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Original article

Early lung ultrasound assessment for the prognosis of patients hospitalized for COVID-19 pneumonia. A pilot study

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ABSTRACT

Objective. – SARS CoV-2 is an epidemic viral infection that can cause mild to severe lung involvement. Newly apprehended knowledge on thoracic imaging abnormalities and the growing clinical experience on the evolution of this disease make the radiographic follow-up of hospitalized patients relevant. The value of consecutive bedside lung ultrasonography in the follow-up of hospitalized patients with SARS CoV-2 pneumonia and its correlation with other clinical and laboratory markers needs to be evaluated.
Methods. – We assessed 39 patients [age: 64 y(60.1–68.7)] with confirmed SARS CoV-2 pneumonia. A total of 24 patients were hospitalized until the follow-up test, 9 were discharged early and 6 required a transfer to critical care unit. Two ultrasound scans of the lung were performed on day 1 and 4 of patients' hospitalization. Primary endpoint was the magnitude of association between a global lung ultrasound score (LUS) and clinical and laboratory markers. Secondary endpoint was the association between the evolution of LUS with the corresponded changes in clinical and laboratory outcomes during hospitalization period.
Results. – LUS score on admission was higher among the deteriorating patients and significantly ($P = 0.038$–0.0001) correlated (Spearman's rho) with the levels of C-reactive protein (0.58), lymphocytes (-0.33), SpO_2 (-0.48) and oxygen supplementation (0.48) upon admission. The increase in LUS score between the two scans was significantly correlated (0.544, $P = 0.006$) with longer hospital stay.
Conclusion. – Lung ultrasound assessment can be a useful as an imaging modality for SARS CoV-2 patients. Larger studies are needed to further investigate the predictive role of LUS in the duration and the outcome of the hospitalization of these patients.

1. Introduction

Since December 2019, outbreaks of the COVID-19 epidemic are a major global health problem. The viral infection can cause mild to severe lung involvement. The development of fast-lane diagnostic tools and prognostic biomarkers is fundamental in order to triage and allocate these patients [1].

Along these lines, lung ultrasound (LUS) has been extensively studied and proven a reliable bedside clinical tool for the evaluation of a variety of thoracic abnormalities in critical care medicine [2,3]. It combines the advantage of ease of use at point of care with an absence of radiation exposure. The use of pulmonary ultrasound has been widely studied in cases of pneumonia, acute respiratory failure and acute respiratory distress syndrome (ARDS) [2,3]. Moreover, using the semi-quantitative method for scoring changes in lung aeration, LUS has shown to have a predictive role in disease severity and mortality in ARDS patients [4]. Additionally, it has shown a value in the follow-up of patients after interventions like prone positioning [5] and in determining the appropriate level of positive end-expiratory pressure (PEEP) to prevent alveolar derecruitment during expiration in ARDS [6].

Nevertheless, the clinical impact of early quantitative lung ultrasound assessments in patients hospitalized with SARS-COV-2 pneumonia has not been investigated so far. Accordingly, in this pilot study we aimed to explore bedside LUS for the rapid assessment of the severity of SARS-COV-2 pulmonary infection in patients hospitalized with proven COVID-19 pneumonia.

We hypothesized that an ultrasonographic marker of lung aeration could be of added value to known clinical and biochemical markers and to assist the management of SARS CoV-2 patients.

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2. Materials and methods

2.1. Study approval and registration

This was a single-center ancillary prospective observational study of consecutive subjects admitted to a low care COVID-19 ward between 02-04-2020 and 24-04-2020. The study was part of a larger observational study that was registered with Clinical-Trials.gov, registration number NCT04327570 that aims to provide an in-depth characterization of clinical and immunological features of patients hospitalized because of COVID-19 infection. The study was approved by the Institutional Review Board of the University Hospitals KU Leuven (study ID s60207). All participants provided written informed consent before entering the study.

2.2. Study participants

Eligible subjects had to meet the following inclusion criteria for lung ultrasound evaluation: SARS-CoV-2 infection confirmed by a positive RT-PCR for SARS-CoV-2 RNA of a respiratory sample and admission to the non-critical COVID-19 ward. Subjects who met the following criteria were excluded: a concurrent diagnosis of (non) cardiogenic pulmonary edema; admission to the non-critical COVID-19 ward for palliative care or sedation; inability to provide informed consent.

2.3. Study design

Two ultrasound scans of the lung were performed on eligible patients with imaging protocols and scoring systems being applied. The first examination was performed within 12 h after admission (scan 1). The follow-up evaluation (i.e., scan 2) was performed between 96 to 120 h after the scan 1 (i.e., day 4) if the patient was still hospitalized at that time. A flowchart with the study procedures and the number of participants is shown in Fig. 1.

2.4. Demographic, clinical, and laboratory data assessment

Patient demographic data, clinical, and laboratory characteristics namely: presenting symptoms, peripheral capillary oxygen saturation (SpO_2), supplemental oxygen flow if needed, white blood cell count in peripheral blood sample, lymphocyte count, platelet count, C-reactive protein levels (CRP), lactate dehydrogenase levels (LDH), hemoglobin A1c, d-dimers and creatinine clearance on the day of admission and on the day of the follow-up ultrasound evaluation were retrieved from the electronic medical file of the patients. Additional clinical data, namely the duration of their hospitalization was extracted at discharge. A clinical classification was applied to summarize each patient's condition at the time of hospital admission, according to the American Thoracic Society (ATS ≥ 3) minor criteria for defining severe community-acquired pneumonia [7].

2.5. Lung Ultrasound and score assessment

Lung ultrasound was performed with a GE Healthcare LOGIQ E9 ultrasound system, dedicated to the COVID19 wards of our institution. To correctly identify the artifactual images of the lungs, the harmonic imaging was disabled, and the reject post-processing was mitigated. The focus was set at the level of the pleural line and depth was set at 15 cm from the pleural line. All ultrasound examinations were performed bedside by the same physician (AK), who was not a member of the treating team. The examiner remained blinded to the electronic file of the patient, including other imaging studies. The echographer was dressed in full personal protection gear (PPE) and all unnecessary parts, besides the 3.5-MHz curved array probe used, were removed from the machine.

Based upon the patients' mild to median clinical impairment, their ability to perform the needed body relocations, and our aim for scanning the surface of the entire thorax, the 12–region lung ultrasound scoring method was used [8,9]: each examined hemithorax was systematically divided into six regions: anterior, lateral and posterior (according to anatomical landmarks set by anterior and posterior axillary lines) with each third of the hemithorax subsequently divided in half, superior and inferior. Patients were examined in the supine and lateral positions. The lateral position was used for the posterior lung surface examination.

All adjacent intercostal spaces were explored via longitudinal and cross-sectional views in all 12 regions to perform a comprehensive examination. For each of the scanned 12 regions per patient, multiple images were taken during an entire respiratory cycle. Lung aeration was measured using the LUS score as follows: for each given region of interest, points were allocated according to the worst ultrasound pattern observed: normal: 0; well-separated B-lines: 1; coalescent B-lines: 2; and consolidation: 3. A LUS score ranging between 0 and 36 was calculated as the sum of each region. The following additional ultrasound findings were noted if present: pleural fluid and pleural line anatomic abnormalities. Upon completion of the examination, the apparatus was initially wiped clean from top down before exiting the room. Wiping was repeated outside the room, while excess moisture on the screen was avoided. Representative images from every region were extracted from the machine and stored in the patient's medical file.

2.6. Statistical analysis

Data are presented as median and interquartile range (IQR, 25%–75%). Shapiro-Wilk test was applied to test to normality of the data. For the longitudinal approach of the analysis, baseline correlations between LUS scores and initial scores of lymphocyte count (lymph), C-reactive protein (CRP), Lactate dehydrogenase
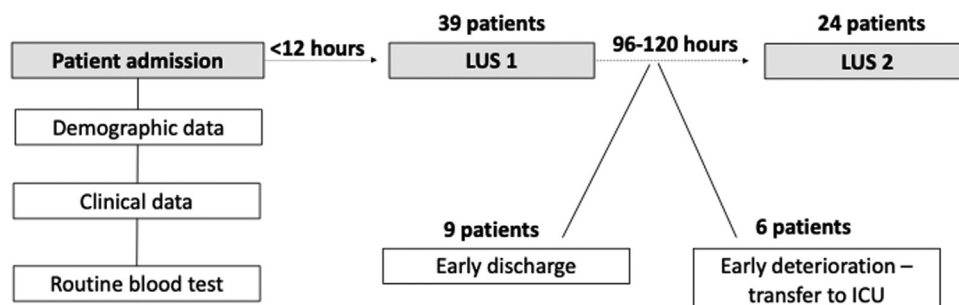

Fig. 1. Flowchart with the study procedures and the number of participants. LUS= lung ultrasound score, ICU= intensive care unit.

Table 1
Baseline demographics, clinical and laboratory findings for the three groups and for the total sample of the study.

Variables	Group A= Hospitalization until at least the follow-up test	Group B= Severity downgrade (Early Discharge)	Group C= Severity upgrade (Death–transfer to ICU)	Total sample of the study
N (% of total)	24 (61.5)	9 (23.1)	6 (15.4)	39
Gender M, (%)	14 (35.9%)	6 (15.4%)	4 (61.5%)	24 (61.5%)
Age, years	67.5 (56.5–70.6)	58 (55–68.5)	67 (56.8–87)	64 (56–72)
BMI	25.7 (22.80–32.05)	26.6 (24.25–29.20)	28.4 (25.83–32.18)	26.4 (23.8–29.5)
Days of symptoms	6 (5–9.25)	7 (4–10.5)	7 (6.25–11)	7 (5–10)
Lung ultrasound score (LUS)	9 (6.25–13.75)	10 (6–12)	17 [c] (11.5–21)	10 (7–14)
Presenting symptoms, % fever or respiratory	56.4	17.9	15.4	–
ATS pneumonia severity, % severe	11.5	0	67	–
SpO$_2$, %	92 (91–94)	95 (92.5–96)	91 (88–93)	92 (91–94)
Supplemental Oxygen NC, L/min	2.0 [a] (1–2.75)	0.0 (0–2)	3.0 [a] (1.5–5.5)	2.0 (0–3)
White blood cell count, $10^3/\mu L$	5.705 (4.075–8.387)	6.220 (4.150–7.220)	6.290 (3.375–8.842)	6.130 (4.040–7.630)
Lymphocyte count (Lymph), $10^3/\mu L$	0.950 (0.650–1.525)	1.100 (0.450–1.950)	0.800 (0.400–0.925)	0.900 (0.600–1.400)
Platelet count, $10^3/\mu L$	202 (152.3–265.8)	178 (156–354)	208 (139.5–301.3)	198 (157–279)
C-reactive protein (CRP), mg/L	61.5 (21.4–111.5)	36.4 (9.35–67.95)	77.9 (51–130)	56.0 (21.2–105)
Lactate dehydrogenase (LDH), U/L	289 (237.8–407)	289 (237.5–418)	489 [b] (393.3–556.8)	298 (240–439)
HbA1c, %	6.0 (5.73–7)	5.8 (5.45–6.20)	6.1 (5.70–7.13)	6.0 (5.7–6.9)
D-dimer, ng/mL	595 (380–1061)	632 (143–932)	1067 (304–1508)	665 (376–1371)
Creatinine Clearance, mL/min/1.73 m^2	80 (62.5–10.75)	92 (73.5–96.5)	59 (37.5–79.3)	81 (63–98)
TotHS, days	9 [d] (7–12)	5 (4.5–7)	13 (4.5–26)	8 (6–12)

Data are presented as median and interquartile range (IQR, 25%–75%); SpO$_2$, peripheral capillary oxygen saturation measured by pulse oxymeter; NC, nasal cannula; HbA1c, glycated haemoglobin; TotHS, days of hospitalization. Level of significance was set to be $P < 0.017$ after Bonferroni correction for multiple comparisons.

[a] Significant difference compared to group B ($P = 0.013–0.001$).
[b] Significant difference compared to group A ($P = 0.006$) and with group B ($P = 0.045$).
[c] Significant difference compared to group A ($P = 0.008$).
[d] Significant difference compared to group B ($P = 0.001$).

(LDH), SpO$_2$, supplemental O$_2$, D-dimer and the total duration of hospitalization (TotHS) variables measured during scan 1 were examined by the Spearman's Rho correlation coefficient.

Patients were a posteriori classified into three groups corresponding to their clinical situation and evolution of their hospitalization namely Group A: hospitalized until follow-up test, Group B: early discharge before day-4 because of a downgrading of their clinical status and Group C: clinical deterioration leading to transfer to ICU or death. Mann-Whitney U test was implemented to compare the critical variable scores between the three independent groups. The Bonferroni correction was chosen to reduce the Type I error resulting to a critical significance level of $P = 0.017$. For the cross-sectional analysis, the DeltaLUS, Deltalymph, DeltaCRP, and DeltaLDH were computed as the difference of the scores of LUS, lymph, CRP, and LDH, respectively, between scan 1 and scan 2. Spearman's Rho correlation coefficient was calculated to examine the existence of a significant association between DeltaLUS and the rest of the variables. Additionally, the DeltaLUS has been recoded to a new nominal, two-valued variable (nominal DeltaLUS) assigned the value -1 when DeltaLUS takes negative values or zero (improvement of echographic score or stable status) and 1 when DeltaLUS is positive (deterioration of echographic score). All statistical analyses were performed with IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp software package).

3. Results

3.1. Subject characteristics

Thirty-nine (39) consecutive patients were included in the study and posteriori classified into three distinct groups determined by the progress of their clinical situation (Table 1). Specifically, 24 out of 36 (61.5%) were hospitalized until participating in the follow-up test (Group A), nine patients (23.1%) were discharged early due to improvement of their situation severity (Group B), and six patients (15.4%) were characterized by severity upgrade (death or transfer to ICU, Group C). Demographic, clinical, and laboratory data of all participants and the respective groups are presented in Table 1.

3.2. Clinical and laboratory markers

No significant changes were found in demographic characteristics between the three groups (Table 1). In terms of clinical and laboratory variables, oxygen supplementation was significantly lower in GROUP B compared to the other groups. LDH was found to be significantly higher in Group C compared to GROUP A ($P = 0.006$) and was tended to be greater compared to Group B ($P = 0.045$). Lymphocyte count tended to be lower in Group C as compared to other groups. LUS score was found to be significantly higher in Group

Table 2
Correlation coefficients between lung ultrasound score (LUS) and baseline demographics, clinical and laboratory variables recorded during the 1st scan.

Variables	LUS (1st scan)	
	Spearman's Rho	P-value
Age	−0.044	0.792
Gender	−0.242	0.138
SpO_2	−0.482	0.002
Supplemental Oxygen NC	0.483	0.002
C-reactive protein (CRP)	0.580	< 0.0001
D-dimer	0.202	0.217
Lactate dehydrogenase (LDH)	0.284	0.080
Lymphocyte count (Lymph)	−0.334	0.038

SpO_2, peripheral capillary oxygen saturation measured by pulse oximeter; NC, nasal cannula.

Table 3
Correlation coefficients amongst changes in lung ultrasound score (LUS) and the demographics data, clinical and laboratory responses recorded between 1st and 2nd scan.

Variables	Delta LUS (2nd–1st scan)	
	Spearman's Rho	P-value
Age	0.272	0.199
Gender	0.220	0.301
Delta Lymphocyte count (Lymph)	0.027	0.900
Delta C-reactive protein (CRP)	0.356	0.088
Delta Lactate dehydrogenase (LDH)	0.303	0.150

C compared to GROUP A ($P = 0.008$) and tended to be significantly greater compared to GROUP B ($P = 0.028$). Total number of days of hospitalization was found to be significantly greater in Group C compared to GROUP B ($P = 0.008$) and tended to be significantly greater compared to GROUP A ($P = 0.028$).

3.3. Associations between LUS and clinical and laboratory markers during the 1st scan

Table 2 presents the correlations coefficients between LUS and clinical and laboratory markers recorded during the 1st scan. Specifically, we found significant association between LUS and peripheral lymphocyte count (Rho = −0.334, $P = 0.038$), CRP (Rho = 0.58, $P = < 0.0001$), SpO_2 at admission (Rho = −0,482, $P = 0.002$) and O_2 supplementation (Rho = 0.483, $P = 0.002$).

3.4. Associations between LUS and clinical and laboratory markers responses between 1st and 2nd scan

Table 3 presents the correlations coefficients amongst changes in lung ultrasound score (LUS) and the demographics data, and the changes in clinical and laboratory data recorded between 1st and 2nd scan. No significant correlations were found between changes in LUS (Delta LUS) and age, gender and changes in Lymph, CRP, LDH (Table 3).

Fig. 2 depicts the correlation coefficient between DeltaLUS and TotHS (Rho = 0.544, $P = 0.006$) in a scatterplot. We also identified that the values of TotHS differ significantly between the two categories of the nominal DeltaLUS ($P = 0.011$). More specifically, positive values of DeltaLUS corresponded to greater number of days in hospital (TotHS) (Fig. 3).

4. Discussion

To our knowledge, this is a well-structured, prospective study that employed early, consecutive lung ultrasound examinations for the direct assessment in less than 12 hours and the follow-up of patients hospitalized with COVID-19 pneumonia on a low-care
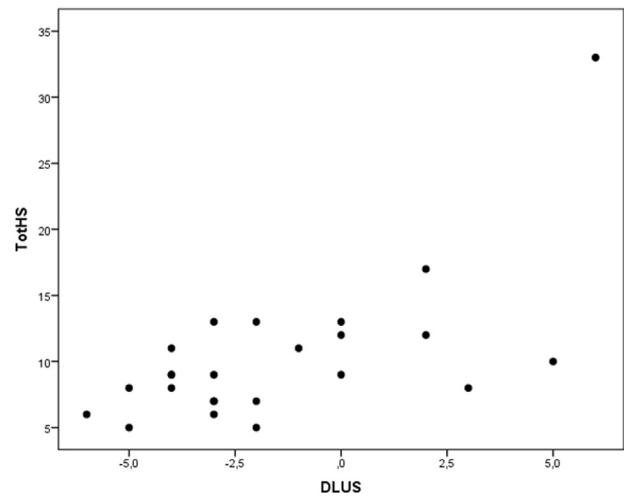

Fig. 2. Scatterplot presenting the association between values of TotHs and changes in lung ultrasound score recorded between 1st and 2nd scan (DeltaLUS). Spearman's correlation coefficient (Rho = 0.544, $P = 0.006$, $n = 24$ patients).
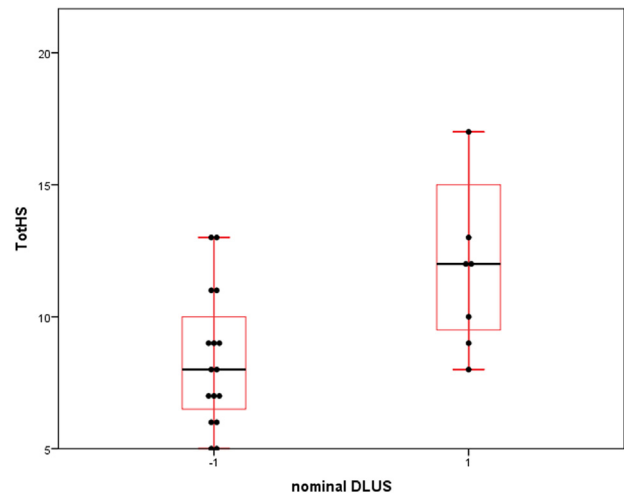

Fig. 3. Box plot of total days of hospitalization (TotHS) for the two categories of nominal changes in lung ultrasound score recorded between 1st and 2nd scan (DeltaLUS, positive and negative).

unit. The main strengths of the study derive from the execution of two ultrasound examinations and the well-defined scheduling of the tests during the first hours of hospitalization, thus providing a detailed view of the evolution of the disease. We identified that during the direct assessment, LUS significantly correlated with biochemical markers that have documented to predict the outcome of the hospitalization of patients with COVID-19. In addition, we observed that the evolution of LUS was associated with the duration of hospitalization.

During the COVID-19 pandemic, the first prospective observational studies demonstrated the range of lung parenchyma abnormalities, which can often develop before respiratory manifestations and PCR detection [10,11]. In affected patients, lung ultrasound examination has revealed a constellation of patterns and signs at different time-markers during the course of their disease. While not pathognomonic for the disease, these findings on lung ultrasonography appear to correlate with the findings on chest CT scans and vary from scattered B-line to coalescent B-lines ("waterfall sign") and in the most severe form, lung consolidation and complete loss of aeration. Secondary features include peripheral lung abnormalities that can cause disruption and thickening of

the pleural line with or without the presence of tiny pleural effusions, with the finding of a substantial pleural effusion being rare [12]. Lung ultrasound has been shown to be of use for the follow-up of the radiographical evolution of the pulmonary infiltrates as it detects the dynamic changes associated with COVID-19 pneumonia [13,14].

There has been an attempt to standardize the quantitative method used for the evaluation of lung aeriation during this pandemic. Point-of-Care Ultrasound (POCUS) with an eight-zone technique has been proposed to review lung condition and potentially assess changes or resolution over time for patients hospitalized for COVID-19 infection [15]. This method was also chosen for clinical practicability in the ICU setting [16]. The extended, 12-point ultrasound technique is based on the same principle of examination and evaluation of the lung but involves 12 zones, 6 at each hemithorax: upper and lower parts of the anterior, lateral, and posterior regions. This method has been studied in the ICU setting for the determination of aeration changes in weaning from mechanical ventilation and has shown good correlation as assessed by CT [17,18]. The 12-point systematic approach is also proposed for diagnosis and monitoring of ventilator-associated pneumonia (VAP) [19] and has been shown in a randomized control trial to improve patient outcomes when compared to the standard diagnostic strategy that relies on CXR [20]. We decided to use the 12-point global LUS score since our patients were in stable clinical condition upon admission and consequently hospitalized in the dedicated COVID-19 wards and not the ICU. They were able to follow the examiner's instructions to take the lateral position used for the posterior lung surface examination. This is important in COVID-19 patients because it has been reported from CT studies that multiple lobes are involved and particularly the lower lobes with a mostly peripheral distribution [21,22].

The initial examination of our patients at admission and the correlation of radiographic findings with biomarkers showed a significant association between LUS and lymphocyte count (Rho = −0.334) and between LUS and CRP (Rho = 0.580). Both increased levels of CRP and lymphopenia have been identified as independent risk factors for disease severity cohort of 99 consecutively hospitalized patients, while lymphopenia is also a risk factor for prolonged hospital stay [23]. Other studies have also attempted to define predictive biomarkers; in a retrospective, single-center study of 99 COVID-19 positive cases confirmed by real-time RT-PCR, 86% had an increased C-Reactive protein and 75% had increased levels of LDH, while only 25% presented initially with lymphopenia [24]. In a larger cohort of 239 patients hospitalized for Covid-19 infection, most patients had high levels of lactate dehydrogenase (74.7%), D-dimer (62.3%) and C-reactive protein (64.9%). C-reactive protein and lactate dehydrogenase were also statistically significant predictors of clinical deterioration [25]. Researchers have also developed a machine learning-based model that was used to predict the mortality rates of patients with COVID-19 more than ten days in advance with more than 90% accuracy, using three biomarkers (LDH, hs-CRP and lymphocytes), together with a clinical route [26]. In another study a combination of clinical and biochemical markers was used in an attempt to define COVID-19-associated hyperinflammatory syndrome [27].

In our cohort, we classified our patients to three groups corresponding to the evolution of their hospitalization. The group with the best evolution and the shortest duration of stay had the lowest CRP level, low LDH, and the highest median number of lymphocytes. These patients, along with the ones who did the follow-up LUS on Day-4, had significantly low LUS in comparison to those with the rapid deterioration and the worse prognosis. The similar score between groups A and B underlines the limitations of a single ultrasound measurement and the need of a close monitoring of the radiographical and clinical evolution of the disease. Finally, from

the group of patients who were in the second group and remained in the ward long enough to perform the follow up echo, a favorable evolution of the lung aeriation depicted by LUS was correlated with a shorter duration of hospitalization. The change of the ultrasonographic score of the lung was independent of the evolution of other biochemical markers and was also independent of the age or the sex of the patients.

This study has limitations. This is a single-center study, and all measurements were performed by the same examiner, in order to avoid unnecessary exposure of personnel and because of the scarcity of protective equipment during the first wave of the pandemic. Additionally, the study was focused in patients hospitalized in the ward and no clinical or imaging follow-up was performed to the patients of group-c. Nevertheless, it is a prospective study of COVID-19 patients that were hospitalized on the ward of a tertiary hospital. LUS seems to correlate with baseline clinical (SpO_2) and biochemical parameters (LDH, lymphocytosis) of disease severity in COVID-19. LUS can be of additional value to the initial evaluation and stratification for hospitalized patients by providing both a qualitative and a quantitative value of the disease severity. Moreover, it could be a useful tool for the radiographical follow-up and an added predictive marker of disease progression since DeltaLUS correlates with the length of hospital stay. Broader studies with more patients and more consecutive LUS evaluations during hospitalization are needed to verify our finding and evaluate the sensitivity and specificity of this disease-severity market for COVID-19 pneumonia.

5. Conclusions

In conclusion, this pilot study demonstrated that lung ultrasound assessment may provide as a useful imaging modality for hospitalized patients with SARS CoV-2. The results showed an association between the ultrasound data and clinical or biological criteria known to have a prognostic impact as well as association between the severity of the ultrasound score and the length of stay. The study provides the initial evidence for future and larger longitudinal studies to investigate the predictive role of LUS on the duration and outcome of the hospitalization in patients with COVID-19 pneumonia.

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