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Early View

Original article

Point-of-care lung ultrasound assessment for risk stratification and therapy guiding in COVID-19 patients. A prospective non-interventional study

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Point-of-care lung ultrasound assessment for risk stratification and therapy guiding in COVID-19 patients. A prospective non-interventional study.

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Take-home messages

- Lung injury caused by COVID-19 can be measured through lung ultrasound (LUS).
- LUS identify COVID-19 patients at a higher risk of complications.
- LUS could support clinical-decision making in COVID-19 patients.

Background: Lung ultrasound (LUS) is feasible for assessing lung injury caused by COVID-19. However, the prognostic meaning and time-line changes of lung injury assessed by LUS in COVID-19 hospitalized patients, is unknown.

Methods: Prospective cohort study designed to analyze prognostic value of LUS in COVID-19 patients by using a quantitative scale (LUZ-score) during the first 72 hours after admission. Primary endpoint was in-hospital death and / or admission to the intensive care unit. Total length of hospital stay, increase of oxygen flow or escalate medical treatment during the first 72 hours, were secondary endpoints.

Results: 130 patients were included in the final analysis; mean age was 56.7 ± 13.5 years. Time since the beginning of symptoms until admission was 6 days (4 - 9). Lung injury assessed by LUZ-score did not differ during the first 72 hours (21 points [16-26] at admission vs 20 points [16-27] at 72 hours; p = 0.183). In univariable logistic regression analysis estimated PaO2/FiO2 (HR 0.99 [0.98 – 0.99]; p=0.027) and LUZ-score > 22 points (5.45 (1.42 – 20.90); p=0.013) were predictors for the primary endpoint.

Conclusions: LUZ-score is an easy, simple and fast point of care ultrasound tool to identify patients with severe lung injury due to COVID-19, upon admission. Baseline score is predictive of severity along the whole period of hospitalization. The score facilitates early implementation or intensification of treatment for COVID-19 infection. LUZ-score may be combined with clinical variables (as estimated PAFI) to further refine risk stratification.

Introduction

COVID-19 is a systemic disease caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)[1, 2]. The virus emerged in China in late 2019 and quickly spread worldwide, challenging healthcare systems and becoming the most devastating pandemic in over a century[3]. In essence, it is a multisystem disease, with special tropism for lungs, where may lead to a severe respiratory failure, ultimately causing the need for mechanical ventilation and high fatality[4]. None of the therapies tested so far, except for low-dose systemic corticosteroids in most severely patients, have shown efficacy in reducing mortality[5]. Therefore, early detection of lung involvement, and anticipation of respiratory complications in COVID-19 patients would be of enormous assistance for clinicians in order to individualize patient management and anticipate the need for mechanical ventilation.

Not surprisingly, COVID-19 has resulted in a diagnostic challenge, since many patients present a dissociation between symptoms and radiological findings (e.g., in around a third of patients, infiltrates in chest X-ray are absent)[2, 6, 7]. Since first outbreak began[1], attempts have been made to improve early diagnosis and potential complications of COVID-19 infection. Due to its sensitivity, pulmonary computed tomography (CT) has been postulated as the "gold standard" to detect lung involvement[8, 9]. However, lung CT has some limitations, — especially when repeated examinations are required: equipment is not always available due to high demand, radiation exposure, the need to move around the patient, or the subsequent need of enhanced environmental cleaning after its use, all of them inconvenient and time-consuming. For all these reasons, lung ultrasound (LUS) and point of care ultrasound (POCUS)[10] have been positioned as a potential alternative for the management of patients with COVID-19.

We hypothesize that LUS is useful to quantify lung injury produced by COVID-19 during admission. Furthermore, we believe that the degree of lung injury might be related to prognosis and, hence, LUS may help in therapeutic decision-making during the first 72 hours. If true, LUS could help to design more effective and earlier treatment strategies in patients admitted for COVID-19 infection.

The goals of the study were: 1) To analyze the prognostic value of lung damage estimated by LUS at admission. 2) Validate a specific quantitative scale for lung injury in patients with COVID-19 using LUS. 3) Analyze whether the changes in lung lesions quantified through LUS during the first 48-72 hours of admission, can identify patients with a worse prognosis. 4) Analyze the correlation between analytical and clinical variables and the severity of lung damage quantified by LUS.

Material and methods

Study design and setting

Prospective cohort study carried out in the Infectious Diseases and Internal Medicine departments of tertiary, university teaching center between July and October 2020. The study consisted of two phases. First to analyze the role of LUS in COVID-19 patients, and second, aiming to identify blood biomarkers with potential clinical utility. Results included in this article refer to the first phase of the study.

Inclusion criteria: 1) Age ≥ 18 years. 2) Informed consent granted. 3) Confirmed diagnosis of SARS-CoV2 (COVID-19) infection by nasopharyngeal polymerase chain reaction (PCR) or specific serology (IgM and / or IgG) with sign or symptoms of clinically active respiratory infection. Exclusion criteria: 1) Intensive Care Unit (ICU) admission. 2) Refusal of the patient to participate. 3) Functional dependence (Barthel index <50 points). 4) Moderate / Severe cognitive impairment (Pfeiffer scale), 5) Advanced chronic obstructive pulmonary disease (COPD) (FEV1 <30%) or a history of emphysema and / or pulmonary fibrosis, 6) Active cancer.

Variables and definitions

Patients were assessed three times during hospitalization: 1) “Admission” (first 24 hours upon admission). 2) “Control” (between 48 and 72 hours later) and 3) “discharge” (the day prior to discharge). In each time point, lung involvement was quantified using a LUS protocol (see below), vital signs were recorded (blood pressure, heart rate, oxygen saturation, and respiratory

therapy), PAFI (PaO2/FiO2) index was estimated from FiO2 and oxygen saturation (ePAFI), and patient's dyspnea was quantified using Borg scale (From 1 [minimum] to 10 [maximum]). Routine blood laboratory data (Complete blood count -CBC-, biochemistry, coagulation, and blood gasses) were recorded. Additional blood samples were bio banked, after the patient's consent, and kept at -80 ºC for future analysis (Aragón Health System Biobank).

Lung ultrasound

Lung US examinations were performed with the UPROBE-C5PL wireless ultrasound device (Leleman ©), convex probe of 3.5 to 5 MHz, with a gain between 80-100 dB, and a maximum depth of between 160 and 220 mm. Images and videos were stored (Ipad 10.2. Apple ©). Researchers responsible for LUS were Internal Medicine specialists, with extensive experience in clinical ultrasound (more than two years and more than 180 thoracic LUS explorations)[11–13].

In each examination, 12 areas were analyzed according to previous studies[14] (2 anterior, 2 lateral and 2 posterior for each lung). Given the progressive nature of ultrasound changes in COVID-19, a score between 0 and 4 points was assigned to each quadrant according to the pattern of observed findings, resulting in a total score between 0 and 48 points (0 point: A lines and normal pleural line; 1 point: A lines coexist with isolated and small “b” lines; 2 points: A lines disappear and multiple "B" lines are seen alternating with preserved lung parenchymal spaces. Pleural line thickens and small "bites" may be seen; 3 points: "B" lines merge and form a giant "B" line that fills the entire intercostal space. Pleural line is blurred, "bites" appear more frequently; 4 points: Pleural line is broken and subpleural consolidations (1 to 1,5 cm deep) are observed. “Sun rays” and “Waterfall” patterns coexists.) (Figure 1,supplementary figure 5 and supplementary multimedia) -we called this protocol “*Lung Ultrasound Zaragoza Score*” (LUZ-Score). In case of multiple patterns coexisting in the same lung quadrant (according to the intercostal space analyzed), the finding with highest score was annotated. Number of affected areas, presence of sub-pleural consolidations and presence of pleural effusion were also recorded.

Outcomes

Primary endpoint was defined as the combined occurrence of in hospital-death or transfer to the ICU for invasive mechanical ventilation. The following secondary outcomes were also considered: 1) Length of hospital stay until discharge in patients not requiring ICU. 2) Whether an increase in flow oxygen during the 72 hours following admission was required, and 3) change to more aggressive medical treatment (defined as adding remdesivir or convalescent plasma, or either starting corticosteroids or increasing dexamethasone dose) during the 72 hours after admission.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (Interquartile range), as appropriate. Categorical variables were expressed as percentages. To perform the comparative analysis between normal continuous variables, the Student's t test and ANOVA were used. Those variables that did not follow normality were compared using the Mann-Whitney and Kruskal Wallis U tests. Categorical variables were compared using the chi-square test. The analysis of the different correlations between continuous variables was carried out using the Pearson or Spearman test.

Sample size was calculated based on the number of blood samples required to carry out phase 2 of the study (see study design section). Final objective was to collect 100 serum samples from patients with complete follow-up (baseline, control and discharge). To account for the consequences of healthcare pressure during recruitment phase, an approximate percentage of losses of 30% were estimated, marking a final goal of 130 inclusions.

In univariable and multivariable logistic regression analysis, LUZ-Score was dichotomized based on a cut-off value selected from ROC analysis of its primary endpoint predictive value. Multivariable logistic regression model was designed to identify factors independently associated with the need of ICU transfer during admission or intra-hospital death. Candidate predictors were selected from the univariable analysis when p-value < 0.200, and entered at a

single step in the multivariable analysis. Age was also included in the model. Bootstrap with 1000 replicates was performed, testing the stability of the model. Continuous candidate variables were transformed using logarithmic polynomials if necessary.

Confidence intervals included were 95% (95% CI), establishing statistical significance with a p lower than 0.05. Statistical analysis was carried out with Statistical Package for the Social Sciences (SPSS) version 24.0 for Windows).

The study complied with the fundamental guidelines of the Helsinki declaration guidelines (CEICA, Ref. C.P.-C.I. PI20/248, May 13Th, 2020).

Results

Baseline characteristics (Table 1)

Lung ultrasound

A total of 341 examinations were performed (130 at admission, 124 at control, and 87 at discharge). Pulmonary involvement observed through LUZ-Score did not vary between baseline and control phases (21 [10] vs 20 [11]; p = 0 .183), although significant decrease was observed at discharge (13 [12]; p = <0.001) (Figure 2 and supplementary table 1). Number of lung areas affected neither varied significantly during the first 72 hours of admission (9 [3] vs. 9 [4]; p = 0.077). The most affected lung fields were lower right lobe (R6 = 69.2%) and lower left lobe (L6 = 65.2%), followed by lateral portion of upper left lobe (L3 = 58.5%) and lateral portion of upper right lobe. (R3 = 56.2%) (Supplementary table 1).

Stratification of population according to LUZ-Score (tertiles) did not show significant differences in baseline characteristics or in comorbidities (Table 1). However, those patients with greater pulmonary involvement (LUZ-Score > 75 percentile), presented a higher degree of respiratory failure by estimated PAFI (p = < 0.001), as well as a higher dyspnea score by Borg scale (p =0.031). Patients with greater LUS alterations (LUZ score > 75 percentile), presented higher concentrations at admission of aspartate transaminase (p= 0.044), lactate dehydrogenase

(p= < 0.001), D-Dimer (p=0.037), C-reactive protein (p= 0.013) and Interleukin 6 (p= < 0.001). The proportion of patients who received treatment with systemic steroids (p=0.001) and remdesivir (0.009) was higher among patients with greater initial lung involvement quantified by LUZ-Score (Table 1).

LUZ score showed significant correlations with variables related to respiratory function as ePAFI (r=-0.516; p=<0.001) or Borg scale (r=0.228; p=0.009); lung-tissue biomarkers as lactate dehydrogenase (r=0.395; p=<0.001); and with markers of systemic inflammation such as C-reactive protein (r=0.286; p=0.001) or IL-6 (r=0.383; p=< 0.001). (Supplementary table 2 & Supplementary Figure 2).

Outcomes

Thirteen out of 130 patients reached primary endpoint (10.1%): 12 patients required admission to ICU for invasive mechanical ventilation, and another died of bacteremia associated with a central venous catheter. A baseline LUZ-Score of 22 was the point of maximum sensitivity for the primary endpoint (Sensitivity = 76.9%; Specificity = 62.1%; AUC = 0.693; p = 0.023) (Supplementary Figure 3).

The median length of hospital stay for patients not requiring admission to ICU was 8 days (IQR 6). At control phase, oxygen administration had to be increased in 37 patients (32.7%), and 44 (37.9%) needed to change to more aggressive medical treatment. Patients with a baseline LUZ score > 75 percentile, presented a significantly higher proportion of events for the primary endpoint (25%; p = 0.016), a longer length of stay without being transferred to intensive care (9 days [IQR 6]; p = 0.003), and required a significant increase in oxygen administration at control (41.7%; p = 0.037). (Table 2). Kaplan-Meier curves showing how baseline LUZ score stratification might help predicting patients at higher risk of primary endpoint can be found in the supplementary material (Supplementary Figure 4).

Univariable logistic regression analysis identified estimated ePAFI (HR 0.99 [0.98 – 0.99]; p=0.027) and LUZ score at baseline > 22 (HR 5.45 (1.42 – 20.90); p=0.013) as potential

predictors for primary endpoint (Supplementary Table 3). In the multivariable logistic regression, after adjusting for confounders and bootstrapping (Table 3), LUZ-Score at baseline > 22 points (cut-off with highest sensibility) was identified as an independent predictor for the primary endpoint (HR 5.25 [0.84 – 32.84]; p = 0.038) (Table 3).

Discussion

In this study we monitor lung injury through LUS in patients hospitalized due to COVID-19. We herein propose a quantitative score based on LUS to estimate severity of the disease. Our main results show that LUZ-Score at admission identifies patients with more severe lung injury and can accurately predict poor outcomes. The score does not change over the first 72 h of hospital stay, meaning that it is fully informative upon admission.

Given the extensive lung involvement in COVID-19 patients, LUS may have some potential utility in the management of acutely ill patients[15, 16]. Some studies have reported an improvement in lung involvement assessment in COVID-19 by using LUS in the context of ED and ICU[17, 18], but we only have found two prospective studies analyzing the prognostic value of LUS during the first pandemic wave of COVID-19 (March & April 2020)[19]. The first included 80 patients (17 outpatients, 42 hospitalized and 21 with orotracheal intubation or death), initially admitted to ED. Authors used a quantitative scale (LUS-score) —based on measurements in ten areas of the chest— identifying those patients with the greatest probability of admission at the intensive care unit. The second one[20], included 120 patients, using a similar quantitative scale, based only in six areas, and including COVID-19 patients admitted either to medical ward or intensive care unit. Of these patients, only 20 patients (16.6%) were monitored during the study. Authors concluded that LUS rapidly identifies pulmonary involvement and provides risk stratification. Despite the novelty and importance of these findings, both studies had some limitations. Sample heterogeneous, as both outpatients and hospitalized in medical ward or at the ICU were included. Furthermore, they did not provide data about changes in treatment guided by the score, nor about follow-up in LUS score (*Lichter Y et al*[20]. only monitored 20 patients). In addition, these studies were carried out during the

first pandemic wave, thus their results may not effectively translate to the current situation, since some effective therapies, such as dexamethasone[21] or remdesivir[22], are being used in a more systematic fashion than before.

In our patients, LUZ-Score did not change during the first 72 hours after admission (p=0.183), what underlines the importance of the early assessment of the lung. Postero-inferior and supero-lateral areas of both lungs were the regions more commonly and more severely involved. This pattern is similar to that described in other studies using LUS in COVID-19[18, 19, 23]. One striking finding from our study, not previously reported, was that although lung injury decreased significantly at discharge (21 points [IQR 10] at admission vs. 13 points [IQR 12] at discharge: p= < 0.001) most patients still had ultrasound lung findings. Whether these findings indicate an active or evolving injury remains to be clarified. Whatever the meaning, this is a clear expression of the heterogeneity of clinical picture of COVID-19 infection and the dissociation between clinical and radiological development. Furthermore, the persistence of lung artifacts at discharge should prompt medical community to address the follow-up of these patients from a comprehensive perspective, which must include a close monitoring of lung function and potential residual lesions.

In our cohort, patients with the highest LUZ-Score (> 75 percentile) at baseline had longer duration of symptoms, self-reported more dyspnea through the Borg scale, had a significantly lower estimated PAFI and higher concentration of lactate dehydrogenase, C - reactive protein and Interleukin- 6. In keeping with the perception of a greater degree of severity, patients with a higher LUZ-Score had been treated at admission more often with systemic steroids (93.1%; p = 0.001) and remdesivir (44.8%; p = 0.009). In short, LUS and quantification of lung damage using LUZ score identified the most severely affected patients, as showed by significant correlation with other measures of severity such as clinical or analytical parameters and indirectly through the treatment they received.

Our results open a new tool to assist the management of patients with COVID-19. Quantification of lung injury through an objective measure, such as LUZ-Score, offers the

opportunity for an early identification of the most severe patients, and, as a consequence, the early implementation and proper allocation of most intense treatment in those COVID-19 patients.

One can extract relevant information from our study. First, patients with more severe respiratory symptoms at admission, had higher LUZ score (> 75 percentile), and experienced more frequently death from all causes or admission to ICU (25%; p = 0.009). Second, baseline LUZ-Score above 22 points, along with estimated PAFI, were identified in the univariable logistic regression model as predictors for the primary end-point (Table 3). LUZ-Score > 22 points remained significant in the final multivariable model, after adjusting for potential confounders and bootstrapping (HR 5.25 [0.84 – 33.84]; p=0.038). The fact that confidence intervals were wide and included the unit deserves some consideration. Probably, a higher power would have been obtained with a larger sample size, but we were limited by the availability of US equipment and trained staff, the need for higher safety precautions, and the work overload associated to the current pandemic situation. Sample size was besides calculated on biomarker expected predictive power, and limited by available funding. One should also take into account that the study's primary endpoint was hard (death and/or ICU admission). On the other hand, the fact that the result is significant after bootstrapping reflects its consistency and strongly supports a potential utility of ultrasound along with other clinical variables, such as estimated PAFI. This is especially important in a disease with highly variable clinical expression, and frequently dissociated from data yielded by other complementary examinations.

We suggest LUZ-Score as an easy, simple and fast point of care ultrasound tool in patients with COVID-19 to stratify risk upon admission in combination with other clinical and analytical variables. According to our results, admission LUS can help clinicians to implement COVID-19 treatment (either by the early increase of O2 flow or by escalating other therapies), in those cases more severely involved. Given the advantages of LUS, this technique can be repeated as many times as needed and everywhere, which confer additional advantages for its clinical use.

Limitations

The study was carried out in a single center, so their results cannot be generalizable. We did not analyzed correlations between LUS and CT due to the study design. The sample size was designed based on the collection of samples for biomarkers analysis, which could have underestimated power of multivariable logistic regression analysis. Finally, although all physicians who took LUS images had a large previous experience in LUS, this technique is operator-dependent, and could have influenced final results.

Conclusions

Lung ultrasound and LUZ-Score allow quantifying degree of pulmonary involvement in patients with COVID-19. There are no changes in the score during the first 72 hours of admission, which reinforces the importance of the very first ultrasound assessment, which should be performed soon after admission. A baseline admission LUZ-Score > 22 is a predictor of ICU admission or in-hospital death. Despite the improvement in clinical condition, ultrasound lung artifacts remain at discharge in a proportion of patients. This particular finding has not been previously reported and its significance is not clear.

Conflict of interest

The authors declare no conflict of interest.

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Table 1: Baseline characteristics according to LUZ score at baseline (tertiles).

Variable	TOTAL	LUZ < 13	LUZ 13 - 26	LUZ > 26	P-Value
Total size (N)	130	32 (24.6)	69 (53.1)	29 (22.3)	
Age (years)	56.7 ± 13.5	54.0 ± 13.2	56.3 ± 14.7	60.5 ± 10.0	0.173
Gender-Male (n[%])	80 (61.5)	20 (62.5)	43 (62.3)	17 (58.6)	0.935
Duration of symptom (days)	6 (5)	4.0 (5.0)	6.0 (3.0)	8.0 (5)	**0.003**
Time until COVID confirmation (Days)	-2 (6)	-1.5 (7)	-2.0 (6)	-3.0 (6)	0.315
Comorbidities (n[%]):					
• Hypertension	50 (38.5)	11 (34.4)	24 (34.8)	15 (51.7)	0.250
• Heart failure	4 (3.1)	2 (6.3)	2 (2.9)	0 (0.0)	0.366
• Dyslipidemia	37 (28.5)	11 (34.4)	15 (21.7)	11 (37.9)	0.187
• Coronary artery disease	5 (3.8)	2 (6.3)	2 (2.9)	1 (3.4)	0.712
• Diabetes	22 (16.9)	5 (15.6)	9 (13.0)	8 (27.6)	0.210
• History of smoking	40 (30.8)	8 (25.0)	21 (30.4)	11 (37.9)	0.548
• COPD/Asthma	13 (10.0)	5 (15.6)	6 (8.7)	2 (6.9)	0.457
• Atrial/flutter fibrillation	5 (3.8)	3 (9.4)	1 (1.4)	1 (3.4)	0.155
• CKD	6 (4.6)	2 (6.3)	2 (2.9)	2 (1.5)	0.607
Clinical variables					
• BMI (Kgs/m2)	28.7 (6.2)	29.0 (5.4)	28.8 (7.4)	28.3 (6.0)	0.625
• SBP (mmHg)	126.8 ± 16.5	129.7 ± 15.9	125.2 ± 16.0	128.1 ± 14.7	0.731
• DBP (mmHg)	77.2 ± 10.8	75.7 ± 12.9	76.8 ± 9.8	79.5 ± 8.5	0.315
• HR (bpm)	81.4 ± 2.2	80.6 ± 15.6	80.7 ± 11.6	84.8 ± 9.9	0.217
• Estimated PAFI (mmHg)	382 (92)	429 (0)	355 (93)	346 (73)	**< 0.001**
• Borg scale for dyspnea (points)	4 (5)	3 (5)	4 (6)	5 (4)	**0.031**
Laboratory:					
• Urea (mg/dL)	34 (20)	34.5 (23.5)	33.0 (20.5)	35.0 (16.0)	0.448
• Creatinine (mg/dL)	0.9 (0.29)	0.97 (0.18)	0.88 (0.31)	0.89 (0.30)	0.241

Variable (Continue)	TOTAL	LUZ < 13	LUZ 13 - 26	LUZ > 26	P-Value
Laboratory:					
• Aspartate transaminase (U/L)	38 (25)	30 (16)	39 (26)	43 (22)	**0.044**
• Alanine transaminase (U/L)	30 (29)	34 (24)	30 (33)	30 (37)	0.816
• Creatin phophokinase (U/L)	94 (91)	131 (110)	89 (86)	83 (64)	0.460
• Lactate deshidrogenase (U/L)	306 (146)	254 (109)	307 (166)	394 (183)	**<0.001**
• C-Reactive Protein (mg/L)	64.2 (81.2)	36.7 (58.8)	67.5 (75.5)	86.8 (104.9)	**0.013**
• Ferritin (ng/mL)	729 (855)	737 (721)	670 (770)	954 (1414)	0.248
• Hemoglobin (g/dL)	14.2 (2.1)	14.2 (2.0)	14.1 (2.4)	14.1 (1.9)	0.275
• Total leucocytes (x 1000)	5.5 (3.1)	5.7 (3.8)	5.9 (3.2)	5.0 (3.1)	0.479
• Total lymphocytes (x 1000)	0.9 (0.6)	0.9 (0.7)	1.0 (0.6)	0.8 (0.6)	0.250
• D-Dimer (ng/mL)	731 (661)	739 (903)	658 (654)	891 (743)	**0.037**
• Fibrinogen (mg/dL)	777 (213)	723 (207)	793 (220)	785 (231)	0.182
• Interleukine-6 (pg/mL)	42.34 (26.6)	25.4 (22.5)	45.4 (28.0)	46.4 (46.9)	**<0.001**
Therapies (n[%])					
• Colchicine	8 (6.2)	2 (6.3)	4 (5.8)	2 (6.9)	0.979
• Plasma	1 (0.8)	0 (0.0)	1 (1.4)	0 (0.0)	0.641
• Remdesivir	45 (34.6)	4 (12.5)	28 (40.6)	13 (44.8)	**0.009**
• Systemic corticosteroids	99 (76.2)	17 (53.1)	55 (79.7)	27 (93.1)	**0.001**
• Medium dose of corticosteroids (Dexametasone [mg])	6 (3)	6 (1)	6 (3)	6 (3)	0.596
• Low molecular weight heparin	124 (95.4)	28 (87.5)	67 (97.1)	28 (96.6)	**0.044**

Variables are expressed as mean ± standard deviation or median (Interquartile range) BMI: Body Mass Index; CKD: Chronic Kidney Disease (estimated glomerular filtration rate < 60 mL/min/173m2 CKD-EPI-Creatinine method); COPD: Chronic Obstructive Pulmonary Disease; DBP: Diastolic Blood Pressure; HR: Heart Rate; SBP: Systolic Blood Pressure.

Table 2: Outcomes by LUZ lung ultrasound score at baseline.

Variable	TOTAL	LUZ < P25	LUZ P25 – P75	LUZ > P75	P-Value
Primary outcome (n[%]):					
• **ICU admission and/or death**	13 (10.1)	3 (9.4)	3 (4.3)	7 (25.0)	**0.016**
Secondary outcomes:					
• **Length of stay (days)**	8 (6)	5 (6)	8 (4)	9 (6)	**0.003**
• **Necessity of higher O2 therapy at 48/72 hours (n[%])**	42 (34.1)	5 (16.1)	27 (39.7)	10 (41.7)	**0.037**
• **Necessity to update COVID-19 treatment at 48/72 hours (n[%])**	52 (40.9)	9 (29.0)	29 (42.0)	14 (51.9)	0.199
• **Necessity of higher O2 therapy or update COVID-19 treatment at 48/72 hours (n[%])**	62 (50.4)	11 (35.5)	35 (51.5)	16 (66.7)	0.067

ICU: Intensive Care Unit. ***Bold results*** *are statistical significant.*

Table 3: Univariable and multivariable logistic regression model for the primary combined endpoint all-cause mortality and/or ICU admissions**.

	UNIVARIABLE		MULTIVARIABLE	
Variable	**HR (CI 95%)**	**P-Value**	**HR (CI 95%)**	**P-Value**
Age	1.02 (0.97 – 1.06)	0.351	1.03 (0.97 – 1.10)	0.287
Dyslipidemia	2.35 (0.73 – 7.53)	0.151	1.53 (0.32 – 7.20)	0.586
Diabetes	2.42 (0.67 – 8.70)	0.176	0.99 (0.15 – 6.44)	0.992
Estimated PAFI	0.99 (0.98 – 0.99)	**0.027**	0.99 (0.98 – 1.00)	0.640
CPK	1.00 (1.00 – 1.00)	0.098	1.00 (0.99 – 1.00)	0.109
Total Lymphocytes	1.06 (0.97 – 1.17)	0.175	1.03 (0.92 – 1.15)	0.563
LUZ lung ultrasound baseline score >22* **	5.45 (1.42 – 20.90)	**0.013**	5.25 (0.84 – 32.84)	**0.038***

CPK: Creatin Phosphokinase.

*Significant after a bootstrap of 1000 replicates.

**Complete Univariable analysis can be consulted at Supplementary Table 5.

*** Point of highest sensibility and specificity (Sensitivity = 76·9%; Specificity = 62·1%; AUC = 0.693; p = 0.023).

Figure legends

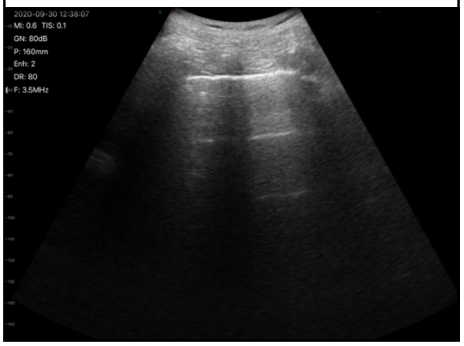
Figure 1: Lung ultrasound Zaragoza score (LUZ-score)

Figure 2: Box plots showing LUZ-score distribution at baseline (red), control (yellow) and discharge (green).

Foodnote: *U-Mann Whitney test between LUZ-score at baseline and LUZ-score at baseline and discharge.

LUNG ULTRASOUND ZARAGOZA (LUZ) SCORE

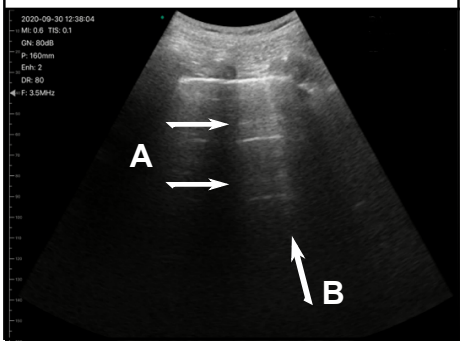
NORMAL



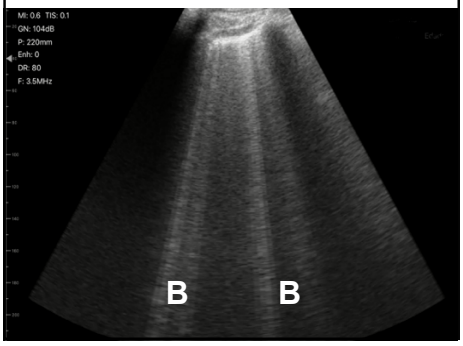
LUZ SCORE

Normal	=	0 points
Initial	=	1 point
Sun Rays	=	2 points
Waterfall	=	3 points
Consolidation	=	4 points

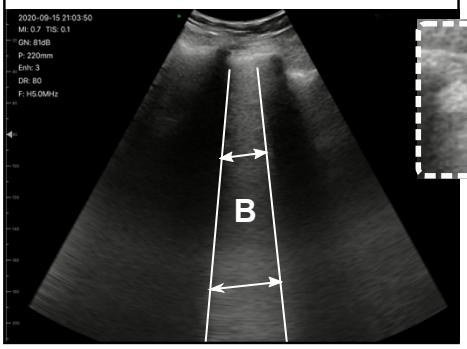
INITIAL



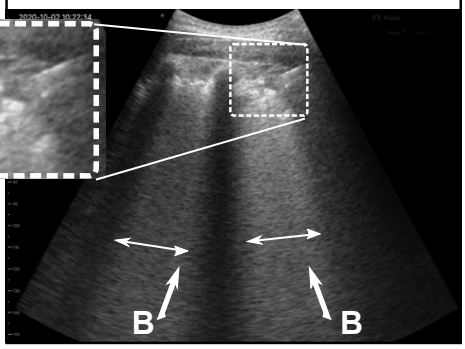
SUN RAYS

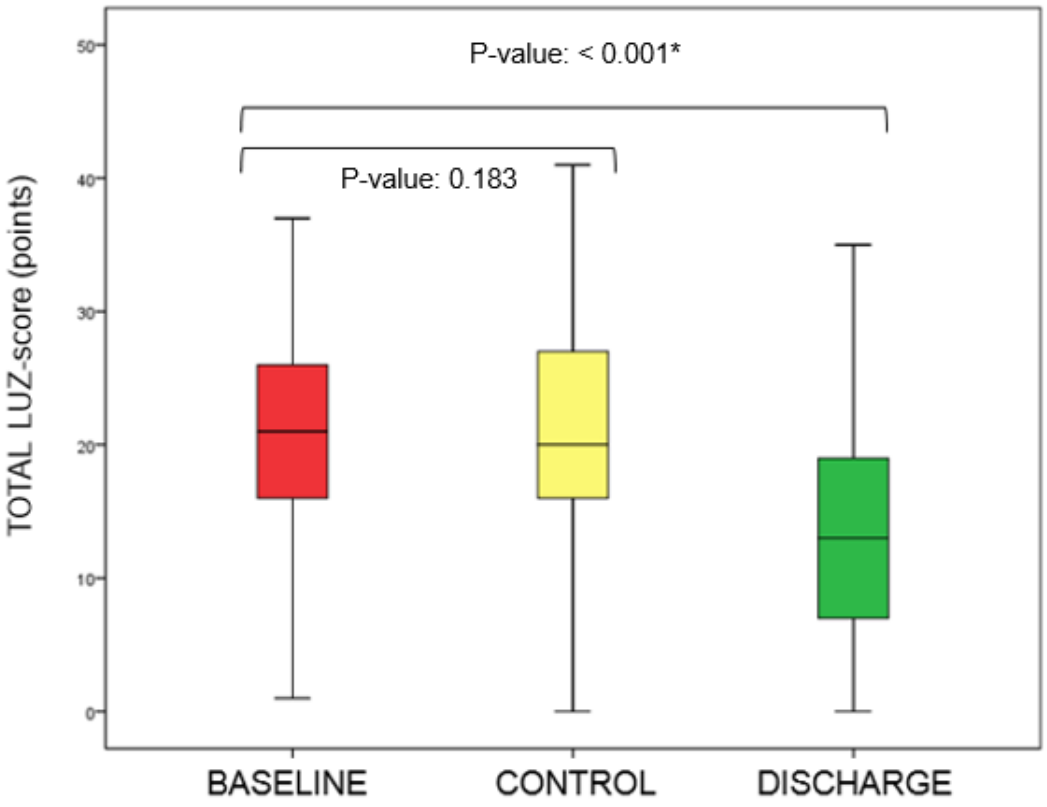


WATERFALL



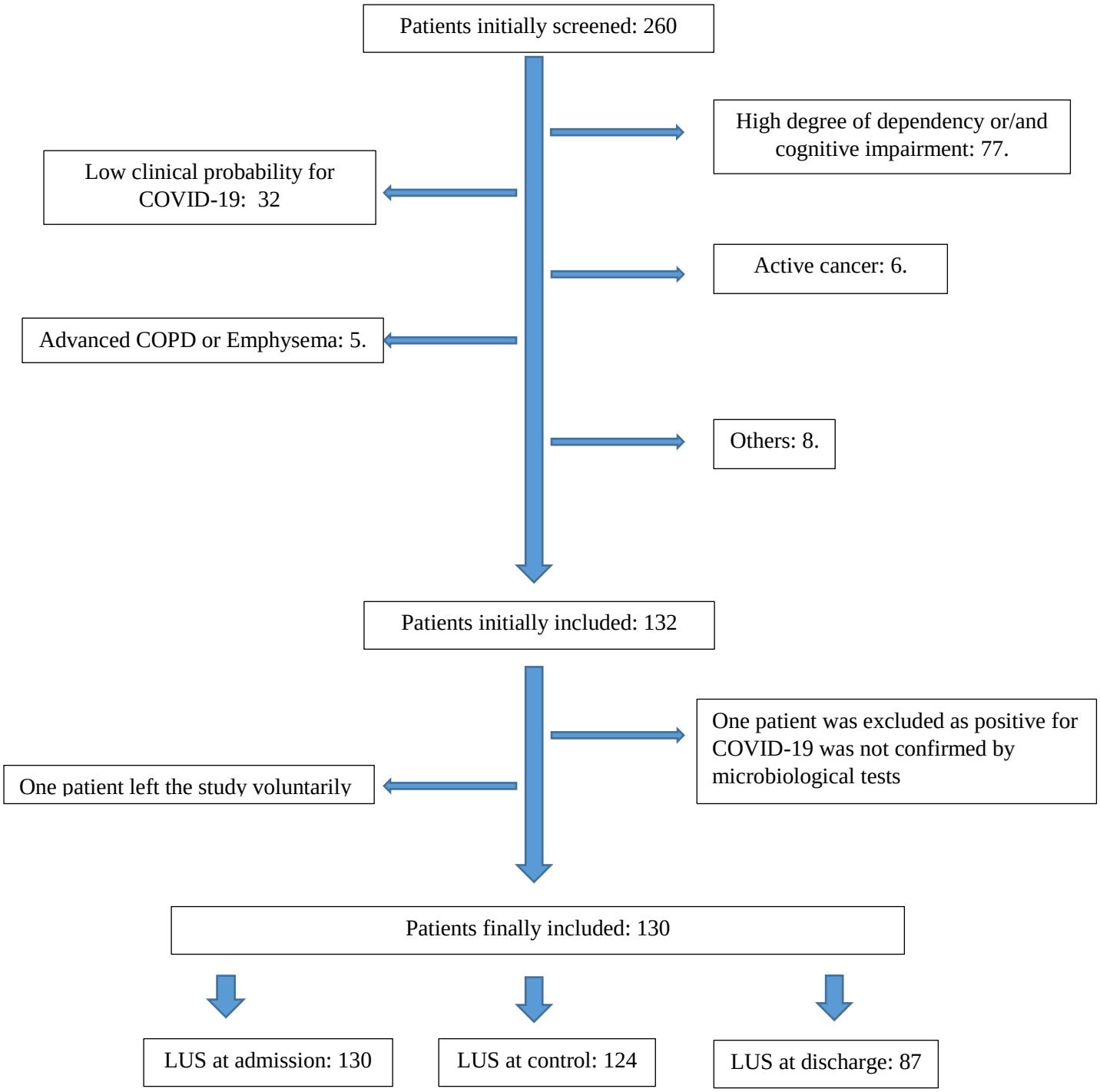
CONSOLIDATION





*U-Mann Whitney test between LUZ-score at baseline and LUZ-score at baseline and discharge.

Supplementary figure 1: Inclusion Flow chart



Supplementary table 1: Lung ultrasound results by LUZ-score at baseline, control and discharge.

Variable	BASELINE	CONTROL	DISCHARGE
N	130	124	87
Lung areas (Score [median] / Frequency[%])			
R1	2.0 (55.4)	2.0 (54.8)	1.0 (46.0)
R2	1.5 (41.5)	1.0 (37.9)	0 (23.0)
R3	2.0 (56.2)	2.0 (56.5)	1.0 (37.9)
R4	1.0 (35.4)	1.0 (46.0)	0 (33.3)
R5	2.0 (40.8)	2.0 (40.3)	1.0 (31.0)
R6	3.0 (69.2)	3.0 (67.7)	2.0 (55.2)
L1	2.0 (50)	2.0 (54.8)	1.0 (31.0)
L2	0 (23.1)	0 (25.8)	0 (13.8)
L3	2.0 (58.5)	2.0 (58.1)	2.0 (35.6)
L4	1.0 (40.0)	2.0 (52.4)	0 (33.3)
L5	1.0 (36.9)	1.0 (42.7)	0 (31.0)
L6	3.0 (65.4)	3.0 (64.5)	2.0 (40.2)
Total LUZ Score (points)	21 (10)	20 (11)	13(12)
Total of lung areas affected (n)	9 (3)	9 (4)	7 (5)

Continuous variables are expressed as mean ± standard deviation or median (interquartile range).

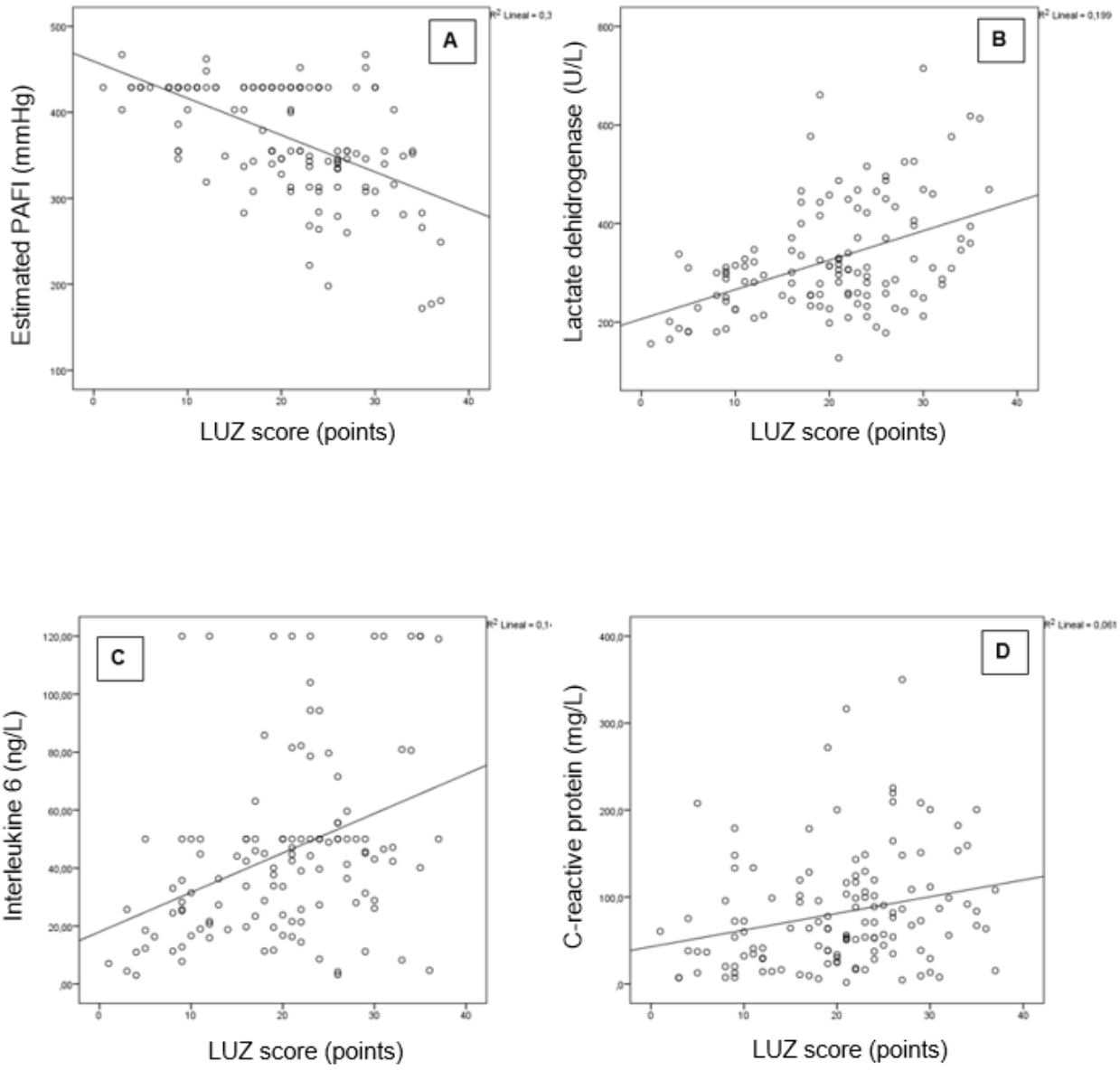
R1: right antero-superior area; R2: right antero-inferior area; R3: upper and right lateral area; R4: lower and right lateral area; R5: right postero-superior area; R6: right postero-inferior area. L1: left antero-superior area; L2: left antero-inferior area; L3: upper and left lateral area; L4: lower and right lateral area; L5: left postero-superior area; L6: left postero-inferior area.

Supplementary table 2: Correlation analysis between the LUCOZ score at admission and clinical and analytical variables at admission.

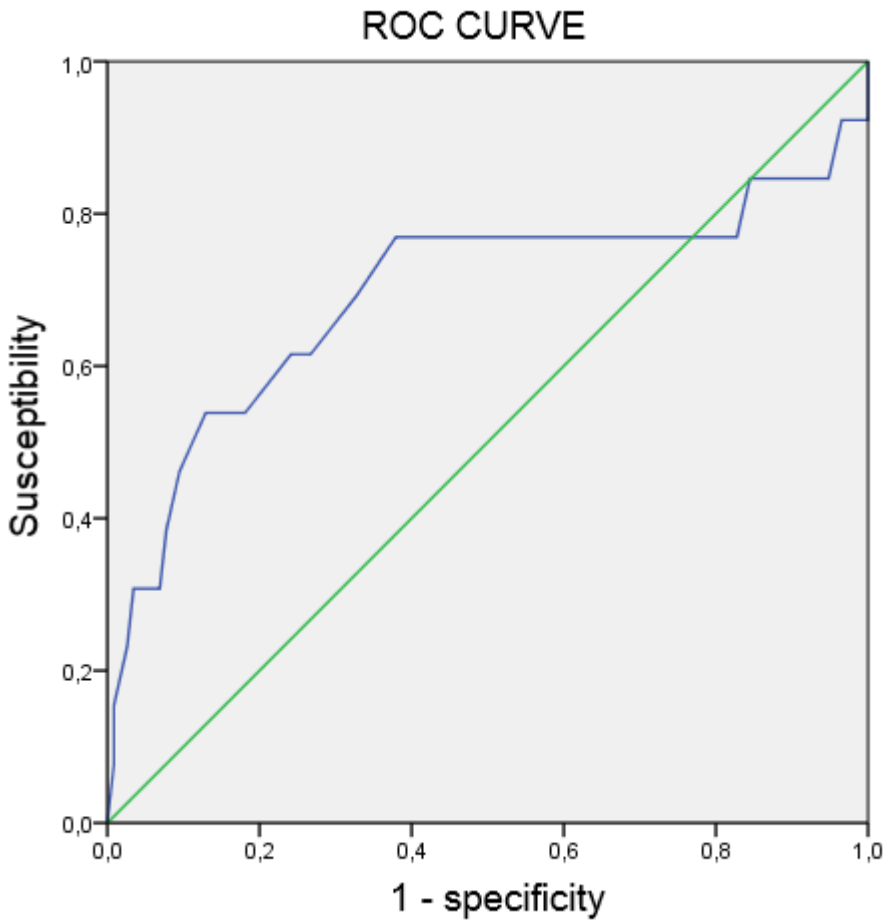
Variable	Rho Spearman	P-value
BMI (Kgs/m2)	-0.113	0.253
SBP (mmHg)	-0.055	0.536
DBP (mmHg)	0.077	0.383
Hr (B.p.s.)	0.197	**0.025**
ePAFI (mmHg)	-0.516	**<0.001**
Creatinine (mg/dL)	-0.165	0.060
Reactive C-protein (mg/L)	0.286	**0.001**
Aspartate transaminase (U/L)	0.180	**0.046**
Lactate dehidrogenase (U/L)	0.395	**<0.001**
Creatinine Kinase (U/L)	-0.062	0.515
Ferritin (ng/mL)	0.134	0.133
Total leucocites (x 1000)	-0.005	0.157
Total linfocites (x 1000)	-0.152	0.086
D-Dimer (ng/mL)	0.157	0.078
IL-6 (pg/mL)	0.383	**<0.001**
Borg Scale (points)	0.228	**0.009**
Hemoglobine (g/dL)	-0.028	0.750

BMI: Body Mass index; DBP: Diastolic Blood Pressure; IL: Interleukine; SBP: Systolic Blood Pressure.

Supplementary figure 2: Correlation graphs between the LUZ score on admission and A) PAFI; B) Lactate dehydrogenase; C) Interleukine-6 and D) C-Reactive Protein.

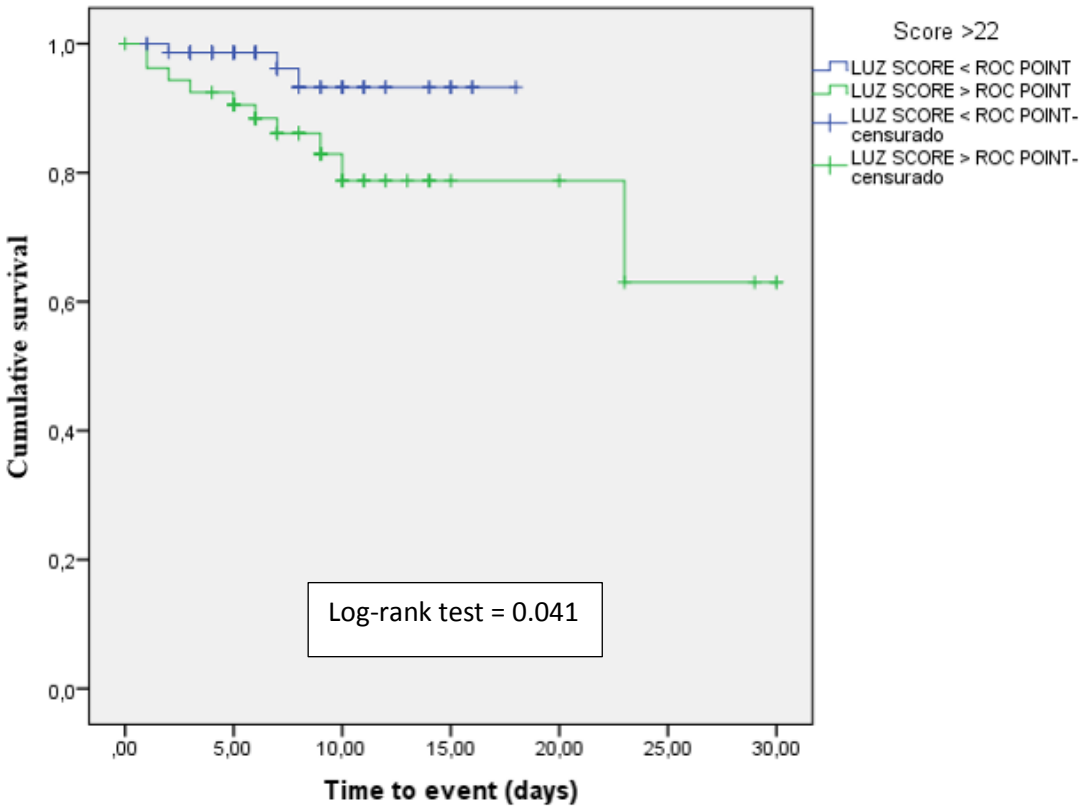


Supplementary figure 3: ROC curve for the primary composite end-point by LUZ-score at baseline.



LUZ score cut-off for primary outcome: 22.5 points (S= 76.9%; E=62.1%; AUC: 0.693; p=0.023)

Supplementary Figure 4: Survival Kaplan-Meier curves for the composite primary end-point (ICU admission and/or all-cause mortality) by LUZ-score at baseline (higher point of Sensitivity and 1-Specificity).



	0	5	10	15	20	25	30
LUZ score ≤ ROC point (≤ 22 points)	75	47	17	4	0	0	0
LUZ score > ROC point (> 22 points)	55	44	17	7	6	3	0

Number at risk

Supplementary table 3: Univariable and multivariable logistic regression analysis for the primary composite end-point.

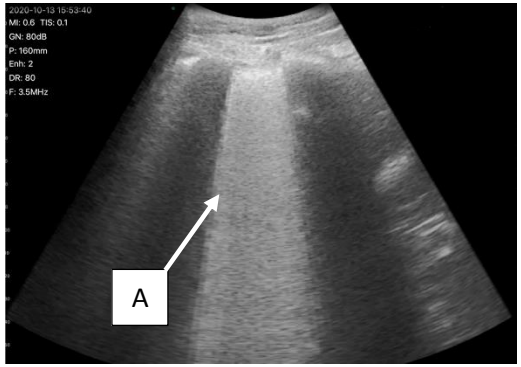
UNIVARIABLE			MULTIVARIABLE	
Variable	**HR (IC 95%)**	**P-Value**	**HR (IC 95%)**	**P-Value**
Age	1.02 (0.97–1.06)	0.351	1.03 (0.97 – 1.10)	0.287
Gender-Male	1.02 (0.31 – 3.32)	0.970		
Duration of symptom (days)	1.00 (0.94 – 1.07)	0.875		
Comorbidities (if present)				
• Hypertension	1.98 (0.62 – 6.27)	0.246		
• Heart failure	0	0.999		
• Dyslipidemia*	2.35 (0.73 – 7.53)	0.151	1.53 (0.32 – 7.20)	0.586
• Coronary artery disease	2.33 (0.24 – 22.6)	0.465		
• Diabetes*	2.42 (0.67 – 8.70)	0.176	0.99 (0.15 – 6.44)	0.992
• History of smoking	1.44 (0.44 – 4.73)	0.542		
• COPD/Asthma	1.73 (0.34 – 8.85)	0.507		
• Atrial/flutter fibrillation	2.33 (0.24 – 22.60)	0.465		
• CKD	0	0.999		
Clinical variables				
• BMI	1.05 (0.95 – 1.16)	0.320		
• SBP	1.01 (0.97 – 1.04)	0.516		
• DBP	0.99 (0.94 – 1.04)	0.759		
• HR	1.01 (0.97 – 1.06)	0.499		
• Estimated PAFI*	0.99 (0.98 – 0.99)	**0.027**	0.99 (0.98 – 1.00)	0.640
• Dyspnea Borg scale	1.06 (0.85 – 1.3)	0.592		
• Oxygen_saturation				
Laboratory				
• Urea	0.99 (0.96 – 1.02)	0.619		
• Creatinine	2.43 (0.51 – 11.47)	0.260		
• Aspartase transaminase	0.98 (0.95 – 1.01)	0.259		
• Alanin transaminase	0.97 (0.94 –1.01)	0.204		
• Creatin phophokinase*	1.00 (1.00-1.00)	0.098	1.00 (0.99 – 1.00)	0.109
• Lactate deshidrogenase	1.00 (0.99 – 1.00)	0.539		
• C-Reactive protein	1.00 (0.99 –1.00)	0.959		
• Ferritin	1.00 (0.99 – 1.00)	0.329		
• Hemoglobin	0.84 (0.58 – 1.23)	0.391		
• Total of leucocites	1.03 (0.92 – 1.15)	0.529		
• Total of lymphocites*	1.06 (0.97 – 1.17)	0.175	1.03 (0.92 – 1.15)	0.563
• D-Dimer	1.00 (0.99 – 1.00)	0.586		
• Fibrinogen	1.00 (0.99 – 1.00)	0.779		
• Interleukine-6	1.00 (0.98 – 1.02)	0.475		
Lung ultrasound analysis				
LUZ baseline score*	5.45 (1.42 – 20.90)	**0.013**	5.25 (0.84 – 32.84)	**0.038****

**Candidate variables finally included in the multivariable logistic regression model.*

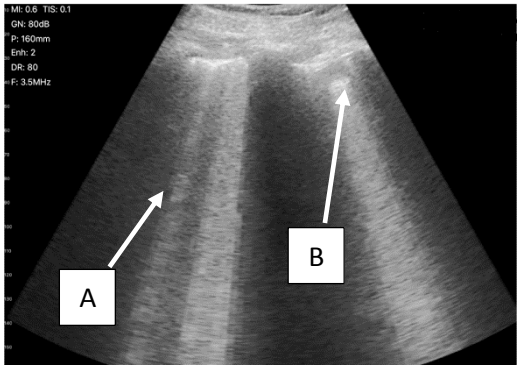
***After a bootstrap of 1000 replicates.*

Supplementary figure 5: LUS findings between: A) Patient with needed for mechanical ventilation after 24 hours of admission and B) Patient with good evolution and fast discharge after 72 hours of admission.

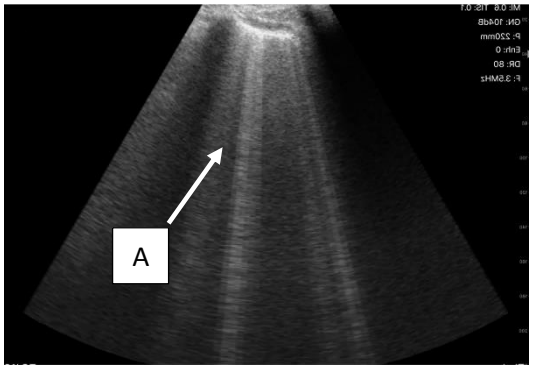
A) Pictures corresponding to three of the twelve lung areas explored. Patient showed advanced findings (Sun rays/waterfall patterns and one subpleural consolidation in the left lower posterior quadrant. Total LUZ-score= 28 points). After 24 hours of admission, acute respiratory failure developed (Estimated PAFI < 200) and admission to the ICU for mechanical ventilation was needed.



Waterfall sign (A) observed at lower left lateral quadrant.

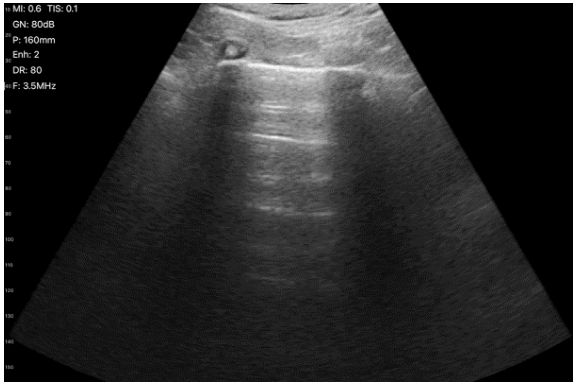


Sun rays pattern (A) and subpleural consolidation (B) observed at left lower and posterior quadrant

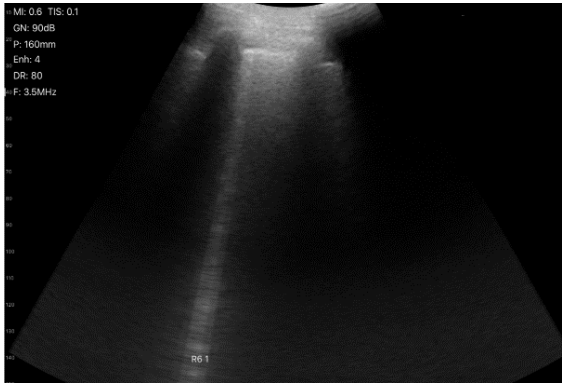


Sun rays pattern (A) observed at right lower and posterior quadrant

B) Pictures corresponding to two of the twelve lung areas explored. LUS did not detected advanced findings of viral pneumonia (LUZ score=5) and patient was admitted for supervision. After 72 hours, patient was discharged without any sign of respiratory complication.



Normal A lines observed.



Isolated “b” line (starting pattern) observed at right lower and posterior quadrant.