# Serial lung ultrasound in monitoring viral pneumonia: the lesson learned from COVID-19

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**Lung ultrasound is a reliable tool to predict the risk of respiratory deterioration in hospitalised patients with COVID-19. A low score on admission and the absence of progression in 48 h rule out future deterioration with intensive care requirement.** https://bit.ly/43dYqi4

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## Abstract

*Background* Lung ultrasound (LUS) has proven to be useful in the evaluation of lung involvement in COVID-19. However, its effectiveness for predicting the risk of severe disease is still up for debate. The aim of the study was to establish the prognostic accuracy of serial LUS examinations in the prediction of clinical deterioration in hospitalised patients with COVID-19.

*Methods* Prospective single-centre cohort study of patients hospitalised for COVID-19. The study protocol consisted of a LUS examination within 24 h from admission and a follow-up examination on day 3 of hospitalisation. Lung involvement was evaluated by a 14-area LUS score. The primary end-point was the ability of LUS to predict clinical deterioration defined as need for intensive respiratory support with high-flow oxygen or invasive mechanical ventilation.

*Results* 200 patients were included and 35 (17.5%) of them reached the primary end-point and were transferred to the intensive care unit (ICU). The LUS score at admission had been significantly higher in the ICU group than in the non-ICU group (22 (interquartile range (IQR) 20–26) *versus* 12 (IQR 8–15)). A LUS score at admission ⩾17 was shown to be the best cut-off point to discriminate patients at risk of deterioration (area under the curve (AUC) 0.95). The absence of progression in LUS score on day 3 significantly increased the prediction accuracy by ruling out deterioration with a negative predictive value of 99.29%.

*Conclusion* Serial LUS is a reliable tool in predicting the risk of respiratory deterioration in patients hospitalised due to COVID-19 pneumonia. LUS could be further implemented in the future for risk stratification of viral pneumonia.

## Introduction

More than 2 years have passed since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, which has caused more than 6 million deaths worldwide [1].

SARS-CoV-2 infection can manifest in a wide range of conditions, from asymptomatic forms to severe pneumonia and multiorgan dysfunction. Given this heterogeneity in the clinical evolution, the identification of risk and predictive factors for severe disease should be one of the key research topics. Being able to predict and stratify which patients will be at risk of deterioration is crucial for monitoring and early initiation of treatment.

Numerous studies have identified negative host-related prognostic factors, such as age, gender and comorbidities, and various prognostic markers such as radiological and laboratory findings [2–4]. Although there is no consensus regarding the best diagnostic procedure for prognostic assessment, the radiological evaluation of lung involvement seems to be a reliable tool according to WHO recommendations [5].

High-resolution computed tomography (HRCT) has demonstrated high level of accuracy for diagnosing and monitoring COVID-19 pneumonia [6–8], but it has several limitations in clinical practice due to limited availability, high-cost, radiation exposure and need for patient transfer.

However, lung ultrasound (LUS) is accessible, low-cost, nonionising, repeatable and portable, minimising the risk of cross-contamination. Several studies have reported a good correlation of LUS with HRCT [9, 10] and clinical outcomes [11–13]. However, few of these reports have studied the prognostic accuracy of serial LUS explorations [14–16].

Thus, the aim of this study is to determine the reliability of serial LUS for monitoring COVID-19 pneumonia.

## Methods

### *Ethics statement*

Ethics approval was obtained prior to the start of the study by the Medical Ethics Committee of Vall d'Hebron Barcelona University Hospital (PR(AG)267/2020). Oral informed consent was obtained from all the patients before their inclusion and this information was registered in their clinical history.

### *Study design*

This single-centre prospective cohort study evaluated patients hospitalised for COVID-19 between 21 November 2020 and 30 May 2021 at Vall d'Hebron University Hospital, Barcelona, Spain.

Patients hospitalised for COVID-19 were consecutively recruited and oral consent was required, according to the local protocol for SARS-COV2 infection control. SARS-CoV-2 infection was confirmed by a positive nasopharyngeal real-time multiplex polymerase chain reaction (PCR) assay according to WHO criteria [1]. Exclusion criteria were intensive care unit (ICU) requirement at admission and any pre-existing chronic pulmonary disease, such as interstitial lung disease, emphysema and lung cancer.

Baseline information was retrieved from medical records including age, sex, comorbidities and Charlson comorbidity index (CCI). Routine blood laboratory data and chest radiographs obtained at admission were recorded. Clinical data about hospitalisation, complications and treatment provided were also recorded. Respiratory support was recorded for each patient, including low-flow oxygen, high-flow oxygen (HFO), noninvasive mechanical ventilation (NIMV) and invasive mechanical ventilation (IMV).

### *Lung ultrasound*

All recruited patients underwent LUS within 24 h from admission. Serial explorations during hospitalisation were planned on day 3 and day 5 (at 48 and 96 h from the first LUS, respectively).

The sonographic protocol consisted of a complete examination of all intercostal spaces, which were divided into 14 thoracic areas (three posterior, two lateral and two anterior for each lung) (figure 1) [17]. For each of the 14 zones, a score from 0 to 3 was given depending on the severity of lung involvement by the following sonographic findings (figure 2) [18]:

- Score 0: regular pleural line and presence of horizontal artifacts (A-lines).
- Score 1: presence of B-lines that do not merge (defined as laser – such as vertical hyperechoic artefacts that arise from the pleural line extending to the bottom of the screen, moving synchronously with lung sliding [19]). Pleural line is usually blurred.
- Score 2: multiple coalescent B-lines. Pleural line is usually broken and small subpleural consolidated areas can be present.
- Score 3: presence of a large consolidated area or tissue-like pattern (complete loss of lung aeration).

If two or more patterns coexisted in the same lung area, the finding with a highest score was counted. The total LUS score was calculated by summing the scores of the 14 zones (range 0–42).

LUS examinations were performed using a Sonosite M-Turbo system equipped with a 2–5-MHz convex transducer. All the examinations were conducted by a team of four pulmonologists with experience in LUS

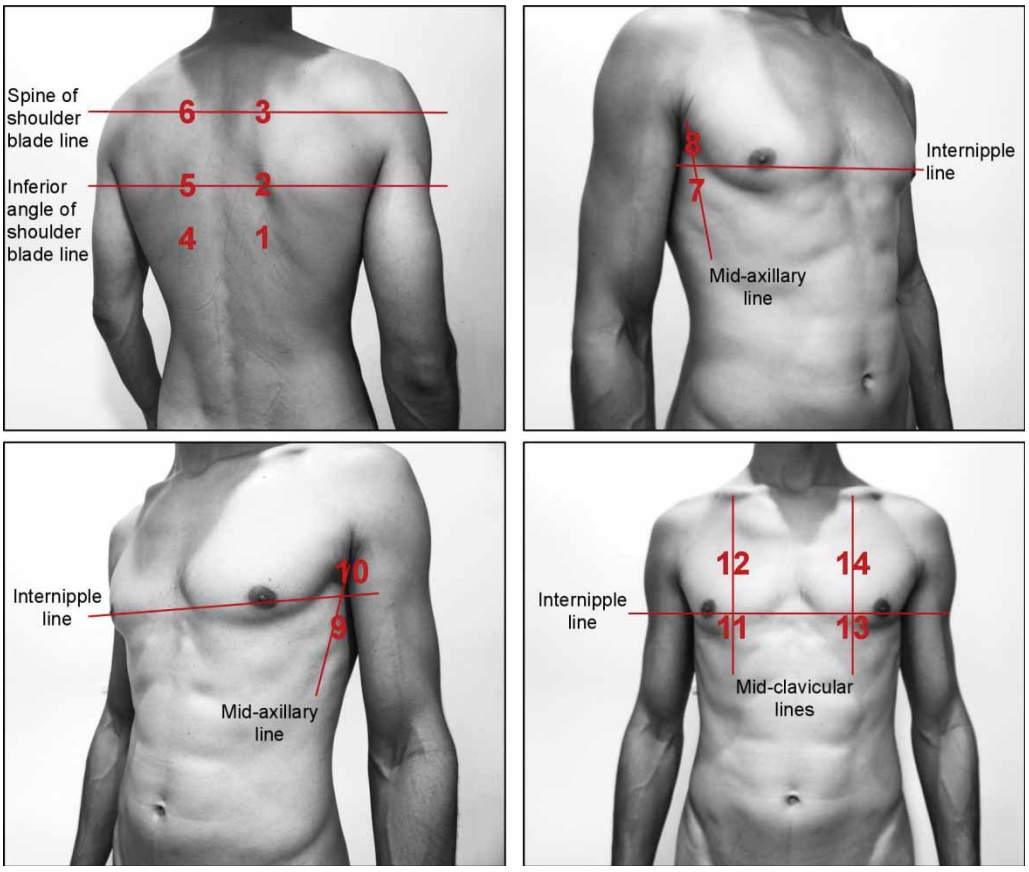


FIGURE 1 Thoracic areas and anatomical landmarks. Adapted with permission from Soldati *et al.* [17].

and previous publications in this field. The investigators were blinded to any clinical information other than the visible physical signs.

The interobserver agreement was evaluated retrospectively by a blinded and simultaneous review of 350 saved clips by the four examiners.

### *End-points*

The primary end-point was to establish the accuracy of LUS score in the prediction of clinical deterioration defined as need for intensive respiratory support (HFO, NIMV or IMV).

### *Statistical analysis*

All data were analysed using Stata software (StataCorp. 2017; Stata statistical software: Release 15 College Station, TX, StataCorp LLC, USA). Descriptive analysis was performed according to the presence or not of the primary end-point. Patients who reached the primary end-point were classified as the ICU group, as all patients with intensive respiratory support (HFO and IMV) requirement were transferred to the ICU.

For the qualitative variables, frequencies and percentages were compared using the chi-square test. For the quantitative variables, means±SD and medians (interquartile range (IQR)) were calculated and compared using ANOVA or Kruskal–Wallis test.

The normality of the distribution was analysed using the Shapiro–Wilk test. The p-value was computed from the Spearman rank correlation coefficient when the variable was continuous and from the chi-square test if the variable was categorical. Statistical significance was set at $p<0.05$. A simple size calculation was not performed.

A Pearson correlation analysis was performed between clinical and laboratory data and the LUS score. Receiver operating characteristic (ROC) curves were plotted to analyse the area under the curve (AUC).

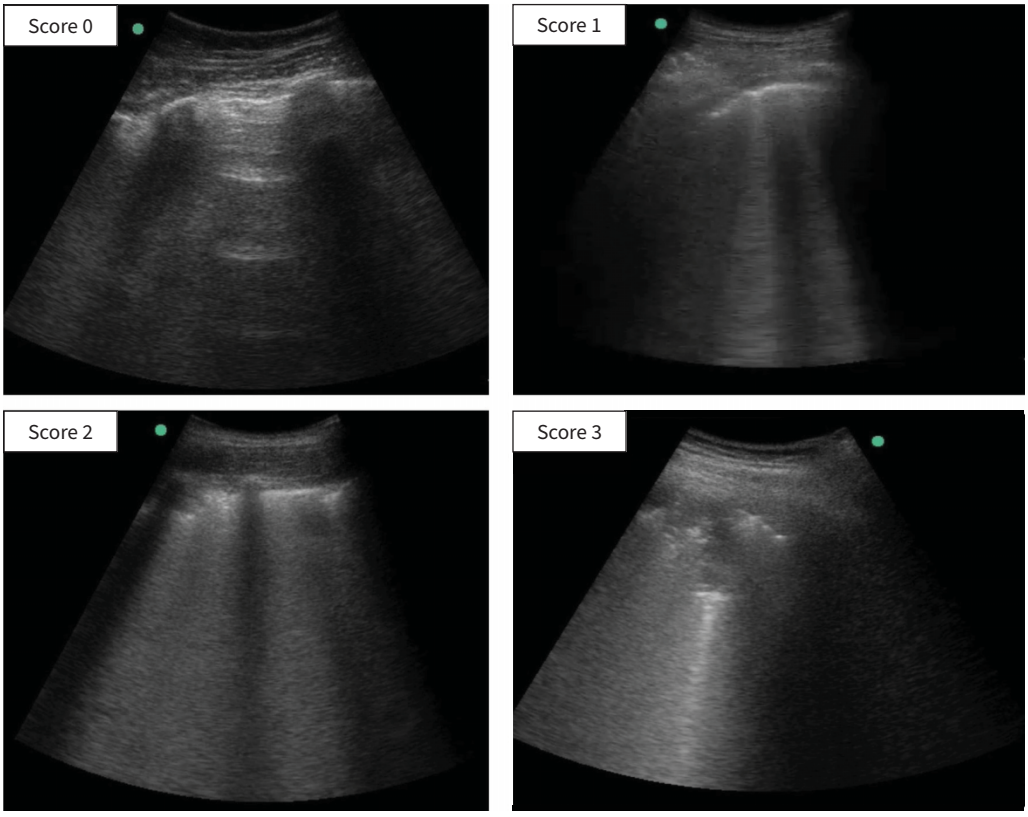


FIGURE 2 Lung ultrasound scores. Score 0: regular pleural line and presence of A-line pattern. Score 1: presence of B-lines that do not merge. Score 2: coalescent B-lines with a small subpleural consolidated area. Score 3: presence of a large consolidated area.

A cut-off point in the LUS score was obtained according to the Youden index to evaluate the primary end-point. LUS interobserver agreement was evaluated for 350 measurements, by using a contingency table and calculating the kappa index of agreement.

Univariate and multivariate models were performed to evaluate the prognostic variables according to the primary end-point. The multivariate model was performed using the LASSO variable selection method.

## Results

200 patients hospitalised for COVID-19 were included. Baseline demographic and clinical characteristics are shown in table 1.

### *Lung ultrasound findings*

All the 200 patients underwent LUS during the first 24 h after admission (day 1). Follow-up LUSs were performed on 96 patients on day 3 and on 27 patients on day 5 of hospitalisation. Serial examinations were not performed in cases of early discharge, ICU transfer and sonographer unavailability (figure 3).

LUS findings are presented in supplementary table 1. LUS at admission showed that 31% of all the thoracic areas evaluated were normal (score 0). The most common pathological finding was the presence of B-lines, isolated (score 1) in 40.3% and coalescent (score 2) in 27.9% of all areas. Only 0.8% of the explored areas showed a score 3. Pleural effusion was present in six patients. Regarding the distribution of abnormalities (scores 1–3), posterior areas were the most affected, with pathological findings in 87.2%. Additionally, 70.4% of lateral areas and 55.3% of anterior areas showed abnormalities. Only five patients (2.5%) had a unilateral involvement.

Median LUS score at admission was 13 (IQR 9.0–17.5). Follow-up LUS showed median scores of 14 (IQR 10–17) and 11 (IQR 8–16) on days 3 and 5, respectively.

**TABLE 1** Baseline characteristics of the study population

| Characteristic | |
|---|---|
| **Age, median (IQR)** | 55 (49–66) |
| **Gender, n (%)** | |
| Male | 132 (66) |
| Female | 68 (34) |
| **SARS-CoV-2 vaccination (first dose), n (%)** | 7 (3.5) |
| **Overweight, n (%)** | |
| BMI >25 | 80 (40) |
| BMI >30 | 69 (34.5) |
| **Tobacco consumption, n (%)** | |
| Never-smokers | 147 (73.5) |
| Past-smokers | 43 (21.5) |
| Active-smokers | 10 (5) |
| **Comorbidities, n (%)** | |
| Arterial hypertension | 62 (31) |
| Dyslipidaemia | 57 (28.6) |
| Diabetes | 31 (15.5) |
| COPD | 13 (6.5) |
| Asthma | 13 (6.5) |
| Localised solid tumour | 11 (5.5) |
| OSAS | 9 (4.5) |
| Connective tissue disease | 7 (3.5) |
| Liver disease | 5 (2.5) |
| Chronic renal disease | 4 (2) |
| Myocardial infarction | 4 (2) |
| Peptic ulcer disease | 4 (2) |
| Congestive heart failure | 3 (1.5) |
| Peripheral vascular disease | 3 (1.5) |
| Stroke | 3 (1.5) |
| Cancer | 2 (1) |
| **CCI, median (IQR)** | 1.5 (0.5–3.0) |

IQR: interquartile range, BMI: body mass index; OSAS: obstructive sleep apnoea syndrome; CCI: Charlson comorbidity index.

LUS score at admission showed a moderate positive correlation with interleukin-6 (IL-6) (r=0.43) and a moderate negative correlation with $SpO_2/FIO_2$ ratio at the time of the exploration (r=−0.46). Other correlations are showed in supplementary table 2.

### *Outcomes*

Among the 200 patients enrolled, 35 patients (17.5%) presented respiratory deterioration requiring ICU transfer for HFO (25 patients; 12.5%) or IMV (10 patients; 5%), and only 2 (1%) patients died. All these patients presented acute respiratory distress syndrome (ARDS) defined as a $SpO_2/FIO_2$ ratio <235 and radiographic bilateral involvement [20, 21]. Patient data during hospitalisations are shown in table 2.

Patients in the ICU group were significantly older and presented with higher CCI and more laboratory data alterations, such as lower platelets, higher dimer-D, aspartase transaminase, lactate dehydrogenase and IL-6. At admission, they presented a worse $SpO_2/FIO_2$ ratio and ROX index, defined as the ratio ($SpO_2/FIO_2$)/respiratory rate. There was no significant difference in time from symptom onset to hospitalisation between the two groups (table 2).

LUS score at admission was significantly higher in the ICU group than in the non-ICU group (22 (IQR 20–26) *versus* 12 (IQR 8–15)). The ROC curve analysis showed that a LUS score at admission ⩾17 was the best cut-off point to discriminate patients at risk of ICU transfer (supplementary figure 1). This value represented the best compromise between sensitivity (97.1%) and specificity (84.9%). The corresponding negative and positive predictive values were 99.3% and 57.6%, respectively, and the AUC was 0.95.

Regarding follow-up, 96 patients underwent LUS on day 3. Patients in the non-ICU group presented a median change in LUS score of 0.0 (IQR −2.0–1.5) between day 3 and day 1 while patients in the ICU

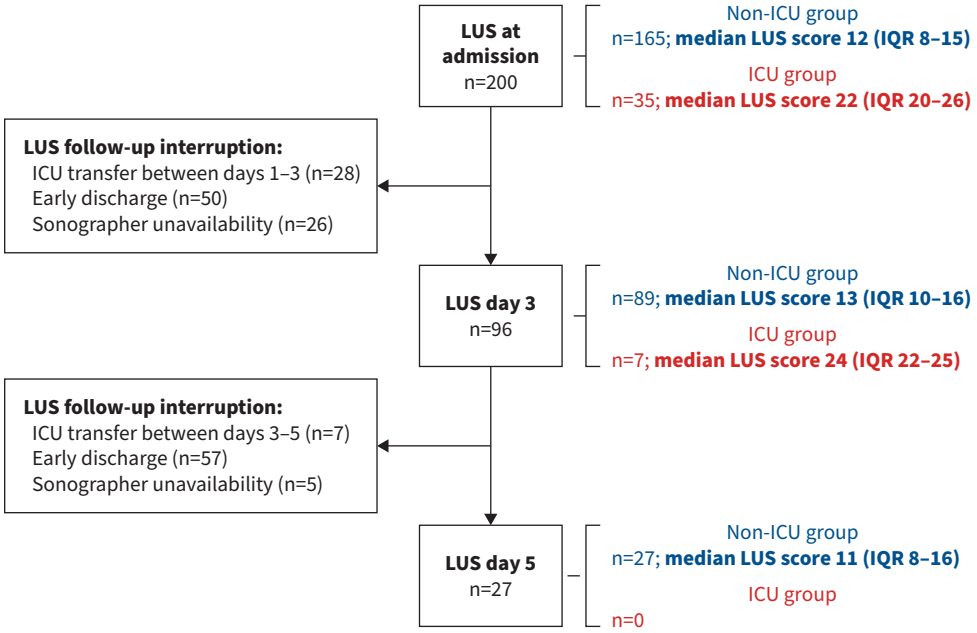


FIGURE 3 Flowchart of patients included in the study. ICU group: patients with subsequent deterioration. Non-ICU group: patients with clinical stability until discharge. LUS: lung ultrasound.

group presented a median change in LUS score of +5.0 (IQR 4.0–6.0) between day 3 and day 1 (table 3 and figure 4).

The absence of progression of LUS score on day 3 significantly increased the prediction accuracy for ICU transfer (specificity and predictive positive value increased to 94.55% and 79.07%, respectively).

Only a small subgroup of 27 patients underwent LUS on day 5. All these patients remained clinically stable and presented a median change in LUS score of −2.0 (IQR −5.0–0.0) between day 5 and day 3.

Univariate logistic regression analysis identified age, CCI, comorbidities (COPD, obstructive sleep apnoea syndrome, hypertension, dyslipidaemia), laboratory data (aspartate aminotransferase, lactate dehydrogenase, IL-6), $SpO_2/FIO_2$ ratio, ROX index and LUS score, as potential predictors for the primary end-point (table 4). Of all the variables included in the univariate analysis, the LASSO method identified the LUS score as an independent predictor for the primary end-point (OR 1.64, 95% CI 1.40–1.93; p<0.0001).

The LUS score showed a good interobserver agreement with a kappa value of 0.869.

## Discussion

The present study suggests that LUS is a reliable tool for monitoring lung injury in COVID-19 hospitalised patients. The main finding is that a low LUS score at admission shows an excellent negative predictive value for respiratory worsening. Furthermore, the progression of LUS scores on serial examinations, particularly at day 3 from admission, is also useful to discriminate patients who will likely present clinical deterioration. This study reinforces the usefulness of serial LUS in COVID-19, which was a controversial issue. To our knowledge, we report the largest single-centre cohort managing this topic.

Sonographic features of COVID-19 pneumonia have been described in several studies [22–25]. In this sense, our study confirms previously published data regarding patient characteristics and sonographic abnormalities in this infection. A B-line pattern (isolated or in confluent presentation) was the most frequent finding, followed by pleural abnormalities and subpleural consolidations. Large consolidations and pleural effusion were uncommon. Regarding distribution, almost all patients presented a bilateral involvement and greater affectation of infero-posterior areas, also in line with previous studies [9–12].

**TABLE 2** Clinical and laboratory data during hospitalisations

| | Non-ICU group (n=165) | ICU group[#] (n=35) | Total (n=200) | p-value |
|---|---|---|---|---|
| **Days from symptom onset to hospitalisation (IQR)** | 7 (5–10) | 7 (6–10) | 8 (6–10) | 0.2359 |
| **Length of hospital stay, days** | 5 (3–6) | 14 (11–28) | 5.5 (3–8) | 0.0000 |
| **Admission reasons, n (%)** | | | | |
| Oxygen support needed | 81 (49.1) | 30 (85.7) | 111 (55.5) | 0.0000 |
| Chest radiograph infiltrates | 79 (47.9) | 5 (14.3) | 84 (42) | 0.0000 |
| Others | 5 (3) | 0 (0) | 5 (2.5) | 0.2970 |
| **Respiratory status at admission** | | | | |
| $SpO_2/FIO_2$ ratio, median (IQR) | 447.6 (373.1–461.9) | 365.4 (309.7–395.8) | 408.3 (369.2–457.1) | 0.0000 |
| ROX index, median (IQR) | 23.1 (20.2–25.4) | 19.0 (15.5–21.4) | 22.6 (19.0–25.4) | 0.0000 |
| CURB-65 ⩾2, n (%) | 19 (11.5) | 9 (25.7) | 28 (14) | 0.0560 |
| **Chest radiograph infiltrates at admission, n (%)** | | | | |
| Absent | 9 (5.5) | 0 (0) | 9 (4.5) | 0.0003 |
| Present unilaterally | 30 (18.2) | 0 (0) | 30 (15) | |
| Present bilaterally | 126 (76.4) | 35 (100) | 161 (80.5) | |
| **Complications, n (%)** | | | | |
| Worst $SpO_2/FIO_2$ (IQR) | 404 (365–457) | 160.0 (113.0–190.0) | 373.0 (329.5–452.0) | 0.0000 |
| Pulmonary embolism | 1 (0.6) | 1 (2.9) | 2 (1) | 0.3201 |
| Sepsis | 0 (0) | 1 (2.9) | 1 (0.5) | 0.1750 |
| Acute heart failure | 0 (0) | 1 (2.9) | 1 (0.5) | 0.1750 |
| Acute kidney failure | 2 (5.7) | 2 (5.7) | 4 (2) | 0.2350 |
| Death | 0 (0) | 2 (5.7) | 2 (1) | 0.0299 |
| **Maximum respiratory support, n (%)** | | | | |
| Low-flow oxygen | 94 (57) | 0 (0) | 94 (47) | 0.0000 |
| High-flow oxygen | 0 (0) | 25 (71.4) | 25 (12.5) | 0.0000 |
| Invasive mechanical ventilation | 0 (0) | 10 (28.6) | 10 (5) | 0.0000 |
| **Treatments, n (%)** | | | | |
| Dexamethasone | 105 (63.6) | 35 (100) | 140 (70) | 0.0128 |
| Antibiotics | 12 (7.3) | 19 (54.3) | 31 (15.5) | <0.0001 |
| Antiviral therapy | 0 (0) | 1 (2.9) | 1 (0.5) | 0.1750 |
| **Laboratory data at admission, mean (IQR)** | | | | |
| Haemoglobin | 13.7 (12.6–14.6) | 13.8 (12.3–15.0) | 13.7 (12.6–14.6) | 0.7151 |
| Leukocytes | 6.1 (4.7–7.8) | 6.3 (4.8–8.6) | 6.2 (4.8–7.9) | 0.6250 |
| Lymphocytes | 1.1 (0.8–1.4) | 0.9 (0.6–1.3) | 1.1 (0.7–1.4) | 0.1667 |
| Platelets | 199 (156–258) | 179 (139–223) | 191 (153–251) | 0.0371 |
| Fibrinogen | 5.2 (4.5–5.9) | 5.2 (4.6–5.7) | 5.2 (4.5–5.9) | 0.8189 |
| D-dimer | 176 (119–267) | 228 (167–410) | 185 (127–295) | 0.0061 |
| Urea | 29.0 (22.0–39.0) | 30.0 (24.0–38.0) | 29.5 (23.0–38.5) | 0.3393 |
| Creatinine | 0.8 (0.6–0.9) | 0.8 (0.6–1.0) | 0.8 (0.6–0.9) | 0.1425 |
| Bilirubin | 0.5 (0.4–0.7) | 0.6 (0.5–0.7) | 0.5 (0.4–0.7) | 0.4491 |
| Aspartase transaminase | 37 (28–51) | 49.0 (36.0–67.0) | 39.5 (29.0–55.5) | 0.0041 |
| Alanin transaminase | 29 (20–52) | 29.0 (21.0–48.0) | 29.0 (20.5–51.5) | 0.5159 |
| Lactate dehydrogenase | 302 (253–364) | 372 (315–426) | 315 (265–386) | 0.0041 |
| C-reactive protein | 6.7 (3.5–11.7) | 9.0 (5.8–18.0) | 7.0 (3.5–12.1) | 0.0639 |
| Ferritin | 440 (230–808) | 608 (294–1060) | 450 (239–869) | 0.0859 |
| Interleukin-6 | 32.0 (16.7–55.0) | 83.2 (36.0–138.3) | 36.3 (17.8–67.6) | 0.0000 |

ROX index ($SpO_2/FIO_2$)/respiratory rate; ICU: intensive care unit; IQR: interquartile range; $SpO_2$: peripheral oxygen saturation; $FIO_2$: inspiratory oxygen fraction. [#]: patients admitted to ICU anytime during protocol.

There is no consensus on which is the best scale to quantify these findings. A recent systematic review has shown the excessive diversity of scores used in COVID-19 LUS studies, calling for a homogenisation of protocols [26]. We implemented a 14-area LUS score, such as the one proposed by Soldati *et al.* [17], which has shown a good correlation with HRCT and clinical outcomes [27, 28]. In contrast to this score, we restricted "score 3" to the presence of large consolidations or tissue-like patterns, as the discrimination between white lung patterns and coalescent B-lines is sometimes challenging.

Several studies have reported a good prognostic value of a single LUS exploration for clinical outcomes in COVID-19, such as for the risk of ICU admission and mortality [29–32] or as a prediction of stability for safe discharge [33, 34]. However, only few prospective studies have attempted to analyse the prognostic value of serial LUS examinations [14–16].

**TABLE 3** Lung ultrasound (LUS) total scores on serial examinations

| | Non-ICU group | ICU group[#] | Total | p-value |
|---|---|---|---|---|
| **LUS day 1** | 165 patients | 35 patients | 200 patients | |
| Score, median (IQR) | 12 (8–15) | 22 (20–26) | 13 (9–17.5) | 0.0000 |
| **LUS day 3** | 89 patients | 7 patients | 96 patients | |
| Score, median (IQR) | 13 (10–16) | 24 (22–25) | 14 (10–17) | 0.0000 |
| **LUS day 5** | 27 patients | 0 patients | 27 patients | |
| Score, median (IQR) | 11 (8–16) | | 11 (8–16) | 0.0000 |
| **Change on LUS score day 3–day 1, median (IQR)** | 0.0 (−2.0; 1.5) | 5.0 (4.0–6.0) | 0.0 (−2.0; 1.5) | 0.0000 |
| **Change on LUS score day 5–day 3, median (IQR)** | −2.0 (−5.0; 0.0) | N/A | −2.0 (−5.0; 0.0) | |

ICU: intensive care unit; IQR: interquartile range. [#]: patients admitted to ICU anytime during protocol.

The first study conducted by Casella *et al.* [14] reported that both LUS at admission and after 72 h were correlated with ICU admission and death. However, the change between the first and second LUS score was not analysed. Rubio-Gracia *et al.* [15] also reported that LUS score at admission predicted ICU transfer and death. Follow-up explorations showed that LUS score did not change during the first 72 h and decreased at discharge, so did not provide additional information. In contrast, Torres-Macho *et al.* [16] showed the usefulness of serial LUS examinations. In fact, this large multicentric cohort study showed that absence of progression in the LUS score used for this purpose at 72–96 h from admission predicted minimal risk of death or IMV with a NPV of 99%. Unfortunately, this study did not provide data on the number of sonographers involved or give a clear interobserver agreement calculation – a key factor in this kind of evaluation with high operator-dependence.

In our report, LUS score was identified as an independent predictor for ICU transfer in the multivariate analysis. Additionally, a LUS score <17 at admission was able to discard this unfavourable outcome with a NPV of 99.3%.

In line with Torres-Macho *et al.* [16], our study also showed that a follow-up LUS examination is useful to predict clinical outcomes. The absence of progression of LUS score on day 3 demonstrated subsequent clinical stability. However, an increase of the score on day 3 was associated with a high risk of clinical deterioration. Consequently, the incorporation of a control LUS exploration on day 3 significantly increased the prediction accuracy of this technique for ICU transfer (specificity and PPV increased to

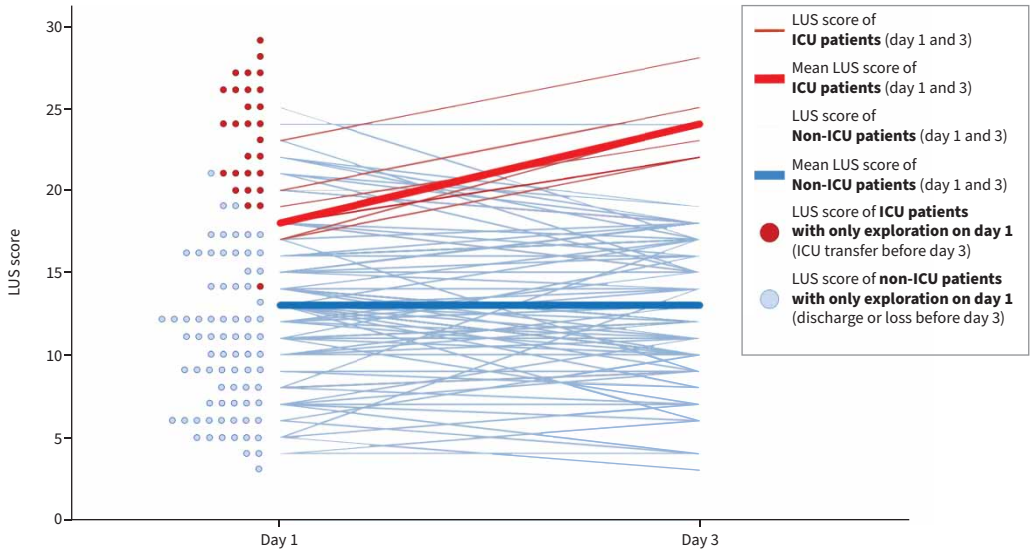


**FIGURE 4** Changes in lung ultrasound (LUS) scores between day 3 and day 1 of admission regarding the forthcoming intensive care unit (ICU) requirement.

**TABLE 4** Univariate logistic regression analysis for intensive care unit transfer

| Variable | OR | (95% CI) | p-value |
|---|---|---|---|
| **Age** | 1.04 | (1.01–1.08) | 0.013 |
| **Female gender** | 0.74 | (0.33–1.64) | 0.457 |
| **Overweight** | | | |
| BMI >25, n (%) | 0.86 | (0.32–2.30) | |
| BMI >30, n (%) | 1.62 | (0.63–4.15) | |
| **Tobacco consumption** | | | |
| Never-smokers | 1 | | 0.005 |
| Past-smokers | 3.61 | (1.64–7.96) | |
| Active-smokers | 0.75 | (0.09–6.25) | |
| **Comorbidities (if present)** | | | |
| Hypertension | 2.52 | (1.19–5.31) | 0.015 |
| Dyslipidaemia | 2.18 | (1.02–4.64) | 0.043 |
| Diabetes | 1.43 | (0.53–3.87) | 0.140 |
| COPD | 3.27 | (1.00–10.68) | 0.049 |
| Asthma | 0.37 | (0.05–2.98) | 0.354 |
| Active cancer | 1.05 | (0.22–5.09) | 0.951 |
| OSAS | 6.71 | (1.70–26.43) | 0.007 |
| Connective tissue disease | 1.94 | (0.36–10.43) | 0.440 |
| Liver disease | 4.94 | (0.67–36.33) | 0.117 |
| Chronic renal disease | 1.59 | (0.16–15.73) | 0.693 |
| Myocardial infarction | 1.59 | (0.16–15.73) | 0.693 |
| Congestive heart failure | 2.40 | (0.21–27.19) | 0.481 |
| Peripheral vascular disease | 9.94 | (0.88–112.83) | 0.063 |
| Stroke | 9.94 | (0.88–112.83) | 0.063 |
| CCI, median (IQR) | 1.25 | (1.04–1.50) | 0.019 |
| **Clinical variables** | | | |
| Days from symptoms onset to hospitalisation | 0.96 | (0.86–1.06) | 0.397 |
| $SpO_2/FIO_2$ ratio at admission | 0.98 | (0.97–0.99) | 0.0001 |
| ROX index at admission | 0.76 | (0.68–0.85) | 0.0000 |
| Pulmonary embolism | 4.82 | (0.29–79.03) | 0.270 |
| **Laboratory data** | | | |
| Haemoglobin | 1.04 | (0.82–1.32) | 0.748 |
| Leukocytes | 1.06 | (0.92–1.22) | 0.451 |
| Lymphocytes | 0.57 | (0.25–1.29) | 0.177 |
| Platelets | 0.995 | (0.99–1.00) | 0.074 |
| Fibrinogen | 0.93 | (0.63–1.36) | 0.697 |
| D-dimer | 1.00 | (1.000–1.002) | 0.036 |
| Urea | 1.01 | (0.99–1.03) | 0.328 |
| Creatinine | 1.83 | (0.79–4.23) | 0.156 |
| Bilirubin | 2.72 | (0.64–11.61) | 0.177 |
| Aspartase transaminase | 1.01 | (1.00–1.02) | 0.006 |
| Alanin transaminase | 1.01 | (1.00–1.01) | 0.146 |
| Lactate dehydrogenase | 1.004 | (1.001–1.008) | 0.006 |
| C-reactive protein | 1.04 | (0.99–1.09) | 0.094 |
| Ferritin | 1.001 | (1.000–1.001) | 0.089 |
| Interleukin-6 | 1.02 | (1.01–1.02) | 0.000 |
| **Lung ultrasound** | | | |
| LUS score at admission | 1.64 | (1.40–1.93) | 0.0000 |

ROX index: ($SpO_2/FIO_2$)/respiratory rate. OR: odds ratio; BMI: body mass index, OSAS: obstructive sleep apnoea syndrome; CCI: Charlson comorbidity index; IQR: interquartile range; $SpO_2$: peripheral oxygen saturation; $FIO_2$: inspiratory oxygen fraction; LUS: lung ultrasound.

94.55% and 79.07%, respectively). Figure 5 gives a proposal for a clinical algorithm for using LUS as a predictor for ICU transfer.

Only 27 patients underwent LUS on day 5, and all of them presented a favourable evolution. The mean LUS score on day 5 decreased; however, its prognostic relevance could not be calculated due to the low numbers of subjects remaining in the study.

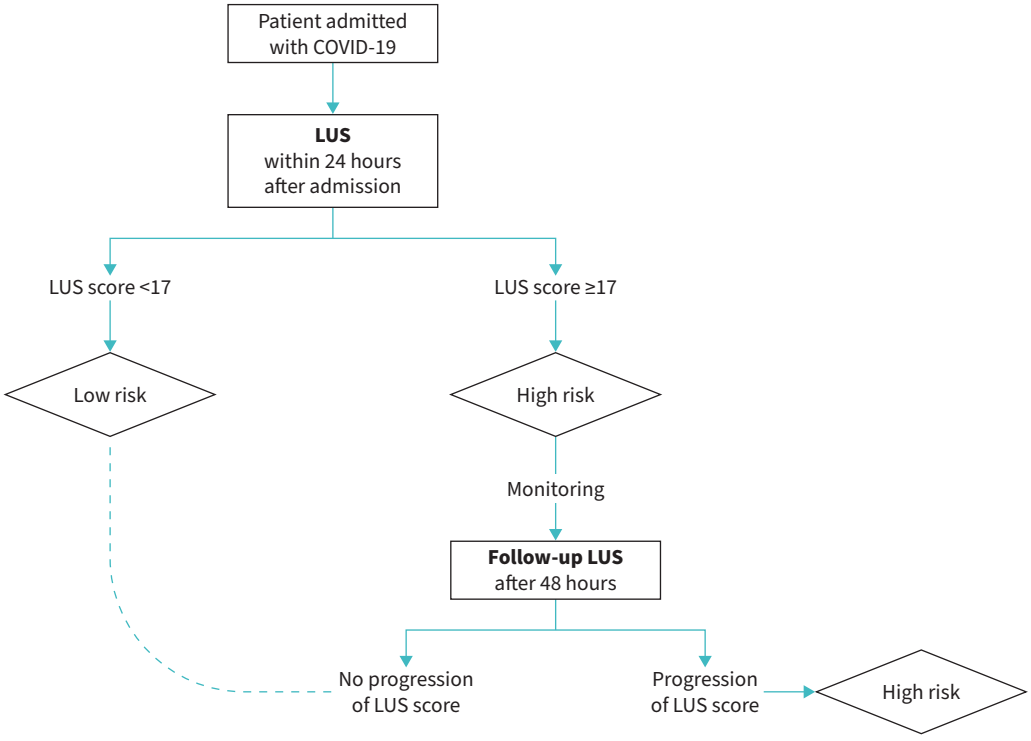


FIGURE 5 Proposal for a clinical algorithm for use of lung ultrasound (LUS) as a predictor for intensive care unit transfer.

Our findings have relevant implications for clinical practice. Prediction of respiratory deterioration is essential in COVID-19, given its heterogeneous clinical presentation and the fast progression to severe disease. After more than 2 years of pandemic, there is no consensus on which tools have the best prognostic value. Surprisingly, LUS is absent in most protocols despite the existing evidence on its usefulness [35–37]. Our study shows that evaluation of lung involvement by LUS is related to clinical outcomes and predicts respiratory deterioration. Its application as a stratification tool could be helpful not only for detecting and monitoring high-risk patients, but also for identifying low-risk patients who can be safely discharged, thus optimising health resources. Finally, its technical features (accessible, low-cost, nonionising and portable) support its reliability on large pandemic populations.

Although there is not yet enough evidence, in the future it is possible that LUS could be used for the management of other viral pneumonias. Respiratory viruses are responsible for up to 30% of community acquired pneumonia (CAP) cases in adults and 60% in children, and these rates could rise, particularly with the increase of rapid diagnostic tests that are able to distinguish between viral and bacterial infections [38–40]. The previous literature on the use of LUS in management of pneumonia is limited to children [41, 42] and adults in intensive care (respiratory distress, mechanical ventilation, *etc.*) [43, 44]. In addition, bacterial pneumonias usually differ from viral pneumonias in their clinical and radiological progression. Despite this heterogeneity, our results support the need for further studies to confirm the prognostic role of LUS in management of pneumonia of any cause.

### *Strengths and limitations*

The present study has some remarkable strengths. Firstly, it is the largest prospective single-centre cohort published for this objective. It is a real-life study as LUS was performed during hospitalisation by pulmonologists. All the LUS explorations were performed by only four sonographers with experience in LUS, using the same equipment and achieving an excellent interobserver agreement. However, this is also a limitation, since the fact that this is a single-centre study could impact on the generalisability of results.

In this sense, another important limitation is the type of population and the time the study took place, during the second wave of the coronavirus outbreak. The significant number of young participants with few comorbidities, and the more conservative protocols in use at that time of the pandemic, had relevant

implications on clinical management. Examples of this are the high percentage of patients hospitalised for mild pneumonias and the transfer to ICU to every patient with an HFO requirement. It is important to point out that this is a mostly unvaccinated population, which could also influence the extrapolation of the results. Unfortunately, the viral strains causing pneumonia in our patients could not be determined during our study although it is likely they were mostly Alpha variants, according to the local epidemiology at the time.

Finally, the significant loss of follow-up, especially for early discharges, made it impossible to perform control LUS examinations on all patients. In particular, LUS on day 5 was performed on a limited number of patients, which did not allow the interpretation of these data. It is likely that patients with milder symptoms were excluded from this follow-up due to early discharge, thus generating a potential selection bias; however, the present study was able to assess the risk of respiratory deterioration with a sufficient level of confidence.

### *Conclusion*

Serial LUS is a reliable tool in predicting the risk of respiratory deterioration in patients hospitalised for viral pneumonia due to COVID-19. A score <17 at admission rules out a forthcoming respiratory worsening with ICU transfer. Patients with a LUS score ⩾17 should be monitored and undergo a control examination in 48 h, which in absence of progression would also rule out a future deterioration. Taking into consideration the multiple practical advantages of this technique (low-cost, ease, no radiation), we hope that our results will promote further investigation on the role of LUS as prognostic tool in other types of pneumonia, particularly in case of new epidemics/pandemics.

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Author contributions: D. Clofent is the guarantor of the paper and takes full responsibility for the content of the manuscript, including data and analysis. D. Clofent, M. Culebras and E. Polverino conceived and designed the study, analysed the data, and drafted the manuscript. D. Clofent, A. Felipe-Montiel, G. Granados and M. Arjona-Peris performed lung ultrasound examinations in all patients. A. Álvarez, K. Loor, P. Bosch-Nicolau, A. Felipe-Montiel, F. Pilia and M. Sáez critically reviewed the manuscript for relevant intellectual content. All the authors critically reviewed and approved the final version of the manuscript.

Access to data: Requests to access the datasets should be directed to david.clofent@vallhebron.cat.

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