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Original Article

The association of lung ultrasound images with COVID-19 infection in an emergency room cohort

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Summary

Lung ultrasound could facilitate the triage of patients with suspected COVID-19 infection admitted to the emergency room. We developed a predictive model for COVID-19 diagnosis based on lung ultrasound and clinical features. We used ultrasound to image the lung bilaterally at two anterior sites, one and two hands below each clavicle, and a posterolateral site that was the posterior transverse continuation from the lower anterior site. We studied 100 patients, 31 of whom had a COVID-19 positive reverse transcriptase polymerase chain reaction. A positive test was independently associated with: quick sequential organ failure assessment score ≥1; ≥3 B-lines at the upper site; consolidation and thickened pleura at the lower site; and thickened pleura line at the posterolateral site. The model discrimination was an area (95%CI) under the receiver operating characteristic curve of 0.82 (0.75–0.90). The characteristics (95%CI) of the model's diagnostic threshold, applied to the population from which it was derived, were: sensitivity, 97% (83–100%); specificity, 62% (50–74%); positive predictive value, 54% (41–98%); and negative predictive value, 98% (88–99%). This model may facilitate triage of patients with suspected COVID-19 infection admitted to the emergency room.

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Introduction

The current coronavirus disease 2019 (COVID-19) pandemic is caused by the severe acute respiratory syndrome coronavirus 2 strain (SARS-CoV-2), with many patients admitted to the emergency room with suspected COVID-19 infection [1]. The results of RNA reverse transcriptase polymerase chain reaction (RT-CR) diagnostic oropharyngeal swabs may be unavailable for 48 h after collection [2]. This delay can lead to unnecessary isolation of many patients that may exceed a hospital's resources.

Lung ultrasound can contribute to the diagnosis of acute respiratory failure in the emergency room, for instance the 'bed-side lung ultrasound in emergency' (BLUE) protocol [3]. Lung ultrasonographic characteristics of COVID-19 disease have been recently described [4]. Lung ultrasound could facilitate rapid, simple and reliable triage of patients with suspected COVID-19 infection admitted to the emergency room and may inform prognosis [5].

We aimed to develop a model for COVID-19 diagnosis in patients presenting to the emergency room with possible infection, based on the association of lung ultrasound and clinical features with positive viral swabs. Our secondary objectives were to study the associations between these and admission to the intensive care unit, respiratory complications and mortality.

Methods

The University Medical Centre review board approved this observational study, which we conducted from March to April 2020 and that we report as strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [6]. Participants gave informed consent. We studied adults admitted to the emergency room whose lungs were imaged with ultrasound by the emergency physician for suspected COVID-19 infection as part of the BLUE protocol and who had a SARS-CoV-2 RT-PCR test [3].

We excluded pregnant women or patients unable to give informed consent or patients with suspected or proven chronic interstitial lung disease. We did not analyse patients whose ultrasound scans were poor due to an acoustic barrier, for instance pneumothorax or subcutaneous emphysema.

We used a convex array transducer and ultrasound system (C5-2s™ and TE7, Mindray™; Shenzhen, China) to identify abnormalities consistent with possible COVID-19 disease: thickening of the pleural line with irregularity; B-lines in a variety of patterns, including focal, multifocal and confluent; and consolidation in a variety of patterns (Fig. 1a) [4, 7, 8]. The 'bed-side lung ultrasound in emergency' (BLUE) protocol interrogates the lung bilaterally at upper and lower anterior sites and at a posterolateral site (Fig. 1b) [9]. We only counted the number of B-lines at the upper and lower sites as they are present in around 25% of healthy subjects elsewhere [8, 10]. The number of B-lines was counted in a short-axis scan between two ribs. Two experts who had performed at least 50 lung ultrasound scans interpreted stored images, unaware of patients' SARS-CoV-2 RT-PCR status (SB, PG) [11].

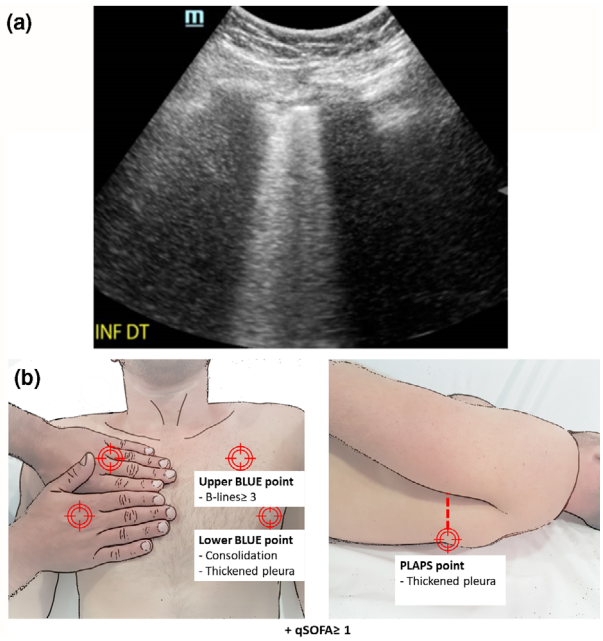

Figure 1 (a) Lower anterior chest subpleural consolidation associated with thickened pleura. (b) The 'bed-side lung ultrasound in emergency' (BLUE) protocol interrogates three points in each hemithorax. The two anterior sites are under one (upper) and two (lower) hands placed below each clavicle. The posterolateral site is the posterior transverse continuation from the lower anterior site, interrogated as posterior as possible in the supine patient

We recorded baseline characteristics, including age, sex, BMI, medical history and medications. We also recorded heart rate, mean arterial pressure and pulsed oxygen saturation. We calculated the quick sequential organ failure assessment (qSOFA) score and the Glasgow coma scale, respiratory rate and systolic arterial pressure [12]. We measured lymphocyte count, C-reactive protein and the ratio of arterial oxygen partial pressure to inspired fraction oxygen (PaO_2/F_IO_2). The primary outcome was the SARS-CoV-2 RT-PCR result, which we defined as negative if COVID-19 was not detected by two RT-PCRs [13]. The secondary outcomes were admission to intensive care; respiratory complications (acute respiratory distress syndrome (ARDS), pulmonary embolism and secondary bacterial infection); and mortality 14 days after inclusion, recorded by one investigator (AL) who was not informed of lung ultrasound results or COVID-19 status.

We calculated that we would need 100 patients to have a 80% power to demonstrate an ultrasound diagnostic accuracy of 18% and 12% for sensitivity and specificity, assuming their true values to be 50%, at an alpha threshold of 5%, if 30% of patients presenting to the emergency room with suspected COVID-19 had SARS-CoV-2 detected by up to two RT-PCR. We used the Agostino-Pearson test for normality of data distribution. We used Student's t-test, Mann–Whitney test, Chi-square test or Fisher test, as appropriate. We used logistic regression to model the associations of lung ultrasound and clinical features with admission to intensive care, respiratory complications and mortality. We constructed a multivariate logistic model with ultrasound variables that associated with outcome ($p < 0.05$), constrained by elastic net penalisation, with the L2 ridge parameter α set to 0.9 and the optimal L1 Lasso parameter λ determined by 10-fold cross-validation [14, 15]. In this multivariate logistic model, we categorised the number of B-lines ≥ 3 and < 3 in accordance with the international definition of interstitial syndrome [7]. We used the area under the receiver operating characteristic curve and the highest

Youden index to define model discrimination and diagnostic threshold, respectively. Inter-observer agreement between the two experts concerning qualitative ultrasound signs (signs present or absent) was evaluated using a Kappa concordance coefficient and agreement on quantitative evaluations (number of B-lines detected at the upper and lower sites) using an intraclass correlation coefficient. We used R for analyses (Core Team®, 2017, Vienna, Austria).

Results

We included 100 adults of whom 31 had a positive SARS-CoV-2 RT-PCR (Table 1 and Fig. 2). The qSOFA score (≥ 1) and four ultrasound signs were independently associated with a positive test (Table 2). The area (95%CI) under the receiver operating characteristic curve for the multivariate equation was 0.82 (0.75–0.90). The optimal model value for diagnosis was −1.35, recursively characterised (95%CI) in

Table 1 Characteristics of 100 patients presenting to the emergency room with possible COVID-19 infection. Values are mean (SD), number (proportion) or median (IQR [range])

	SARS-CoV-2 RT-PCR		
	Positive (n = 31)	**Negative (n = 69)**	**p value**
Age; years	66.8 (16.3)	68.7 (16.4)	0.98
Females	20 (65%)	39 (56%)	0.60
BMI; $kg.m^{-2}$	30.0 (3.19)	26.4 (3.98)	0.06
Medical history			
High blood pressure	21 (68%)	36 (52%)	0.22
Coronary heart disease	2 (6%)	13 (19%)	0.19
Smoking	2 (6%)	21 (30%)	0.01
Peripheral arterial disease	2 (6%)	4 (6%)	0.74
Stroke	7 (23%)	9 (13%)	0.36
Diabetes	3 (10%)	7 (10%)	0.77
Dyslipidaemia	10 (32%)	21 (30%)	0.96
Medication			
ACE inhibitor	5 (16%)	11 (16%)	0.79
Angiotensin receptor blocker	8 (26%)	10 (15%)	0.28
NSAID	0	1 (1%)	0.68
qSOFA score	1 (0-1 [0-2])	0 (0-1 [0-1])	0.003
Heart rate; min^{-1}	97 (80-115 [70-127])	88 (80-105 [67-134])	0.22
Mean arterial pressure; mmHg	96.0 (12.9)	97.5 (17.4)	0.68
Oxygen saturation; %	95 (93-98 [85-100])	97 (93-99 [82-100])	0.22
Lymphocyte count; $10^9.l^{-1}$	1.5 (1.0-2.1 [0.6-3.6])	2.0 (1.8-2.2 [0.6-3.9])	0.01
C-reactive protein; $mg.l^{-1}$	118 (71-151 [14-327])	42 (12-125 [0-29])	0.005
P_aO_2/F_iO_2	298 (119)	338 (105)	0.12
Chest ultrasound sites			
Upper and lower anterior			
B lines	6 (2-10 [0-30])	3 (1-7 [0-16])	0.04
Confluent B-lines	3 (10%)	0	0.04
Thickened pleural line	24 (77%)	26 (38%)	< 0.001
Consolidation	17 (54%)	11 (16%)	< 0.001
Posterolateral			
Confluent B-lines	10 (32%)	8 (12%)	0.03
Thickened pleural line	24 (77%)	26 (38%)	< 0.001
Consolidation	18 (58%)	23 (33%)	0.04

ACE, angiotensin-converting-enzyme; BLUE, bed-side lung ultrasound in emergency; NSAID, nonsteroidal anti-inflammatory drug; P_aO_2/F_iO_2, arterial oxygen partial pressure to fractional inspired oxygen; qSOFA, quick sequential organ failure assessment; SARS-CoV-2 RT-PCR, severe acute respiratory syndrome coronavirus 2 reverse transcription polymerase chain reaction

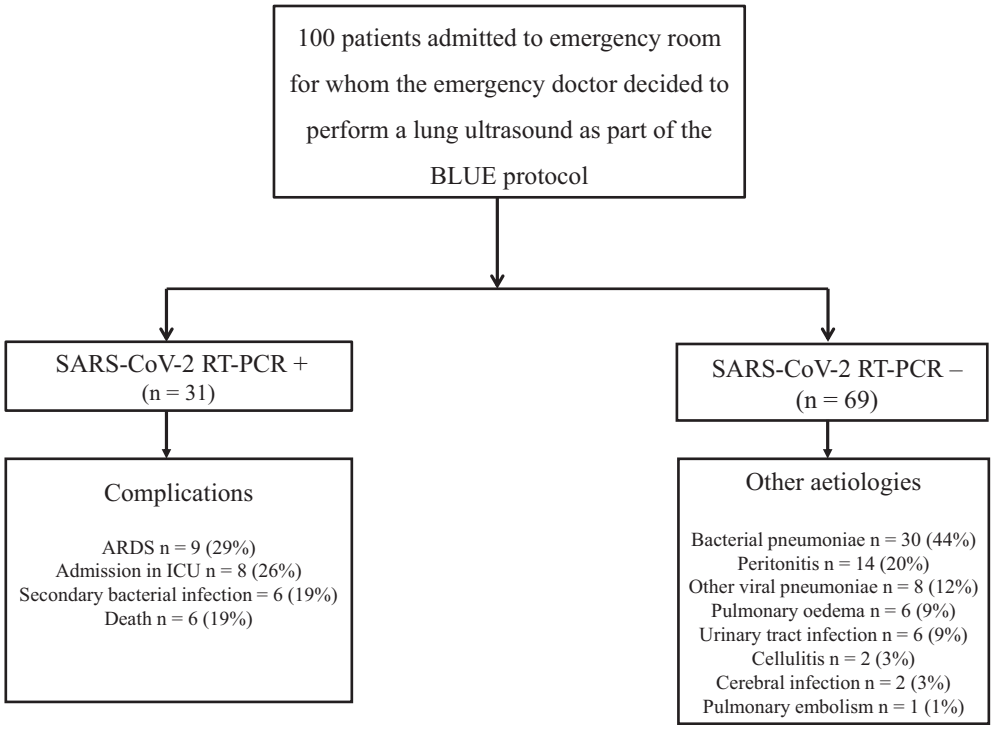

Figure 2 Study flow chart detailing complications in case of positive RT-PCR and other aetiologies in case of negative RT-PCR. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; RT-PCR, reverse transcription polymerase chain reaction

the derivation population by: sensitivity, 97% (83–100%); specificity, 62% (50–74%); positive predictive value, 54% (41–98%); and negative predictive value, 98% (88–99%).

Nine patients (29%) with a positive SARS-CoV-2 RT-PCR developed ARDS, six (19%) developed a secondary bacterial infection and none developed a pulmonary embolism. The odds ratio (95%CI) for subsequent ARDS in patients with COVID-19 was independently associated with three variables: ≥ 3 upper site B-lines, 1.7 (1.3–2.3), p = 0.001; ≥ 3 lower site B-lines, 1.0 (1.0–1.1), p = 0.03; and PaO_2/F_IO_2 ratio, 1.00 (1.00–1.01), p = 0.006. The same variables were associated with admission to the ICU, OR (95%CI): 1.6 (1.2–2.1), p = 0.003; 1.0 (1.0–1.1), p = 0.016; and 1.00 (1.00–1.01], p = 0.02, respectively. No associations were found between other respiratory complications and lung ultrasound variables.

Six patients (19 %) with a positive SARS-CoV-2 RT-PCR died during the study period. Mortality was not associated with lung ultrasound variables. The inter-observer agreement was good, with a Kappa concordance coefficient of 0.89 (95%CI [0.67–1.00]). The intraclass correlation coefficient for the agreement on quantitative evaluations was 0.92 (95%CI [0.81–0.97]).

Table 2 Lung ultrasound characteristics and qSOFA score independently associated with COVID-19

	Coefficients	Odds ratio (95%CI)
Intercept	−1.95	
qSOFA score ≥ 1	0.05	1.05 (1.01-1.10)
Chest ultrasound site findings		
Upper sites B lines ≥ 3	0.42	1.52 (1.31-1.79)
Lower sites thickened pleura	0.55	1.73 (1.49-1.98)
Lower sites consolidation	0.87	2.39 (2.07-2.69)
Posterolateral sites thickened pleura	0.68	1.97 (1.72-2.22)

qSOFA, quick sequential organ failure assessment

Discussion

We found that a combination of clinical features and lung ultrasound signs were independently associated with positive SARS-CoV-2 RT-PCR. Subsequent development of adult respiratory distress syndrome and ICU admission were also associated with lung ultrasound signs.

Chest computed tomography (CT) imaging has been strongly recommended because it is very sensitive for detecting early disease [16]. The early stages of COVID-19 infection are characterised by bilateral ground glass opacification, accompanied by interlobular thickening and

consolidation, predominantly in the peripheral and subpleural middle and lower lobes [17, 18]. However, the transportation of potentially infectious and unstable patients for CT limits its use [4].

Lung ultrasound has several advantages compared with CT. It is non-irradiating and non-invasive. It can be learned quickly and its use in the emergency room has generated great interest [7, 19–23]. Decontamination of the equipment is straightforward [24]. The abnormalities observed on CT are accompanied by ultrasound signs, which include B-lines that become more extensive with disease progression, accompanied by pleural thickening and subpleural consolidation [25, 26].

The signs associated with COVID-19 diagnosis in our model are consistent with other studies [4, 25]. The most common sign was thickening of the pleural line in the inferior and posterolateral sites, which is indicative of pneumonia or ARDS [7]. Consolidation is common to bacterial pneumonitis and did not independently associate with COVID-19 diagnosis [7]. Occasional B-lines may indicate chronic changes and are common to a number of diseases, but at least three lines indicate interstitial syndrome and greater numbers are associated with disease severity and higher mortality [4, 5, 7, 8, 10, 26–28]. The qSOFA score is a simplified version of the SOFA score that aims to identify patients more likely to suffer serious outcomes after infection [12]. Few patients with COVID-19 are haemodynamically compromised, which may limit its utility [29, 30].

Our study had several limitations. The first was the interpretation of B-lines in the upper chest, as a diffuse and heterogeneous distribution of B-lines with thickening of the pleura also occurs with chronic interstitial lung disease, whom we excluded from the study [31]. Lung ultrasound can distinguish between cardiogenic and non-cardiogenic pulmonary oedema, particularly through careful examination of the pleura [32, 33]. Lung ultrasound signs are not particularly specific for infections, although the bilateral distribution of changes in COVID-19 can help differentiate it from influenza and bacterial pneumonias [7, 34, 35]. The performance of our model will be limited in part by the sensitivity of the SARS-CoV-2 RT-PCR test, which misdiagnoses one quarter of COVID-19 patients as negative, a rate that we tried to reduce by performing two tests on each patient. It is possible that the performance of a model might be improved by imaging with ultrasound more lung areas, but any improvement might not justify the additional time [3, 5, 31, 36].

In conclusion, the association of BLUE protocol lung ultrasound signs and qSOFA with COVID-19 diagnosis could facilitate more effective triage of patients presenting to emergency departments with suspected COVID-19 infection. This model should be tested on an independent cohort.

Acknowledgements

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