Point-of-care ultrasound use in COVID-19: a narrative review

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Background and Objective: The coronavirus disease 2019 (COVID-19) pandemic that began in early 2020 resulted in significant mortality from respiratory tract infections. Existing imaging modalities such as chest X-ray (CXR) lacks sensitivity in its diagnosis while computed tomography (CT) scan carries risks of radiation and contamination. Point-of-care ultrasound (POCUS) has the advantage of bedside testing with higher diagnostic accuracy. We aim to describe the various applications of POCUS for patients with suspected severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in the emergency department (ED) and intensive care unit (ICU).

Methods: We performed literature search on the use of POCUS in the diagnosis and management of COVID-19 in MEDLINE, Embase and Scopus databases using the following search terms: "ultrasonography", "ultrasound", "COVID-19", "SARS-CoV-2", "SARS-CoV-2 variants", "emergency services", "emergency department" and "intensive care units". Search was performed independently by two reviewers with any discrepancy adjudicated by a third member.

Key Content and Findings: Lung POCUS in patients with COVID-19 shows different ultrasonographic features from pulmonary oedema, bacterial pneumonia, and other viral pneumonia, thus useful in differentiating between these conditions. It is more sensitive than CXR, and more accessible and widely available than CT scan. POCUS can be used to diagnose COVID-19 pneumonia, screen for COVID-19-related pulmonary and extrapulmonary complications, and guide management of ICU patients, such as timing of ventilator weaning based on lung POCUS findings.

Conclusions: POCUS is a useful and rapid point-of-care modality that can be used to aid in diagnosis, management, and risk stratification of COVID-19 patients in different healthcare settings.

Keywords: Coronavirus disease 2019 (COVID-19); point-of-care testing; ultrasonography; emergency medical services; diagnosis

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Introduction

Global pandemics are rising threats facilitated by pathogen spillover from wild animal species into humans driven by ecological alterations from climate change and accelerated by the steady growth of intercontinental air travel (1,2). This threat was evident in the past 3 years by the coronavirus disease 2019 (COVID-19) pandemic that spread worldwide from early 2020. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections resulted in significant number of fatalities from respiratory tract infections. The initial diagnosis of this novel virus was hampered by lack of adequate sensitive and specific tests, with false negative rates as high as 30% in the initial reverse transcriptase polymerase chain reaction (RT-PCR) tests that were developed to detect the virus (3). Chest X-ray (CXR) is also poorly sensitive in detecting pulmonary infections (4).

Comparatively, computed tomography (CT) scan of the chest is more sensitive (5). Unique CT features of thickened interlobular and intralobular septa on a background of ground-glass opacity, commonly known as "crazy-paving pattern" have been described (6). However, CT scan involves higher doses of radiation and needs to be performed in a dedicated radiography suite. The risks of contamination and increased resource utilisation in disinfection after every patient are also considerable.

Point-of-care ultrasound (POCUS) has the advantage of being able to be performed at the bedside without transporting critically ill patients to radiology suites or contaminating other areas and has easy user trainability. Lung ultrasound (LUS) have been shown to possess higher sensitivity and accuracy in detecting pathologies as compared to CXR (7,8). Apart from identifying lower respiratory tract involvement, bedside POCUS can be useful in discovering pulmonary and extrapulmonary complications related to COVID-19.

The aim of this narrative review is to describe the various applications of POCUS to diagnose, manage and prognosticate patients with suspected SARS-CoV-2 infection, primarily in the emergency department (ED) and intensive care unit (ICU). We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1403/rc).

Methods

We performed a literature search of published studies on the use of POCUS in the diagnosis and management of COVID-19 in MEDLINE, Embase and Scopus databases using the following search terms: "ultrasonography", "ultrasound", "COVID-19", "SARS-CoV-2", "SARS-CoV-2 variants", "emergency services", "emergency department" and "intensive care units". Study team members conducted independent searches of articles and any discrepancy between two members was resolved by a third independent co-investigator. Our inclusion criteria were studies that evaluated the use of POCUS in the diagnosis, management, and prognosis of COVID-19 among adult patients aged 16 years and above, in the emergency and intensive care settings. All English language and peer-reviewed articles that were published from January 2020 to November 2022 were eligible for inclusion. References of narrative reviews were searched to include the original articles. Articles that were not published in English, studies involving animals, evaluating only paediatrics patients or ultrasound not performed at bedside as point-of-care testing, conference proceedings and abstracts were excluded. The search strategy is summarised in *Table 1*.

Discussion

Pathophysiology of COVID-19 infection and its complications

COVID-19 is caused by SARS-CoV-2 that belongs to the family Coronaviridae, so named due to its homology with SARS-CoV that led to SARS in the years 2002 to 2003, which inflicted high mortality among infected individuals (9). Transmitted via respiratory droplets or direct contact with contaminated surfaces (10), SARS-CoV-2 enters the upper respiratory tract, binds to angiotensin-converting enzyme 2 receptors on nasal epithelial cells (11), replicates within these cells and subsequently invades the upper airways. Most patients are able to mount an immune response to adequately control the infection at this stage.

In some patients, SARS-CoV-2 continues to invade and replicate within the type 2 alveolar epithelial cells in the lungs (12). These infected pneumocytes release cytokines and inflammatory markers such as interleukins and tumour necrosis factors, as well as more viral particles (13), resulting in cellular apoptosis and diffuse alveolar damage. In the early stages, this appears as single or multiple ground-glass lesions mainly in the peripheral lung and subpleural areas (14). The cycle repeats within the adjacent type 2 alveolar epithelial cells causing diffuse alveolar damage and endothelial dysfunction with progression to acute

Table 1 Search strategy

Items	Specification
Date of search	30 November 2022
Databases and other sources searched	MEDLINE, Embase and Scopus databases
Search terms used	"Ultrasonography"; "ultrasound"; "COVID-19"; "SARS-CoV-2"; "SARS-CoV-2 variants"; "emergency services"; "emergency department"; "intensive care units"
Timeframe	January 2020 to November 2022
Inclusion and exclusion criteria	Inclusion criteria: (I) original peer-reviewed articles; (II) study setting in emergency departments and intensive care units; (III) English language papers; (IV) focused on diagnosis, management, and prognosis of COVID-19 infections
	Exclusion criteria: (I) not point-of-care ultrasound; (II) studies involving animals and studies evaluating only paediatrics patients; (III) conference proceedings, abstracts; (IV) entirely non-English language papers
Selection process	Two independent reviewers searched the databases, and any discrepancy was resolved by a third study team member

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

respiratory distress syndrome (ARDS) (15).

The cytokine storm induced by SARS-CoV-2 also triggers the production of interleukin-6 which in turn stimulates hepatocytes to synthesize fibrinogen, plasminogen activator inhibitor and C-reactive protein (16). This provokes a prothrombotic state locally in the pulmonary vasculature and systemically in the peripheral venous and arterial systems, leading to complications such as venous thrombosis, strokes, acute myocardial infarction, and pulmonary embolism (PE) (17).

Ultrasound findings in COVID-19 infection

In the early course of COVID-19, pathological changes first occur in the peripheral regions of the lungs and thereafter progress centrally. These changes appear as ground-glass opacities on CT scan with a peripheral distribution and a predilection for the lower lobes of the lungs. In later stages, dense consolidations develop bilaterally in multiple lobes (18,19). These initial peripheral changes in the lungs allow POCUS to be a suitable modality to evaluate patients with suspected or confirmed COVID-19 pneumonia (20).

As COVID-19 pneumonia is an acute interstitial disease (21), this appears on ultrasound as B-lines (*Figure 1*), which are discrete vertical hyperechoic lines arising from the pleural line extending to the bottom of the ultrasound screen without fading (22). The "light beam" sign (23) has been described in early phases of COVID-19 pneumonia, referring to B-lines that look like shining bands appearing intermittently with normal lung pattern in the background due to segmental areas of involvement alternating with normal lung tissue (24). Presence of 3 or more B-lines between 2 ribs in a single scan is more likely to be pathological (25). In early stages of COVID-19 pneumonia, there are focal B-lines, progressing to confluent and multifocal B-lines with subpleural consolidations as the infection advances (20). Confluent B-lines have been described as "shining white lung" (26), "torchlight" sign (27) and "waterfall" sign (28).

Pleural abnormalities are also common in patients with COVID-19 pneumonia, exhibiting sonographic features of thickening, irregularity or fragmented pleural lines (29). Subpleural consolidations may then progress to large consolidations, which are poorly vascularised or avascular with occasional air bronchograms on Doppler imaging (30). This contrasts with bacterial pneumonia where blood flow signal is good on colour Doppler imaging in consolidations, making POCUS a useful modality to differentiate the aetiology of pneumonia at the bedside (28). B-lines are the most common findings on LUS in patients with COVID-19 pneumonia (59–92%), followed by irregular pleural lines (59.3–78%) and subpleural consolidations (35–55.3%) (31-33). Pulmonary hepatisation and pleural effusion (*Figure 1*) are rarely found in patients with COVID-19 (31). Distribution of abnormalities are mainly in the lateral and posterior areas of the lung with bilateral involvement (34,35). Pathological lung findings on ultrasound over the course of COVID-19 infection increases in the first 2 weeks, followed

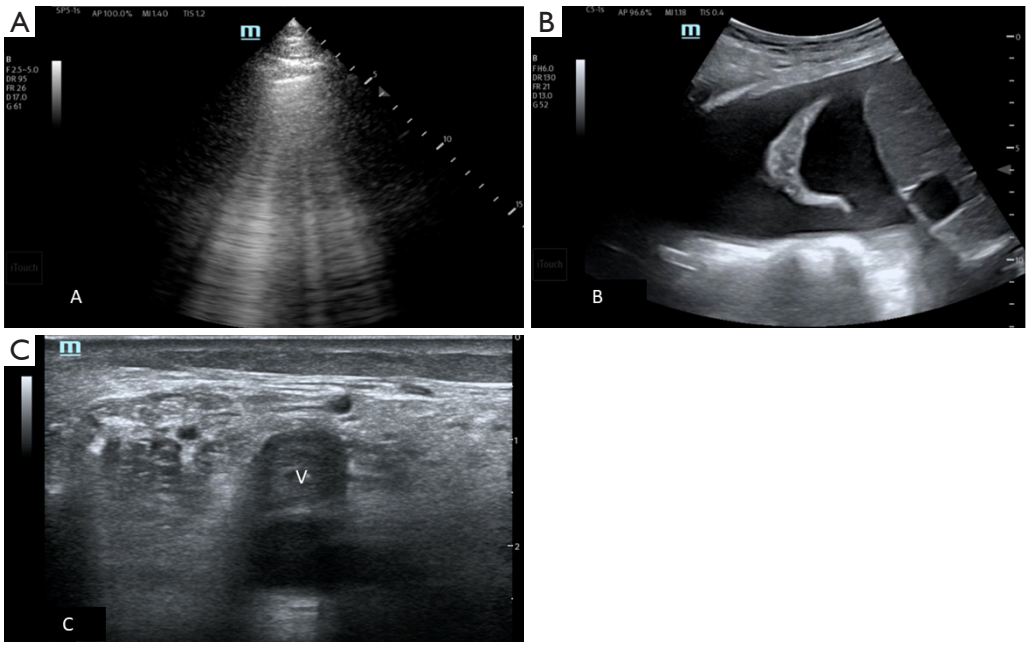

Figure 1 Sonographic examples. "M" denotes probe orientation marker. (A) B-lines seen on lung ultrasound; (B) pleural effusion; (C) thrombus seen in popliteal vein (denoted as V).

Table 2 Comparison of ultrasound findings in various conditions

Condition	B-lines	Pleural lines	Consolidation	Pleural effusion
COVID-19 pneumonia	Diffused and fixed	Irregular	(I) Subpleural; (II) lateral and posterior lung areas; (III) bilateral, multiple lobes; (IV) hepatisation rare; (V) poorly vascularised or avascular on Doppler	Rare
Bacterial pneumonia	Less diffuse than COVID-19	Irregular	(I) More extensive, large consolidation; (II) circumscribed and fewer lobes; (III) can have hepatisation; (IV) good blood flow on colour Doppler imaging	More common than COVID-19
Viral pneumonia (e.g., influenza)	Less common than COVID-19	Irregular pleural lines less common than COVID-19	Less common than COVID-19	More common than COVID-19
Cardiogenic pulmonary oedema	Focal, symmetrical, homogenous and gravity related	Not irregular	None	More common than COVID-19

COVID-19, coronavirus disease 2019.

by a gradual decrease in the subsequent 2 weeks (36).

Table 2 summarises the differences in LUS findings in various conditions compared to COVID-19 pneumonia. Although B-lines are also seen in patients with cardiogenic pulmonary oedema, these tend to be focal, symmetrical, homogenous (22), and in dependent regions (24). In patients with COVID-19, the B-lines are often fused and fixed (28), with additional findings of irregular or thickened pleural lines (25,37) which are not present in cardiogenic pulmonary oedema. Compared to viral pneumonia, there are higher incidences of B-lines, irregular pleura and subpleural consolidations but lower likelihood of pleural effusion in COVID-19 pneumonia (38). In contrast, bacterial community-acquired pneumonia has more extensive

consolidation and/or hepatisation that are circumscribed and restricted to fewer lobes of the lung, while LUS findings in COVID-19 tend to be bilateral, involving multiple lobes (29) interspersed with areas of normal lung parenchyma. Deep machine learning algorithms have been used to analyse LUS videos of B-lines to differentiate between COVID-19, non-COVID-19 respiratory distress syndrome and pulmonary oedema, and these algorithms seem to perform significantly better than physicians' ability to differentiate the various conditions (39).

Aside from LUS, there is a role in using POCUS to detect complications related to COVID-19 infection. Cardiac complications such as myocarditis, right ventricular dysfunction and acute myocardial infarction have been reported in patients with COVID-19 (26). Point-of-care echocardiography is able to identify the circulatory status, type of shock as well as evaluate for right heart dysfunction and left heart function at bedside (40). POCUS of the deep venous system of the lower limbs may be utilised to diagnose complications like deep venous thrombosis (DVT) (*Figure 1*) (36).

POCUS examinations are used frequently by emergency physicians at the patient's bedside (41) as it gives immediate actionable results, allows for serial examinations, and reduces the patient's exposure to ionising radiation. Transporting patients to another location such as for CT scan in a radiology suite can also be avoided, thus reducing transmission risk of COVID-19 as well as risk of deterioration during transport (42). Notwithstanding, POCUS has limitations of requiring an adequately experienced operator to acquire suitable images and to subsequently interpret the images accurately (35). Interobserver variability may influence the image acquisition, interpretation of ultrasound findings and assigned severity. It is, however, ubiquitous even in lower resource healthcare settings and the skills can be readily acquired by physicians (43). Previous studies have shown that interobserver variability in ultrasound findings and LUS scoring among physicians experienced in POCUS have substantial and good agreement (27,33,44-46).

Ultrasound protocols

High frequency linear array transducers or low frequency curvilinear transducers are recommended to obtain optimal LUS images in patients with suspected COVID-19 pneumonia (47). A linear probe acquires more optimal images of the pleural line appearance and subpleural changes whereas a curvilinear probe provides a panoramic view from the pleural line to identify B-lines and consolidations (48,49). Handheld pocket-sized ultrasound devices have been shown to have good agreement with standard POCUS scanners when visualising interstitial patterns, consolidation and calculation of LUS score in ICU patients (50) as well as patients with COVID-19 (51,52). Therefore, handheld pocket-sized ultrasound devices or wireless transducers may be preferable compared to larger POCUS machines during a pandemic as it is more convenient to sheath with single use plastic covers (53) and easier to disinfect.

Ultrasound protocols described in the literature since the emergence of COVID-19 vary among institutions. Common protocols for lung POCUS include scanning 6-, 8-, 12- or 14-zone on the chest (27,52-56), with the 12-zone protocol being the most frequently used. Bedside Lung Ultrasound in Emergency (BLUE) protocol was first described in 2008 by Lichtenstein *et al.* as a quick method to diagnose the aetiology for acute respiratory failure (57). *Figure 2* illustrates the differences in the various protocols (43,58,59). A higher number of regions scanned would give a more representative picture of the overall lung involvement but the trade-off is the time required to perform the scan in busy emergency settings. A study that compared the 6-, 8- and 12-zone protocols in COVID-19 pneumonia showed that the 8-zone protocol has the least sensitivity of 81%, while the 6- and 12-zone lung protocols have good sensitivities of 89.5% and 91.4%, respectively (43). The suboptimal sensitivity in the 8-zone protocol is likely because the posterior aspects of the hemithorax are not included and COVID-19 has a predilection towards the posterior lobes. Hence, this makes the 6-zone protocol a good screening tool and clinicians can proceed with scanning the 12 zones if abnormalities are identified (43).

To maximise yield and reduce operator's exposure to COVID-19, Duggan *et al.* proposed an alternative 6-zone protocol in a seated upright or prone position covering the posterior, superior lateral and inferior lateral zones using a lawnmower technique (*Figure 2D*) (35). This method focuses on the areas with the highest yield of abnormal findings and optimizes provider safety by having the provider positioned behind the patient and reducing the number of zones and time required to scan (35).

Diagnostic accuracy of LUS

Timely identification of COVID-19 pneumonia is crucial as patients may deteriorate abruptly into respiratory

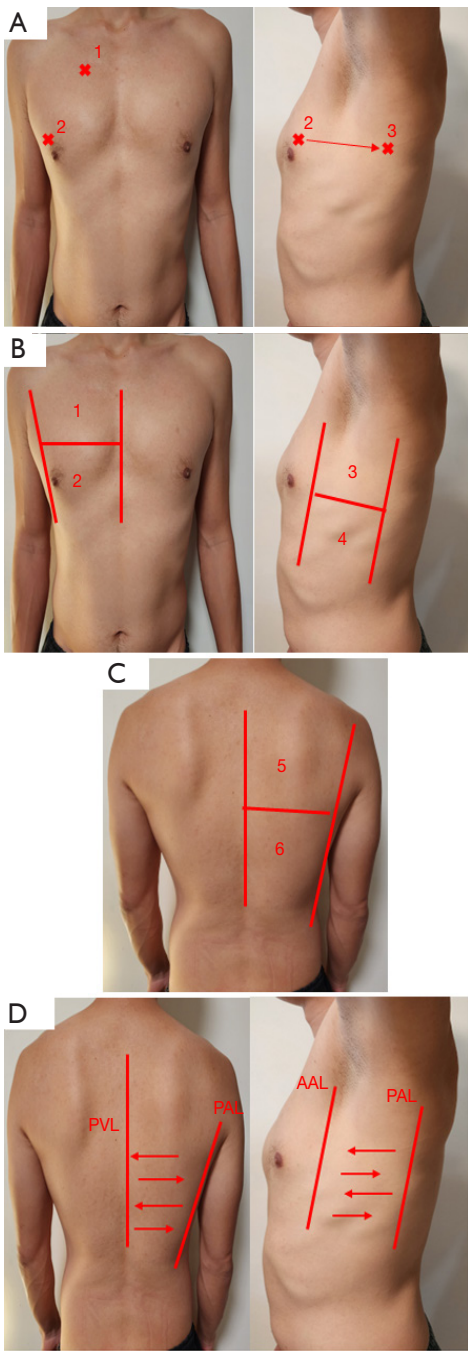

Figure 2 Ultrasound protocols. (A) 6-zone protocol: 1—upper BLUE point; 2—lower BLUE point; 3—PLAPS (extends posteriorly from lower BLUE point to posterior axillary line). (B) 8-zone protocol: utilises 4 sites on each hemithorax, the anterior and lateral aspects of the chest, which are further divided into upper and lower zones. 1—anterior upper zone; 2—anterior lower zone; 3—lateral upper zone; 4—lateral lower zone. (C) 12-zone protocol: incorporates the 8 zones and posterior upper and lower segments of the hemithorax. 14-zone protocol (not shown): incorporates 8-zone protocol; posterior hemithorax divided into 3 zones instead of 2. 5—posterior upper zone; 6—posterior lower zone. (D) Alternative method by Duggan *et al.*: the transducer is positioned in a sagittal plane with the probe marker pointed cranially, sliding the probe back and forth the hemithorax between PAL and PVL up to the mid-scapular border. The operator then scans the area between PAL and AAL in a lawnmower fashion inferiorly to superiorly. PVL, paravertebral line; PAL, posterior axillary line; AAL, anterior axillary line; BLUE, Bedside Lung Ultrasound in Emergency; PLAPS, posterolateral alveolar and/or pleural syndrome.

failure despite relatively mild respiratory discomfort being reported (60). Delayed invasive mechanical ventilation has been shown to be associated with increased mortality (61). In the very early stages of the pandemic, there were scarce availability of molecular tests to diagnose COVID-19, which in turn led to delayed recognition of pneumonia. Currently, a plethora of low-cost, easily accessible rapid antigen tests are employed to quickly diagnose COVID-19. However, the low sensitivity of CXR (62) and limited access to more accurate CT scans (63) have hampered the ability to identify COVID-19 pneumonia for early intervention.

LUS plays a crucial role in the diagnosis and staging of many lung diseases (22) and has been integrated in many clinical diagnostic pathways of SARS-CoV-2 pneumonia due to its potentially useful screening and diagnostic capabilities. LUS is a quick, non-invasive, non-radiating and repeatable diagnostic tool to identify pulmonary manifestation of COVID-19 (64). A study by Huang *et al.* showed that LUS was superior to CT in detecting smaller peri-pulmonary lesions and pleural effusion (28).

Several studies demonstrated high diagnostic accuracy [high sensitivity and negative predictive value (NPV)] of LUS for identification of COVID-19 pneumonia (23,34,56,65-71) (*Table 3*). A study by Haak *et al.* reported high sensitivity of 89% and NPV of 93% compared with RT-PCR or CT scan in diagnosing COVID-19 pneumonia (69). When integrated with history, physical examination and RT-PCR test in the early clinical assessment, LUS was a valuable screening tool for patients with suspected COVID-19 in the ED (56,70).

In a multicentre study involving 20 EDs in Europe and USA, Volpicelli *et al.* used mutually exclusive LUS patterns categorised as low, high, intermediate, or alternative probabilities to determine the diagnosis and clinical phenotype (mild, mixed, or severe) of patients suspected of having COVID-19 (23). The combination of clinical phenotypes and LUS patterns of probability could rapidly identify patients with SARS-CoV-2 infection at the bedside, thereby allowing rapid triage in the ED. Peyrony *et al.* compared the diagnostic performance for COVID-19 LUS (bilateral B-lines), clinical gestalt, physician examination and chest radiograph findings (71). LUS outperformed chest radiographs in the presence of high clinical probability for COVID-19. A retrospective study from Bolzano, Italy used LUS as a triage tool to quickly determine the disposition of patients to be isolated or discharged. The overall sensitivity and specificity of their LUS protocol was 70% and 77%, respectively. The sensitivity improved to 95% when a cut-off value of ≥3 was used (34).

Most studies that attempted to ascertain the diagnostic performance of LUS yielded a high sensitivity for the diagnosis of COVID-19 (*Table 3*). However, the observed disparity in diagnostic performances between studies likely were due to differences in reference standards used and variations in the LUS protocols employed. Comparisons were made between LUS and CXR for the diagnosis of COVID-19 pneumonia. LUS consistently outperformed CXR in excluding the disease.

The purported higher accuracy of CT in detection of interstitial pneumonia caused by COVID-19 was investigated by several studies that compared the LUS against it. CT was used in the early phases of the pandemic to diagnose COVID-19 pneumonia (72) but its limitations of higher radiation exposure, safety of transferring unstable patients for scans, contamination and potential nosocomial spread, limited mobility, and resource consumption restricted its use (73). It is also not recommended by the American College of Radiology as a first line tool to screen or diagnose COVID-19 (74). A systematic review of 9 studies involving 531 patients compared the agreement between LUS and CT. The pooled overall agreement was 81% on the background of very high heterogeneity between studies (75). LUS was widely accepted as an equally accurate alternative to CT in diagnosis and evaluation of COVID-19 pneumonia in the emergency or intensive care settings given its safety and accessibility.

A prospective study in a Spanish ED correlated LUS findings with CT in COVID-19 patients (76). Results obtained from 51 consecutive patients showed good correlation of LUS findings with positive CT scans suggestive of COVID-19 with an odds ratio of 13.3. Another study by Yang *et al.* reported that LUS was more sensitive than CT in the diagnosis of regional alveolar-interstitial pattern, alveolar-interstitial syndrome, consolidation and pleural effusion (77).

LUS in diagnosis of COVID-19 pneumonia in pregnant patients

Pregnant patients are at an increased risk of developing severe disease, are more likely to be admitted to the ICU and requiring mechanical ventilation (78). Although the radiation risk of CXR in pregnancy is generally considered small, it could be a major source of anxiety for the parents and the obstetrician (79). The risk is higher in CT, particularly to the foetus during the first trimester (80). Therefore, the use of LUS is regarded as a more suitable

Table 3 Diagnostic performance of lung ultrasound in COVID-19

Study	Country	Protocol	Setting	Sample size	Reference standard	Test	Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR–
Volpicelli (23)	USA, Italy, Spain, UK	8 zones (patterns categorized into high, intermediate and low probabilities)	20 EDs	1,462	RT-PCR	HighLUS	60	89	93	49	5.45	0.45
						HighLUS + IntLUS	90	53	82	70	1.91	0.19
Zanforlin (34)	Bolzano, Italy	20 zones [score 0 (no consolidation] to score 5 (large consolidation with air bronchograms)]	ED	111	RT-PCR, CXR, CT, ABG	LUS	70	77	69	68	3.04	0.39
Bianchi (56)	Florence, Italy	12 zones (atypical B or C, multiple consolidations, ARDS patterns)	ED	360	RT-PCR	LUS	86	71	65	89	2.97	0.20
Di Gioia (66)	Northeast Italy	12 zones (coalescent B-lines, irregular/thickened pleural line, subpleural consolidations)	3 EDs	235	Clinical, RT-PCR, CXR, CT, ABG	LUS	86	91	87	91	9.56	0.15
Haak (69)	Netherlands	12 zones (irregular pleural line, waterfall B-lines, subpleural consolidations, small pleural effusion)	ED	97	RT-PCR or CT	LUS	89	59	47	93	2.17	0.19
Pivetta (70)	Turin, Italy	Clinical evaluation + 12 zones (focal or diffuse interstitial syndrome associated with spared areas, subpleural consolidations, and irregular or thickened pleural line)	ED	228	RT-PCR	LUS	94	95	94	95	18.8	0.06
Comparison with CXR												
Sorlini (65)	Milan, Italy	12 zones (interstitial lung syndrome, interstitial lung pattern, white lung, subpleural consolidations)	ED	384	RT-PCR	LUS	92	65	89	73	2.63	0.12
						CXR	74	56	84	42	1.68	0.46
Gibbons (67)	PA, USA	Protocol not stated	ED	143	CT	LUS	98	33	82	82	1.46	0.06
						CXR	70	44	80	32	1.25	0.68
Pare (68)	MA, USA	12 zones (B-lines)	ED	43	RT-PCR	LUS	89	56	77	75	2.02	0.20
						CXR	52	75	78	48	2.08	0.64
Peyrony (71)	France	Bilateral B-lines	ED	391	RT-PCR	LUS	77	89	90	75	7	0.26
						CXR in high clinical probability	74	78	84	66	3.36	0.33

COVID-19, coronavirus disease 2019; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio of a positive test; LR–, likelihood ratio of a negative test; CXR, chest X-ray; ARDS, acute respiratory distress syndrome; ED, emergency department; RT-PCR, reverse transcriptase polymerase chain reaction; CT, computed tomography; ABG, arterial blood gas; HighLUS, high probability lung ultrasound pattern for COVID-19 pneumonia; IntLUS, intermediate probability lung ultrasound pattern for COVID-19 pneumonia; LUS, lung ultrasound.

Table 4 Two-tier scale for PE using LUS findings and Well's score

Variable	Area-under-curve value	Sensitivity (%)	Specificity (%)
LUS findings[†]	0.729	76.9	71.4
Well's score[‡]	0.813	90.0	70.0
LUS findings + Well's score[§]	0.944	100.0	80.0

[†], LUS findings: high/probable versus possible/unlikely; [‡], Well's score: ≥2 versus <2; [§], LUS findings + Well's score: Well's score ≥2 and high/probable LUS versus Well's score <2 and possible/unlikely LUS. PE, pulmonary embolism; LUS, lung ultrasound.

alternative since it is free of ionising radiation and safe for use in pregnancy. WHO guidelines recommend that ultrasound be used as a complementary method for diagnostic evaluation of COVID-19 in pregnant women with standard infection prevention and control measures (81). Obstetricians are generally proficient with the use of ultrasound. Hence, a systematic approach to perform LUS has been proposed by Moro *et al.* for pregnant patients, with particular emphasis on lung changes indicative of COVID-19 pneumonia (82).

The utility of LUS in pregnancy was highlighted in a case series of 8 pregnant COVID-19 patients in Türkiye, where 7 of 8 patients had commencement or change in their treatment based on LUS findings of serious lung involvement (83). Four of these 7 patients had either no symptoms, initial negative RT-PCR, or initial negative CT. Using a semi-quantitative LUS score, an Italian study of 44 pregnant women who were positive for SARS-CoV-2 infection found significant differences between symptomatic and asymptomatic patients, mainly increase in diffuse B-lines and light beams in symptomatic patients (84).

LUS scores

AB_1B_2C LUS score (85)

LUS score is a validated tool for assessing lung aeration, originally used in ARDS (30,86). Each lung zone that is scanned is given a score from 0 to 3 based on the ultrasound findings and a total score, also known as the lung aeration score, is tabulated from 12 zones. A score of 0 is given for normal lung sliding with A-lines or <3 isolated B-lines, score of 1 for 3 or more well-defined B-lines, score of 2 for confluent B-lines or small areas of consolidations <1 cm, and score of 3 for consolidations >1 cm (33,46,87). The highest scores are tabulated from each of the 12 zones to give a global score, sometimes referred to as the Lung Aeration Score, ranging from 0, where all zones are well aerated to 36, where all zones are consolidated (50). An observational study from Romania used this score on 16 thoracic zones for diagnosis, monitoring and prognostic stratification of COVID-19 patients. The AB_1B_2C score was generated by scanning the lung involvement in 16 thoracic areas (LUS score range 0 to 48), each area providing a score of 0 to 3 depending on the LUS pattern seen. A cut-off value of >22 predicted severe COVID-19 [area under the receiver operating characteristic curve (AUROC): 0.69] and >29 predicted transfer to ICU with a specificity of 97.7% and sensitivity of 80% (85), while a score of <13 corresponded with milder disease (21). Similar findings were obtained in other cohorts, where higher LUS Score correlated with higher severity of disease (51) and the need for intensive respiratory support, requirement of non-rebreather mask, high-flow nasal cannula (HFNC) or mechanical ventilation (33).

Lung Ultrasound Severity Index (LUSI) (59)

The LUSI was derived from a single centre prospective observational study of 159 consecutive patients who were suspected of having COVID-19 to measure the quality and extent of lung involvement. It involves scanning 12 thoracic areas with findings in each zone assigned points that are subsequently tabulated in a LUSI calculator. The 63.5% of patients with final diagnosis of COVID-19 had higher LUSI compared to non-COVID-19 patients, resulting in an AUROC of 0.72 in distinguishing between the two groups. An estimation of the degree of extension of lung lesions to the pulmonary surface using LUS also correlated significantly with the severity on CT imaging (88).

COVILUS (89)

Derived from the BLUE protocol (58), the COVILUS score (range between 1 and 6) was validated in an independent cohort of 100 patients in the ED who were suspected of contracting COVID-19. The score had an AUROC of 0.92, and a score of ≥4 achieved a sensitivity of 94% in predicting a positive SARS-CoV-2 test and ≥3 B-lines were independently associated with subsequent ARDS.

Other modified scoring models have also been proposed such as including pleural line abnormalities (53) in the scoring and using the interstitial lung disease Buda scoring system (29).

ICU admission prediction and risk stratification in ED

As the pandemic unfolded, risk stratification and prognostication of patients with COVID-19 became increasingly important to preserve the healthcare system capacity and efficiently utilise limited resources. LUS-based scoring systems were formulated for the prognostication of COVID-19 patients. Some examples are the LUS score, COVID-19 Worsening Score (COWS) and Point-of-care ultrasound Lung Injury Score (PLIS). These scores could be useful adjuncts for risk stratification to determine disease severity, predicting outcomes like the need for intubation, risk of ICU admission and mortality.

LUS score

The presence of LUS features such as bilateral lung involvement, B-profile, spared areas and confluent B-lines or waterfall sign were significantly associated with increasing disease severity (31). Those who required ICU admission were found to have higher rate of anterior (77% *vs.* 39%) and lateral (92% *vs.* 50%) subpleural consolidation, and less likely to have A-lines in >50% of lung zones on the initial ultrasound scans (0% *vs.* 27%) compared to those who did not need ICU care (90).

In addition to specific pulmonary features on ultrasound, the LUS score seemed to correlate with the extent of disease severity and respiratory failure. Patients who died from COVID-19 at presentation in the ED were found to have a mean LUS score of 11 (91). While a low LUS score <5 has an NPV of 100% for the need for ICU admission (33), a higher LUS score and higher proportion of pathologic lung area involvement were associated with higher risk of ICU admission and death (92). Ciurba *et al.* used an LUS score cut-off of >29 to predict the need for ICU admission with a sensitivity of 80% and specificity of 97.7% (85). A higher LUS score was associated with the need for intensive respiratory support or mechanical ventilation, SpO_2/FiO_2 ratio below 357 as well as length of stay of ≥9 days (21). A multiple logistic regression model from a Mexican cohort by Manzur-Sandoval *et al.* found that an LUS score of ≥19 was significantly associated with mortality (hazard ratio =2.55) (93). Meanwhile, a study by Lugara *et al.* on Southern Italian COVID-19 patients found that increased LUS score correlated with elevated lactate levels and an increased need for ventilation (94).

COWS

COWS (range from 0–1) combines LUS and the previously validated COVID-GRAM score (GRAM) (95) variables to categorize patients into low and high risk (96). Five predictive variables (LUS score >15, number of comorbidities, days from symptom onset, dyspnoea at presentation, and PaO_2/FiO_2 ratio) were selected to derive an optimal accuracy threshold of 0.183. Those below this threshold were considered low risk, and unlikely to require ICU monitoring.

PLIS

The PLIS score ranges from 0–6 points and comprises a combination of method of respiratory support with two major COVID-19 LUS findings of interstitial alveolar syndrome (bilateral B-lines) and lung consolidations (97). It correlated closely with Sequential Organ Failure Assessment (SOFA) scores and every point increase in PLIS score was associated with higher risk of ICU admission and death.

Ultrasound to guide management in intensive care units

Monitoring progression of disease

The LUS score has shown to be highly sensitive in predicting ICU admission; every 1-point rise in LUS increases the odds of ICU admission by almost 50% (98,99). Patients admitted to the ICUs have higher LUS score on admission than those who did not require hospitalisation or were admitted to non-critical care wards (98-100), and all ICU patients had abnormal LUS findings on admission (101). The "beam line" or "waterfall" artifacts describing confluent B-lines originating from regular pleural lines classically associated with early COVID-19 pneumonia were only noticed in a small proportion of ICU patients (24,36). ICU patients more commonly had findings of confluent B-lines with pleural irregularity and thickening as well as a "starry sky" pattern of consolidation where bright infiltrates are interspersed between normal lung parenchyma mostly in the peripheral and posterior zones, and these abnormalities correspond to higher LUS scores (100). This may suggest that patients with such ultrasound findings should be monitored in a high acuity area, if not already so.

Studies which evaluated the utility of serial LUS exams on admission and at pre-defined intervals (2- to 7-day

intervals) showed that increasing LUS score correlated with worsening of disease and predicted the need for mechanical ventilation and mortality (36,99,101,102). The disappearance of B-lines due to increasing consolidation depleting air from subpleural lung tissue correlated with clinical deterioration. With recovery, consolidations became less solid with air bubbles i.e., the appearance of air bronchograms (103). Number of lung parenchymal abnormalities increased before improvement from the third week onwards in survivors (36), although median LUS scores remained elevated at ICU discharge and there was no difference in scores between survivors and non-survivors (104). In severely ill COVID-19 patients initiated on venovenous extracorporeal membrane oxygenation (VV ECMO), patients with a decreasing LUS score were capable of being weaned from VV ECMO while those with no change or increasing LUS scores required longer duration of VV ECMO or died (103). These findings indicate that POCUS lung is a useful modality in monitoring progress of COVID-19 pneumonia during the illness.

When to intubate and extubate

The assessment of respiratory failure requiring intervention in the form of invasive or non-invasive ventilation (NIV) was of concern, especially when prudent use of limited resources was needed as the number of COVID-19 patients admitted to ICU increased (105). POCUS enabled identification of patients who were at risk of deterioration requiring mechanical ventilation, monitoring progress of these intubated patients including related complications such as pneumothorax, pleural effusions, ventilator associated pneumonia, and in determining when the patient can be extubated.

Zieleskiewicz *et al.* showed that LUS score was doubled in mechanically ventilated patients (21), and all patients requiring mechanical ventilation had LUS score >19 (21,106-108). LUS score was significantly lower at day 7 of ICU admission for those who did not require invasive ventilation versus those who were intubated (106). Majority of patients (92%) with increasing LUS score at day 7 required invasive ventilation compared to only 57% in the group with decreasing LUS score (106). Hence, serial LUS measurements in ICU patients may be useful to predict the need for mechanical ventilation, to support patients' respiratory functions in a timely fashion. During mechanical ventilation, LUS continued to be a valuable tool in monitoring respiratory failure and response to titration of mechanical ventilation, as worsening LUS score has been shown to significantly correlate with deteriorating ventilation parameters such as positive end expiratory pressure, FiO_2 and PaO_2/FiO_2 ratio (101,106). The global LUS score was associated with successful extubation (109), independent of when the ultrasound was performed and severity of disease. LUS score also showed a higher trend in patients with post-extubation acute respiratory failure compared to successfully extubated patients (87).

NIV and HFNC have been used as treatments for patients with respiratory failure with the aim of avoiding intubation (110-113). Apart from using clinical parameters such as increasing respiratory effort and oxygen requirements, the LUS was studied as an objective measure to predict failure of NIV. LUS score was significantly lower in patients who were successfully treated with HFNC and NIV compared to patients who required intubation (114). LUS ≥12 gave the most accurate cut-off value for prediction of NIV failure with a sensitivity of 88% and specificity of 93%. LUS may aid clinicians in identifying patients at high risk of NIV failure and allow for early intervention before clinical deterioration.

Sonographic evaluation of the thickness of the diaphragm, such as the diaphragmatic thickening fraction (DTF) and the diaphragmatic motion, may also be useful adjuncts in monitoring respiratory status in severely ill patients. A pilot study by Corradi *et al.* evaluated the utility of DTF, which is the ratio of the difference between diaphragmatic thickness at the end of inspiration and expiration to the end-expiratory thickness. DTF was found to be inversely correlated with the success of continuous positive airway pressure in COVID-19 patients with respiratory failure (115). Meanwhile, Pivetta *et al.* reported in their proof-of-concept study that lower motion or excursion of the diaphragm (measured in M-mode) combined with age and LUS achieved a modest AUROC of 0.75 to predict poorer outcomes at 30 days (116).

Diaphragmatic ultrasound was evaluated to predict extubation success in ICU patients (117) and to identify patients at risk of NIV failure. It can be used to assess for diaphragmatic dysfunction, defined as a reduced maximum thickening fraction during maximum inspiratory pressure (118,119). Diaphragmatic ultrasound is easily accessible, non-invasive and can be employed at bedside to determine diaphragmatic thickness, thickening fraction and excursion (116). In particular, the DTF has been shown to correlate with the pressure-generating capacity of the muscle, work of breathing, and respiratory effort. Previous studies have shown that DTF of less than 20% was a measure of

diaphragmatic dysfunction and can predict failure of weaning from mechanical ventilation (120) whereas successful weaning required DTF values of ≥30% (121). This has implications on the number of ventilator days and length of stay in the ICU. However, in a study on patients with COVID-19 pneumonia by Vetrugno *et al.*, the use of diaphragmatic ultrasound was not shown to be helpful in predicting extubation success in this cohort, with similar DTF values across the extubation success and failure groups (118). In patients on NIV, a higher likelihood of NIV failure requiring intubation was seen in those with lower initial DTF values (115). The accuracy of the DTF for continuous positive airway pressure ventilation failure in COVID-19 patients returned 21.4% as the best threshold value (AUROC: 0.944).

Detection of ICU complications

Apart from severity of infection, ICU patients are also at risk of complications, related to both disease progression and treatment related such as ventilator associated pneumonia (VAP). Early detection and treatment of VAP with appropriate antibiotics may improve survival, reduce ventilated days and ICU length of stay (122). POCUS was used to monitor lung parenchymal changes especially when serial trending of biomarkers in detecting VAP can be costly (122). Moreover, LUS score can be easily assessed at bedside and has been shown to increase in VAP (87).

A large majority of COVID-19 ICU survivors develop ICU-acquired muscle weakness which can last up to a month post-ICU admission (123). Muscular ultrasonography is used to evaluate the muscular echogenicity, which is affected by the composition of intramuscular fat and connective tissue. A higher muscle echogenicity of parasternal intercostal and diaphragm muscles (indicating poorer muscle quality) negatively correlated with survival in COVID-19-related ARDS (124). There may be a role in nutritional supplements to reduce muscle atrophy during prolonged ICU stay if wasting is detected on POCUS.

Additionally, patients with severe COVID-19 pneumonia who are intubated are at higher risk of other nosocomial infections, such as maxillary sinusitis, which contributes to the overall severity and mortality in this group of patients (125). Ultrasonography has a high predictive value of 85% compared to the gold standard of bacterial growth in cultures in the material obtained during surgical drainage (126) and is useful as a bedside tool for diagnosis and follow-up. This allows the patient to be diagnosed and treated at the bedside without exposing the patient to the dangers of intra-hospital transfers.

Patients who were intubated for COVID-19 pneumonia had higher cumulative incidence of venous thromboembolic events (30% to 36.8%) compared to those who were intubated for other causes (5% to 11%) despite prophylactic anti-coagulation therapy (127-129). This was corroborated by incidences of 29.4% to 37.3% seen in other studies (17,128,130,131). In an ICU multi-organ POCUS study, ultrasound detection of thrombosis in either femoral or popliteal veins together with low ejection fraction had high specificity for mortality (132). Most thrombotic events only occurred after the first week from ICU admission (127), hence physicians should be aware of this late complication of severe COVID-19 pneumonia. The use of POCUS by emergency physicians or intensivists is an excellent modality in diagnosing venous thromboembolic events such as DVT and PE at the bedside and to guide management. It can be repeated at regular intervals, minimises the need for transporting critically ill patients and reduces nosocomial spread of the virus as portable ultrasound devices can be wrapped and easily disinfected (133,134).

Ultrasound as a predictive tool

Development of severe disease

A study done by Zieleskiewicz *et al.* found that LUS score was significantly associated with severity on chest CT (21), which is the gold standard for assessment of serious COVID-19 pneumonia (135). LUS score >23 predicted severe COVID-19 pneumonia diagnosed by CT and <13 excluded severe COVID-19 pneumonia with both specificity and sensitivity more than 90% (21), suggesting that CT may only be required for patients with an intermediate score between 13 and 23 to determine the severity of disease.

Patients with cardiac dysfunction on ultrasound were found to have lower PaO_2/FiO_2 ratio compared to patients without cardiac dysfunction, leading to higher rates for intubation and ICU admission (136). In patients with COVID-19 and PE, those with a larger right ventricular diameter on ultrasound required oxygen support more often (137), and hence may be a potentially useful tool for risk stratification.

Mortality

Higher LUS scores were associated with increased risk of mortality (59,101,107,138). Numerous cut-off values from 18 to 26 have been evaluated, with varying predictive accuracies (101,107,138). Risk-stratifying patients by their

National Early Warning Score (NEWS) subgroups and LUS score further improved the prediction of mortality. Patients with a NEWS ≥7 and a LUS score ≥20 had 27 times higher risk of mortality compared to patients who had LUS score <20 (98).

Apart from LUS score, other POCUS findings were also useful in mortality prediction. Serial ultrasonography using LUS and Focused UltraSound for Intensive Care heart (FUSIC Heart) were able to risk-stratify patients with COVID-19. The CORONA study found an association between LUS score, right ventricular dysfunction, and mortality (139).

Echogenicity of other important respiratory muscles can be assessed by POCUS—low echogenicity is characterised by lean muscle tissue, whereas fat and connective tissue within the muscles constitute high echogenicity (140). Formenti *et al.* reported that the echogenicity score for both parasternal intercostal muscles, diaphragm and rectus femoris were significantly lower in patients who survived compared to those who died (124). Although the exact cause of how COVID-19 affects the muscle echogenicity is unclear, the authors postulate that there could be potential benefit of proactive early therapies to preserve respiratory and peripheral muscle structure, which could reduce the number of days on the ventilator.

Readmission

Protocols for safe discharge of low risk COVID-19 patients from the ED combining clinical characteristics and imaging results have been used with good effect (141,142). The use of LUS as part of these clinical pathways improved prediction of hospitalisation and mortality. Discharged patients with negative LUS had lower likelihood of readmissions or 30-day mortality (143,144).

Ultrasound to screen for COVID-19-related complications

COVID-19 associated coagulopathy has been described in affected patients causing venous thromboembolism, acute stroke, clotting of vascular access catheters and dialysis circuits due to a prothrombotic state and is associated with higher morbidity and mortality (17,145,146). This may be due to the interplay between vascular dysfunction, dysregulated inflammation, and immune thrombosis unique to patients with COVID-19 (147,148). In the pre-COVID-19 era, POCUS was used for detection of venous thromboembolic (VTE) events such as PE and DVT. Its use to screen for VTE increased during the pandemic (149). POCUS for diagnosis of DVT has low rates of false positive or negative results, even when performed by relatively inexperienced physicians with minimal training (17), with specificity close to 90% (150), thereby allowing the initiation of anti-coagulation without need for further formal investigations. Although ICU patients have higher incidence of DVT as described above, any patients with COVID-19 were at risk of thromboembolic events (151). Patients who were found to have thrombosis in the common femoral vein have higher mortality compared to patients without thrombosis (50% *vs.* 16%) (132). POCUS enables rapid DVT screening even in the less severely ill patients to facilitate better resource allocation.

Other than DVT, POCUS can be used to evaluate for suspected PE. Mathis *et al.* suggested an ultrasound diagnostic criterion for PE based on the size and number of subpleural consolidations (152), which are amongst COVID-19 specific sonographic signs (153,154). LUS findings for probability of PE can be divided into high (≥2 subpleural consolidations of ≥1 cm), probable (1 subpleural consolidation ≥1 cm), possible (≥2 subpleural consolidations of <1 cm) and low or unlikely (when no consolidations were detected) (150,155). Performing a multi-organ POCUS that includes LUS, focused cardiac ultrasound and compression ultrasound of the femoral and popliteal veins increases the sensitivity of detecting PE compared to single-organ POCUS. A positive multi-organ POCUS, defined as either a high PE likelihood on LUS or DVT or right ventricular strain has the highest sensitivity of 87.5% compared to single-organ POCUS findings of more than two subpleural consolidations (sensitivity 70.8%) and right ventricular strain (sensitivity 40%) alone (150,156). A two-tier scale using both Well's score and lung POCUS findings can also improve the diagnostic accuracy of PE (*Table 4*) (155). The use of POCUS in a diagnostic pathway to rule out PE in patients with COVID-19 has the potential to reduce the amount of CT pulmonary arteries, especially at the height of the pandemic in overwhelmed hospital systems.

Conclusions

Emerging infectious diseases and global pandemics are evolving public health threats that will continue to pose challenges to healthcare systems worldwide. POCUS is an indispensable, rapid and reasonably accurate point-of-care modality that can be used to aid diagnosis, management, risk stratification and prognostication in patients suspected

to have COVID-19.

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Footnote

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