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Development and Validation of an Acute Respiratory Distress Syndrome Prediction Model in Coronavirus Disease 2019: Updated Lung Injury Prediction Score

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Abstract

Objective: To develop and validate an updated lung injury prediction score for coronavirus disease 2019 (COVID-19) (c-LIPS) tailored for predicting acute respiratory distress syndrome (ARDS) in COVID-19.

Patients and Methods: This was a registry-based cohort study using the Viral Infection and Respiratory Illness Universal Study. Hospitalized adult patients between January 2020 and January 2022 were screened. Patients who qualified for ARDS within the first day of admission were excluded. Development cohort consisted of patients enrolled from participating Mayo Clinic sites. The validation analyses were performed on remaining patients enrolled from more than 120 hospitals in 15 countries. The original lung injury prediction score (LIPS) was calculated and enhanced using reported COVID-19–specific laboratory risk factors, constituting c-LIPS. The main outcome was ARDS development and secondary outcomes included hospital mortality, invasive mechanical ventilation, and progression in WHO ordinal scale.

Results: The derivation cohort consisted of 3710 patients, of whom 1041 (28.1%) developed ARDS. The c-LIPS discriminated COVID-19 patients who developed ARDS with an area under the curve (AUC) of 0.79 compared with original LIPS (AUC, 0.74; $P<.001$) with good calibration accuracy (Hosmer-Lemeshow $P=.50$). Despite different characteristics of the two cohorts, the c-LIPS's performance was comparable in the validation cohort of 5426 patients (15.9% ARDS), with an AUC of 0.74; and its discriminatory performance was significantly higher than the LIPS (AUC, 0.68; $P<.001$). The c-LIPS's performance in predicting the requirement for invasive mechanical ventilation in derivation and validation cohorts had an AUC of 0.74 and 0.72, respectively.

Conclusion: In this large patient sample c-LIPS was successfully tailored to predict ARDS in COVID-19 patients.

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The limited benefit of pharmacologic and nonpharmacologic interventions in established acute respiratory distress syndrome (ARDS) underscores the importance of preventive strategies in at-risk populations. Early identification of at-risk patients is crucial for implementing evidence-based preventive strategies known to improve patient outcomes and for evaluating future potential strategies.[1,2] Predictive clinical tools in ARDS are therefore useful in both clinical practice and research. The lung injury prediction score (LIPS) is a validated ARDS prediction tool that has been used to enroll at-risk patients in ARDS prevention clinical trials.[3]

The coronavirus disease 2019 (COVID-19) pandemic was responsible for an unprecedented increase in hospitalized patients with acute respiratory failure. The most severe end of this spectrum was ARDS, with considerable associated health care use and mortality.[4,5] Determining those patients with COVID-19 and acute respiratory failure at highest risk for ARDS development can be important clinically for triage decision-making and can help facilitate enrollment of the highest-risk patients into ARDS prevention clinical trials.[2,3] The risk factors for ARDS in critically ill patients are relatively well-described.[3,6] However, several features of ARDS in COVID-19 patients are distinct from non−COVID-19−associated ARDS.[7-11] There is currently limited data on COVID-19−specific ARDS risk prediction modeling.[12-14] The predictive ability of the LIPS tool is unclear in COVID-19 patients and, although LIPS has been shown to have a discriminatory effect to some extent in predicting ARDS in COVID-19 patients, it must be tailored for COVID-19 ARDS.[13,15]

In this study, we aimed to develop and validate an updated lung injury prediction score for COVID-19 patients (c-LIPS) using the VIRUS (Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study) Registry.[16,17]

PATIENTS AND METHODS

This was a registry-based cohort study using data from the VIRUS registry (Mayo Clinic Institutional Review Board: 20-002610). Informed consent was waived under Common Rule 45 CFR 46.116. Both derivation and validation analyses were conducted on the VIRUS registry patients.

Study Patients

All COVID-19 patients admitted to participating hospitals are eligible for VIRUS registry.[17] Patients from Minnesota sites for whom research authorization is not available and readmissions of previously enrolled patients were excluded.[18] Study data were recorded and managed using the Research Electronic Data Capture (REDCap) system.[19] REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.[19] The data was then stored in a central database.

Patients enrolled in the VIRUS registry between January 2020 and January 2022 were evaluated for inclusion. To ensure adequate granularity for the development of the score, the derivation analyses were conducted solely on patients enrolled from participating Mayo Clinic sites (Mayo Clinic Rochester, Mayo Clinic Florida, Mayo Clinic Arizona, Mayo Clinic Health System Eau Claire, and Mayo Clinic Health System Mankato). For validation analyses, all patients enrolled from sites contributing to the registry (other than Mayo Clinic institutions) were screened and patients from 121 sites located in 18 countries were included. Patients younger than 18 years of age and patients with missing hospital discharge status were excluded. In addition, patients whose ARDS development time could not be determined due to missing data, who qualified for ARDS at hospitalization, or who developed ARDS within the first day were also excluded (Figure 1).

Predictor Variables

Risk factors related to the development of ARDS and other adverse disease outcomes

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(eg, critical disease and death) in COVID-19 in prior research were assessed for model development.[12,14,15,20-35] Data were retrieved from the VIRUS registry including demographics, comorbidities, social history, disease presentation, laboratory findings, and vital signs. Because the tool was designed to predict ARDS risk early in the hospital course, only vital signs and laboratory findings recorded for the first day of admission were assessed.

Outcomes

The primary outcome was the development of ARDS during admission, using a modified version of the Berlin definition as (1) a partial pressure of arterial oxygen to fractional inspired oxygen (PaO_2/FiO_2) ratio of less than or equal to 300 mm Hg[36] or oxygen saturation (SpO_2)/FIO_2 for patients with missing PaO_2 data using previously validated equations to convert SpO_2 data to estimated PaO_2[37,38]; and (2) a positive end-expiratory pressure of greater than or equal to 5mm H_2O given by either invasive or noninvasive mechanical ventilation,[36] or need for high-flow nasal cannula (HFNC).[39]

Bilateral pulmonary opacities could not be ascertained in all patients due to limited availability of radiological data in the VIRUS registry. Considering that bilateral pulmonary opacity is the most common radiological finding in COVID-19 (>80%), this was not considered a major limitation.[40]

A sensitivity analysis was also conducted excluding patients who were only on HFNC as the highest level of oxygen support (those patients who were never on mechanical ventilation support). Secondary outcomes were the requirement for invasive mechanical ventilation, increase in the WHO ordinal scale score during admission, in-hospital mortality, 6-month mortality, and discharge disposition (home or any type of care facility). The performance of this model for secondary outcomes was compared with recently developed COVID-19–related prediction tools — the 4C Mortality and 4C Deterioration scores.[41,42]

Statistical Methods

Median (range) was used to describe continuous data, whereas frequencies and percentages were used to summarize categorical data. Patient factors associated with ARDS development were evaluated using univariate logistic regression. Those patient factors that were statistically significant ($P<.05$) in the univariate analyses were then included in multivariate modeling.

The Multivariate Imputation by Chained Equations package in R was used to replace missing laboratory values in both the model development and model validation data sets. In the model development data set (n=3710), the missing values included: leukocyte count (n=126, 3.4%), lymphocyte count (n=291, 7.8%), platelets (n=127, 3.4%), glucose (n=138, 3.7%), lactate (n=1382, 37.3%), C-reactive protein (CRP) (n=533, 14.4%), ferritin (n=925, 24.9%), and blood urea nitrogen (n=138, 3.7%). These missing data were assumed to be missing at random. Imputations were calculated using multivariate linear regression models to predict the missing values using one replication (single imputation). Finally, a complete data set was constructed.

The development of the c-LIPS model proceeded in five stages. First, multivariate logistic regression analysis, using backwards elimination variable selection, was used for determining factors significantly associated with ARDS development. That is, in the multivariate model, all the patient factors were statistically significant. Second, the set of statistically significant laboratory values, resulting from stage one, were categorized using locally weighted scatterplot smoothing plots and prior literature[43-48] and clinical judgement. Third, the categorized laboratory values and the current LIPS variables were entered into a multivariate logistic regression model for predicting ARDS. Fourth, the coefficients from the model developed in stage three were used for deriving the c-LIPS points for each categorical predictor. The final c-LIPS score is the sum of these points. Finally, the receiver operating characteristic (ROC) curve for the c-LIPS score was plotted

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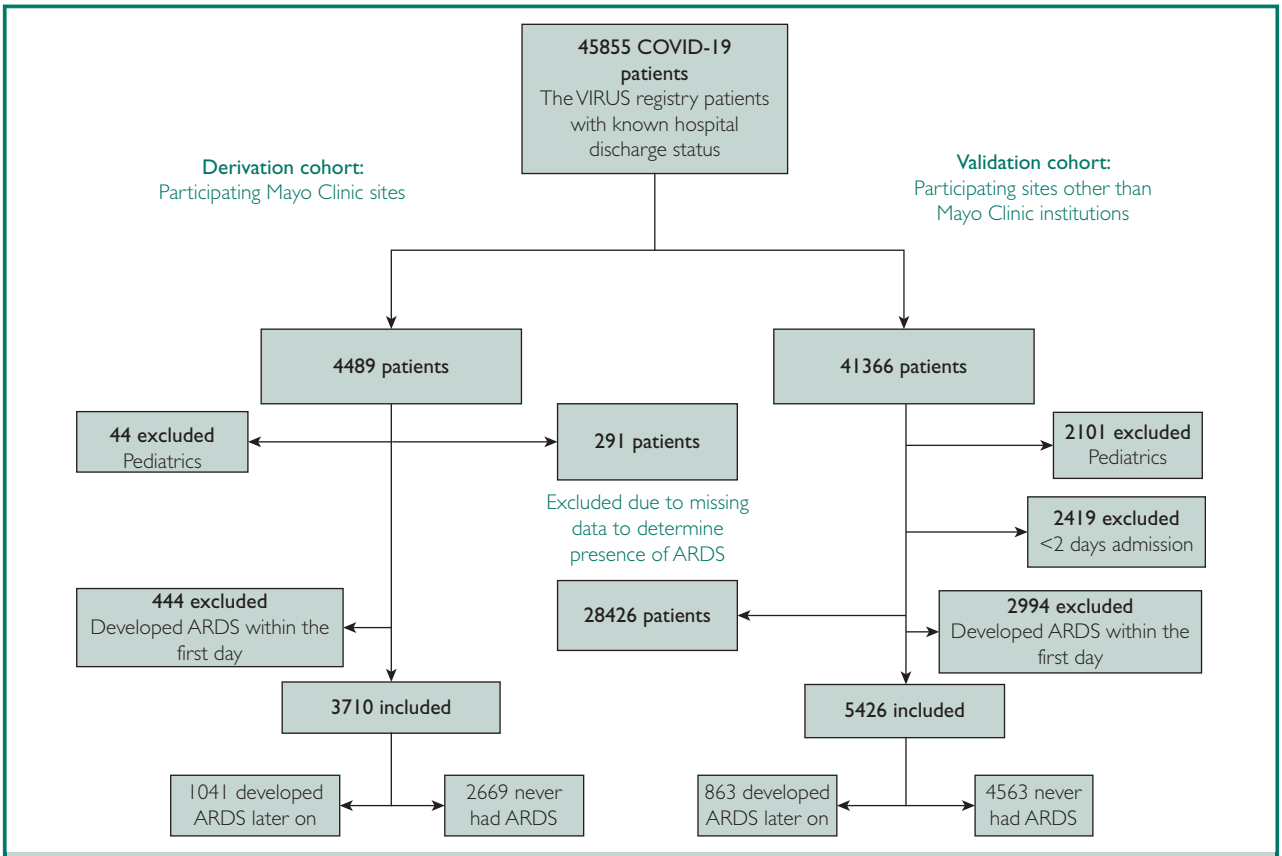

FIGURE 1. Flowchart for the identification of study patients. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease-2019; VIRUS, Viral Infection and Respiratory Illness Universal Study.

and the area under the curve (AUC) was calculated. Diagnostic test statistics (sensitivity and specificity) were calculated. The Hosmer-Lemeshow statistic was used to assess the model's calibration. R statistical software was used for all analyses (R Foundation for Statistical Computing, version 3.4). De Long's test was used to compare the ROC curves using MedCalc Statistical Software version 19.1 (MedCalc Software bv). All tests were two-sided with a statistical significance of *P* less than or equal to .05.

RESULTS

Figure 1 depicts the flowchart for subject identification. Baseline characteristics of the development and validation cohort are outlined in Table 1.

The original LIPS scores were calculated using the available data points at the time of admission. To enhance the performance of the LIPS score in COVID-19 ARDS, additional variables found to be significantly associated with ARDS development including smoking history, aspartate aminotransferase (AST), CRP, lactate, ferritin, glucose, and lymphocytes were included in the c-LIPS model.

Derivation Cohort

The derivation cohort included 3710 patients, of whom 1041 (28.1%) developed ARDS during their admission period. The median LIPS on admission was 3.5 (IQR, 2.5-4.5). The LIPS score distinguished patients who developed ARDS from those who did not with an AUC of 0.74 (95% CI, 0.72 to 0.76) (Figure 2). The median c-LIPS score (Table 2) on admission was 6 (IQR, 4.5-8). The c-LIPS score had an AUC of 0.79 (95% CI, 0.77 to 0.81) for predicting ARDS. The ROC curves for both LIPS and

TABLE 1. Baseline Information[a,b]

Characteristics	Derivation cohort (n=3710)		Validation cohort (n=5426)	
	Availability in the dataset, %		Availability in the dataset, %	
Age, y	100	66 (53-77)	98.5	59 (45-71)
Male	100	2094 (55.2)	100	3127 (57.6)
Race and ethnicity	100		100	
American Indian		94 (2.5)		22 (0.4)
Asian		144 (3.9)		1942 (35.8)
Black or African American		207 (5.6)		677 (12.5)
Hispanic		366 (9.9)		839 (15.5)
Native Hawaian		10 (0.3)		2 (0)
Other/unknown		87 (2.3)		191 (3.5)
White		2802 (75.5)		1753 (32.3)
LIPS[c]	100	3.5 (2.5-4.5)	100	2 (1-3)
Smoking, ever	100	1568 (42.2)	93	934 (17.2)
CRP, mg/L	86	64 (27-115)	46	22 (4-96)
Lactate, mmoL/L	63	1.5 (1.1-2)	25	1.5 (1-2.1)
Ferritin, μg/L	75	476 (218-959)	36	466 (199-897)
Glucose, mg/dL	96	123 (106-160)	48	129 (106-188)
Lymphocyte, $\times 10^9$/L	92	0.87 (0.59-1.30)	58	1.51 (0.79-32)
AST, U/L	90	39 (28-58)	58	36 (25-54)

[a]AST, aspartate aminotransferase; CRP, C-reactive protein; LIPS, lung injury prediction score.
[b]Data are presented as median (interquartile range) or n (%).
[c]Missing data for the LIPS variables were considered as normal[3]; for others, single imputation was performed.

c-LIPS are outlined in Figure 2. The frequency of patients who developed ARDS at different c-LIPS cutoffs is shown in Figure 3. The sensitivity analyses for different cutoff points of c-LIPS are provided in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). The model was well calibrated (Hosmer-Lemeshow P=.50) and calibration plot with good calibration accuracy is shown in Supplemental Figure 1 (available online at http://www.mayoclinic proceedings.org). The c-LIPS score was superior to the LIPS score in predicting ARDS development (difference in AUC of 0.047 [95% CI, 0.034 to 0.061]; P<.001).

A sensitivity analysis was performed excluding 503 (13.6%) patients with HFNC use as the highest level of oxygen support (those patients who were never on mechanical ventilation support). Among remaining 3207 patients, 538 (16.8%) developed ARDS during admission. The models showed similar performance with an AUC of 0.75 (95% CI, 0.73 to 0.78) and an AUC of 0.78 (95% CI, 0.76 to 0.80) for LIPS and c-LIPS, respectively.

Secondary outcomes of interest are outlined in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org). The performance of c-LIPS was good with regards to predicting the need for invasive mechanical ventilation (AUC, 0.74 [95% CI, 0.71 to 0.78]) and in-hospital mortality (AUC, 0.71 [95% CI, 0.67 to 0.75]). The performance of c-LIPS was modest for predicting clinical worsening on the WHO ordinal scale score (AUC, 0.68 [95% CI, 0.66 to 0.70]). The performance of c-LIPS was relatively poor in predicting discharge to any type of subacute or long-term care facility (AUC, 0.52 [95% CI, 0.50 to 0.55]). The ROCs of c-LIPS with regards secondary outcomes are shown in the Supplemental Figure 2 (available online at http://www.mayoclinicproceedings.org). A sample group

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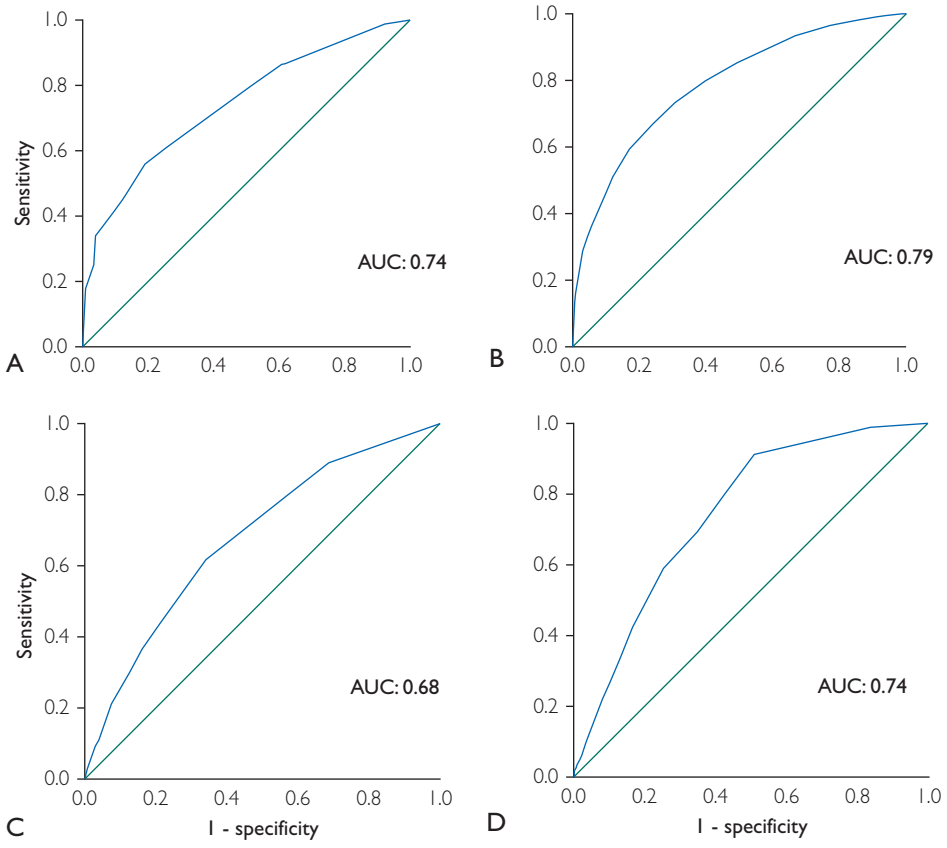

FIGURE 2. Receiver operating characteristic curves for the lung injury prediction score (LIPS) and coronavirus disease 2019 lung injury prediction score (c-LIPS) for classification of acute respiratory distress syndrome in derivation and validation cohorts. A, LIPS in the development cohort. The area under the receiver operating characteristic curve (AUC) was 0.74 (95% CI, 0.72 to 0.76). B, c-LIPS in the derivation cohort. The AUC was 0.79 (95% CI, 0.77 to 0.81). C, LIPS in the validation cohort. The AUC was 0.68 (95% CI, 0.66 to 0.7). D, c-LIPS in the validation cohort. The AUC was 0.74 (95% CI, 0.73 to 0.76).

of patients demonstrating score calculation is shown in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org).

We also tested 4C Mortality and 4C Deterioration scores' performance in our derivation dataset. The 4C Deterioration model was not able to discriminate the development of ARDS (AUC, 0.48 [95% CI, 0.45 to 0.50]); however, it performed better in predicting the requirement for invasive mechanical ventilation (AUC, 0.65 [95% CI, 0.61 to 0.70]). Meanwhile, the 4C Mortality score had an AUC of 0.72 (95% CI, 0.68 to 0.76) and 0.75 (95% CI, 0.73 to 0.78) in discriminating in-hospital mortality and 6-month mortality, respectively.

Validation Cohort

The validation cohort included 5426 patients from 121 sites. The incidence of ARDS in the validation cohort was 15.9% (n=863). The median LIPS in the validation cohort was 2 (IQR, 1-3) and it had an AUC of 0.68 (95% CI, 0.66 to 0.7) for predicting ARDS. The median c-LIPS score was 3 (IQR, 2-5), with an AUC of 0.74 (95% CI, 0.73 to 0.76) (Figure 2). Figure 3 shows the frequency of patients who developed ARDS at different

TABLE 2. Predictive Variables for Acute Respiratory Distress Syndrome Development in the Derivation Cohort[a,b]

Coefficients		Estimate	P[c]	Points assigned
LIPS score[d]	100%	0.6452	< .001	As is
AST	> 43 U/L	0.4045	< .001	1
CRP	50 to 100 mg/L	0.6050	< .001	1
	>100 mg/L	0.9224	< .001	2
Ferritin	>500 μg/L	0.4045	< .001	1
Glucose	>180 mg/dL	0.4243	< .001	1
Lactate	2-4 mmol/L	0.2871	.048	0.5
	>4 mmol/L	0.4523	.01	1
Lymphocyte count	$<0.8 \times 10^9$/L	0.3882	< .001	1
Smoking, ever	Yes	0.1686	.048	0.5

[a]AST, aspartate aminotransferase; CRP, C-reactive protein; LIPS, lung injury prediction score.
[b]The cutoff points were selected according to the literature as well as clinical experience.[43-48]
[c]Comparative analyses were performed in the derivation cohort.
[d]Components of the LIPS that were available in the dataset include predisposing conditions (such as shock, sepsis, and pneumonia) and risk modifiers (such as alcohol abuse, obesity, hypoalbuminemia, chemotherapy, fraction of inspired oxygen levels, tachypnea, oxygen saturation levels, acidosis, and diabetes mellitus).

c-LIPS cutoffs. Supplemental Table 1 shows the sensitivity analyses for various cutoffs. The difference between the AUC for LIPS vs c-LIPS was 0.067 (95% CI, 0.053 to 0.080; $P<.001$).

The model's calibration declined in the validation set with lower prevalence. However, when comparing the expected and observed frequencies, they demonstrated with reasonable calibration. The calibration plot is shown in Supplemental Figure 1.

Supplemental Table 2 shows secondary outcomes of interest and their frequency in the validation cohort. When we looked at the performance of the c-LIPS in predicting secondary outcomes, the AUC for determining invasive mechanical ventilation was 0.72 (95% CI, 0.70 to 0.74). In terms of other secondary outcomes, the AUC for in-hospital mortality was 0.67 (95% CI, 0.65 to 0.69), for progression on the WHO ordinal scale was 0.69 (95% CI, 0.67 to 0.71); and predicting discharge to a subacute or long-term care facility was 0.56 (95% CI, 0.54 to 0.59).

DISCUSSION

In this large, multicenter cohort study, we assessed the performance of the existing, previously validated, LIPS score for predicting COVID-19–related ARDS and then developed a modified score, c-LIPS, that incorporated predictors specific to the COVID-19 population. The c-LIPS score offered better discriminatory performance for predicting ARDS development than the LIPS score alone. Specifically, in the validation cohort, a c-LIPS score on admission of greater than 3 conferred a 10% or greater chance of ARDS development. Interestingly, in the validation cohort, the frequency of ARDS reached to greater than 30% by c-LIPS score of 6, and did not considerably increase further after that threshold (Figure 3).

In our derivation cohort, the model was well calibrated (Hosmer-Lemeshow $P=.50$). As expected, calibration modestly declined in the validation set with lower prevalence of ARDS. When the expected and observed frequencies that are similar were compared, the model showed reasonable calibration. The prevalence of ARDS differed between the derivation and validation datasets (n=1041 of 3710 [28.1%] vs n=863 of 5426 [15.9%], respectively), which could be attributed to the fact that all five hospitals in the derivation set were tertiary care facilities. In contrast, the validation cohort was

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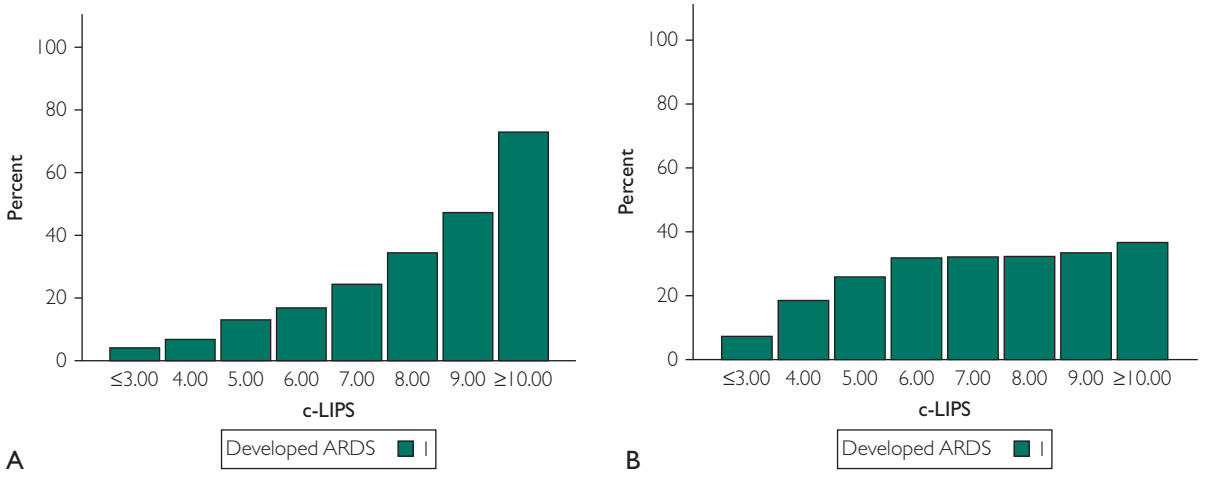

FIGURE 3. The frequency of patients who developed acute respiratory distress syndrome for different coronavirus disease 2019 lung injury prediction score levels. A, Derivation cohort. B, Validation cohort. ARDS, acute respiratory distress syndrome; c-LIPS, coronavirus disease 2019 lung injury prediction score; LIPS, lung injury prediction score.

gathered from a variety of settings, including academic, community, and private hospitals. Another potential explanation for the dissimilarity is that the derivation cohort was confined to the United States, whereas the validation analyses were performed on patients from a global dataset. Possible differences in health care resources and policies may have influenced admission criteria in these settings.

To improve the performance of the LIPS for predicting ARDS in COVID-19 patients, we enhanced it with routinely available data variables that have been shown to be associated with adverse outcomes in COVID-19 patients including smoking history, lymphocyte count, AST, CRP, lactate, ferritin, and glucose levels.[12,14,20,22,24,29,30,33,34,49] Although there was considerable missingness in this cohort, likely registry-specific only, these additional variables have been routinely reported in other COVID-19–related studies reflecting clinical practice. Some of the key variables from the original LIPS model (eg, high-risk trauma or surgery) were not available in our dataset. Thus, we calculated the LIPS assuming that patients did not have these risk factors.[3] Because these variables are typically not relevant to the setting of COVID-19, this assumption is likely acceptable. In the original LIPS study, the presence of diabetes mellitus if accompanied by sepsis was found to be associated with a decreased likelihood of ARDS development. We were unsure if diabetes had the same effect on COVID-19 patients. Therefore, we ran a sensitivity analysis excluding diabetes and overall model performance was unchanged. To increase the convenience of calculation of the score, we have categorized them according to the levels.

Initially, we attempted to build a model for predicting ARDS by treating some variables (CRP, AST, blood urea nitrogen, lactate, platelets, and leukocytes) as continuous while classifying others (lymphocytes, glucose, and ferritin) as normal or abnormal, and including estimates in the calculation

rather than assigning scores. The AUC for this method was 0.80 (95% CI, 0.78 to 0.81%) in the derivation cohort. Because the version with classified points achieved nearly as good discriminatory performance, we decided to use the model with assigned scores rather than keep some as continuous in the model for the sake of simplicity and uniformity, as well as to be consistent with the original LIPS methodology.

Various prediction models have been developed to determine the likelihood of adverse outcomes in COVID-19 patients. However, the outcomes of interest in those studies were typically mortality or composite outcomes indicating clinical worsening.[23,27,29-31,33] We tested the performances of 4C Mortality and 4C Deterioration scores, both of which were developed using a large multinational dataset, in our derivation cohort. The 4C Mortality score showed modest performance in predicting mortality, but poor performance in predicting ARDS development.[42] The 4C Deterioration score had lower performance overall than the 4C Mortality score.[41] Importantly, neither of these scores were developed to predict ARDS development and as such it is not surprising that model performance was lower than for c-LIPS.

Although there has been some prior work on developing prediction tools that assess risk of progression to ARDS in hospitalized COVID-19 patients, these have major methodological limitations that preclude wider use.[12,14] For example, Seo et al[12] developed a four-predictor model using 37 ARDS patients in Korea. Of the four predictors chosen, CRP is the only one featured in c-LIPS. In addition to small sample size and limited generalizability, this model had no validation phase. Another model was developed using machine learning methodologies from 76 ARDS patients in China.[14] Clinical predictors shared with c-LIPS include lymphocyte count, AST, CRP, obesity, and lactate. This study also had a small sample size, limited external validation, and relied on region-specific severity scoring systems that are not widely used. One recent model (eARDS) was developed using machine learning methodologies using a large multicenter cohort. It focused on key vital sign derangements (eg, heart rate, respiratory rate, SpO_2) that were predictive of clinical deterioration and ARDS development up to 12 hours before ARDS development. Although this model had good performance and was rigorously developed, its role is primarily as an early warning system for already hospitalized patients rather than a risk predictor at the time of hospitalization. In contrast, c-LIPS provides prediction of ARDS development at the time of hospitalization, potentially days before ARDS development. All three studies outlined were also from the early months of the pandemic when therapeutics (eg, steroids, immune modulators, and antivirals) were limited, health care systems often overburdened, and newer COVID-19 variants were not yet prevalent.[50,51]

Our study has several strengths that are worth emphasizing. The development cohort included patients from multiple sites in geographically different settings that encompass a diverse patient population while ensuring highly granular data access in a unified electronic health care record. The management of the development cohort was also relatively uniform because our institution had a standardized approach to management of COVID-19 patients including criteria for intensive care unit transfer and ARDS management. Another important strength of our study was the large, robust international validation cohort, which included patients from academic, community, and private hospitals from more than 15 countries, which enhanced the generalizability of our results. Additionally, due to the large amount of data available, we were able to test the model's performance in predicting other outcomes, such as mortality and discharge disposition. Although there were notable differences in the baseline characteristics of the derivation and validation cohorts including age, race, incidence of ARDS, and inflammatory markers, the performance of the c-LIPS was similar in both cohorts, again emphasizing the generalizability of this tool.[41,42] Importantly, the factors chosen

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for c-LIPS are also routinely collected during hospital admission, indicating that this score can have wider applicability.

Study Limitations

The main limitation of the study was the lack of reliable radiological data which impelled us to use a modified version of the Berlin criteria instead of the original definition. Another important limitation was reliance on retrospectively collected electronic health record data, which had a high rate of missing variables. This precluded us from testing some variables that could have been relevant to the COVID-19 ARDS process. The stepwise approach to variable selection for our model was important and thus patients with missing data were not excluded but handled through imputation. All five derivation centers are tertiary care facilities, which may have resulted in a referral bias. However, showing that the test performed well in the multicenter validation analyses might alleviate the concerns about its generalizability. Additionally, the inclusion of parameters as categorized variables with assigned scores over continuous variables eliminates some critical information. However, for the sake of simplicity and uniformity with the original LIPS model, we adopted the model with cutoff values. We attempted to ameliorate the impact of dichotomization by categorizing certain clinically important severity indicators (CRP and lactate) into three categories rather than two. Ultimately, our model's discriminatory performance using the cutoffs was nearly as good as the model with continuous variables. Another limitation was that, because the employment of some treatment strategies (ie, corticosteroids and antivirals) were directly related to the disease severity at the time of presentation, we could not test the impact of early exposure to these treatments on ARDS development. Lastly, we were not able to consider the impact of the different circulating variants in the study.

CONCLUSION

In this large database of COVID-19 patients, we tested the performance of the LIPS in predicting ARDS and enhanced its performance by including laboratory tests which are routinely performed in COVID-19 patients. The new model, c-LIPS, performed well in the international external validation cohort. Although the modest positive predictive value may limit routine clinical use, c-LIPS can be used as a predictive enrichment tool to enroll high-risk patients into ARDS prevention studies and clinical trials.

POTENTIAL COMPETING INTERESTS

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ARDS,** acute respiratory distress syndrome; **AST,** aspartate aminotransferase; **AUC,** area under the curve; **c-LIPS,** lung injury prediction score for COVID-19 patients; **COVID-19,** coronavirus disease 2019; **CRP,** C-reactive protein; **HFNC,** high-flow nasal cannula; **LIPS,** lung injury prediction score; **PaO_2/FiO_2,** partial pressure of arterial oxygen to fractional inspired oxygen ratio; **ROC,** receiver operating characteristic; **SCCM,** Society of Critical Care Medicine; **SpO2,** oxygen saturation; **VIRUS,** Viral Infection and Respiratory Illness Universal Study

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