# Predictive Role of Lung Injury Prediction Score in the Development of Acute Respiratory Distress Syndrome in Korea

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**Purpose:** Early recognition and therapeutic intervention are important in patients at high risk of acute respiratory distress syndrome (ARDS). The lung injury prediction score (LIPS) has been used to predict ARDS development; however, it was developed based on the previous definition of ARDS. We investigated the predictive role of LIPS in ARDS development according to its Berlin definition in the Korean population.

**Materials and Methods:** This was a retrospective study that enrolled adult patients admitted to the intensive care unit (ICU) at a single university-affiliated hospital in Korea from September 1, 2018, to August 31, 2019. LIPS at the time of ICU admission and the development of ARDS were evaluated.

**Results:** Of the 548 enrolled patients, 33 (6.0%) fulfilled the Berlin ARDS definition. The LIPS for non-ARDS and ARDS groups were 4.96±3.05 and 8.53±2.45, respectively ($p<0.001$); it was significantly associated with ARDS development (odds ratio 1.48, 95% confidence interval, 1.29−1.69; $p<0.001$). LIPS >6 predicted the development of ARDS with a sensitivity of 84.8% and a specificity of 67.2% [area under the curve (AUC)=0.82]. A modified LIPS model adjusted for age and severity at ICU admission predicted ICU mortality in patients with ARDS (AUC=0.80), but not in those without ARDS (AUC=0.54).

**Conclusion:** LIPS predicted the development of ARDS as diagnosed by the Berlin definition in the Korean population. LIPS provides useful information for managing patients with ARDS.

**Key Words:** Acute lung injury, respiratory distress syndrome, respiratory insufficiency, prediction model, critical illness

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome that involves extensive damage to the lung parenchy-

ma caused by direct or indirect injury. After Ashbaugh, et al.[1] first reported 12 patients with ARDS in 1967, there was no consensus definition for a long time. The American-European Consensus Conference (AECC) definition was proposed in 1994,[2] after which it was subsequently revised to the current Berlin definition in 2012.[3] According to the LUNG SAFE Study, the prevalence of severe ARDS was 23.4% and the mortality was 46.1%, showing a very poor prognosis as an isolated clinical syndrome.[4] Several clinical trials have been conducted regarding the treatment of ARDS. However, with the exception of low-tidal volume ventilation,[5] most of those studies failed to improve the mortality rate. There are good reasons for the approaches towards ARDS to have changed from focusing on treatment following the development of ARDS to performing interventions in high-risk groups before the development of

ARDS.[6-8] First, ARDS has a high mortality rate, but treatment strategies are quite limited. Second, preclinical studies have demonstrated the efficacy of initiating treatment before clinical injury occurs.[9,10] Therefore, it is essential to develop a clinical prediction tool for early recognition and treatment in high-risk groups.

In 2011, Trillo-Alvarez, et al.[11] presented a lung injury prediction score (LIPS) for evaluating the risks and predisposing factors for ARDS. At the time of initial emergency room (ER) arrival or before undergoing high-risk surgery, patients with risk factors for ARDS should undergo early therapeutic intervention if their LIPSs exceed 4 points. A limitation of this study was that it was conducted in a single center with a small sample. The United States Critical Illness and Injury Trial Group (USCIITG) subsequently conducted a large-scale multicenter study demonstrating LIPS to be an effective tool for predicting ARDS development.[12] However, these two studies were conducted under the AECC definition of ARDS, and the definition of ARDS has recently been revised to the Berlin definition.[3] In addition, the previous studies were conducted in Western countries. Therefore, the purpose of this study was to analyze the role of LIPS in predicting the development of ARDS according to the current Berlin definition and to examine its applicability in the Korean population.

## MATERIALS AND METHODS

### Study population and design
This study retrospectively evaluated medical records of the admitted patients in a single university-affiliated hospital from September 1, 2018, to August 31, 2019. All patients over 18 years of age who had been admitted to the intensive care units (ICU) for medical illness were included. We excluded patients who were pregnant and those who were admitted for simple observation (<24 hours) following procedures such as endoscopy or coronary intervention, and those who had been readmitted for the same morbidities. The Institutional Review Board approved the study protocol (IRB No. 2019AS0042) and waived the requirement for informed consent.

### Data collection and definition
We collected demographic data as well as information regarding the reason for admission, predisposing factors, and modifiable risk factors for ARDS. We assessed the LIPS within 6 hours following an ER visit or within 12 hours before entering the ICU from the general ward. Simultaneously, we assessed the severity index within 24 hours following ICU admission. The severity index was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score and Simplified Acute Physiology Score (SAPS) III. Additionally, we measured the P/F ratio at admission, defined as the ratio of arterial oxygen partial pressure ($PaO_2$) to fractional inspired oxygen ($FiO_2$), to check the degree of oxygenation. We recorded the duration of mechanical ventilation applied with a mechanical ventilator, duration of ICU stay, hospital day, ICU mortality, and hospital mortality. We analyzed the results of patients who did not have ARDS at the time of their ICU admission but later developed ARDS during their ICU stay. We defined ARDS according to the Berlin definition, and the critical care specialist investigated the presence of ARDS by reviewing the medical records based on the 7th Korean Standard Classification of Disease.

### Lung injury prediction score
The LIPS used the same scheme as the previous USCIITG study (Supplementary Table 1, only online).[12] We assigned scores ranging from 0 to 15.5 according to the weights of predisposing conditions and risk factors. The higher the score, the greater the risk of ARDS development. In case where the albumin and pH values of blood were not checked, they were assumed to be normal. In the case of emergency surgery, we added 1.5 points, and in the case of sepsis with diabetes, we subtracted 1 point.

### Statistical analysis
All categorical variables are expressed as numbers and percentages, and continuous variables are expressed as means and standard deviations. Chi-square or Fisher's exact test was used to determine the associations between categorical variables, and Student's t-test or Mann–Whitney U test was used to compare the means in continuous variables. Logistic regression and receiver operating characteristic curve analyses were used for the primary outcome analysis. The Youden index was used to determine the cut-off value of LIPS to predict the development of ARDS. All statistical analyses were performed using SPSS (ver. 20.0; IBM Corp., Armonk, NY, USA) and MedCalc (ver.18.5; MedCalc Software, Mariakerke, Belgium). $p$-values less than 0.05 were considered statistically significant.

## RESULTS

A total of 548 patients were enrolled during the study period. The mean age of the patients was 66.20±15.50 years, and 335 (61.1%) were male. The most common reason for admission was pneumonia (n=174, 31.8%). ARDS was diagnosed in 33 (6.0%) patients. Compared to the patients without ARDS, pneumonia [147 (28.5%) vs. 27 (81.8%), $p<0.001$], and mechanical ventilator support were more common [221 (42.9%) vs. 28 (84.8%), $p<0.001$] and the severity evaluated by SAPS III was higher (67.09±17.56 vs. 85.64±17.26, $p<0.001$) in the patients with ARDS. The ICU mortality rate was 20 (60.6%) in patients with ARDS and 200 (38.8%) in patients without ARDS; it was significantly higher in patients with ARDS ($p$=0.02) (Table 1 and 2).

The mean LIPS of patients was 5.18±3.14, which was signifi-

cantly higher in ARDS group (4.96±3.05 in non-ARDS group and 8.53±2.45 in ARDS group, $p<0.001$). The LIPS in non-ARDS group ranged from 0 and 6, and scores from 3−5 were more frequent. However, in ARDS group, LIPS was distributed be- tween 6 and 12 and the peak point was at 9−10 (Fig. 1A). The frequency of ARDS development according to LIPS is depicted in Fig. 1B. For every 1 point increase in LIPS, the risk of ARDS development increased 1.48 times [95% confidence in-

**Table 1.** Baseline Characteristics of the Patient by the Development of Acute Respiratory Distress Syndrome (ARDS)

|  | Total (n=548) | ARDS group (n=33) | Non-ARDS group (n=515) | p value |
|---|---|---|---|---|
| Sex, male | 335 (61.1) | 22 (66.7) | 313 (60.8) | 0.50 |
| Age (yr) | 66.20±15.50 | 67.64±13.94 | 66.11±15.61 | 0.58 |
| Reason for admission |  |  |  | <0.001 |
| Pneumonia | 174 (31.8) | 27 (81.8) | 147 (28.5) |  |
| Cardiovascular disease | 78 (14.2) | 0 (0) | 78 (15.1) |  |
| Urinary tract infection | 53 (9.7) | 2 (6.0) | 51 (9.9) |  |
| Renal failure | 39 (7.1) | 1 (3.0) | 38 (7.4) |  |
| Gastrointestinal bleeding | 34 (6.2) | 0 (0) | 34 (6.6) |  |
| Others | 170 (31.0) | 3 (9.1) | 167 (32.4) |  |
| LIPS | 5.18±3.14 | 8.53±2.45 | 4.96±3.05 | <0.001 |
| APACHE II | 20.94±8.71 | 28.58±8.60 | 20.45±8.50 | <0.001 |
| SAPS III | 68.21±18.08 | 85.64±17.26 | 67.09±17.56 | <0.001 |
| P/F ratio (mm Hg)* | 234.74±150.90 | 131.95±130.92 | 241.22±149.84 | <0.001 |
| Application of MV | 249 (45.4) | 28 (84.8) | 221 (42.9) | <0.001 |
| Duration of MV (days)† | 10.00±18.25 | 8.93±11.47 | 10.14±18.95 | 0.74 |
| Length of ICU stay (days) | 8.57±13.63 | 9.61±12.02 | 8.51±13.73 | 0.65 |
| Length of hospital stay (days) | 21.69±23.66 | 19.70±17.00 | 21.82±24.03 | 0.62 |
| ICU mortality | 220 (40.1) | 20 (60.6) | 200 (38.8) | 0.02 |
| In-hospital mortality | 222 (40.5) | 21 (63.3) | 201 (39.0) | 0.01 |

LIPS, lung injury prediction score; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS III, Simplified Acute Physiology Score III; MV, mechanical ventilation; ICU, intensive care unit.
Data are presented as a n (%) or means±standard deviations.
*The results of 506 patients without missing values. P/F ratio is the ratio of arterial oxygen partial pressure to fractional inspired oxygen, †Durations were measured only in the patients who underwent MV.

**Table 2.** Parameters of Lung Injury Prediction Score between the Groups With and Without Acute Respiratory Distress Syndrome (ARDS)

|  | Total (n=548) | ARDS group (n=33) | Non-ARDS group (n=515) | p value |
|---|---|---|---|---|
| Predisposing condition |  |  |  |  |
| Shock | 241 (44.0) | 219 (42.5) | 22 (66.7) | 0.01 |
| Aspiration | 54 (9.9) | 52 (10.1) | 2 (6.1) | 0.76 |
| Sepsis | 262 (47.8) | 231 (44.9) | 31 (93.9) | <0.001 |
| Pneumonia | 174 (31.8) | 147 (28.5) | 27 (81.8) | <0.001 |
| High-risk surgery | 11 (2.0) | 11 (2.1) | 0 (0.0) | 0.87 |
| High-risk trauma | 4 (0.7) | 4 (7.8) | 0 (0.0) | 1.00 |
| Risk modifier |  |  |  |  |
| Alcohol abuse | 48 (8.8) | 47 (9.1) | 1 (3.0) | 0.35 |
| Obesity | 24 (4.4) | 23 (4.5) | 1 (3.0) | 1.00 |
| Hypoalbuminemia | 225 (41.1) | 204 (39.6) | 21 (63.6) | 0.01 |
| Chemotherapy | 41 (7.5) | 32 (6.2) | 9 (27.3) | <0.001 |
| FiO₂ >0.35 | 334 (60.9) | 303 (58.8) | 31 (93.9) | <0.001 |
| Tachypnea | 179 (32.7) | 161 (31.3) | 18 (54.5) | 0.01 |
| SpO₂ <95% | 222 (40.5) | 198 (38.4) | 24 (72.7) | <0.001 |
| Acidosis | 228 (41.6) | 212 (41.2) | 16 (48.5) | 0.47 |
| Diabetes mellitus | 139 (25.4) | 132 (25.6) | 7 (21.2) | 0.68 |

FiO₂, fraction of inspired oxygen; SpO₂, oxygen saturation by pulse oximetry.
Data are presented as n (%).
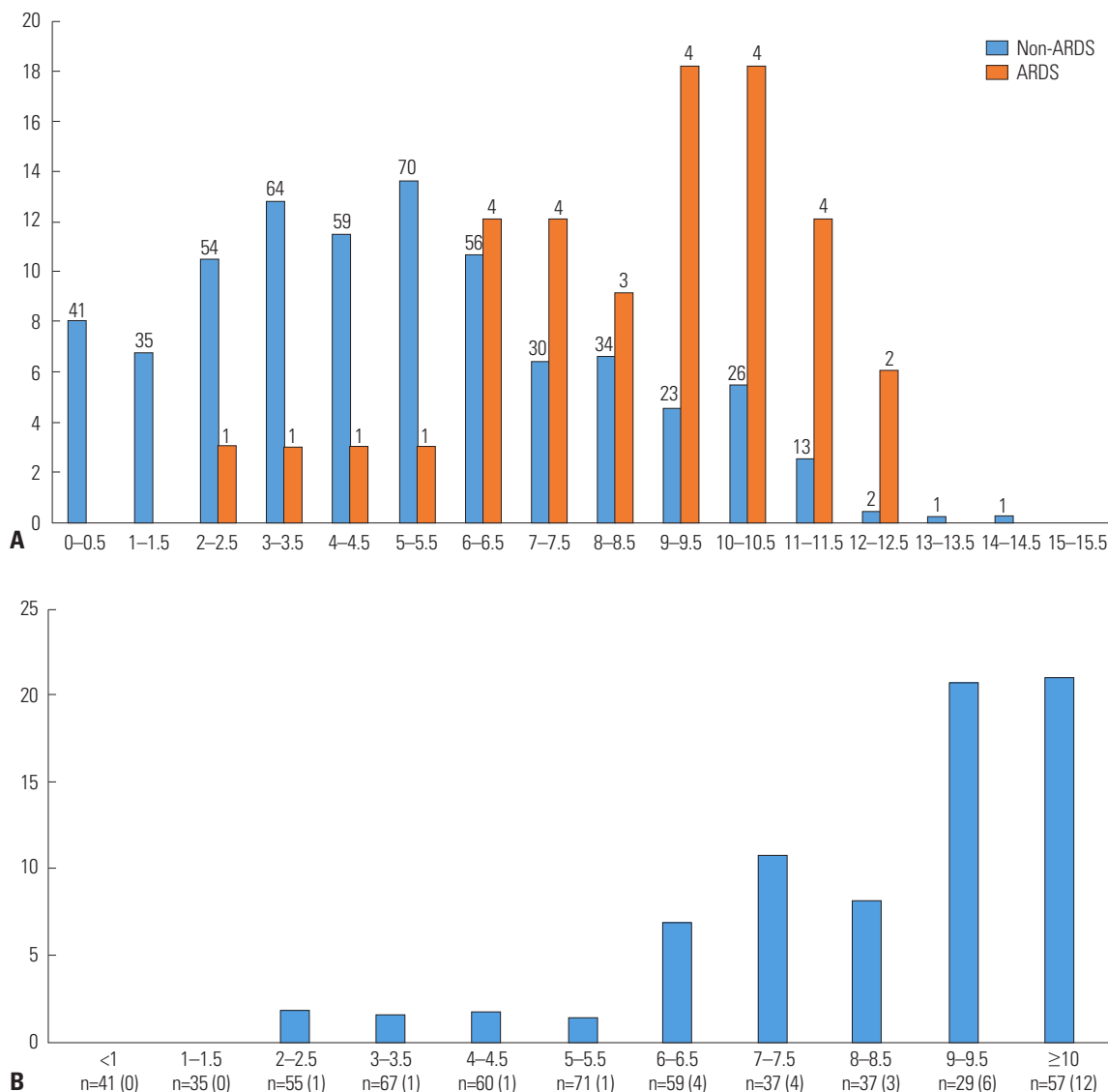
**Fig. 1.** Distribution of patients according to the lung injury prediction scores (LIPSs) and the development of acute respiratory distress syndrome (ARDS) according to LIPS. (A) The bar represents the percentage of patients with ARDS according to the LIPS, and the number above the bar indicates the number of patients in each LIPS range. (B) The bar represents the percentage of patients with ARDS development, and the number of patients according to the LIPS is depicted at the bottom of the graph. The numbers in parentheses indicate the number of patients with ARDS development.

terval (CI) 1.29–1.69, $p<0.001$]. The area under the curve (AUC) of LIPS for ARDS development was 0.82 (95% CI 0.75–0.88), and LIPS predicted the development of ARDS with a sensitivity of 84.8% and specificity of 67.2% when it exceeded 6 (Fig. 2).

Among the predisposing factors or risk modifiers of ARDS in LIPS, chemotherapy markedly increased the risk of developing ARDS with an odds ratio (OR) of 3.62 (95% CI 1.37–9.58, $p=0.01$). Furthermore, pneumonia (OR 2.03, 95% CI 1.18–3.50, $p=0.01$), shock (OR 1.64, 95% CI 1.13–2.39, $p=0.01$), oxygen saturation by pulse oximetry ($SpO_2$) <95% (OR 1.62, 95% CI 1.14–2.32, $p=0.01$), and tachypnea (OR 1.54, 95% CI 1.04–2.28, $p=0.03$) were also important factors that were related to the development of ARDS (Table 3).

In the patients with ARDS, the modified LIPS model adjusted for age and severity of patients at ICU admission significantly

predicted ICU mortality with an AUC of 0.80 (95% CI 0.63–0.92, $p<0.001$), although LIPS failed to predict ICU mortality in patients with ARDS (AUC=0.58). However, in patients without ARDS, both LIPS and modified LIPS failed to predict ICU mortality (AUC=0.54, AUC=0.58, respectively) (Fig. 3).

## DISCUSSION

This study was conducted to investigate the role of LIPS in predicting ARDS development according to the Berlin definition in a Korean population admitted to medical ICU. LIPS was significantly higher in patients with ARDS, and the risk of ARDS was positively related with LIPS. LIPS efficiently predicted the development of ARDS and the prognosis of patients with ARDS,

but for not those without ARDS, in the medical ICU.

Although ARDS has high prevalence and mortality, there is no effective treatment other than low-tidal volume ventilation. Therefore, it is crucial to develop a model that can prevent lung injury and provide early treatment by predicting high-risk patients before ARDS develops. Several lung injury prediction models have been introduced previously, but there are some limitations in their general application.[13-15] LIPS is a scoring

system devised by Trillo-Alvarez, et al.[11] in 2011 to predict ARDS development by scoring the risk factors and predisposing conditions for ARDS. LIPS has the following advantages compared to previous prediction models. First, it is easy to assess from general clinical data as it is related to ARDS prediction. Second, LIPS can be measured before ICU admission; therefore, it can be used to predict ARDS development more quickly. Third, invasive blood test results other than those of arterial blood pH
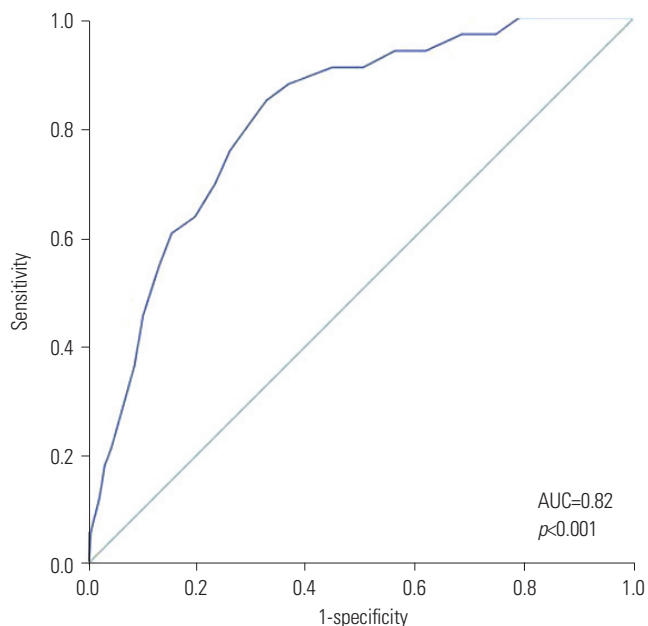


**Fig. 2.** The receiver operating characteristic curve for lung injury prediction scores related to acute respiratory distress syndrome development in the Korean population. AUC, area under the curve.

**Table 3.** The Relationship between Lung Injury Prediction Score Parameters and Acute Respiratory Distress Syndrome Development

| | OR | 95% CI | *p* value |
|---|---|---|---|
| Predisposing condition | | | |
| Shock | 1.64 | 1.13–2.39 | 0.01 |
| Aspiration | 0.48 | 0.22–1.03 | 0.06 |
| Sepsis | 4.99 | 0.97–25.75 | 0.06 |
| Pneumonia | 2.03 | 1.18–3.50 | 0.01 |
| High-risk surgery | - | - | - |
| High-risk trauma | - | - | - |
| Risk modifier | | | |
| Alcohol abuse | 0.31 | 0.04–2.33 | 0.26 |
| Obesity | 0.67 | 0.09–5.11 | 0.70 |
| Hypoalbuminemia | 2.15 | 0.94–4.89 | 0.07 |
| Chemotherapy | 3.62 | 1.37–9.58 | 0.01 |
| $FiO_2$ >0.35 | 2.06 | 0.97–4.40 | 0.06 |
| Tachypnea | 1.54 | 1.04–2.28 | 0.03 |
| $SpO_2$ <95% | 1.62 | 1.14–2.32 | 0.01 |
| Acidosis | 1.16 | 0.82–1.65 | 0.41 |
| Diabetes mellitus | 1.28 | 0.54–3.02 | 0.57 |

OR, odds ratio; CI, confidence interval; $FiO_2$, fraction of inspired oxygen; $SpO_2$, oxygen saturation by pulse oximetry.
Data are presented as n (%).
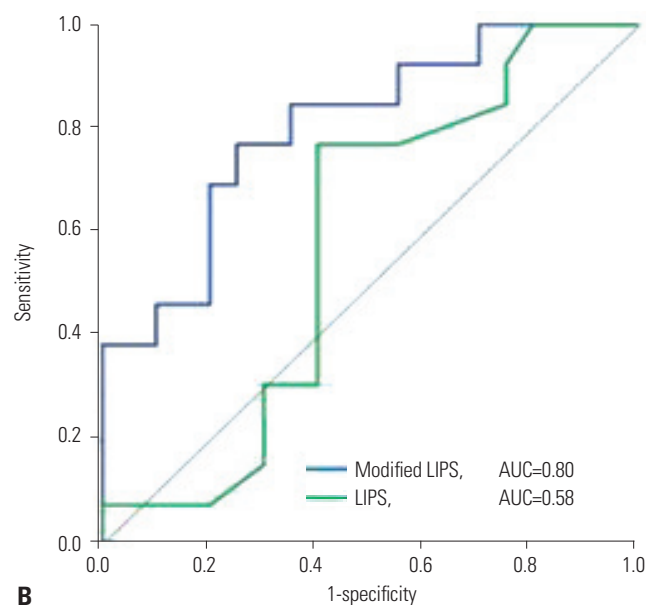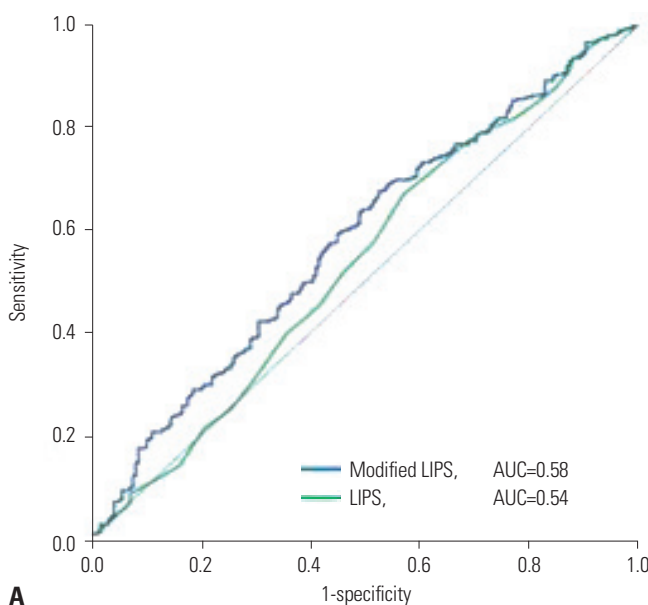


**Fig. 3.** Mortality prediction using the original lung injury prediction score (LIPS) and modified LIPSs model in the patients with and without acute respiratory distress syndrome (ARDS). (A) Mortality prediction in the non-ARDS group using LIPS and modified LIPS. (B) Mortality prediction in the ARDS group using LIPS and modified LIPS. AUC, area under the curve.

and venous blood albumin are not required. However, LIPS was proposed based on the previous AECC definition, which was revised to the Berlin definition in 2012. Further research is needed to evaluate the applicability of LIPS to the new definition of ARDS. Some studies were performed to evaluate the usefulness of LIPS in predicting ARDS development by the Berlin definition[16,17]; however, most of these studies were conducted in Western countries, and no proper evidence was found regarding the application of LIPS in the Korean population.

The results of this study showed that LIPS had a significant correlation with the development of ARDS when the score exceeded 6, and not 4, as reported in the USCIITG–LIPS study.[11] The different cut-off values of LIPS in our study may be due to the disease severities of patients at ICU admission. The APACHE II score was 20.94 in this study, whereas it was 9 in the previous study, and the mean age of patients included was 66.2 years in our study and 57.0 years in the USCIITG–LIPS study.[11] This is because we enrolled patients who were admitted to the medical ICU. However, the predictability of LIPS for ARDS development in our study was not inferior to that of previous studies. The sensitivity and specificity reported in our study was 84.8% and 67.2%, respectively, and that of the USCIITG–LIPS study was 69% and 78%, respectively. Moreover, several studies have suggested a higher cut-off point of LIPS for ARDS prediction.[17,18]

In this study, pneumonia was the most common condition in both of the groups, and it was significantly higher in ARDS group than that in non-ARDS group. This result was consistent with a previous study.[4] The mortality rate in our study was higher than that in the original study, especially in ARDS group. Considering the APACHE II scores and SAPS III of enrolled patients, the expected mortality rate was approximately 40−50%,[19] but the mortality in our study was high. This may be because the proportion of patients with severe ARDS was high, and the mean P/F ratio was less than 150 mm Hg. A previous study showed a hospital mortality rate of 68.0% at a P/F ratio ≤150 mm Hg, although it had a small sample size.[20]

Furthermore, we evaluated the relationship between LIPS and patient prognosis. Although the LIPS itself did not show a significant result, the modified LIPS model adjusted for age and patient severity at ICU admission was a good predictor of ICU mortality in patients with ARDS but not in those without. Considering that the elements deciding LIPS include factors that reflect the severity of patients at diagnosis of ARDS, the results suggest that the mortality of ARDS is related to the predisposing conditions or risk modifiers that contributed to the development of ARDS, rather than the severity of patients graded at ICU admission. Accordingly, the modified LIPS model did not work for mortality prediction in patients without ARDS. This result was consistent with those of previous studies that reported mortality predictors of ARDS.[17]

This study had the following limitations. First, when there were missing values of serum albumin (30.8%) and arterial pH (7.7%), the values were assumed to be normal, which may

have affected the results of this study. However, LIPS was designed to predict ARDS in the early stage of the disease; therefore, even in the original study, the parameters of serum albumin and arterial pH, which require an invasive process for the result, were regarded as normal when they were not evaluated. Moreover, the missing rates of serum albumin and arterial pH were higher in the original study (43.4% in albumin, and 26.8% in pH) than in our study.[11] Second, its generalizability is limited since it was conducted at a single university-affiliated hospital. Finally, the patients enrolled in our study were admitted to the ICU from ER or general ward. Therefore, due to the severity and characteristics of the patients, the group was highly heterogeneous. However, the purpose of our study was to investigate the predictability of ARDS development in high-risk patients admitted to the medical ICU and to determine the possibility of predicting ARDS using LIPS in this group of patients.

In conclusion, when the LIPS exceeded 6 points, the predictive power of ARDS development was high, and the incidence of ARDS increased 1.48 times for each point. Therefore, LIPS may be useful for predicting ARDS development by the Berlin definition in critically ill patients admitted to the medical ICU in Korea.

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Conceptualization: Je Hyeong Kim. Data curation: Beong Ki Kim, Sua Kim, Chi Young Kim, Yu Jin Kim, and Seung Heon Lee. Formal analysis: Beong Ki Kim, Sua Kim, and Jae Hyung Cha. Investigation: Beong Ki Kim and Sua Kim. Methodology: Sua Kim and Jae Hyung Cha. Project administration: Chi Young Kim, Yu Jin Kim, and Seung Heon Lee. Resources: Beong Ki Kim and Sua Kim. Software: Beong Ki Kim and Sua Kim. Supervision: Je Hyeong Kim. Validation: Beong Ki Kim. Visualization: Beong Ki Kim. Writing—original draft: Beong Ki Kim. Writing—review & editing: Sua Kim and Je Hyeong Kim. Approval of final manuscript: all authors.

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