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Lung ultrasound in COVID-19 pneumonia: correlations with chest CT at hospital admission

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Short title: Ultrasound-CT correlation in COVID-19

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ABSTRACT

Background- Lung ultrasound (LUS) is an accurate, safe and cheap tool assisting the diagnosis of several acute respiratory diseases. The diagnostic value of LUS in the workup of coronavirus disease-19 (COVID-19) in the hospital setting is still uncertain.

Objectives- The aim of this observational study was to explore correlations of the LUS appearance of COVID-19-related pneumonia with CT findings.

Methods- Twenty-six patients (14 M, age 64 ± 16) urgently hospitalized for COVID-19 pneumonia, who underwent chest CT and bedside LUS on the day of admission, were enrolled in this observational study. CT images were reviewed by expert chest radiologists, who calculated a visual CT score based on extension and distribution of ground-glass opacities and consolidations. LUS was performed by clinicians with certified competency in thoracic ultrasonography, blind of CT findings, following a systematic approach recommended by ultrasound guidelines. LUS Score was calculated according to presence, distribution and severity of abnormalities.

Results- All participants had CT findings suggestive of bilateral COVID-19 pneumonia, with an average visual scoring of $43\pm 24\%$. LUS identified four different possible abnormalities, with bilateral distribution (average LUS score 15 ± 5): focal areas of non-confluent B-lines, diffuse confluent B-lines, small subpleural microconsolidations with pleural line irregularities, large parenchymal consolidations with air bronchograms. LUS score was significantly correlated with CT visual scoring ($r=0.65$, $p<0.001$), and oxygen saturation in room air ($r=-0.66$, $p<0.001$).

Conclusion- When integrated with clinical data, LUS could represent a valid diagnostic aid in patients with suspect COVID-19 pneumonia, reflecting CT findings.

INTRODUCTION

Thoracic imaging, either with chest X-ray (CXR) or computed tomography (CT), is an essential part of the diagnostic route of Coronavirus Disease 19 (COVID-19) in patients admitted to hospital with fever or respiratory symptoms [1]. Ground-glass opacities (GGO), local or bilateral patchy shadowing and interstitial abnormalities are the most common alterations described in CXRs and CTs [1].

The sensitivity of CT for diagnosing COVID-19 pneumonia is 97%, when considering the results of reverse-transcription polymerase-chain reaction (RT-PCR) tests as gold standard [2]. Despite potential lack of specificity of the COVID-19 pneumonia-related CT findings, the specific epidemic contingency makes CT an accurate tool to stratify patients based on imaging patterns [2-5], predicting poor outcomes and the need for ventilation [6]. However, the use of CT scanning in the context of COVID-19 pandemic strictly relies on the local resources and expertise.

Bedside lung ultrasound (LUS) is a widely available diagnostic tool, complementary to physical examination, that can provide a large amount of diagnostic information in several respiratory diseases and settings [7]. In the hands of experienced clinicians, LUS diagnostic accuracy for bacterial pneumonia is similar to chest CT [8, 9]. The advantages of LUS are more obvious in older patients with multimorbidity and mobility-limitations, for whom high-quality CXR and CT scans are difficult to obtain [9].

Recently, it has been suggested that point-of-care LUS can be useful for both diagnosing and monitoring COVID-19 patients [10, 11]. COVID-19 pneumonia-related pulmonary abnormalities are often located in the subpleural regions of the lung, thus increasing the likelihood of insonation during ultrasound examinations. As reported by small case-series studies, COVID-19 pneumonia can be associated with multifocal B-lines, bilateral subpleural consolidations and pleural thickening [12-14], reflecting abnormalities detectable on chest CT [14]. However, correlation between LUS

and CT findings in patients urgently hospitalized for severe COVID-19 pneumonia is still uncertain [10].

The primary aim of this observational study was to describe LUS patterns in a group of patients with severe COVID-19 pneumonia admitted to an acute-care hospital, and to explore correlations of these findings with both chest CT and clinical features.

METHODS

Study design, population and setting

The study population included patients admitted to the Internal Medicine and Critical Subacute Care Unit of Parma University-Hospital, Italy for suspect COVID-19 pneumonia in March 2020. Only patients who underwent both chest CT and bedside LUS within 24 hours from ward admission were included. Critical conditions, requiring intensive care support at the moment of admission, and presence of severe cardio-respiratory illness other than COVID-19 were considered as exclusion criteria.

The study protocol was approved by the Ethics Committee of Area Vasta Emilia Nord, Emilia-Romagna Region, under the ID 235/2020/OSS/AOUPR. Due to retrospective design of the study, informed consent signature was waived, in compliance with Italian law.

CT technique

All patients included in the study underwent high-resolution CT (HRCT) immediately before ward admission, as part of the Emergency Department evaluation route of suspect COVID-19 cases set at Parma University-Hospital [15].

HRCTs were performed with either a 128-row scanner (SOMATOM Definition Edge, Siemens Healthineers, Erlangen, Germany) or a 16-row scanner (SOMATOM Emotion, Siemens Healthineers, Erlangen, Germany). All HRCT scans were performed in supine position at end inspiration, without intravenous administration of contrast media. The acquisition parameters were set at range 100-140 kVp on the 128-row scanner (automatic selection of tube voltage by CareKv, Siemens Healthineers) and fixed 110 kVp on the 16-row scanner, 80 reference mAs, pitch 1.0–1.5, and collimation 0.625–1.0 mm. Reconstruction parameters for lung images: slice thickness 1.0 mm, increment 0.7-1.0 mm, sharp reconstruction algorithm (B157 or B70s, respectively), lung window (width, 1600 HU; level, –600 HU). Reconstruction parameters for mediastinal images: slice

thickness 2.0 mm, increment 1.5 mm, medium reconstruction algorithm (Br36 or B31s, respectively), mediastinal window (width, 400 HU; level, 30 HU). Images were reconstructed by Advanced Modeled iterative reconstruction (ADMIRE) strength 3 on the 128-row scanner, filtered back projection (FBP) on 16-row scanner.

Visual scoring of CT images

A chest radiologist with 17 years of experience in chest imaging retrospectively reviewed the HRCT scans, defining presence and extent of thoracic abnormalities. Notably, extent of GGO and consolidation was visually scored at the nearest 5% on the whole lungs. The distribution was described as follows: a) axial distribution: predominantly peripheral (within the outer third of the lung), predominantly central, or mixed; b) cranio-caudal distribution: predominantly upper (above the carina), middle (between the carina and the right inferior pulmonary vein) or lower (below the inferior pulmonary vein) [16]; c) bilateral or unilateral involvement; d) lobar involvement was accounted over 6 lobes (lingula considered as a single lobe). Description of the pattern was tabulated into the various HRCT categories of our local COVID-19 protocol [17].

CT images were also classified according to the COVID-19 Reporting and Data System (CO-RADS) score, which is based on the level of suspicion of pulmonary involvement in SARS-CoV-infection [18].

Ultrasound procedures and analysis of images

Within 24 hours from ward admission and CT scanning, bedside LUS was performed, as part of routine diagnostic evaluation adopted in our medical unit even before the emergence of COVID-19 outbreak, by an ultrasound-certified expert clinician with more than five years of experience in lung ultrasonography, who was blind of chest CT findings. LUS was performed as a complement to physical examination and integrated with it, and operators wore adequate personal protective

equipment. A portable ultrasound system (Esaote MyLab Alpha™, Esaote, Genova, Italy) with convex 3.5-5 MHz and linear 4-8 MHz probes, dedicated to COVID-19 patients, was used. Covers for probes and ultrasound machine console were used during examinations.

Examinations were performed in compliance with expert recommendations [19], with the patient in sitting position, systematically scanning the front and the back side of each hemithorax. Convex probe was first used to provide a panoramic view of pleural line and ultrasound artifacts associated with lung parenchyma status (A-lines, comet-tail artifacts such as B-lines, consolidations). Linear probe was then used for a more detailed study of pleural line appearance and subpleural abnormalities.

Each hemithorax was split into anterior-lateral sectors and posterior sectors, and each sector was then divided into upper and lower halves using the third intercostal space as reference, as to obtain four areas for each hemithorax, according to our previously published research [20]. Images were saved on the ultrasound software and reviewed by operators after the exam, to avoid unnecessary prolonged contact with patients. The presence, site and distribution of abnormalities, such as B-lines, pleural line thickening or break, consolidations and air bronchograms, was detected.

Abnormal findings in each scan were also graded according to the scoring system (Lung Ultrasound Score) proposed by Soldati et al (0=regular pleural line, A-lines present; 1=indented pleural line, focal B-lines; 2=broken pleural line, subpleural consolidations; 3=white lung with or without consolidations) [11].

Clinical data

Clinical information of each patient, including vital signs and oxygen saturation in room air at the moment of ward admission, SARS-CoV-2 testing, timing of symptom onset and main comorbidities, was also collected from each clinical record.

Statistical analyses

Data were analyzed with Stata v.16 (StataCorp LLC, College Station, Texas, US). Data were expressed as percentages or mean \pm standard deviation. The correlation of Lung Ultrasound Score with CT visual score and oxygen saturation in room air was calculated with Spearman correlation index. Abnormalities detectable on HRCT were grouped into two categories, namely a first group showing either consolidations or diffuse GGO and a second group where only patchy GGO could be detected. Comparison tests were used for continuous variables as appropriate: Student t test for independent variables, or Mann-Whitney U test.

RESULTS

Twenty-six patients (14 M, 12 F; mean age 64 ± 16), were included in the study. The most frequent symptoms of presentation were fever (96% of cases), cough (81%) and dyspnea (38%). At admission, the duration of symptoms was on average 7 ± 3 days. Seventeen patients (65%) required oxygen support, including eight (31%) with high-flows (≥ 15 L/minute). Twenty-two patients tested positive for SARS-CoV-2 RT-PCR at admission. The remaining four patients had COVID-19 diagnosis confirmed with RT-PCR testing later during hospital stay. Baseline clinical features of patients are summarized in Table 1.

Twenty-one patients had CT findings typical of COVID-19 pneumonia (CO-RADS score 5), while five patients had equivocal findings for pulmonary involvement of COVID-19 (CO-RADS score 3). The extension of parenchymal involvement, measured by visual scoring, was in average $43\pm 24\%$. Bilateral involvement was detected in 100% of cases, with abnormal findings involving all six pulmonary lobes in 88% of cases. GGO, subpleural lines, fat vessel sign and crazy paving pattern were the most frequent abnormalities (Table 2).

LUS showed bilateral abnormalities in all patients, with an average Lung Ultrasound Score of 15 ± 5 . Diffuse B-lines, focal B-lines with spared areas, interstitial involvement with multiple subpleural microconsolidations were the most frequently detected patterns (Table 2, Figure 1). In 50% of cases, larger consolidations were also detected, and dynamic air bronchogram sign could also be documented in two cases. Pleural effusion of mild severity could be detected in only one patient, while all other examinations revealed no pleural effusion.

The Lung Ultrasound Score showed a significant positive correlation with CT visual score ($r=0.65$, $p<0.001$) (Figure 2a) and a negative correlation with oxygen saturation at admission ($r=-0.66$, $p<0.001$). No significant correlation could be found between lung ultrasound score and duration of symptoms before assessment.

After stratification of Lung Ultrasound Scores in two groups, namely above and below average, the former showed higher extent of HRCT abnormalities, as compared to individuals whose Lung Ultrasound Scores were below average value ($p=0.016$) (Figure 2b).

Patients with HRCT depicting either consolidation or diffuse GGO showed higher Lung Ultrasound Scores as compared to those individuals with HRCTs showing only patchy GGO abnormalities ($p=0.005$) (Figure 2c).

Nine patients out of twenty-six (34%) died during hospital stay. Compared with survivors, they were older (age 75 ± 8 vs 57 ± 15 , $p=0.003$), had higher baseline visual CT scores ($57\pm 26\%$ vs $35\pm 19\%$, $p=0.02$), but their Lung Ultrasound Score was not different than that of survivors (16 ± 5 vs 15 ± 6 , $p=0.71$).

DISCUSSION

At hospital admission, COVID-19-related alveolar-interstitial pneumonia was associated with lung ultrasound abnormalities reflecting chest CT alterations. The most frequent ultrasound presentation were focal areas of interstitial syndrome (either non-confluent or confluent B-lines) with possible presence of small, multiple subpleural consolidations and indentation of pleural line. In some cases, overt consolidations with air bronchograms could be detected, while pleural effusion was present in only few cases. The Lung Ultrasound Score, calculated according to type, extension and severity of ultrasound abnormalities, showed a statistically significant correlation with analogue CT severity score and oxygen saturation in room air.

These findings are coherent with expert opinions and case-series previously published in the literature [10-15]. However, the significant correlation between ultrasound and CT scores allows to make a step forward in defining a role for LUS in the clinical management of COVID-19 pneumonia. In patients urgently admitted with respiratory symptoms and fever, the integration of clinical and anamnestic data with LUS findings could represent an important aid for diagnosis of COVID-19 and for addressing patients to the most appropriated care path, especially in situations where CT diagnostics is not immediately available.

Soldati et al. recently suggested the use of LUS for triaging patients with symptoms compatible with pneumonia in the pre-hospital setting or at the moment of first Emergency Department (ED) evaluation [11]. This application of LUS could be particularly useful considering that, during the pandemic peak, many COVID-19 patients, especially if older and multimorbid, may have atypical clinical presentation and no evident history of contact with individuals who tested positive for SARS-CoV-2 [21-22]. Recent data also suggest that early LUS evaluation of patients with respiratory symptoms in ED can result in significant changes in patient management [23], and this could be particularly useful in the COVID-19 pandemic, where misdiagnoses may have relevant consequences in terms of infection spread. The use of ultraportable handheld devices could be of

particular interest in this emergency setting, as recently demonstrated for interventional applications [24]. The correlation between Lung Ultrasound Score and CT visual score in COVID-19 supports the implementation of this technique and the design of larger, prospective studies evaluating the outcomes of LUS in different settings of COVID-19 care.

The ultrasound imaging findings of COVID-19 pneumonia are similar to those previously described in cases of viral pneumonia of different etiology, including H1N1 and H7N9 influenza viruses [25-30]. In that situations, lung ultrasound was effectively used for diagnosing Acute Respiratory Distress Syndrome (ARDS), for monitoring response to intensive care treatments and for detecting bacterial superinfections [25-30]. Such applications could be useful also in the context of COVID-19 pneumonia [10, 11], and should be carefully evaluated in future studies. Notably, we observed higher Lung Ultrasound Scores in patients with consolidation or diffuse GGO abnormalities detectable on HRCT, as compared to individuals showing patchy GGO.

Despite the findings of our study support the use of bedside LUS in the evaluation of patients with suspect COVID-19, ultrasound should not be considered a substitute for chest CT for several reasons. First, the correlation between the severity of ultrasound abnormalities and CT visual score was suboptimal, albeit statistically significant. This suggests that ultrasound may be less accurate than CT for stratification of severity of lung involvement in COVID-19. Moreover, the false negative and false positive rates of LUS findings in COVID-19 pneumonia is still uncertain in comparison with CT. The interobserver agreement of LUS is also uncertain in COVID-19 pneumonia, albeit it was demonstrated as good to excellent in several other respiratory diseases [31-32]. The limited availability of ultrasound equipment dedicated to isolated patients may also be an important barrier for the use of this technique in the context of COVID-19 patients [33].

We must also acknowledge that the ultrasonographic signs of COVID-19 pneumonia can be present in other respiratory and cardiovascular diseases, including pulmonary fibrosis and congestive heart failure [34, 35]. Confluent or non-confluent B-lines with pleural line thickening and subpleural

nodules are the key abnormalities associated with idiopathic or secondary pulmonary fibrosis [34, 36]. Diffuse B-lines also represent a well-known index of pulmonary congestion usually responding to diuretic treatment [35, 37]. The integration of the clinical and epidemiological context with ultrasound findings is therefore necessary for the differential diagnosis between COVID-19 pneumonia and other conditions with similar ultrasonographic appearance. The detection of pleural effusion, which is rare in COVID-19 (less than 6% of cases according to a recent meta-analysis of CT findings [38]) and very frequent in congestive heart failure, may represent an important element for the formulation of a correct diagnosis.

From this perspective, LUS represents a technologic complement of physical examination orienting the diagnostic suspect in patients with a clinical history compatible with COVID-19 pneumonia [10, 11]. This is the framework in which LUS examinations were performed in the present study. LUS should therefore be considered as a guide, and not a substitute, for the prescription of more consolidated diagnostic techniques, such as CXR and CT. It is also noteworthy that neither LUS nor traditional imaging can be able to detect SARS-CoV-2 infection when pulmonary involvement is not present [39]. Similarly, none of these diagnostic techniques can help to distinguish viral pneumonia caused by other respiratory viruses from COVID-19 pneumonia [39]. Thus, integration of imaging with clinical and anamnestic data is always mandatory to reach a correct diagnosis even in the context of a pandemic [39]. LUS could also represent a promising tool for monitoring the evolution of pulmonary involvement of COVID-19 after baseline traditional imaging (CXR or CT). Some limitations of our study should be considered. The small sample size and absence of prospective evaluation of LUS during the clinical course of COVID-19 pneumonia are the most obvious ones. LUS may in fact be very useful for monitoring the evolution of pulmonary lesions with treatments [11]. Recent data also suggest that CT findings are able to predict adverse outcomes in COVID-19 pneumonia [6]. The small size of the present study population prevented to explore whether the extension and severity of abnormal LUS findings can provide some prognostic

information in COVID-19 pneumonia. Finally, the ultrasound evaluation was not performed exactly at the same time of HRCT, albeit during the same day, generating a possible bias in the correlation of the two imaging techniques.

However, this study represents one of the first clear demonstrations that a significant correlation between chest CT and LUS exists in COVID-19 pneumonia, supporting the use of LUS for an early detection and clinical management of this disease. Future studies should clarify the impact of LUS implementation in the clinical management of COVID-19 in different settings, including community care, Emergency Department triage, Intensive Care Units and follow-up of recovering patients.

CONCLUSIONS

In patients urgently hospitalized for suspect COVID-19 pneumonia, LUS is associated with recognizable patterns, including focal areas of confluent or non-confluent B-lines, multiple bilateral subpleural consolidations and indentation of pleural lines. These abnormalities reflect chest CT findings and their severity correlates with chest CT visual score in a positive way. When integrated with clinical data, LUS represents a safe and effective diagnostic technique with great potential for improving diagnosis and management of COVID-19 pneumonia in hospital and community settings.

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Statement of Ethics

The study protocol was approved by the Ethics Committee of Area Vasta Emilia Nord, Emilia-Romagna Region, under the ID 235/2020/OSS/AOUPR. Due to retrospective design of the study, informed consent signature was waived, in compliance with Italian law. The study was conducted in accordance with the Declaration of Helsinki.

Disclosure statement

The authors have no conflict of interest to declare.

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Author contribution

A.N., N.S., T.M. and A.T. designed the study. A.N., M.D.Z., G.M. and A.P. conducted the study and collected data. A.T., G.M. and A.O. analyzed the data. M.B., E.G.B. and T.M. gave support in the conduction of the study and revised the manuscript for important intellectual content. A.T. drafted the manuscript.

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TABLE 1

Overview of baseline demographic and clinical characteristics of patients with suspect COVID-19 who underwent both CT and lung ultrasound testing at hospital admission.

Males, n (%)	14 (54)
Age, years	64±16
Fever, n (%)	25 (96)
Cough, n (%)	21 (81)
Dyspnea, n (%)	10 (38)
Symptom duration before assessment, days	7±3
Oxygen saturation in room air, %	94±5
Need for oxygen therapy, n (%)	17 (65)
No comorbidities, n (%)	7 (27)
Comorbidities, number	1.5±1.3
Chronic respiratory diseases prevalence, %	3 (12)

TABLE 2

Overview of the main chest CT and ultrasound findings of 26 patients admitted with suspect COVID-19 who performed both examinations within a 24-hour time frame at hospital admission.

CT findings	
Bilateral involvement, n (%)	26 (100)
Mixed axial distribution, n (%)	21 (81)
Involvement of six pulmonary lobes, n (%)	23 (88)
Predominance of basal, medial or apical lobe involvement, n (%)	6 (23)
Ground-glass opacities, n (%)	26 (100)
Subpleural lines, n (%)	13 (50)
Fat vessel sign, n (%)	15 (58)
Crazy paving sign, n (%)	4 (15)
Basal consolidations, n (%)	2 (8)
Centrolobular nodules, n (%)	1 (4)
Pleural effusion, n (%)	1 (4)
Lymphadenopathy, n (%)	2 (8)
CT visual score, %	43±24%
Ultrasound findings	
Bilateral involvement, n (%)	26 (100)
Predominance of basal, medial or apical lobe involvement, n (%)	3 (12)
Pattern of areas of alveolar-interstitial syndrome with distinct B-lines, n (%)	7 (27)
Pattern of areas of alveolar-interstitial syndrome with confluent B-lines (white lung), n (%)	17 (73)
Subpleural consolidations, n (%)	17 (73)
Parenchymal consolidations, n (%)	13 (50)
Lung Ultrasound Score	15±5

FIGURE LEGENDS

Figure 1- Appearance of COVID-19-related alveolar-interstitial pneumonia at bedside lung ultrasound. A) Non-confluent B-lines (comet-tail artifacts) with spared areas of normal lung parenchyma showing A-lines (horizontal artifacts). B) Confluent B-lines with “white lung” pattern and spared areas of normal lung parenchyma showing A-lines. C) Diffuse, non-confluent B-lines reflecting homogeneous interstitial involvement of lung parenchyma. D) Subpleural microconsolidations with indentation of pleural line, associated with a non-confluent focal B-line pattern. E) Overt subpleural consolidation with air bronchograms. F) Spared area showing A-lines corresponding to a region of normally ventilated lung parenchyma without alveolar-interstitial involvement.

Figure 2- Spearman correlation between Lung Ultrasound Score and CT visual scoring (panel A). The CT visual score was significantly different ($p=0.016$) between patients with Lung Ultrasound Score below and above the median value (panel B). The Lung Ultrasound Score was also significantly different ($p=0.005$) in patients who exhibited consolidation and/or diffuse GGO at chest CT vs those who had a patchy GGO pattern (panel C).