● *Original Contribution*

LUNG ULTRASOUND CAN PREDICT THE CLINICAL COURSE AND SEVERITY OF COVID-19 DISEASE

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Abstract—Coronavirus disease 2019 (COVID-19) compromises the lung in large numbers of people. The development of minimally invasive methods to determine the severity of pulmonary extension is desired. This study aimed to describe the characteristics of sequential lung ultrasound and to test the prognostic usefulness of this exam in a group of patients admitted to the hospital with COVID-19. We prospectively evaluated patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection admitted to our hospital between April and August 2020. Bedside lung ultrasound exams were performed at three time points: at inclusion in the study, after 48 h and on the seventh day of follow-up. Lung ultrasound scores were quantified according to the aeration loss in each of eight zones scanned. Sixty-six participants were included: 42 (63.6%) in the intensive care unit and 24 (36.3%) in the ward. Lung ultrasound scores were higher in participants admitted to the intensive care unit than in those admitted to the ward at the time of inclusion (16 [13−17] vs. 10 [4−14], $p < 0.001$), after 48 h (15.5 [13−17] vs. 12.5 [8.2−14.7], $p = 0.001$) and on the seventh day (16 [14−17] vs. 7 [4.5−13.7], $p < 0.001$) respectively. Lung ultrasound score measured at the time of inclusion in the study was independently associated with the need for admission to the intensive care unit (odds ratio = 1.480; 95% confidence interval, 1.093−2.004; $p = 0.011$) adjusted by the Sequential Organ Failure Assessment score. (E-mail: ceciliag.ravetti@gmail.com) © 2021 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: COVID-19, Lung ultrasound, Intensive care, SARS-CoV-2.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first described in China in December 2019, and rapidly spread worldwide. Today, coronavirus disease 2019 (COVID-19), the disease caused by the new beta coronavirus, affects more than 37 million people around the world, and more than one million have died (WHO, 2020). COVID-19 diagnosis requires isolation of RNA from clinical samples or a high clinical suspicion associated with typical images on chest computerized tomography, such as peripheral ground-glass opacities mainly in the lower regions of the lungs (Fang et al. 2020).

In critically ill patients, with severe hypoxemia requiring mechanical invasive ventilatory support, transport for chest imaging is both clinically dangerous and associated with a higher risk of virus transmission during transportation (Simpson et al. 2020). Bedside lung ultrasonography (LUS) has proven useful for evaluating COVID-19 patients, with several studies describing the main characteristic findings of this exam (Convissar et al. 2020; Peng et al. 2020; Soldati et al. 2020). As it is non-invasive and does not expose patients to ionizing radiation, LUS is an excellent alternative to other methods of diagnosing and monitoring the pulmonary

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condition of patients with suspected or confirmed COVID-19. Moreover, it may reduce the need for patient transport and its related risks.

Lichter et al. (2020) showed that LUS score measured at admission strongly correlates with the need for invasive mechanical ventilation and mortality in people infected with SARS-CoV-2. That study included 120 participants, but only 20 were sequentially screened with a second exam.

Perrone et al. (2020) also evaluated COVID-19 patients admitted to wards, analyzing 14 windows at two time points: admission and discharge. The study included 52 participants, and observed a positive correlation between LUS score and worsening disease.

The present study aimed to describe the characteristics of sequential LUS and to test the prognostic usefulness of this exam in a group of patients admitted in a tertiary hospital, both intensive care units and wards, with suspected COVID-19.

METHODS

This study was carried out at Hospital das Clínicas, Universidade Federal de Minas Gerais. We used a convenient sampling protocol to include patients admitted between April and August 2020. During this period all adults (age ≥ 18 y) admitted to the units dedicated to the care of COVID-19 patients (a 23-bed ward and an 18-bed intensive care unit [ICU]) were assessed for potential eligibility. Exclusion criteria were COVID-19 non-confirmation by reverse transcription polymerase chain reaction, a more probable differential diagnosis at the time of inclusion, exclusive palliative care at the moment of first assessment for the study and high probability of death within 24 h of inclusion. The local ethics committee approved the study (protocol number 30437020.9.3001.5124), and all participants signed an informed consent form.

The first priorities to admit patients to the ICU were hemodynamic instability with noradrenaline requirement (>0.1 μg/kg/min), acute kidney injury with hemodialysis requirement, endotracheal intubation for invasive mechanical ventilation and post-cardiac arrest. Secondary priorities were median arterial pressure <65 mm Hg or systolic blood pressure <90 mm Hg, oxygen saturation <93% in room air, pulmonary infiltration rapidly progressive (50% in 24−48 h) and National Early Warning Score ≥ 7.

Clinical and epidemiologic data were prospectively collected using electronic charts. The prevalence of comorbidities such as chronic obstructive pulmonary disease, asthma, systemic arterial hypertension, heart failure, diabetes mellitus, coronary artery disease, obesity, solid organ neoplasm, hematological neoplasm, solid organ or hematopoietic stem cell transplantation and chronic renal replacement therapy requirement was also registered. Finally, we calculated the Sequential Organ Failure Assessment (Vincent et al. 1996) score for all participants included in the study, and the APACHE II (Knaus et al. 1985) score in those admitted to the ICU.

Ultrasound exams were performed at three time points, with 3−4 s image acquisition (recorded) in each area: at inclusion in the study, after 48 h and on the seventh day after inclusion. The images were acquired by the same physician, who is experienced in intensive care and in performing point-of-care ultrasound examinations at the bedside (Gómez Ravetti et al. 2020). The US protocol was adapted from Soummer et al. (2012) and included four areas in each hemithorax: anterior (2° inter-costal space at a mid-clavicular line), lateral (anterior axillary line at 5° inter-costal space), posterior (posterolateral alveolar or pleural syndrome) and costophrenic (Fig. 1).

A Terason t3000 portable ultrasound machine (Terason Ultrasound, Burlington, MA, USA) and Sonosite M-Turbo (Sonosite, Bothell, WA, USA) were used with a sector transducer (3.5−5 MHz). The depth was adjusted between 5 and 10 cm at the beginning of the exam. In lateral areas, according to visualized costophrenic zones, some deeper images were obtained (15 cm) to determine the presence of pleural effusion and
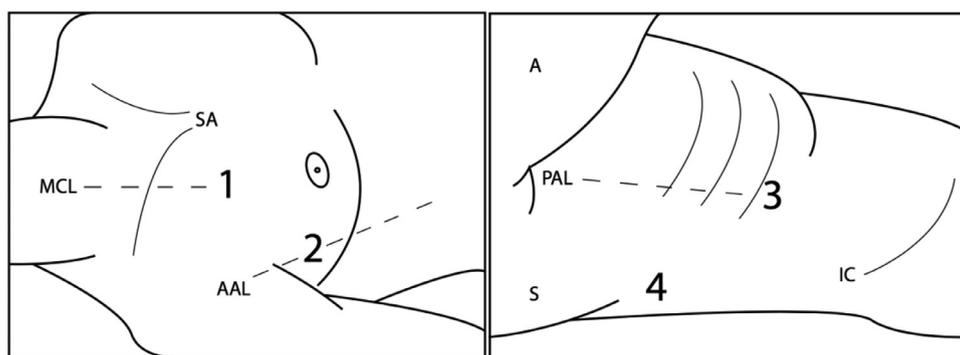

Fig. 1. Thorax ultrasound protocol regions scanned.

consolidation. For better visualization of the pleura, a linear probe (5−10 MHz) was used whenever required. The linear probe was mainly used to diagnose or rule out pneumothorax or barotrauma related to mechanical ventilation.

According to the images found in each assessed area, pulmonary aeration was quantified through a previously defined scoring rubric (Soummer et al. 2012): 0 points for A-lines with lung sliding, 1 point for more than three well-defined B-lines, 2 points for coalescent B-lines, 3 points for consolidation and 1 point if pleural effusion is present in each hemithorax. A B-line was defined as a vertical, hyperechoic, dynamic line that originates in the pleural line and moves synchronously with lung sliding. A well-defined B-line pattern was characterized by more than three B-lines in an intercostal space which the operator could count. Coalescent B-line patterns were characterized by B-lines that the operator could not quantify because they were so numerous and tended to merge (Fig. 2). The score ranged from 0 to 26 points, with higher values meaning greater loss of aeration.

Statistical analysis

Data are described as proportion, central tendency and distribution. Qualitative variables were compared with χ^2 or Fisher's exact test, as recommended. Quantitative variables were compared by the Mann−Whitney U test or Kruskal−Wallis test, as indicated according to normal or non-normal distribution. The Friedman test was used to compare quantitative variables within the same group. To investigate whether LUS was associated with outcome, we built a logistic regression model. All explanatory variables with a $p < 0.05$ were included in this model. Moreover, we built a Kaplan−Meier survival curve according to the LUS score and compared it with a log-rank test. LUS score was included as a dichotomous variable for which the cutoff was set using a receiver operating characteristic curve and the Youden test.

A two-tailed p value <0.05 was considered significant for all analyses. The REDCap platform (REDCap, Nashville, TN, USA) was used to collect the data, and SPSS version 22.0 (IBM, Chicago, IL, USA) was used for statistical analysis.

RESULTS

We assessed 82 patients for eligibility, and 66 with confirmed SARS-CoV-2 infection were included in the final analysis. COVID-19 diagnosis was confirmed by reverse transcription polymerase chain reaction test by nasopharyngeal swab in most participants (93.3%), or combination of a highly suggestive clinical scenario and
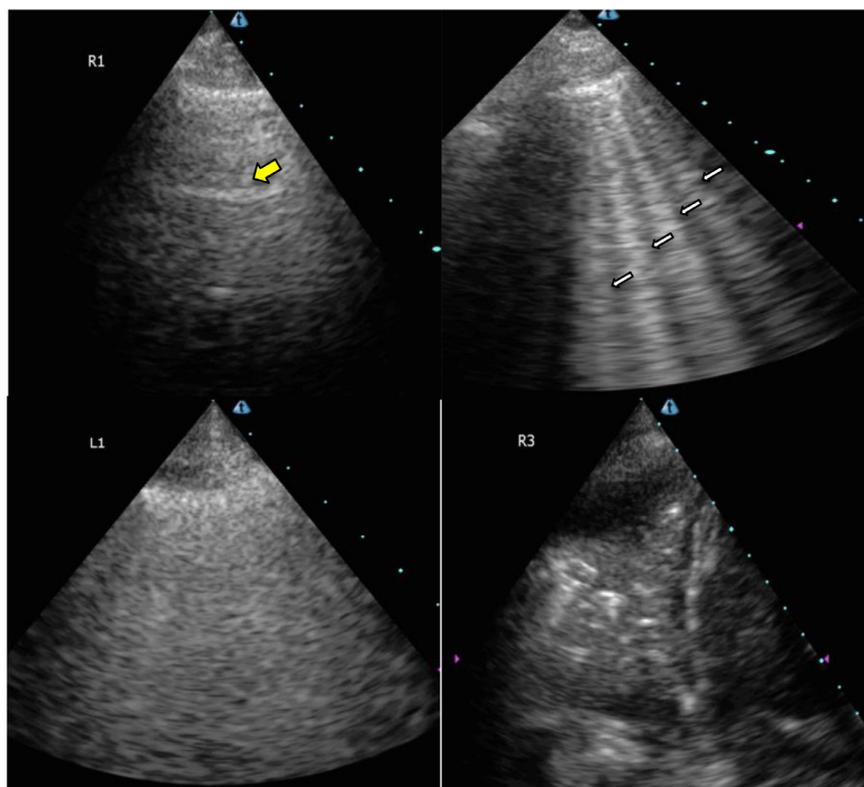

Fig. 2. Ultrasound lung patterns in COVID-19.

typical findings on chest computed tomography in the rest. Forty-two participants (63.6%) were admitted to the ICU and 24 (36.3%) to the ward. The median (interquartile range) age was 63.5 (46.7−72) y; 30 (45.5%) were female and 36 (54.5%) male. The most common comorbidities were hypertension (59.1%), diabetes mellitus (34.8%) and obesity (24.2%). Dyspnea was present at hospital admission in more than 80% of participants. Thirty-three (78.6%) of the 42 participants admitted to the ICU were mechanically ventilated, and 23 (69.7%) of those 33 died. The overall hospital mortality in the study sample was 36.9%, and the mortality in the subgroup initially admitted to the ICU was 58.5%. Taken as a whole, the ICU group had dyspnea more frequently, had higher Sequential Organ Failure Assessment scores on admission and spent more time in the hospital than those admitted to the ward (Table 1).

LUS according to admission destination at the time of inclusion

LUS scores were significantly higher among participants initially admitted to the ICU than those admitted to the ward; these differences were observed at the time of inclusion, on day 3 and on day 7 (Fig. 3).

We further compared the tendency of LUS scores measured on days 1, 3 and 7 between the two groups. There was no significant within-group difference in participants
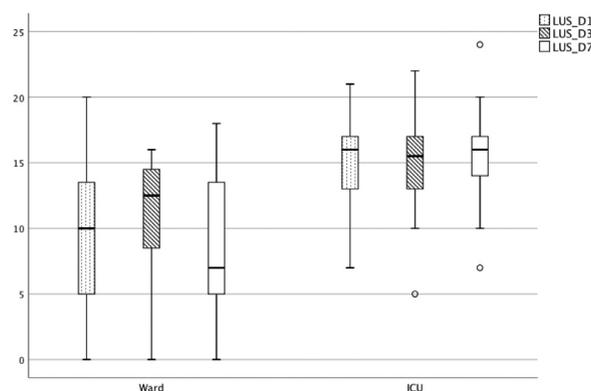

Fig. 3. Comparison between median lung ultrasound scores according to intensive care unit admission requirement.

admitted to the ward (respectively, 10 [4−14], 12.5 [8.2−14.7] and 7 [4.5−13.7]; $p = 0.152$) or to the ICU (16 [13−17], 15.5 [13−17] and 16 [14−17]; $p = 0.583$).

In an analysis adjusted for severity (*i.e.,* Sequential Organ Failure Assessment score), the LUS score measured at the time of inclusion in the study was independently associated with the need for ICU admission (odds ratio = 1.480; 95% confidence interval, 1.093−2.004; $p = 0.011$).

LUS findings stratified by the need for ICU admission

The LUS artifacts (A-lines, well-defined B-lines, coalescent B-lines and consolidation) for each

Table 1. Demographic and clinical characteristics of participants

Characteristic	All (*N* = 66)	Ward (*n* = 24)	ICU (*n* = 42)	*p*
Age (y)	63.5 (46.7−72)	60 (46−70)	64 (50−72)	0.323
Male sex	36 (54.5)	10 (41.7)	26 (61.9)	0.112
Comorbidities	60 (90.9)	22 (91.7)	36 (85.7)	0.700
Hypertension	39 (59.1)	12 (50)	27 (64.3)	0.256
Diabetes	23 (34.8)	8 (33.3)	15 (35.7)	0.845
Obesity	16 (24.2)	4 (17.4)	12 (29.3)	0.292
COPD/Asthma	12 (18.8)	5 (20.8)	7 (16.7)	0.618
HF	6 (9.4)	2 (8.3)	4 (9.5)	1.000
Cardiovascular disease	10 (15.1)	5 (20.8)	5 (11.9)	0.477
Solid neoplasm	10 (17.2)	3 (12.5)	7 (16.7)	0.736
Solid organ transplantation	7 (10.6)	4 (16.7)	3 (7.1)	0.246
Symptoms				
Dyspnea	54 (81.8)	13 (54.2)	41 (97.6)	<0.001
Cough	47 (71.2)	18 (75)	29 (69)	0.607
Fever	38 (57.6)	15 (62.5)	23 (54.8)	0.541
SOFA score	4 (2−7)	1.5 (1−3)	5 (3−9)	<0.001
Leukocyte count (× 10³)	9.09 (5.02−11.89)	5.58 (3.58−8.81)	10.52 (7.84−13.55)	<0.001
Neutrophil count (× 10³)	7.57 (3.48−9.97)	3.54 (2.28−6.87)	8.60 (5.62−11.87)	<0.001
Lymphocyte count (× 10³)	0.81 (0.58−1.38)	1.09 (0.60−1.62)	0.74 (0.58−1.08)	0.080
CRP (mg/L)	158 (60−215)	81 (52−163)	175 (71−233)	0.011
LOS (d)	14 (7.2−26.7)	13 (6−16)	18 (10−33)	0.032
Dexamethasone	38 (59.4)	9 (37.5)	31 (73.8)	0.004
ATB use	62 (93.9)	20 (83.3)	42 (100)	0.015
IMV requirement	33 (50)	0	33 (78.6)	<0.001
Hospital mortality	24 (36.9)	0	24 (58.5)	<0.001

COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ICU = intensive care unit; IMV = invasive mechanical ventilation; LOS = length of stay; SOFA = Sequential Organ Failure Assessment; ATB = antibiotics; HF = heart failure.
Data are presented as number (%) or median (interquartile range).

pulmonary region assessed at the time of inclusion in the study were compared according to the need for ICU or ward admission. Participants admitted to the ward showed more prevalence of A lines in the right and left hemithorax in the eight windows than those admitted to the ICU (Fig. 4). Likewise, the ICU group showed more B-lines (well defined and coalescent) in upper windows (R1, R2, R3, L1, L2 and L3) than the ward group.

Accordingly, median LUS scores were significantly higher among participants who died during hospitalization than those who did not on day 1 (16 [14−17] vs. 12 [8−16], $p = 0.001$), day 3 (15.5 [13−17.7] vs. 14 [11−16], $p = 0.025$) and day 7 (15 [14.2−17] vs. 14 [6.7−16], $p = 0.029$).

Mortality among participants with LUS scores > 12 at inclusion was significantly higher than among those with lower scores (2 [83%] vs. 22 [91.7%], $p < 0.001$),

and their cumulative survival during follow-up was significantly lower (Fig. 5).

DISCUSSION

In this study, a LUS score for pulmonary aeration loss quantified at bedside was independently associated with the need for ICU admission among patients admitted with COVID-19, adjusted by the severity. Also, sequential lung scores measured after 48 h and on the seventh day of follow-up were higher in those admitted to the ICU than those in the ward. Likewise, the ICU group showed more prevalence of B-lines in the upper lung regions.

Since the beginning of the pandemic, several studies on LUS in COVID-19 have been published (Buonsenso et al. 2020; Peng et al 2020;
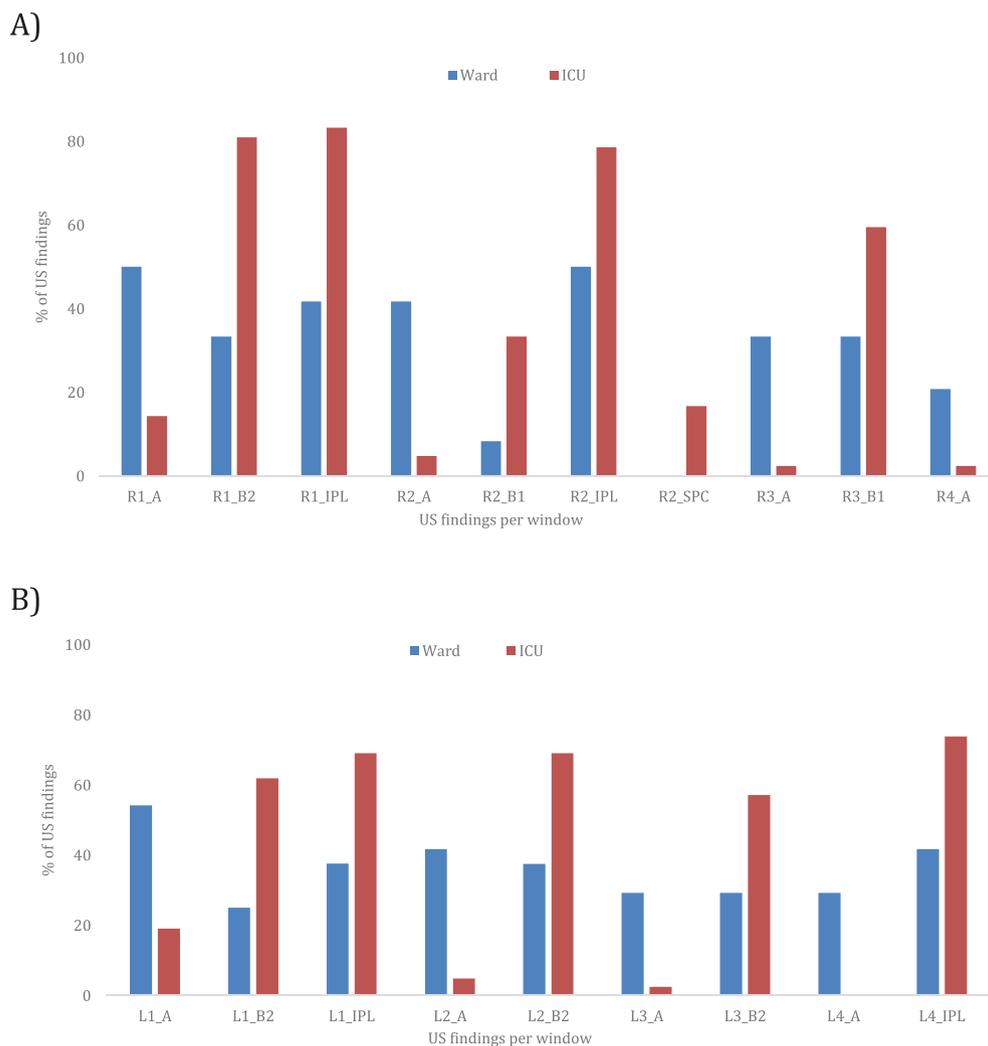
A)

B)

Fig. 4. Comparison between lung ultrasound findings according to intensive care unit admission requirement: (a) right hemithorax. (b) left hemithorax.
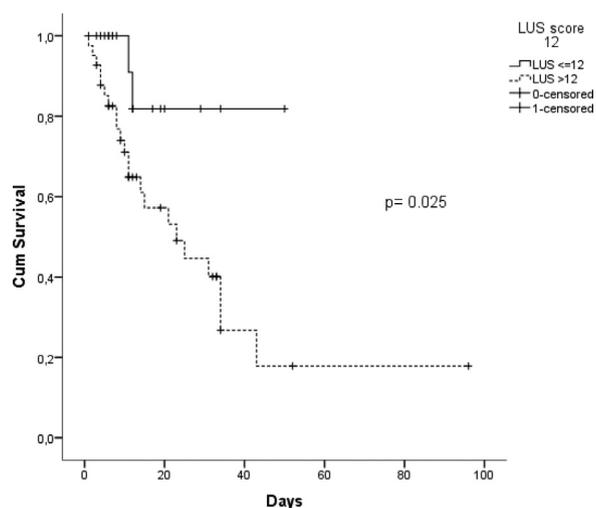
Fig. 5. Kaplan−Meier curves to compare hospital mortality according to lung ultrasound score at time of inclusion.

Soldati et al. 2020). Our findings on LUS are in agreement with previously published data showing impaired aeration predominantly in posteroinferior regions, identified by the presence of B-lines with different patterns—from well-defined B-lines to coalescence ("white lung")—pleural "thickening" and subpleural consolidations (Smith et al. 2020; Volpicelli et al. 2020; Xing et al. 2020).

Lichter et al. (2020) carried out a study with LUS in 120 COVID-19 patients. They performed a first exam at the time of hospital admission in all participants, and a second exam in a subgroup of 20 participants who required orotracheal intubation. This study demonstrated that the pulmonary score measured at admission was associated with the composite outcome of need for invasive mechanical ventilation or death. These findings are in line with our results showing more significant loss of aeration in patients who required ICU admission and died during hospitalization.

Bonadia (2020) demonstrated in 41 patients with COVID-19 that in the first ultrasound exam performed at the emergency department, the rates of pathologic lung areas involved and the scores of aeration loss were higher among those who were admitted to the ICU or died during hospitalization. In accordance with our results, the ultrasound showed interesting results to differentiate the severity of the disease.

Our study sequentially evaluated lung ultrasound in a larger number of COVID-19 patients with different disease severities, assessed at three time points. We hypothesized that by doing so, we would be able to monitor the evolution of lung compromise (*i.e.,* aeration loss) during the first week of the disease, which could help predict the need for ICU admission and eventual

death. Our data suggest that LUS findings can be added to other clinical and laboratory data to render the decision-making process regarding care management more accurate. In other scenarios of severe pulmonary disease, pulmonary ultrasonography has proven useful, both in diagnosis (Lichtenstein and Mezière 2008) and in monitoring positive end-expiratory pressure adjustment (Bouhemad et al. 2011) and the response to antibiotic treatment in cases of ventilator-associated pneumonia (Bouhemad et al. 2010). Previous studies have demonstrated the evolution of pulmonary lesions in the convalescence period, from consolidation to A-line patterns (Peng et al. 2020; Xing et al. 2020). Using this method in a systematic protocol would avoid patient transport for computed tomography scans, as well as the exposure of health workers to chest X-ray. Moreover, in low-resource environments and remote areas such as the Amazon region, LUS can be a portable alternative to help manage COVID-19.

Our results highlight the importance of performing a bedside lung ultrasound to determine disease severity and to quantify aeration loss in patients admitted with SARS-CoV-2 infection.

Mento et al. (2020), in a multi-center study, compared four LUS protocols (4, 8, 12 and 14 scanned areas) in COVID-19 patients, and showed that 12-area acquisition had a better correlation between time scanned and accuracy. Similarly, a CLUE protocol with 12 lung areas has been recommended in COVID-19 patients, and suggested as useful in emergency-department clinicians' decision making (Manivel et al. 2020). We quantified aeration loss differently, measuring in eight lung windows according to previous studies (Soummer et al. 2012; Millington et al. 2018) with critically ill patients, because most of our participants were admitted to the ICU. Our eight scanned zones proved to be sufficient to differentiate groups according to severity and outcomes. In our opinion, this approach could be useful in severe COVID-19.

Perrone et al. (2020) and Smargiassi et al. (2020) used 14 areas in LUS of people with COVID-19. In both studies, the authors evaluated patients admitted to the wards differently from our cohort of participants. In our study, participants were admitted mostly to the ICU, where position change required further effort, because most of them were under mechanical ventilation or had high oxygen demand. However, we scanned the whole pulmonary area and recorded 3−4 s of each area, totaling a minimum of 32 s per participant.

In this study, we used a phased-array probe to scan the lungs, as recommended for some experts with people who are critically ill (Mojoli et al. 2019), and a linear probe was used only in situations when barotrauma or pneumothorax was a concern. We hypothesized that during the COVID-19 pandemic, when health professionals'

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exposure has to be limited, this approach could have underestimated disease severity, despite our results proving different between the groups.

Another limitation is that this was a single-center study with a small number of participants. However, the prospective design, along with the protocol of sequential LUS imaging in patients admitted to the hospital with COVID-19, is a positive aspect of the study, and can contribute to anticipating the need for ICU admission.

CONCLUSION

Bedside lung ultrasound proved to be a suitable method for determining severity of illness in people admitted to the hospital with SARS-CoV-2 infection. The lung ultrasound scores measured at three time points were higher in those who required ICU admission and died during hospitalization.

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