Lung ultrasound in ruling out COVID-19 pneumonia in the ED: a multicentre prospective sensitivity study

Carmine Cristiano Di Gioia, Nicola Artusi, Giovanni Xotta, Marco Bonsano, Ugo Giulio Sisto, Marzia Tecchiolli, Daniele Orso, Franco Cominotto, Giulia Amore, Stefano Meduri, Roberto Copetti

ABSTRACT

Purpose Early diagnosis of COVID-19 has a crucial role in confining the spread among the population. Lung ultrasound (LUS) was included in the diagnostic pathway for its high sensitivity, low costs, non-invasiveness and safety. We aimed to test the sensitivity of LUS to rule out COVID-19 pneumonia (COVIDp) in a population of patients with suggestive symptoms.

Methods Multicentre prospective observational study in three EDs in Northeastern Italy during the first COVID-19 outbreak. A convenience sample of 235 patients admitted to the ED for symptoms suggestive of COVIDp were tested for COVIDp using standard constituted by: clinical gestalt, real-time PCR test, radiological and blood gas results. Of the 235 enrolled patients, 90 were diagnosed with COVIDp (fever, cough or shortness of breath) from 17 March 2020 to 26 April 2020 was enrolled. All patients underwent a sequential assessment involving: clinical examination, LUS, CXR, and arterial blood gas. The index test under investigation was a standardised protocol of LUS compared with a pragmatic composite reference standard constituted by: clinical gestalt, real-time PCR test, radiological and blood gas results. Of the 235 enrolled patients, 90 were diagnosed with COVIDp according to the reference standard.

Results Among the patients with suspected COVIDp, the prevalence of SARS-CoV-2 was 38.3%. The sensitivity of LUS for diagnosing COVIDp was 85.6% (95% CI 76.6% to 92.1%); the specificity was 91.7% (95% CI 86.0% to 95.7%). The positive predictive value and the negative predictive value were 86.5% (95% CI 78.8% to 91.7%) and 91.1% (95% CI 86.1% to 94.4%) respectively. The diagnostic accuracy of LUS for COVIDp was 89.4% (95% CI 84.7% to 93.0%). The positive likelihood ratio was 10.3 (95% CI 6.0 to 17.9), and the negative likelihood ratio was 0.16 (95% CI 0.1 to 0.3).

Conclusion In a population with high SARS-CoV-2 prevalence, LUS has a high sensitivity (and negative predictive value) enough to rule out COVIDp in patients with suggestive symptoms. The role of LUS in diagnosing patients with COVIDp is perhaps even more promising. Nevertheless, further research with adequately powered studies is needed.

Trial registration number NCT04370275.

INTRODUCTION

An early diagnosis plays a crucial role in identifying infectious patients to contain the pandemic’s spread and appropriately cohort patients in medical settings. In this context, the ED represents the first assessment point for potentially infected patients. Real-time PCR (RT-PCR) tests to detect SARS-CoV-2 RNA are the operational gold standard for detecting COVID-19 disease in clinical practice. RT-PCR performed on lower respiratory specimens (bronchial aspirate and bronchoalveolar fluid) represents the test with the highest reported diagnostic accuracy (93%) but not routinely performed in the ED setting. A more suitable and practical strategy to sample biological material is through a nasopharyngeal mucosal layer swab (NPS). While highly specific, the sensitivity RT-PCR by NPS ranges between 60% and 97%, depending on the study. A meta-analysis of diagnostic test accuracy studies reported the pooled sensitivity of RT-PCR to be 87.8% and specificity in the range of 87.7%–100%. For the newest tests, the sensitivity ranges from 70% to 85%, and the specificity ranges from 95% to 99%. SARS-CoV-2 testing through RT-PCR on NPA swab samples is logistically practical, but results are not immediate, and it does not provide information regarding the severity of disease in the tested population.

Therefore, further clinical assessment and diagnostic workup are required to identify those infected patients developing COVID-19 pneumonia (COVIDp). The thoracic high-resolution CT scan is a useful diagnostic tool in assessing patients with confirmed SARS-CoV-2 or high pretest probability and worsening respiratory compromise. However, it is not practical as a screening tool due to its high
Clinical ASUGI unit (ICU). Therefore, we applied a pragmatic approach analysing the dated definition of the sonographic findings pathognomonic of bacterial pneumonia (close to 100%). Finally, it represents a useful tool for monitoring patients in the ED and intensive care unit (ICU).

The aim of this study is to determine the sensitivity of LUS in the diagnosis of COVIDp in a population with suggestive symptoms.

MATERIALS AND METHODS

Study design

This prospective study was conducted between 17 March 2020 and 26 April 2020.

Setting

Between 17 March 2020 and 26 April 2020, 307 patients with suggestive symptoms for COVID-19 were evaluated in the three study centres. Patients with suspected COVIDp were enrolled at admission to one of three EDs in Northeast of Italy by convenience sampling based on the presence of the sonographers: ASUFC Latisana Hospital (census about 25,000 patients/year), ASUGI Cattinara in Trieste (census about 150,000 patients/year) and Borgo Roma in Verona (census about 40,000 patients/year). Clinical data were registered prospectively without interfering with usual clinical practice.

Population

Patients were eligible if they presented with one of these symptoms: fever, cough, or shortness of breath and met the epidemiological criteria that were in place during the first stages of the epidemic outbreak (coming from a geographical area with a high incidence of COVID-19 or direct contact with a subject infected with SARS-CoV2). Exclusion criteria were age less than 18 years, pregnancy, major trauma and cardiac arrest.

Index test (LUS diagnosis)

The LUS examinations were performed by one of five emergency medicine residents (three in Trieste, one in Latisana and one in Verona) with standardised training in thoracic ultrasound (following the certification of competence by the Italian Society of Emergency Medicine, SIMEU). The sonographers were blinded to the RT-PCR result for SARS-CoV-2 but not for the patient’s clinical presentation. The images were evaluated by describing the ultrasound findings classified as bilateral B-lines, consolidations, small subpleural consolidations, thickening and irregularities of the pleural line, pleural effusion for every thoracic area (‘Definitions’ on online supplemental material). Each sonographer diagnosed COVIDp based on the comprehensive picture of the LUS. The protocol used for LUS evaluation was performed by analysing 12 anterior and posterior thoracic areas (figure 1). At present, there is no consensus on a validated definition of the sonographic findings pathognomonic of COVIDp. Therefore, we applied a pragmatic approach analysing the presence of the following artefacts, typical of interstitial pneumonia:

- Presence of local or diffuse interstitial syndrome (ie, coalescent B-lines).
- Irregular/thickened pleural line.
- Subpleural consolidations.

In the absence of criteria defined by guidelines or by consensus at the time of the study, to diagnose pulmonary involvement from COVID-19 and optimise the sensitivity of the LUS, we considered sufficient even a single thoracic area suggestive of interstitial disease to consider the ultrasound examination as positive.

In order to assess interindividual reliability, 3 min video clips for each scanned area for each patient enrolled were recorded and re-evaluated by every sonographer to assess a posteriori the agreement among the sonographers. Aware of the suboptimal reference standard, we also evaluated a posteriori the agreement between the diagnosis made by the sonographer and that produced by the radiologist through CXR (and chest CT scan, when present).

The equipment used was described in online supplemental material.

Reference standard

An adjudication committee—composed of three expert emergency physicians with more than 20 years of experience (FC, RC and GA)—retrospectively (approximately a couple of days after data collection) established the adjudicated diagnosis of COVIDp based on the clinical history and evaluation, the arterial blood gas, CXR, the RT-PCR test (Roche Cobas SARS-CoV-2 essay and Liaison MDX DiaSorin, in Trieste and Latisana; Roche Cobas SARS-CoV-2 essay and Alplex 2019 n-CoV Assay, in Verona) on the NPS performed in the ED (usually 4 hours of processing time) and chest CT scan images if requested by the physician on duty during patient assessment. The radiographic images were reviewed by an experienced radiologist (SM) who categorised the final report into ‘suggestive’ or ‘non-suggestive’ for COVID-19p based on the Radiological Society of North America consensus criteria.

Each committee member evaluated the available clinical documentation and proposed the diagnosis. In case even one of the three members did not agree with the other members, the whole committee discussed the case in the plenary session.

In order to assess the degree of reliability among the members of the adjudication committee, we also assessed the agreement between the members of the adjudication committee a posteriori before an eventual plenary discussion to establish the diagnosis of questionable cases. Aware that the reference standard is
suboptimal, we also assessed the degree of agreement between the sonographers and the adjudication committee.

Aims
The study’s primary aim was to establish LUS sensitivity in diagnosing COVP to safely rule out interstitial pneumonia in patients with suspected SARS-CoV-2 infection. We also described the ultrasound findings found to identify a possible characteristic pattern of COVID-19 pneumonia.

The secondary aims were to verify any statistically significant differences in the demographic, clinical or laboratory characteristics between patients with COVID-19p and patients without COVP and verify the agreement among sonographers as well as between sonographers and the adjudication committee, and between the members of the adjudication committee. Finally, we retrospectively tested the agreement between the different diagnoses produced by the radiographic methods (sonographer’s diagnosis for LUS and a radiologist’s diagnosis for CXR).

Sample size
We calculated the sample size based on the estimated prevalence of COVID-19p of about 40% in our population. The null hypothesis was that LUS was at least 90% sensitive and 70% specific in diagnosing COVID-19p. We calculated it was necessary to enrol at least 183 patients for adequate sensitivity and 409 for adequate specificity.11 Therefore, the study is adequately powered to assess LUS sensitivity only.

Statistical analysis
For the index test, we calculated: sensitivity, specificity, positive and negative likelihood ratios and overall diagnostic accuracy. Moreover, we calculated positive predictive value (PPV) and negative predictive value (NPV) related to SARS-CoV-2 prevalence in our study population.

We divided our sample into two groups according to the adjudicated diagnosis of COVID-19 pneumonia (ie, COVID-19+ and COVID-19–) and compared their demographic and clinical characteristics. Categorical variables are expressed as absolute values, and statistical significance between the two groups was calculated using Pearson’s χ² test or Fisher’s exact test when appropriate. Due to their non-parametric distribution, continuous variables are shown as the median value (and IQR). Statistical significance between the two groups was calculated using the Kruskal-Wallis test. A two-tailed p value of ≤0.05, corrected for multiplicity through the Benjamini-Hochberg method, was considered statistically significant.

Cohen’s test between two groups (or Fleiss’s test between more than two groups) was used to evaluate the agreement between LUS diagnosis, CXR diagnosis and final diagnosis by the adjudication committee as described previously. According to the k value obtained, agreement was defined as slight (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) or almost perfect (0.81–1).

All statistical analyses were performed using the R-CRAN project V3.6.1, ‘irr’, ‘part’, ‘caret’ and ‘compareGroups’ packages were implemented.

Patient and public involvement
This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

### RESULTS
From 17 March 2020 to 26 April 2020, we enrolled 238 patients with suspected COVP. Of these, three were excluded from the final analysis because of incomplete data, so the final sample was 235 patients (figure 2). Ninety patients (38.3%) were diagnosed as COVID-19+ following the evaluation by the adjudication committee (figure 2). In the plenary session, the adjudication committee discussed 24 cases: 18 for uncertain radiographic diagnosis and 6 for a debated final diagnosis of COVP. The agreement between the three members of the adjudication committee was 0.91 (K Fleiss). After discussion, all members of the adjudication committee reached an agreement.

The LUS diagnosis was 89 patients with COVP (table 1). There were 77 true positives, 12 false positives, 133 true negatives and 13 false negatives. The LUS sensitivity for diagnosing COVP was 85.6% (95% CI 76.6% to 92.1%); the specificity was 91.7% (95% CI 86.0% to 95.7%). Overall diagnostic accuracy was 89.4% (95% CI 84.7% to 93.0%) (table 1). The PPV and the NPV were, respectively, 86.5% (95% CI 78.8% to 91.7%) and 91.1% (95% CI 86.1% to 94.4%). The LR+ was

### Table 1
<table>
<thead>
<tr>
<th>COVP+</th>
<th>COVP−</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUS+</td>
<td>77</td>
<td>12</td>
</tr>
<tr>
<td>LUS−</td>
<td>13</td>
<td>133</td>
</tr>
</tbody>
</table>

COVP+, COVID-19 pneumonia; LUS, lung ultrasound.
The agreement between LUS diagnosis and diagnosis by the adjudicating committee was 0.77. The agreement between radiologist on duty’s diagnosis through chest radiography and adjudicated diagnosis was 0.28 (p value=1.52 × 10^{-05}). The agreement between LUS and radiologist on duty’s diagnosis through chest radiography was 0.36 (p value=1.99 × 10^{-08}).

DISCUSSION

The investigated study protocol demonstrated satisfactory sensitivity in the diagnosis of COVIDp. Applied in the context of a population with high prevalence, the calculated NPV supports the usefulness of LUS as a diagnostic tool to rule out suspected interstitial pneumonia secondary to SARS-CoV-2 infection.

Compared with Pivetta et al—a similar study by setting, disease prevalence and population characteristics—our research shows a lower sensitivity for LUS in diagnosing COVIDp (85.6% vs 94.4%). Sorlini et al, who conducted a similar study with a larger sample, found a sensitivity of around 92%, therefore in line with the results of Pivetta et al. The discrepancy between these studies and ours could be ascribed to gene amplification via nasopharyngeal swab as the reference standard. As described previously, the sensitivity of the various gene amplification systems on nasopharyngeal swabs is not optimal. Furthermore, the positivity for SARS-CoV2 infection does not necessarily imply lung involvement such as COVIDp. It is conceivable that the patients who test positive for viral gene amplification systems on nasopharyngeal swabs may present subclinical signs of infection even in the presence of negative results from the nasopharyngeal swab (also due to the variability related to how the procedure is performed). Lieveld et al achieved a sensitivity of 92% and specificity of 80%. The Authors considered eligible patients who had undergone chest...
In the appraised literature, we could not identify a single predominant pattern for COVIDp.6 19 The finding of bilateral B-lines, which proved to be an evocative finding for COVIDp in our study, is common to other interstitial pulmonary diseases and presents a low specificity. Interstitial lung diseases other than COVIDp could be confounding factors.9 20 Although the homogeneous distribution and absence of pleural line irregularities are, as far as we observed, more typical of cardiogenic pulmonary oedema rather than COVID-19p (even in the more advanced stages with an ARDS appearance), it cannot be excluded that there may be overlapping clinical pictures. Indeed, the literature seems to identify a cohort of patients more susceptible to SARS-CoV2 infection in cardiopathic patients.21 This limitation is particularly relevant when evaluating a massive population of older people, many of whom are cardiopathic.

Similarly, patients with previous interstitial disease (eg, COPD) may present difficult pictures to interpret. However, it should be noted that these clinical pictures can be difficult to evaluate, even via a chest CT scan. In any case, according to our observation and considering the literature published so far,22 the presence of confluent B lines up to the white lung, associated with small subpleural consolidations and irregularities of the pleural line, in the presence of a sufficient pre-test probability, constitute a pattern suggestive of the COVID-19p.

We also noticed that minimal pleural effusion might occur, possibly due to an inflammatory response. This finding is of considerable significance as pleural effusion, contrary to what is usually believed,23 is not a useful sign to rule out COVID-19 or viral pneumonia.24 A recent meta-analysis including five studies reports a prevalence of pleural effusion detected by ultrasound of 14%.25

We report that few patients (5) had a normal LUS (bilateral A-line pattern) and tested positive at the NPS: three of them had presented more vivid symptoms of SARS-CoV2 infection 15–20 days before, with mild symptoms at the time of the visit; still, they came to the ED for diagnostic confirmation. The period between the onset of the first symptoms and access to the ED was variable. Some patients remained symptomatic for up to 20 days after the first mild symptoms.26 Evaluating how much the diagnostic delay related to the onset of symptoms might have affected the diagnostic accuracy of the LUS is difficult.

As proposed by other authors, the high sensitivity of LUS suggests that it could be a useful tool for excluding patients at low risk of developing pulmonary involvement from COVID-19.27 28 The promising results in LUS specificity for COVIDp advocate for further research with adequately powered studies to consolidate the role of LUS in ruling-in patients with COVIDp. This goal would be more important considering that most patients show non-specific symptoms such as tachycardia and tachypnoea, which are common to other emergent conditions such as pain, stress or anxiety. However, ageusia and anosmia are late and, above all, not very specific signs for COVIDp.

The results describing the diagnostic accuracy of LUS can constitute the basis for designing and implementing a diagnostic algorithm that integrates sonography as part of the first-line investigations.

**Limitations**

The study sample was recruited using a convenience recruiting strategy, and therefore the study could suffer from a bias. Enrolment was only possible when one of the sonographers was present, and this may have introduced a systematic error for not being able to consecutively enrol all suspected COVID-19 patients.

**Table 3** Comparison between the main characteristics of the positive COVID-19 group and the negative COVID-19 group

<table>
<thead>
<tr>
<th>Hospital, n (%)</th>
<th>COVID-19+ (n=90)</th>
<th>Covid-19− (n=145)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latisana</td>
<td>2 (2)</td>
<td>15 (10)</td>
<td></td>
</tr>
<tr>
<td>Trieste</td>
<td>64 (71.1)</td>
<td>114 (79)</td>
<td></td>
</tr>
<tr>
<td>Verona</td>
<td>24 (27)</td>
<td>16 (11)</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>47 (52)</td>
<td>69 (48)</td>
<td>0.367</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>67 (54–81)</td>
<td>73 (52–83)</td>
<td>0.849</td>
</tr>
<tr>
<td>Comorbidity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>5 (6)</td>
<td>10 (7)</td>
<td>0.893</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>31 (34)</td>
<td>58 (40)</td>
<td>0.475</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (17)</td>
<td>26 (18)</td>
<td>0.943</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>7 (8)</td>
<td>16 (11)</td>
<td>0.555</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24 (27)</td>
<td>49 (34)</td>
<td>0.316</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>9 (10)</td>
<td>19 (13)</td>
<td>0.633</td>
</tr>
<tr>
<td>Pneumopathy (other from COPD)</td>
<td>7 (8)</td>
<td>20 (14)</td>
<td>0.222</td>
</tr>
<tr>
<td>Liver failure</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 (6)</td>
<td>12 (8)</td>
<td>0.601</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>10 (11)</td>
<td>13 (9)</td>
<td>0.755</td>
</tr>
<tr>
<td>Clinical signs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>67 (74)</td>
<td>81 (56)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Cough</td>
<td>50 (56)</td>
<td>67 (46%)</td>
<td>0.227</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>51 (57)</td>
<td>80 (55)</td>
<td>0.975</td>
</tr>
<tr>
<td>ABG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mm Hg) (IQR)</td>
<td>65.6 (55.9–78.2)</td>
<td>75.1 (66.0–87.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg) (IQR)</td>
<td>35.3 (31.4–39.7)</td>
<td>36.6 (33.0–41.3)</td>
<td>0.115</td>
</tr>
<tr>
<td>FiO₂ (%) (IQR)</td>
<td>21.0 (21.0–21.0)</td>
<td>21.0 (21.0–21.0)</td>
<td>0.101</td>
</tr>
<tr>
<td>PaO₂/FiO₂ (mm Hg) (IQR)</td>
<td>290 (219–343)</td>
<td>332 (284–400)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ox. suppl.</td>
<td>18 (20)</td>
<td>15 (16)</td>
<td>0.180</td>
</tr>
<tr>
<td>Lactate (mg/dL) (IQR)</td>
<td>9.0 (8.0–14.0)</td>
<td>10.0 (7.0–17.0)</td>
<td>0.306</td>
</tr>
<tr>
<td>6 min walking test (positive)</td>
<td>15 (17)</td>
<td>7 (5)</td>
<td>0.039*</td>
</tr>
</tbody>
</table>

The asterisk (*) indicates the statistically significant differences.

ABG, arterial blood gas; Ox. suppl., oxygen supplementation.
patients during the study period. However, we have tried to limit this bias by intensifying the presence of the sonographers as much as possible (82% of potentially eligible patients were enrolled).

Furthermore, we conducted the study in a phase of the pandemic (March–April 2020) in which the prevalence of the disease was particularly high, which may have influenced the diagnostic accuracy results we found, especially regarding the clinical gestalt component. The clinical history and clinical presentation were made as objective as possible through questionnaires in which symptoms and signs were specified; nevertheless, the sonographs were not concealed from this information. Therefore, we cannot exclude that a certain amount of confirmatory bias may have influenced the results: this could have increased a not completely reliable specificity. However, the sensitivity of LUS cannot have been affected by this bias, except to some degree of underestimation.

The study’s main limitation is the absence of a single reference standard investigation for the diagnosis of COVIDp. CT scan was performed only in a selected percentage of our population (mirroring the usual clinical practice). When the patients were recruited, serological tests were not available, and the role of these tests in the early SARS-CoV-2 diagnosis in ED has yet to be demonstrated.29 Probably, the most accurate comparison would have been between LUS and chest CT+bronchoalveolar lavage for each patient. However, this would have been difficult to achieve in reality, both due to the lack of resources considering the high influx of patients suspected of COVIDp and for ethical reasons (not all patients with COVIDp require invasive procedure and—probably—in many patients chest CT would not add prognostic value).30

Furthermore, the CT scan was consulted (though not exclusively) by the adjudication committee so that it may have resulted in a lack of homogeneity in the accuracy of the reference standard adopted by our study.

The literature agrees that the posterior thoracic areas offer the best sensitivity in viral pneumonia.18 The supine position of the bedridden patient may be a limitation to the sensitivity. This limitation is non-specific for patients with COVID-19p only, but every patient is forced to the supine position due to severe clinical conditions.

All study subjects lacked follow-up clinical data beyond the result of the culture or microbiological samples. Therefore, we were unable to assess the role of LUS in predicting patient clinical progress. The pragmatic protocol designed for our study reflects the current practice in the EDs involved. Unfortunately, when the study was performed, there were no resources available to deploy an effective follow-up strategy.

In order to provide a more solid correlation between LUS findings and the severity of clinical presentation, the study population would have required a more exhaustive characterization. However, this goal was outside the scope of our study, which aimed to investigate the role of LUS in detecting cases of COVIDp in a patient population suspected of COVID-19.

CONCLUSION
In the context of a population with high SARS-CoV-2 prevalence, LUS has a high sensitivity enough to play a role in ruling out COVID-19 pneumonia. The role of LUS in diagnosing patients with COVID-19 pneumonia is perhaps even more promising. Nevertheless, further research with adequately powered studies is needed.


