operating characteristic curves for combination value, APACHE II, NLR and Vte for predicting NIV failure APACHE II, acute physiology and chronic health evaluation II; Vte, expired tidal volume; NLR, neutrophil/lymphocyte ratio.

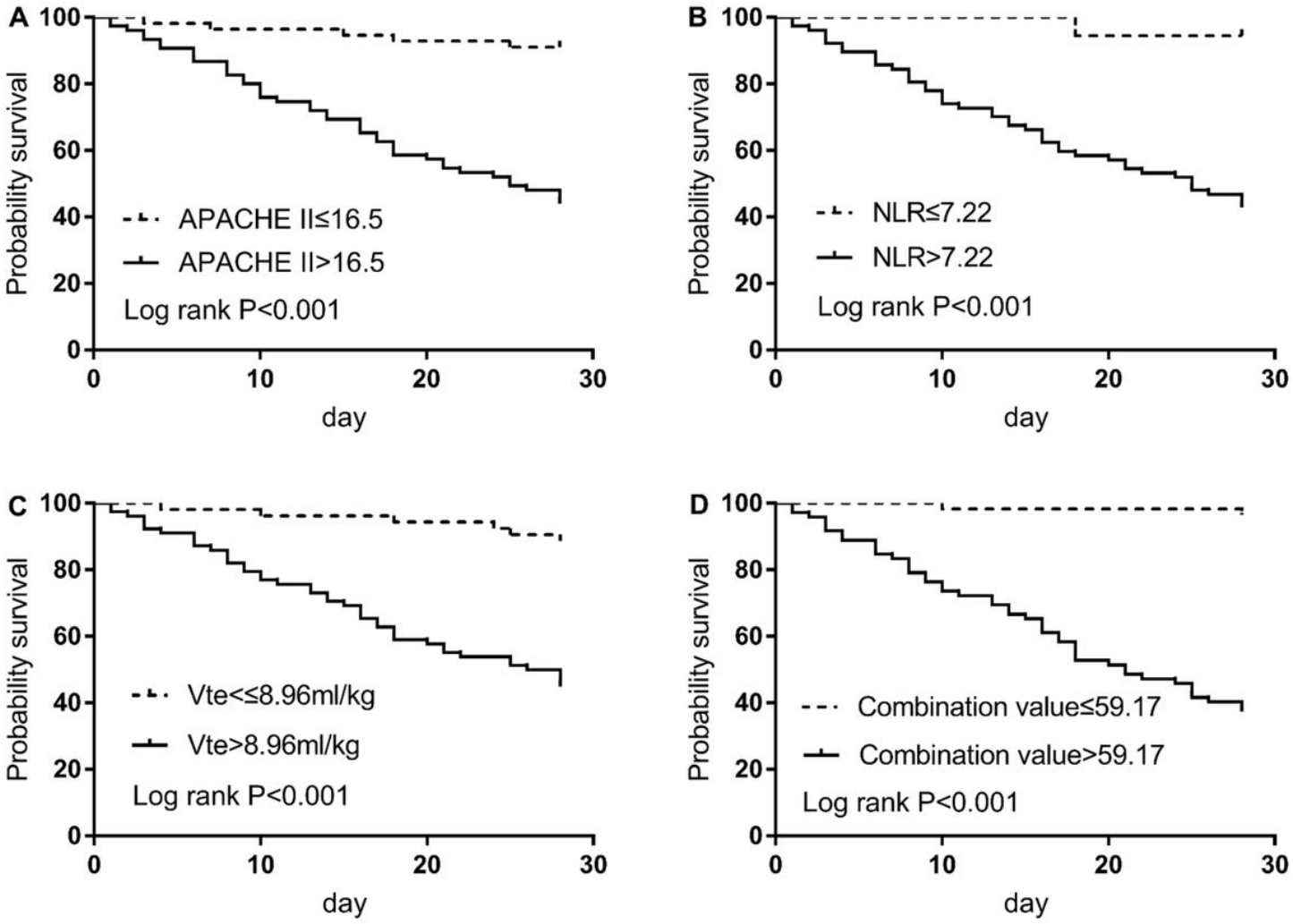

Figure 3

Kaplan-Meier curves for 28-day survival categorized by APACHE II (A), NLR (B), Vte (C), and combination value levels (D). APACHE II, acute physiology and chronic health evaluation II; NLR, neutrophil/lymphocyte ratio. Vte. expired tidal volume.