

Early identification of patients at risk for acute respiratory distress syndrome among severe pneumonia: a retrospective cohort study

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Background: Severe pneumonia is the predominant cause for acute respiratory distress syndrome (ARDS). Identification of ARDS from patients with severe pneumonia remains a significant clinical problem due to the overlap of clinical presentations and symptoms. Early recognition of risks for ARDS from severe pneumonia is of great clinical value.

Methods: From April 2014 to December 2015, patients with severe pneumonia at admission were retrieved from the hospital database, of which ARDS developed within 7 days were further identified. We compared the demographic and clinical characteristics at admission between severe pneumonia patients with and without ARDS development, followed by analysis of potential predictors for ARDS development and mortality. Multivariate logistic regression and receiver operating characteristic (ROC) curves were performed to screen independent risk factors and identify their sensitivity in predicting ARDS development and prognosis.

Results: Compared with severe pneumonia without ARDS development, patients with ARDS development had shorter disease duration before admission, higher lung injury score (LIS), serum fibrinogen (FiB), and positive end-expiratory pressure (PEEP), lower Marshall score, sequential organ failure assessment score and proportion of cardiovascular and gastrointestinal diseases, but similar mortality. Serum FiB >5.15 g/L [adjusted odds ratio (OR) 1.893, 95% confidence interval (CI): 1.141–3.142, P=0.014] and PEEP >6.5 cmH₂O (adjusted OR 1.651, 95% CI: 1.218–2.237, P=0.001) were independent predictors for ARDS development with a sensitivity of 58.3% and 87.5%, respectively, and pH <7.35 (adjusted OR 0.832, 95% CI: 0.702–0.985, P=0.033) was an independent risk factor for ARDS mortality with a sensitivity of 95.2%.

Conclusions: ARDS development risk could be early recognized by PEEP >6.5 cmH₂O and serum FiB >5.15 g/L in severe pneumonia patients, and pH <7.35 is a reliable prognostic factor in predicting ARDS mortality risk.

Keywords: Acute respiratory distress syndrome (ARDS); severe pneumonia; risk factors; fibrinogen (FiB); positive end-expiratory pressure (PEEP); pH

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Introduction

Acute respiratory distress syndrome (ARDS) is a type of acute diffuse and inflammatory lung injury with an estimated mortality of approximately 40% (1-5). It is a form of pulmonary edema without cardiogenic origin and can be induced by either pulmonary or systemic inflammatory process such as pneumonia and severe acute pancreatitis. The clinical landmarks of ARDS are severe refractory hypoxemia and acutely progressing in disease course, which usually results in difficulty and failure in the treatment of patients with ARDS status (6,7). Therefore, early recognition of patients with high risk for developing ARDS and the subsequent prevention of its progress is of great value in critical care units (8,9).

Severe pneumonia has been reported as the predominant cause in pulmonary originated ARDS, and identification and diagnosis of ARDS from patients with severe pneumonia remains a significant clinical problem due to the overlap of clinical presentations and symptoms in both diseases (10,11). Although studies have demonstrated numerous risk factors for the development of ARDS including aspiration, inappropriate mechanical ventilation (MV), extrapulmonary sepsis, polytrauma, and pancreatitis (1,12), and the prognosis of ARDS such as acute cor pulmonale, Cytomegalovirus seroprevalence, shock on hospital admission, and acute physiology, age, chronic health evaluation II (APACHE II) score (13-15), but most of these risk factors are also true in patients with severe pneumonia. Therefore, identification of risk of ARDS development in patients with severe pneumonia seems more challenging and more practical to clinicians.

Recently, an acute lung injury (ALI) prediction model, the Lung Injury Prediction Score (LIPS), was introduced and validated to discriminate patients at high risk of ALI before intensive care unit admission (8,16). It integrates the risk factors and modifiers present at the time of hospital admission with the aim of determining population at high risk before ALI onset. In spite of the potential power of early identification, the underlying diseases and causes for ALI and ARDS were diverse, and specific factors should be considered in an individual disease, therefore, integrated assessment might contribute to potential underestimation in certain disease conditions. In postoperative patients, Kim *et al.* and Chen *et al.* separately reported risk factors for ARDS development in patients underwent pneumonectomy and valvular heart surgery, and they identified that low predicted postoperative forced expiratory volume in 1 second, high

perfusion fraction of resected lung, old age, presence of liver cirrhosis, massive blood transfusion, and tricuspid valve replacement resulted in higher prevalence of ARDS (17,18). Nevertheless, relevant studies in specific patients with severe pneumonia are scarce, which intrigued and drove us investigating potential risk factors for patients with severe pneumonia progressed to ARDS.

Based on the ambiguous perceptions and heterogeneous patients investigated, we hypothesized that individual risk factors should be associated with ARDS development in patients with severe pneumonia; therefore a retrospective case-control study was conducted to further identify risk factors associated with ARDS development and prognosis in order to early recognize ARDS from severe pneumonia and determine the optimal treatment strategies.

Methods

From April 2014 to December 2015, patients were screened for eligibility once they were admitted to respiratory and infectious intensive care unit (RICU) of West China Hospital, Sichuan University. Patient information was retrieved from our previous randomized control trial (10), and the study protocol was approved by the Institutional Ethical Committee for Clinical and Biomedical Research of West China Hospital [No. ChiCTR-TRC-14004163; Universal Trial Number (UTN): U1111-1152-2390]. Written informed consent was obtained from the legal substitute decision makers or lineal consanguinity for each patient. All methods were performed in accordance with the relevant guidelines and regulations released by the Chinese National Institutes of Health and the Clinical Trial Center of West China Hospital.

Study design

Two individual steps of comparison and analysis were performed in our study, in which eligible patients were classified into severe pneumonia patients who developed ARDS and those who did not, and patients with ARDS development were further divided into survival and dead groups. In step 1, we compared the demographic, clinical and prognostic characteristics on admission between patients with and without ARDS development to screen the potential indicators for ARDS development. In step 2, we divided patients with ARDS development into survival and death to analyze the related risk factors for ARDS mortality.

Participants

Patients with severe pneumonia on admission were included in our retrospective analysis based on the consensual criteria released by Infectious Diseases Society of America and American Thoracic Society, which met either major criteria (acute respiratory failure requiring invasive MV and septic shock with need for vasopressors) or at least three minor criteria (respiratory rate ≥ 30 bpm, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ≤ 250 , blood urea nitrogen (BUN) ≥ 20 mg/dL, white blood cell count $< 0.4 \times 10^9/\text{L}$, platelet count $< 100 \times 10^9/\text{L}$, body temperature < 36 °C, multilobar infiltrates, confusion/disorientation, and hypotension requiring aggressive fluid resuscitation) (19). Severe pneumonia patients with ARDS development were defined as ARDS occurring within 7 days after admission according to the 1994 American-European Consensus Conference Definition: (I) acute onset of respiratory symptoms; (II) bilateral infiltrates in chest radiograph; (III) left atrial hypertension and cardiogenic pulmonary edema ruled out by echocardiography; (IV) severe hypoxemia with $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg (2).

We excluded patients if they had alternative pulmonary diseases regardless of the presence of pneumonia such as acute exacerbation of chronic obstructive pulmonary disease, asthma, and pulmonary thromboembolism, or underwent fatal and life-threatening comorbidities including but not limited to aggressive carcinoma with unstable clinical conditions, and cerebral injury. Patients with immunosuppressive therapy were also excluded in our study.

Treatment strategies

Pathogens identification was conducted upon the patients' admission by blood, sputum, or urine culture for bacteria and fungi, or chemiluminescence for virus specific IgM in serum, and empirical and subsequent pathogen-directed antimicrobial therapies were administered according to the consensus guidelines (19). For mechanical ventilation, "lung protective ventilation" and "open-lung approach" were performed, and we used volume-controlled mode to target the tidal volume of 6 mL/kg of predicted body weight with allowances for 4 to 8 mL/kg and the plateau airway pressures of not exceeding 30 cmH₂O. Positive end-expiratory pressure (PEEP) was adjusted by FiO_2 to meet the $\text{PaO}_2 \geq 55$ mmHg or oxygen saturation of pulse oximetry (SpO_2) $\geq 88\%$ (3,20). On the basis of analgesia by fentanyl, we sedated the patients with midazolam and/or propofol

to meet the goal of Richmond Agitation-Sedation Scale between -2 and -4 (21). Additional treatment strategies such as organ function support, circulation stabilization, nutrition and internal environment maintenance were implemented in accordance with corresponding guidelines.

Clinical and laboratory measurements and recordings

Scoring systems for disease severity

APACHEII, LIPS, lung injury score (LIS), Marshall, sequential organ failure assessment (SOFA), and gas exchange, organ failure, cause, associated disease (GOCA) scoring systems were used to assess disease severity upon patients' admission. APACHE II is a disease classification system used to stratify acutely ill patients prognostically by risk of death via 14 basic physiologic principles (22). LIPS consists of 2 major risks: (I) predisposing conditions, including shock, aspiration, sepsis, pneumonia, high-risk surgery, and high-risk trauma; (II) risk modifiers, containing alcohol abuse, body mass index (BMI) > 30 kg/m², hypoalbuminemia, chemotherapy, $\text{FiO}_2 > 35\%$, respiratory rate > 30 bpm, $\text{SpO}_2 < 95\%$, pH < 7.35 , and diabetes mellitus (8). SOFA and Marshall scores are organ failure assessment tools developed by consensus in a group of critical care physicians in 1994 and by Marshall through investigating 692 critically ill patients in 1995, respectively, both of which consist of scores from six organ systems and is graded from 0 to 4 according to the degree of dysfunction (23,24). LIS is a score for lung injury released by Murray in 1988, which classify extent of lung injury into 3 categories (25).

Clinical manifestations and laboratory measurements

At admission, all patients' clinical characteristics including disease histories and durations, symptoms and vital signs, as well as medication histories were recorded. We also recorded the details of treatment for each patient during hospitalization, such as MV settings, type and dose of analgesics and sedatives, and usage of vasopressors and muscle relaxants. Echocardiography and chest computed tomography were performed on the first day of admission, and, at the same time, we also collected the venous and arterial blood to do the blood type measurement, blood cell counting, hepatic, renal and cardiac function test, coagulation analysis, cellular and humoral immunity analysis, and blood gas analysis. For cellular and humoral immunity analysis, we measured the total T cells and their subtypes including CD4+ helper T cells and CD8+ cytotoxic T cells, and complement concentrations. Blood,

sputum, and urine samples were collected upon admission to screen the pathogen by culturing or chemiluminescence.

Statistical analysis

Data collection and statistical analysis were performed separately by two independent investigators. Continuous variables were reported as mean \pm standard deviation, while dichotomous variables were reported as frequency and proportion. We used SPSS 21.0 [Copyright (c) SPSS Inc. 1989–2007] to test the hypothesis, and statistical significance was rendered as a two-sided P value of <0.05 .

Independent-sample Student's *t*-test and Chi-square test or Fisher's exact test were conducted to compare demographic, clinical and prognostic characteristics between patients who developed ARDS and those who did not. Univariate logistic regression with unadjusted odds ratio (OR) and 95% confidence interval (CI) was performed to identify potential parameters for ARDS development and mortality. Significant predictors with $P < 0.1$ in the univariate logistic regression model were then verified by the multivariate logistic regression to filter the independent risk factors, which were further depicted in receiver operating characteristic (ROC) curves to calculate the area under the curve (AUC) for evaluation of their accuracy in discriminating ARDS from severe pneumonia and death from survival. Cutoff points were identified as Youden index (= sensitivity + specificity - 1) reached the maximum, and the respective sensitivity and specificity were also calculated. We also performed the correlation matrixes and the variance inflation factors analyses for the variables in the multivariable regression model to evaluate the potential correlations and multicollinearity among individual variables.

Results

A total of 666 patients in RICU were screened for eligibility, and eventually 157 patients with severe pneumonia were included in our final analysis, of which 43 patients developed ARDS while 114 patients did not, which resulted in a proportion of 27% of ARDS development in patients with severe pneumonia. The hospital mortality of patients with ARDS development reached 22 (51.2%); while for patients without ARDS development it was 58 (50.8%). The study flow was summarized in *Figure 1*.

Demographic, clinical and microbiological characteristics between severe pneumonia patients with and without ARDS development

APACHE II, LIPS, and LIS were calculated to be higher while Marshall, SOFA, and GOCA were lower in patients with ARDS development, but significant differences were only found in LIPS, LIS, Marshall and SOFA (*Table 1*). Patients with ARDS development had less cardiovascular (27.9% vs. 50.9%) and gastrointestinal (9.3% vs. 38.6%) diseases. However, we did not find any significant differences between the two groups in gender, age, BMI, or other comorbid diseases including diabetes, renal diseases, connective tissue diseases, dermatosis, or metabolic diseases.

Table 2 showed that, compared with patients without ARDS development, disease duration before admission was significantly shorter, proportion of lower extremities edema, PaO₂/FiO₂, BUN and myoglobin were significantly lower, while body temperature, serum fibrinogen (FiB) and C-reactive protein were significantly higher in patients with ARDS development, but we did not find significant difference in echocardiography, blood types, or cellular and humoral immunity.

A total of 12 species of bacteria, 6 species of fungi, and 13 species of viruses were detected. We did not notice any significant differences in bacteria, fungi, or virus between two groups (*Table 3*). However, we found that sputum had the highest pathogen detection rate, and bacteria were the predominant microbes in patients with severe pneumonia, of which *Acinetobacter Bauman* and *Candida* were the leading bacterium and fungus.

Treatment and outcome characteristics between severe pneumonia patients with and without ARDS development

In comparison of patients without ARDS development, patients with ARDS development used more invasive MV, higher PEEP or expiratory positive airway pressure, FiO₂ during invasive MV and non-invasive MV, and dosages of midazolam and use of muscle relaxants (*Table 4*). However, the need of antibiotics, corticosteroids, diuretics and blood transfusion were similar between the two groups.

During treatment, patients with ARDS development had significantly less delirium than patients without ARDS development, but we did not find significant difference in new-onset septic shock, duration of MV, ICU stay, or mortality (*Table 5*).

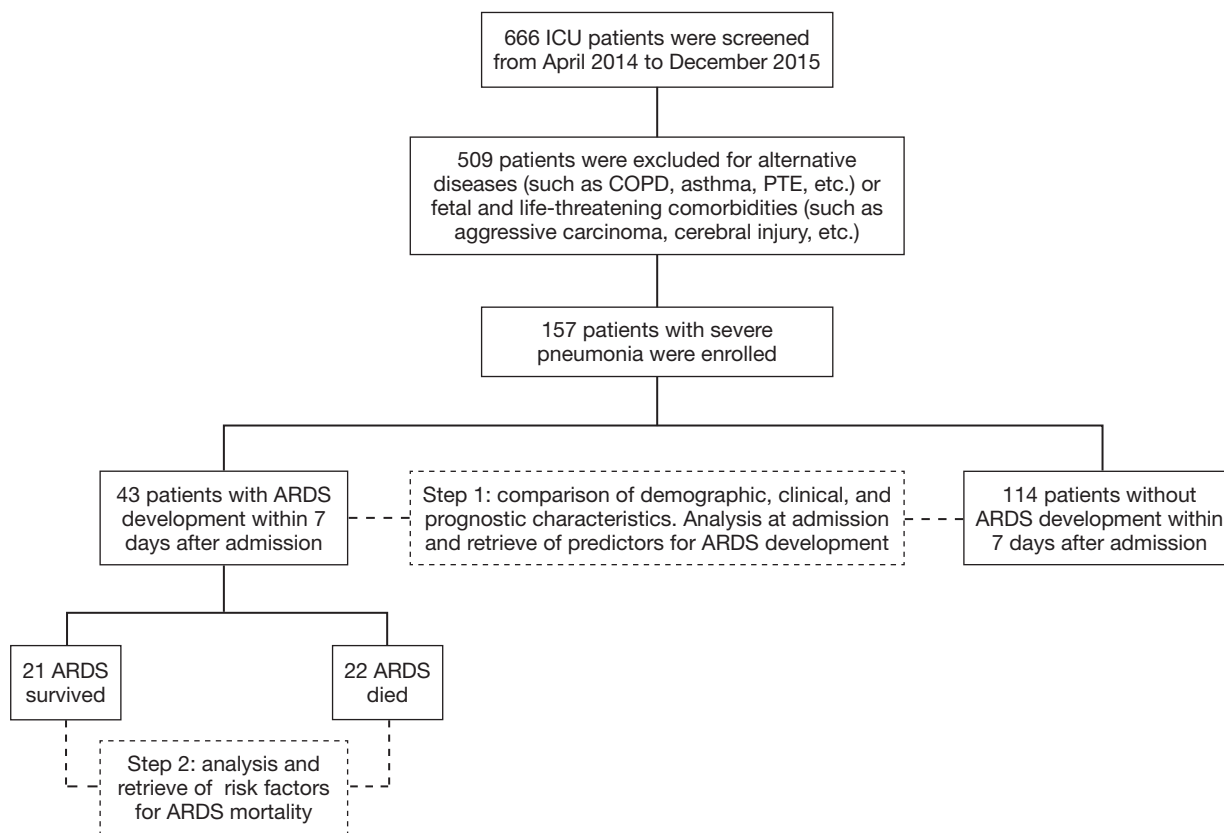


Figure 1 Study flow diagram. ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PTE, pulmonary thromboembolism.

Predictors and risk factors for ARDS development and prognosis among severe pneumonia

Tables 6,7 summarized the potential risk factors involving ARDS development and prognosis, respectively, which showed that gastrointestinal diseases, SpO₂, PaO₂/FiO₂, and BUN were inversely associated with ARDS development, while LIS score, body temperature, serum FiB, PEEP, FiO₂ during invasive MV, and use of muscle relaxants were in positive correlation with ARDS development; and BMI and pH were in negative correlation with ARDS mortality, while male patients, age, APACHE II score, and serum creatinine were positively associated with ARDS mortality. However, multivariate logistic regression revealed that serum FiB (adjusted OR 1.893, 95% CI: 1.141–3.142, P=0.014) and PEEP (adjusted OR 1.651, 95% CI: 1.218–2.237, P=0.001) were independent risk factors for ARDS development, and pH (adjusted OR 0.832, 95% CI: 0.702–0.985, P=0.033) was independent risk factor for ARDS mortality. In the correlation matrixes analysis, we found significant

correlations between gastroenteric diseases and BUN, body temperature and PaO₂/FiO₂, PaO₂/FiO₂ and BUN, PEEP and PaO₂/FiO₂, and muscle relaxants and gastroenteric diseases, PaO₂/FiO₂ and PEEP in multivariate logistic regression model for ARDS development, while for ARDS mortality, gender and creatinine, and pH and creatinine had potential correlations. (Data not shown) However the variance inflation factor analyses of both outcomes did not show significant multicollinearity (data not shown).

In discrimination of ARDS from severe pneumonia, ROC curves of serum FiB and PEEP resulted in an AUC of 0.661 (95% CI: 0.525–0.797, P=0.034) and 0.833 (95% CI: 0.733–0.934, P<0.001), respectively, and an cutoff point of 5.15 g/L for serum FiB with a sensitivity and specificity of 58.3% and 68.4% and of 6.5 cmH₂O for PEEP with a sensitivity of 87.5% and a specificity of 65.8% (Figure 2). Similarly in identification of ARDS mortality, the AUC of pH was calculated to be 0.778 (95% CI: 0.641–0.915, P=0.002) with a cutoff point of 7.35 yielding a sensitivity and specificity of 95.2% and 54.5%, respectively (Figure 3).

Table 1 Baseline characteristics between severe pneumonia patients with and without ARDS development

Parameters	SP with ARDS development (n=43)	SP without ARDS development (n=114)	P
Demographics			
Gender (male, %)	25 (58.1)	71 (62.3)	0.635
Age (years)	56.09±18.51	60.98±18.80	0.147
BMI (kg/m ²)	22.26±2.45	22.48±8.29	0.891
Smoking history (%)	10 (23.3)	45 (39.5)	0.057
Disease severity			
APACHE II	16.81±4.96	16.50±4.57	0.708
Marshall	1.49±1.61	2.27±2.33	0.044
SOFA	4.30±2.25	5.47±2.73	0.013
LIS	2.58±0.50	2.03±0.75	<0.001
LIPS	7.08±0.70	3.31±0.51	<0.001
GOCA	4.91±1.31	5.14±1.51	0.372
Comorbidities (%)			
Cardiovascular diseases	12 (27.9)	58 (50.9)	0.010
Diabetes	9 (20.9)	25 (21.9)	0.892
Renal diseases	6 (14.0)	28 (24.6)	0.150
Connective tissue diseases	3 (7.0)	16 (14.0)	0.227
Dermatosis	2 (4.7)	5 (4.4)	1.000
Gastrointestinal diseases	4 (9.3)	44 (38.6)	<0.001
Metabolic diseases	2 (4.7)	4 (3.5)	0.666

APACHE II, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; GOCA, gas exchange, organ failure, cause, associated disease; LIPS, lung injury prediction score; LIS, lung injury score; SOFA, sequential organ failure assessment; SP, severe pneumonia.

Discussion

In our study, we found that, in patients who developed ARDS within 7 days after admission, disease duration before admission was shorter, LIS score, body temperature, FiB, C-reactive protein, PEEP, expiratory positive airway pressure, FiO₂ during invasive and non-invasive MV, dosages of midazolam, proportion of invasive MV and muscle relaxants were higher, while Marshall and SOFA score, SpO₂, PaO₂/FiO₂, BUN, myoglobin, cardiovascular and gastrointestinal diseases, and lower extremities edema were lower than those in patients without ARDS development. Serum FiB and PEEP were independent risk factors for ARDS development, and pH was independent risk factor for ARDS mortality, of which FiB >5.15 g/L and PEEP >6.5 cmH₂O determined ARDS risk with a power

of 58.3% and 87.5% in sensitivity and 68.4% and 65.8% in specificity, respectively, while pH <7.35 resulted in higher risk of mortality with a sensitivity of 95.2% and specificity of 54.5%.

Severe pneumonia is a one of the major causes for ICU admission and leads to a high risk of morbidity and mortality even with potent antibiotic therapy and sufficient respiratory support (19,26-28). As described in introduction, ARDS is a severe lung injury with high mortality but lack effective treatment and severe pneumonia is the predominant cause of ARDS, therefore the treatment failure for severe pneumonia might result from ARDS development afterward. It has been reported that many treatments targeting the mechanisms identified in promising preclinical studies fail to improve patient outcomes partially due to the delayed recognition of patients at risk and the

Table 2 Clinical characteristics and laboratory analysis between severe pneumonia patients with and without ARDS development

Parameters	SP with ARDS development (n=43)	SP without ARDS development (n=114)	P
Clinical characteristics			
Disease duration (days)	7.14±4.34	12.07±9.35	0.001
Lower extremities edema (%)	9 (20.9)	47 (41.2)	0.018
Body temperature (°C)	37.48±1.01	36.90±0.84	<0.001
Respiratory rate (bpm)	25.98±8.11	24.32±6.73	0.197
Heart rate (bpm)	113.37±24.70	105.70±24.27	0.081
SBP (mmHg)	114.86±19.91	123.21±23.04	0.037
DBP (mmHg)	67.67±15.69	71.68±17.18	0.185
SpO ₂ (%)	93.95±6.97	96.30±5.11	0.022
Imaging			
Echocardiography			
Left ventricle (cm ²)	45.77±6.55	44.54±5.57	0.308
Right ventricle (cm ²)	20.13±2.89	20.30±3.17	0.805
Ejection fraction (%)	60.65±13.57	64.09±8.32	0.080
Pericardial effusion (%)	9 (22.5)	26 (26.5)	0.621
Chest CT (%)			
Pleural effusion	28 (66.7)	80 (70.2)	0.674
Laboratory analysis			
Blood types (%)			
Type A	8 (28.6)	17 (26.2)	0.809
Type B	4 (14.3)	18 (27.7)	0.163
Type AB	3 (10.7)	6 (9.2)	1.000
Type O	13 (46.4)	24 (36.9)	0.390
Arterial blood gas			
pH	7.38±0.07	7.39±0.09	0.497
PaO ₂ /FiO ₂ (mmHg)	112.10±41.41	163.07±90.14	<0.001
PaCO ₂ (mmHg)	42.87±11.08	40.98±11.91	0.368
HCO ₃ ⁻ (mmol/L)	24.73±5.07	23.84±5.12	0.358
Blood cell analysis			
Hemoglobin (g/L)	106.33±22.08	100.97±24.47	0.212
Hematocrit (%)	32.70±6.19	34.01±32.30	0.792
Platelet (10 ⁹ /L)	182.79±96.39	160.10±88.70	0.165
WBC (10 ⁹ /L)	12.66±6.08	13.37±8.34	0.610
Neutrophils (%)	87.98±12.53	88.72±7.56	0.655

Table 2 (continued)

Table 2 (continued)

Parameters	SP with ARDS development (n=43)	SP without ARDS development (n=114)	P
Biochemical analysis			
TB (μmol/L)	11.27±6.15	12.78±12.62	0.453
ALT (IU/L)	33.35±32.92	75.83±198.65	0.186
AST (IU/L)	53.51±35.95	147.06±581.31	0.294
ALP (IU/L)	93.65±45.80	116.14±90.71	0.123
GGT (IU/L)	62.26±52.66	101.04±234.64	0.285
Albumin (g/L)	27.61±4.88	28.03±4.93	0.627
BUN (mmol/L)	8.81±5.52	12.00±7.92	0.016
Creatinine (μmol/L)	84.84±51.73	119.20±118.81	0.069
Glucose (mmol/L)	9.41±5.52	8.98±3.62	0.570
LDH (IU/L)	475.40±248.66	585.28±1,171.80	0.544
Coagulation analysis			
PT (s)	13.66±2.68	14.54±3.60	0.155
INR	1.21±0.23	1.27±0.31	0.308
APTT (s)	40.44±25.06	39.34±20.74	0.783
FiB (g/L)	5.15±2.15	4.20±1.95	0.010
D-dimer (mg/L FEU)	231.31±1,407.25	8.30±8.40	0.094
Myocardial biomarkers			
Myoglobin (ng/mL)	139.21±221.74	383.27±704.43	0.029
Troponin (ng/L)	62.95±112.62	261.17±1,318.12	0.333
BNP (ng/mL)	3,124.86±5,813.54	5,085.94±8,506.06	0.172
Inflammatory biomarkers			
Procalcitonin (ng/mL)	2.98±5.06	7.39±18.35	0.136
CRP (ng/L)	184.31±126.83	129.31±112.81	0.030
Interleukin-6 (ng/mL)	905.87±1,368.17	452.33±1,086.52	0.076
Cellular immunity (%)			
CD3 cell	60.52±13.94	56.37±16.64	0.215
CD4 cell	27.63±13.65	28.42±13.59	0.782
CD8 cell	29.49±14.92	24.82±15.59	0.150
Humoral immunity (g/L)			
Complement 3	0.8474±0.2410	0.7647±0.2569	0.126
Complement 4	0.2198±0.0755	0.1988±0.0781	0.205

ARDS, acute respiratory distress syndrome; CT, computed tomography; DBP, diastolic blood pressure; HCO₃⁻, bicarbonate ion; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂/FiO₂, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SBP, systolic blood pressure; SP, severe pneumonia; SpO₂, oxygen saturation of pulse oximetry; WBC, white blood cell count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; FiB, fibrinogen; GGT, gamma-glutamyltranspeptidase; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; SP, severe pneumonia; TB, total bilirubin.

Table 3 Microbiological analysis between severe pneumonia patients with and without ARDS development

Parameters	SP with ARDS development (n=43) [n (%)]	SP without ARDS development (n=114) [n (%)]	P
Sputum culture			
Bacteria			
Acinetobacter bauman	24 (60.0)	62 (56.4)	0.690
Pseudomonas aeruginosa	5 (12.5)	19 (17.3)	0.481
Klebsiella pneumoniae	2 (5.0)	9 (8.2)	0.728
Burkholderia cepacia	2 (5.0)	7 (6.4)	1.000
Stenotrophomonas maltophilia	4 (10.0)	6 (5.5)	0.458
Enterobacter cloacae	3 (7.5)	5 (4.5)	0.440
Serratia marcescens	2 (5.0)	2 (1.8)	0.289
Escherichia coli	0 (0.0)	4 (3.6)	0.574
Haemophilus influenzae	0 (0.0)	2 (1.8)	1.000
Bacillus mirabilis	0 (0.0)	2 (1.8)	1.000
Staphylococcus aureus	0 (0.0)	5 (4.5)	0.325
Fungi			
Candida albicans	8 (25.0)	33 (38.4)	0.175
Oidium tropioale	1 (3.1)	9 (10.5)	0.283
Candida glabrata	1 (3.1)	4 (4.7)	1.000
Candida krusei	0 (0.0)	3 (3.5)	0.562
Candida parapsilosis	0 (0.0)	1 (1.2)	1.000
Aspergillus fumigatus	2 (4.9)	3 (2.7)	0.613
Blood culture			
Bacteria			
Staphylococcus aureus	0 (0.0)	0 (0.0)	–
Acinetobacter bauman	3 (8.3)	11 (12.5)	0.756
Escherichia coli	0 (0.0)	1 (1.1)	1.000
Burkholderia cepacia	0 (0.0)	1 (1.1)	1.000
Enterococcus faecium	0 (0.0)	1 (1.1)	1.000
Pseudomonas aeruginosa	0 (0.0)	1 (1.1)	1.000
Urine culture			
Bacteria			
Escherichia coli	1 (10.0)	2 (4.9)	0.488
Klebsiella pneumoniae	1 (10.0)	2 (4.9)	0.488
Acinetobacter bauman	0 (0.0)	3 (7.3)	1.000
Enterococcus faecium	0 (0.0)	3 (7.3)	1.000

Table 3 (continued)

Table 3 (continued)

Parameters	SP with ARDS development (n=43) [n (%)]	SP without ARDS development (n=114) [n (%)]	P
Fungi			
Oidium tropioale	0 (0.0)	1 (2.6)	1.000
Candida glabrata	1 (11.1)	2 (5.1)	0.472
Candida albicans	0 (0.0)	7 (17.9)	0.320
Serum viral IgM			
Herpes simplex virus	6 (17.1)	12 (15.2)	0.792
Cytomegalovirus	1 (2.9)	2 (2.5)	1.000
Epstein-Barr virus	3 (16.7)	7 (10.8)	0.446

ARDS, acute respiratory distress syndrome; SP, severe pneumonia.

subsequent development of the full-blown syndrome (8), thus early identification of patients at high risk of ARDS development from those with severe pneumonia could potentially help for early intervention and prevent severe pneumonia patients from developing fatal ARDS because these two conditions require different treatment. For high risk of ARDS, preventive strategies may be required such as protective MV optimization (low tidal volume, high PEEP), restrictive transfusion, sepsis management, as well as conservative fluid strategy (29). Furthermore, some novel treatments are now under investigations but they are all based on early recognition of ARDS, such as prehospital use of inhaled steroids, aspirin, or heparin (30-32). Our study about the risk factors for ARDS development in severe pneumonia further enriches and highlights the limited knowledge in such an area and is of clinical importance and practice.

Scoring systems are reliable and convenient tools for clinicians to evaluate disease severity in critically ill patients, of which APACHE II, Marshall, SOFA, and LIS are the most commonly used scores, and we also included LIPS as a novel lung injury prediction system. Our study demonstrated that Marshall and SOFA were significantly lower while LIPS and LIS were dramatically higher in patients with ARDS development than that in patients without ARDS development, but no significant difference was found in APACHE II or GOCA between the two groups. Based on the significant difference in LIPS score between patients with and without ARDS development, we are confident to conclude that the classification of patients and the results in our study are convincing. Inconsistent results in these scoring systems may be attributable to

the differences in evaluation of organ systems in each score system. In LIS score, degree of hypoxemia, lung compliance, PEEP and infiltrates in chest X-ray were assessed, while degree of hypoxemia, platelet count, bilirubin, hypotension and creatinine were appraised in Marshall and SOFA score. In our study, we also notified that, in patients with ARDS development, $\text{PaO}_2/\text{FiO}_2$ was lower and PEEP was higher, which mainly resulted in higher LIS score in patients with ARDS development. At the meantime, the comorbid cardiovascular and gastrointestinal diseases, in which hypotension due to coronary artery disease and hyperbilirubinemia induced by hepatic dysfunction accounted for majority, were lower in patients who developed ARDS, which might offset the effect of lower $\text{PaO}_2/\text{FiO}_2$ in Marshall and SOFA score. Therefore, APACHE II is more likely to be rendered as a comprehensive assessment tool, while LIS, Marshall and SOFA should be used in priority under certain clinical conditions.

Refractory hypoxemia and decreased lung compliance, resulted from increased permeability in pulmonary vascular as well as increased alveoli trapping and loss of aerated tissue, are clinical hallmarks for ARDS (1). MV is a validated treatment strategy for ARDS, in which low tidal volume of 4 to 6 mL/kg combined with high PEEP and FiO_2 were termed as “lung protective ventilation” and “open lung approach” and were demonstrated to be effective and safe in improving oxygenation without inducing barotrauma (20,33). In our study, PEEP and FiO_2 in patients with ARDS development was significantly higher than those in patients without ARDS development, which was in accordance with the pathophysiological

Table 4 Treatment strategies between severe pneumonia patients with and without ARDS development

Parameters	SP with ARDS development (n=43)	SP without ARDS development (n=114)	P
MV (%)	43 (100.0)	106 (93.0)	0.108
Invasive MV (%)	39 (90.7)	86 (75.4)	0.034
Frequency (bpm)	15.13±3.76	13.92±3.06	0.060
Tidal volume (mL)	467.40±60.09	454.00±69.50	0.394
Inspiratory pressure (cmH ₂ O)	17.00±4.28	15.47±3.40	0.293
PEEP (cmH ₂ O)	9.18±2.99	6.86±3.40	<0.001
FiO ₂ (%)	81.28±19.53	71.51±23.24	0.024
Non-invasive MV (%)	4 (9.3)	20 (17.5)	0.201
IPAP (cmH ₂ O)	13.00±1.16	12.20±2.51	0.543
EPAP (cmH ₂ O)	6.50±1.29	5.00±1.03	0.018
FiO ₂ (%)	75.00±20.82	53.00±16.89	0.031
Analgesics and sedatives (mg/d)			
Midazolam	61.77±49.26	43.19±51.21	0.044
Propofol	460.74±424.05	309.50±448.94	0.060
Fentanyl	0.83±0.48	0.66±0.51	0.057
Vasopressors (%)	29 (67.4)	64 (56.1)	0.199
Muscle relaxants (%)	10 (23.3)	6 (5.3)	0.002
Antibiotics			
No. of antibacterial agents	3.49±2.26	3.97±5.97	0.605
No. of antifungal agents	0.56±0.50	0.61±0.69	0.682
No. of antiviral agents	0.16±0.53	0.11±0.35	0.502
Venous corticosteroids (%)	30 (69.8)	72 (63.2)	0.439
Venous diuretics (%)	36 (83.7)	101 (88.6)	0.414
Insulin (%)	19 (44.2)	47 (41.2)	0.738
Blood products (%)			
Albumin	38 (88.4)	97 (85.1)	0.597
RBC	11 (25.6)	37 (32.5)	0.404
Platelet	1 (2.3)	12 (10.5)	0.116
Plasma	7 (16.3)	26 (22.8)	0.371
Cryoprecipitate	1 (2.3)	2 (1.8)	1.000

ARDS, acute respiratory distress syndrome; EPAP, expiratory positive airway pressure; FiO₂, fraction of inspired oxygen; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; RBC, red blood cell; SP, severe pneumonia.

characteristics of ARDS. However, the level of PEEP in patients who developed ARDS in our study was comparatively lower than that reported by Meade (9.18±2.99 vs. 14.6±3.4 cmH₂O) but similar with that reported in our

previous study (9.18±2.99 vs. 10.3±3.2 cmH₂O) (3,10), and the inconsistency may be due to body weight and height as well as races differed in the included patients because higher PEEP may be required in patients with lower

Table 5 Outcomes measures between severe pneumonia patients with and without ARDS development

Parameters	SP with ARDS development (n=43)	SP without ARDS development (n=114)	P
Delirium (%)	2 (4.7)	20 (17.5)	0.038
New-onset septic shock (%)	9 (20.9)	24 (21.1)	0.987
Duration of MV (days)	13.23±12.88	13.89±13.85	0.786
Invasive MV (days)	12.28±12.99	11.55±14.06	0.769
Duration of ICU stay (days)	15.09±13.66	16.29±14.75	0.645
Duration of hospital stay (days)	21.95±16.96	26.82±20.47	0.167
Mortality (%)	22 (51.2)	58 (50.9)	0.975
ICU mortality	12 (27.9)	29 (25.4)	0.754
Out of ICU mortality	10 (23.3)	29 (25.4)	0.778
Cause of death			
Respiratory failure	14 (63.6)	22 (37.9)	0.039
MODS	2 (9.1)	28 (48.3)	0.001
DIC	3 (13.6)	4 (6.9)	0.386
Septic shock	3 (13.6)	4 (6.9)	0.386

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; ICU, intensive care unit; MODS, multiple organ dysfunction syndrome; MV, mechanical ventilation; SP, severe pneumonia.

chest wall compliance induced by overweight. In addition, we also found that, compared with patients without ARDS development, the need of invasive MV, sedatives and muscle relaxants was significantly higher in patients with ARDS development, which further demonstrated the treatment difficulty in ARDS and the urgency and essentiality of early recognition of ARDS.

Since its first report in 1967, ARDS has been defined all the way as an acute onset of bilateral pulmonary infiltration, which induces severe oxygenation dysfunction (2,34). Moreover, recent Berlin definition further limited the timing of ARDS to be less than a week (1). Pneumonia is a form of lung infection, which results in patches in chest imaging (35,36). A wide variety of pathogenic microbes may cause pneumonia, thus the disease duration of pneumonia is solely determined by the pathogen's biological properties. In our study, we found shorter disease duration before admission in patients with ARDS development, which further highlighted the importance of timing for ARDS diagnosis as well as its difference from severe pneumonia. However, to our knowledge, most studies predicting ARDS and investigating prognostic risk factors did not take the timing into consideration, which may lead to heterogeneity in patients as well as inaccuracy in results. Therefore,

abiding by the timing defined by Berlin definition, we retrieved and validated potential risk factors to early identify ARDS from patients with severe pneumonia.

In our univariate logistic regression, LIS score, gastrointestinal diseases, muscle relaxants, body temperature, PaO₂/FiO₂, BUN, level of serum FiB, and PEEP were further identified to be associated with ARDS development in addition to SpO₂ and FiO₂ reported in LIPS, but only serum FiB and PEEP were shown to be independently associated with ARDS onset in patients with severe pneumonia in multivariate logistic regression. Moreover, ROC curve demonstrated the high reliability of PEEP in a cutoff point of 6.5 cmH₂O, and the relatively low reliability of serum FiB in a cutoff point of 5.15 g/L. In the Berlin definition, a minimum level of PEEP (5 cmH₂O) was included in the diagnosis of ARDS with consideration of influences in PaO₂/FiO₂. However, that minimum PEEP of 5 cmH₂O was resulted from a consensus of professionals and other requirement of a minimum PEEP levels were not evaluated as they were selected by the panel using face validity criteria to ensure compatibility with prior definitions (1). Therefore, a minimum PEEP of 5 cmH₂O was not suitable for any clinical conditions and different minimum levels of PEEP may be demanded in certain disease

Table 6 Univariate and multivariate logistic regression analysis of risk factors for ARDS development in severe pneumonia

Characteristics	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	P	OR (95% CI)	P
Disease severity				
Marshall	0.877 (0.693–1.108)	0.271	–	–
SOFA	0.873 (0.723–1.054)	0.157	–	–
LIS	3.278 (1.501–7.156)	0.003	–	–
Comorbidities (%)				
Cardiovascular diseases	0.565 (0.213–1.502)	0.253	–	–
Gastrointestinal diseases	0.181 (0.048–0.684)	0.012	0.095 (0.007–1.349)	0.082
Clinical characteristics				
Disease duration (days)	0.901 (0.722–1.126)	0.359	–	–
Lower extremities edema (%)	0.451 (0.154–1.320)	0.146	–	–
Body temperature (°C)	1.906 (1.157–3.142)	0.011	1.607 (0.755–3.421)	0.219
SpO ₂ (%)	0.888 (0.803–0.981)	0.020	–	–
Laboratory analysis				
PaO ₂ /FiO ₂ (mmHg)	0.991 (0.983–0.999)	0.023	1.000 (0.985–1.014)	0.949
BUN (mmol/L)	0.914 (0.836–0.998)	0.046	0.930 (0.797–1.085)	0.356
FiB (g/L)	1.357 (1.042–1.769)	0.024	1.893 (1.141–3.142)	0.014
Myoglobin (ng/mL)	0.997 (0.994–1.001)	0.101	–	–
CRP (ng/L)	1.002 (0.998–1.006)	0.317	–	–
Treatment strategies				
Invasive MV (%)	2.316 (0.585–9.160)	0.231	–	–
PEEP (cmH ₂ O)	1.461 (1.176–1.816)	0.001	1.651 (1.218–2.237)	0.001
FiO ₂ (invasive, %)	1.030 (1.005–1.056)	0.020	–	–
EPAP (cmH ₂ O)	3.889 (0.574–26.361)	0.164	–	–
Midazolam (mg/d)	1.006 (0.997–1.016)	0.200	–	–
Muscle relaxants (%)	6.714 (1.250–36.061)	0.026	0.483 (0.046–5.104)	0.483
Outcomes				
Delirium (%)	0.410 (0.081–2.087)	0.283	–	–

ARDS, acute respiratory distress syndrome; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; EPAP, expiratory positive airway pressure; FiB, fibrinogen; FiO₂, fraction of inspired oxygen; LIS, lung injury score; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; OR, odds ratio; PaO₂/FiO₂, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; SOFA, sequential organ failure assessment; SpO₂, oxygen saturation of pulse oximetry.

circumstances, just as a higher PEEP of 6.5 cmH₂O reported in our study. As for the discrimination capacity of serum level of FiB, several studies have demonstrated that coagulation and fibrinolytic pathways play an active role in modulating systemic inflammatory processes in patients with severe sepsis and the

severity of abnormalities in these pathways correlates with clinical outcomes, of which plasminogen activator inhibitor-1, impairing fibrinolysis by the inhibition of tissue plasminogen activator and urokinase and resulting in accumulation of FiB, was found to be an independent risk factor for mortality in

Table 7 Univariate and multivariate logistic regression analysis of risk factors for ARDS mortality in severe pneumonia

Characteristics	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	P	OR (95% CI)	P
Demographics				
Gender (male, %)	5.525 (1.461–20.898)	0.012	7.600 (0.738–78.24)	0.088
Age (years)	1.041 (1.002–1.080)	0.037	1.021 (0.958–1.089)	0.517
BMI (kg/m ²)	0.654 (0.433–0.988)	0.044	0.611 (0.371–1.007)	0.611
Disease severity				
APACHE II	1.169 (1.013–1.350)	0.033	–	–
Laboratory analysis				
pH (per 0.01 point)	0.823 (0.720–0.940)	0.004	0.832 (0.702–0.985)	0.033
Hemoglobin (g/L)	1.032 (0.999–1.065)	0.056	–	–
BUN (mmol/L)	1.155 (0.998–1.336)	0.053	–	–
Creatinine (μmol/L)	1.023 (1.002–1.045)	0.031	1.011 (0.982–1.041)	0.451
INR	211.450 (0.825–54,184.171)	0.058	–	–
Myoglobin (ng/mL)	1.006 (0.999–1.014)	0.104	–	–

APACHE II, acute physiology, age, chronic health evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; INR, international normalized ratio; OR, odds ratio.

patients with ARDS (37-39).

A large number of prognostic factors have been verified in previous studies, including factors in clinical characteristics, physiological parameters, genetic polymorphisms, biomarkers and scoring systems (15). In our study, we found that higher mortality in patients with ARDS was associated with older age, higher APACHE II score, creatinine level and use of vasopressors and new-onset septic shock, but lower BMI and pH, which were in accordance with the recent findings (40,41). However, multivariate logistic regression analysis showed that all these parameters were confounding factors except for pH, which had a high sensitivity of 95.2% in a cutoff point of 7.35. The value of pH in our study was higher than that reported in the studies by Brun-Buisson and Villar (7.35 *vs.* 7.30), and the difference may due to the inconsistency in patients selection (42,43). Controversies lies in the association between PaO₂/FiO₂ at the onset of ARDS and the adverse outcomes in ARDS (42-45), but our study revealed that initial PaO₂/FiO₂ is not an independent predictor of mortality, which we suspected was attributed to the insignificant difference in PEEP because PaO₂/FiO₂ has been reported to vary depending on ventilator strategy and is sensitive to ventilator settings (46), and early change of PaO₂/FiO₂ being too likely to be

associated with outcomes in ARDS (10,47).

Limitations for our study included: Firstly, relatively small sample size, which may lead to insignificant differences of some potential predictors in statistical analysis; Secondly, inadequate parameters recorded such as but not limited to alcohol abuse condition, respiratory mechanisms including inspiratory plateau pressure and lung compliance, early alteration of PaO₂/FiO₂, as well as some candidate genes; Thirdly, FiO₂ was excluded in our study due to the correlation with PaO₂/FiO₂, which might omit this potential risk factor for ARDS because PaO₂/FiO₂ depended on FiO₂ and FiO₂ changes would change the disease classification (48); Finally, the potential overlap and correlation between individual risk factors, such as gastroenteric diseases and urea nitrogen level, body temperature and PaO₂/FiO₂, and PaO₂/FiO₂ and PEEP in the correlation matrix analysis (data not shown), may offset and cover the role of some risk factors in the multivariate logistic regression.

Conclusions

Patients with ARDS development have different clinical characteristics and need distinct treatment strategies

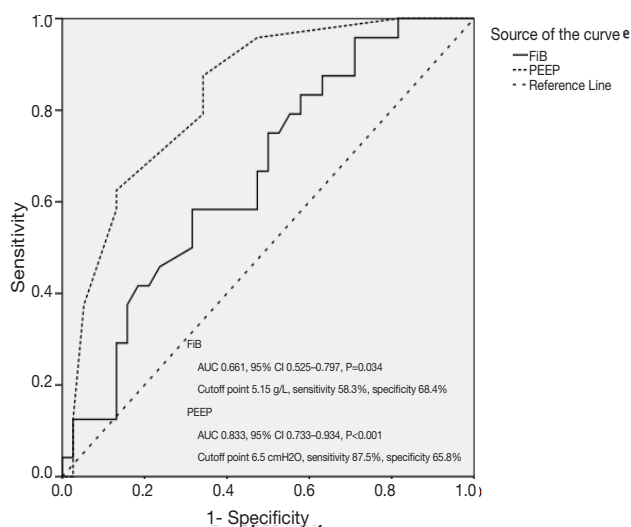


Figure 2 ROC curves of FiB and PEEP in identifying risks for ARDS development in severe pneumonia. ROC curves show accuracy and power of FiB and PEEP in distinguishing patients at risk of ARDS from patients with severe pneumonia. The solid line represented FiB, while the dotted line represented PEEP. The AUC of FiB and PEEP was 0.661 (95% CI: 0.525–0.797, P=0.034) and 0.833 (95% CI: 0.733–0.934, P<0.001), and the cutoff point was calculated to be 5.15 g/L and 6.5 cmH₂O with a sensitivity of 58.3% and 87.5% and a specificity of 68.4% and 65.8%, respectively. ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; FiB, fibrinogen; PEEP, positive end-expiratory pressure; ROC, receiver operating characteristic.

compared to patients with severe pneumonia. A minimum of PEEP >6.5 cmH₂O and level of serum FiB >5.15 g/L could sensitively distinguish patients at high risk of ARDS from severe pneumonia, and pH <7.35 is a reliable prognostic factor in predicting risk of mortality in patients with ARDS. More future studies are warranted to further validate and explore potential predictors and possible mechanisms to improve treatment efficacy and create novel treatment strategies for patients with ARDS.

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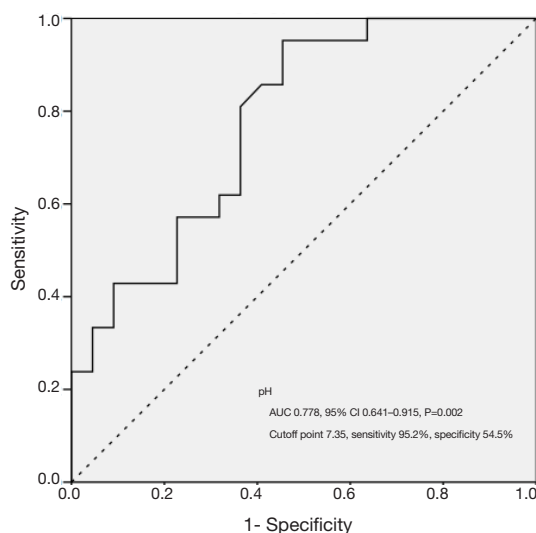


Figure 3 ROC curve of pH in identifying risks for ARDS mortality in severe pneumonia. ROC curve presents accuracy and power of pH in predicting risk of mortality for patients with ARDS. The solid line represented pH, and the AUC was 0.778 (95% CI: 0.641–0.915, P=0.002) with a sensitivity of 95.2% and a specificity of 54.5% at a cutoff point of 7.35. ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

Footnote

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

Ethical Statement: The study protocol was approved by the Institutional Ethical Committee for Clinical and Biomedical Research of West China Hospital (No. ChiCTR-TRC-14004163; Universal Trial Number (UTN): U1111-1152-2390) and written informed consent was obtained from all patients.

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