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Letter to the Editor

In COVID-19 patients with mild or moderate respiratory failure, duration and type of symptoms influence the diagnostic accuracy of lung ultrasound

Dear Editor

The SARS-CoV-2 pandemic has placed considerable pressure on healthcare systems worldwide, forcing hospitals to implement strict infection control measures aimed at isolating all suspected cases. To preserve hospital capacity, this triage must be accurately and rapidly performed. As the most frequent clinical presentation of hospitalized patients with SARS-CoV-2 infections is pneumonia, and as RT-PCR and rapid antigen/antibody tests are vulnerable to shortages during epidemics, delaying test results, lung-imaging techniques have been included into the diagnostic workup. Lung Ultrasonography (LUS) offers several advantages over computed tomography, such as low cost, global accessibility even in countries with limited resources, absence of radiation and the possibility to be performed by clinicians at the bedside.

A recent systematic review showed highly variable LUS sensitivity and specificity in diagnosing SARS-CoV-2 pneumonia, ranging from 68% to 97%, resp. 21% to 79%, depending on the study design and the care setting [1]. Since most LUS studies have been performed in the outpatient, emergency or intensive care settings [1,2], we conducted a prospective observational study aimed to determine the diagnostic accuracy of LUS in patients with symptoms suggestive of SARS-CoV-2 infection, admitted to an internal medicine ward. This population represent the majority of patients actually hospitalized with a SARS-CoV-2 infection. We also investigated clinical and biological variables that may influence the diagnostic accuracy of LUS.

We defined a suspected case of SARS-CoV-2 infection according to international criteria (WHO, 2020). Patients who met these criteria were admitted to the internal medicine ward if hemodynamically stable, with an O_2 saturation $\geq$90% on $<$ 6 L/min supplementary oxygen and a respiratory rate $<$30 per min. Patients exceeding these clinical severity criteria were directly transferred to the intensive care unit and not enrolled into this study. We also excluded patients with an established alternative diagnosis on admission, for whom a LUS was not performed within 48 h of admission, or who refused to participate to the study. The study protocol was approved by the local Ethics Committee.

All patients had a nasopharyngeal swab for RT-PCR performed at admission by a dedicated team. In the presence of gastrointestinal symptoms, a rectal swab was also obtained. In patients with a first negative RT-PCR test but a persisting clinical suspicion, a second set of swabs was obtained 24 h after the first test. A patient was considered as having a SARS-CoV-2 infection if any of the RT-PCR returned positive.

LUS examinations were performed within 24–48 h from admission by a team of 5 trained examiners, blinded to RT-PCR results (see Supplementary material). LUS procedure was standardized for all examiners, as described elsewhere [3–5]. Standardization was also ensured using a structured *case report form* that examiners completed immediately after each examination. Findings were reported in 6 lung quadrants for each side [3,4]. Basing on validated criteria on SARS-CoV-2 pneumonia patterns, each LUS examination was classified as "*Likely Pneumonia*", "*Unlikely Pneumonia*" and "*Uncertain Pneumonia*" [5] (eTable 1, Supplementary material).

We performed between-group comparisons utilizing the chi-square or Fisher's exact test for categorical variables and student's *t*-test or Kruskal-Wallis test for continuous variables. Diagnostic capacity of LUS was assessed by computing sensitivity, specificity, positive and negative predictive values and corresponding 95% confidence intervals using SARS-CoV-2 RT-PCR result as gold standard. Since RT-PCR results are binary variables, while LUS include the third possibility of "uncertain" result, we determined the diagnostic accuracy of LUS clustering "uncertain" results first with " likely pneumonia "; then with " unlikely pneumonia " to enable statistical analyses. Given the dichotomous nature of such ultrasonographic findings (likely/unlikely pneumonia) and of the clinical symptoms (present/absent), we computed the area under the receiver operating curve (ROC) as (sensitivity+specificity)/2. The diagnostic capacity of clinical symptoms and ultrasonographic findings was further tested with logistic regression utilizing the SARS-CoV-2 RT-PCR result as the dependent variable after adjusting for age, gender, WBC count, presence of fever, dry cough and dyspnea.

Between 01.03.2020 and 01.07.2020, 197 patients were screened for eligibility and data from 145 patients where available for analysis. SARS-CoV-2 prevalence in our population was 42% (62/145). Patients with a positive RT-PCR result had a higher BMI (27.8 $\pm$ 5.3 vs 24.8 $\pm$ 6.3 kg/m^2, $p = 0.007$) and were less likely to have COPD as comorbidity. Fatigue, fever $\geq$ 38 °C and dry cough were significantly more prevalent in RT-PCR positive patients. Both RT-PCR positive and negative patients had mild respiratory failure (mean supplementary oxygen need of 1.5 L O2/min during the first 24 h from admission) (eTable 2, Supplementary material).

LUS detected pneumonia in 46/62 (74.2%) RT-PCR positive and 23/83 (27,7%) of RT-PCR negative patients (e**Table 3,** Supplementary material). When considering "uncertain" results as "likely pneumonia ", we obtained moderate sensitivity, specificity, negative predictive value and area-under-the ROC-curve (AUROC) (79%, 61.4%, 79.7% resp 0.70). When considering "uncertain" results such as "unlikely pneumonia", sensitivity slightly decreased (74.2%), but specificity increased to 72.3% (AUROC 0.73) (Table 4). Two systematic reviews reported higher sensitivity of LUS (86–97%) in predicting RT-PCR positivity, but, unlike our study, included patients with severe and very severe SARS-CoV-2 infections [1,2]. Our results are in line with a recent large prospective multicenter study that showed a sensitivity of LUS ranging from 31% in patients with mild symptoms and without respiratory failure, to 69% in patients with severe respiratory failure [6].

While the overall accuracy of the LUS in our study was moderate, it

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Table 4
Overall performance of LUS for the diagnosis of SARS-CoV-2 pneumonia and performance according to different clinical variables (95% CI)*.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC (%)
LUS "Uncertain" considered as "pneumonia likely"	79 (67 – 88)	61 (50 – 72)	60 (49 – 71)	80 (68 – 89)	0.70 (0.63 - 0.78)
LUS "Uncertain" considered as "pneumonia unlikely	74 (61 – 84)	72 (61 – 82)	67 (54 – 78)	79 (68 – 87)	0.73 (0.66- 0.81)
Symptoms > 7 days *($n = 40$)	90 (73–98)	70 (35–93)	90 (73–98)	70 (35–93)	0.8 (0.64–0.96)
Dry cough present * ($n = 53$)	80 (63–91)	89 (65.–98)	93 (78–99)	69 (47–87)	0.84 (0.74–0.94)
Fever ($\geq$ 38 °C) * ($n = 84$)	74 (58.–86)	75 (60–87)	76 (60–88)	74 (58–86.	0.75 (0.65–084)
Dyspnea present * ($n = 71$)	86 (70–95)	66 (48–81)	72 (56–84)	82 (63–94)	0.76 (0.66–0.85)

LUS : Lung Ultrasonography, PPV : Positive predictive value ; NPV : Negative predictive value; AUROC: Area under the ROC curve.
* In this analysis "uncertain LUS" was considered as "pneumonia unlikely".

resulted to be excellent in the subgroup of patients with dry cough on admission (AUROC 0.84; 95%-CI 0.74–0.94; sensitivity 80% (95%-CI 63–91%) and specificity 89% (95%-CI 65–98). More interestingly, LUS sensitivity, specificity and AUROC were excellent (90% (95%-CI 73–98%) resp. 0.8 (95%-CI 0.64–0.96)) in patients with symptoms lasting more than 7 days (Table 4).

There are several possible explanations to these findings. A meta-analysis of small case series showed that 37% of asymptomatic patients did not display lung lesions on CT scan [7]. This could also have been the case in our study, since a significant proportion (42%) of the participants did not have dyspnea at admission and required a low average supplemental oxygen. Moreover, it has been shown, that early in the course of infection imaging studies can be negative [8]. A retrospective study of CT scans on hospitalized patients did not detect lung opacities in 56% of SARS-CoV-2 patients with symptoms for 0–2 days, compared with those symptomatic for 3–5 days (9%) and >6 days (4%) [9]. Similarly, in our study, RT-PCR positive patients without detectable pneumonia had a significantly shorter duration of symptoms than those with detectable pneumonia (median of 3 days (IQR 1–5) vs. 8 days (IQR 7–13), p 0.001). (eTable 2, Supplementary material).

After adjustment for age, BMI, symptoms (fever, dry cough, dyspnea) and WBC count using logistic regression, LUS findings remained significantly associated with RT-PCR status (OR 4.83, 95%-CI 1.62–14.4).

In the 23 patients displaying pneumonia on LUS despite a negative RT-PCR, final diagnosis at discharge was pneumonia in 15 (63%), including 4 (17.4%) with a high likelihood of SARS-CoV-2 pneumonia based on typical clinical presentation and CT scan images (eTable 5, supplementary material). These results confirm that LUS is a good diagnostic tool for pneumonia [10].

Several studies have been published regarding the use of LUS in the context of the SARS-CoV-2 pandemic, but to the best of our knowledge this is one of the few prospective studies addressing the diagnostic accuracy of LUS in a selected population of patients with mild or moderate respiratory failure [1] and the first reporting the effect of symptoms duration on the diagnostic accuracy of LUS.

This study presents some limitations. In case of an uncertain LUS result, we did not systematically perform a CT or a follow-up examination. This decision was left to the discretion of the clinicians in charge of the patient. However, we performed a sensitivity analysis considering the uncertain LUS results first as pneumonia and then as no-pneumonia, and we did not find major differences in the diagnostic accuracy. Moreover, during the study period, very few patients with structural lung diseases (COPD, interstitial lung disease, lung cancer) were hospitalized and no case of Influenza was detected. Thus, our results could have overestimated the accuracy of LUS and should not be generalized to these patients.

The current pandemic has allowed for an incredible acceleration in the use of LUS as a diagnostic tool and our study contributes to clarify under which conditions LUS results can be considered reliable. However, with the emergence of new viral variants, each presenting a different prevalence of pneumonia, further research will be needed to specify in which patients and situations LUS will be most useful in the diagnostic workup of SARS-CoV-2 infections, particularly outside pandemic peaks.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.08.029.

References

[1] Islam N, et al. Thoracic imaging tests for the diagnosis of COVID-19. Cochrane Database Syst Rev 2021;3(3). https://doi.org/10.1002/14651858.CD013639.pub4. Cd013639 DOI.
[2] Pecho-Silva S, et al. Pulmonary Ultrasound in the Diagnosis and Monitoring of Coronavirus Disease (COVID-19): a Systematic Review. Ultrasound Med Biol 2021;47(8):1997–2005. https://doi.org/10.1016/j.ultrasmedbio.2021.04.011.
[3] Soldati G, et al. Proposal for International Standardization of the Use of Lung Ultrasound for Patients With COVID-19: a Simple, Quantitative, Reproducible Method. J Ultrasound Med 2020. https://doi.org/10.1002/jum.15285. DOI.
[4] Cogliati C, et al. Lung ultrasound in COVID-19: insights from the frontline and research experiences. Eur. J. Intern. Med. 2021;90:19–24. https://doi.org/10.1016/j.ejim.2021.06.004.
[5] Millington SJ, et al. Lung Ultrasound for Patients With Coronavirus Disease 2019 Pulmonary Disease. Chest 2021;159(1):205–11. https://doi.org/10.1016/j.chest.2020.08.2054.
[6] Volpicelli G, et al. Lung ultrasound for the early diagnosis of COVID-19 pneumonia: an international multicenter study. Intensive Care Med 2021;47(4):444–54. https://doi.org/10.1007/s00134-021-06373-7.
[7] Tsikala Vafea M, et al. Chest CT findings in asymptomatic cases with COVID-19: a systematic review and meta-analysis. Clin Radiol 2020;75(11). https://doi.org/10.1016/j.crad.2020.07.025. p. 876.e33-876.e39 DOI.
[8] Pan F, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2020;295(3):715–21. https://doi.org/10.1148/radiol.2020200370.
[9] Bernheim A, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): relationship to Duration of Infection. Radiology 2020;295(3):200463. https://doi.org/10.1148/radiol.2020200463.
[10] Orso D, Guglielmo N, Copetti R. Lung ultrasound in diagnosing pneumonia in the emergency department: a systematic review and meta-analysis. Eur J Emerg Med 2018;25(5):312–21. https://doi.org/10.1097/mej.0000000000000517.

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