Review Article

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The role of lung ultrasonography in evaluation of COVID-19 pneumonia

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ABSTRACT

After a few months it emerged in Wuhan (China), Coronavirus Disease 2019 (COVID-19) caused by 2019 novel coronavirus (2019-nCoV) was declared as a pandemic by the World Health Organization (WHO). Diagnosis of the disease is mainly based on real time polymerase chain reaction (PCR) test by nasopharyngeal swab. However, due to excess of numbers of false-negative PCR test results, chest computed tomography (CT) is commonly used as a supplementary modality. However, CT has some disadvantages. Firstly, a normal chest CT scan does not exclude the diagnosis of COVID-19 pneumonia. Additionally, the radiation exposure and a weak diagnostic value are other challenges. When the infection is limited to upper respiratory system or performed in the early stage, false-negative results may be obtained on CT scan. Recently lung ultrasonography (LUS) has emerged as a easy-to-use, cost-effective and radiation-free tool in diagnosis, management and follow-up of COVID-19 pneumonia. In this narrative review, our aim is to clarify the utility of LUS in COVID-19 pneumonia with its advantages and disadvantages. We also aimed to guide clinicians to use LUS as a practical tool.

Keywords: COVID-19, Lung ultrasonography, Pneumonia

INTRODUCTION

Following a series of pneumonia in Wuhan in December 2019, etiological agent was defined as 2019 novel coronavirus (2019-nCoV). Then, the disease spread throuhout the World and declared as a "pandemic" by the World Health Organization (WHO). The disease was named as coronavirus disease 2019 (COVID-19). The diagnosis of COVID-19 is mainly based on a combination of Real time polymerase chain reaction (PCR) test and chest computed tomography (CT). Even before the pandemic, lung ultrasonography (LUS) was being used as an accurate tool for point-of-care diagnosis of many chest conditions, particularly pneumonia, pulmonary edema and pleural effusion, in either emergency and critical care settings.

The role of Chest x-ray (CXR) is limited in COVID-19 diagnosis. Besides, thorax CT has several disadvantages even if it has a great sensitivity. Hence, recently, the role of LUS in respiratory status evaluation and decision-making is being debating by the scientific World.⁴

Today, the LUS findings of COVID-19 are well-established in the literature. B-lines, pulmonary consolidation, and a thickened pleural line may be given as examples (Figure 1).⁵

Clarifying the histopathological mechanism of COVID-19 may help understanding the LUS findings of COVID-19. The histopathology during the initial phases of COVID-19 pneumonia is characterised by diffuse alveolar damage with vascular congestion, patchy

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inflammatory cellular infiltration (B lines) and intraalveolar oedema, while interstitial thickening and patchy reparative processes show ongoing reparative process. The progressive stage of COVID-19 pneumonia manifests as gravitational consolidation, which is similar to acute respiratory distress syndrome (ARDS). Meanwhile, alveolar congestion, haemorrhagic necrosis, flaking, oedema and fibrosis may exist which is called the "white lung". Therefore, pulmonary consolidation can be graded using LUS images of patients with viral infection.6 In summary, COVID-19 patients share common LUS findings such as B-lines and shred signs. However, patients with refractory COVID-19 have more ground-glass (GGO) signs, consolidation patterns and pleural effusion. 7 Given the fact that the large difference in acoustic impedance between air and lung tissue results in the reflection of the ultrasound wave at the lung surface and consequently the loss of most ultrasound energy, LUS has a high diagnostic accuracy for interstitial syndrome and alveolar consolidation, which is superior to chest radiograph. In the literature, LUS has been recommended for the diagnosis and management of pneumonia.^{8,9} The low cost and radiation-free nature of an ultrasound examination encourages clinicians to utilize ultrasonography in the diagnosis of pulmonary diseases. 10

In this narrative review, our aim is to investigate the utility of LUS in diagnosis and prognosis in COVID-19 pneumonia in all aspects.

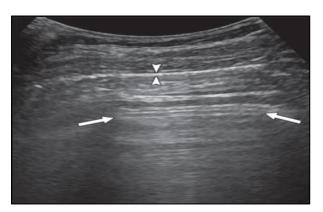


Figure 1: Pleural line is shown between arrowheads as a hyperechoic line. Arrows indicate posterior horizontal echogenic lines, which are called A-lines.⁵

METHODS

We performed a narrative review by entering keywords "COVID-19", "pneumonia", "ultrasonography" and "coronavirus" to the scientific database "Pubmed©". Following a detailed investigation regarding relevance to our review, a total of 110 publications were involved into the study. Those written in another language than English were excluded. Also, those without full-texts or an explanatory abstract were excluded. Finally, a total of 77 articles (reviews, original articles, case reports and series, correspondences and letters) were discussed in details by

two reviewers. In case of a disagreement, it was consulted with the 3rd reviewer.

LUS FINDINGS IN COVID-19 PNEUMONIA

It is well-desribed in the literature that COVID-19 causes certain patterns in LUS. The best-defined patterns are B lines (light beam patterns) which may give the lung shining "White Lung" appearance. Irregularity of the pleural line, subpleural pulmonary consolidations and poor blood flow also occur in bilateral patchy clusters, and are mainly visible in the posterior and inferior areas (Figure 2).¹¹ It is also known that, in COVID-19 pneumonia, LUS findings are predominantly located in the posterior and lateral lung zones bilaterally.¹²

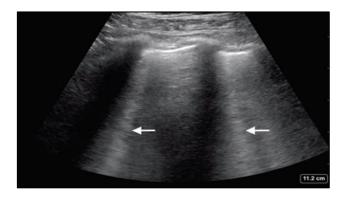


Figure 2: White arrows show B lines. B lines in COVID-19 occur in large numbers, both in separate and coalescent forms (light-beam patterns), and can give the appearance of a shining white lung. 11

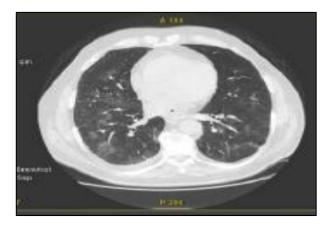


Figure 3: Bilateral and diffuse ground-glass opacity (GGO) and consolidations in multiple lobes as a typical computerized tomography finding in COVID-19 pneumonia.²⁹

Use of LUS in COVID-19 disease management is mainly based on detection of inflammatory fluid "exudate" filling in alveolar sacs in the lung that lie below the visceral pleura. The lung is composed of a honeycomb structure of alveolar sacs wherein oxygen and carbon dioxide exchange with blood flow to and from the heart occurs. Within these alveolar sacs, epithelial Type II

pneumocytes lined on the surface of the sacs, secretes surfactant that maintains the sacs open and free of extraneous debris. These cells are responsible for a specific receptor expression for Angiotensin Converting Enzyme 2 (ACE2). When the pneumocytes are infected by the virus, they produce viral RNA and immune system attacks them with cytokines. Products of the immune system begins to fill the alveoli which in turn compromises their ability for gas Exchange. These filled alveoli can be detected with LUS. If long vertical rays (B-lines) are detected, pneumonia is considered. 13 Normally, the US beam is unable to penetrate the airfilled alveoli due to acoustic reflection at the tissue air interface. When there is fluid within the alveoli secondary to infection, however, the US beam is able to be transmitted across the pleural line into the fluid and thus a B-line in the image is formed.¹⁴ Some of the sound leaks out of this cavity and returns to the US system, and with each transmit cycle additional acoustic energy is coupled into the resonance chamber. 13

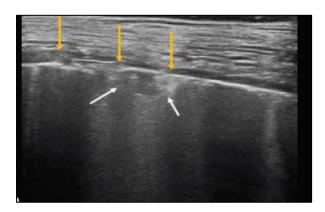


Figure 4: Yellow arrows show discontinued pleural line and white arrows show small sub-pleural consolidation.⁵²

B-lines are the most common ultrasound sign, subpleural consolidations are those that most impact the respiratory condition.^{15,16} In numerous studies, LUS findings were denoted as a discontinuous, thickened, and irregular pleural line, B-lines in a variety of patterns, including multifocal. coalescent: and consolidations (small multifocal, nontranslobar, and translobar); rarely, localized pleural effusion; and the appearance of A-lines in previously affected areas during the recovery phase. 16,17,18 B-lines are hyperechoic artifacts arising from single points along the pleural line and projecting to the bottom of the screen. They are thought to originate from locally increased tissue density which enhances reverberation from alveoli and distal airways. Three or more well-spaced B-lines (a "B-profile") are associated with interstitial syndromes. Unilateral B-lines are commonly observed in interstitial pneumonia of bacterial origin. Accordingly, unilateral consolidation also is more common in bacterial pneumonia. Sometimes septa can be seen floating in effusions, which is more typical of bacterial or fungal infection. However, in COVID-19 pneumonia, large pleural effusions occur rarely. So, when pleural effusion is present, another origin instead of COVID-19 or a superimposed infection should be considered. 19 In a report, an artefact moving rapidly with sliding, at times creating an 'on-off' effect as it appears and disappears from the screen was described and named as 'light beam'.²⁰ Millington et al. categorized LUS findings of COVID-19 in terms of probability. According to this categorization, bilateral and multifocal B-lines in posterior and inferior regions with or without small consolidations accompanied with a light beam pattern was an indicator of high probability. Unilateral B-lines accompanied with or without peripheral consolidations indicated intermediate probability. An isolated large lobar consolidation with air bronchograms, a large pleural effusion, or diffuse and very symmetrical B-lines with a gravity-related distribution indicates alternative diagnoses such as bacterial pneumonia, pleural effusion, and cardiogenic pulmonary edema, etc. These findings are indicators of alternate LUS pattern which is between intermediate and low probability LUS patterns. In low probability, a generalized bilateral A-line pattern with lung sliding may be observed. This may be seen in pulmonary embolism and physician must keep it in mind that pulmonary embolism may also be associated with an existing COVID-19 and absence of LUS findings of COVID-19 does not exclude COVID-19.21

In summary, fused multifocal B-lines under the pleura, thickening and edema in affected tissues, interruption of pleural line, patchy-strip-nodular consolidation involving a bronchogram, insufficient blood supply in color Doppler ultrasound may be observed in COVID-19 pneumonia.²²

ADVANTAGES OF LUS IN COVID-19 PNEUMONIA

In the early stages of COVID-19 pneumonia, X-ray is usually normal.²³ It is known that LUS was more sensitive in detecting B-lines in lower lung fields.^{24,25}

It was also reported that LUS had a similar diagnostic accuracy in COVID-19 pneumonia when compared to cest CT.²⁶ Moreover, it was reported that LUS might detect lesions that do not appear in CT.^{27,28}

Some radiologists do not recommend CT as a primary diagnostic tool in COVID-19 pneumonia and do not include CT in diagnostic criteriae. At the same time, CT plays an essential role in anticipation of mild invasive ventilation in COVID-19 patients. Most common CT findings are bilateral GGOs in posterior and peripheral lungs and consolidation (figure 3).²⁹ At the other hand, some recommend routine use of chest computed tomography in case of COVID-19 suspicion due to high rate of false-negative results obtained in RT-PCR performed by nasopharyngeal swab.³⁰

Recently, LUS is being widely used by clinicians for pneumonia diagnosis with sensitivity and specificity of 92% and 93%, respectively. As the pandemic emerged, LUS has become the first-line radiological tool in patients with suspected pneumonia.³¹

In a study by Fonsi et al., LUS had good reliability in terms of sensitivity, specificity, positive predictive value, and negative predictive value.³² LUS provides early triage in the Emergency Department. It is a useful, rapid and safe tool in COVID-19 pneumonia diagnosis due to its high sensitivity and negative predictive value, It also prevents invasive, cost-intensive, and time-consuming tests.^{33,34} LUS is also adventageous with its radiation-free, flexible and cost-effective nature. Since it is performed at bed-side, it reduces nasocomial transmission and provides a better patient cooperation.^{16,35} Patients movement is restricted in an isolated room and radiation exposure to healthcare staff is limited.¹³

For performing LUS, fewer people are required. When compared to CT, there is less equipment to clean. LUS may also be used in children, pregnant women and unstable patients, safely. ^{28,36}

LUS with portable and pocket devices allows to save sources and time since it may be performed in ED, ICU an deven at home of the patients. It has advantage of reproducibility that allows appropriate triage and determination of disease severity via line artefacts. 37,38 When performed by ED physicians, prognosis may be determined by LUS. In the ED, ICU admission may be predicted by LUS.3 LUS findings correlate with disease severity and those who require hospitalization may be discriminated in the ED.³⁹ Patients with ARDS may be observed with LUS in terms of progression and need for X-ray and CT may be reduced.⁴⁰ LUS plays an important role in monitoring patients for improvement or deterioration.²¹ Scoring systems based on LUS findings help determine need for invasive mechanical ventilation and predict mortality.41 Pulmonary pathologies and progression of mechanical ventilation may be detected bedside. Complications like pleural effusion, pneumothorax, and atelectasis may be monitored.⁴² With LUS, residual damage may be determined in patients who meet discharge criteria. 43 A complete normalization of lung is obtained in LUS 5 weeks following discharge.⁴⁴

When anterior region of the lung is affected, the risk for requiring noninvasive respiratory support (NIRS) increases. Hence, LUS may predict patients more likely to need NIRS.⁴⁵

In a study, patients with verified COVID-19 disease hospitalized at the ICU and treated with ventilator and extracorporal membrane oxygenation (ECMO) were evaluated with LUS for pulmonary changes and the authors concluded that LUS might be used as a primary imaging modality for pulmonary assessment reducing the use of chest X-ray in COVID-19 patients treated with

ventilator and ECMO.⁴⁶ Identification of different lung morphologies early after the start of invasive ventilation and decision on adjunctive therapies are possible with LUS. Depending on LUS findings, early after initiation of invasive ventilation, invasive ventilation can be planned.⁴⁷

It is clear that diagnosis and follow-up of consolidations, atelectasis, interstitial and alveolar edema, pneumothorax, and pleural effusion can be evaluated by LUS. Numerous protocols were recommended for this purpose. The first and the most popular one is BLUE protocol. The BLUE protocol evaluates six areas in each hemithorax There are numerous pleuropulmonary disorders. protocols in the literature for different thoracic regions. The anterosuperior and anteroinferior regions are evaluated on the anterior surface of the thorax (limited by the anterior parasternal and anterior axillary lines). The upper and lower lateral regions are evaluated on the lateral surface (limited by the anterior axillary and posterior axillary lines). Finally, the posterosuperior and posteroinferior regions are evaluated on the posterior surface (posterior to the posterior axillary line. Some protocols evaluate 14 areas (two anterior, two lateral and three posterior areas in each hemithorax) and constitute a scoring system based on findings.⁴⁸ It was reported that scoring systems based on B-line were correlated with oxygen parameters, and thus, LUS can be used for COVID-19 pneumonia severity estimation.⁴⁹ determine disease severity, a scoring system to avoid subjectivity and the operator-dependence of the exam was suggested by Soldati et al. According to this system, normal LUS pattern characterized by regular pleural line and A-lines is score 0 vertical artifacts are described. The pleural line appears indented with several B-lines is score 1. A broken pleural line with dark and white consolidation areas are score 2 and large regions of white lung is score 3.50,51

In some cases, COVID-19 diagnosis is made by bronchoalveolar lavage fluid in patients with negative nasopharyngeal swab. Persistently negative nasopharyngeal swab is explained by low viral load but it is known that viral particles have been isolated in BAL. In those cases, LUS also may be utilized for bronchoalveolar lavage fluid collection (Figure 4).⁵²

LUS may also be used for COVID-19 pneumonia diagnosis in children. Similar pathologies such as bilateral findings including pleural line irregularities such (fragmentation and small subpleural consolidations), scattered and coalescing B-lines, consolidations with air bronchograms, and pleural effusions were identified in children with COVID-19 pneumonia.⁵³

Another advantage of LUS is that it can be learnt via online conferences (webinars). This form of education may be successfully applied in the teaching and learning of lung ultrasound techniques.⁵⁴ Moreover, Pivetta et al. reported that a patient self-performed lung ultrasound in

the home with a hand-held device under the guidance of a physician using a novel teleguidance platform is also possible. Maximum isolation, thus, can be obtained.⁵⁵

PREVENTION AND PROTECTIVE CLOTHING

LUS should be performed in an understanding that prioritize both clinical utility and decreased nasocomial disease spread.¹²

According to Centers for Disease Control and Prevention (CDC), N95 masks are only recommended in aerosol-generating interventions (intubation, bronchoscopy, etc.). Hence, during LUS, surgical masks are enough as personal equipment.²² In the isolation room, transducers may be placed inside sterile sheaths, and US machines may be dressed in sterile covers to perform each examination in order to prevent virus transmission. When the examination ends, machines and transducers were sterilized in a designated isolation room and were placed into new sterile covers.⁵⁶

CHALLENGES IN LUS EXAMINATION

On the other hand, LUS also has some disadvantages. An accurate LUS performing requires training and a detailed LUS examination may be time consuming. Prolonged examnination time may result in more exposure of the clinician to the virus at the bedside.⁵⁷ Although LUS may support physical examination, a nasopharyngeal swab should be required most of the time.⁵⁸ Particularly in the pediatric group, but also in adults, there is a lack of adequate data on usefulness of LUS in the literature.59 It was reported that LUS had limited clinical use in identifying consolidations.49 With LUS, only the pathologies near the pleural surface can be observed. It is difficult to detect deep and intrapulmonary lesions and posterobasal regions. Hence, it is difficult to assess "White Lung" which is a prominent finding of COVID-19.60,61 Some pathologies attributed to COVID-19 pneumonia such as to pulmonary congestion, ARDS and B-lines may also be determined in heart failure, nephrotic syndrome, pneumonia, minimal pleural effusion, hydropneumothorax, fibrosis, emphysema, exacerbations of chronic obstructive pulmonary diseases, and lymphangitis. Also, B-lines may be visible in healthy subjects. LUS was reported to be a safe tool only when pleural effusion is present, however, pleural effusion is a rare finding of COVID-19 pneumonia. It was also reported that LUS may cause virus spread more than expected. 62,63 In the presence of cavitations, LUS may induce tissue damage. Air pockets in lung tissue can oscillate with the pressure changes of the oscillating acoustic pulse and enter cavitation. Such a complication has not been yet but animal studies revealed that capillary hemorrhage at diagnostic frequencies is possible.⁶⁴ Besides, it should be kept in mind that LUS is highly dependent to performer and can only determine pathologies on peripheral sites. 65 LUS sensitivity is strongly linked to swab testing.66 A study has shown that lesions (as well as the worst ones) in COVID-19 pneumonia are posteriorly and laterally located and LUS is inadequate in detecting these regions.⁶⁷ There is a lack of knowledge regarding regarding the optimal technique, the number and topography of areas that must be detected and patient positioning.⁶⁸ In order to obtain a higher sensitivity and specificity, experienced operators are required.⁶⁹ The operator should be aware of sonographic patterns of COVID-19 and other pathologies that manifest the same changes.²⁸ Even though LUS score correlates with survival, oxygenation, ventilation, and IL-6, compliance was not found to correlate with the degree of abnormalities found in LUS.⁷⁰

Even though diffused B-line is commonly detected in COVID-19 pneumonia, it must be kept in mind that different viral pneumonias have similar sonographic features.⁷¹

CONCLUSION

Evaluation of patients with COVID-19 is important in many aspects. LUS not only evaluates findings of pneumonia but also cardiac function, diaphragm function and thrombotic tendency due to COVID-19 pneumonia. Even though CT is the widely accepted "gold standart" imaging tool in COVID-19, there are some concerns about CT regarding virus spread inducement. With its advantages (ease of use at point of care, repeatability, absence of radiation exposure, and low cost), LUS is known to be superior to Chest X-ray. Recent studies have shown that it may also be as useful as CT. Currently, it is reasonable to consider CT and LUS as complementary tools rather than competetive tools. They seperately answer various clinical questions. While CT scan offers a better and comprehensive view of the lung and can also help identify complications such as infarction, embolism, emphysema; therefore, CT scanning is always helpful in case of sudden worsening of clinical conditions or for an initial assessment of moderate to severe patients if feasible in the setting where the patient is evaluated, LUS can be used as a first level exam during the first evaluation in the emergency department or even at home to distinguish lowrisk from high-risk patients, as these would need second level exams or admission/discharge. Efforts to determine a standardized approach that various specialists can perform still continue.51 With appropriate protection measures, number of LUS in COVID-19 pneumonia is rising. Many operators could apply the technique with the help of on on-line e-learning sources.

As a summary, there are 3 main fields of use of LUS in COVID-19 at the moment: primary screening and diagnosis of lung involvement in patients presenting at the emergency room with a suspicion of COVID-19, daily routine, or as occasion requires (such as deterioration of oxygen saturation), and monitoring of patients hospitalized in general wards, and daily and regular monitoring of patients (with or without

mechanical ventilation) in the intensive care unit. Portable devices for LUS to determine both the disease and its severity seems to gain importance in the near future. These devices may also be used for evaluation of the patients from a distance without hospitalization. We conclude that, even though it has disadvantages when compared to CT, LUS is a promising diagnostic tool for COVID-19 pneumonia. When performed by experienced staff, it may also be used for prognosis prediction.

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