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Point-of-Care Lung Ultrasound Predicts Severe Disease and Death Due to COVID-19: A Prospective Cohort Study

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OBJECTIVES: The clinical utility of point-of-care lung ultrasound (LUS) among hospitalized patients with COVID-19 is unclear.

DESIGN: Prospective cohort study.

SETTING: A large tertiary care center in Maryland, between April 2020 and September 2021.

PATIENTS: Hospitalized adults (≥ 18 yr old) with positive severe acute respiratory syndrome coronavirus 2 reverse transcriptase-polymerase chain reaction results.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: All patients were scanned using a standardized protocol including 12 lung zones and followed to determine clinical outcomes until hospital discharge and vital status at 28 days. Ultrasounds were independently reviewed for lung and pleural line artifacts and abnormalities, and the mean LUS Score (mLUSS) (ranging from 0 to 3) across lung zones was determined. The primary outcome was time to ICU-level care, defined as high-flow oxygen, noninvasive, or invasive mechanical ventilation, within 28 days of the initial ultrasound. Cox proportional hazards regression models adjusted for age and sex were fit for mLUSS and each ultrasound covariate. A total of 264 participants were enrolled in the study; the median age was 61 years and 114 participants (43.2%) were female. The median mLUSS was 1.0 (interquartile range, 0.5–1.3). Following enrollment, 27 participants (10.0%) went on to require ICU-level care, and 14 (5.3%) subsequently died by 28 days. Each increase in mLUSS at enrollment was associated with disease progression to ICU-level care (adjusted hazard ratio [aHR], 3.61; 95% CI, 1.27–10.2) and 28-day mortality (aHR, 3.10; 95% CI, 1.29–7.50). Pleural line abnormalities were independently associated with disease progression to death (aHR, 20.93; CI, 3.33–131.30).

CONCLUSIONS: Participants with a mLUSS greater than or equal to 1 or pleural line changes on LUS had an increased likelihood of subsequent requirement of high-flow oxygen or greater. LUS is a promising tool for assessing risk of COVID-19 progression at the bedside.

KEY WORDS: cohort studies; COVID-19; severe acute respiratory syndrome coronavirus 2; survival analysis; ultrasonography

Point-of-care lung ultrasound (LUS) has been used for the evaluation of a range of cardiopulmonary conditions in emergency and critical care settings although, to date, implementation protocols have varied across settings. LUS offers benefits over traditional imaging modalities including portability, instantaneous results, lower costs, and lack of exposure to ionizing radiation. LUS has been proposed as an essential tool in evaluating patients with COVID-19 pneumonia to prevent nosocomial spread of disease (1). Ultrasound

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hardware can be cleaned easily and reduces the burden on personnel and resources that would be required for traditional chest imaging. LUS may be able to identify patients at risk for decompensation requiring higher level of care in resource-limited settings or in regions with limited ICU capacity during a COVID-19 surge.

Despite the potential utility of LUS in COVID-19 management, standardized and evidence-based clinical use has not been fully established. The most widely studied and reported findings are based on the LUS score, originally developed in 2011 and used for assessment of aeration for titration of positive end-expiratory pressure (2). This scoring system includes a 0–3-point grade per six lung zones totaled from each hemithorax (3). This has been adopted for prognostication for non–COVID-19 acute respiratory distress syndrome (4) and was subsequently evaluated as a part of candidate models for COVID-19 prognostication (5–9). Among individuals with COVID-19, the LUS score has been associated with relevant chest CT findings and predicts the extent of parenchymal disease as well as mortality (5). However, modified scores have limitations and have not been widely adopted. Modifications to scores had been based on early anecdotal reports and resulted in multiple scoring systems without protocol standardization and unclear generalizability. The LUS scores predicate on being able to sum all 12 zones, which can be challenging to obtain in tenuous patients.

The aim of this study was to determine the association between baseline LUS findings and the ultimate degree of COVID-19 severity or death. We evaluated a mean LUS Score (mLUSS) to determine risk of progression to ICU-level care (i.e., either high-flow oxygen, noninvasive, or invasive mechanical ventilation). We hypothesized that the mLUSS would be associated with an increased risk of disease progression to requiring ICU-level care.

METHODS

We enrolled adults (≥18 years old) who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on reverse transcriptase-polymerase chain reaction (RT-PCR) and were admitted to Johns Hopkins Hospital in Baltimore, Maryland, into a larger COVID-19 prospective cohort after verbal informed consent, between April 2020 and September 2021 as a convenience sample. This protocol was approved by the Johns Hopkins University Institutional Review Board (IRB00245545). Participants were enrolled after admission throughout the enrollment period or from the emergency department starting December 2020. After screening SARS-CoV-2 RT-PCR positive patients admitted to Johns Hopkins Hospital (n = 2,270) during this period, 264 participants had LUS performed as part of a subcohort of a parent biorepository protocol (n = 723) with patients consecutively enrolled depending on LUS-trained research staff availability (**Fig. 1**).

LUS was standardized with 6-second clips from 12 lung zones with six lung zones on each side as previously described (10). All images were collected with a Lumify S4 phased array probe (Philips, Amsterdam, the Netherlands) using the application's lung scan settings. Research coordinators without prior ultrasound experience were trained to perform a standardized, point-of-care ultrasound (POCUS) research protocol to characterize lung abnormalities in COVID-19. A clinician certified in critical care ultrasonography reviewed the initial ultrasound scanning sessions until operators were proficient and graded 95.7% of 497 scans as satisfactory. Research coordinators rather than clinicians were used to improve objectivity and to avoid interfering with clinical care. Study personnel were subsequently masked to clinical information and recorded LUS reads identifying and characterizing A lines (**Fig. S1*A***, http://links.lww.com/CCX/B31), B lines (**Fig. S1, *B*** and ***C***, http://links.lww.com/CCX/B31), pleural effusions (**Fig. S1*D***, http://links.lww.com/CCX/B31), pleural line abnormalities (**Fig. S1*E***, http://links.lww.com/CCX/B31), and consolidations (**Fig. S1*F***, http://links.lww.com/CCX/B31). The pleural line was considered abnormal if it was irregular, fragmented, discontinuous, or greater than or equal to 0.5 cm in thickness. Consolidations were required to be greater than or equal to 0.25 cm in at least one dimension. Although hospitalized, study visits with LUS scans occurred on study days 0, 3, 7, and weekly for up to 90 days. The scan on parent study day 0 or the first subsequent study day (5.3% of participants) was used for this analysis. Baseline demographics, comorbid conditions, physiologic variables, WBC count, and oxygen requirements were determined using the Hopkins Precision Medicine Analytics Platform (11), and duration of symptoms at enrollment was determined through medical chart review. Date of death by 28 days from enrollment was determined using the Precision

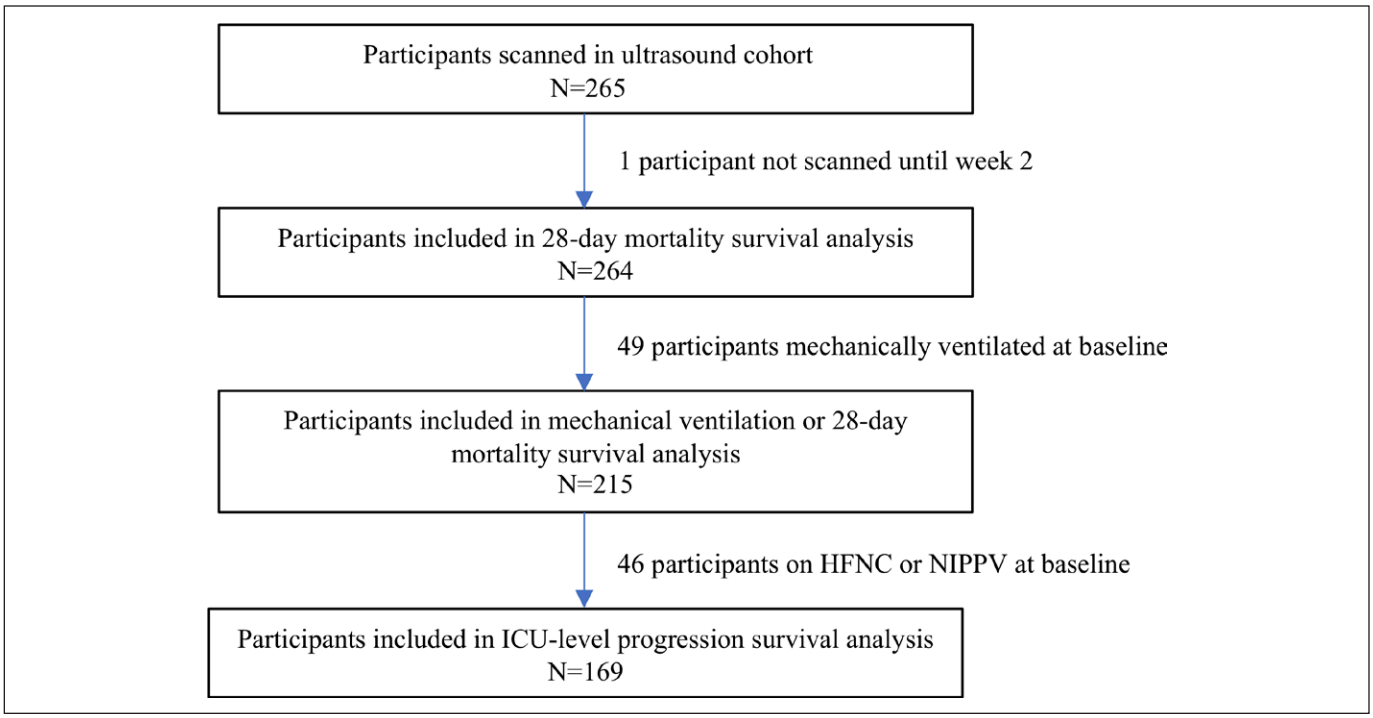

Figure 1. Flow diagram of enrollments and total participants included in survival analyses. HFNC = high-flow nasal cannula, NIPPV = noninvasive positive pressure ventilation.

Medicine Analytics Platform, medical chart review, and review of the regional Maryland, Washington DC, and Virginia health information exchange (12).

As previously described (13), the LUS score was calculated for each zone with 1 point for discrete B lines, 2 points for coalescent B lines, and 3 points for lung consolidation. The mLUSS ranges from 0 to 3, with a higher score signifying higher severity. The mLUSS was calculated out of total available zones to include participants with missing zones rather than a sum to determine the utility of the original and most studied LUS score (2) for COVID-19 prognostication with the flexibility to include less than 12 lung zones. The Pearson correlation coefficient of the mLUSS between masked ultrasound clip readers was determined for the participants who were available (61 consecutive patients or 23% of the cohort). Participants were divided into severity groups at baseline based on severity at the time of POCUS or peak severity prior to POCUS: on room air or nasal cannula supplemental oxygen (moderate disease), on high-flow nasal cannula (HFNC) or noninvasive positive pressure ventilation (NIPPV) (moderately severe), or on invasive mechanical ventilation (severe disease). Summary statistics were performed by comparing baseline demographics (i.e., sex, age, race, ethnicity, medical comorbidities) and duration post symptom onset between severity groups using Kruskal-Wallis tests.

Progression to ICU-level care was defined as newly requiring either HFNC, noninvasive ventilation, or invasive mechanical ventilation during the hospitalization. To determine the association between baseline LUS characteristics and future risk, this outcome was restricted to study participants not requiring more than supplemental oxygen via low-flow nasal cannula at baseline (among those with moderate disease at baseline, $n = 164$) (Fig. 1). Secondary outcomes included 28-day mortality (all baseline severity groups, $n = 264$) and 28-day progression to invasive mechanical ventilation or 28-day death (among those with moderate or moderately severe disease, $n = 215$) (Fig. 1). A Kaplan-Meier plot was created to compare risk over time between those at the 25th and 75th mLUSS percentile. After checking the proportional hazards assumption, Cox proportional hazards regression models were used to evaluate the differences in risk of death and risk of death or subsequent invasive mechanical ventilation plus 28-day death as a function of baseline % of lung fields with A lines, % with B lines, % with consolidations, % with pleural line abnormalities, % with pleural effusions, or the mLUSS. For comparison, models were individually fit with the classical LUS Score using a sum, physiologic

variables (i.e., respiratory rate, heart rate, and temperature), WBC count, and the Severe Inflammatory Response Syndrome Score (SIRS, composite score with range 0 [best] to 4 [worst] points). Unadjusted analyses and analyses adjusting for age and biologic sex were performed. Harrell's C-index (*C*-statistic) was calculated for each model to determine the accuracy of prediction of each model (14). Sensitivity analyses included restricting the population to those with all 12 lung zones, excluding 16 participants who were asymptomatic and adding adjustment for baseline severity. Data were analyzed in R (v4.0.2) and Stata, Version 16.0 (StataCorp LLC, College Station, TX).

RESULTS

Of 264 participants, the median age was 61 years (interquartile range [IQR], 48–68 yr), and 43.2% ($n = 114$) were female (**Table 1**). The study participants were racially and ethnically diverse with 47.7% of the population ($n = 126$) identified as Black and 16.7% ($n = 44$) identified as Hispanic. The median time from symptoms onset until ultrasound scan was 9.27 days (IQR, 5.2–14.3 d), and the median mLUSS at baseline was 1.00 (IQR, 0.50–1.30) overall. Comorbid illness was common. The majority of participants (74.2%) had hypertension, and 42.4% participants had diabetes mellitus (Table 1). Diagnoses of congestive heart failure (33.0%) and chronic obstructive pulmonary disease (36.4%) were also common. Most participants were overweight (median 29.0 kg/m^2; IQR, 25.4–33.2 kg/m^2). At baseline, 169 participants required only ambient oxygen or nasal cannula supplemental oxygen, and an additional 46 participants (18.7%) were requiring HFNC or NIPPV (**Table 2**). Last, 49 participants (16.3%) required invasive mechanical ventilation at the time of initial ultrasound scanning. During hospitalization, the most frequent treatments included dexamethasone (63.6% of participants), remdesivir (50.0%), or tocilizumab (9.1%).

Baseline Cross-Sectional Differences in POCUS Findings by Severity

At enrollment, participants with severe illness were later in their course of illness (median: 16.33 d post symptom onset; IQR, 11.08–28.29 d) compared with those with moderately severe (median: 9.29 d; IQR, 7.03–13.92 d) or moderate illness (median 7.38 d; IQR, 4.08–11.22 d) (Table 2). A lines were the most common finding among lung zones scanned (median 75.0% of lung fields; IQR, 58.3–91.7%), with a stepwise decrease in proportion of lung zones affected in moderately severe disease (median 69.7%; IQR, 51.8–87.1%) followed by severe disease at enrollment (54.6%; IQR, 25.0–66.7%) (Table 2). B lines were more likely to be present among those with severe disease (median 75.0%; IQR, 60.0–100%) or moderately severe disease (median 81.8%; IQR, 67.9–100%) compared with moderate cases (median 57.1%; IQR, 27.3–75.0%). Similarly, participants requiring invasive mechanical ventilation at enrollment had higher percent of pleural line abnormalities (median 25.0%; IQR, 9.1–50%) compared with moderately severe (median 0.0%; IQR, 0.0–15.6%) or moderate (median 0.0%; IQR, 0.0–16.7%) disease. Pleural effusions were mostly absent across severity levels, and those with a pleural effusion were a median 9.73 days (IQR, 5.17–16.21 d) post symptom onset, no different than the overall cohort (Mann-Whitney *U* test $p = 0.23$). The mLUSS was lower for moderate disease (median, 0.83; IQR, 0.33–1.17) compared with a stepwise increase in moderately severe disease (median, 1.11; IQR, 1.00–1.50) followed by severe critical disease (1.25; IQR, 1.00–1.67). The Pearson correlation coefficient of the mLUSS between readers was high at 0.77 among 61 participants with an available matched masked LUS read (**Fig. S2**, http://links.lww.com/CCX/B31).

Risk of Disease Progression

When evaluating the 28-day risk of progression to severe COVID-19, multiple baseline POCUS variables were found to be associated with severity progression using Cox proportional hazards regression. Each point increase in the mLUSS was associated with disease progression to ICU-level care (adjusted hazard ratio [aHR], 3.61; 95% CI, 1.27–10.22) and 28-day mortality (aHR, 3.10; 95% CI, 1.29–7.50; *C*-statistic = 0.760), but not the composite outcome of invasive mechanical ventilation or death (aHR, 2.99; 95% CI, 0.81–11.02; *C*-statistic = 0.743) (**Figs. 2** and **3** and **Table 3**) (**Table S1**, http://links.lww.com/CCX/B31). The sum LUS Score correlated highly with the mLUSS (Spearman correlation coefficient = 0.92). Inference was unchanged when adjusting for total number of available lung zones with an increased risk of progression to ICU-level care (aHR, 4.04; 95%

TABLE 1.
Participant Baseline Demographics

Characteristics	Total (*N* = 264)
Age, yr, median (IQR)	61.00 (48.75–68.00)
Female, *n* (%)	114 (43.18)
Race, *n* (%)	
Asian	7 (2.65)
Black	126 (47.73)
White	80 (30.30)
Other	49 (18.56)
Ethnicity, *n* (%)	
Hispanic	44 (16.67)
Non-Hispanic	220 (83.33)
Smoking, *n* (%)	
Never	149 (56.44)
Current	23 (8.71)
Former	80 (30.30)
Median body mass index, kg/m^2, median (IQR)	29.00 (25.4–33.2)
Comorbidities, *n* (%)	
Cancer	25 (9.5)
Congestive heart failure	87 (33.0)
Chronic obstructive pulmonary disease	96 (36.4)
Diabetes mellitus	112 (42.4)
Hypertension	196 (74.2)
HIV/AIDS	12 (4.6)
Liver disease	54 (20.5)
Symptoms onset until LUS scan, d, median (IQR)	9.27 (5.2–14.3)
Physiologic or laboratory variables–median (IQR)	
Respiratory rate (breaths per minute, maximum value on day of ultrasound)	22 (19–32)
Heart rate, beats per minute (maximum value on day of ultrasound)	91 (80–104)
Temperature (maximum value on day of ultrasound), °C	36.9 (36.6–37.4)
Temperature (minimum value on day of ultrasound), °C	36.1 (35.8–36.4)
WBC count (maximum value on day of ultrasound), × 10^9 cells/L	7.59 (5.22–10.62)
WBC count (minimum value on day of ultrasound), ×10^9 cells/L	7.08 (5.17–10.24)
Severe Inflammatory Response Syndrome (points)	2 (1–3)
Total lung zones scanned, median (IQR)	9 (7–12)
Mean LUS Score, median (IQR)	1.00 (0.50–1.30)
A-line lung fields, %, median (IQR)	0.75 (0.58–0.92)
B-line lung fields, %, median (IQR)	0.67 (0.38–0.84)
Pleural line abnormality lung fields, %, median (IQR)	0.00 (0.00–0.18)

IQR = interquartile range, LUS = lung ultrasound.

TABLE 2.

Cross-Sectional Differences in Lung Ultrasound Findings by Severity at Baseline

Oxygen Requirement Severity at Baseline Scan	Moderate: Ambient or Low-Flow Nasal Cannula (*N* = 169)	Moderately Severe: High-Flow Nasal Cannula or Noninvasive Positive Pressure Ventilation (*N* = 46)	Severe: Ventilation at LUS (*N* = 49)	*p*[a]
Age, yr, median (IQR)	60.00 (46.00–68.00)	63.00 (55.25–69.00)	61.00 (53.00–67.00)	< 0.001
Female, *n* (%)	84 (49.70)	18 (39.13)	12 (24.49)	0.006
Race, *n* (%)				0.232
Asian	1 (0.59)	5 (10.87)	1 (2.04)	
Black	92 (54.44)	18 (39.13)	16 (32.65)	
White	49 (28.99)	15 (32.61)	16 (32.65)	
Other	26 (15.38)	8 (17.39)	15 (30.61)	
Ethnicity, *n* (%)				0.445
Hispanic	25 (14.79)	8 (17.39)	11 (22.44)	
Non-Hispanic	144 (85.21)	38 (82.61)	38 (77.55)	
Smoking, *n* (%)				0.265
Never	103 (60.95)	25 (54.34)	21 (42.86)	
Current	15 (8.88)	3 (6.52)	5 (10.20)	
Former	48 (28.40)	18 (39.13)	14 (28.57)	
Median body mass index, kg/m^2, median (IQR)	27.56 (24.18–32.88)	29.98 (26.75–33.17)	30.80 (27.05–34.58)	0.054
Comorbidities, *n* (%)				
Cancer	20 (11.83)	0 (0.00)	5 (10.20)	0.051
Congestive heart failure	50 (29.59)	15 (32.61)	22 (44.90)	0.141
Chronic obstructive pulmonary disease	65 (38.46)	15 (32.61)	16 (32.65)	0.620
Hypertension	125 (73.96)	35 (76.09)	36 (73.47)	0.957
Liver disease	32 (18.93)	11 (23.91)	11 (22.45)	0.720
Diabetes	69 (40.83)	19 (41.30)	24 (48.98)	0.605
HIV/AIDS	8 (4.73)	4 (8.70)	0 (0.00)	0.126
Symptoms onset until LUS scan, d, median (IQR)	7.38 (4.08–11.22)	9.29 (7.03–13.92)	16.33 (11.08–28.29)	<0.001
Physiologic variables, median (IQR)				
Respiratory rate (breaths/min, maximum value on day of ultrasound)	20 (18–25)	34 (27–42)	28 (20–37)	< 0.001
Heart rate, beats/min (maximum value on day of ultrasound)	90 (80–100)	87 (78–99)	102 (90–116)	< 0.001
Temperature (maximum value on day of ultrasound), °C	36.9 (36.5–37.4)	36.8 (36.5–37.1)	37.2 (36.8–37.7)	0.008
Temperature (minimum value on day of ultrasound), °C	36.0 (35.8–36.3)	36.0 (35.8–36.2)	36.3 (35.9–36.6)	0.021
WBC count (maximum value on day of ultrasound), × 10^9 cells/L	6.64 (4.48–9.26)	8.54 (6.77–9.76)	11.19 (8.35–15.40)	< 0.001
WBC count (minimum value on day of ultrasound), × 10^9 cells/L	6.40 (4.48–9.07)	8.24 (6.21–9.71)	10.50 (7.09–14.37)	< 0.001
Severe Inflammatory Response Syndrome (points)	2 (1–2)	2 (1–2)	2 (2–3)	< 0.001
Ultrasound variables, median (IQR)				
Mean LUS Score	0.83 (0.33–1.17)	1.11 (1.00–1.50)	1.25 (1.00–1.67)	< 0.001
A-line, % lung fields	86 (67–100)	70 (52–87)	55 (25–67)	< 0.001
B-line, % lung fields	57 (27–75)	82 (68–100)	75 (60–100)	< 0.001
Pleural effusion, % lung fields	0 (0–8.3)	0 (0–8.3)	0 (0–37)	0.10
Pleural line abnormality, % lung fields	0 (0–17)	0 (0–16)	25 (9–50)	< 0.001

IQR = interquartile range, LUS = lung ultrasound.

[a]Kruskal-Wallis test by ranks.

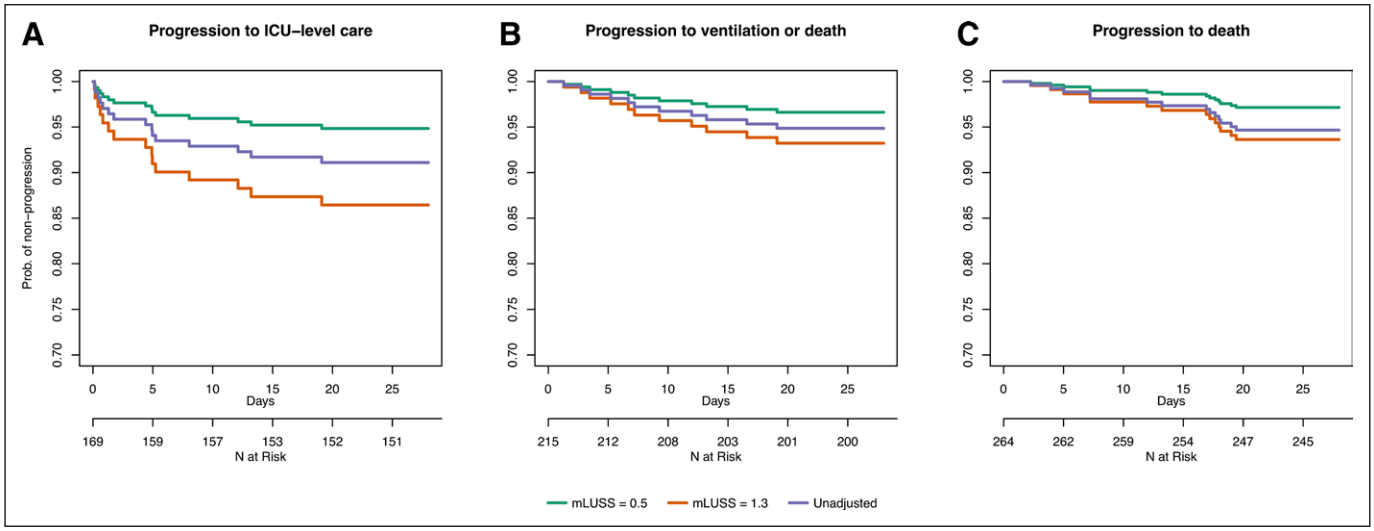

Figure 2. Kaplan-Meier time to progression by 75th percentile (1.3) versus 25th percentile (0.5) mean Lung Ultrasound Score (mLUSS) from time of lung ultrasound scan.

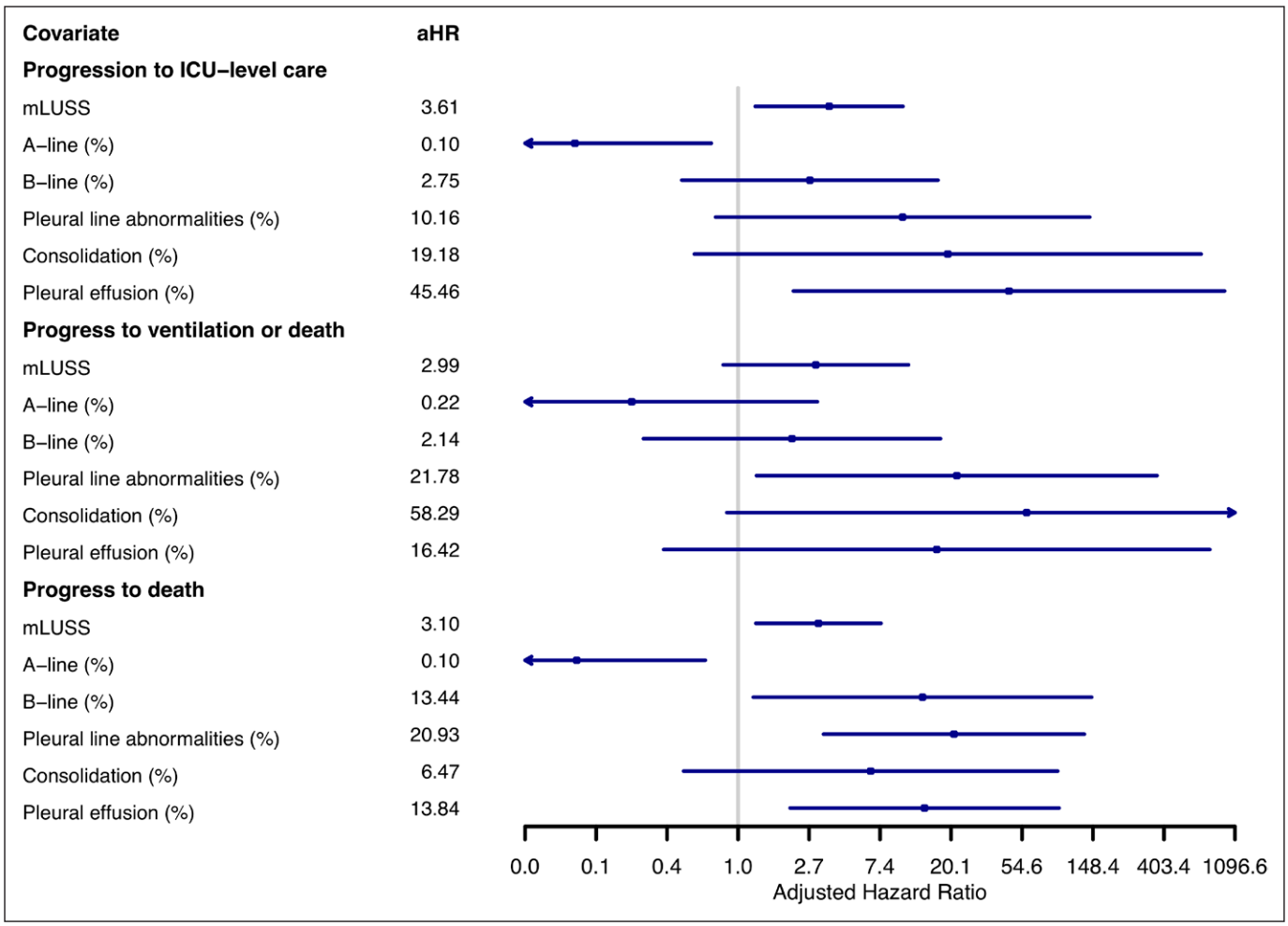

Figure 3. Forest plot of hazard ratios (HRs) of lung ultrasound (LUS) variables from individually fit models adjusting for age and sex for progression to severe disease. aHR = adjusted HR, mLUSS = mean LUS Score.

TABLE 3.
Cox Proportional Hazard Regression Models for Progression to ICU-Level Care Adjusted for Age and Sex (*N* = 169)

Covariates	Adjusted Hazard Ratio (95% CI)	*p*	Concordance (SE)
Duration of symptoms (d)	0.979 (0.901–1.064)	0.623	0.563 (0.067)
Ultrasound characteristics			
Mean Lung Ultrasound Score	3.607 (1.274–10.215)	**0.016**	0.680 (0.064)
A-lines (% lung fields)	0.100 (0.015–0.686)	**0.019**	0.697 (0.064)
B-lines (% lung fields)	2.750 (0.452–16.712)	0.272	0.590 (0.064)
Consolidation (% lung fields)	19.181 (0.540–680.960)	0.105	0.601 (0.068)
Pleural effusion (% lung fields)	45.460 (2.181–947.701)	**0.014**	0.640 (0.069)
Any pleural line abnormalities (% lung fields)	10.157 (0.728–141.644)	0.085	0.657 (0.053)
Thick (≥ 0.5cm) pleural line (% lung fields)	10.726 (0.133–863.768)	0.289	0.639 (0.063)
Irregular pleural line (% lung fields)	15.408 (0.806–294.672)	0.069	0.655 (0.053)
Fragmented pleural line (% lung fields)	38.754 (0.648–2,318.788)	0.080	0.600 (0.066)
Clinical variables			
Oxygen saturation (minimum value on day of ultrasound), %	0.911 (0.848–0.979)	**0.011**	0.670 (0.074)
Respiratory rate (maximum value on day of ultrasound), breaths/min	1.061 (1.019–1.105)	**0.004**	0.705 (0.064)
Heart rate, beats/min (maximum value on day of ultrasound)	1.001 (0.973–1.030)	0.927	0.550 (0.063)
Temperature (maximum value on day of ultrasound), °C	1.085 (0.559–2.107)	0.809	0.567 (0.063)
Temperature (minimum value on day of ultrasound), °C	1.069 (0.285–4.012)	0.921	0.569 (0.066)
WBC count (maximum value on day of ultrasound), × 10^9 cells/L	0.948 (0.827–1.087)	0.444	0.566 (0.072)
WBC count (minimum value on day of ultrasound), × 10^9 cells/L	0.952 (0.824–1.100)	0.508	0.555 (0.072)
SIRS (continuous)	1.301 (0.805–2.102)	0.282	0.571 (0.071)
SIRS, ≥ 2 points	1.114 (0.404–3.075)	0.834	0.553 (0.065)

SIRS = systemic inflammatory response syndrome.
Boldface values indicates statistical significance ($p < 0.05$).

CI, 1.36–12.01) or death (aHR, 2.45; 95% CI, 1.10–5.46), but not the composite outcome of invasive mechanical ventilation or death (aHR, 3.00; 95% CI, 0.82–11.07). Additionally, the directionality of the findings was consistent when adjusting for history of congestive heart failure (aHR, 4.93; 95% CI, 1.60–15.21), chronic lung disease (aHR, 3.34; 95% CI, 1.21–9.24), and body mass index (BMI) (aHR, 3.53; 95% CI, 1.20–10.37). Similarly, inference was unchanged when excluding asymptomatic individuals with each increase in the mLUSS associated with risk of progression to ICU-level care (aHR, 3.07; 95% CI, 1.04–9.07), death (aHR, 2.94; 95% CI, 1.21–7.15), but not invasive mechanical ventilation or death together (aHR, 2.69; 95% CI, 0.66–11.05). There was no interaction observed between duration of symptoms and mLUSS ($p = 0.98$) (data not shown).

Individual LUS characteristics were associated with disease progression. The presence of any type of B line was not associated with an increased risk of progression to ICU-level care (among those not on NIPPV, HFNC, or invasive mechanical ventilation) (aHR, 2.75; 95% CI, 0.45–10.22) but was associated with 28-day mortality compared with those without any B lines (aHR, 13.44; 95% CI, 1.24–145.76) (Fig. 3 and Table 3) (**Table S2**, http://links.lww.com/CCX/B31). Except for A lines, all studied individual POCUS variables (i.e., B lines, pleural line changes, consolidations, and pleural effusions) had an increased risk of progression to ICU-level care, death, and death or invasive mechanical ventilation but did not always meet statistical significance. Accordingly, A lines, which are generally present in the absence of

B lines, were associated with a decreased risk of progression to ICU-level care (aHR, 0.10; 95% CI, 0.02–0.69) and 28-day mortality (aHR, 0.10; 95% CI, 0.02–0.63). Pleural abnormalities were independently associated with invasive mechanical ventilation plus death (aHR, 21.78; 95% CI, 1.30–365.95) and death (pleural line aHR, 20.93; 95% CI, 3.34–131.30). These findings were qualitatively the same with the type of abnormality (i.e., irregular, thickened, or fragmented) (Table 3).

Ultrasound variable *C*-statistic estimates, particularly mLUSS (*C*-statistic = 0.680) and % A lines (*C*-statistic = 0.697), were similar to respiratory rate (*C*-statistic = 0.705) and oxygen saturation % (*C*-statistic = 0.670) and better than temperature, heart rate, WBC count, or SIRS for accuracy of prediction of progression to ICU-level care (Table 3). Pleural abnormalities had a high *C*-statistic predicting invasive mechanical ventilation or death with (*C*-statistic = 0.806) and without (*C*-statistic = 0.758) adjustment for baseline severity (Table S1, http://links.lww.com/CCX/B31). Adjustment for baseline severity resulted in the highest C-statistics for predicting 28-day death and severity adjustment resulted in *p* values greater than 0.05 for all ultrasound, physiologic, and SIRS variables (Table S2, http://links.lww.com/CCX/B31).

DISCUSSION

We observed mLUSS and multiple individual LUS findings were associated with a subsequent increased oxygen requirement or death in a prospective cohort. Although many studies to date have used retrospective clinical data, we conducted a prospective cohort study with standardized time points, probes, and protocols for image acquisition. Participants with fewer A lines or more irregular pleural lines, consolidations, or pleural effusions were more likely to have or to require a higher levels of care. POCUS had high accuracy in prediction of respiratory support requirements compared with commonly used variables of respiratory rate or oxygen saturation and performed better than SIRS. The mLUSS correlated well between ultrasound readers and could be used for patients with difficult to scan lung zones. These findings demonstrate the prognostic value of individual LUS findings or the mLUSS in assessing anticipated disease severity trajectories of COVID-19 without necessarily requiring all 12 lung zones in patients where a full examination may be challenging (e.g., endotracheal intubation, prone positioning, or chemically paralyzed).

Although there have been few large studies (5, 8), LUS has been shown to be associated with radiographic and clinical severity among adults hospitalized with COVID-19. B lines, pleural line irregularities, and large parenchymal consolidations have correlated with CT findings and oxygen saturation (15). In a systematic review of 43 studies, the presence of focal, multifocal, and/or confluent B lines and the presence of pleural irregularities were common among individuals with COVID-19 (16). We identified similar POCUS associations and, additionally, found pleural effusions to be associated with disease progression, potentially due to decreased oncotic pressure during severe illness. Mechanistically, the degree and magnitude of LUS abnormalities throughout lung zones reflects the extent of lung disease and is intuitively directly related to severe disease trajectories. LUS compares favorably with CT as a gold standard for identifying severe COVD-19 with an area under the curve of 0.78 (95% CI, 0.68–0.87; $p < 0.001$) (17). Rubio-Garcia et al (9) examined the LUS among 130 patients with COVID 19 and demonstrated an increased risk of mortality among individuals with a high modified LUS score (hazard ratio, 5.25; 0.84–32.84). The investigators however did not describe individual features of the LUS such as A lines, B lines, and pleural disease and used a high cutoff to optimize sensitivity (9). In contrast to our findings of pleural irregularities among more severely ill participants, hospital-based cohort in Iran identified pleural thickening to be present in 95% of participants, but the undescribed criteria may have been lower than our greater than or equal to 0.5 cm cutoff (18). Although other studies have generally used a sum of all 12 lung zones (5, 8, 9, 19, 20), our study found the risk estimates were unchanged when some lung fields were not obtainable due to clinical instability. Our study is consistent with prior publications and provides evidence that LUS can prognosticate hospitalized patients using available lung zones.

Adoption of LUS has varied in hospital settings largely a result of lack of familiarity as well as difference in approaches, techniques, and nomenclature (21). However, research coordinators were trained with standardized protocols, and images were satisfactory

and correlated well. Standardization of scans reduced the risk of bias related to direct performance by medical caregivers. This suggests that LUS scanning could be expanded to nonclinicians, including but not limited to nursing staff, respiratory therapists, or medics in the field. Although the value of immediate information to a performing clinician should not be ignored or undervalued, extending the expertise of LUS performance to additional healthcare workers could be more scalable than LUS by clinicians alone.

Biomarker and therapeutic research has identified the importance of phase of disease as indicated by duration of symptoms (22). A small ICU cohort in Saudi Arabia was observed to have a decrease in LUS abnormalities beginning in week 3 of illness (7). However, inference was unchanged after adjusting for duration of symptoms or interaction with duration in our Cox regression models. POCUS results appeared to be generalizable regardless of adjustment for days since symptom onset for determining risk of decompensation toward ICU-level care. Changes in LUS findings or the role of LUS for identifying patients who would benefit from treatments were not evaluated here due to a limited sample size (data not shown), but studies are ongoing to evaluate longitudinal LUS for estimating risk of severe disease and treatment response.

There were limitations to the present study. First, not all participants were enrolled prior to admission, and as this was a hospital-based protocol, generally had a minimum requirement of oxygen. Not all participants were enrolled on the day of admission, and some had their first scan a few days after enrollment which may have diminished the effect size of differences in POCUS findings. However, we found that results were stable regardless of duration of symptoms. Additionally, those hospitalized with incidental asymptomatic SARS-CoV-2 infection may be less comparable to those with moderate severity, although a sensitivity analysis was conducted and demonstrated no change in prognostic utility of mLUSS between groups. Different baseline severities led to sample size limitations in some of the survival analyses leading to wide CIs, including between mLUSS and risk of progression to ventilation or death or after baseline severity adjustment, but the qualitative inference was consistent across outcomes and remains important. Although this cohort was scanned based on trained research personnel availability, the age, sex, BMI, and baseline comorbid conditions were a representative sample of the previously described patient population in the Johns Hopkins Hospital network (23). This was a single-center study and occurred prior to dominance of the omicron variant, but work is ongoing to validate findings in multiple centers to improve our understanding of the external validity and diagnostic accuracy among additional populations including nonhospitalized individuals with COVID 19. A single probe type was used for a rapid scanning protocol. However, granular pleural line details may have been more accurately identified with the addition of a linear ultrasound probe (24). Last, although the mLUSS provide valuable prognostic information, additional LUS features such as pleural effusions or pleural line changes appear to be useful prognostic findings and should be evaluated for incorporation into models with subsequent validation. Future research with machine learning and unsupervised approaches can help optimize LUS for clinical use.

CONCLUSIONS

Individual LUS findings and the mLUSS across available lung zones on lung POCUS are associated with ultimate oxygen requirement or death among hospitalized patients.

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