Journal of Intensive Care Medicine
2022, Vol. 37(12) 1614-1624

DOI: 10.1177/08850666221111731
journals.sagepub.com/home/jic
SAGE

Point-of-care Lung Ultrasound, Lung CT and NEWS to Predict Adverse Outcomes and Mortality in COVID-19 Associated Pneumonia

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Abstract

Introduction: The appraisal of disease severity and prediction of adverse outcomes using risk stratification tools at early disease stages is crucial to diminish mortality from coronavirus disease 2019 (COVID-19). While lung ultrasound (LUS) as an imaging technique for the diagnosis of lung diseases has recently gained a leading position, data demonstrating that it can predict adverse outcomes related to COVID-19 is scarce. The main aim of this study is therefore to assess the clinical significance of bedside LUS in COVID-19 patients who presented to the emergency department (ED). **Methods:** Patients with a confirmed diagnosis of SARS-CoV-2 pneumonia admitted to the ED of our hospital between March 2021 and May 2021 and who underwent a 12-zone LUS and a lung computed tomography scan were included prospectively. Logistic regression and Cox proportional hazard models were used to predict adverse events, which was our primary outcome. The secondary outcome was to discover the association of LUS score and computed tomography severity score (CT-SS) with the composite endpoints. **Results:** We assessed 234 patients [median age 59.0 (46.8-68.0) years; 59.4% M), including 38 (16.2%) in-hospital deaths for any cause related to COVID-19. Higher LUS score and CT-SS was found to be associated with ICU admission, intubation, and mortality. The LUS score predicted mortality risk within each stratum of NEWS. Pairwise analysis demonstrated that after adjusting a base prediction model with LUS score, significantly higher accuracy was observed in predicting both ICU admission (DBA −0.067, $P = .011$) and in-hospital mortality (DBA −0.086, $P = .017$). **Conclusion:** Lung ultrasound can be a practical prediction tool during the course of COVID-19 and can quantify pulmonary involvement in ED settings. It is a powerful predictor of ICU admission, intubation, and mortality and can be used as an alternative for chest computed tomography while monitoring COVID-19-related adverse outcomes.

Keywords

COVID-19, pneumonia, lung ultrasound (LUS) score, computed tomography severity score (CT-SS), mortality, emergency medicine

Introduction

Coronavirus disease 2019 (COVID–19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is severely affecting public health worldwide. It is frequently associated with a pneumonia that can progress to acute respiratory distress syndrome (ARDS), multi-organ dysfunction, and even death.[1] Frontline healthcare providers are continuously challenged to ascertain the seriousness and urgency of COVID-19 cases to improve clinical decision making, provide high-quality medical services, and effectively allocate available resources.[2] Therefore, development of validated clinical and radiological risk assessment tools is essential to triage and allocate these patients, especially on admission to an emergency department (ED).

Several risk stratifying models, such as national early warning score (NEWS), peripheral perfusion index (PPI), computed tomography severity score (CT-SS), and lung ultrasound (LUS) score, were extensively investigated to evaluate the severity of lung injury in COVID-19.[3–5] In this context,

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the NEWS is a well validated prognostication tool that has proven to be effective in ED settings and has shown merit in predicting COVID-19-associated adverse events (eg, viral pneumonia or ARDS) but necessitates seven physiologic variables to compute.[3–6] Chest CT has been proposed as a significant determinant for COVID-19 diagnosis and follow-up but the risk of ionizing radiation, high cost, challenges related to infection control, and lack of continuous monitoring limits its value, especially for critically ill patients.[7]

LUS examination is a well-established and broadly used diagnostic imaging technique in the primary assessment or follow-up of patients with pneumonia and acute respiratory failure and has the added advantage of affordability, lack of ionizing radiation, and ease of use. It has a clear advantage over standard chest x-ray and is comparable with chest CT for the assessment of pneumonia and ARDS.[8] However, data on its significance in diagnosis and monitoring of COVID-19-associated pneumonia is still unclear. Hence, in the present study we evaluate LUS as a substitute to CT for predicting COVID-19-related adverse outcomes including intensive care unit (ICU) admission, intubation, and death. This has the potential to diminish the need for lung CT examination and its associated side effects and costs. To achieve this goal, we established and validated a multivariable risk stratification tool for ICU admission/intubation and mortality by utilizing a combination of LUS score, CT-SS, and NEWS in COVID-19 patients.

Materials and Methods

Study Design and Patient Eligibility

This prospective cohort-based study was undertaken at the Training and Research Hospital of Canakkale Onsekiz Mart University (COMU). COVID-19 patients who underwent LUS and CT scans were consecutively recruited from the same hospital between March 2021 and May 2021. All the patients were from the COMU Medical Center's ED and had disease confirmed by reverse transcription polymerase chain reaction (RT-PCR) of nasal and pharyngeal swab samples.

Inclusion criteria for study entry were age older than 18 years, positive SARS-CoV-2 in respiratory tract specimens detected by RT-PCR, and patients with no missing medical data. The exclusion criteria were defined as: (1) pregnant patients; (2) patients already intubated at the time of ED admission; (3) lung operation history; (4) chronic obstructive lung

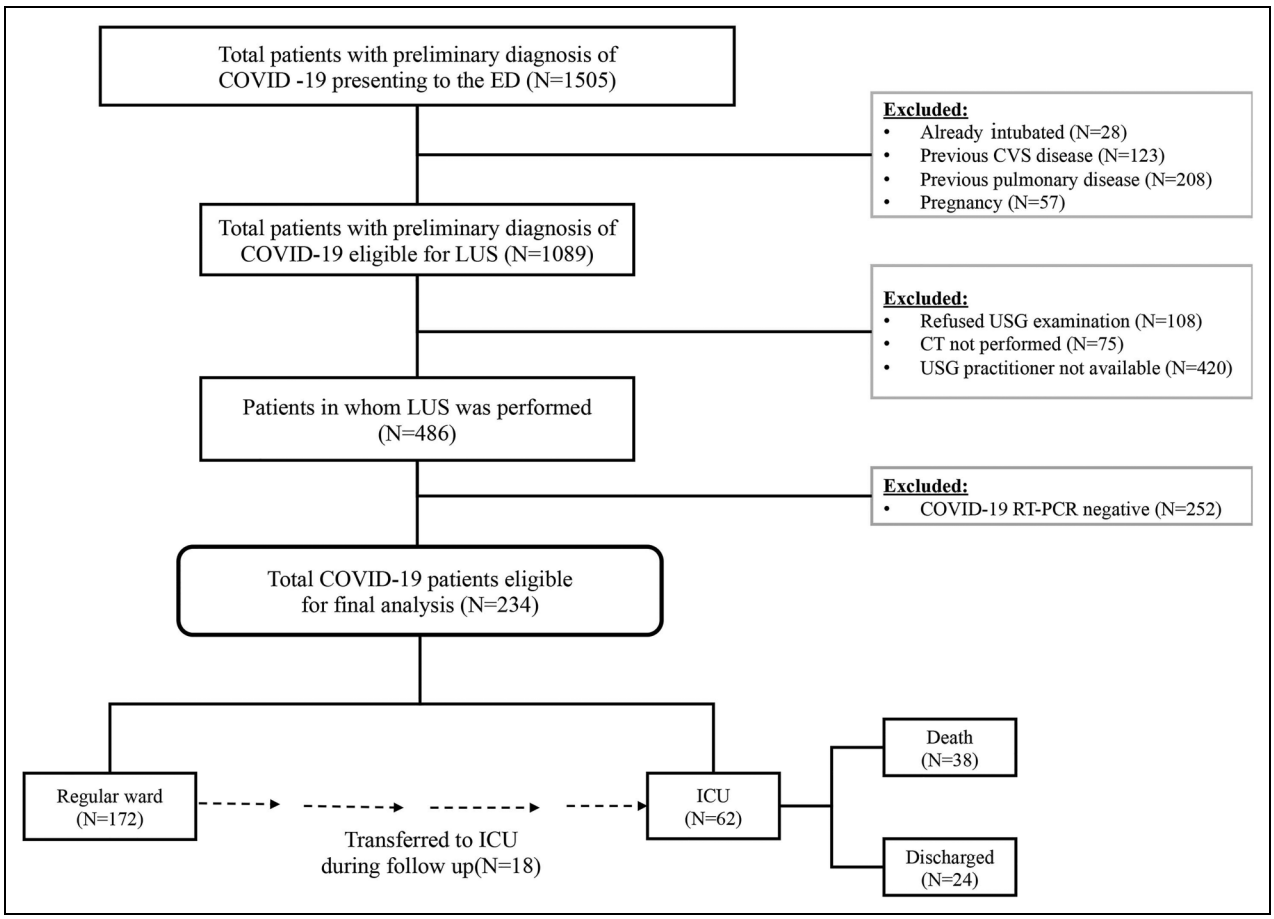

Figure 1. Study flowchart illustrating patient selection. ED; Emergency Department, CVS; Cardio Vascular System, LUS; Lung Ultrasound, USG; Ultrasonography, CT; Computed Tomography, RT-PCR; Real-time Polymerase Chain Reaction, ICU; Intensive care unit.

disease and cardiovascular system disease; (5) patients with a malignant tumor; (6) patients for whom a CT scan was not performed. The flow chart of the study selection process is summarized in Figure 1.

Approval for the study was granted by the COMU Ethics Committee (Approval No: 2011-KAEK-27/2021-E.2100019772). Written informed consent was obtained after the procedure(s) had been fully explained.

Clinical Data Assessment

Clinical, laboratory, and demographic characteristics of the COVID-19 patients were collected from the COMU Hospital Information and Management System. Patient information that derived from the hospital electronic health record database allowed us to analyze the following clinical, laboratory, and demographic variables: age, sex, vital parameters at ED arrival, complete blood cell counts, laboratory values, chronic medical histories, discharge status, ED disposition (home, hospital admission, ICU admission, intubation, and death). Clinical examination and initial laboratory work-up were conducted within 4 h of ED admission. All patients were followed up from admission until hospital discharge or death.

Screening Tools and Outcome Measures

The CT-SS is a commonly used risk stratifying tool that initially emerged for evaluating the severity of lung involvement in ARDS on lung CT images.[9] It is a validated tool for severity measurement in COVID-19 patients.[10] Total score ranges from 0 to 25 and an increase in the score is reported to be associated with worse prognosis in COVID-19.

The LUS protocol consists of assessment of 12 different lung zones (the upper and lower parts of the anterior, lateral, and posterior aspects of the left and right thoracic regions) as reported by Bouhemad et al[11] We allocated the points for each lung zone according to the worst ultrasound pattern registered in each of the 12 regions studied: 0 points – normal aeration; 1 point – moderate loss of lung aeration with three or four B lines issued from the pleural line; 2 points – severe loss of lung aeration with multiple coalescent vertical B lines issued either from the pleural line or from juxta-pleural consolidations; 3 points – lung consolidation with the existence of a hypoechoic poorly defined tissue pattern including either hyperechoic punctiform images or hyperechoic tubular images. The final LUS is the sum of points in all 12 zones and ranges from 0 to 36. Examples of LUS findings, including the B line patterns, lung consolidations, abnormalities of the pleural line, and the lesion distribution, are illustrated in Figure 2.

Clinical severity was measured by the NEWS.[12] The NEWS (0-20; higher = worse) consists of seven physiological parameters (body temperature; heart and respiratory rate; supplemental oxygen requirement; blood oxygen saturation; systolic blood pressure, and level of consciousness) and is used to identify patients with high-risk in acute care conditions and proved to be related with ICU admission, intubation, and death.[13]

The primary and secondary foci of this study are ICU admission and intubation and mortality. In this case, ICU admission is defined as patients who did not discharge from the hospital after ED admission and were hospitalized in an ICU either directly from ED or from a regular ward. Intubation is defined as the first endotracheal tube insertion in a non-intubated patient. The outcome measure for in-hospital mortality is defined as death that occurred at any time during the hospital stay.

Emergency Department Workflow and LUS Protocol

After the admission of the patient, a triage nurse separately evaluated patients who present in the ED and isolate/separate patients at high risk for having COVID-19 in single-person rooms with doors closed or designated COVID-19 waiting areas. After evaluation by a senior ED physician, eligible patients for study inclusion were assessed by an emergency medicine specialists with at least four years practice in point-of-care emergency ultrasonography. LUS evaluations were performed at the bedside and both of the ultrasonographers were blinded to the clinical details and tomographic findings. Interobserver variability (IOV) for LUS score was established by an independent blinded and qualified observer, who measured the LUS score in 24 randomly selected COVID-19 patients. IOV was evaluated using the Bland-Altman method and the within-subject coefficient of variation. The within-subject coefficient of variation which is an index of a measurement's reliability serves as a scale-free, unitless estimate of variation expressed as a percentage.

The specialists used a Samsung HM70A portable ultrasound machine (Samsung Medison, Seoul, South Korea) with 2- to 5-MHz convex probes. LUS examination started by adjusting the ultrasound machine to lung pre-set to depth of 150 mm and probe placed vertically on the ribs. All preventive measures for droplet and contact isolation were undertaken according to the standard protocols. The ultrasound probe was placed in a single used sterile cover.

The patient was preferably positioned in a sitting position. In the case of clinical worsening or poor patient compliance, LUS examination was conducted with the patient in a supine or semi recumbent position. Where possible, the posterior zones of the lung were examined while the patient was in a seated position or, if not suitable, by turning the patient to a lateral decubitus position on both sides. The ultrasound probe was positioned vertically perpendicular to the ribs. Each lung zone was inspected for no less than one complete respiratory cycle.

Computed Tomography Imaging

Computed tomography imagings were performed using a dedicated CT scanner (Asteion TSX-021B; Toshiba Corporation, Tokyo Japan). The voltage of the tube was set at 120 kVp and the tube current was set to 150 mAs. The CT scan images were analyzed by an experienced radiology specialist.

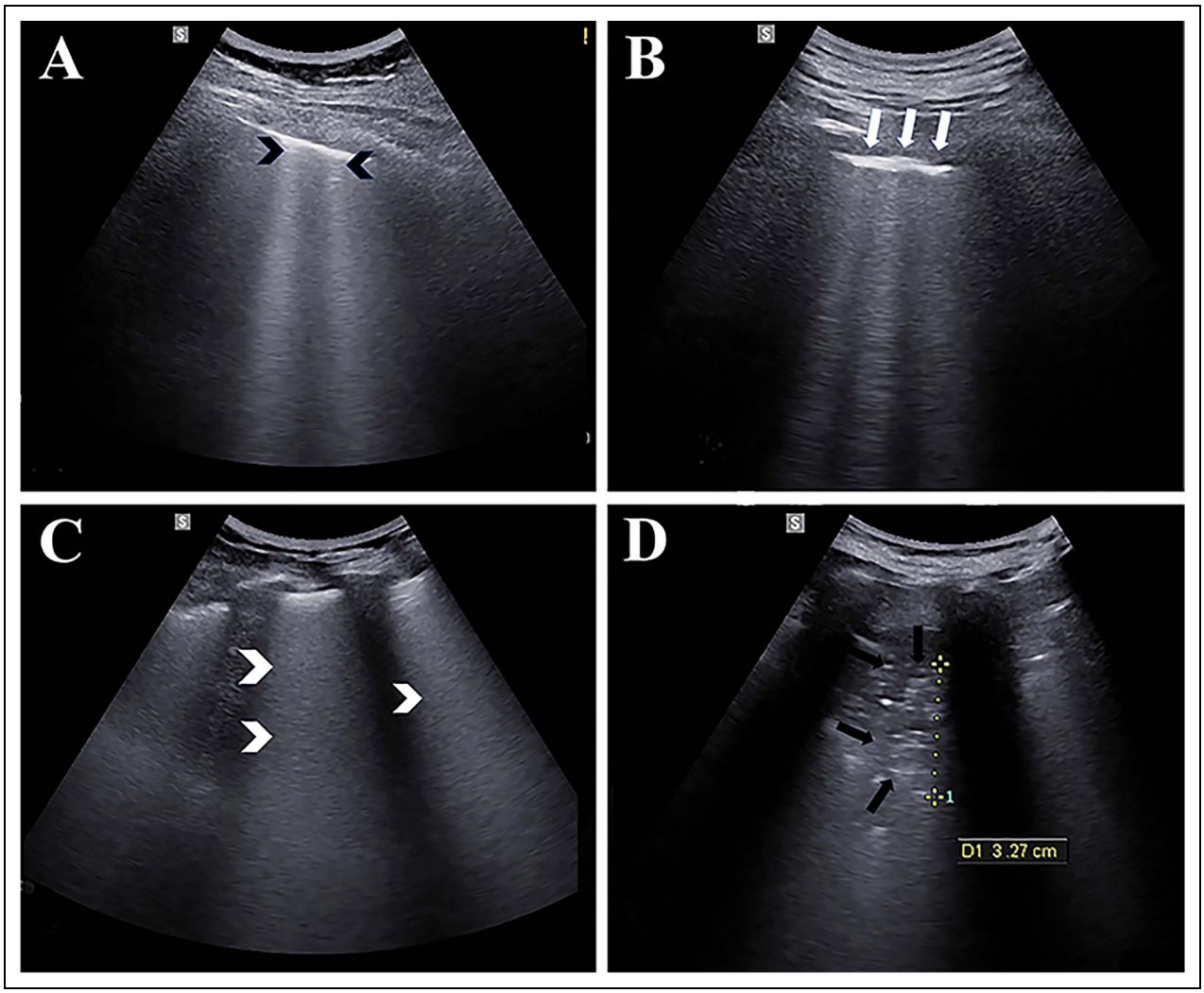

Figure 2. Ultrasonographic images and lung ultrasound (LUS) score in COVID-19. (A) B1 line: the presence of multiple, well-defined, regularly spaced B lines (black arrowhead), LUS score: 1. (B) B2 line: the presence of coalescent B lines (white arrow), LUS score: 2. (C) Confluent B lines and loss of pulmonary aeration (white arrowhead), LUS score: 3. (D) Lung consolidation: the presence of a tissue pattern (black arrow), LUS score: 3.

All volumetric chest CTs were evaluated at a lung window of 1600 WW and 550 WL and a mediastinal window of 400 WW and 40 WL using 2D coronal and sagittal planes for optimal evaluation. The scans were initially appraised as negative or positive for typical findings of COVID-19 pneumonia as defined by the RSNA Consensus statement.[14]

To quantify the severity of COVID-19 pneumonia, a thin-section CT score was designated on the basis of the area involved. This scoring system is a modification of a method formerly used to refer interstitial pneumonia and idiopathic pulmonary fibrosis and demonstrated to be highly correlated with the extent of fibrosis manifested in pathologic specimens.[15]

Statistical Analysis

Descriptive statistics were presented as median (interquartile range—IQR) for the non-normally distributed variables, and as number and percentage (%) for nominal variables. The Shapiro–Wilk test was used to assess the normality assumption. The significance of the difference between the groups in terms of the median values was analyzed using a Mann-Whitney U test. Categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test. Spearman's correlation test was used to perform correlation analysis. Odds ratios (95% confidence intervals) of the independent clinical parameters were calculated with univariable and multivariable logistic regression models to predict the outcome variables (ICU admission, intubation, and mortality). A multivariable logistic regression analysis was built by performing stepwise variable selection on those variables with a univariate P value $<$ .25. The Hosmer and Lemeshow test was computed to detect goodness of fit in the multivariable models; a nonsignificant p value indicated a good fit. Covariate adjusted receiver operating characteristic (ROC) curve analysis using multivariable logistic regression was performed to identify diagnostic accuracy measures and calculate the areas under the receiving operator curves (AUROC). The DeLong test was then used for a pairwise

comparison of AUROCs.[16] All statistical analyses were conducted using SPSS 19.0 for Windows (IBM Corp., Armonk, NY, USA) and R software version 3.6.2. All *P* values of less than .05 were considered to indicate statistical significance.

Results

Overall, 234 patients aged over 18 years with a positive SARS-CoV-2 RT-PCR test for whom LUS and CT scans were conducted between March 2021 and May 2021 were included in the study. The median patient age was 59.0 years (IQR 46.75-88.0 years). Of the 234 patients, 62 (26.4%) were followed in ICU and 38 (16.4%) were deceased. Patients admitted to ICU and those who were deceased were older with a median age of 66.0 (IQR 58.0-71.5, $P < .001$) and 68.0 (IQR 60.5-74.5, $P < .001$), respectively. The majority of those admitted to ICU (72.5%) and deceased were male (73.6%). Initial presentation with low oxygen (O2) saturation ($P < .001$), high respiratory rate ($P < .001$), low PPI ($P < .001$) and high d-dimer ($P < .001$) levels were more commonly present in non-survivors. High NEWS, CT-SS and LUS score were found both in ICU admitted patients and non-survivors ($P < .001$ for all). Table 1 presents demographic, clinical, and laboratory characteristics of all patients with regard to final outcome.

We established a univariable and multivariable logistic regression analysis in our study group to reveal the role of distinct demographic and clinical factors with several scoring systems to predict ICU admission, intubation, and mortality (Table 2). A univariable analysis revealed that each year in age increased the rate of ICU admission/intubation and mortality 4.1% (95% CI: 1.019-1.062) and 5.8% (95% CI: 1.030-1.087) respectively. In COVID 19 patients, a 1-point increase in CT-SS and LUS score was associated with x1.29 and x1.21 increased ICU admission/intubation rate and x1.26 and x1.19 increased mortality rate, respectively. After univariable analysis, we performed a multivariable logistic regression analysis. For both ICU admission and mortality in COVID-19 patients age, CT-SS, and NEWS were found to be significant factors that affect final outcome (Table 2).

ICU admission, intubation, and mortality in COVID-19 patients according to levels of NEWS and LUS score are presented in Table 3. Mortality prediction varied remarkably within NEWS subgroups depending on the LUS score. Similarly, classifying patients by LUS score significantly improved prediction of mortality across the NEWS subgroups. Patients with a NEWS ≥ 7 and a LUS score > 20 had the highest odds ratio 24.430 (8.790-67.896) for crude model, 22.829 (7.714-67.558) for adjusted model. Similar improvements for prediction of ICU admission and intubation were also observed (Table 3).

We analyzed the impact of LUS score and CT-SS on the discriminating accuracy of different ICU admission and mortality models (Table 4). First, we created a base model to recognize patients at high risk (higher age, male gender, and elevated d-dimer levels) for ICU admission and mortality. Pairwise analysis demonstrated that after adjusting the base model with the LUS score, a significant higher accuracy was observed in

Table 1. Comparison of Baseline Characteristics of COVID-19 Patients According to Both Admission and Survival Status.

	Ward admission (n = 172)	ICU admission (n = 62)	*P*-value	Patients alive (n = 196)	Patients deceased (n = 38)	*P*-value
Characteristics	Median (IQR)/n (%)	Median (IQR)/n (%)		Median (IQR)/n (%)	Median (IQR)/n (%)	
Age(years)	57.0 (44.0-65.0)	66.0 (58.0-71.5)	<.001	57.5 (44.0-65.25)	68.0 (60.5-74.5)	<.001
Male	94 (54.7)	45 (72.5)	.014	111 (56.6)	28 (73.6)	.036
Vital signs at triage						
Saturation(%)	97.0 (94.0-99.0)	82.5 (72.0-90.0)	<.001	96.0 (91.75-98.25)	81.5 (72.0-88.0)	<.001
Heart rate (beat/min)	86.0 (79.0-99.0)	89.0 (76.8-110.0)	.078	86.5 (78.0-100.0)	90.0 (79.8-113.5)	.093
Respiratory rate(min)	20.0 (17.0-22.0)	24.0 (22.0-26.0)	<.001	20.0 (17.75-24.0)	24.0 (21.0-28.0)	<.001
SBP (mm/Hg)	130.0 (118.0-140.0)	131.5 (115.0-140.3)	.936	130.0 (118.0-139.0)	131.0 (110.0-141.3)	.493
DBP (mm/Hg)	79.0 (70.0-88.0)	79.0 (64.8-88.0)	.358	79.5 (70.0-88.0)	77.5 (64.0-88.3)	.114
PPI	2.8 (1.4-4.2)	1.4 (0.63-2.25)	<.001	2.45 (1.4-4.1)	0.98 (0.47-2.5)	<.001
Complete blood count						
WBC ($mm^3 \times 10^3$)	6.83 (5.0-9.0)	9.75 (6.39-13.68)	<.001	7.0 (5.1-9.1)	11.0 (7.4-17.0)	<.001
Hgb (mg/dl)	13.5 (12.11-14.5)	12.95 (11.6-14.33)	.149	13.3 (12.0-14.5)	13.0 (11.6-14.7)	.681
Htc(%)	40.0 (36.0-43.1)	39.0 (35.03-42.8)	.217	40.0 (35.78-43.03)	39.1 (35.35-43.55)	.739
Platelet ($mm^3 \times 10^3$)	200.0 (160.0-251.0)	215.0 (173.5-295.5)	.322	203.0 (160.8-260.8)	214.0 (171.0-268.0)	.885
D-Dimer (ng/ml)	201.0 (116.0-416.0)	597.0 (347.8-1947.8)	<.001	223.0 (120.0-469.3)	563.0 (279.0-1591.0)	<.001
NEWS	2.0 (0.0-5.0)	9.0 (7.0-10.0)	<.001	3.5 (1.0-7.0)	9.0 (7.8-10.3)	<.001
CT-SS	5.0 (2.0-10)	17.0 (12.0-20.0)	<.001	6.0 (2.75-11.0)	18.0 (13.75-20.25)	<.001
LUS score						
Global LUS score	9.0 (4.0-15.0)	22.0 (15.0-26.0)	<.001	10.0 (4.75-16.0)	22.5 (19.0-26.25)	<.001
LUS score right lung	5.0 (2.0-8.0)	11.5 (7.75-13.0)	<.001	5.0 (2.0-9.0)	12.0 (7.75-13.0)	<.001
LUS score left lung	5.0 (2.0-7.0)	10.0 (8.0-13.0)	<.001	5.0 (2.0-8.0)	11.0 (8.0-13.0)	<.001

Data represented Median IQR (Inter Quartile Range) or n (%).

Abbreviations: WBC, White Blood Cell; Hgb, hemoglobin; Htc, hematocrit; PPI, Peripheral Perfusion Index; SBP, sistolic blood pressure; DBP, diastolic blood pressure; ICU, Intensive Care Unit; NEW score, National Early Warningscore; CT-SS, Computed Tomography Severity Score; LUS score, Lung Ultrasound Score.

Table 2. Univariable and Multivariable Logistic Regression Analysis for the Prediction of ICU/Intubation and Mortality.

	ICU/intubation (n = 62)				Death (n = 38)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age	1.041 (1.019-1.062)	<.001	1.043 (1.009-1.078)	.012	1.058 (1.030-1.087)	<.001	1.066 (1.027-1.106)	.001
Gender M[F(ref)]	2.196 (1.166-4.139)	.015	2.135 (0.910-5.011)	.081	2.144 (0.987-4.656)	.054	2.123 (0.800-5.631)	.131
LUS score	1.217 (1.153-1.285)	<.001			1.198 (1.128-1.272)	<.001		
CT-SS	1.296 (1.212-1.385)	<.001	1.113 (1.008-1.229)	.035	1.269 (1.179-1.366)	<.001	1.157 (1.037-1.292)	.009
NEW score	1.700 (1.474-1.961)	<.001	1.376 (1.122-1.687)	.002	1.539 (1.332-1.778)	<.001	1.245 (1.005-1.543)	.045
PPI	0.980 (0.920-1.045)	.540			1.005 (0.956-1.057)	.837		
D-Dimer	1.001 (1.001-1.002)	<.001	1.001 (1.000-1.001)	.029	1.001 (1.001-1.002)	<.001		

Abbreviations: LUS score, Lung Ultrasound Score; CT-SS, Computed Tomography Severity Score; PPI, Peripheral Perfusion Index; NEW score, National Early Warning score.

Table 3. ICU Admission, Intubation and Mortality in COVID-19 Patients According to Levels of NEWS, LUS Score and CT-SS.

	ICU/intubation				
		OR (95% CI)		OR (95% CI)	
	N ICU/intubation/*N* total (%)	Crude model	*P*	Adjusted model[a]	*P*
NEWS < 7 (REF)	11/151 (7.3)				
NEWS ≥ 7/LUSS < 20	10/83 (12.0)	7.444 (2.725-20.341)	<.001	7.320 (2.591-20.679)	<.001
NEWS ≥ 7/LUSS ≥ 20	41/55 (74.5)	28.140 (12.216-64.823)	<.001	25.518 (10.714-60.717)	<.001
	Mortality				
		OR (95% CI)		OR (95% CI)	
	N died /*N* total (%)	Crude model	*P*	Adjusted model[a]	*P*
NEWS < 7 (REF)	6/151 (3.9)				
NEWS ≥ 7/LUSS < 20	4/28 (14.3)	4.633 (1.161-18.497)	.030	4.999 (1.187-21.075)	.028
NEWS ≥ 7/LUSS ≥ 20	28/55 (50.9)	24.430 (8.790-67.896)	<.001	22.829 (7.714-67.558)	<.001

Abbreviations: OR, odds ratio; CI, Confidence Interval; ICU, Intensive Care Unit; LUS score, Lung Ultrasound Score; NEW score, National Early Warning Score.
[a]The adjusted model included Age and Sex.

predicting both ICU admission (DBA −0.067, $P = .011$) and in-hospital mortality (DBA −0.086, $P = .017$). Similarly, after adjusting the base model with CT-SS, a significant higher accuracy was observed in predicting both ICU admission (DBA −0.084, $P = .001$) and in-hospital mortality (DBA −0.109, $P = .002$) (Table 4).

We performed ROC curve analysis to predict ICU admission, intubation, and mortality according to LUS score and CT-SS on admission to ED (Table 5). Based on the ROC curves, the best cut-off value for LUS score to predict ICU admission and intubation was >11 with a sensitivity of 90.3% and a specificity of 60.4%, while for CT-SS, the best cut-off value was >10 with a sensitivity of 82.2% and a specificity of 79.6%. Similar analysis was also conducted for mortality and is presented in Table 5.

We also performed ROC curve analysis to compare predictive performances of LUS score and CT-SS in conjunction with the base model that was designed to identify high risk patients for ICU admission and mortality. Both of these variables significantly predicted ICU admission (ROC AUC = 0.897, $P < .001$ for base model + LUS score and AUC = 0.914, $P < .001$ for base model + CT-SS) and mortality (ROC AUC = 0.880, $P < .001$ for base model + LUS score and AUC = 0.903, $P < .001$ for base model + CT-SS) (Figure 3). The difference between AUCs was further tested for the significance by pairwise comparison of ROC curve analysis. Considering the DBA (0.017), no significant difference in terms of predicting ICU admission was indicated in the pairwise comparison for base model + LUS score and base model + CT-SS ($P = .057$), but there was a significant difference in terms of predicting mortality (DBA 0.023, $P = .037$) (Table 6). Correlation analysis between LUS score and CT-SS revealed a strong and consistent correlation between these two scores (Spearman's Rho = 0.944 and $P < .001$).

Discussion

In this study, we analyzed the predictive performance of LUS score in combination with CT-SS and NEWS to predict ICU

admission, intubation, and mortality in the context of COVID-19. Our findings demonstrate that a higher LUS score is significantly related to ICU admission, intubation, and mortality in crude and adjusted multivariable logistic regression analysis. Moreover, predictive models incorporating LUS score and CT-SS were more accurate than those that did not include tomographic and ultrasonographic findings. However, pairwise comparisons of ROC curves confirmed a slight superiority of CT-SS in predicting mortality in comparison with LUS score; both of the AUCs (0.880 for LUS score and 0.903 for CT-SS) exceeded the value of 0.850. Therefore, the present study emphasizes the significance of adding a validated imaging technique to generally used prognostication tools when estimating the possibility of progression to severe disease and mortality in hospitalized COVID-19 patients.

The identification of COVID-19 patients at risk of increased morbidity and mortality in ED settings is important as it can allow healthcare providers to stratify treatment strategy and effectively manage healthcare resources. Thus, it is not surprising to see ongoing attempts to develop prognostic scoring systems that can predict a poor clinical course for patients with COVID-19.[17] More than two dozen prognostic scoring systems were published in just over 16 months since COVID-19 was announced as a pandemic by the World Health Organization.[18] The majority of these models suggest male gender, old age, hypertension, cigarette smoking, obesity, IL-6, ferritin, and d-dimer levels as prognostic factors for adverse events.[19] However, many of these prognostic models were developed as simplified scoring systems or nomograms and although their predictive performance in the initial derivation is admirable, the validity of these models has not been demonstrated across independent research studies.[20] In this context, recent studies report that imaging findings including x-ray, ultrasonography, and CT could have auxiliary value to clinical prognostic tools in selecting COVID-19 patients with increased risks of negative outcomes regardless of disease stage.[21–23] Therefore, for this study, we examined the single and combined performance of LUS score, CT-SS, and distinct clinical and biochemical prognostic factors and analyzed the effect of LUS score and CT-SS on the discriminating accuracy of different mortality models to discover an efficient prognostication tool for patients with COVID-19.

Over the last few decades, LUS has emerged as a valuable, non-invasive diagnostic technique that can be applied at the bedside for both adult and pediatric patients and is particularly suited for identification, grading, and follow-up of the severity of pulmonary involvement.[24,25] Due to its relatively low cost, bedside availability, absence of ionizing radiation, and repeatability of the method there has been a resurgent use of LUS in COVID-19 patients.[25] Although there is no general consensus in studies about the most effective and precise LUS protocol, 8-zone/0–24 score and 12-zone/0–36 score protocols are the most widely used in COVID-19 patients.[25,26] In this study, we used a 12-zone/0–36 score protocol and found that increased LUS scores were associated with worsening of the disease and death where a LUS score of >14 had an AUC of 0.838 for mortality after ED admission (Table 6). This result

Table 4. Impact of the LUS Score and CT-SS on the Discrimination Accuracy of Mortality Models.

		Area under the ROC curve (95% CI)	Area under the ROC curve (95% CI)		Pairwise Analysis				
						95% CI			
Prognostic model		Without LUS score	With LUS score	DBA	SE	Lower	Upper	Z statistic	*P*
Base Model = Age, gender and D-dimer	ICU/intubation	0.830	0.897	−0.067	0.220	−0.119	−0.015	−2.535	.011
	death	0.794	0.880	−0.086	0.247	−0.157	−0.015	−2.378	.017
		Area under the ROC curve (95% CI)	Area under the ROC curve (95% CI)		Pairwise Analysis				
						95% CI			
Prognostic model		Without CT-SS	With CT-SS	DBA	SE	Lower	Upper	Z statistic	*P*
Base Model = Age, gender and D-dimer	ICU/intubation	0.830	0.914	−0.084	0.215	−0.136	−0.032	−3.176	.001
	death	0.794	0.903	−0.109	0.238	−0.177	−0.041	−3.148	.002

Abbreviations: ROC, Reciever Operating Caracterictics; CI, Confidence Interval; SE, standart error;DBA,difference between areas; ICU (Intensive Care Unit); LUS score, Lung Ultrasound Score; CT-SS, Computed Tomography Severity Score.

Table 5. ROC Curve Analysis to Predict ICU Admission, Intubation and Mortality According to Initial LUS Score and CT-SS on Admission to Emergency Department.

	Cut-off	AUROC (95% CI)	Sensitivity % (95% CI)	Specifity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy % (95% CI)
ICU/intubation							
LUS score	>11	0.852(0.799-0.905)	90.32(80.12-96.4)	60.47(52.74-67.82)	45.16(40.22-50.2)	94.55(88.92-97.4)	98.38(62.0-74.28)
CT-SS	>10	0.876(0.828-0.923)	82.26(70.47-90.8)	79.65(72.85-85.4)	59.3(51.47-66.68)	92.57(87.88-95.54)	80.34(74.66-85.23)
Mortality							
LUS score	>14	0.838(0.771-0.906)	81.58(95.97-92.26)	66.84(59.77-73.38)	32.29(27.09-37.97)	94.93(90.49-97.35)	69.23(62.89-75.08)
CT-SS	>13	0.865(0.809-0.921)	76.32(59.76-88.56)	83.67(77.74-88.56)	47.54(38.66-56.58)	94.8(91.12-97.0)	82.48(76.99-87.12)

Abbreviations: LUS score, Lung Ultrasound Score; CT-SS, Computed Tomography Severity Score; CI, Confidence Interval; AUROC, area under curve receiver operating characteristics;PPV, positive predictive value; NPV, negative predictive value.

is similar to previous reports, which suggests that LUS could allow a semi-quantitative assessment of the extravascular lung water and, indirectly, of the blood oxygen levels and therefore, a low level of LUS score indicates less impaired aeration of the pulmonary parenchyma in COVID-19 patients.[23,27,28]

This study also demonstrated the power of the LUS score to identify different levels of mortality risk within the NEWS strata. According to both crude and adjusted models, we found that COVID-19 patients with a NEWS ≥ 7 have increased ICU admission, intubation, and mortality risk, and that inclusion of the LUS score significantly increased the accuracy in identifying those patients who have increased risk for ICU admission, intubation, and mortality. Patients with a NEWS ≥ 7 and a LUS score ≥ 20 had a 27.05 times (95% C.I.: 8.979-81.521) higher risk of mortality compared to patients who had a LUS score < 20. However, to the best of our knowledge, this is the first study to assess the effectiveness of LUS score combined with CT-SS and NEWS for the prediction of mortality in COVID-19 patients. Markarian et al[29] recently demonstrated that an early LUS score can predict clinical severity according to NEWS in patients with dyspnea due to COVID-19. Our data indicates the importance of adding LUS findings to other clinical and laboratory data to improve the decision-making process regarding healthcare management.

The present study not only evaluated ultrasonographic findings for risk stratification but also investigated the role of CT as a prognostication tool in COVID-19 patients. To quantify the degree of CT findings, a semi-quantitative scoring method previously used by Zhou et al[30] and Abbasi et al[31] was applied. The degree of pulmonary involvement was quantified by using a thin-section lung CT. Our results revealed that non-survivors had significantly elevated CT-SS even after adjustment for both clinical and laboratory parameters. Moreover, combining CT-SS with a prognostic model comprising high risk patients significantly increased the accuracy of identifying patients at high risk for ICU admission, intubation, and death. Other recent studies also established a clear link between negative outcomes and CT-SS similar to our findings.[3,31–33] Despite the superiority of CT over other imaging modalities during the COVID-19 pandemic, the elevated infection risk, and the necessity of moving unstable patients make lung CT a limited choice. The American College of Radiology has advised against the systematic use of CT; it should be reserved for hospitalized, symptomatic patients with specific clinical indications for CT.[14] Based on the substantial evidence that lung lesions associated with SARS-CoV2 are mainly located peripherally and sub-pleurally,[34,35] ultrasound can determine pulmonary lesions in a prompt and effective manner. Therefore, LUS could be an optimal imaging modality as it is available at the bedside, performed directly by the in-charge physicians, and could provide reliable information about COVID-19-related adverse outcomes.

Our results demonstrate that LUS score is an important predictor of clinical deterioration and death in COVID-19 patients, and also confirms that COVID-19-associated lung injury that is quantified by LUS is significantly associated with the

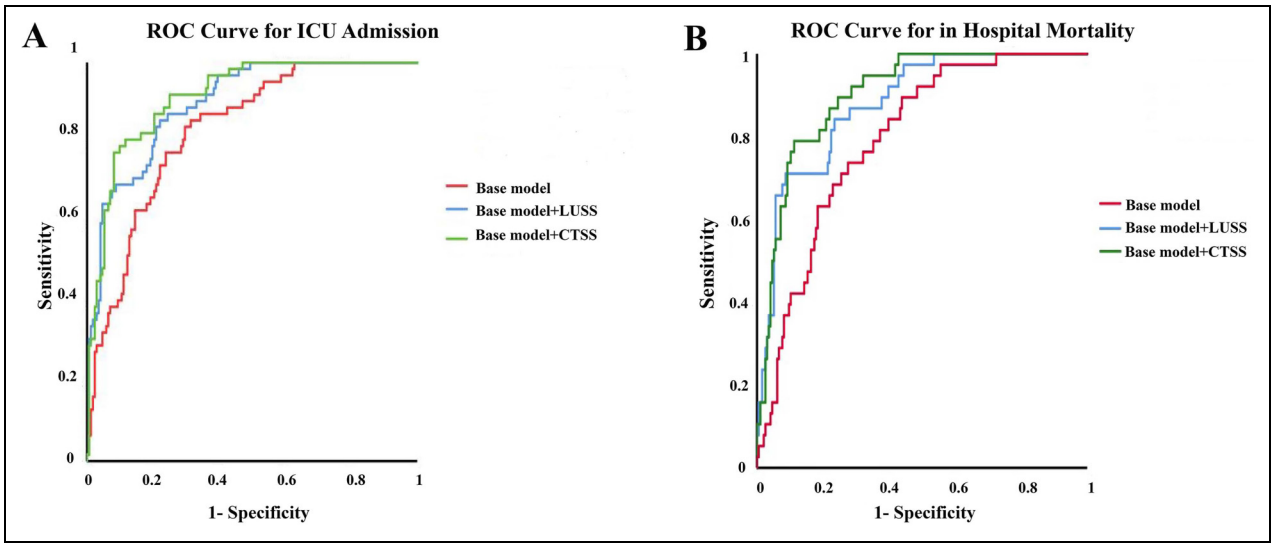

Figure 3. Receiver operating characteristic (ROC) curve analysis of the prognostic models incorporating LUS score and CT-SS for the prediction of (A) ICU admission/intubation and (B) mortality.

Table 6. Pairwise Comparisons of Receiver Operating Characteristic Curves.

				95% CI			
	AUC	DBA	SE	Lower	Upper	Z statistics	*P*-value
ICU/intubation							
Base model + CT-SS vs Base model + LUS score	0.914 vs 0.897	0.017	0.198	0.001	0.034	2.047	.057
Death							
Base model + CT-SS vs Base model + LUS score	0.903 vs 0.880	0.023	0.221	0.001	0.044	2.088	.037

Abbreviations: ICU, intensive care unit; AUC, area under curve; DBA, difference between areas; SE, standart error; CI, Confidence Interval; LUS score, lung ultrasound score; NEW score, national early warning score; CT-SS, computed tomography severity score.

pulmonary involvement appraised by CT-SS. Although CT is regarded as the most sensitive diagnostic tool for detecting the degree of parenchymal lung disease, our findings suggest that LUS could be a practicable alternative to CT in the initial evaluation of pulmonary involvement in COVID-19. In fact, the peripheral with or without peribronchovascular distribution of COVID-19 makes LUS an ideal tool for the detection of these abnormalities.[36,37] The demonstration of a positive and linear correlation between LUS score and CT-SS in this study is comparable to those reported by Lieveld et al[36] Tana et al.[38] Both studies suggest that LUS and CT-SS are strongly comparable and useful to quantify the parenchymal impairment with accuracy and predict negative outcomes in COVID-19 patients. A similar result was also reported by Zhu et al[39] in a small population of COVID-19 patients with pneumonia of different degrees of severity and found a substantial correlation between LUS and lung CT score, with a correlation coefficient of 0.82 ($P < .001$), indicating LUS as an alternative modality to the CT scan for evaluating disease severity. Thus, LUS has great potential to have wide-reaching impact when routinely included in a screening tool in ED settings, because chest CT is not recommended for routine screening due to concerns regarding potential infectivity and constraints on resources during the COVID-19 pandemic. Therefore, it is reasonable to suggest that integrating LUS into standard diagnostic and management considerations for the rest of this pandemic and potential next pandemics would offer the advantages of easy implementation, affordability, repeatability, and reducing stress on conventional radiological resources.[40,41]

While this study investigated the combined predictive capacity of several prognostication scores in patients with COVID-19, there are several limitations. First, although this is a prospective cohort-based study with a sufficiently large sample size to make an inference about the outcomes, the extrapolations of the conclusion may not be strong enough to be appropriate for other COVID-19 patients. Second, USG examinations of the thorax sometimes fail to screen back because patients with severe disease are usually in the supine position. Finally, detection of lung lesions with USG that is located in the center of the lungs is somewhat limited and therefore the predictive accuracy of the LUS might have been reduced.

In conclusion, LUS can quantify and prognosticate lung involvement in COVID-19 and has good correlation and

agreement with CT based risk stratifying systems. Moreover, combining risk stratification tools such as LUS score, CT-SS, and NEWS may help predict the likelihood of COVID-19 patient progression to severe illness or death, thus enabling physicians to perform early diagnosis and timely interventions, which could reduce the morbidity and mortality rates related to COVID-19.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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