Usefulness of lung ultrasound in the early identification of severe COVID-19: results from a prospective study

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Abstract

Aim: There is growing evidence regarding the imaging findings of coronavirus disease 2019 (COVID-19) in lung ultrasound (LUS); however, its role in predicting the prognosis has yet to be explored. The aim of the study was to assess the relationship between lung ultrasound findings with the degree of respiratory failure measured by the PaO2/FiO2 ratio (PaFi) and the prognosis of these patients: need for non-invasive mechanical ventilation (NIMV), admission to the Intensive Care Unit (ICU) and mortality. Material and method: Prospective, longitudinal and observational study performed in patients with confirmed COVID-19 underwent a LUS examination and laboratory tests. Results: A total of 107 patients were enrolled: 93.4% with bilateral involvement and 73.83% presented at least one consolidation. A good inverse correlation (Rho Spearman coefficient -0.897) between the ultrasound score and PaFi was obtained. The AUC for identification of patients with more severe respiratory failure, a moderate and severe ARDS, was 0.97 (CI 95%: 0.95-1) and a cut-off score of 34.5 showed a sensitivity of 0.94 and a specificity of 0.91. The Kappa index showed a high concordance (0.83) of the classification by ultrasound lung involvement and ARDS. Conclusions: The combination of the ultrasound score and the presence of respiratory failure can easily identify patients with a higher risk to present complications.

Keywords: Coronavirus disease 2019 (COVID-19); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); lung ultrasound (LUS); lung score

Introduction

The first cases of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were reported at the end of December 2019 and in March 2020 the World Health Organization declared a pandemic. At present, the virus continues to spread around the world; there are more than 115 million confirmed cases and more than 2.5 million deaths (https://covid19.who.int/).

A significant percentage of COVID-19 patients will develop pneumonia [1] and 15-20% require hospitalization due to respiratory failure. Acute respiratory distress syndrome (ARDS) due to COVID-19 is the main cause of death [2].

Risk factors associated with poor outcomes are age above 65 years, some chronic diseases (cardiovascular, pulmonary and chronic kidney diseases), active malignancy, diabetes mellitus and obesity, among others. Hypoxemia (baseline oxygen saturation <95%) and some
abnormal laboratory findings such as lymphopenia and significant elevation of acute-phase reactants are also prognostic. The extent of lung lesions detected on chest X-ray or computed tomography (CT) [1,3] have also been associated with a poor prognosis.

The most reliable imaging method to diagnose COVID-19 pneumonia is chest CT [4], although chest X-ray is the most common imaging method used in most of the medical centers owing to its wide availability.

Lung ultrasound (LUS) is an ideal alternative to chest X-ray as it is safe, rapid, can be performed at the bedside, from outpatient facility or hospital and has a good correlation with CT findings [5]. Numerous studies have demonstrated that LUS has a higher diagnostic accuracy for pneumonia than the chest X-ray [6-7]. In addition, the main ultrasound features associated with COVID-19 pneumonia have been described [8]. However, few studies have correlated these findings with the patient’s prognosis [9-10].

The main purpose of this study was to assess the relation between the LUS findings in the acute phase of SARS-CoV-2 infection with the degree of respiratory failure measured by the partial pressure arterial oxygen and fraction of inspired oxygen and the prognosis of these patients: need for non-invasive mechanical ventilation (NIMV), admission to the Intensive Care Unit (ICU) and mortality. The secondary objectives were to describe the most relevant LUS findings associated with SARS-CoV-2 pneumonia and to assess which demographic, comorbidities, clinical and laboratory findings were associated with a more severe lung involvement.

Material and method

Patient selection

This was a prospective, longitudinal and observational study performed in Europe’s largest COVID-19 field hospital, Ifema in Madrid, opened during the first wave of the pandemic (21st of March to 1st of May 2020). A total of 3,814 patients were admitted during that period.

Inclusion criteria consisted of: 1) confirmed COVID-19 cases [11] with positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) or positive antigen/antibody test for SARS-CoV-2; 2) probable COVID-19 cases [11] as any severe acute respiratory infection who meets clinical, laboratory and radiological criteria, in the absence of any other identified cause; 3) mild, moderate or severe disease as classified according to the National Institutes of Health (NIH) COVID-19 Guidelines [12]; 4) Absence of critical illness at the time of inclusion according to the classification of the NIH COVID-19 Guidelines [12]; 4) age above 18 years; 5) signing of the informed consent to participate in the study. Exclusion criteria consisted of all patients who declined to participate and cognitive impairment or inability to understand the objectives of the study.

A random sample of the 1710 patients who met the inclusion criteria during the period of two weeks in April 2020 (7th to 20th) were recruited. Each patient gave informed consent and the study was approved by the Research Ethics Committee of our University Hospital. (protocol number 20/16).

Initial patient assessment and data collection

Epidemiological and clinical data were collected at inclusion using an electronic case report form and were included in an anonymized database. We also collected the laboratory tests results at admission and the clinical evolution (complications, mechanical ventilation support, ICU admission and mortality).

Ultrasound data collection

All LUS exams were performed by a single research team of three internal medicine physicians with long experience in Point-of-Care Ultrasound (certified by the ultrasound working group of the Spanish Internal Medicine Society).

The LUS examinations were performed at the patient’s bedside using two cart-based ultrasound machines (SONOSCAPE X3 Exp™ and Esaote MyLab Omega™) equipped with a curvilinear array transducer with an abdominal preset. The ultrasound exam was performed following a 13-area protocol (3 in the posterior area and 2 lateral of each lung, 2 anterior of the right lung and 1 in the anterosuperior left lung) [13]. We omitted the left anteroinferior area due to the opposition of the heart.

In the LUS exam, we assessed the presence of the following COVID-19 typical findings [5,8]: irregular pleural line or focal B lines; focal or confluent B lines; subpleural (<1 cm) or lobar consolidation (>1 cm).

We assigned a score to each pathological finding: Interstitial involvement: 2 points: irregular-discontinuous pleural line and / or <3 B-lines; 4 points: ≥3 B-lines; 6 points: very confluent B lines (white lung: “lung rockets”); Consolidation: subpleural consolidation (+0.5 points) or consolidation >1 cm (+1 point); Bilateral distribution: +1 point. We summed the findings at each of the 13-areas (“score”), ranging from 0 to 92 points.

PaFi (PaO2/FiO2)

The partial pressure arterial oxygen and fraction of inspired oxygen (PaFi = PaO2/FiO2 x 100) was calculated from each patient at the moment of the LUS exam as an indicator of ARDS according to the Berlin Criteria [14]: PaFi ≥300 mmHg: no ARDS; PaFi 200-299 mmHg: mild ARDS; PaFi 100-199 mmHg: moderate ARDS; PaFi <100 mmHg: severe ARDS.
In cases where arterial blood gas analysis was not available, this relation was obtained by pulse oximetric saturation (SpO₂) using the Severinhause-Ellis SaFi-PaFi equivalence equation [15,16].

**Statistical analysis**

Continuous variables were presented as mean and standard deviation (+/-), count and proportions for categorical variables. The baseline characteristics, clinical, laboratory variables of mild-moderate patients (score <35) were compared with severe-critical patients (score ≥35), as well as the ultrasound score and PaFi to the severity of the ARDS and the risk of complications according to LUS involvement (critical patients compared to the rest).

To assess normality a Kolmogorov-Smirnov test was performed. For continuous variables that have a normal distribution, we used a T-Student and the Mann-Whitney test for those who do not have normal distribution. For comparison of more than two groups, the Analysis of variance (ANOVA) was used. For categorical variables that have a normal distribution, the Chi-square hypothesis testing was performed.

The correlation between the continuous variables PaFi and score was analyzed using Rho-Spearman, as it does not have a normal distribution and the Kappa index was used for categorical variables.

The area under the curve (AUC) was calculated with the receiver operating characteristic (ROC) curve to determine the ability of the score to identify patients with more severe respiratory failure. Results were expressed as odds ratio (OR) along with its 95% confidence interval. We assumed a p-value of 0.05 for statistical significance. Analyses were conducted with the statistical IBM SPSS software v24.0 (SPSS Inc., Chicago, IL, USA).

**Results**

In our study, 115 patients who met the inclusion criteria were identified. Of these, 8 patients refused to participate. Thus, 107 patients were finally included and completed the follow-up. Baseline demographics, patient characteristics and relevant laboratory results are summarized in table I.

Patients were admitted to the Ifema field hospital transferred from any emergency department from our city, on an average of 2.51±3.95 days since arrival to the hospital of origin; symptom onset occurred 5.37±2.65 days before and LUS was performed at 12.93±4.51 days.

According to the ultrasound findings, 100 patients (93.4%) had bilateral involvement, and the most frequently affected were the posteroinferior and the lateral areas; 79 patients (73.83%) presented at least one consolidation, 76 patients (71.02%) had <1 cm subpleural consolidations and 27 patients (25.23%) larger than 1 cm. Mild pleural effusion was present in only 4 patients, bilateral in one patient.

Table II shows a good inverse correlation (Rho Spearman coefficient -0.897) between the ultrasound score and PaFi. A higher LUS involvement was associated with a lower PaFi, represented by a nonlinear regression. The following quadratic equation was obtained: \( R^2 = 0.872 \).

Figure 1 shows the ROC curve of the score as a method of identifying patients with more severe respiratory failure according to the Berlin Criteria (mortality greater than 31%) [14]. The AUC was 0.97 (CI 95%: 0.95-1) and a cut-off score of 34.5 showed a sensitivity of 0.94 and a specificity of 0.91.

The relation between the score and ARDS was graphically represented in a box plot in figure 2, divided horizontally in 4 groups according to the score and the mild to critical LUS involvement. According to this, in our study, 23 patients had mild involvement versus 23 without ARDS, 10 patients had moderate involvement versus 12 with mild ARDS, 39 patients had severe involvement versus 40 with moderate ARDS, and 35 patients with critical involvement versus 32 with severe ARDS. The Kappa index showed a high concordance (0.83) of the classification by LUS involvement and ARDS.

**Relation between ultrasound score and prognostic factors**

Possible differences in demographics and clinical characteristics between the ultrasound groups (mild-to-moderate and severe-to-critical) were analyzed (Table I),

![Fig 1. Receiver operating characteristic (ROC) curve for identification of patients with moderate and severe Acute respiratory distress syndrome (ARDS). Cut-off value of 34.5 (asterisk).](image_url)
Table I. Demographics, clinical characteristics and ultrasound severity classification of patients included at hospital admission (n = 107).

|                         | Total N = 107 | Mild to moderate LUS (score < 35) N = 33 | Severe to critical LUS (score ≥ 35) N = 74 | p-value |
|-------------------------|---------------|------------------------------------------|------------------------------------------|---------|
| **Sex**                 |               |                                          |                                          |         |
| Male                    | 61 (57)       | 17 (51.51)                                | 44 (59.46)                               | 0.443   |
| Female                  | 46 (42)       | 16 (48.48)                                | 30 (40.54)                               | 0.443   |
| **Age**                 |               |                                          |                                          |         |
| Mean age (years)        | 55.64 ±13.28  | 54.30 ±14.64                              | 56.23±12.68                              | 0.753   |
| 20-35                   | 8 (7.48)      | 4 (12.12)                                 | 4 (5.41)                                 | 0.660   |
| 35-50                   | 24 (22.43)    | 6 (18.18)                                 | 18 (24.32)                               | 0.660   |
| 50-65                   | 45 (42.06)    | 14 (42.42)                                | 31 (441.89)                              | 0.660   |
| 65-80                   | 26 (24.30)    | 7 (21.21)                                 | 19 (25.68)                               | 0.660   |
| ≥80                     | 4 (3.74)      | 2 (6.06)                                  | 2 (2.70)                                 | 0.660   |
| **Ethnicity**           |               |                                          |                                          |         |
| Caucasian               | 56 (52.34)    | 19 (57.58)                                | 37 (50.0)                                | 0.218   |
| Hispanic                | 50 (46.73)    | 13 (39.40)                                | 37 (50.0)                                | 0.218   |
| Arab                    | 1 (0.93)      | 1 (3.03)                                  | 0 (0)                                    | 0.218   |
| **Medical history**     |               |                                          |                                          |         |
| Obesity                 | 38 (35.51)    | 9 (27.27)                                 | 29 (39.19)                               | 0.234   |
| Hypertension            | 32 (29.91)    | 10 (30.30)                                | 22 (29.73)                               | 0.952   |
| Overweight              | 22 (20.56)    | 7 (21.21)                                 | 15 (20.27)                               | 0.91    |
| Dyslipemia              | 19 (17.76)    | 3 (9.09)                                  | 16 (21.62)                               | 0.117   |
| COPD/Asthma             | 17 (15.89)    | 10 (30.30)                                | 7 (9.46)                                 | 0.06    |
| Diabetes Mellitus       | 11 (10.28)    | 6 (18.18)                                 | 5 (6.76)                                 | 0.07    |
| Chronic Heart Disease   | 9 (8.41)      | 4 (12.12)                                 | 5 (6.76)                                 | 0.356   |
| SAHS                    | 7 (6.54)      | 2 (6.06)                                  | 5 (6.76)                                 | 0.893   |
| Malignancy              | 8 (7.48)      | 1 (3.03)                                  | 7 (9.46)                                 | 0.243   |
| **Symptoms at admission** |           |                                          |                                          |         |
| Fever                   | 91 (85.04)    | 26 (78.79)                                | 65 (87.83)                               | 0.225   |
| Cough                   | 74 (69.16)    | 23 (69.69)                                | 51 (68.92)                               | 0.827   |
| Dyspnea                 | 66 (61.68)    | 20 (60.61)                                | 46 (62.16)                               | 0.878   |
| Abdominal symptoms      | 58 (54.20)    | 20 (60.61)                                | 38 (51.35)                               | 0.375   |
| Malaise/Fatigue         | 50 (46.73)    | 14 (42.42)                                | 36 (48.65)                               | 0.255   |
| Anosmia or dysgeusia    | 33 (30.84)    | 15 (45.46)                                | 18 (24.32)                               | 0.029   |
| Arthromyalgia           | 32 (29.91)    | 10 (30.30)                                | 22 (29.73)                               | 0.952   |
| Cephalrea               | 18 (16.82)    | 7 (21.21)                                 | 11 (14.86)                               | 0.418   |
| **Laboratory results at admission** | | | | |
| White blood cell /μL    | 6816 ±2956    | 7013 ±3148                                | 6754 ±2847                               | 0.688   |
| Lymphocyte /μL          | 1113 ±614     | 1569 ±835                                 | 937 ±381*                                | <0.0001 |
| D dimer (ng/dL)         | 1990 ±7917*   | 1121.79 ±1332*                            | 2441.24 ±9542*                           | 0.117   |
| C reactive Protein (mg/L)| 98 ±89.2*    | 61.4 ±73.04*                              | 113.1 ±90.33*                            | 0.007   |
| Ferritin (ng/mL)        | 830 ±699*     | 620.5 ±570.9*                             | 904.1 ±740.6*                            | 0.392   |
| **Physical exam at admission** | | | | |
| Oxygen Saturation       | 93.94 ±4.03   | 95.20 ±3.16                               | 93.42 ±4.34                              | 0.302   |
| Hypoxemia               | 33 (30.84)    | 7 (21.21)                                 | 26 (35.14)                               | 0.150   |
| Respiratory failure     | 21 (19.63)    | 2 (6.06)                                  | 18 (24.32)                               | 0.025   |
| **Patient status at admission** [21] | | | | |
| Mild                    | 16 (14.95)    | 16 (48.48)                                | 0 (0)                                    | <0.0001 |
| Moderate                | 57 (53.27)    | 13 (39.39)                                | 44 (59.46)                               | <0.0001 |
| Severe                  | 34 (31.77)    | 4 (12.12)                                 | 30 (40.54)                               | <0.0001 |

The results are expressed as number (%) or mean±standard deviation. LUS: lung ultrasound; COPD: chronic obstructive pulmonary disease; SAHS: sleep apnea/hypopnea syndrome. * Abnormal parameters according to laboratory reference values
without significant differences. Patients with severe-to-critical lung involvement had significantly lower white blood cell count and higher C-reactive protein levels than those with mild-to-moderate involvement (p < 0.05).

Complications

Table III shows the incidence of complications of the patients according to the LUS involvement. As seen, patients with critical lung involvement (score ≥50; n=35) had a significantly higher relative risk of requiring noninvasive mechanical ventilation (NIMV) (5.14; CI 95%: 2.18-12.11), ICU admission (12.34; CI 95%: 2.92-52.17), need for invasive mechanical ventilation (IMV) (20.57; CI 95%: 2.74-154.39) and death (6.17; CI 95%: 0.67-57.21).

Discussion

Although chest CT might offer a more accurate way to diagnose COVID-19 lung involvement, due to the scale of the pandemic, its routine use for this purpose is not available in most hospitals. Therefore, alternatives such as chest X-ray and LUS should be explored. Several studies have shown that LUS has a greater sensitivity than chest X-ray [17] and has a good correlation with chest CT [5].

The main ultrasound findings seen in SARS-CoV-2 pneumonia are well defined: the interstitial involvement (various patterns of B-lines), consolidation and irregularities of the pleural line [18,19]. While none of these pathologic abnormalities are specific, in the adequate clinical scenario, the bilateral and patchy distribution (areas of sparing) may aid in the diagnosis [8,18,20].

Furthermore, LUS can have an important role in the monitoring and prognosis of these patients. For this purpose, it is essential a standardization of the scanning areas to be scanned and the scoring system for each finding. In our study, we have followed the standardization proposed by Soldati et al [13], in which each hemithorax is divided into 7 areas (3 posterior, 2 lateral and 2 anterior). We finally decided to exclude the left anteroinferior area due to the common opposition of the heart. Unfortunately, there is still no consensus in this regard, complicating the reproducibility of the results, even more as more flexible approaches are being proposed [21-23].

There are also no uniform criteria with regard to the scoring method. In many studies, consolidations have higher score than B-lines [13,22]. However, when assessing the severity of the lung involvement in COVID-19 it might be more relevant the extension of the affected lung areas rather the presence of consolidations [8]. In our scoring system we have prioritized the number of ab-

Table II. Lung ultrasound score and PaFi.

| PaFi  | Score  | Multiple Comparisons | Mean difference | p-value |
|-------|--------|----------------------|-----------------|---------|
| No ARDS | 403.13 ± 55.73 | 10.28 ± 8.11 | Mild ARDS | -21.84 | <0.0001 |
|        |        |                     | Moderate ARDS  | -31.60  | <0.0001 |
|        |        |                     | Severe ARDS   | -51.40  | <0.0001 |
| Mild ARDS | 246.33 ± 22.62 | 32.13 ± 6.89 | No ARDS      | 21.84   | <0.0001 |
|        |        |                     | Moderate ARDS | -9.76   | <0.0001 |
|        |        |                     | Severe ARDS  | -29.56  | <0.0001 |
| Moderate ARDS | 149.65 ± 33.37 | 41.89 ± 6.10 | No ARDS     | 31.60   | <0.0001 |
|        |        |                     | Mild ARDS    | 9.76    | <0.0001 |
|        |        |                     | Severe ARDS | -19.80  | <0.0001 |
| Severe ARDS | 87.53 ± 7.91  | 61.69 ± 8.51 | No ARDS    | 51.40   | <0.0001 |
|        |        |                     | Mild ARDS   | 29.56   | <0.0001 |
|        |        |                     | Moderate ARDS | 19.80  | <0.0001 |

The results are expressed as mean ± standard deviation. ARDS: Acute Respiratory Distress Syndrome; PaFi: PaO2/FiO2
normal lung areas. Therefore, we decided to give a higher score to the bilaterality of the lung injury. It should also be taken into account that the consolidation might follow a focal interstitial involvement (B-lines).

Our study shows that our “score” had a good to excellent correlation (Rho Spearman coefficient -0.897) with the severity of the respiratory failure (PaFi). Lower correlation coefficients results had been reported between the severity and the extent of the lung injury and the respiratory failure [23]. This fact would support the reliability of our score. In this sense, patients with severe (score 35-50) or critical (score ≥ 50) LUS involvement had a significantly higher risk of requiring mechanical ventilation support, ICU admission, longer hospital stay, complications (i.e., thromboembolic disease) and mortality. Patients with a score above 50 (critical involvement) had a 5 times higher risk of needing intubation, 12 times higher risk for ICU admission and 20 times higher for requiring noninvasive mechanical ventilation. These findings are striking and of undoubted benefit since it will allow us to better stratify the severity of our patients and more appropriately establish who will need closer clinical surveillance.

Another striking result is that 17 of the 19 patients that were diagnosed with thromboembolic event (3 proximal deep vein thrombosis and 16 pulmonary embolism) had a score above 35 (severe to critical lung involvement). Thromboembolic events are common in COVID-19 patients [24,25]; however, the need to screen for deep vein thrombosis in hospitalized patients remains controversial [26,27]. In addition to the positive D-dimer result, deep vein thrombosis should be ruled-out in patients with severe or critical LUS involvement [27].

The distribution of COVID-19 ultrasound abnormal findings in our cohort are similar to those reported in previous studies [8]. Most of the patients had a bilateral involvement, with a predominance of an interstitial involvement (B-lines) especially in the posteroinferior areas. We noticed a high presence of subpleural consolidations (<1 cm). While these lesions are not specific to COVID-19, they had been only described in a limited number of lung processes, such as pulmonary infarction [28]. Several theories had been suggested that these subpleural consolidations seen in COVID-19 correspond to microthrombus of small-caliber pulmonary arteries, not evident on pulmonary CT angiography [29,30].

There are several limitations to acknowledge. First of all, the sample size is relatively small and this limits the statistical power of some of the results. Ultrasonography, as an operator-dependent imaging modality, is subjective to the experience and skill of the examiner and a certain degree of collaboration from the patients. Although this could limit the external validity of our results, this limitation is inherent to any studies involving the use of ultrasound. This research group acknowledges that it would have been useful to have a comparator such as chest CT (reference standard) at the time the LUS was performed. Unfortunately, at that moment, chest CT was not available for the vast majority of our patients. Moreover, since patients were transferred from other hospitals, LUS could not be performed with the first physician encounter, but only during admission.

In conclusion, our study suggests an excellent relationship between an ultrasound scoring system (“score”) that estimates the lung involvement and the presence of respiratory failure of the patients. Moreover, patients with a higher score were more prone to present complications, such as thromboembolic disease, ventilatory support, admission to the ICU and mortality. This would improve detection of the patients who are most likely to benefit from more intensive monitoring and therapy.

Conflict of interest: none
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