



UNIL | Université de Lausanne

Unicentre

CH-1015 Lausanne

<http://serval.unil.ch>

Year : 2021

Lung ultrasonography for risk stratification in patients with COVID-19: a prospective observational cohort study

Brahier Thomas

Brahier Thomas, 2021, Lung ultrasonography for risk stratification in patients with COVID-19: a prospective observational cohort study

Originally published at : Thesis, University of Lausanne

Posted at the University of Lausanne Open Archive <http://serval.unil.ch>

Document URN : urn:nbn:ch:serval-BIB_D2D8CB60AD9D0

Droits d'auteur

L'Université de Lausanne attire expressément l'attention des utilisateurs sur le fait que tous les documents publiés dans l'Archive SERVAL sont protégés par le droit d'auteur, conformément à la loi fédérale sur le droit d'auteur et les droits voisins (LDA). A ce titre, il est indispensable d'obtenir le consentement préalable de l'auteur et/ou de l'éditeur avant toute utilisation d'une oeuvre ou d'une partie d'une oeuvre ne relevant pas d'une utilisation à des fins personnelles au sens de la LDA (art. 19, al. 1 lettre a). A défaut, tout contrevenant s'expose aux sanctions prévues par cette loi. Nous déclinons toute responsabilité en la matière.

Copyright

The University of Lausanne expressly draws the attention of users to the fact that all documents published in the SERVAL Archive are protected by copyright in accordance with federal law on copyright and similar rights (LDA). Accordingly it is indispensable to obtain prior consent from the author and/or publisher before any use of a work or part of a work for purposes other than personal use within the meaning of LDA (art. 19, para. 1 letter a). Failure to do so will expose offenders to the sanctions laid down by this law. We accept no liability in this respect.



UNIL | Université de Lausanne

Faculté de biologie
et de médecine

UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de médecine
Service des maladies infectieuses

Lung ultrasonography for risk stratification in patients with COVID-19: a
prospective observational cohort study

THESE

préparée sous la direction de la Docteure Noémie Boillat Blanco
et la co-supervision du Professeur Olivier Hugli

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Thomas Brahier

Médecin diplômé de la Confédération Suisse
Originaire de Coeuve

Lausanne
2021



UNIL | Université de Lausanne

Faculté de biologie
et de médecine

UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de médecine
Service des maladies infectieuses

Lung ultrasonography for risk stratification in patients with COVID-19: a
prospective observational cohort study

THESE

préparée sous la direction de la Docteure Noémie Boillat Blanco
et la co-supervision du Professeur Olivier Hugli

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Thomas Brahier

Médecin diplômé de la Confédération Suisse
Originaire de Coeuve

Lausanne
2021



UNIL | Université de Lausanne

Faculté de biologie
et de médecine

*Ecole Doctorale
Doctorat en médecine*

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Directeur.trice de thèse

Dre Noémie Boillat Blanco

Co-Directeur.trice de thèse

Prof. Olivier William Hügli

Expert.e

Prof. Jean-Yves Meuwly

**Vice-Directeur de l'Ecole
doctorale**

Prof. John Prior

la Commission MD de l'Ecole doctorale autorise l'impression de la thèse de

Monsieur Thomas Brahier

intitulée

***Lung ultrasonography for risk stratification in patients
with COVID-19: a prospective observational cohort study***

Lausanne, le 11 février 2021

*pour Le Doyen
de la Faculté de Biologie et de Médecine*


**Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale**

Résumé du travail :

Après avoir passé un mois dans le service des maladies infectieuses du CHUV en temps qu'étudiant de 6^{ème} année en 2018, j'ai demandé à Dre Boillat Blanco si je pouvais réaliser une année de recherche sous sa supervision dans le domaine des infections respiratoires basses aux urgences. Avec le Professeur Hugli et la Dre Boillat Blanco, nous avons alors mis en place une cohorte prospective observationnelle d'infections respiratoires basses aux urgences du CHUV afin d'optimiser la prédiction de la pneumonie acquise en communauté. Pour chaque patient inclus, nous réalisons un ultrason pulmonaire ainsi que des prélèvements biologiques (prise de sang, frottis nasopharyngé et oropharyngé et urine). Après avoir été formé à l'échographie pulmonaire par le Dr Pantet (soins intensifs, CHUV) et le Prof. Fumeaux (soins intensifs, Nyon), j'ai acquis une bonne maîtrise de cet examen. Nous avons travaillé sur la mise en place de la cohorte de début octobre 2019 jusqu'au 6 février 2020, date à laquelle nous avons inclus notre premier patient.

Début mars, les premiers patients atteints de la maladie à coronavirus 2019 (COVID-19) se sont présentés aux urgences du CHUV. Les patients correspondant à nos critères, ont été inclus et ont bénéficié d'un ultrason pulmonaire. Après avoir réalisé quelques examens, j'ai distingué plusieurs patterns radiologiques suggestifs d'une atteinte à SARS-CoV-2. Nous avons alors décidé d'explorer cette nouvelle voie ; une lettre d'intensivistes chinois relatant leur utilisation de l'ultrason pulmonaire dans le contexte de la pandémie a fini de nous convaincre de réorienter notre projet initial afin d'être le plus utile dans ce nouveau contexte épidémiologique.

La pandémie à SARS-CoV-2 a surchargé et surcharge encore de nombreux hôpitaux à travers le monde. Des outils de tri fiables, rapides et accessibles rapidement sont nécessaires afin d'allouer les ressources médicales de manière la plus juste et efficace possible. Rapidement dans la pandémie, des études ont montré que l'atteinte pulmonaire au CT-scanner corrèle et pourrait prédire la sévérité clinique. Malheureusement, son utilisation augmente l'exposition aux rayons X, est coûteuse et requiert le déplacement de patients contagieux dans l'hôpital. L'ultrason pulmonaire étant réalisable au lit du patient, non irradiant et ayant une bonne valeur diagnostique pour la pneumonie pourrait être une bonne alternative.

Nous avons pour objectif de décrire les atteintes pulmonaires à l'ultrason chez les patients avec COVID-19 et d'évaluer la capacité prédictive de cet outil pour l'évolution clinique.

En utilisant un score ultrasonographique validé pour évaluer la ventilation pulmonaire chez les patients avec syndrome de détresse respiratoire aigu non COVID-19, nous avons pu mettre en évidence la capacité de l'ultrason pour prédire l'hospitalisation chez les patients se présentant aux urgences. Comme notre échantillon était relativement petit, nous n'avons pas montré de différences significatives entre les patients qui nécessiteront une hospitalisation et ceux seront intubés ou mourront dans les 7 jours. Nous pouvons supposer qu'il s'agissait d'un manque de puissance car une publication israélienne publiée depuis rapporte cette différence.

En conclusion, l'ultrason pulmonaire avec ses avantages cités précédemment est un très bon outil de triage dans les centres d'urgences et permettrait d'éviter une surcharge des hôpitaux. Ces résultats doivent être confirmés dans une cohorte de validation.

L'automatisation de la lecture des images par intelligence artificielle permettra à des personnes non formées d'utiliser cette technique ce qui la rendra encore plus accessible notamment dans les pays à plus faible revenu. Nous travaillons déjà dans cette direction avec un laboratoire d'intelligence artificielle de l'EPFL. Des cours de formations à l'ultrason pulmonaire pour les cliniciens pourraient mener à une démocratisation de cette technique et à une utilisation rapide de nos résultats au cours de cette seconde vague de cas de COVID-19.

Lung Ultrasonography for Risk Stratification in Patients with Coronavirus Disease 2019 (COVID-19): A Prospective Observational Cohort Study

Thomas Brahier,¹ Jean-Yves Meuwly,² Olivier Pantet,³ Marie-Josée Brochu Vez,⁴ Hélène Gerhard Donnet,⁴ Mary-Anne Hartley,^{5,6} Olivier Hugli,⁴ and Noémie Boillat-Blanco¹

¹Infectious Diseases Service, University Hospital and University of Lausanne, Lausanne, Switzerland, ²Department of Radiology, University Hospital and University of Lausanne, Lausanne, Switzerland, ³Intensive Care Unit, University Hospital and University of Lausanne, Lausanne, Switzerland, ⁴Emergency Department, University Hospital and University of Lausanne, Lausanne, Switzerland, ⁵Digital Global Health Department, Center for Primary Care and Public Health, University of Lausanne, Lausanne, Switzerland, and ⁶Machine Learning and Optimization Laboratory, École polytechnique fédérale de Lausanne, Lausanne, Switzerland

Background. Lung ultrasonography (LUS) is a promising pragmatic risk-stratification tool in coronavirus disease 2019 (COVID-19). This study describes and compares LUS characteristics between patients with different clinical outcomes.

Methods. Prospective observational study of polymerase chain reaction–confirmed adults with COVID-19 with symptoms of lower respiratory tract infection in the emergency department (ED) of Lausanne University Hospital. A trained physician recorded LUS images using a standardized protocol. Two experts reviewed images blinded to patient outcome. We describe and compare early LUS findings (≤ 24 hours of ED presentation) between patient groups based on their 7-day outcome (1) outpatients, (2) hospitalized, and (3) intubated/dead. Normalized LUS score was used to discriminate between groups.

Results. Between 6 March and 3 April 2020, we included 80 patients (17 outpatients, 42 hospitalized, and 21 intubated/dead). Seventy-three patients (91%) had abnormal LUS (70% outpatients, 95% hospitalized, and 100% intubated/dead; $P = .003$). The proportion of involved zones was lower in outpatients compared with other groups (median [IQR], 30% [0–40%], 44% [31–70%], 70% [50–88%]; $P < .001$). Predominant abnormal patterns were bilateral and there was multifocal spread thickening of the pleura with pleural line irregularities (70%), confluent B lines (60%), and pathologic B lines (50%). Posterior inferior zones were more often affected. Median normalized LUS score had a good level of discrimination between outpatients and others with area under the ROC of .80 (95% CI, .68–.92).

Conclusions. Systematic LUS has potential as a reliable, cheap, and easy-to-use triage tool for the early risk stratification in patients with COVID-19 presenting to EDs.

Keywords. COVID-19; triage tool; lung ultrasound; LUS score.

The coronavirus disease 2019 (COVID-19) pandemic has overwhelmed the health systems in several high-income settings [1] and is now spreading in low-income countries. There is a critical need for accessible and low-cost methods to stratify risk for evidence-based resource allocation [2]. While the majority of patients with COVID-19 have a pauci-symptomatic or asymptomatic course, some may rapidly deteriorate, leading to hospitalization and the need for respiratory support. It has been suggested that early identification of patients at high risk of respiratory compromise is associated with lower mortality [3]. Several studies have shown the predictive value of computed tomography (CT) imaging, where the extent and patterns of lung involvement correlated well with severity of COVID-19 on admission

to the hospital. Other studies have described a progression of lung anomalies on consecutive chest CTs during the course of the disease, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities and, finally, consolidation [4]. However, CT imaging has important limitations in triaging patients during the context of COVID-19, not only due to its limited availability, high cost, and exposure to radiation but, more critically, due to its immobile nature, thus necessitating the movement of infectious patients [5]. Point-of-care ultrasound applied to the lung is a promising alternative diagnostic tool, which can shorten time-to-diagnosis for the etiology of acute dyspnea, as well as stratify severity in the emergency department (ED) [6]. It is widely used in routine practice of Swiss EDs, can be performed at the bedside without radiation exposure, and is easy to use in patients requiring protective isolation. So far, the use of lung ultrasonography (LUS) in COVID-19 has only been described in cohorts of hospitalized patients with severe disease [7–10]. However, it has already shown excellent performance to detect non-COVID-19 pneumonia, compared with CT as a reference standard [11], and matches the discriminative power of CT in patients with acute respiratory distress syndrome (ARDS) [12].

Received 9 June 2020; editorial decision 11 September 2020; published online 17 September 2020.

Correspondence: T. Brahier, Service of Infectious Diseases, University Hospital of Lausanne (CHUV), Rue du Bugnon 46, 1011 Lausanne, Switzerland (thomas.brahier@chuv.ch).

Clinical Infectious Diseases® 2021;XX(X):1–8

© The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/ciaa1408

Lung ultrasonography has potential in the pragmatic triage of patients with COVID-19, especially in low-resource settings. This study aims to describe LUS characteristics in a prospective cohort of patients with COVID-19 and explore their predictive capacity for risk stratification.

METHODS

Study Design and Participants

This study is nested in a prospective cohort study of patients with lower respiratory tract infections, which started on 6 February 2020 in the ED of the Lausanne University Hospital, Switzerland. We prospectively screened consecutive adult patients (age ≥ 18 years) presenting to the ED with an acute lower respiratory tract infection (cough, sputum, dyspnea, or chest pain for < 21 days) [13]. Patients with COVID-19 confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by a nasopharyngeal swab were included in this study. Patients were excluded if LUS could not be performed within 24 hours of admission or if the patient was receiving therapeutic prone ventilation before the LUS.

The study team collected patients' data using a standardized electronic case report form in REDCap (Research Electronic Data Capture). We assessed day 7 outcome by checking the electronic health record and we classified patients in 3 groups—group 1: outpatients (absence of admission within 7 days of inclusion); group 2: hospital admission within 7 days of inclusion; and group 3: intubation and/or death within 7 days of inclusion.

Lung Ultrasonography

A trained physician (T. B.) in LUS performed all LUS at inclusion in the ED. Acquisition was standardized according to the “10-zone method” [14, 15]. Two images (sagittal and transverse) and 5-second videos were systematically recorded in

every zone with a Butterfly IQ (Butterfly Network, Guilford, CT, USA), using the lung preset.

The study physician (T.B.) and an expert radiologist (J.-Y. M.) standardized the reporting of pathological LUS features based on COVID-19 patterns (Figure 1; Supplementary Figures 1 and 2, Supplementary Video 1) [7, 16]. For every zone, the following patterns were reported: (1) normal appearance (A lines, < 3 B lines), (2) pathologic B lines (≥ 3 B lines), (3) confluent B lines, (4) thickening of the pleura with pleural line irregularities (subpleural consolidation < 1 cm), or (5) consolidation (≥ 1 cm). The presence of pleural effusion was also recorded. The LUS score, used as a correlate of loss of lung tissue aeration, as well as a normalized LUS score (nLUS score) corrected for the number of examined zone were calculated in every patient [12, 16, 17].

Blinded to patient outcome, both physicians independently filled the standardized report. Discordance between the 2 readers was resolved by a third expert (O. P.).

Supplementary Table 1 shows the potential correlation of visible features between CT and LUS images based on physical explanations behind their generation in several retrospective human studies [8, 18–21], an animal study [22], and biomedical analysis [23].

Statistical Analyses

STATA (version 15.0; StataCorp, College Station, TX) and R Core Team (2019) statistical software were used for analyses. Differences between the 3 groups were evaluated by 1-way analysis of variance (ANOVA), Kruskal-Wallis, or chi-square test, as appropriate. A bilateral P value $< .05$ was considered indicative of statistical significance. The κ coefficient was calculated to measure the interrater agreement between the 2 LUS readers.

The prognostic accuracy of the LUS score, the nLUS score, and the proportion of LUS-affected zones to predict outcome was assessed by calculating the area under the receiver operating characteristic curve (AUROC). We determined the

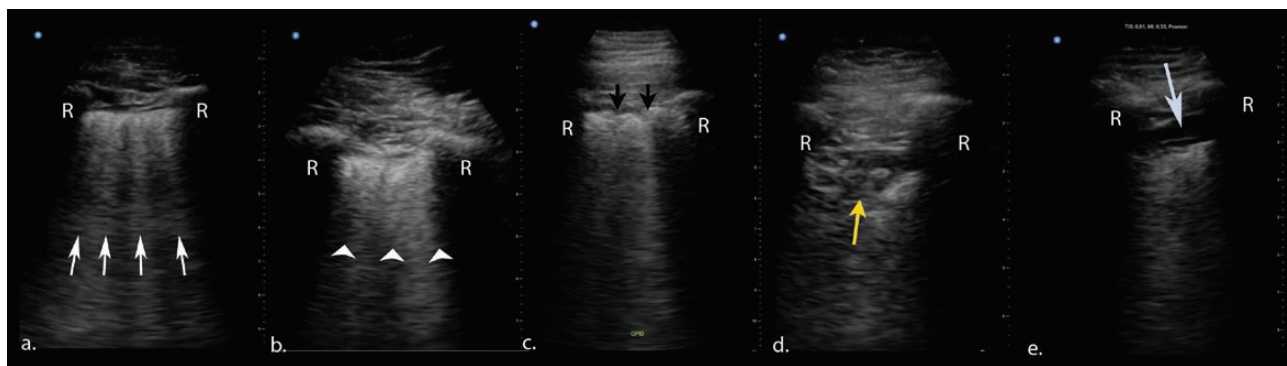


Figure 1. Pathological patterns of lung ultrasound observed in COVID-19, with a convex probe and a large field of view, on sagittal scans. Rib shadowing (R) is visible on the sides of the images. A, Four B lines (small white arrows) spreading out from the pleural surface. B, Confluent B lines (white arrowheads) shaping a curtain covering the depth of the image (white lung). C, Thickening of the pleural line with small (< 1 cm) irregularities (small black arrows). D, Large consolidation (> 1 cm) (yellow arrow). E, Small pleural effusion (large white arrow) forming a hypoechoic line between the thoracic wall and the lung.

optimal nLUS score cutoff by choosing the value with the best sensitivity and a specificity superior to 50%.

Ethics Approval

Ethical approval was granted by the Swiss Ethics Committee of the canton of Vaud (CER-VD 2019-02283).

RESULTS

Demographic and Clinical Characteristics

From the 165 successive adult patients prospectively included in the acute lower respiratory tract infection cohort at the time of ED presentation between 6 March and 3 April 2020, 86 patients had a positive nasopharyngeal RT-PCR for SARS-CoV-2 and were included in this nested study (Supplementary Figure 3). Six patients were excluded due to a more than 24-hour delay in LUS recording or to ventral decubitus position. The remaining 80 patients with COVID-19 included in this analysis were then classified into 3 groups according to outcome evaluated at day 7 after inclusion: 17 (21%) outpatients without secondary hospitalization, 42 (52%) patients admitted to the hospital, and 21 (26%) patients who died or were intubated (15 intubated, 5 deaths, 1 intubated who subsequently died). After inclusion in the ED, 20 patients were discharged home, 3 of whom had a secondary hospitalization after a median of 3 days (interquartile range [IQR], 3.0–3.5 days). Five patients were intubated upon inclusion (<24 hours) and 11 were later intubated after a hospital admission with a median duration of 2 days (IQR, 2.0–2.3 days). Six patients died after a median of 2.5 days of hospitalization (IQR, 1.3–4.5 days).

Table 1 shows demographic and clinical characteristics and laboratory results of the study population by group. Overall, the mean age was 62 years (SD, 17 years) and 34 (42%) patients were female. Outpatients were significantly younger than patients in the other 2 groups (mean of 51 years; $P = .002$). At inclusion, the median duration of symptoms was 7 days (IQR, 6–11 days) and was not different between groups. The most common symptoms were cough (91%), fever (83%), and dyspnea (75%). Dyspnea occurred with increasing frequency across severity groups ($P = .014$). Heart and respiratory rates were lower in outpatients compared with patients in the other 2 groups (median: 78 beats/minute vs 91 beats/minute, $P = .002$, and 20 breaths/minute vs 24 breaths/minute, $P = .002$, respectively). Leukocyte count and C-reactive protein were significantly and gradually higher with increasing severity.

Overall, 8 patients (10%) had a CT scan and 95% had a chest X-ray. X-rays were abnormal in 76% and outpatients had fewer abnormal X-rays than patients in the other 2 groups (38.5% vs 84%; $P < .001$). Among 10 patients with a normal chest X-ray (9 in the hospitalized group, 1 in the intubated/died group), 9 had LUS abnormalities.

Lung Ultrasonography Findings

At ED inclusion, 73 patients (91%) had an abnormal LUS, the proportion of which increased progressively across severity groups to reach 100% in intubated/died patients ($P = .001$) (Table 2).

A total of 735 lung zones were explored with LUS in all patients. A median of 10 zones were recorded for each patient (IQR, 9–10); 10 zones (IQR, 10–10) in outpatients, 10 zones (IQR, 9–10) in hospitalized patients, and 8 zones (IQR, 8–10) in intubated/died cases.

Lung ultrasonography examination showed abnormalities in 351 of 735 (48%) zones. The proportion of involved zones was significantly lower in outpatients compared with patients in the other 2 groups (median of 30%; IQR, 0–40%; $P < .001$). Patients who died or were intubated had the highest proportion of pathological zones (median of 70%; IQR, 50–88%) (Figure 2).

Abnormalities were bilateral in 63 (80%) patients and multifocal in 68 (85%) patients. Abnormalities were predominant in postero-inferior and lateral zones compared with others zones (60/75 [80%, $P < .001$] and 61/80 [76%, $P < .001$], respectively) (Table 2, Figure 3). With increased severity, lung anomalies affected both apical and basal lung regions (Supplementary Figure 4) and were more bilaterally distributed.

The patterns seen on LUS in decreasing severity order were thickening of the pleura with pleural line irregularities (present in 56/80 [70%] of patients), confluent B lines (present in 48/80 [60%] of patients), pathologic B lines (present in 40/80 [50%] of patients), and consolidations (present in 20/80 [25%] of patients) (Table 2, Figure 3).

In terms of the predominant abnormal LUS pattern, outpatients mostly had a “nonconfluent B lines” pattern, while the other 2 groups more frequently presented with a “thickening of the pleura with pleural line irregularities” pattern (Supplementary Figure 5). While the patterns of “pathologic B lines” and “confluent B lines” were more commonly identified in anterior compared with posterior zones (43/80 [54%] and 24/75 [32%], respectively; $P = .006$), “thickening of the pleural line irregularities” and “consolidation” patterns were more often visualized in posterior compared with anterior zones (53/75 [71%] and 15/80 [19%], respectively; $P < .001$) (Figure 3). Pleural effusion was present in 20 (27%) patients, 17 of which (85%) were classified as minor (<5 mm).

Lung Ultrasound Score

The median LUS score was 10 (IQR, 5–15) and the median nLUS score was 1.1 (IQR, 0.5–1.7). Outpatients had a significantly lower LUS score and nLUS score compared with the 2 other groups (median nLUS of 0.5 in outpatients vs 1.1 in hospitalized patients [$P < .001$] and versus 1.5 in patients who were intubated/died [$P < .001$]) (Figure 4). The nLUS score was not significantly different between hospitalized patients and those who required intubation or died (median nLUS score, 1.1 vs 1.5; $P = .34$).

Table 1. Characteristics of Study Participants at the Time of Inclusion in the Emergency Department, Classified According to Their Day 7 Clinical Outcome

	All Patients (N = 80)	Outpatients (n = 17)	Hospitalized Patients (n = 42)	Patients Intubated or Who Died (n = 21)	P
Demographics					
Female sex, n (%)	34 (42)	9 (53)	17 (40)	8 (38)	.608
Age, mean (SD), years	62 (17)	51 (18)	62 (17)	70 (10)	.002
Age distribution, n (%)					.002
<50 years	21 (26)	10 (56)	10 (24)	1 (4.8)	
50–65 years	23 (29)	3 (17)	15 (36)	5 (24)	
>65 years	36 (45)	4 (24)	17 (40)	15 (71)	
Residence in nursing home, n (%)	8 (10)	0 (0)	4 (10)	4 (19)	.291
Current smoker, n (%)	1 (1.3)	1 (6)	0 (0)	0 (0)	.153
Alcohol misuse, n (%)	8 (10)	2 (12)	3 (7)	3 (16)	.572
Coexisting disorder, n (%)					
Any	58 (72)	12 (71)	31 (74)	15 (71)	.961
Hypertension	39 (49)	6 (35)	23 (54.8)	10 (48)	.396
Diabetes	16 (20)	3 (18)	11 (26)	2 (9.5)	.286
Obesity	22 (39)	4 (29)	12 (30)	7 (41)	.606
Asthma	19 (24)	6 (35)	10 (24)	3 (14)	.318
Cardiovascular disease ^a	10 (12)	1 (5.9)	5 (12)	4 (19)	.468
Chronic obstructive pulmonary disease	3 (4)	0 (0.0)	2 (4.8)	1 (4.8)	.657
Neurological disorders ^b	12 (15)	1 (5.9)	4 (9.5)	7 (33)	.022
Active cancer	3 (3.8)	0 (0)	1 (2.4)	2 (9.5)	.244
Hepatitis or liver cirrhosis	2 (2.5)	0 (0)	1 (2.4)	1 (4.8)	.644
Chronic renal failure ^c	3 (3.8)	0 (0)	2 (4.8)	1 (4.8)	.657
Chronic inflammatory diseases	4 (5.0)	2 (12)	2 (4.8)	0 (0)	.253
Symptoms					
Duration, median (IQR), days	7 (6, 11)	7 (5, 10)	8 (7, 12)	9 (4, 10)	.485
History of fever, n (%)	64 (83)	14 (82)	34 (81)	16 (89)	.750
Cough, n (%)	71 (91)	16 (94)	39 (93)	16 (84)	.484
Dyspnea, n (%)	59 (75)	8 (47)	33 (79)	18 (90)	.008
Vital signs at inclusion in ED					
Temperature, median (IQR), °C	37.5 (36.8, 38.4)	37 (37, 38)	37.6 (37, 38)	38 (37, 38)	.626
Systolic blood pressure, median (IQR), mmHg	132 (119, 142)	131 (115, 138)	134 (126, 144)	124 (117, 141)	.079
Heart rate, median (IQR), beats/minute	85 (78, 97)	78 (75, 83)	90 (81, 99)	91 (82, 98)	.006
Respiratory rate, median (IQR), breaths/minute	24 (18, 28)	20 (17, 22)	24 (18, 29)	26 (24, 31)	.001
Respiratory rate ≥22 breaths/minute, n (%)	47 (62)	6 (37)	25 (60)	16 (89)	.006
Oxygen therapy, n (%)	31 (41)	0 (0)	18 (44)	13 (68)	<.001
Saturation, median (IQR), FiO ₂	4.4 (2.9, 4.6)	4.6 (4.6, 4.6)	4.2 (3, 4.5)	2.6 (1.3, 4.3)	<.001
Glasgow coma scale <15, n (%)	2 (2.6)	0 (0)	0 (0)	2 (10)	.044
Laboratory findings at inclusion in ED					
Leukocyte count, median (IQR), Giga/L	6.2 (4.9, 8.5)	5 (4.3, 6.0)	6.3 (5.0, 7.3)	8.9 (6.2, 10)	<.001
Hemoglobin, median (IQR), g/L	140 (129, 149)	146 (142, 152)	137 (125, 146)	135 (131, 149)	.070
Platelet count, median (IQR), Giga/L	209 (162, 282)	223 (163, 256)	210 (165, 294)	185 (158, 275)	.798
C-reactive protein, median (IQR), mg/L	72 (30, 147)	30 (9, 40)	72 (24, 143)	141 (89, 229)	<.001
Glucose, median (IQR), mmol/L	6.6 (5.6, 8)	5.8 (5.2, 6.7)	6.6 (5.6, 7.5)	7.8 (7.0, 9.7)	.011
Creatinine, median (IQR), μmol/L	91 (77, 113)	91 (68, 94)	91 (74, 115)	94 (88, 129)	.049
Radiologic, n (%)					
Chest radiograph performed	76 (95)	13 (76)	42 (100)	21 (100)	<.001
Infiltrate on chest radiograph	58 (76)	5 (38)	33 (79)	20 (95)	<.001
CT scan performed	8 (10)	1 (6)	4 (9.8)	3 (14)	.690

Missing values: smoking status, 1; alcohol use, 3; obesity, 23; duration of symptoms, 8; fever, 3; cough, 2; dyspnea, 1; vital signs, 12; blood count, 1; C-reactive protein, 2; glucose, 22; chest radiograph and CT scan, 4.

Abbreviations: CKD, chronic kidney disease; CT, computed tomography; ED, emergency department; FiO₂, fraction of inspired oxygen; IQR, interquartile range.

^aHeart failure, coronary disease.

^bStroke, dementia, Parkinson's.

^cStage III–V according to CKD classification.

Table 2. Lung Ultrasound Characteristics of Study Participants at Inclusion in the Emergency Department According to Clinical Outcome at Day 7

	All Patients (N = 80)	Outpatients (n = 17)	Hospitalized Patients (n = 42)	Patients Intubated or Who Died (n = 21)	P
Abnormal lung ultrasound	73 (91)	12 (70)	40 (95)	21 (100)	.003
Distribution					
Multifocal	68 (85)	11 (64)	39 (93)	18 (86)	.023
Bilateral	63 (80)	10 (59)	35 (85)	18 (86)	.053
Identified patterns					
Normal appearance	76 (95)	17 (100)	39 (93)	20 (95)	.521
Pathologic B lines (≥3)	40 (50)	7 (41)	16 (38)	17 (81)	.004
Confluent B lines (white lung)	48 (60)	8 (47)	27 (64)	13 (62)	.463
Thickening of the pleura with pleural line irregularities	56 (70)	6 (35)	34 (81)	16 (76)	.002
Consolidations (>1 cm)	20 (25)	1 (5.9)	12 (29)	7 (33)	.209
Pleural effusion					
Bilateral	6 (30)	1 (50)	3 (27)	2 (28)	.808
<5 mm	17 (85)	2 (100)	8 (73)	7 (100)	.236

Data are presented as n (%) unless otherwise indicated.

The LUS score, the nLUS score, and the proportion of affected zones had a good level of discrimination between outpatients and all admitted patients (including those who were intubated or died) with AUROCs of .77 (95% confidence interval [CI], .63–.90), .80 (95% CI, .68–.92), and .78 (95% CI, .67–.89), respectively. The optimal nLUS score cutoff to differentiate between outpatients and admitted patients including those who were intubated or died was 0.6 (sensitivity, 81%; specificity, 59%; positive-predictive value, 88%; negative-predictive value, 45%; positive likelihood ratio, 1.97; negative likelihood ratio, 0.32). If this nLUS score had been used at the first ED visit, it would have correctly recommended primary hospitalization for the 3 patients who were initially discharged (later returning for secondary hospitalization).

The LUS score, the nLUS score, and the proportion of affected zones had a poor level of discrimination between patients who died or were intubated and the other 2 groups.

Interobserver Consistency of Lung Ultrasonography Interpretation

The 2 observers found good reproducibility for all explored zones, with a κ of 0.74 based on the standardized ultrasound report. The reproducibility was excellent to differentiate normal and abnormal zones with a κ of 0.90.

DISCUSSION

Despite the potential of LUS as a cheap, portable, and accessible point-of-care triage tool in acute respiratory disease (especially in low-resource settings), a multinational consensus recently stated that the lack of studies limited specific recommendations for the management of patients with COVID-19 [24]. Using a standardized approach in a prospective ED cohort of 80 patients, we described the characteristics of LUS findings in COVID-19 pneumonia. Most patients presented abnormal LUS with bilateral and multifocal involvement, as previously shown in a large CT-scan study [25]. The most common patterns seen on LUS in decreasing frequency were thickening of the pleura with pleural line irregularities, confluent B lines, pathologic B lines, and rarely, consolidations and minor pleural effusions. Abnormalities affected all lung regions but were more frequent in posterior and inferior zones. Lung ultrasonography findings also evolved with increasing disease severity, both in anatomic scope (progressing from unilateral to bilateral and pan-lung involvement) and pathological type (progressing from the “nonconfluent B lines” pattern to “irregular pleural thickening”).

Our findings are consistent with the existing literature on radiology presentation in COVID-19 and shed more light on the LUS characteristics of COVID-19. A meta-analysis of 7 small

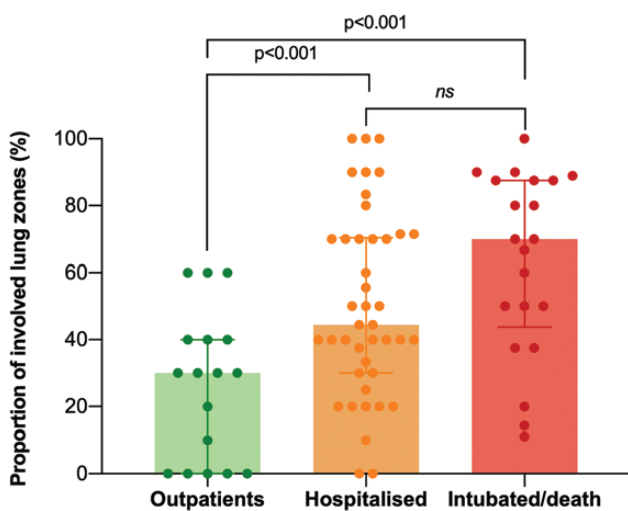


Figure 2. Proportion of lung zones affected in the different-severity patient groups: outpatients, admitted patients, and patients intubated and/or who died. Boxplot with median and interquartile range. Abbreviation: ns, not significant.

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1408/5907893 by guest on 19 June 2021

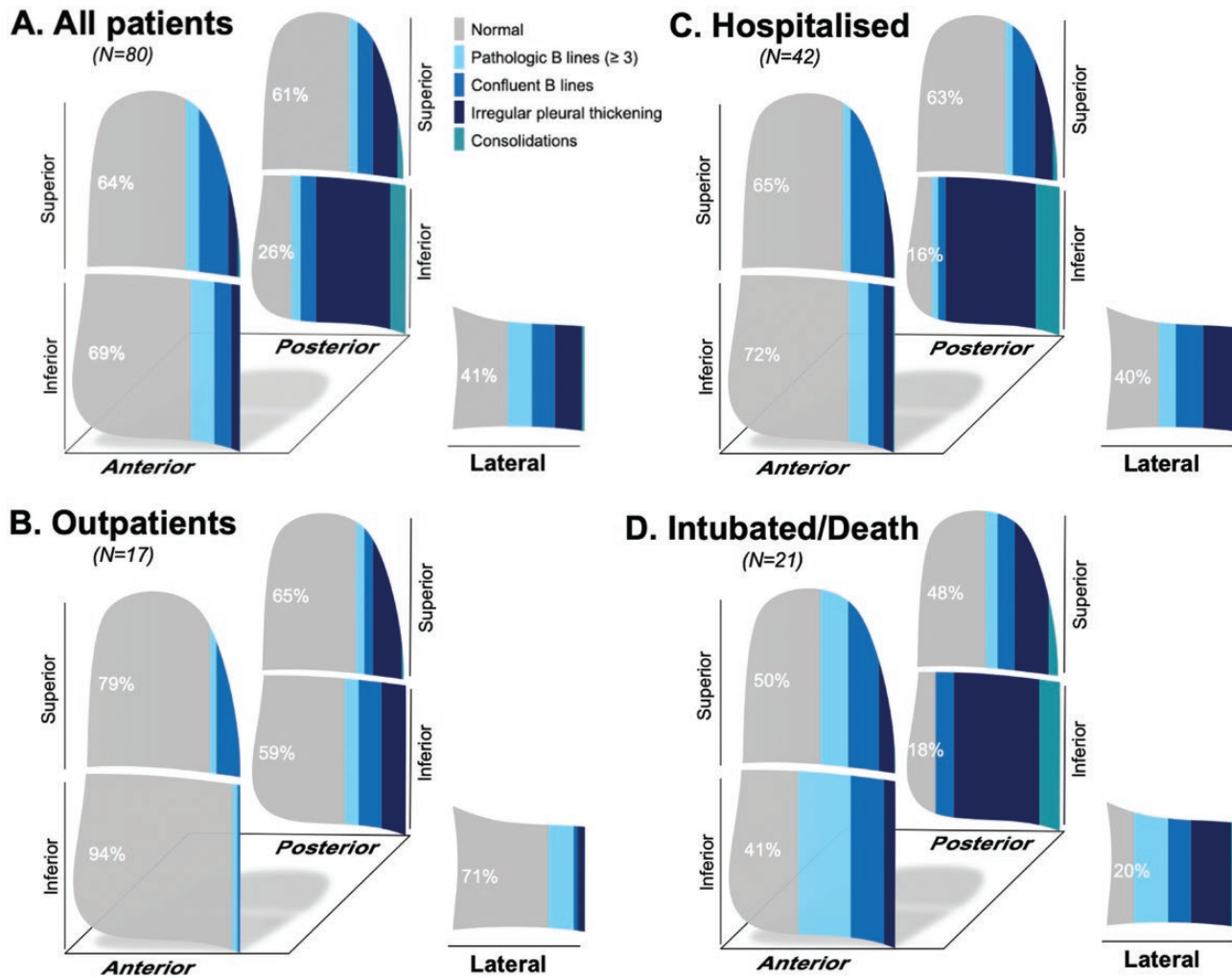


Figure 3. A–D, Distribution of the different lung ultrasound patterns in the different examined lung zones in all patients and according to patient outcome.

observational studies describing a total of 122 patients evaluated the typical characteristics of LUS in COVID-19. The identified patterns are similar to those in our study [26]. The LUS

imaging characteristics described in our and other studies are nonspecific, sharing similarities with those of other viral infections such as influenza and ARDS of any cause [12, 27].

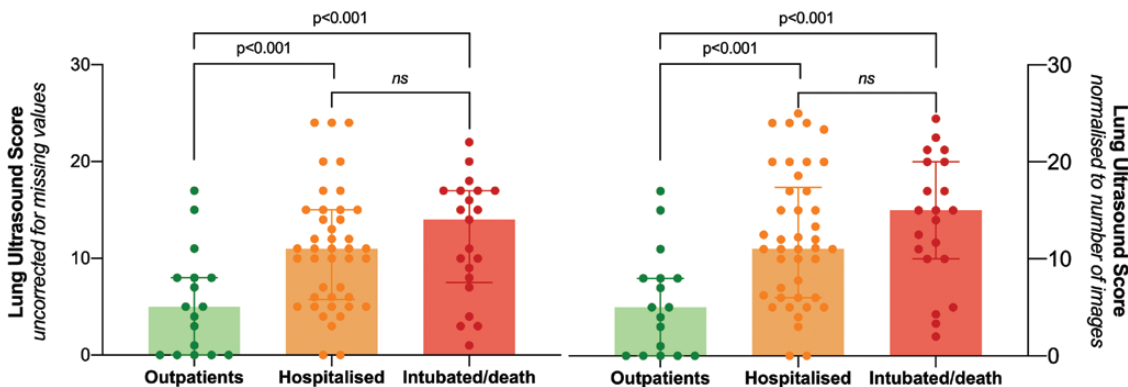


Figure 4. Boxplot [with medians and interquartile ranges] of the lung ultrasound score and the normalized lung ultrasound score according to patient outcome. Abbreviation: ns, not significant.

Our study is the first to analyze the prognostic value of LUS findings in ED patients with COVID-19 including outpatients who had less severe disease. So far, studies have only reported LUS findings in hospitalized patients and thus are not useful for early risk stratification and resource allocation in outpatients. We describe a significant relationship between the clinical severity of COVID-19 pneumonia and the anatomic extent and nature of lung pathology detected by LUS, suggesting the utility of LUS in early risk stratification of patients with COVID-19.

We also describe a risk gradient in LUS findings that can be summarized in a simple ordinal scoring system (LUS score), which was able to discriminate between outcome groups in ED triage. The LUS score can be used to quantify the loss of lung aeration and is thus useful for monitoring patients with ARDS. This simple LUS scoring method may help in assessing COVID-19 disease severity and support ED triage to decide on admission or close monitoring. Previous studies have evaluated the LUS score in patients with COVID-19. In the intensive care unit, the LUS score was higher in patients with refractory respiratory failure compared with others [28]. A good correlation existed between the LUS score and a CT-scan severity score. Both scores correlated with clinical severity [18, 21]. In our study, LUS score also increased progressively according to clinical severity. However, we did not have the power to predict intubation and/or death with good accuracy.

To our knowledge, our study is the first including the complete range of disease severity (ie, outpatients and patients who were intubated or died). Our findings provide additional evidence that the LUS score could be used as a triage tool to decide on admission. The role of LUS to evaluate several respiratory diseases such as pneumonia and ARDS has been widely documented [11, 12]. Lung ultrasonography has several advantages over chest CT, such as its ease of use at point-of-care, low cost, absence of radiation, reproducibility, and a reduced risk of nosocomial infection through its portability (reducing patient transport to imaging suites and lengthy disinfection protocol for the CT suite) [29, 30]. Lung ultrasonography allows a rapid assessment of severity at presentation in the ED. This study also shows that physicians with basic training in ultrasound (1-day theoretical course and 20 supervised acquisitions) are able to identify pathology with excellent concordance compared with experts: a critical proof-of-concept for its rapid deployment in COVID-19 and for its general use in low-resource settings.

This study does not correlate LUS with chest CT imaging. However, current recommendations specify that CT imaging should not be used for screening and is rather reserved for hospitalized, symptomatic patients, with specific indications [31]. Interestingly, 2 studies showed that the LUS and CT-scan scores have good agreement in the assessment of clinical severity [18, 21]. Excluding chest CT from the inclusion criteria eliminates a potential selection bias. On the other hand, we cannot propose a direct correlation between CT imaging and LUS.

Acquisition of LUS is dependent on the accessibility of anatomic sites, which is sometimes challenging in respiratory patients unable to mobilize. Indeed, this study reported approximately 15% of missing values in posterior lung regions, which were mostly in severely ill patients. We mitigated this bias by normalizing our score according to the number of available zones.

Nevertheless, the discriminatory power of the score reveals that the predictive capacity of accessible zones is already highly informative. Work is underway to identify the most informative zones and devise personalized imputations for such missing values. Lung ultrasonography image interpretation is operator dependant, which is a potential disadvantage of this technique. However, in our study, we found a good agreement between the 2 observers. Furthermore, using a standardized procedure and a predefined scoring method could minimize this limitation.

In conclusion, LUS is a promising tool for early risk stratification in COVID-19. Lung involvement visualized with ultrasound correlates with disease severity and summarizing this into a simple ordinal scoring system has potential to discriminate patients requiring hospitalization in the ED and thus better allocate scarce resources.

Work is ongoing to confirm these findings in a larger outpatient cohort.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. T. B., O. H., N. B.-B.: study conception, study design, study performance, study management, data analysis, data interpretation, and manuscript writing. J.-Y. M., O. P.: lung ultrasound images review, data interpretation, and critical review of the manuscript. M.-J. B. V., H. G. D.: acquisition of the data, interpretation of the data, and critical review of the manuscript. M.-A. H.: data interpretation, visualizations, and critical review of the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. T. B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments. The authors thank all the patients who accepted to participate and make this study possible. We thank Professor Carron, head of the emergency department, who supported the study. We thank all healthcare workers of the emergency department, internal medicine ward, infectious disease service, and intensive care unit of the University Hospital of Lausanne, who managed patients with COVID-19. We are grateful to Dr Loïc L'hopitalier for his assistance in the preparation and set-up of the study. We thank Hugo Schmutz for his support in preparing Figure 3. We thank Professor Fumeaux who trained the investigator in the lung ultrasonography.

Disclaimer. The funding body had no role in the design of the study and collection, analysis and interpretation of data, and or writing the manuscript.

Financial support. This work was supported by an academic award of the Leenaards Foundation (to N. B.-B.).

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Tanne JH, Hayasaki E, Zastrow M, Pulla P, Smith P, Rada AG. Covid-19: how doctors and healthcare systems are tackling coronavirus worldwide. *BMJ* **2020**; 368:m1090.
2. World Health Organization. Home care for patients with COVID-19 presenting with mild symptoms and management of their contact. Geneva, Switzerland: World Health Organization, **2020**.
3. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care* **2020**; 10:33.
4. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* **2020**; 20:425–34.
5. Hao W, Li M. Clinical diagnostic value of CT imaging in COVID-19 with multiple negative RT-PCR testing. *Travel Med Infect Dis* **2020**; 34:101627.
6. Zanobetti M, Scorpiniti M, Gigli C, et al. Point-of-care ultrasonography for evaluation of acute dyspnea in the ED. *Chest* **2017**; 151:1295–301.
7. Peng QY, Wang XT, Zhang LN; Chinese Critical Care Ultrasound Study Group (CCUSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic. *Intensive Care Med* **2020**; 46:849–50.
8. Lu W, Zhang S, Chen B, et al. A clinical study of noninvasive assessment of lung lesions in patients with coronavirus disease-19 (COVID-19) by bedside ultrasound. *Ultraschall Med* **2020**; 41:300–7.
9. Poggiali E, Dacrema A, Bastoni D, et al. Can lung US help critical care clinicians in the early diagnosis of novel coronavirus (COVID-19) pneumonia? *Radiology* **2020**; 295:E6.
10. Vetrugno L, Bove T, Orso D, et al. Our Italian experience using lung ultrasound for identification, grading and serial follow-up of severity of lung involvement for management of patients with COVID-19. *Echocardiography* **2020**; 37:625–7.
11. Orso D, Guglielmo N, Copetti R. Lung ultrasound in diagnosing pneumonia in the emergency department: a systematic review and meta-analysis. *Eur J Emerg Med* **2018**; 25:312–21.
12. Mayo PH, Copetti R, Feller-Kopman D, et al. Thoracic ultrasonography: a narrative review. *Intensive Care Med* **2019**; 45:1200–11.
13. Woodhead M, Blasi F, Ewig S, et al; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections—full version. *Clin Microbiol Infect* **2011**; 17:E1–59.
14. Rambhia SH, D'Agostino CA, Noor A, Villani R, Naidich JJ, Pellerito JS. Thoracic ultrasound: technique, applications, and interpretation. *Curr Probl Diagn Radiol* **2017**; 46:305–16.
15. Volpicelli G, Elbarbary M, Blaivas M, et al; International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med* **2012**; 38:577–91.
16. Soldati G, Smargiassi A, Inchingolo R, et al. Proposal for international standardization of the use of lung ultrasound for patients with COVID-19: a simple, quantitative, reproducible method. *J Ultrasound Med* **2020**; 39:1413–9.
17. Li L, Yang Q, Li L, et al. [The value of lung ultrasound score on evaluating clinical severity and prognosis in patients with acute respiratory distress syndrome.] *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* **2015**; 27:579–84.
18. Deng Q, Zhang Y, Wang H, et al. Semiquantitative lung ultrasound scores in the evaluation and follow-up of critically ill patients with COVID-19: a single-center study. *Acad Radiol*. doi:10.1016/j.acra.2020.07.002
19. Lomoro P, Verde F, Zerboni F, et al. COVID-19 pneumonia manifestations at the admission on chest ultrasound, radiographs, and CT: single-center study and comprehensive radiologic literature review. *Eur J Radiol Open* **2020**; 7:100231.
20. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. *Eur Radiol* **2020**; 30:4381–9.
21. Zieleskiewicz L, Markarian T, Lopez A, et al; AZUREA Network. Comparative study of lung ultrasound and chest computed tomography scan in the assessment of severity of confirmed COVID-19 pneumonia. *Intensive Care Med* **2020**; 46:1707–13.
22. Jambrik Z, Gargani L, Adamicza A, et al. B-lines quantify the lung water content: a lung ultrasound versus lung gravimetry study in acute lung injury. *Ultrasound Med Biol* **2010**; 36:2004–10.
23. Soldati G, Demi M, Inchingolo R, Smargiassi A, Demi L. On the physical basis of pulmonary sonographic interstitial syndrome. *J Ultrasound Med* **2016**; 35:2075–86.
24. Rubin GD, Ryerson CJ, Haramati LB, et al. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. *Chest* **2020**; 158:106–16.
25. Zhu J, Zhong Z, Li H, et al. CT imaging features of 4121 patients with COVID-19: a meta-analysis. *J Med Virol* **2020**; 92:891–902.
26. Mohamed MFH, Al-Shokri S, Yousaf Z, et al. Frequency of abnormalities detected by point-of-care lung ultrasound in symptomatic COVID-19 patients: systematic review and meta-analysis. *Am J Trop Med Hyg* **2020**; 103:815–21.
27. Testa A, Soldati G, Copetti R, Giannuzzi R, Portale G, Gentiloni-Silveri N. Early recognition of the 2009 pandemic influenza A (H1N1) pneumonia by chest ultrasound. *Crit Care* **2012**; 16:R30.
28. Zhao L, Yu K, Zhao Q, et al. Lung ultrasound score in evaluating the severity of coronavirus disease 2019 (COVID-19) pneumonia. *Ultrasound Med Biol* **2020**; 46:2938–44.
29. Nakajima K, Kato H, Yamashiro T, et al. COVID-19 pneumonia: infection control protocol inside computed tomography suites. *Jpn J Radiol* **2020**; 38:391–3.
30. Pan L, Wang L, Huang X. How to face the novel coronavirus infection during the 2019–2020 epidemic: the experience of Sichuan Provincial People's Hospital. *Intensive Care Med* **2020**; 46:573–5.
31. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. **2020**. Available at: <https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection>. Accessed 1 September 2020.