Predictive value of combination of lung injury prediction score and receptor for advanced glycation end-products for the occurrence of acute respiratory distress syndrome

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Abstract. The present study evaluated the predictive value of the combination of the lung injury prediction score (LIPS) and receptor for advanced glycation end-products (RAGE) for the occurrence of acute respiratory distress syndrome (ARDS) in critically ill patients with ARDS risk factors. A total of 551 patients with risk factors of ARDS were divided into an ARDS group and a non-ARDS group. LIPS was computed within 6 h of admission into the ICU, and the plasma concentration of RAGE was detected within 24 h of admission. Multivariate analysis was performed to identify independent associations, and the predictive values for ARDS occurrence were assessed with receiver operating characteristic (ROC) curve. Within 7 days after admission into the ICU, ARDS occurred in 176 patients (31.9%). Multivariate analysis demonstrated that LIPS [odds ratio (OR), 1.282; 95% confidence interval (CI), 1.108-1.604], RAGE levels (OR, 2.359; 95% CI, 1.351-4.813) and Acute Physiology and Chronic Health Evaluation II score (OR, 1.167; 95% CI, 1.074-1.485) were independently associated with ARDS occurrence. ROC curves demonstrated that the area under curve (AUC) of LIPS, RAGE levels and their combination was 0.714 [standard error (SE), 0.023; 95% CI, 0.670-0.759], 0.709 (SE, 0.025; 95% CI, 0.660-0.758) and 0.889 (SE, 0.014; 95% CI, 0.861-0.917), respectively. The AUC of LIPS combined with RAGE levels was significantly higher compared with those of LIPS (0.889 vs. 0.714; Z=6.499; P<0.001) and RAGE (0.889 vs. 0.709; Z=6.282; P<0.001) levels alone. In conclusion, both LIPS and RAGE levels were independently associated with ARDS occurrence in critically ill patients with ARDS risk factors, and had medium predictive values for ARDS occurrence. Combination of LIPS with RAGE levels increased the predictive value for ARDS occurrence.

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Key words: acute respiratory distress syndrome, lung injury prediction score, receptor for advanced glycation end-products, receiver operating characteristic curve

Introduction

Acute respiratory distress syndrome (ARDS), characterized by refractory hypoxemia and noncardiogenic pulmonary edema, is an acute inflammatory process of the lungs induced by insults to the alveolar-capillary membrane (1-3). ARDS develops most often in the setting of sepsis, pneumonia, severe trauma or aspiration of gastric contents and exists in ~10% of all patients admitted to the intensive care units (ICU) worldwide (4). Despite progress in the improvement of treatments of underlying conditions and organ support, ARDS is still a major cause of ICU morbidity and mortality (5,6). Therefore, accurate prediction of ARDS at an early stage would be useful for decreasing its morbidity and mortality.

The lung injury prediction score (LIPS), proposed by Trillo-Alvarez *et al* (7), can be used to assess the predisposing factors and risks of ARDS. However, the positive predictive value (PPV) of this score is low and limits its application in clinic (8). Biomarkers can improve the prediction of ARDS but they cannot diagnose ARDS definitely (9). Previous studies have identified several promising candidate biomarkers, including receptor for advanced glycation end-products (RAGE), angiopoietin-2, plasminogen-activator-1, interleukin-8, microRNA (miR)-181a, miR-92a, miR-424, procollagen peptide I and III, surfactant protein D, Fas and Fas ligand, acetaldehyde, 3-methylheptane, and octane (3,10,11). These biomarkers can be integrated into the clinical prediction models for ARDS risk. For example, integration of angiopoietin-2 levels into LIPS significantly elevates the predictive value for ARDS with favorable sensitivity and specificity (12).

As a biomarker of lung epithelium injury, RAGE is associated with the increased risk for occurrence of ARDS (13). In the present study, the independent associations between LIPS, RAGE and occurrence of ARDS in critically ill patients with ARDS risk factors were verified, and the values of LIPS, RAGE and their combination for predicting occurrence of ARDS were evaluated. The aim was to provide an accurate tool for the prediction of ARDS occurrence.

Table I. Univariate analysis results between the ARDS and non-ARDS groups.

Parameter	All patients (n=551)	ARDS group (n=176)	Non-ARDS group (n=375)	χ^2/t-test	P-value
Age, years	59.96±19.21	60.23±18.71	59.84±19.45	0.225	0.830
Male	441 (75.1%)	129 (73.3%)	285 (76.0%)	0.469	0.490
BMI, kg/m^2	23.97±3.46	24.07±3.41	23.92±3.48	0.478	0.650
Reasons for admission					
Operation	32 (5.8%)	11 (6.3%)	21 (5.6%)	0.093	0.760
Cardiopulmonary resuscitation	16 (2.9%)	5 (2.8%)	11 (2.9%)	0.004	0.950
Trauma	121 (22.0%)	30(17.0%)	91 (24.3%)	3.645	0.056
Respiratory disease	314 (57.0%)	111 (63.1%)	203 (54.1%)	3.901	0.048
Acute abdominal disease	31 (5.6%)	7 (4.0%)	24 (6.4%)	0.858	0.350
Others	37 (6.7%)	12 (6.8%)	25 (6.7%)	0.094	0.760
LIPS	5.40±2.43	6.17±2.54	5.04±2.38	4.967	<0.001
APACHE II score	16.81±7.47	19.23±7.79	15.67±7.32	5.098	<0.001
Length of ICU stay, days	7.07±3.25	7.38±3.46	6.92±3.15	1.497	0.140
Use of vasopressors	145 (26.3%)	58 (33.0%)	87 (23.2%)	5.878	0.015
Methods of respiratory support					
Invasive mechanical ventilation	241 (43.7%)	80 (45.5%)	161 (42.9%)	0.309	0.580
Non-invasive ventilation	122 (22.1%)	41 (23.3%)	81 (21.6%)	0.200	0.660
Non-invasive and invasive mechanical ventilation	70 (12.7%)	33 (18.8%)	37 (9.9%)	8.523	0.004
Oxygen inhalation through the nasal tube	162 (29.4%)	54 (30.7%)	108 (28.8%)	0.204	0.650
TC, mmol/l	4.20±1.40	4.24±1.47	4.18±1.36	0.457	0.660
TG, mmol/l	1.30±0.64	1.29±0.62	1.31±0.65	-0.348	0.740
HDL-C, mmol/l	1.29±0.60	1.26±0.57	1.30±0.61	-0.751	0.460
LDL-C, mmol/l	2.63±1.12	2.68±1.17	2.61±1.09	0.669	0.500
RAGE levels, μg/l	1.08±0.38	1.85±0.64	0.72±0.26	22.566	<0.001

Data are presented as either mean ± SD or n (%). RAGE, receptor for advanced glycation end-products; BMI, body mass index; ARDS, acute respiratory distress syndrome; LIPS, lung injury prediction score; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

Materials and methods

Patients. In this prospective observational study, a consecutive cohort of 819 patients with risk factors of ARDS were enrolled from the ICU of Chongqing University Jiangjin Hospital (Chongqing, China) between May 2020 and April 2021. These 819 patients included 613 male patients (74.8%) and 206 female patients (25.2%) with a mean age of 60.12±19.15 years (range, 18-91 years). The inclusion criteria included presence of one or more risk factors and informed consent (11). The exclusion criteria included: i) Developing ARDS before initial blood collection and assessment; ii) <7 days of hospital stay, resulting in unfeasibility of determining the clinical outcome; iii) rehospitalization; iv) failure in collecting blood within 24 h of admission into the ICU; v) mortality of the patient within 6 h of admission; vi) a history of chronic interstitial lung disease; vii) diagnosed as congestive heart failure; and viii) failure to conduct chest computed radiography or computed tomography within 7 days of admission. The present study was approved by the Ethical Committee of Chongqing University Jiangjin Hospital (approval no. JJ2020017031) and carried out strictly following the guidelines of the Declaration of Helsinki. Written informed consent was obtained from the study participants prior to study commencement.

Data collection. Demographic data, baseline clinical information, ARDS risk factors, ARDS risk modifiers and laboratory parameters were collected. LIPS was computed within 6 h of admission into the ICU as previously described (7,14). At the same time, the Acute Physiology and Chronic Health Evaluation (APACHE) II score was computed within 24 h of admission to evaluate the severity index. Blood collection was performed within 24 h of admission.

RAGE detection. Blood samples were collected using EDTA as an anti-coagulant within 24 h of admission into the ICU, and centrifugation of 1,006.2 x g for 10 min at room temperature was performed to obtain plasma. The plasma concentration of RAGE was detected using a human receptor for advanced glycation endproducts ELISA kit (cat. no. ZN2383; Beijing

Table II. Multivariate analysis results between the ARDS and non-ARDS groups.

Parameter	β	SE	Wald χ^2	OR	95% CI	P-value
RAGE levels	0.947	0.252	6.068	2.359	1.351-4.813	<0.001
APACHE II score	0.728	0.235	3.094	1.167	1.074-1.485	0.002
LIPS	0.531	0.196	2.397	1.282	1.108-1.604	0.018
Non-invasive and invasive mechanical ventilation	0.422	0.168	1.635	1.529	0.703-3.072	0.117
Use of vasopressors	0.294	0.103	0.538	1.396	0.592-2.903	0.374
Admission due to respiratory disease	0.433	0.125	1.704	1.609	0.711-4.106	0.103
Admission due to trauma	0.391	0.112	1.517	1.498	0.679-3.104	0.122

ARDS, acute respiratory distress syndrome; RAGE, receptor for advanced glycation end-products; LIPS, lung injury prediction score; APACHE, Acute Physiology and Chronic Health Evaluation; β, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

Baiolaibo Technology Co., Ltd.) following the manufacturer's instructions strictly. This kit has a detection range of 78-5,000 pg/ml and sensitivity of <2 pg/ml.

Primary outcome. The primary endpoint was ARDS occurrence within 7 days. ARDS was diagnosed by two experienced clinicians (Department of Critical Care Medicine, Chongqing University Jiangjin Hospital, Chongqing, China) independent from the present study according to the Berlin definition for ARDS (1). The two clinicians were blinded to the concentration of plasma RAGE and LIPS. The diagnosis of sepsis, severe sepsis and septic shock were determined according to the previously reported criteria (15).

Statistical analysis. SPSS version 20.0 (IBM Corp.) was used to carry out statistical analysis. The Kolmogorov-Smirnov test was employed to assess the normality of continuous variables. For normally distributed variables, Student's t-test was employed to perform univariate analysis (intergroup comparison between ARDS group and non-ARDS group). The χ^2 test was employed to perform univariate analysis of categorical variables. The variables with P<0.10 in the univariate analysis were then included in binary logistic regression model to perform multivariate analysis, aiming for identifying independent associations between LIPS, RAGE levels and ARDS occurrence. The values of LIPS, RAGE levels and their combination in predicting ARDS occurrence were assessed using the receiver operating characteristic (ROC) curve. For the prediction tool of LIPS combined with RAGE levels, the probability obtained from binary logistic regression analysis was used as a new indicator for the prediction of ARDS occurrence. *Z* test was employed to perform the comparison of the area under curve (AUC) between different prediction methods. P<0.05 was considered to indicate a statistically significant difference.

Results

General information. A total of 819 patients with risk factors of ARDS were enrolled during the study period, and 551 patients were included in the final analysis. A total of 45 patients were excluded due to developing ARDS before initial blood collection and assessment, 34 patients were excluded due to a hospital stay that was <7 days, 11 patients were excluded due to rehospitalization, 86 patients were excluded due to failure in collecting blood within 24 h after admission, 2 patients were excluded due to death within 6 h after admission, 17 patients were excluded due to a history of chronic interstitial lung disease, 14 patients were excluded due to diagnosed as congestive heart failure and 59 patients were excluded due to failure in conducting chest computed radiography or computed tomography within 7 days after admission.

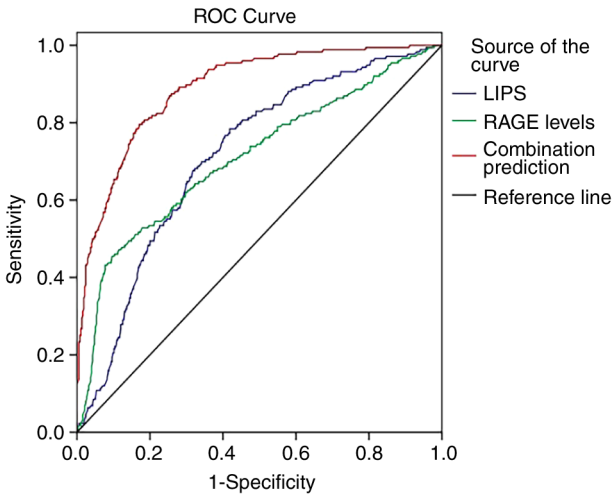

Figure 1. ROC curves of LIPS, RAGE levels and their combination in predicting acute respiratory distress syndrome occurrence in critically ill patients with ARDS risk factors. RAGE, receptor for advanced glycation end-products; LIPS, lung injury prediction score; ROC, receiver operating curve.

These 551 patients included 414 males (75.1%) and 137 females (24.9%) with an average age of 59.96±19.21 years. The reasons for admission included respiratory disease (57.0%), trauma (22.0%), operation (5.8%), acute abdominal disease (5.6%), cardiopulmonary resuscitation (2.9%) and others (6.7%). Within 7 days after admission into the ICU, ARDS occurred in 176 patients (31.9%) (Table I).

Univariate analysis. Univariate analysis (Table I) was conducted between the ARDS and non-ARDS groups, which demonstrated that LIPS, RAGE levels, APACHE II score,

Table III. Clinical utility indexes of LIPS, RAGE levels and their combination in predicting ARDS occurrence.

Parameter	Best cut-off	Sensitivity, %	Specificity, %	Accuracy, %	FPR, %	FNR, %	PPV, %	NPV, %
LIPS combined with RAGE levels	-	87.50	89.10	88.60	21.00	6.20	79.00	93.80
LIPS	5.42 points	63.60	67.70	66.40	51.90	20.10	48.10	79.90
RAGE levels	1.13 μg/l	55.10	71.20	66.10	52.70	22.80	47.30	77.20

RAGE, receptor for advanced glycation end-products; LIPS, lung injury prediction score; FNR, false negative rate; FPR, false positive rate; NPV, negative predictive value; PPV, positive predictive value.

non-invasive and invasive mechanical ventilation, use of vasopressors and admission due to respiratory disease were significantly different (P<0.05), and the remaining variables were not (P>0.05). However, the P-value of admission due to trauma was <0.10.

Multivariate analysis. Multivariate analysis was conducted with inclusion of LIPS, RAGE levels, APACHE II score, non-invasive and invasive mechanical ventilation, use of vasopressors and admission due to respiratory disease and trauma. The results demonstrated that LIPS, RAGE levels and APACHE II score were independently associated with ARDS occurrence with adjustment for non-invasive and invasive mechanical ventilation, use of vasopressors, admission due to respiratory disease and trauma (Table II).

ROC analysis. ROC curves (Fig. 1) were employed to evaluate the values of LIPS, RAGE levels and their combination in predicting ARDS occurrence. The results demonstrated that the AUCs of LIPS, RAGE levels and their combination were 0.714 [standard error (SE), 0.023; 95% confidence interval (CI), 0.670-0.759], 0.709 (SE, 0.025; 95% CI, 0.660-0.758) and 0.889 (SE, 0.014; 95% CI, 0.861-0.917), respectively. The AUC of LIPS combined with RAGE levels was significantly higher compared with those of LIPS and RAGE levels alone (0.889 vs. 0.714, Z=6.499, P<0.001; 0.889 vs. 0.709, Z=6.282, P<0.001). The clinical utility indexes were calculated (Table III), which demonstrated that the sensitivity, specificity and accuracy of combination prediction were 87.5, 89.1 and 88.6%, respectively.

Discussion

The incidence of ARDS has decreased following progress in the management of critically ill patients (16). However, mortality among patients with ARDS still remains high at up to 46.1% for severe ARDS (6). In order to further decrease the disease burden of ARDS, it is not adequate to focus on the treatment following the occurrence of ARDS (17). Firstly, the strategies for treatment of ARDS are quite limited and there is no effective strategy other than low-tidal volume ventilation (18). Secondly, preclinical studies have confirmed the effectiveness of initiating treatment prior to occurrence of clinical injury (19,20). Thus, it is important to develop an accurate prediction tool for the early identification of at-risk patients. The general aim is to decrease the incidence of ARDS by administering the therapies for ARDS prevention for at-risk patients.

LIPS can be used to stratify patients at risk for ARDS by predisposing conditions for ARDS and scoring the risk factors. It was derived from a multicenter study including >5,000 patients with risk factors for ARDS and included 22 items associated with risk modifiers, physiologic data and predisposing conditions (7). Its predictive value is relatively high with an AUC of 0.80-0.84. A LIPS exceeding 4 points yields a sensitivity of 69%, specificity of 78% and negative predictive value (NPV) of 97%, but PPV was only 18%. Kim *et al* (21) investigated the predictive value of LIPS for the occurrence of ARDS in adult patients admitted to ICUs in the Korean population. Their results showed that LIPS is significantly correlated with the occurrence of ARDS, and LIPS >6 points yields a sensitivity of 84.8% and specificity of 67.2% with an AUC of 0.82 for predicting the occurrence of ARDS. Moreover, a modified LIPS with adjustment for severity at ICU admission and age can be applied in predicting ICU mortality in patients with ARDS (21). Xu *et al* (12) demonstrated that LIPS is also associated with ARDS occurrence in critically ill patients with ARDS risk factors in the Chinese population with an AUC of 0.704 for the prediction of ARDS occurrence. The AUC increased to 0.803 after combining angiopoietin-2 levels with LIPS, and the PPV increased to 58.19% correspondingly (12).

The biomarkers of ARDS are hypothesized to reflect its pathophysiological process characterized with high permeability alveolar oedema, alveolar-capillary membrane injury and migration of inflammatory cells (22). A previous study demonstrated that biomarkers associated with alveolar tissue injury can predict ARDS occurrence, whereas those associated more with inflammation can predict ARDS mortality (23). As a biomarker of lung epithelium injury, RAGE is constitutively expressed on all cells at low levels, but its expression is significantly upregulated in the lung epithelium, especially in alveolar type-I cells (24). RAGE is involved in a number of cellular processes, including vascular smooth muscle proliferation and migration, microtubule stabilization, apoptosis, neuroinflammation, excitotoxicity, neurodegeneration, oxidative stress, corneal healing, and mitochondrial function (25-27). Its activation can regulate propagation of the inflammatory response, which is considered to be particularly relevant to ARDS (28). Calfee *et al* (29) reported elevated plasma levels of RAGE among patients with severe ARDS and its association with mortality among patients with ARDS

ventilated with high tidal volume. Later studies demonstrated the association of soluble RAGE (sRAGE) with outcome and severity of patients with ARDS (30,31). Jabaudon *et al* (32) showed that the sRAGE level is higher in patients with ARDS with or without sepsis compared with that in patients who only have sepsis but not ARDS. Additionally, the authors indicated that the sRAGE level is associated with severity of lung injury but not with outcome. Subsequently, two studies focusing on panels of biomarkers have indicated the role of RAGE as a valuable candidate for diagnosing ARDS (33,34). A recent meta-analysis showed that the plasma RAGE level is positively correlated with increased risk of ARDS occurrence, but is not correlated with mortality in patients with ARDS (13).

In the present study, both LIPS and RAGE levels were independently associated with ARDS occurrence, and could be applied in predicting ARDS occurrence with medium values (AUC, 0.714 and 0.709). LIPS combined with RAGE levels elevated the predictive value significantly with an AUC of 0.889, and the clinical utility indexes also improved significantly, especially PPV up to 79.0%. Additionally, APACHE II score was also independently associated with ARDS occurrence in the present study. However, on the one hand, it has been studied extensively; on the other hand, it needs a long time to obtain the required parameters and costs more compared with LIPS. Therefore, the focus was primarily on analyzing LIPS and RAGE levels as biomarkers for ARDS.

The main limitation of the present study was no inclusion of all relevant biomarkers, and the prediction tool only integrated RAGE. In the next step, future studies will develop a more accurate prediction tool by integrating multiple biomarkers of different properties.

In conclusion, both LIPS and RAGE levels were independently associated with ARDS occurrence in critically ill patients with ARDS risk factors, and could be applied in predicting ARDS occurrence with medium values. LIPS combined with RAGE levels elevated the predictive value for ARDS occurrence significantly.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JY was responsible for acquisition of data and drafting the article. AW was responsible for acquisition of data and revising the article. BW was responsible for acquisition of data and revising the article. JD was responsible for the conception and design, analysis and interpretation of data, and critically reviewing the article. JY, AW and BW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Chongqing University Jiangjin Hospital (approval no. JJ2020017031) and carried out strictly following the guidelines of the Declaration of Helsinki. Written informed consent was obtained from the study participants prior to study commencement.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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