Lung Ultrasound Score to Predict Outcomes in COVID-19

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BACKGROUND: Patients with coronavirus disease 2019 (COVID-19) can develop severe bilateral pneumonia leading to respiratory failure. We aimed to study the potential role of lung ultrasound score (LUS) in subjects with COVID-19. METHODS: We conducted an observational, prospective pilot study, including consecutive subjects admitted to an intermediate care unit due to COVID-19 pneumonia. LUS is a 12-zone examination method for lung parenchyma assessment. LUS was performed with a portable convex transducer, scores from 0 to 36 points. Clinical and demographic data were collected at LUS evaluation. Survival analysis was performed using a composite outcome including ICU admission or death. Subjects were followed for 30 d from LUS assessment. RESULTS: Of 36 subjects included, 69.4% were male, and mean age was 60.19 ± 12.75 y. A cutoff LUS ≥ 24 points showed 100% sensitivity, 69.2% specificity, and an area under the receiver operating characteristic curve of 0.85 for predicting worse prognosis. The composite outcome was present in 10 subjects (55.6%) with LUS ≥ 24 points, but not in the group with lower LUS scores ($P < .001$). Subjects with LUS ≥ 24 points had a higher risk of ICU admission or death (hazard ratio 9.97 [95% CI 2.75–36.14], $P < .001$). Significant correlations were observed between LUS and S_{pO_2}/F_{IO_2}, serum D-dimer, C-reactive protein, lactate dehydrogenase, and lymphocyte count. CONCLUSIONS: LUS ≥ 24 points can help identify patients with COVID-19 who are likely to require ICU admission or to die during follow-up. LUS also correlates significantly with clinical and laboratory markers of COVID-19 severity.
Key words: COVID-19; lung ultrasound; intermediate respiratory care unit; ICU; pneumonia; ARDS.
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Introduction

Coronavirus disease 2019 (COVID-19) is a viral infection by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with COVID-19 develop lung damage, which can lead to respiratory failure and ARDS.[1] Approximately 26% of hospitalized patients with COVID-19 pneumonia require admission in the ICU.[1,2] The rapid increase in infected patients with severe disease highlights the need for better diagnostic and prognostic tools to improve patient care and health care resource administration.[3,4]

Different clinical, laboratory, and imaging features have been associated with severe COVID-19 pneumonia. P_{aO_2}/F_{IO_2} and its equivalent, S_{pO_2}/F_{IO_2}, may be relevant for the severity assessment of patients with COVID-19 with respiratory failure.[2,5-8] Furthermore, several blood markers have been described in severe cases, such as a high white blood cell count, low lymphocyte count, and elevated D-dimer, lactate dehydrogenase (LDH), and C-reactive protein, among others.[1,2,5,7,9] Regarding imaging features, the main finding in chest computed tomography (CT) of patients with COVID-19 is bilateral ground-glass opacities predominantly in lower lobes,[10] which has been significantly higher in nonsurviving individuals.[1] Nevertheless, patients with severe illness may have difficulty in accessing chest CT depending on their clinical respiratory and hemodynamic status and the risk of contamination. In addition to these limitations, data on the prognostic values and clinical implications of the aforementioned features in patients with COVID-19 are scarce. Therefore, more information is needed to improve prediction and early detection of clinical impairment.

Lung ultrasound use has increased as a diagnostic and monitoring tool in critically ill patients.[11] Ultrasonographic patterns have been useful for assessing pneumonia, atelectasis, pleural effusion, pulmonary edema, pneumothorax, and ARDS,[12-14] as well as for monitoring respiratory response in patients with invasive ventilation.[15-17] In this

regard, lung ultrasound score (LUS) may be used as a semi-quantitative index for the assessment of lung aeriation loss and prediction of clinical outcomes in patients in the ICU.[13,15,18] Recently, lung ultrasound has been recommended for the evaluation of patients with COVID-19 because of its bedside utility and the minimal involvement of health care professionals.[16,19,20] However, the value of lung ultrasound in this disease is still to be fully studied. We aim to assess the potential role of LUS as a prognostic tool in the management of patients with COVID-19.

QUICK LOOK

Current knowledge

Severe COVID-19 is a global health care concern. A significant number of patients will need critical care attention. Finding clinical and radiological prognostic factors will help identify subjects who may need critical support.

What this paper contributes to our knowledge

Lung ultrasound score had the accuracy to identify severe COVID-19 clinical evolution. Lung ultrasound score correlated significantly with clinical and laboratory markers of COVID-19 severity. Lung ultrasound is an simple and noninvasive bedside tool useful in patients with critical COVID-19 illness.

Methods

Data Collection and Design

An observational, prospective pilot study was performed on consecutive subjects admitted to the intermediate respiratory care unit (IMCU) of a tertiary care hospital in Barcelona, Spain, throughout the month of April 2020. The study protocol was approved by the local ethics committee (PR260/20). Informed consent was obtained from all subjects included in the study. All procedures performed in this study involving human subjects were in accordance with the ethics standards of the institution as well as the 1964 Helsinki Declaration. The inclusion criterion was admission to the IMCU due to respiratory failure related to COVID-19 pneumonia. All subjects were diagnosed with a positive polymerase chain reaction for SARS-CoV-2 from nasopharyngeal swab and the presence of patchy infiltrates on chest radiography. Subjects were transferred to the IMCU directly from the emergency department or from general wards when respiratory support with high-flow nasal cannula oxygen therapy or noninvasive ventilation was required. Exclusion criteria were recent admission to the ICU, invasive mechanical ventilation, suspected or proven respiratory infection by another pathogen and respiratory failure due to any etiology other than COVID-19. Demographic, clinical, radiological, and laboratory data were collected for all subjects at the time of LUS evaluation, which was performed the day they were admitted into the IMCU. However, some of the subjects were already admitted into the emergency department or other medical facilities before. Subjects were followed-up until 30 d from lung ultrasound assessment.

Lung Ultrasound Evaluation

A complete lung ultrasound examination was performed after admission to the IMCU by a trained pulmonologist blinded to subjects' clinical information. A Lumify C5-2 convex transducer (Philips, Amsterdam, The Netherlands) set into lung configuration was used, equipped with a portable tablet and the Lumify app. During examination, the portable tablet device and the transducer were wrapped in single-use protection to reduce contamination and improve sterilization. Tablet and transducer were sterilized following recent recommendations after examination.[21]

Ultrasound findings were reported using the LUS according to current recommendations.[16] Briefly, LUS evaluates lung parenchyma following a 12-zone examination of the thorax.[15,17,22] Anterior (midclavicular line), lateral (midaxillary line), and posterior (paravertebral line) chest wall regions were divided in 2 parts (superior and inferior). Posterior exploration was performed when subjects were able to sit or tilt sideways. When this was not possible, it was substituted with posterior axillary line exploration. The transducer was placed longitudinal to the ribs to enhance pleural and lung exploration.[23,24] Each region was then scored following recommendations for point-of-

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care lung ultrasound: lung sliding with A-lines or < 3 isolated B-lines scored 0; multiple well-defined B-lines (B1) scored 1; multiple coalescent B-lines (B2) or white lung scored 2; and subpleural consolidation scored 3. The sum of the scores defined the LUS, ranging from 0 to 36 points.[22,25]

Subjects were divided into 2 groups depending on lung ultrasound assessment, corresponding to severe alveolo-interstitial involvement (LUS ≥ 24) and mild to moderate alveolo-interstitial involvement (LUS < 24). A survival analysis was performed using a composite event for worse clinical outcome defined as ICU admission or death. ICU admission criteria included cardiopulmonary arrest, sudden fall in level of consciousness, invasive ventilation requirement, and shock. LUS correlations with clinical and blood severity markers were evaluated. Accuracy values for prediction of poor clinical outcomes for these features were studied using criteria for ARDS[6] and cutoff values identified in severe cases from previous studies.[2,5,7,8]

Statistical Analysis

Categorical data are described as frequency and percentages, and differences were evaluated using the chi-square test or Fisher exact test when required. Continuous variables are expressed as mean ± SD for normally distributed variables or median and interquartile range (IQR) otherwise. Differences in continuous variables were analyzed with analysis of variance or the Student *t* test or their corresponding nonparametrical tests when required (eg, Kruskal-Wallis and Mann-Whitney U tests). Predictive accuracy and optimal cutoff point for LUS for the prediction of the composite outcome was estimated using the bootstrap technique for receiver operating characteristic curve analysis. Accuracy values were calculated for LUS and disease severity markers. Kaplan-Meier survival analysis was used to evaluate time to ICU admission or death. Due to the absence of events in one group, the univariate hazard ratio was calculated using the Mantel-Haenszel approach for variables showing significant differences between subjects with and without the composite event. $P < .05$ was considered statistically significant. Data were analyzed using GraphPad Prism 8.2.1 (GraphPad Software, San Diego, California) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

Of 36 subjects with severe COVID-19 pneumonia hospitalized in the IMCU were included, 25 (69.44%) were male, and mean age was 60.19 ± 12.85 y. Twenty-three subjects (63.9%) were transferred to the IMCU from the general ward due to respiratory impairment during admission, and 13 (36.1%) were admitted directly from the emergency department. The most frequent comorbidity was hypertension (50.00%), obesity (38.9%) and dyslipidemia (30.6%). Demographic and clinical characteristics of included subjects are described in Table 1. The composite outcome of ICU admission requirement or death was described in 10 subjects (27.8%), and hospital discharge during the 30-d follow-up was possible in 26 (72.2%) subjects. All reported deaths were related to respiratory complications. No significant differences were identified between discharged subjects and those requiring ICU admission or deceased regarding medical history, active treatment during admission, peripheral blood leukocytes, and serum ferritin.

LUS Accuracy

Median LUS was 23.5 points (IQR 16-27); median time from hospital admission to lung ultrasound evaluation was 6.5 d (IQR 3-11.25). The most frequent ultrasound findings were B2-lines (41% of the explored zones), followed by subpleural consolidations (25%) and B1-lines (18.1%). Normal lung parenchyma, described as A-lines, was identified in 16% of explored areas.

The optimal cutoff point for LUS was estimated at 24 points. LUS ≥ 24 showed an area under the receiver operating characteristic curve of 0.846 and an accuracy of 77.8%. Eighteen subjects (50%) had a LUS ≥ 24, and 18 (50%) presented with LUS < 24. No significant differences in time from hospital admission to lung ultrasound evaluation were observed between groups. Subject characteristics according to LUS are described in Table 1, and LUS accuracy values are presented in Table 2.

Clinical Outcomes

The composite outcome was described in 10 subjects (55.6%) with LUS ≥ 24 points, but not in the lower LUS group ($P < .001$). Seven participants (19.4%) required ICU admission, and 5 (13.9%) died during follow-up. Two of the deceased subjects had been already transferred to the ICU. LUS was higher in subjects with the observed composite outcome (median 26.5 points [IQR 25.5-28.25] vs 19 points [IQR 16-24], $P = .004$). Kaplan-Meier survival analysis identified a significant difference between LUS groups regarding the composite outcome (Fig. 1). Among subjects with LUS ≥ 24 points, survival at 7 d from lung ultrasound assessment was 50% (95% CI 31.50–79.40%), compared to 100% in subjects with lower LUS. Subjects with LUS ≥ 24 had a significantly higher risk of having worse clinical outcomes

Table 1. Subject Characteristics at the Time of Evaluation

	Subjects ($N = 36$)	Lung Ultrasound Score		P
		< 24 points ($n = 18$)	≥ 24 points ($n = 18$)	
Subject background				
Age, y	60.2 ± 12.8	56.6 ± 12.5	63.8 ± 12.3	.09
Male	25 (69.4)	14 (77.8)	11 (61.1)	.47
Smoking history	6 (16.7)	1 (5.6)	5 (27.8)	.18
Hypertension	18 (50.0)	7 (38.9)	11 (61.1)	.32
Dyslipidemia	11 (30.6)	6 (33.3)	5 (27.8)	> .99
Diabetes	6 (16.7)	4 (22.2)	2 (11.1)	.66
Obesity	14 (38.9)	8 (44.4)	6 (33.3)	.73
COPD	1 (2.8)	1 (5.6)	0	> .99
Asthma	3 (8.3)	2 (11.1)	1 (5.6)	> .99
Cardiopathy	2 (5.6)	1 (5.6)	1 (5.6)	> .99
Hepatopathy	4 (11.1)	2 (11.1)	2 (11.1)	> .99
History of malignancies	5 (13.9)	1 (5.6)	4 (22.2)	.34
Chronic kidney disease	3 (8.3)	1 (5.6)	2 (11.1)	> .99
Severity assessment				
S_{pO_2}/F_{IO_2}	162 (76.8)	191 (101.3)	126.5 (39.3)	< .001
Lung ultrasound score	23.5 (11)	16 (6.8)	27 (3.8)	< .001
Laboratory blood tests				
Lactate dehydrogenase, U/L	366.5 (191)	328 (73.3)	440.5 (288.8)	.001
C-reactive protein, mg/L	22.3 (57.7)	12.1 (5.7)	45.5 (23.4)	.068
Ferritin, μg/L	911.5 (510.8)	911 (312.6)	926.4 (722.9)	.39
Leukocyte count, $\times 10^9$/L	9.8 (7.1)	8.8 (4.7)	12.7 (6.7)	.068
Lymphocyte count, $\times 10^9$/L	0.98 (0.88)	1.63 (0.98)	0.86 (0.27)	.002
D-dimer, μg/L	504 (686)	367 (446.5)	783 (2282)	.01
Treatment				
Lopinavir/ritonavir	18 (50)	10 (55.6)	8 (44.4)	.74
Hydroxychloroquine	36 (100)	18 (100)	18 (100)	> .99
Azithromycin	14 (38.9)	8 (44.4)	6 (33.3)	.73
Systemic corticosteroids	35 (97.2)	17 (94.4)	18 (100)	> .99
Tocilizumab	22 (61.1)	11 (61.1)	11 (61.1)	> .99
Low molecular weight heparin	33 (91.67)	15 (83.3)	18 (100)	.23
Respiratory support				.045
Air-entrainment mask	9 (25)	6 (33.3)	3 (16.7)	
Non-rebreather mask	2 (5.6)	1 (5.6)	1 (5.6)	
High-flow nasal cannula	16 (44.4)	10 (55.6)	6 (33.3)	
Noninvasive ventilation	9 (25)	1 (5.6)	8 (44.4)	
Outcomes				
ICU admission	7 (19.4)	0	7 (19.4)	< .001
Deaths	5 (13.9)	0	5 (13.9)	< .001
In the IMCU	3 (60)	NA	3 (60)	
In the ICU	2 (40)	NA	2 (40)	
Time to event	7 (9.5)	NA	7 (9.5)	
Discharged	26 (72.2)	17 (94.4)	9 (50)	.009
Follow-up time, d	11 (11)	8 (6.8)	16.5 (14)	.034

Data are presented as n (%), mean ± SD, or median (interquartile range).
IMCU = intermediate respiratory care unit
NA = not applicable

compared to those with lower LUS (hazard ratio 9.97 [95% CI 2.75–36.14], $P < .001$).

Regarding hospital stay, a statistically significant difference was observed in time from lung ultrasound exploration to hospital discharge between subjects with LUS ≥ 24 and subjects with LUS < 24 (median 18 vs 8 d, respectively, $P = .001$). At 7 d from ultrasound exploration, 8 subjects (44.4%) of those with LUS < 24 were discharged, whereas

Table 2. Hazard Ratio and Accuracy Values of Lung Ultrasound Score and Other Severity Markers for the Prediction of ICU Admission or Death

	Reference Value	Hazard Ratio (95% CI)	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Area Under ROC
Lung ultrasound score ≥ 24 points	NA	9.97 (2.75–36.14)*	100%	69.2%	100%	55.6%	0.85
$S_{pO_2}/F_{IO_2} < 235$	NA	3.57 (0.58–21.99)	100%	23.1%	100%	33.3%	0.62
D-dimer > 500 μg/L	0–250 μg/L	2.39 (0.67–8.65)	70%	57.7%	83.3%	38.9%	0.64
Lactate dehydrogenase > 400 U/L	0–224 U/L	3.96 (1.06–14.72)*	70%	69.2%	85.7%	46.7%	0.70
C-reactive protein > 10 mg/L	0–5 mg/L	4.64 (1.13–18.97)*	100%	34.6%	100%	37%	0.67
Lymphocyte count < 0.8 × 10^9/L	1.30–3.40 mg/L	1.79 (.43–7.35)	40%	76.9%	76.9%	40%	0.59

* Log-rank test: $P < .05$.
NA = not applicable

all of the subjects with LUS ≥ 24 were still hospitalized. Furthermore, hospital discharge within 14 d from lung ultrasound assessment was achieved in 4 (22.2%) subjects of the LUS ≥ 24 group versus 14 (77.8%) of the subjects with LUS < 24. At 30 d of follow-up from lung ultrasound assessment, only 1 subject (5.6%) with lower LUS was still hospitalized (95% CI 0.83–37.32), whereas 4 (22.22%) surviving subjects with LUS ≥ 24 were still admitted (95% CI 14.70–71.70).

LUS and Severity of Disease

We investigated varying cutoffs of the LUS. Lowering the cutoff to 20 points or 22 points resulted in an important loss of specificity to ∼ 50% while maintaining a sensitivity of 100%. An increase in the cutoff to 26 points or 28 points achieved a higher specificity (> 75%) but reduced sensitivity to < 60%. The receiver operating characteristic curve is shown in Figure 2.

There was a significant correlation between LUS and S_{pO_2}/F_{IO_2} (r = –0.674, $P < .001$) and blood laboratory tests such as D-dimer (r = 0.424, $P = .01$), C-reactive protein (r = 0.373, $P = .02$), LDH (r = 0.460, $P = .004$), and lymphocyte count (r = –0.487, $P = .002$), as presented in Figure 3.

We compared the predictive accuracy values of LUS with clinical and analytical severity markers showing significant correlations to assess its added diagnostic power (Table 2).

Discussion

This pilot study has demonstrated that LUS could help identify subjects with COVID-19 who are likely to have worse clinical outcomes. LUS also showed significant correlations with clinical and blood severity markers. Therefore, lung ultrasound may be a useful tool for the assessment of subjects with COVID-19.

The severity of COVID-19 pneumonia and the rapid transmission of the virus have led to a worldwide increase in the burden of critical care units.[26] In our study, 7 (19.4%) subjects required admission to the ICU and 5 (13.9%) died during follow-up. Of this latter group, 3 subjects were already in the ICU. This proportion of subjects with worse clinical evolution is higher than what was initially observed in reports from China,[2,8] but it is similar to studies from recent cohorts in the United Kingdom[27] and the United States.[5] Notably, subjects in our study who required ICU admission or died did not show significant differences regarding age, gender, or clinical history. This highlights the importance of identifying accurate prognostic tools for the assessment of subjects with COVID-19 to improve patient management and the administration of health care resources.

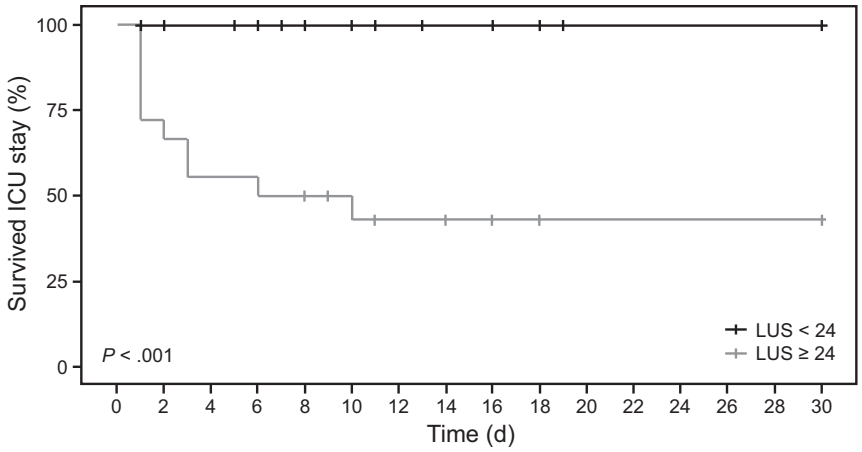

Fig. 1. Kaplan-Meier analysis for ICU admission requirement or death according to lung ultrasound score (LUS).

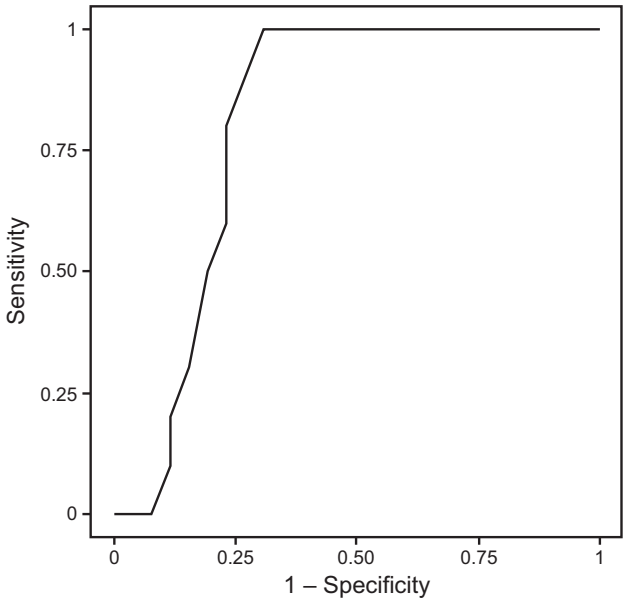

Fig. 2. Receiver operating characteristic curve for lung ultrasound score.

Lung ultrasound is a low-cost, harmless, and easy-to-clean imaging tool that provides useful information of pleural and lung parenchymal integrity. During the COVID-19 pandemic, few studies have reported the utility of lung ultrasound for the assessment of critically ill subjects due to the possibility of bedside application requiring a single examiner.[22,28,29] However, strong evidence favoring its routine use in this disease is scarce.[30] Our results with the LUS indicate the important role that lung ultrasound may have in the management of subjects with COVID-19 in an IMCU environment. This validated index for the assessment of lung parenchymal damage[16,22,30] is independently associated to 28-d mortality in shock patients.[15] Similar results were observed in our pilot cohort, as subjects with higher LUS had a significantly higher risk of worse clinical outcomes. We studied different cutoff values, and a LUS $\geq$ 24 points showed the highest accuracy for predicting ICU admission or death. Results reported by Burian et al[31] showed similar accuracy values for chest CT features and serum inflammation markers in subjects with COVID-19 who required ICU management.[31] However, lung ultrasound may be a simpler and faster option for predicting clinical evolution and adjusting patient care.

Severe COVID-19 also leads to longer hospital stay. However, current evidence is limited, as more severe subjects were still hospitalized at the time of publication of most recent studies.[27] Median hospital stay in our cohort was 11 d (IQR 7-18) after lung ultrasound assessment in the IMCU. Subjects with higher LUS had a significantly longer hospital stay (median 18 vs 8 d from lung ultrasound evaluation for subjects with LUS $\geq$ 24 and $<$ 24 points, respectively, $P = .001$). Also, subjects with lower LUS were more likely to be discharged from the hospital during any measured time period. Thus, lung ultrasound evaluation may also help identify subjects with better prognosis in subjects with severe COVID-19 illness.

Lung ultrasound correlation with clinical features has already been described in critically ill subjects,[18] but data are scarce for COVID-19. In our study, we identified that LUS correlated positively with clinical markers associated with COVID-19 severity, such as D-dimer, C-reactive protein, and LDH, and correlated negatively with S_{pO_2}/F_{IO_2} and lymphocyte count. We investigated the possible added value of LUS for the prediction of worse clinical prognosis. Briefly, $S_{pO_2}/F_{IO_2} < 235$ identified all cases with worse prognosis but had a high false positive rate (specificity 23.1%). D-dimer $>$ 500 μg/L, LDH $>$ 400 U/L, and lymphocyte count $< 0.8 \times 10^9$/L predicted only 30%, 70%, and 40% of subjects who died or required ICU admission, respectively, in contrast to the 100% sensitivity of LUS $\geq$ 24 points. On the other hand, C-reactive protein $>$

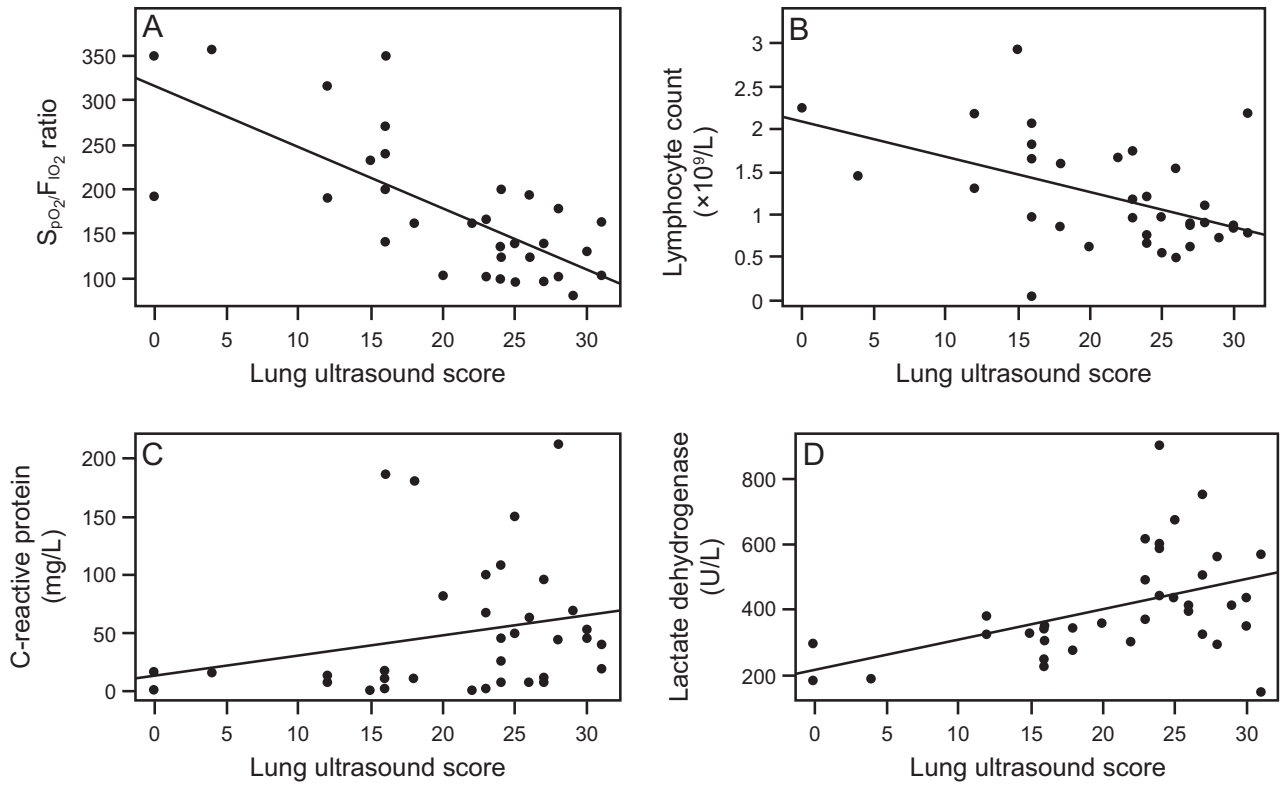

Fig. 3. Correlation between the lung ultrasound score and disease severity markers. (A) S_{pO_2}/F_{IO_2}; (B) lymphocyte count; (C) C-reactive protein; (D) lactate dehydrogenase.

10 mg/L showed a similar high sensitivity but lower specificity values. Moreover, regardless of its predictive accuracy for poor clinical outcomes, lung ultrasound provides visual information of pathophysiological changes in the lung that may further guide patient management. Therefore, LUS could be used alongside these other clinical and laboratory findings for the assessment of subjects with severe COVID-19 illness, especially during a pandemic situation were hospital resources and ICU availability may be limited.

There are some limitations to this study. This is a single-center pilot study with a small number of subjects. However, our cohort has characteristics similar to those included in other COVID-19 series.[8,27,32] Another limitation is the lung ultrasound assessment at a single time point. Further studies are necessary to evaluate the role of repeated lung ultrasound scoring during admission. Due to the COVID-19 pandemic situation and the different clinical presentations for each subject, it was not possible to perform LUS at the same time point for all included subjects. A high proportion of subjects were evaluated after being transferred to the IMCU from the general ward; therefore, time from hospital admission to LUS assessment differed between subjects. Nevertheless, our assessment was performed when subjects presented with respiratory impairment, which may be a more clinically important time for evaluation. Furthermore, there were no significant differences between time from symptom onset and hospital admission to LUS assessment between subject groups.

Conclusions

LUS $\geq$ 24 points may help identify patients with COVID-19 who are likely to require ICU admission or die during follow-up. LUS also correlated significantly with clinical and laboratory markers of COVID-19 severity.

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