

A modified acute respiratory distress syndrome prediction score: a multicenter cohort study in China

Jianfeng Xie¹, Ling Liu¹, Yi Yang¹, Wenkui Yu², Maoqin Li³, Kaijiang Yu^{4,5}, Ruiqiang Zheng⁶, Jie Yan⁷, Xue Wang⁸, Guolong Cai⁹, Jianguo Li¹⁰, Qin Gu¹¹, Hongsheng Zhao¹², Xinwei Mu¹³, Xiaochun Ma¹⁴, Haibo Qiu¹

¹Department of Critical Care Medicine, Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, China; ²Department of Critical Care Medicine, Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, China; ³Department of Critical Care Medicine, Xuzhou Central Hospital, Xuzhou 221009, China; ⁴Department of Critical Care Medicine, Harbin Medical University Cancer Hospital, Harbin Medical University, Harbin 150040, China; ⁵Department of Critical Care Medicine, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, China; ⁶Department of Critical Care Medicine, Subei People's Hospital, School of Medicine, Yangzhou University, Yangzhou 225001, China; ⁷Department of Critical Care Medicine, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi 214002, China; ⁸Department of Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China; ⁹Department of Critical Care Medicine, Zhejiang Hospital, Hangzhou 310013, China; ¹⁰Department of Critical Care Medicine, Zhongnan Hospital, Wuhan University, 430071, Wuhan, China; ¹¹Department of Critical Care Medicine, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, China; ¹²Department of Critical Care Medicine, The First Affiliated Hospital of Nantong University, Nantong 226001, China; ¹³Department of Critical Care Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, China; ¹⁴Department of Critical Care Medicine, The First Hospital of China Medical University, Shenyang 110001, China

Contributions: (I) Conception and design: J Xie, L Liu, Y Yang, KYu, J Li, X Ma, H Qiu; (II) Administrative support: H Qiu; (III) Provision of study materials or patients: J Xie, W Yu, M Li, K Yu, R Zheng, J Yan, X Wang, G Cai, J Li, Q Gu, H Zhao, X Mu, X Ma; (IV) Collection and assembly of data: J Xie, W Yu, M Li, K Yu, R Zheng, J Yan, X Wang, G Cai, J Li, Q Gu, H Zhao, X Mu, X Ma; (V) Data analysis and interpretation: J Xie, L Liu, Y Yang, H Qiu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Haibo Qiu, MD, PhD. Department of Critical Care Medicine, Nanjing Zhongda Hospital, School of Medicine, Southeast University, Nanjing 210009, China. Email: haiboq2000@163.com.

Background: Early recognition of the risks of acute respiratory distress syndrome (ARDS) and prevention of the development of ARDS may be more effective in improving patient outcomes. We performed the present study to determine the ARDS risk factors in a Chinese population and validate a score to predict the development of ARDS.

Methods: This was an observational multicenter cohort study performed in 13 tertiary hospitals in China. Patients admitted into participating intensive care units (ICUs) from January 1 to January 31, 2012, and from January 1 to January 10, 2013, were enrolled in a retrospective derivation cohort and a prospective validation cohort, respectively. In the derivation cohort, the potential risk factors of ARDS were collected. The confirmed risk factors were determined with univariate and multivariate logistic regression analyses, and then the modified ARDS prediction score (MAPS) was established. We prospectively enrolled patients to verify the accuracy of MAPS.

Results: A total of 479 and 198 patients were enrolled into the retrospective derivation cohort and the prospective validation cohort, respectively. A total of 93 (19.4%) patients developed ARDS in the derivation cohort. Acute pancreatitis, pneumonia, hypoalbuminemia, acidosis, and high respiratory rate were the risk factors for ARDS. The MAPS discriminated patients who developed ARDS from those who did not, with an area under the curve (AUC) of 0.809 [95% confidence interval (CI), 0.758–0.859, $P < 0.001$]. In the prospective validation cohort, performance of the MAPS was similar to the retrospective derivation cohort, with an AUC of 0.792 (95% CI, 0.717–0.867, $P < 0.001$). The lung injury prediction score (LIPS) showed a predicted value of an AUC of 0.770 (95% CI, 0.728–0.812, $P < 0.001$) in our patients, which was significantly lower than our score ($P < 0.046$).

Conclusions: The MAPS based on risk factors could help the clinician to predict patients who will develop ARDS.

Trial registration: ClinicalTrials.gov NCT01666834

Keywords: Acute respiratory distress syndrome (ARDS); adult; prediction score; prevention

Submitted Apr 16, 2018. Accepted for publication Sep 06, 2018.

doi: 10.21037/jtd.2018.09.117

View this article at: <http://dx.doi.org/10.21037/jtd.2018.09.117>

Introduction

Acute respiratory distress syndrome (ARDS) is associated with significant morbidity and mortality in patients in intensive care units (ICUs) (1). Since the initial description of ARDS in 1967 (2), a great progress has been made in understanding the pathophysiology of ARDS and advanced treatments for ARDS, such as low tidal volume ventilation (3), higher positive end-expiratory pressure (PEEP) (4), prone position ventilation (5), and early neuromuscular blockade in severe ARDS cases (6). However, the mortality of ARDS patients did not show a significant reduction over time, with a mortality of 40% reported in recent studies (1,7-9).

More recently, the focus has shifted from the treatment of ARDS to early identification and prevention of ARDS (10,11). Thus, it is important to recognize the ARDS risk factors early and eventually prevent its development. Some studies have shown that certain interventions could reduce the incidence of ARDS (12-14). However, the patients enrolled in these trials had various risk factors, which made it difficult to predict ARDS in clinical practice. Therefore, a prediction system for ARDS is needed to anticipate which patients are likely to develop ARDS.

A lung injury prediction score (LIPS) was identified by Trillo-Alvarez and his colleagues to recognize ARDS early (15). Later, they validated and refined the LIPS model through a multicenter cohort study (16). LIPS produced a high predicted value of 0.8 in alerting clinicians about the risk of ARDS (16). However, this study was focused on emergency department (ED) patients, and the risk factors for ARDS may vary in different patient populations. In addition, there are more than 20 variables in LIPS, which may make LIPS complicated to use in a clinical setting. Therefore, we performed a study to establish a modified ARDS prediction score (MAPS) to help clinicians in the early recognition of ARDS in patients who need to be admitted to the ICU.

Methods

Study design

This observational multicenter cohort study was performed in 13 tertiary hospitals in China. The protocol of this study was approved by the Institutional Ethics Committee of Zhongda Hospital (Approval Number 2012ZDIIKY09.0) and registered on clinicaltrials.gov (Registration No. NCT01666834). All patients, or their next of kin, provided consent for the use of their medical records for this study.

There were retrospective derivation cohort patients and prospective validation cohort patients enrolled in our study. We collected the potential risk factors of ARDS in the retrospective cohort. Patients who developed ARDS in the first three days after ICU admission were placed into the ARDS group. After comparing the ARDS patients with the non-ARDS patients, we observed the risk factors of ARDS and built the MAPS. Finally, we prospectively enrolled patients to verify the accuracy of the MAPS.

Study patients

Critically ill patients who were admitted to a participating ICU from January 1 to January 31, 2012, were included in the retrospective derivation cohort and used to set up the prediction model of ARDS. Exclusion criteria for this cohort of patients included the following: patients with chronic respiratory failure, patients with an age of less than 18 years old, patients who were pregnant, patients who had died within 24 hours from ICU admission, patients who fulfilled the ARDS criteria at ICU admission and patients with a referral from another hospital to a participating ICU. The patients who had a lack of data on ARDS risk factors were also excluded.

Patients who admitted into an ICU from January 1 to January 10, 2013, were prospectively enrolled into the

prospective validation cohort. The exclusion criteria of this cohort were the same as the derivation cohort.

Data collection

Trained investigators abstracted data from the electronic medical records of the patients. Baseline characteristics of patients, including sociodemographics, comorbidities and clinical variables, were collected. We collected the data at the time of 24 hours before ICU admission. We also analyzed the data at the time of ICU admission. The worst value during this period was recorded if there was more than one value.

All ARDS risk factors that had been collected in previous studies (15,16) were collected in this study. We also noted other potential ARDS risk factors, such as acute compartment syndrome (17), other immunosuppression conditions besides chemotherapy (18), acute kidney injury (AKI) (19), and blood transfusion (20). Other factors that may affect the ARDS diagnosis, such as cardiac dysfunction and pulmonary embolism, were also recorded.

Definition

ARDS diagnosis was performed according to the Berlin definition established in 2012 (1). The diagnostic criteria included the following: (I) within 1 week of a known clinical insult, or new or worsening respiratory symptoms; (II) chest imaging showing bilateral opacities that were not fully explained by effusions, lobar/lung collapse, or nodules; (III) respiratory failure not fully explained by cardiac failure or fluid overload; and (IV) a $\text{PaO}_2/\text{FiO}_2$ less than or equal to 300 mmHg. All patients diagnosed with ARDS were administered noninvasive or invasive positive pressure ventilation, with PEEP ≥ 5 cmH₂O in our study. Two radiologists, who received the same training for assessment of bilateral infiltrates and diagnosis of ARDS, interpreted the chest radiograph. Any disagreements between the two radiologists were resolved by a discussion with an ICU attending physician, who also received the same training, until a consensus was achieved.

Comparison of MAPS with LIPS

We also recorded all ARDS risk factors and calculated the LIPS score in every included patient. These calculated scores were used to test the accuracy of LIPS in our patients. Afterward, we compared the performance of

MAPS with LIPS

Statistical methods

Data were presented as a number (%) for categorical variables and as a mean (standard deviation) or median (interquartile range) for continuous variables. Regarding the basic characteristics of the patients, we assessed the differences in the categorical variables using χ^2 test or Fisher's exact test, and we assessed the differences in continuous variables with Student's *t*-test or Mann-Whitney *U* test, as appropriate.

Univariate and multivariate logistic regression models were used, with the presence or absence of ARDS in patients as the dependent variable and risk factors of ARDS as the independent variables, to calculate the regression coefficients and to build the corresponding score systems. Forward model selection was used with a threshold *P* value of 0.05 in the multivariate logistic regression model. The model discrimination was then evaluated by the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis. The corresponding 95% confidence interval (CI) and *P* value based on the Mann-Whitney *U* test were calculated as well. The optimum cutoff point that gives the best combination of sensitivity and specificity was determined based on the Youden index.

A *P* value of <0.05 was considered statistically significant. Statistical analyses were carried out using the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

Results

There were 732 patients screened in the retrospective cohort. Among them, 253 patients were excluded because of various exclusion criteria and 479 patients were enrolled to build the prediction system (*Figure 1A*). A total of 222 patients were screened in the prospective cohort. After the exclusion of 24 patients, 198 patients were included to verify the system (*Figure 1B*). The characteristics of both the retrospective cohort and the prospective cohort are presented in *Table 1*.

MAPS establishment of the retrospective derivation cohort

Of the 479 patients finally enrolled in the retrospective derivation cohort, 93 (19.4%) patients developed ARDS in the first three days after ICU admission. The basic characteristics of the ARDS and the non-ARDS patients in

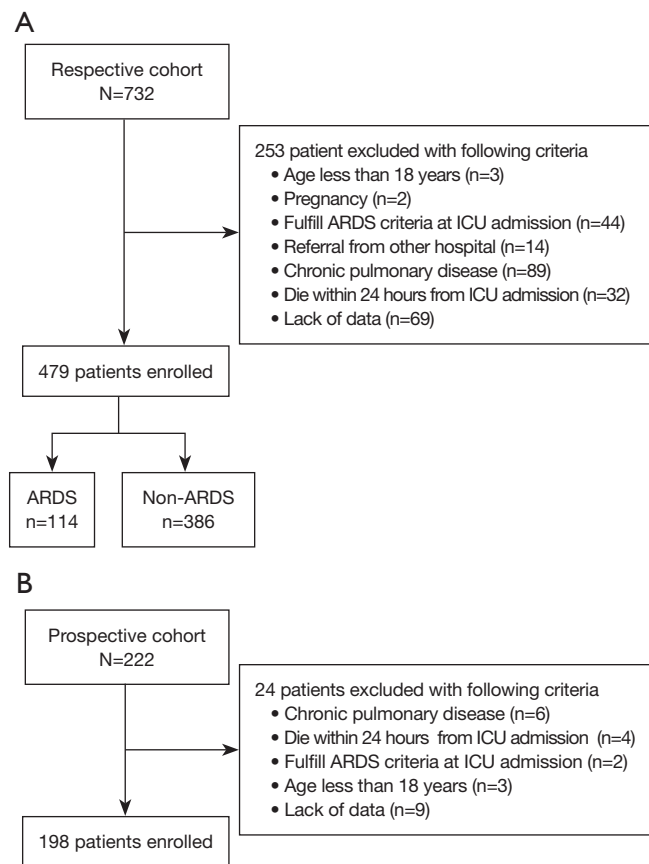


Figure 1 Outline of the screening protocol and case ascertainment. (A) Screening protocol of the retrospective derivation cohort and (B) screening protocol of the prospective validation cohort. ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Table 1 Patient characteristics of both cohort patients

Patient characteristics	Retrospective derivation cohort (n=479)	Prospective validation cohort (n=198)
Demographics		
Age (years)	61±18	62±18
Male	329 (68.7)	143 (72.2)
APACHE II	18±8	19±9
Comorbidities		
Hypertension	203 (42.4)	80 (40.4)
Coronary heart disease	19 (4.0)	14 (7.1)
Diabetes	69 (14.4)	44 (22.2)
Heart dysfunction	95 (19.8)	38 (19.2)
Immunosuppression	19 (4.0)	8 (4.0)

Table 1 (continued)

Table 1 (continued)

Patient characteristics	Retrospective derivation cohort (n=479)	Prospective validation cohort (n=198)
Predisposing conditions		
High risk diseases for ARDS		
Pneumonia	111 (23.2)	68 (34.3)
Aspiration	24 (5.0)	11 (5.6)
Sepsis	119 (24.8)	15 (7.6)
Severe sepsis	76 (15.9)	23 (11.6)
Pancreatitis	48 (10.0)	7 (3.5)
Peritonitis	30 (6.3)	10 (5.1)
ACS	5 (1.0)	0 (0)
AKI	35 (7.3)	14 (7.1)
Shock	96 (20.0)	58 (29.2)
High-risk surgery for ARDS		
Emergency	65 (13.6)	31 (15.6)
Abdomen	80 (16.7)	47 (23.7)
Cardiac surgery	14 (2.9)	10 (5.1)
Orthopedic spine	3 (0.6)	2 (1.0)
Lung	5 (1.0)	1 (0.5)
Head	21 (4.4)	7 (3.5)
High-risk trauma for ARDS		
Traumatic brain injury	29 (6.1)	7 (3.5)
Lung contusion	13 (2.7)	3 (1.5)
Multiple fractures	18 (3.8)	15 (7.6)
Spine injury	2 (0.4)	1 (0.5)
Risk modifiers		
Alcohol abuse	70 (14.6)	26 (13.1)
Smoking	97 (20.3)	34 (17.1)
BMI (kg/m ²)	23±4	22±3
Mechanical ventilation	313 (65.3)	150 (75.8)
Oxygen supplementation >0.35	132 (27.6)	62 (31.3)
Tachypnea (RR ≥30 bpm)	93 (19.4)	35 (17.7)
Acidosis (pH <7.3)	91 (19.0)	56 (28.3)
Hypoalbuminaemia (<30 g/L)	173 (36.1)	100 (50.5)
ICU length of stay (days)	6 (3, 12)	6 (3, 11)
ICU mortality	87 (18.2)	35 (17.7)

Data are presented as mean (SD), median (interquartile range) or n (%) as appropriate. APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; ACS, abdominal compartment syndrome; AKI, acute kidney injury; BMI, body mass index; RR, respiratory rate; ICU, intensive care unit.

Table 2 Univariate comparison of risk factors between patients with ARDS and non-ARDS in retrospective derivation cohort

Patient characteristics	Non-ARDS	ARDS	P value
Subjects, n	386	93	
Predisposing conditions			
High risk diseases for ARDS			
Pneumonia	79 (20.5)	32 (34.4)	0.006
Aspiration	16 (4.1)	8 (8.6)	0.107
Pulmonary embolism	4 (1.0)	0 (0)	1.000
Acute intestinal obstruction	12 (3.1)	4 (4.3)	0.527
Acute pancreatitis	27 (7.0)	21 (22.6)	<0.001
Acute peritonitis	19 (4.9)	11 (11.8)	0.014
Gastrointestinal perforation	16 (4.1)	3 (3.2)	1.000
ACS	0 (0)	5 (5.4)	<0.001
Sepsis	79 (20.5)	30 (32.3)	0.015
Severe sepsis	45 (11.7)	21 (22.6)	0.006
Shock	128 (33.2)	22 (23.7)	0.076
Acute kidney injury	20 (5.2)	15 (16.1)	<0.001
High-risk surgery for ARDS			
Emergence	55 (14.2)	10 (10.8)	0.377
Aortic surgery	4 (1.0)	0 (0)	1.000
Abdominal surgery	65 (16.8)	15 (16.1)	0.885
Cardiac surgery	13 (3.4)	1 (1.1)	0.323
Spine orthopedic surgery	3 (0.8)	0 (0)	1.000
Lung surgery	3 (0.8)	2 (2.2)	0.250
Brain surgery	17 (4.4)	4 (4.3)	1.000
High risk trauma for ARDS			
Traumatic brain injury	23 (6.0)	6 (6.5)	0.858
Pulmonary contusion	8 (2.1)	5 (5.4)	0.145
Multiple fractures	13 (3.4)	5 (5.4)	0.364
Spinal cord injury	1 (0.2)	1 (1.1)	0.351
Risk modifiers			
Alcohol abuse	51 (13.2)	19 (20.4)	0.077
Smoking	75 (19.4)	22 (23.7)	0.363
Comorbidities			
Hypertension	165 (42.7)	38 (40.9)	0.741
Coronary heart disease	18 (4.7)	1 (1.1)	0.143
Diabetes	56 (14.5)	17 (18.3)	0.91

Table 2 (continued)

Table 2 (continued)

Patient characteristics	Non-ARDS	ARDS	P value
Heart dysfunction	93 (24.1)	2 (2.2)	<0.001
Valvular heart disease	20 (5.2)	0 (0)	0.019
Chronic renal dysfunction	40 (10.4)	1 (1.1)	0.004
Hemodialysis	6 (1.6)	2 (2.2)	0.656
Immunosuppression	14 (3.6)	11 (11.8)	0.077
Glucocorticoids use (>30 day)	4 (1.0)	4 (4.3)	0.065
Radiotherapy or chemotherapy	4 (1.0)	4 (4.3)	0.065
Immune system diseases	6 (1.6)	3 (3.2)	0.337
Blood transfusion	146 (37.8)	35 (37.6)	0.973
Mechanical ventilation	250 (64.8)	63 (67.7)	0.588
Vt >10 mL/kg	16 (4.1)	7 (7.5)	0.171
FiO ₂ >35%	101 (26.2)	31 (33.3)	0.165
Tachypnea (RR ≥30 bpm)	57 (14.8)	36 (38.7)	<0.001
Acidosis (pH <7.30)	50 (13.0)	41 (44.1)	<0.001
Hypoalbuminemia (<30 g/L)	110 (28.5)	63 (67.7)	<0.001

Data are presented as n (%) and analyzed using univariate logistic regression models. ARDS, acute respiratory distress syndrome; ACS, abdominal compartment syndrome; ICU, intensive care unit; RR, respiratory rate.

Table 3 Risk factors of ARDS under multivariate logistic regression in retrospective derivation cohort

Risk factors	Multivariate logistic regression			Value
	P value	OR	95% CI	
Acute pancreatitis	0.050	2.147	1.000–4.628	2.0
Pneumonia	<0.001	2.888	1.591–5.424	3.0
Hypoalbuminemia	<0.001	3.627	2.092–6.288	3.5
pH <7.30	0.001	2.942	1.599–5.09	3.0
RR ≥30 bpm	0.040	1.897	1.029–3.496	2.0
Heart failure	<0.001	0.063	0.014–0.275	–3

ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; RR, respiratory rate.

the derivation cohort are shown in *Table 2*. Compared with non-ARDS patients, ARDS patients had higher mortality (15.0% vs. 31.2%, $P<0.001$). The results of the univariate logistic regression analysis of risk factors of ARDS are given in *Table 2*.

A multivariate logistic regression, the ARDS risk factors, and the corresponding points are also shown in *Table 3*, according to the odds ratio (OR) value of the multivariate logistic analysis. The prediction score discriminated well between patients who did and did not develop ARDS,

with an AUC of 0.809 (95% CI, 0.758–0.859, $P<0.001$) (*Figure 2A*). At the cutoff point of 4.0 determined by ROC analysis, the sensitivity and specificity were 0.66 and 0.83, respectively, with a positive predicted value (PPV) of 0.48 and negative predicted value (NPV) of 0.91.

MAPS verification of the prospective validation cohort

One hundred and ninety-eight patients who did not fulfill ARDS criteria at the time of ICU admission were included

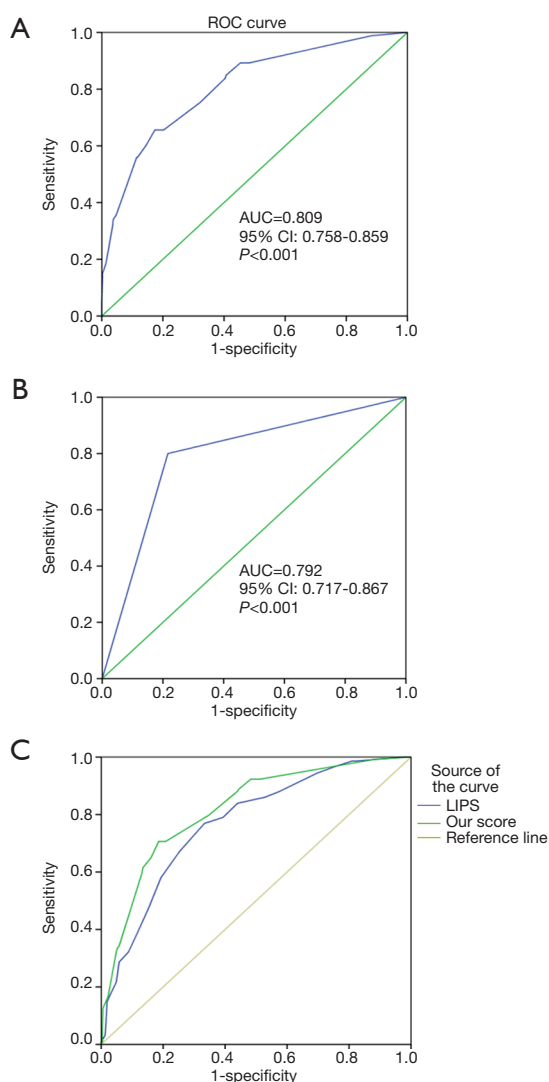


Figure 2 ROC curve for ARDS based on clinical variables. (A) AUC for the prediction score in the retrospective derivation cohort was 0.809 (95% CI, 0.758–0.859, $P<0.001$); (B) AUC for the prediction score in the prospective validation cohort was 0.792 (95% CI, 0.717–0.867, $P<0.001$); (C) AUCs for the prediction score and LIPS in predicting ARDS in all included patients were 0.818 (95% CI, 0.779–0.856, $P<0.001$) and 0.770 (95% CI, 0.728–0.812, $P<0.001$), respectively. Compared to LIPS, the prediction score showed a significantly higher value to predict the development of ARDS in our patients ($P=0.046$). ROC, receiver operating characteristic; ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval.

in the prospective validation cohort. The performance of this prediction score was similar to the retrospective derivation cohort, with an AUC of 0.792 (95% CI, 0.717–0.867, $P<0.001$) (Figure 2B). At the cutoff point

of 4.0, the sensitivity and specificity were 0.66 and 0.83, respectively, with a PPV of 0.48 and an NPV of 0.91.

Comparison of the performance of MAPS with LIPS

We tested the value of LIPS in predicting ARDS in all of the 677 patients enrolled in our study. The performance of LIPS is shown in Figure 2C with an AUC of 0.770 (95% CI, 0.728–0.812, $P<0.001$). Using the cutoff value of 4 from a previous study (16), the sensitivity and specificity were 0.72 and 0.59, respectively, with a PPV of 0.37 and an NPV of 0.87. In all included patients, MAPS showed a predicted value of an AUC of 0.818 (95% CI, 0.779–0.856, $P<0.001$). Compared to LIPS, MAPS showed a significantly higher value in predicting the development of ARDS in our patients ($P=0.046$).

Discussion

There is a limited strategy in improving the outcome of patients with ARDS, and the mortality of patients remains very high, especially after the development of ARDS into a severe condition (3,5,6,21). Thus, it becomes very important to shift from the treatment of ARDS to the prevention of ARDS, in terms of research priorities (10,22,23). The MAPS was set up based on the risk factors of ARDS and had a predictive value, with a sensitivity of 0.66 and a specificity of 0.83. The MAPS was verified by the prospective cohort patients. The present study indicated that MAPS could help us to predict the development of ARDS.

LIPS was identified in a previous study as being able to predict the development of ARDS (15) and was later validated through a multicenter cohort study (16). LIPS had a high value, with an AUC of 0.80, in predicting ARDS development (16). However, these two studies were focused on ED patients. The risk factors of ARDS may be different in various patient populations. We found that the predicted value of LIPS was significantly lower than our prediction score (Figure 2C) for our patients. Moreover, in a recent study, LIPS also showed a low predicted value, with an AUC of 0.70, in a similar patient population to our patient population (24). These results may indicate that LIPS may not be optimal to predict ARDS in patients who need to be admitted into the ICU. More importantly, the LIPS score is very complicated, with more than 20 variables involved in score prediction. Compared to LIPS, the MAPS we proposed, which gave a high predictive value, included only 7 risk factors, which makes it much easier for clinicians to

use in daily practice.

We found some ARDS risk factors that were reported in previous studies, such as sepsis, pneumonia, and aspirations (18,25-30). However, some risk factors, such as alcohol abuse and smoking, were not associated with ARDS in our study. Gajic *et al.* showed that the risk of ARDS development in patients with these risk factors was not high (16). In addition, the risk factors may vary in different populations. In a recent study, which also focused on patients admitted to the ICU, there were no differences in proportions of alcohol abuse, smoking and diabetes between ARDS patients and non-ARDS patients (24).

The incidence of ARDS in our study was much higher than in a previous study (24). However, this high incidence was similar to a survey result in China (31). Because of this, the MAPS produced a higher positive predictive value (PPV) than LIPS (0.48 *vs.* 0.14). Levitt *et al.* compared 33 acute lung injury (ALI) patients with 67 non-ALI patients before mechanical ventilation to identify clinical predictors of progression to acute lung injury. The results showed a higher PPV of their prediction system because of a high proportion of ALI in their study population (32).

MAPS had a high predictive value; however, several issues are worthy of attention. First, we only included the patients who were admitted to the ICU. In addition, we included all patients during a short period in the winter season. Therefore, this result may not be suitable for other patients. Second, the criteria for admission to the ICU may vary among different hospitals. Therefore, MAPS may only be suitable for the ICUs in which the types of patients were similar to the types of patients in our study. Whether our score can be used in the ICUs that received different types of patients needs to be confirmed in a further study. Third, some patients may have evidence of lung injury even prior to positive ventilation (32). Therefore, MAPS cannot distinguish patients at high risk for developing ARDS from patients with early lung injury in our study. Fourth, since the risk factors may vary in different patient populations, our results may not extend to other countries. An international prospective validation cohort study is encouraged to validate our results.

We found that heart failure was a 'protective factor' for ARDS development in MAPS. This could be related to the difficulty of diagnosing ARDS in patients with heart failure because this was an observational study and most patients with heart failure lacked objective data of left ventricle (LV) filling. In our study, the heart failure definition was according to the clinical assessment and medical records

of the patients. This is a limitation of our study. However, in our study, the diagnosis of ARDS was according to the Berlin definition. The chest radiograph was interpreted by two radiologists, who received the same training for assessment of bilateral infiltrates and ARDS independently. We thought this would improve the accuracy of our diagnosis. Indeed, a further study needs to be performed to clarify the role of heart failure in predicting ARDS development. In addition, patients with heart failure are usually combined with increased respiratory rate and hypoalbuminemia. Therefore, our results showed that when we use MAPS, especially for patients with increased respiratory rate and hypoalbuminemia, heart function should also be assessed.

The present study had several other limitations that needed to be expounded. First, even if this was a multicenter study, the sample was relatively small. Second, we excluded all the patients with missing data, even if most of the ARDS risk factors were recorded in our electronic database. There were 69 and 9 patients in the derivation cohort and validation cohort, respectively, who were excluded because of missing data. This exclusion may also induce a biased result, which needs a further study to confirm. Third, the mortality of patients included in our study was approximately 18%. We believe that some patients may have died before they had a chance to fulfill the criteria for ARDS. We did not analyze the competing risk of death in our study and this may also induce a biased result. A further study including a much larger sample size and different types of patients will be needed to improve the predictive value.

Conclusions

In the present study, we developed and validated MAPS to screen for the risk factors of ARDS at ICU admission. Using MAPS may help the clinician to recognize patients who will develop ARDS earlier.

Acknowledgments

Funding: This study was sponsored by a grant from Jiangsu Provincial Key Medical Discipline (grant number: ZDXKA2016025); grants (81571847 and 81601723) from the National Natural Science Foundation of China; a grant (YBJJ1741) from Scientific Research Foundation of Graduate School of Southeast University and a grant (QNRC2016806) from Jiangsu Provincial Medical Youth Talent. We thank all patients for participation in the study,

and all the doctors who participated in this study, for their helpful and continuous support.

Footnote

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

Ethical Statement: The protocol of this study was approved by the Institutional Ethics Committee of Zhongda Hospital (Approval Number 2012ZDIIKY09.0)

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Cite this article as: Xie J, Liu L, Yang Y, Yu W, Li M, Yu K, Zheng R, Yan J, Wang X, Cai G, Li J, Gu Q, Zhao H, Mu X, Ma X, Qiu H. A modified acute respiratory distress syndrome prediction score: a multicenter cohort study in China. *J Thorac Dis* 2018;10(10):5764-5773. doi: 10.21037/jtd.2018.09.117