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ORIGINAL RESEARCH

Infectious Disease

Lung ultrasound in predicting COVID-19 clinical outcomes: A prospective observational study

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Abstract

Study objective: We sought to determine the ability of lung point-of-care ultrasound (POCUS) to predict mechanical ventilation and in-hospital mortality in patients with coronavirus disease 2019 (COVID-19).

Methods: This was a prospective observational study of a convenience sample of patients with confirmed COVID-19 presenting to 2 tertiary hospital emergency departments (EDs) in Iran between March and April 2020. An emergency physician attending sonographer performed a 12-zone bilateral lung ultrasound in all patients. Research associates followed the patients on their clinical course. We determined the frequency of positive POCUS findings, the geographic distribution of lung involvement, and lung severity scores. We used multivariable logistic regression to associate lung POCUS findings with clinical outcomes.

Results: A total of 125 patients with COVID-like symptoms were included, including 109 with confirmed COVID-19. Among the included patients, 33 (30.3%) patients were intubated, and in-hospital mortality was reported in 19 (17.4%). Lung POCUS findings included pleural thickening 95.4%, B-lines 90.8%, subpleural consolidation 86.2%, consolidation 46.8%, effusions 19.3%, and atelectasis 18.3%. Multivariable logistic regression incorporating binary and scored POCUS findings were able to identify those at highest risk for need of mechanical ventilation (area under the curve 0.80) and in-hospital mortality (area under the curve 0.87). In the binary model ultrasound (US)

findings in the anterior lung fields were significantly associated with a need for intubation and mechanical ventilation (odds ratio [OR] 3.67; 0.62–21.6). There was an inverse relationship between mortality and posterior lung field involvement (OR 0.05; 0.01–0.23; and scored OR of 0.57; 0.40–0.82). Anterior lung field involvement was not associated with mortality.

Conclusions: In patients with COVID-19, the anatomic distribution of findings on lung ultrasound is associated with outcomes. Lung POCUS-based models may help clinicians to identify those patients with COVID-19 at risk for clinical deterioration.

Key Words: COVID-19; Lung Ultrasound; Mechanical ventilation; Prediction; ICU admission; Mortality; Clinical outcome; Risk stratification; Diagnostic accuracy

KEYWORDS

COVID-19, clinical outcome, diagnostic accuracy, ICU admission, lung ultrasound, mechanical ventilation, mortality, prediction, risk stratification

1 | INTRODUCTION

1.1 | Background

As of mid-October 2020, the World Health Organization confirmed approximately 40 million cases and 1 million deaths attributable to coronavirus disease 2019 (COVID-19).[1,2] Clinical progression of COVID-19 is variable and can range from patients remaining asymptomatic and able to recover at home to patients developing severe respiratory failure requiring prolonged hospitalization and intensive care.[3–7] Therefore, improving targeted care will require exploring strategies for rapid and accurate prognosis in patients with suspected COVID-19.[8]

COVID-19 exhibits characteristic imaging findings including bilateral, patchy, reticular-nodular opacities, ground-glass opacities, or a "crazy-paving" pattern on CT scan. These findings are typically more prominent in a peripheral and basilar distribution.[9,10] As imaging findings can precede clinical symptoms, imaging studies have been used to predict clinical outcomes and prognosticate disease course.[11] Multiple lung involvement severity scores have been proposed. Generally, data suggest more severe scores correlate with worse clinical outcomes including need for intensive care unit (ICU) admission, mechanical ventilation, and even patient death.[12–18] Existing imaging-based lung severity scores are almost exclusively created using chest x-ray (CXR) or computed tomography (CT) scan. The number of studies focusing on point-of-care ultrasound (POCUS) in this context is limited.

1.2 | Importance

The early identification of patients at risk of adverse clinical outcomes and those who need mechanical ventilation is of interest considering the variable progression pattern in COVID-19 and the need for critical care resources. POCUS is an important imaging modality in identifying lung pathology in many clinical settings. Well-established standardized protocols for cardiopulmonary POCUS aid emergency department and ICU physicians in assessing patients with acute undifferentiated respiratory distress.[19–21] Compared to chest radiography, POCUS demonstrates higher sensitivity and specificity for diagnosing pneumonia, pneumothorax, pleural effusion, and alveolar-interstitial syndrome.[22–26]

Data supporting the use of POCUS in COVID-19 are promising.[27–31] POCUS-based triage algorithms, monitoring strategies, and scoring systems aimed at COVID-19 diagnosis and assessment have been proposed.[32–35] Although existing data suggest the extent of pulmonary findings in POCUS correlate with disease severity, there are few studies formally assessing the predictive capabilities of POCUS in COVID-19.[36,37]

1.3 | Goals of this investigation

Defining the prognostic capabilities of POCUS in COVID-19 may have significant implications for triage and overall management of patients with this global disease. We sought to assess the ability of ED lung POCUS to predict mechanical ventilation and in-hospital mortality in patients with COVID-19.

2 | METHODS

2.1 | Study design and setting

This prospective, observational study took place at the Firouzgar General Hospital and the Masih Daneshvari Hospital, 2 tertiary teaching medical centers in Tehran, Iran. Both hospitals are urban academic ED and trauma centers and care for >100,000 patients per year. This study

was approved by the local ethics committees and institutional review boards.

2.2 | Selection of participants

We included a convenience sample of patients during March to April 2020 (7 weeks) with COVID-like illness and when the study physician sonographer was available to complete POCUS examinations. We included all patients with both polymerase chain reaction (PCR) positive and CT findings compatible with COVID-19. The ultrasonographer was blinded to the PCR and CT scan results at the time of scanning.

Exclusion criteria included critically ill patients who could not tolerate a complete POCUS examination, as well as patients with a known lung malignancy, lobectomy, or active lung tuberculosis. Patients with "do not resuscitate" status were also excluded as this could skew the rate of interventions. Subjects who tested positive for COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) and had a CT scan finding compatible with COVID-19 were included in the final analysis and were monitored toward their completion of hospitalization or death. Informed consent was provided by patients, legal guardians, or next of kin for all participants.

2.3 | Measurements

An emergency physician with >10 years of emergency ultrasound experience performed a complete lung POCUS on each participant at the time of ED presentation. An M-Turbo machine (FUJIFILM SonoSite, Bothell, WA, USA) with a linear transducer (6–13 MHz) and a phased array transducer (2–5 MHz) was used for all POCUS examinations. Six-second clips of each view were recorded electronically and were reviewed by 2 attending emergency physicians with fellowship training in emergency ultrasound for quality control.

For lung POCUS, using a linear transducer a 12-zone bilateral scanning protocol (6 zones per hemithorax) was performed.[35] With patients in supine, semisupine, or lateral decubitus positions, the scanning points on each hemithorax were included:

1. *Anterior Superior (AS)*: On the midclavicular line above the crossing internipple line
2. *Anterior Inferior (AI)*: On the midclavicular line below the crossing internipple line
3. *Axillary (Ax)*: On the midaxillary line above the inter-nipple line
4. *Posterolateral Alveolar and/or Pleural Syndrome (PLAPS-point)*: On the midaxillary line below the inter-nipple line
5. *Posterior Superior (PS)*: On the paravertebral line at the line crossing scapular spine
6. *Posterior Inferior (PI)*: On the paravertebral line above the curtain sign

Emergency physician performing each POCUS provided real-time interpretations of scans for the data mentioned . All POCUS clips were

The Bottom Line

Early detection of lung disease is important for COVID-19 treatment. In this series of 125 emergency department patients with COVID-19-like illness in Iran, abnormal lung ultrasonography finding—particularly those in the anterior lung fields—were associated with the need for intubation and mechanical ventilation. Lung ultrasonography may be helpful in the management of COVID-19.

also independently reviewed by 2 emergency medicine sonographers with extensive ultrasound experiences, for quality assurance purposes. For lung POCUS, each of the 12 lung zones was individually assessed for the presence of pleural line irregularities, pleural thickening, subpleural consolidations (SCs), consolidations, atelectasis, B-lines, pleural effusion, and lung hepatization. If a finding was present in at least 1 of the lung zones, it was deemed positive.

Research associates blinded to the US results and trained in chart review abstracted data from our electronic health record into an Excel (version 16.16; Microsoft, Redmond, WA) spreadsheet after the conclusion of the patient's hospital stay. Patient demographics, comorbidities, clinical presentation, and clinical course/outcome data were collected. Demographic data included age, sex, height, weight, and body mass index. Clinical presentation data included type and duration of symptoms, and whether there was a known COVID-19 exposure. Medical comorbidities, tobacco use history, and history of receiving the influenza vaccine were also collected. Clinical data included vital signs and serum laboratory test results at the time of presentation. Clinical outcomes including intubations and mechanical ventilation, ICU admission, and mortality were collected on daily follow-up and after completion of the hospitalization or death.

2.4 | Outcomes

The primary end point was in-hospital mortality. Outcomes included a need for intubation and mechanical ventilation. We also reported the frequency of ICU admission and ward admission >72 hours, noting that there were no guidelines for ICU or ward admissions. All patients were followed until death or discharge. A research associate trained in data abstraction and blinded to the ultrasound results documented the occurrence of clinical outcomes on their day-by day follow-up and after the completion of hospital course or in-hospital death.

2.5 | Analysis

All statistical analyses were performed in the R statistical programming environment.[38] Descriptive statistics are reported as medians with the 25th and 75th percentile for continuous variables and percentages for

categorical variables. Comparisons between groups were made with the chi-square test with Yates' continuity corrections for categorical variables, respectively. Correction for multiple testing was performed by controlling the false discovery rate with a q-value threshold of 0.1 by the Benjamini and Hochberg method. Each outcome was assessed independently of the others.

As described previously, ultrasound evaluation was performed at 6 sites bilaterally and assessed for 6 possible lung pathologies for a combined 72 possible findings. To simplify the analysis, lung pathology and the sites of involvement were analyzed separately. A subject was said to be positive for a pathology if it was present in at least 1 site in either lung. Similarly, a lung site was said to be involved if any pathology was found in it. In addition to the binary of present/involved or not, a scored metric was calculated by summing the number of sites involved for pathologies, or the number of pathologies involved for sites.

For outcome modeling, a subject was included as a positive if that outcome had occurred during their hospital course. Outcomes modeled included intubation and death. Simple univariate logistic regressions of the ultrasound features were implemented to test for associations between predictors and outcomes. Results of these models were reported with the odds ratios (ORs), 95% confidence intervals (CIs), and coefficient P values. To reduce the risk of overfitting, variables were considered for further inclusion into multivariable models only if the q-value was <0.1. Multivariable logistic regressions were then generated including the previously identified variables. These models then underwent backwards stepwise selection maximizing the Akaike information criterion to generate final models. For the multivariate models, the superior and inferior lung fields were combined into Anterior (AS + AI) and Posterior (PS + PI) variables, which had the advantage of simplifying the model. This had no significant impact on the accuracy of the models.

Test performances of the final models were then calculated using the original data set. We did not have enough subjects for a validation set. For each model, a response operator characteristic curve, area under the curve (AUC), sensitivity, and specificity were calculated. Calibration curves (not shown) and Hosmer-Lemeshow goodness-of-fit testing was then implemented to ensure all models were properly calibrated.

3 | RESULTS

3.1 | Characteristics of study subjects

Demographic data for enrolled patients are reported in Table 1. A total of 125 suspected COVID-19 patients were enrolled, of whom 109 were found to be positive for SARS-CoV-2 by RT-PCR and were included in future analyses. Subjects had a median age of 60 (interquartile range [IQR] 45–70), body mass index of 26 (IQR 25–29), and 67% were male. Prevalent comorbidities included hypertension (33.9%), diabetes (25.7%), coronary artery disease (13.8%), hyperlipidemia (12.8%), heart failure (7.3%), and tobacco use (7.3%). Subjects presented a median of 6 [3–10] days from onset of symptoms and 16.5%

TABLE 1 Patient characteristics and demographic data

n (%)	Overall 109 (100)
Demographics	
Age	60 (45–70)
Male (%)	67 (62.0)
Body mass index	26 (25–29)
Comorbidities	
Hypertension (%)	37 (33.9)
Hyperlipidemia (%)	14 (12.8)
Diabetes (%)	28 (25.7)
Heart failure (%)	8 (7.3)
Chronic kidney disease (%)	3 (2.8)
Coronary artery disease (%)	15 (13.8)
Malignancy (%)	5 (4.6)
Active malignancy (%)	2 (1.8)
Chronic obstructive pulmonary disease (%)	2 (1.8)
Organ transplant (%)	1 (0.9)
Immunosuppressed (%)	3 (2.8)
Smoking (%)	8 (7.3)
Relevant history	
Fever (%)	75 (69.4)
Cough (%)	77 (70.6)
Dyspnea (%)	71 (65.1)
Other respiratory symptoms (%)	32 (29.4)
Gastrointestinal Symptoms (%)	40 (36.7)
Headache (%)	28 (25.9)
Myalgias (%)	55 (50.9)
Chest pain (%)	33 (30.6)
Days from onset	6 (3–10)
Known COVID exposure (%)	18 (16.5)
Laboratory results	
Leukocytes	7.1 (4.9–9.8)
Hemoglobin	13.3 (12.2–14.7)
Platelets	193 (140–283)
Creatine phosphokinase	153 (91–264)
Erythrocyte sedimentation rate	42 (30–58)
C-reactive protein elevation (%)	67 (61.5)
Lactate dehydrogenase (LDH)	546 (417–732)
D-dimer elevation (%)	13 (12.9)
Troponin elevation (%)	5 (5.2)
Medications	
Steroid (%)	32 (29.6)
Antibiotics (%)	103 (95.4)
Antivirals (%)	90 (83.3)
Hydroxychloroquine (%)	78 (72.2)

(Continues)

TABLE 1 (Continued)

n (%)	Overall
	109 (100)
Clinical course	
Admitted (%)	71 (65.1)
ICU (%)	54 (49.5)
Intubation (%)	33 (30.3)
Death (%)	19 (17.4)
Hospital length of stay	7 (3–15)

Continuous variables are shown as medians with interquartile ranges in parentheses. Categorical variables are depicted as the n with percentages in parentheses.

had a known COVID-19 exposure. Of 109 patients 77 (76.2%) required supplemental oxygen including high-flow oxygen therapy and 33/109 cases (30.3%) were intubated with mechanical ventilation. Of 109 patients 71 (65.1%) required hospital admissions with 54/109 (49.5%) ICU admission. In-hospital mortality is reported in 19/109 (17.4%) of patients.

3.2 | Distribution of ultrasound findings

In evaluating 12 lungs' zones (6 per lung), the most common site of involvement were the axillary sites (PLAPS 84.4%, Ax 74.3%), followed by the anterior sites (AI 64.2%, AS 63.3%), and then the posterior sites (PI 56.0%, PS 36.7%). The superior sites were more frequently involved than the inferior sites. In descending order of frequency, the recorded lung findings included pleural thickening (95.4%), B-lines (90.8%), subpleural consolidation (86.2%), consolidation (46.8%), effusions (19.3%), and atelectasis (18.3%). There were no differences between the distribution of findings between the left and right lungs. Anterior, posterior, and axillary lung fields differed in their distribution of findings. In the axillary area, the inferior fields had higher frequencies of atelectasis, 8.3% (CI 5.1%–12.9%) compared to 1.4% (CI 0.4%–4.3%), and effusions, which had an identical distribution. The posterior lung fields also had higher frequencies of nearly all ultrasound lung findings in the inferior field: consolidation 16.5% (CI 12%–22.3%) versus 7.3% (CI 4.4%–11.9%), effusion 5.5% (CI 3%–9.7%) versus 0% (CI 0%–2.2%), pleural thickening 40.8% (CI 34.3%–47.7%) versus 28.4% (CI 22.7%–35%), and subpleural consolidation 29.8% (CI 23.9%–36.4%) versus 14.2% (CI 10%–19.7%). Figure 1 demonstrates the frequencies of the US findings and their geographic distributions in the left and right lungs.

3.3 | Location of US findings and outcomes

We compared the relative frequencies of the US findings and their eventual disposition outcome. There were no differences in the frequency of US findings between outcomes (Figure 2A).
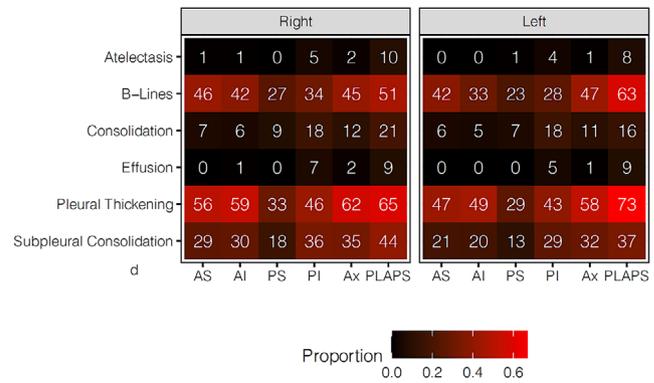
FIGURE 1 Heat map demonstrating the geographical distribution and types of lung POCUS findings among enrolled patients. In each hemithorax, lung zones include anterior superior (AS), anterior inferior (AI), posterior superior (PS), posterior inferior (PI), axillary (Ax), and posterolateral alveolar and/or pleural syndrome (PLAPS)

We then hypothesized that the geographic distribution of findings may be associated with subject outcomes. We performed a similar analysis as previously with the 6 lung sites. The AS lung field was involved in 28.0% of cases who were discharged, but this increased to 60.0% (difference = 32.0%, CI 3.5%–60.5%) in the ward cohort, 71.4% (difference 43.4%, CI 12.9%–73.9%) in the ICU cohort, 85.7% (difference 57.7%, CI 8.9%–26.7%) in the intubation cohort, and 89.5% (difference 61.5%, CI 34.5%–88.5%) in the deceased cohort. A similar pattern was observed for the AI lung site, with 20.0% involvement in those discharged compared to 70.0% (difference 50.0%, CI 23.6%–76.4%), 66.7% (difference 46.7%, CI 16.7%–76.6%), 92.9% (difference 72.9%, CI 46.6%–99.1%), and 89.5% (difference 69.5%, CI 44.0%–95.0%) for the ward, ICU, intubated, and deceased cohorts, respectively.

The posterior lung fields exhibited an increase in frequency between the discharged and ward groups. The PS lung field was involved in 28.0% and 63.3% of discharged and ward groups (difference 35.3%, CI 7.0%–63.6%). The PI lung field was involved in 64.0% and 86.7% of discharged and ward groups (difference 22.7%, CI 3.4%–48.7%). However, in contrast to the anterior lung fields, the posterior lung fields were less involved as severity increased from the ward group. Compared to the ward group, the PS in the ICU, intubated, and deceased group were 15.7% (CI -15.8%–47.2%), 49.0% (CI 18.6%–79.5%), and 52.8% (CI 26.4%–79.2%) less frequent, respectively. Compared to the ward group, the PI in the ICU, intubated, and deceased group were 24.8% (CI -3.4%–52.9%), 51.0% (CI 17.8%–84.1%), and 81.4% (CI 61.3%–100%) less frequent, respectively.

The axillary lung fields were more frequently involved in all admitted groups compared to the discharged group. The Ax field differences were 27.3% (CI 0.1%–54.6%), 20.2% (CI -10.8%–51.2%), 22.6% (CI 12.0%–57.1%), and 22.9% (CI -8.4%–54.3%) for the ward, ICU, intubated, and deceased groups, respectively. The PLAPS field differences were 33.3% (CI 8.5%–58.2%), 30.5% (CI 3.2%–57.8%), 32.9% (CI 3.8%–61.9%), and 29.5% (CI 1.2%–57.8%) for the ward, ICU, intubated, and deceased groups, respectively.
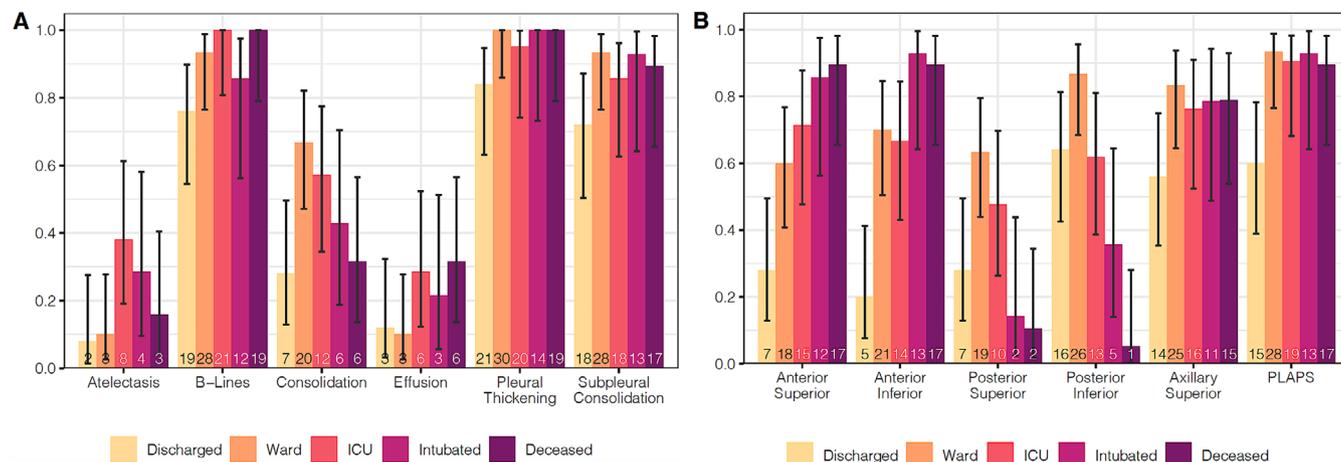
FIGURE 2 (A and B) Relative frequencies of sonographic lung findings and their anatomic distributions based on outcome. Bar heights represent the proportion of subjects that had the finding or region involved. The numbers at the bottom of the bars represent the n involved. Adjacent bars show the outcomes studied from left to right: discharge, admission, ICU use, intubation, and death. Error bars denote the standard error of the proportion. Abbreviation: PLAPS, posterolateral alveolar and/or pleural syndrome

At an individual lung level, anterior involvement alone occurred in 70 samples, posterior alone in 50 samples, and both present in 65 samples. We also performed various combined metrics that performed worse than individual areas. In fact, it performed better when posterior lung field scores were subtracted rather than added to the cumulative scores.

3.4 | Univariate associations of US and outcomes

We performed simple univariate logistic regressions to test the association between sonographic results and outcomes of intubation and death. Each predictor was tested twice: as a binary (whether the predictor was involved or present) and as a scored metric (sum of the number of times the predictor was involved or present). Tables 2 and 3 show the results of the binary and scored univariate regressions of both intubation and death, respectively (Table 2). Similar patterns were found between the 2 outcomes and predictor types (Table 3).

3.5 | Multivariable model of US and outcomes

We generated multivariable models of both outcomes with binary and scored predictors that were found to be significant in the univariate models. The results of these models are summarized in Figure 3. The final intubation models included only the Anterior and Posterior variables. In the binary model, findings in the anterior lung fields had an OR of 3.67 (0.62–21.6) and posterior lung findings had an OR of 0.07 (0.02–0.22). For the scored model, the anterior lung fields had an OR of 1.28 (1.08–1.52) and the posterior lung fields had an OR of 0.66 (0.55–0.8). Both models had moderate performance and were well calibrated (AUC = 0.823 (CI 0.741–0.904) and 0.875 (CI 0.802–0.947; Hosmer-
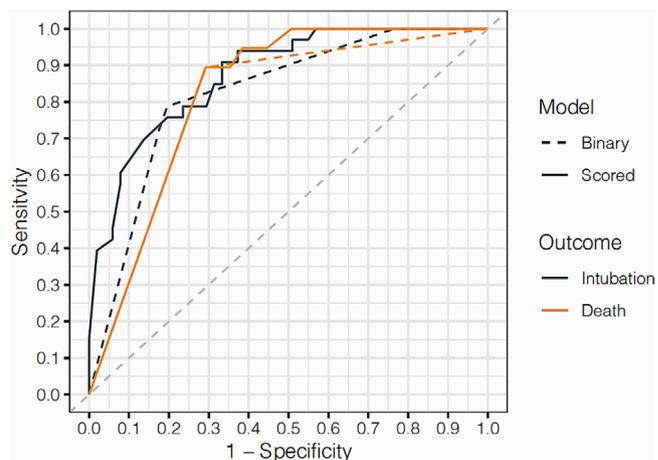
FIGURE 3 Receiver operating characteristic curves of all final models. The color of the line type indicates the outcomes analyzed: intubation (red) and death (black). Binary models are depicted with dashed lines, whereas the scored models with solid lines

Lemeshow goodness-of-fit $P = 0.99$ and 0.57 for binary and scored models, respectively). When modeling death as outcome, only the posterior lung fields were found to be necessary with a binary OR of 0.05 (0.01–0.23) and a scored OR of 0.57 (0.40–0.82). These models performed similarly (AUC = 0.80, CI 0.711–0.891; and 0.825, CI 0.753–0.897; Hosmer-Lemeshow goodness-of-fit $P = 1.0$ and 0.94 for binary and scored models, respectively).

3.6 | Limitations

Limitations to this study include the possibility of selection bias from enrolling a convenience sample of patients with COVID-19 based on

TABLE 2 Results of the univariable logistic regression for the intubation outcome

Variable	OR	(95% CI)	P Value
Binary			
Consolidation	0.34	(0.14–0.84)	0.019
B-lines	0.63	(0.08–4.73)	0.655
Atelectasis	0.98	(0.34–2.85)	0.969
Subpleural consolidation	1.09	(0.24–4.89)	0.913
Effusion	1.75	(0.61–5.01)	0.296
Pleural thickening	3.80	(0.0–Inf)	0.991
PI	0.07	(0.02–0.2)	<0.0001
PS	0.1	(0.03–0.34)	0.0002
PLAPS	0.85	(0.18–4.07)	0.84
Ax	0.91	(0.31–2.68)	0.858
AS	3.95	(1.2–13.03)	0.023
AI	4.57	(1.21–17.22)	0.024
Scored			
Consolidation	0.61	(0.42–0.88)	0.008
Atelectasis	0.85	(0.48–1.48)	0.559
Pleural thickening	0.91	(0.78–1.06)	0.240
Subpleural consolidation	0.92	(0.78–1.1)	0.356
B-lines	0.93	(0.79–1.1)	0.413
Effusion	1.2	(0.69–2.11)	0.520
PI	0.59	(0.46–0.75)	<0.0001
PS	0.6	(0.44–0.81)	0.001
PLAPS	0.9	(0.74–1.09)	0.273
Ax	1.0	(0.82–1.22)	0.976
AI	1.27	(1.01–1.59)	0.037
AS	1.38	(1.11–1.71)	0.003

Reported is the OR (95% CI), and the P value. Abbreviations: AI, anterior inferior; AS, anterior superior; Ax, axillary; CI, confidence interval; OR, odds ratio; PI, posterior inferior; PLAPS, posterolateral alveolar and/or pleural syndrome; PS, posterior superior.

TABLE 3 Results of the univariable logistic regression for the death outcome

Variable	OR	(95% CI)	P Value
Binary			
Consolidation	0.33	(0.11–0.97)	0.044
Atelectasis	0.62	(0.16–2.44)	0.498
Subpleural consolidation	0.86	(0.16–4.68)	0.865
Effusion	2.04	(0.64–6.45)	0.225
Pleural thickening	1.71	(0–Inf)	0.992
B-lines	1.33	(0–Inf)	0.993
PI	0.03	(0–0.21)	0.0006
PS	0.13	(0.03–0.6)	0.0093
PLAPS	0.71	(0.13–3.98)	0.695
Ax	0.94	(0.27–3.3)	0.92
AI	3.01	(0.63–14.4)	0.167
AS	3.78	(0.8–17.9)	0.094
Scored			
Atelectasis	0.56	(0.21–1.46)	0.232
Consolidation	0.59	(0.36–0.97)	0.038
Pleural thickening	0.87	(0.72–1.05)	0.142
Subpleural consolidation	0.93	(0.76–1.14)	0.495
B-lines	0.99	(0.82–1.21)	0.954
Effusion	1.39	(0.76–2.54)	0.282
PI	0.43	(0.25–0.75)	0.003
PS	0.58	(0.36–0.91)	0.018
Ax	0.98	(0.77–1.23)	0.847
PLAPS	1.05	(0.85–1.3)	0.656
AI	1.23	(0.95–1.59)	0.122
AS	1.24	(0.97–1.57)	0.085

Reported is the OR (95% CI), and the P value. Abbreviations: AI, anterior inferior; AS, anterior superior; Ax, axillary; CI, confidence interval; OR, odds ratio; PI, posterior inferior; PLAPS, posterolateral alveolar and/or pleural syndrome; PS, posterior superior.

the availability of physician sonographer. The potential exclusion of the lower acuity patients and those who were discharged from the ED may explain the high prevalence of CT and POCUS findings in our study. However, this potential bias may be less relevant in this cohort as we intentionally were looking at the adverse outcome in those who had established COVID-19 and had higher severity of the disease. The relatively small number of subjects significantly limits the power of the study to detect more nuanced findings. This is compounded by the relatively large number of possible ultrasound findings and their combinations. Thus, for this study, we simplified the search space but recognize that a larger data set may yield even more interesting findings. The high frequency of involvement of certain pathologies and lung sites means there was relatively little variance in the data set, whereas other pathologies were particularly rare. Both can easily lead

to model overfitting; thus, our model would benefit from external validation to corroborate our findings. As for discharged patients, we do not have follow-up data, which could mean discharges were made inappropriately and may have resulted in repeat visits with notable clinical outcomes later.

The ultrasound examinations were performed by an attending physician with extensive experience in POCUS, which may assist with a high intrarater reliability but perhaps limit the generalizability of the study. We also included patients who may clinically needed proning position, but we did not collect data on the duration and frequency of this practice. Expanding this work to include additional institutions and sonographers with variable levels of experience may improve the generalizability of our work.

4 | DISCUSSION

In the present study, we aimed to define the prognostic capabilities of POCUS in patients with COVID-19 for clinical outcomes, such as hospital admission, ICU admission, intubation, and patient death. Although there were no differences in the frequency of ultrasound findings and patient outcomes, geographical distribution of findings demonstrated interesting trends with clinical course. We generated logistic regression models that were able to identify subjects at highest risk of needing mechanical ventilation and highest risk of death. These trends suggest lung POCUS may be a useful tool in assisting emergency physicians in risk-stratifying patients at the point of disposition from the ED.

The most frequently identified lung pathologies on POCUS were pleural thickening, B-lines, and subpleural consolidations, which were found in many subjects with COVID-19. All of these were found at similar levels regardless of disease severity. Thus, these are sensitive markers for disease but not useful for risk stratification given their ubiquitous presence. Interestingly, consolidation, found in nearly half of subjects, was found to be inversely related to the disease severity. This may reflect the presence of an otherwise asymptomatic or mild case of COVID-19 with a concomitant pneumonia, which is easier to treat with antibiotics. Alternatively, consolidation may represent a different, milder phenotype of COVID-19. Atelectasis and effusions were relatively uncommon and did not associate with outcomes.

The largest source of variation was the anatomic distribution of findings. The most common sites of involvement were the axillary sites and anterior sites, with posterior being the least common. All sites had similar distributions of lung pathology. In general, those who were admitted had higher involvement of anterior and axillary lung findings. The exception proved to be the posterior lung fields, in particular the PI site, which has most frequently involved in the discharged groups. The posterior lung fields were found to be inversely associated with disease severity, a somewhat unexpected finding. Although not significant, anterior lung findings increased in frequency with worsening severity and were found to be a significant predictor of intubation in our models. Axillary findings were so common they were not useful for risk stratification.

The models were able to accurately risk stratify those who would eventually be intubated or expire during their course. We were able to generate both scored and binary models that performed similarly. Although the scored models have an overall higher accuracy, the advantage of the binary models is their simplicity. The binary models would allow the sonographer to stop scanning once the first pathology was identified in the posterior and anterior lung fields. Thus, a 12-point lung scan may on occasion be able to be reduced to just 2 points, dramatically decreasing the time required to perform such a scan.

The scanning protocol we used may have affected our findings. We used a 12-zone lung POCUS protocol modified from previously proposed POCUS protocols in COVID-19.[35] Although it is possible including the additional 2 zones may have improved the quality of our data, we find this unlikely. Six-zone bilateral lung POCUS protocols have been proposed for diagnosis of COVID-19.[25] Scanning 12- or 14-zones requires a considerable amount of time the sonographer must spend in the room with a potentially COVID-19-positive patient, thus increasing the infection risk.

In one of the few existing studies assessing the utility of lung POCUS in predicting clinical outcomes in patients with COVID-19, a lung ultrasound score determined by completing a bilateral 12-zone POCUS within 24 hours of patient presentation was associated with severe illness at the time of admission.[36] Patients who clinically deteriorated underwent a second complete POCUS exam at which point the majority of patients demonstrated worsening scores often secondary to loss of aeration in the anterior lung. This is like our findings in that anterior lung findings associated with more severe clinical outcomes. In another recent study by Lieveld et al., they assessed the association between the lung ultrasound and poor outcome including ICU admission and 30-day all-cause mortality. They concluded that the extend of pulmonary involvement detected by lung ultrasound were associated with poor outcome, admission duration, and disease severity.[37]

In a retrospective observational study assessing the association of findings on serial chest CT scans with clinical outcomes in patients with COVID-19, higher lung involvement scores were also found to be associated with higher patient mortality.[39] Interestingly, lung involvement scores showed minimal variability in days 0–5 of illness among all patients; however, scores began to diverge after day 6 of symptom onset. Taken together with the data from Lichter et al., it is possible that serial lung POCUS exams at multiple timepoints across a patient's clinical course may offer more robust prognostic power. As POCUS is often portable, easy to use, and widely available, serial POCUS exams could feasibly be performed on patients on home isolation as well as on admitted patients, thus potentially offering a widely applicable method for risk-stratification of patients with COVID-19. Further investigation on the prognostic capability of serial lung POCUS exams in both populations is warranted.

Among patients presenting to the ED with suspected COVID-19, geographical distribution of lung POCUS findings is associated with clinical outcomes in COVID-19 and may be predictive of the need of mechanical ventilation and in-hospital mortality. Given the wide availability and ease of use of POCUS, defining this tool's ability to accurately predict clinical outcomes in patients with COVID-19 may dramatically affect the healthcare system's approach to this pandemic. Further studies are needed to assess for scanning protocols that can offer definitive diagnostic and prognostic capabilities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MC—study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript. SSK and SAM—study design, acquisition of data, analysis and interpretation, critical revision of the manuscript. ML—analysis and interpretation of data, developing prediction models, critical revision of the manuscript, statistical expertise. SS—acquisition of data, database management, drafting

of the manuscript. NMD—analysis and interpretation of data, drafting manuscript, critical revision of the manuscript, statistical expertise. RT and SY—acquisition of data. HS—study concept and design, data analysis and interpretation, critical revision of the manuscript.

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