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Lung Ultrasound to Assist ICU Admission Decision-Making Process of COVID-19 Patients With Acute Respiratory Failure

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OBJECTIVES: There is only low-certainty evidence on the use of predictive models to assist COVID-19 patient's ICU admission decision-making process. Accumulative evidence suggests that lung ultrasound (LUS) assessment of COVID-19 patients allows accurate bedside evaluation of lung integrity, with the added advantage of repeatability, absence of radiation exposure, reduced risk of virus dissemination, and low cost. Our goal is to assess the performance of a quantified indicator resulting from LUS data compared with standard clinical practice model to predict critical respiratory illness in the 24 hours following hospital admission.

DESIGN: Prospective cohort study.

SETTING: Critical Care Unit from University Hospital Purpan (Toulouse, France) between July 2020 and March 2021.

PATIENTS: Adult patients for COVID-19 who were in acute respiratory failure (ARF), defined as blood oxygen saturation as measured by pulse oximetry less than 90% while breathing room air or respiratory rate greater than or equal to 30 breaths/min at hospital admission. Linear multivariate models were used to identify factors associated with critical respiratory illness, defined as death or mild/severe acute respiratory distress syndrome ($Pao_2/Fio_2 < 200$) in the 24 hours after patient's hospital admission.

INTERVENTION: LUS assessment.

MEASUREMENTS AND MAIN RESULTS: One hundred and forty COVID-19 patients with ARF were studied. This cohort was split into two independent groups: learning sample (first 70 patients) and validation sample (last 70 patients). Interstitial lung water, thickening of the pleural line, and alveolar consolidation detection were strongly associated with patient's outcome. The LUS model predicted more accurately patient's outcomes than the standard clinical practice model (DeLong test: Testing: z score = 2.50, p value = 0.01; Validation: z score = 2.11, p value = 0.03).

CONCLUSIONS: LUS assessment of COVID-19 patients with ARF at hospital admission allows a more accurate prediction of the risk of critical respiratory illness than standard clinical practice. These results hold the promise of improving ICU resource allocation process, particularly in the case of massive influx of patients or limited resources, both now and in future anticipated pandemics.

KEY WORDS: acute respiratory distress syndrome; acute respiratory failure; COVID-19; intensive care unit admission decision-making; lung ultrasound; machine learning

The exponential spread of the novel COVID-19 has revealed constraints in critical care capacity around the globe (1). Accurate and rapid patient prognostication appears to be essential for critical care utilization management and eventually improving outcomes (2). The literature in this

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field is predominantly descriptive, and there is limited empirical evidence on the use of standardized models to assist ICU admission decision-making process (3–5). Many studies have investigated COVID-19 critical care triage based on clinical variables, laboratory measurements, and radiological examination carried out on hospital admission to build predictive models (6–10). However, the vast majority of these studies are based on low-certainty evidence due to their retrospective design, lack of validation, poor reporting, and high risk of bias (11). Furthermore, it has been argued that data collection and analysis processes that are related to these critical care triage models are time-consuming, ineffective in terms of resources allocation, and are not well adapted to the cases of massive influx of patients or limited resource settings (12).

Interestingly, recent studies have demonstrated that lung ultrasound (LUS) gives results that are similar to chest CT and superior to standard chest radiography for evaluation of COVID-19 severity (13). Converging data suggest that a standardized LUS assessment of COVID-19 patients, based on unspecific sonographic semiotics of lung loss aeration (14), allows accurate bedside evaluation of lung and pleura integrity (15), with the added advantage of ease of use at point of care, repeatability, absence of radiation exposure, reduced risk of inhospital severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus dissemination, and low cost (16). We suggest that an LUS-based patient's bedside stratification of lung and pleural damage induced by SARS-CoV-2 infection hold the promise of providing highly needed, innovative and powerful short-term outcome predictors for COVID-19 patients with acute respiratory failure (ARF).

We hypothesize that the accuracy of prediction of COVID-19 critical respiratory illness, defined as death or mild/severe acute respiratory distress syndrome (ARDS) ($Pao_2/Fio_2 < 200$) in the 24 hours following hospital admission based on LUS data, will significantly outperform prediction built upon standard clinical variables collected at the time of hospital admission. The goal of the current study is to assess the performance of a quantified indicator resulting from LUS data gathered at patient's hospital admission for COVID-19, compared with standard procedures to predict critical respiratory illness in the 24 hours following hospital admission. The optimum cutoff will be defined from a derivation cohort and assessed in an independent validation cohort.

MATERIALS AND METHODS

Study Design

This prospective, observational, proof of concept study was done in the Medical Triage Zone of the Purpan University Hospital, Toulouse, France. We compared two predictive models of critical respiratory illness, defined as death or mild/severe ARDS ($Pao_2/Fio_2 < 200$) in the 24 hours after patient's first hospital admission. The whole dataset, including LUS assessment and standard clinical variables, was prospectively collected between July 2020 and March 2021. Patients were managed by emergency physicians according to current guidelines and recommendations (1, 12, 17). Emergency physicians were blinded to LUS data. The study was approved by the ethics committee of the University Hospital of Toulouse, Toulouse, France (Comité Consultatif pour la Protection des Personnes, Ref. 2020-A01225-48); written consent was obtained from all participants. COVID-19 diagnoses were confirmed by positive real-time reverse transcription polymerase-chain-reaction assay for pharyngeal swap specimens. The study protocol was registered under NCT 04474236.

Population

We recruited consecutively admitted adult patients for COVID-19 who were in ARF at hospital admission (**Fig. 1**). To define ARF, we used American Thoracic guidelines for community-acquired pneumonia given the extensive acceptance of this guideline (blood oxygen saturation as measured by pulse oximetry <90% while breathing room air or respiratory rate ≥30 breaths/min) (18). Exclusion criteria were history of long-term oxygen therapy (oxygen used for at least 15 hr/day in patients with severe chronic resting room air hypoxemia), either standard oxygen requirement greater than 15 L/min to maintain a pulse oximetry greater than 92% or need of invasive mechanical ventilation at the time of hospital admission. Indeed, to increase the clinical relevance of our predictive models, we decided to focus on COVID-19 patients with ARF for whom mild/severe ARDS was not universally apparent at the time of the hospital admission.

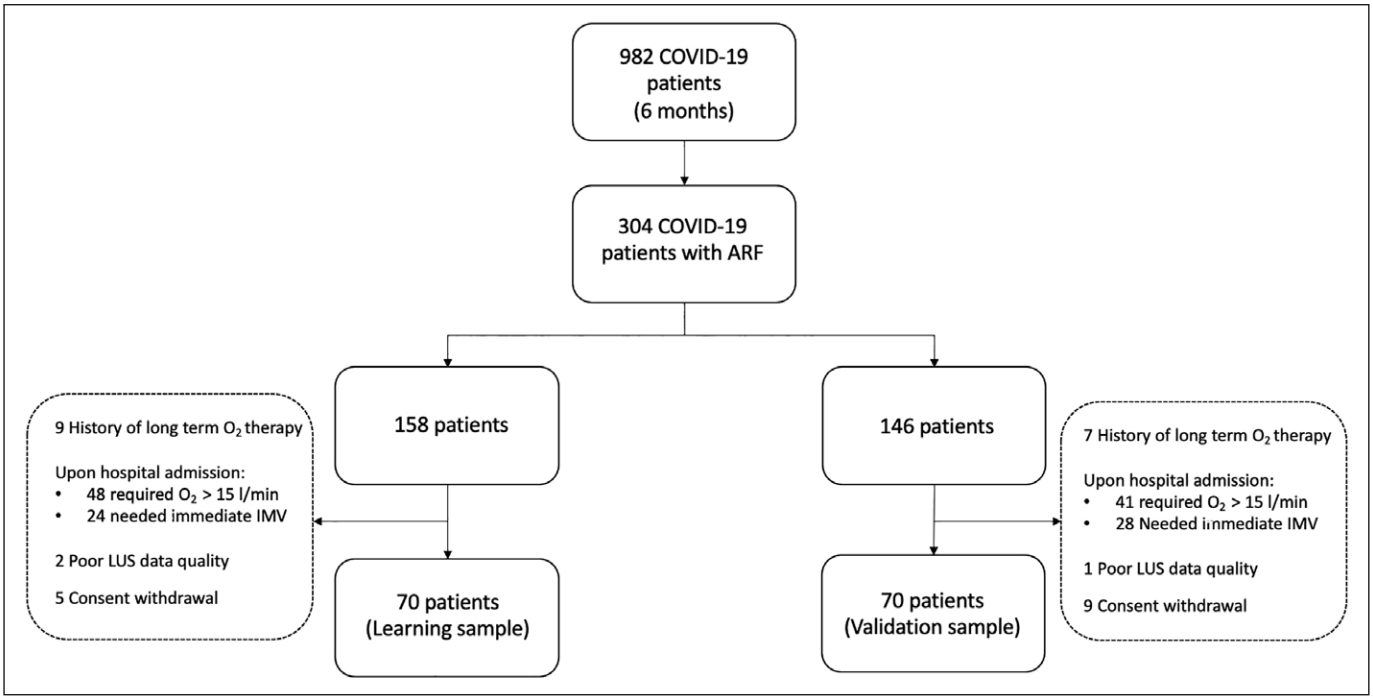

Figure 1. Study flowchart. Longitudinal data from 140 consecutive patients were included in the study. Ultimately, the dataset was split into two time series to enable further analysis: a learning sample (first 70 patients), which was used to establish the best predictive model (10-fold cross-validation and 1,000 bootstrap permutations), and a validation sample (last 70 patients), which has not been used during the previous phase, were employed to test model's generalization. ARF = acute respiratory failure, IMV = invasive mechanical ventilation, LUS = lung ultrasound.

Standard Clinical Assessment

Based on current recommendations for the management of critically ill patients with COVID-19 (1–3) and previous reports about the development and validation of early prognostic tools for COVID-19 patients (19), we prospectively collected predefined clinical data at patient's bedside. To increase the generalizability, the reproducibility, and the clinical relevance of our findings, we decided to only use clinical criteria that are currently considered as being part of standard procedures for first-line medical triage for COVID-19 patients. Following current guidelines and recommendations (1–3, 12, 19), standard variables were collected at hospital admission in the medical triage zone to be used as potential predictors of critical respiratory illness and included: demographic variables, medical history, clinical signs, and symptoms. Demographic variables included sex, age, smoking status, and the Quick Sepsis-related Organ Failure Assessment score for sepsis (20). Medical history included number of comorbidities, chronic obstructive pulmonary disease, diabetes, hypertension, coronary artery disease, cancer, chronic renal disease, and immunodeficiency disease. Clinical signs included categorical and continuous variables: heart rate (beats/min), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), respiratory rate (breaths/min), Spo_2 (%), and standard oxygen flow (L/min). Clinical symptoms comprised fever, cough, dyspnea, anosmia, and diarrhea. The time between first symptoms and hospital admission was also recorded.

Lung Ultrasound Examination

All patients underwent an LUS assessment by investigators who did not participate in patient management (A.A., S.B., B.R., S.S.). These investigators are all senior critical care practitioners, with advanced level of thoracic ultrasound training and who were blinded to patient's outcomes. The level of agreement between raters for the ultrasound findings has been previously reported (21–23). All patients were studied in the semi-recumbent position. LUS assessment was performed with CX 50 Philips Ultrasounds (22100 Bothell-Everett HighwayBothell, WA, USA) and 2- to 4-MHz probes. The investigators used standardized criteria and followed pattern analysis (**Fig. 2**) (24, 25). As previously

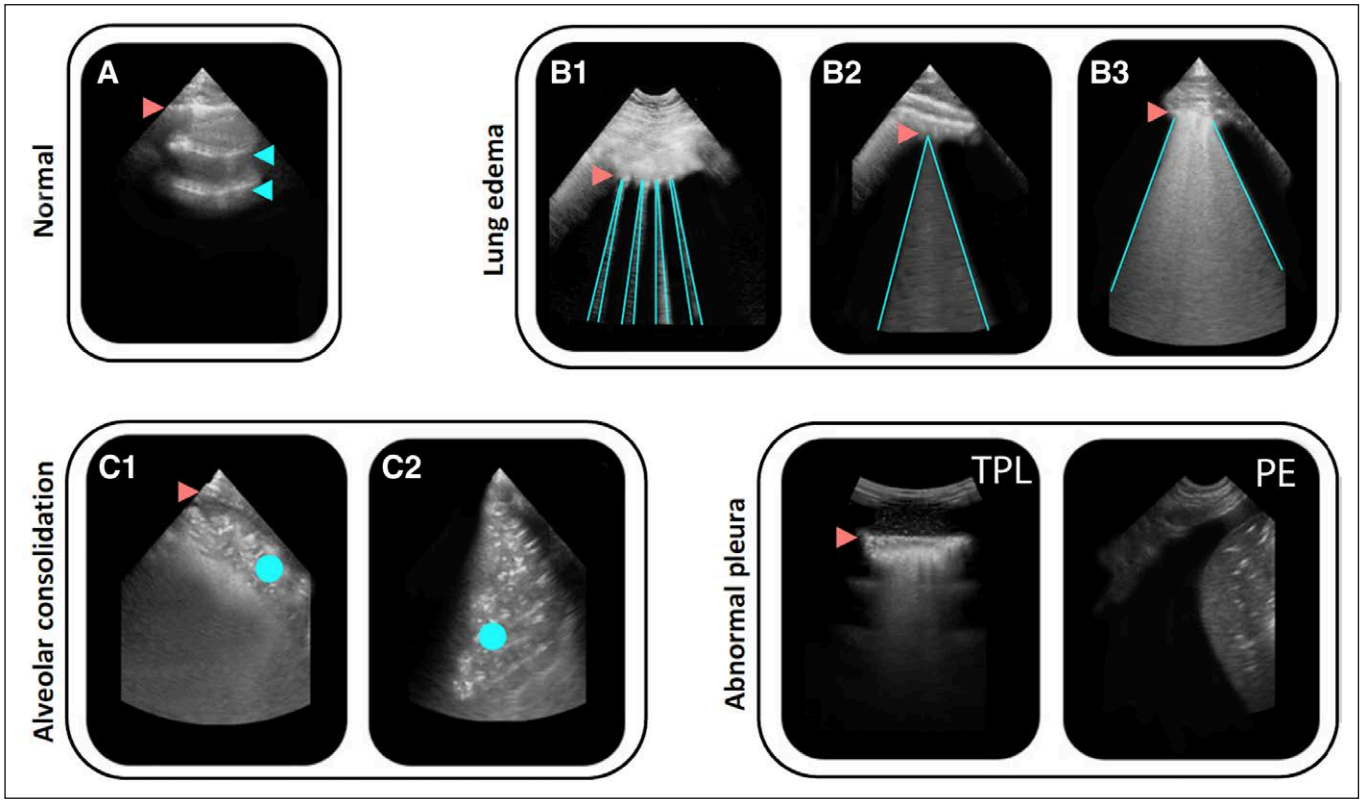

Figure 2. Lung ultrasound patterns. Each of the 12 lung regions assessed per patient was classified using predefined lung ultrasounds profiles (A, B1, B2, B3, C1, C2, TPL, and pleural effusion [PE]). Sonographic LUS signs are not specific of COVID-19 when considered alone. Normal lung sliding (*magenta triangles* indicate the pleural line) with *reverberating horizontal lines* (blue triangles) were described as a profile. Interstitial syndrome was defined as the presence of more than two vertical lines in a given lung sector (depicted between *vertical blue lines*). To allow a semiquantitative assessment, we defined three B-lines patterns: B1 profile (thin, multiple, and well-defined), B2 profile (large and coalescent), and B3 profile ("shining white lung"). As recently reported, we distinguished two patterns of alveolar consolidation (*blue circles*): subpleural nontranslobar (C1 profile) (27) and posterior translobar with occasional mobile air bronchograms (C2 profile). A thickening of the pleural line with pleural line irregularity was considered as abnormal (Thickening of the Pleural Line, TPL), and PE was defined as a hypoechoic collection limited by the diaphragm and the pleura (PE profile). For additional information regarding lung ultrasounds semiotics, please see the "Materials and Methods" section.

described, the chest wall was demarcated from the clavicles to the diaphragm and from the sternum to the anterior axillary line (26). Six quadrants were defined for each hemithorax. The normal pleural line was defined as a horizontal hyperechoic line visible below the rib line. As recently reported from COVID-19 patients (14), thickening of the pleural line with pleural line irregularity was considered as abnormal (Thickening of the Pleural Line, TPL). A normal lung pattern was defined as the presence in a quadrant of lung sliding with reverberating horizontal A lines (A profile). Pleural effusion (PE profile) was defined as a hypoechoic collection limited by the diaphragm and the pleura (24). Alveolar consolidation was defined as the presence of poorly defined heterogeneous wedge-shaped hypoechoic images. As recently reported, we distinguished two patterns of alveolar consolidation during COVID-19: subpleural nontranslobar (C1 profile) (27), which might correspond to peripheral lung embolism (28), and posterior translobar with occasional mobile air bronchograms (C2 profile). Alveolar-interstitial syndrome was defined as the presence of more than two vertical lines B lines in a given lung region. Aiming to specifically address the added value of pulmonary edema semiquantitative LUS assessment, we defined three B-lines patterns: B1 profile (thin, multiple, and well-defined), B2 profile (large and coalescent), and B3 profile ("shining white lung") (29). Each of the 12 lung regions assessed per patient was classified in one of these profiles to define one final pattern for each quadrant. The number of quadrants depicting the same LUS patterns was summed, and the total amount of each profile was computed for further analysis (21–23).

Outcome

Critical respiratory illness, defined as death or mild/severe ARDS (Pao_2/Fio_2 < 200) in the 24 hours following patients' hospital admission, was considered as an unfavorable patient's outcome. To increase the generalizability of our findings, we decide to use neither ICU admission decision nor the specific modalities ventilatory support in our composite main outcome criteria. Indeed, throughout the current pandemic, both criteria for patient's ICU admission and the use of invasive/non-invasive respiratory support have evolved across the time (1) and might also have been influenced by ICU resource's availability during the study period (30).

Statistics Analysis

Continuous data are expressed as mean ± SD and or median (interquartile range) according their distribution. Categorical variables were expressed as numbers and percentages. Two means were compared with Student test or Mann-Whitney *U* test and two proportions with a chi-square test or Fisher exact test. The Pearson correlation or Spearman test were used to test linear correlation. A cross-correlation matrix was applied to the whole dataset to test multicollinearity. Sensitivity, specificity, and diagnostic accuracy were calculated using standard formulas to evaluate the predictive performances of clinical standard and LUS approaches.

First, clinical and LUS data were split into two time series to enable further analysis: a learning sample (first 70 patients) was used to establish the best classification model and validation sample (last 70 patients), which has not been used during the previous phase, was employed to test model's generalization and to avoid the risk of over-fitting. Second, clinical and LUS data, used as independent variables, were employed to estimate partial least square (PLS) regression to predict critical respiratory illness using a linear multivariate model. PLS model does not require the absence of multicollinearity and can be performed when there are more variables than observations. All the variables (independent and dependent) were used without any mathematical treatment. Note that the PLS model used a nonlinear iterative partial least squares (NIPALS) algorithm to implement missing data. To test multicollinearity, we used variable inflation factors (VIFs), which determine the strength of the correlation between independent variables. The determination of the significant PLS principal components (model dimensions) was made by 10-fold cross-validation. Among them, only one component minimized the least square difference between the reference value and the measured parameters. The standardized coefficients and 95% CIs of each parameter were determined using a bootstrap procedure (1,000 permutations). A logistic regression was performed on the PLS component to convert PLS values of each observation into a probability score. Finally, receiver-operating characteristic curves were calculated for each final diagnosis during each both learning and validation phases and compared using the DeLong test (R-library package nsRoc).

The level of agreement between the observers for the ultrasound findings was previously reported (21–23). All statistical tests were two-sided, and $p < 0.05$ was required to reject the null hypothesis. Statistical analysis was performed with the R software (R Foundation, Vienna, Austria) and Tanagra 1.4.50 (Rakotomalala, Lyon University, Lyon, France).

RESULTS

Patients

A total of 305 COVID-19 patients with ARF were prospectively identified at the time of hospital admission (Fig. 1). Among them, 147 did not fulfill at least one inclusion criterion, three had to be excluded because of insufficient LUS data quality, and 14 withdrawn consents. The final cohort consisted of 140 patients, age 62.0 years (51.8–73.0 yr), of whom 42 (30%) were woman. This cohort was split into two independent patient's groups for further analysis: a learning sample (first 70 patients), which was used to establish the best cross-validated classification model, and validation sample (last 70 patients), which has not been used during the previous phase, were employed to test model's generalization (Fig. 1). At inclusion time, patients have a mean Spo_2 of 89.0 (84.2–90.0) and a mean respiratory rate of 27.0 (14.1–32.1) before oxygen therapy onset. Within the 24 hours of follow-up, 53/140 patients (37.8%) developed critical respiratory illness. Indeed, 19 patients died, 34 developed mild/severe ARDS, 67 had moderate ARDS, and 20 were not with ARDS. Among ARDS patients, 17 received

invasive mechanical ventilation, and 84 were treated with nasal high-flow oxygen therapy during the first 24 hours after hospital admission. The mean ICU stay was 12 ± 10 days. The 28-day mortality rate was 31% (43 patients). Further information about patient's demographics and characteristics is provided in Table 1.

LUS Data

Patient's LUS assessments lasted 6 ± 2 min. Overall, 1,680 lung regions were evaluated. In this cohort of COVID-19 patients with ARF, LUS examination allowed the identification of predefined LUS patterns (Fig. 2; **Supplemental Digital Content 1–3**, http://links.lww.com/CCX/B14) as follows (sum and percentage of quadrants depicting the same LUS patterns, respectively): A (618, 37%), B1 (450, 27%), B2, (205, 12%), B3 (207, 12%), C1 (162, 10%), C2 (30, 2%), TPL (305, 18%), and PE (11, 1%). Interestingly, the total amount of lung regions depicting the same LUS pattern was significantly different between patients who were with or without critically respiratory failure during the 24 hours of follow-up (**Fig. 3**; Supplemental Digital Content 1, http://links.lww.com/CCX/B14). It is worth noting that a significant multicollinearity was observed between collected LUS data (VIF > 5; **Supplemental Digital Content 4**, http://links.lww.com/CCX/B15).

Data Modeling

The whole data set of predictors was used to generate two independent linear multivariate models with no a priori hypothesis (**Supplemental Digital Content 5**, http://links.lww.com/CCX/B16). We used PLS methods to build these models because PLS does not require the absence of multicollinearity, and it is well fitted in the case of missing data. The LUS-derived model (Supplemental Digital Content 5, http://links.lww.com/CCX/B16) revealed a significant relationship between the patient's risk of critical respiratory illness and the identification at hospital admission of the following LUS profiles: B2, B3, C1, C2, and TPL. Regarding the standard clinical practice model, it should be noted that among clinical predictors, respiratory rate was the factor who was more significantly associated with patient's outcome (Supplemental Digital Content 5, http://links.lww.com/CCX/B16).

Predictive Values

Overall, the LUS model predicted more accurately patient's outcomes than the standard clinical practice model (DeLong test: Testing: z score = 2.50, p value = 0.01; Validation: z score = 2.11, p value = 0.03). It should be noted that data obtained during the validation study phase confirmed the accuracy and robustness of the cross-validated models that were built during the testing phase (Supplemental Digital Content 6, http://links.lww.com/CCX/B17).

The analysis of PLS "standard coefficient" of each LUS profile yields additional information in terms of critical respiratory illness risk assessment (Supplemental Digital Content 5, http://links.lww.com/CCX/B16). Indeed, detection of A profile was significantly associated with patient's favorable outcome. On the other hand, all the ultrasonographic LUS patterns corresponding to lung edema (B profiles) were significantly associated with patients' outcome. It is worth noting that a gradient effect was observed, meaning that B1 detection, corresponding to absent or minimal pulmonary edema, compared with B2/B3 recognition, related to greater amount of interstitial lung water, was significantly associated with favorable and unfavorable outcomes, respectively. Regarding alveolar consolidation, subpleural topography seemed more linked to unfavorable outcome than a posterior translobar loss of lung aeration (C2). Last but not least, pleura ultrasonographic evaluation demonstrated that PE was not associated with patient's outcome, but the detection of thickening of the pleural line with pleural line irregularity (TPL pattern) was significantly associated with the risk of critical respiratory illness.

The number of lung quadrants depicting the same LUS pattern at patients' hospital admission for each outcome group (patients with or without critical respiratory illness at 24 hr from hospital admission) was significantly different for all LUS profiles but PE (Fig. 3; Supplemental Digital Content 5, http://links.lww.com/CCX/B16). These results are in favor of lung lesion effect, meaning that a greater number of lung regions showing the same pattern are more strongly associated with a definite outcome.

DISCUSSION

Despite many reports of patient characteristics and risk factors for critical illness (31–34), there is little

TABLE 1.
Patient's Characteristics at Hospital Admission

Characteristics	*n* (%)	All Patients (*n* = 140)	24-hr Critical Respiratory Illness		
			Yes (*n* = 53)	No (*n* = 87)	*p*
Age, yr	140 (100)	62.0 (51.8–73.0)	61.0 (49.0–75.0)	63.0 (52.0–72.5)	0.947
Woman, *n* (%)	140 (100)	42 (30)	17 (32)	25 (29)	0.707
Body mass index > 30, *n* (%)	140 (100)	61 (44)	25 (47)	36 (41)	0.598
Active smokers, *n* (%)	135 (96.4)	31 (22.1)	13 (24.5)	18 (20.7)	0.676
Quick Sepsis-related Organ Failure Assessment score, median (IQR)	140 (100)	1.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	0.283
Time between first symptoms and hospital admission, d	129 (92.1)	9.0 (7.0–12.0)	10.0 (8.0–12.0)	9.0 (6.0–12.0)	0.231
Comorbidities, *n* (%) = 140 (100)					
Treated hypertension		84 (60.0)	32 (60.4)	52 (59.8)	1.000
Known diabetes		56 (40.0)	22 (41.5)	34 (39.1)	0.859
Immunodeficiency		16 (11.4)	10 (18.9)	6 (6.9)	0.052
Chronic pulmonary disease		111 (79.3)	43 (81.1)	68 (78.2)	0.830
Chronic liver disease		24 (17.1)	9 (17.0)	15 (17.2)	1.000
Chronic heart failure		27 (19.3)	20 (23.0)	7 (13.2)	0.188
Solid cancer		11 (7.9)	6 (11.3)	5 (5.7)	0.332
Symptoms, *n* (%) =140 (100)					
Fever		102 (72.9)	38 (71.7)	64 (73.6)	0.846
Cough		85 (60.7)	31 (58.5)	54 (62.1)	0.723
Dyspnea		111 (79.3)	41 (77.4)	70 (80.5)	0.672
Anosmia		62 (44.3)	19 (35.8)	43 (49.4)	0.160
Diarrhea		40 (28.6)	14 (26.4)	26 (29.9)	0.703
Admission measures,[a] median (IQR)					
Systolic blood pressure, mm Hg	133 (95)	121.0 (108.0–145.0)	117.0 (102.0–131.5)	131.0 (118.0–146.0)	0.010
Diastolic blood pressure, mm Hg	133 (95)	70.0 (58.0–78.0)	66.0 (58.0–75.0)	71.0 (60.0–80.0)	0.095
Heart rate, beats/min	133 (95)	83.0 (73.0–92.5)	80.5 (69.0–90.5)	84.0 (74.0–93.0)	0.210
Respiratory rate, breaths/min	140 (100)	22.0 (17.0–29.0)	27.0 (18.0–30.0)	21.0 (16.0–27.0)	0.022
Spo_2, %	140 (100)	95.0 (93.8–98.0)	95.0 (93.0–97.0)	95.0 (94.0–98.0)	0.430
Standard O_F flow, L/min	138 (99)	9.0 (6.0–12.0)	9.0 (6.0–12.0)	9.0 (6.0–9.0)	0.328
Confusion	140 (100)	28 (20.0)	14 (26.4)	14 (16.1)	0.191

IQR = interquartile range.

[a]These variables were recorded after oxygen therapy onset.

Results are expressed as median (interquartile range) or *n* (%). Critical respiratory illness was defined as death or mild/severe acute respiratory distress syndrome ($Pao_2/Fio_2 < 200$) in the 24 hr following hospital admission. A *p* value of < 0.05 was considered as statistically significant.

evidence-based guidance available to aid first-line practitioners in safely dispositioning COVID-19 patients with ARF. To the extent of our knowledge, we report for the first time the usefulness of point-of-care LUS assessment to assist medical triage of COVID-19 patients with ARF upon hospital admission. Hence, we observed that compared with standard clinical data, LUS data were significantly associated with the risk of critical respiratory illness 24 hours after hospital admission. We think that our result holds the promise

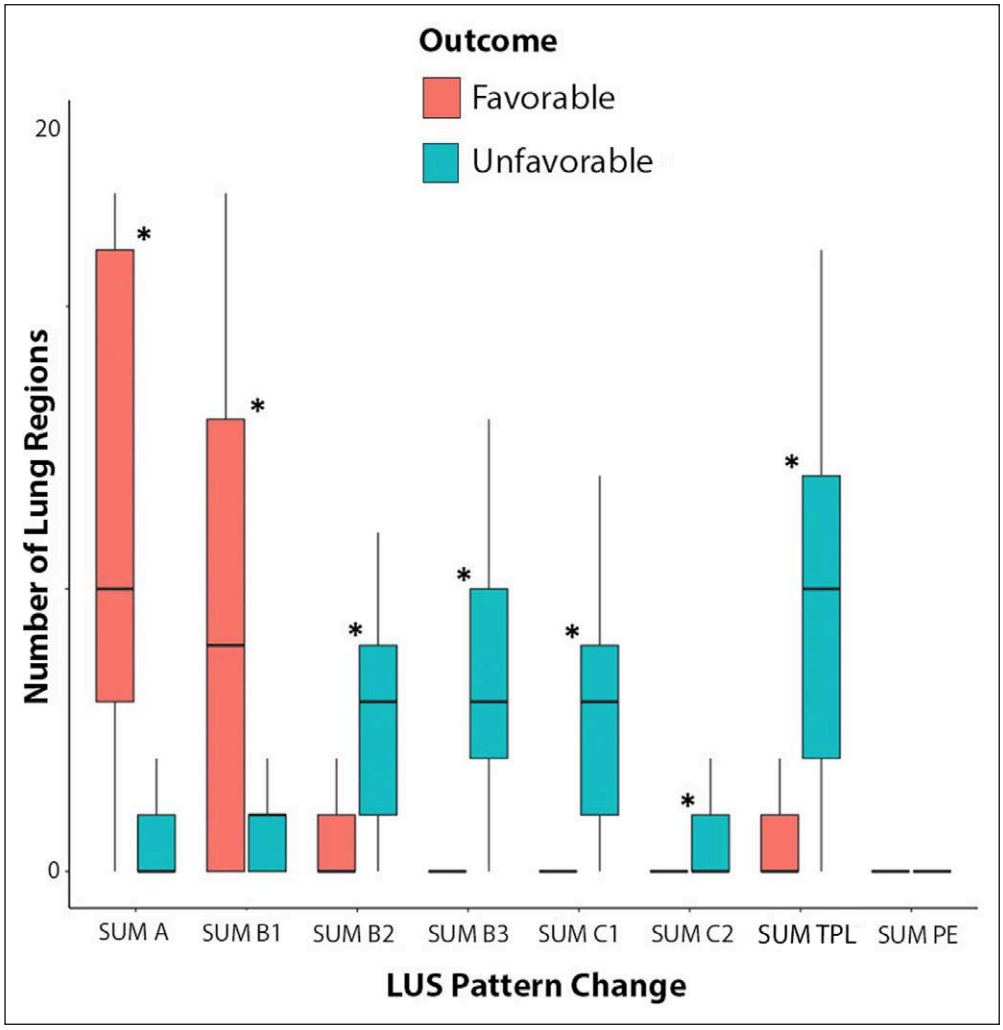

Figure 3. Extent of lung lesions. The number of quadrants depicting the same lung ultrasound patterns (A, B1, B2, B3, C1, C2, TPL, and pleural effusion [PE]) was summed and is represented according patient's outcome (critical respiratory illness at 24 hr from hospital admission). *p* value < 0.05 was considered as statistically significant (*). For additional information, please see Supplemental Digital Content 1, http://links.lww.com/CCX/B14 and **Supplemental Digital Content 6**, http://links.lww.com/CCX/B17.

of significantly improving ICU admission decision-making process and medical resource attribution for these patients, particularly in the case of massive afflux of patients or limited-resource settings.

In agreement with previous in vitro (35) and in vivo (36) reports, which have described the progressive loss of lung aeration as first as a switch from A-lines to a B-pattern, followed by a progressive increasing number of B-lines that coalesce more and more (from B1 to B3 patterns), we observed a significant relationship between the total amount of LUS-detected lung edema and patient's outcome. Indeed, A/B1 patterns and B2/B3 were significantly associated with favorable and unfavorable outcomes, respectively. Interestingly, in addition to well-known unspecific LUS semiotics (24, 26), we also explored the clinical relevance of LUS patterns that have been described in the specific setting of COVID-19. In fact, we observed that lung consolidation (C pattern) was significantly associated with patients' unfavorable outcome, in particular, when lung consolidations were small, anterior, subpleural, and triangular (C1) compared with large, posterior, and ill-defined consolidations (C2). We think that the reported difference between C1 and C2 patterns in terms of outcome prediction might be related to the difference between the underlying pathophysiological mechanisms. In fact, a recent study has suggested that C1 pattern is more typical of COVID-19 patients and might be an indicator for segmental pulmonary embolism (28). Finally, it is worth noting that the detection of thickening of the pleural line with pleural line irregularity (TPL profile) was also associated with unfavorable patient outcome. We suggest that the impact of the detection of these diffuse irregularities of the pleural line in terms of patient's outcome could be related to the fact that TPL pattern is an accurate bedside biomarker (14, 29) of interstitial pulmonary disease.

Our results must be interpreted with caution, and a number of limitations should be borne in mind. The first is related to the limited sample size. Consequently, the reported evidence requires confirmation from large-scale trials with strict recruitment criteria. Clinical and LUS data were split into two time series to enable to first establish the best classification model and then to test

model's generalization. However, external validation has not been performed and may result in overfitting. In addition, we should keep in mind that the reported predictive model was developed for identification of patients' deterioration within the first 24 hours after hospital admission, but its performance for prediction of critical respiratory illness at later time points has not been evaluated. Finally, to increase the generalizability and the clinical relevance of our findings, we decided to only use clinical criteria as standard predictive procedure during first-line medical triage for COVID-19 patients. Further advances will come from studies that will specifically address the added value of LUS data for patients' monitoring and outcome prediction, independently or in combination with additional radiological and laboratory findings. The main strengths of our study are a prospective design, the blinded assessment of LUS data based on predefined criteria, and the use of a standard clinical practice model based on current guidelines for COVID-19 patient's clinical management. As a variant to tree-based predictive algorithms, the reported machine learning model accurately deals with two critical methodological issues that are frequently encountered in LUS studies: 1) LUS data multicollinearity (Supplemental Digital Content 2, http://links.lww.com/CCX/B14), meaning that there is a linear correlation between the detection discrete LUS features (e.g., the thickening of the pleural line pattern—TPL pattern—was mostly observed in patients with subpleural alveolar consolidation—C1 pattern, but was never identified in patients with predominant normal lung patterns—A pattern) and 2) missing data are accurately taken into account and elude further exclusion of patients (Table 1).

During the current study, we specifically addressed the usefulness of LUS data, early collected at the time of hospital admission, to streamline further care of COVID-19 patients with ARF. Our results suggest that LUS holds the promise of significantly improving COVID-19 patients' first-line medical triage, while reducing the need for additional test as chest CT scan or laboratory findings. However, we acknowledge that the valuable information carried by LUS should always be integrated in a broader medical reasoning (37,38) and that triage tools alone, whatever their precision, without ethical support and accurate information about available resources, do not guarantee protective standards for all those involved in a pandemic.

CONCLUSIONS

The pandemic of COVID-19 has seriously challenged the medical organization in many parts of the world. LUS sonographic assessment of COVID-19 patients with ARF at hospital admission allows for a reliable patient's bedside characterization of lung and pleura integrities, providing new predictors of subsequent need for ICU admission. This would give critical lead time to allocate resources most wisely both now and in future anticipated pandemics.

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Pr. Silva takes the responsibility for the content of the article, including the data and analysis. He conceived the study and has personally made contributions to the design of the study, the acquisition of data, and the analysis and interpretation of data. Drs. Aguersif, Sarton, Bouharaoua, Gaillard, Riu, and Pr. Silva have substantially participated at the data acquisition. Drs. Sarton and Bataille have made contribution to the design of the study. Drs. Standarovski, Faucoz, Khallel, Thalamas, Sommet, Morand, and Bataille have contributed to the conception and analysis of data. Drs. Sarton, Bataille, and Pr. Silva wrote the report. All authors have revised the submitted article critically for important

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