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Respiratory Medicine 197 (2022) 106826

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Lung ultrasound findings following COVID-19 hospitalization: A prospective longitudinal cohort study

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ARTICLE INFO

Keywords:
Lung ultrasound
COVID-19
Longitudinal follow-up

ABSTRACT

Background: Lung ultrasound (LUS) is a useful tool for diagnosis and monitoring in patients with active COVID-19-infection. However, less is known about the changes in LUS findings after a hospitalization for COVID-19.
Methods: In a prospective, longitudinal study in patients with COVID-19 enrolled from non-ICU hospital units, adult patients underwent 8-zone LUS and blood sampling both during the hospitalization and 2–3 months after discharge. LUS images were analyzed blinded to clinical variables and outcomes.
Results: A total of 71 patients with interpretable LUS at baseline and follow up (mean age 64 years, 61% male, 24% with acute respiratory distress syndrome (ARDS)) were included. The follow-up LUS was performed a median of 72 days after the initial LUS performed during hospitalization. At baseline, 87% had pathologic LUS findings in ≥1 zone (e.g. ≥3 B-lines, confluent B-lines or subpleural or lobar consolidation), whereas 30% had pathologic findings at follow-up ($p < 0.001$). The total number of B-lines and LUS score decreased significantly from hospitalization to follow-up (median 17 vs. 4, $p < 0.001$ and 4 vs. 0, $p < 0.001$, respectively). On the follow-up LUS, 28% of all patients had ≥3 B-lines in ≥1 zone, whereas in those with ARDS during the baseline hospitalization ($n = 17$), 47% had ≥3 B-lines in ≥1 zone.
Conclusion: LUS findings improved significantly from hospitalization to follow-up 2–3 months after discharge in COVID-19 survivors. However, persistent B-lines were frequent at follow-up, especially among those who initially had ARDS. LUS seems to be a promising method to monitor COVID-19 lung changes over time.
Clinicaltrials.gov ID: NCT04377035.

Abbreviations: LUS, lung ultrasound; CT, computed tomography; AHF, acute heart failure; ARDS, acute respiratory distress syndrome; IQR, interquartile range.

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https://doi.org/10.1016/j.rmed.2022.106826
Received 30 December 2021; Received in revised form 13 March 2022; Accepted 14 March 2022
Available online 2 April 2022

1. Introduction

COVID-19 pneumonia is associated with substantial lung involvement. Lung ultrasound (LUS) is a useful tool in the acute care setting to detect and grade the severity of lung involvement in patients with COVID-19 as LUS is a portable, rapid, non-invasive examination that can be performed at the bedside. The typical findings on LUS frequently detected in patients with COVID-19 pneumonia include pleural line irregularities, multiple and at times confluent B-lines and consolidations [1–5]. The LUS findings observed in patients with COVID-19 correlate well with findings on chest computed tomography (CT) [1,6,7]. LUS has higher sensitivity than chest X-ray for the diagnosis of COVID-19 pneumonia [8,9] and provides prognostic information regarding adverse outcomes in some studies [10–13], although there are heterogenous results regarding the prognostic utility of LUS in the inpatient setting [14,15]. The COVID-19 worsening score including clinically relevant data in addition to LUS findings has proven to accurately identify patients who are less likely to require treatment in the intensive care unit [16]. Moreover, deep-learning based methods for LUS have also shown promising results for detecting COVID-19 pneumonia [17,18].

Several studies have also assessed the dynamic changes in LUS findings during a COVID-19 infection and found that LUS can be used to monitor disease progression during hospitalization [1,19,20]. However, whether the LUS findings detected during the initial COVID-19 infection resolve or persist after hospital discharge is less well investigated. Indeed, pathologic findings on CT have been shown to persist in a substantial number of COVID-19 survivors several months after hospitalization [21–24]. In contrast to CT, LUS can be used for rapid & radiation-free monitoring in the outpatient setting. Moreover, B-lines on LUS are also a common measure of pulmonary congestion in patients with acute heart failure (AHF) [25,26]. LUS findings in patients with COVID-19 pneumonia and AHF may thus overlap, further complicating accurate diagnosis of pulmonary congestion in the acute setting after a prior COVID-19 infection. Therefore, it is important to understand the trajectory of LUS findings after discharge in patients with COVID-19. In this longitudinal cohort study, we sought to investigate the changes in LUS findings from hospitalization for COVID-19 to 2–3 months after discharge.

2. Methods

2.1. Study population

Adult patients hospitalized with laboratory-confirmed SARS-CoV-2 infection at 8 different hospitals in eastern Denmark were enrolled in a prospective, observational, multicenter study (the ECHOVID-19 study) from March 30th to June 3rd, 2020. Patients were enrolled from dedicated COVID-19 non-ICU hospital units. The study design has been described in detail previously [15,27–29]. Upon inclusion, patients underwent LUS, laboratory testing and answered a questionnaire. Surviving participants were invited by telephone for a follow-up examination 2–3 months after hospital discharge. If participants did not respond after 3 attempts of contact on 3 separate days, they were excluded from the follow-up study. At the follow-up examination, participants underwent another LUS examination and laboratory testing. Participants also underwent echocardiography at the time of LUS during hospitalization and at follow-up. These results have been published elsewhere [27,29,30]. For this analysis, we only included participants who had $\leq$1 missing zone on the LUS during hospitalization and at follow-up. Clinical and baseline data as well as in-hospital events were retrieved from the participants' electronic health records after inclusion in the study. The definitions of hypertension, diabetes mellitus, hypercholesterolemia, heart failure and ischemic heart disease have been described previously [27]. Development of acute respiratory distress syndrome (ARDS) during hospitalization was defined according to the Berlin Criteria [31]. Venous thromboembolic events consisted of CT-confirmed pulmonary embolism and/or ultrasound-verified deep vein thrombosis [29]. All included patients provided written informed consent. The study was conducted in accordance with the 2nd Declaration of Helsinki. The ECHOVID-19 Study is registered at Clinicaltrials.gov (NCT04377035).

2.2. LUS examination

The LUS examinations were performed with standard echocardiographic equipment using a phased-array transducer (1.7–3.3 MHz) in sagittal orientation. The baseline LUS examination was performed using the portable Vivid IQ 4D Ultrasound System (GE Healthcare, Horten, Norway). The follow-up LUS examination was performed using Vivid 9 Ultrasound System (GE Healthcare, Horten, Norway). Both LUS examinations were performed by trained investigators and followed a standardized 8-zone protocol (4 zones on each hemithorax) [26]. Fig. 1 illustrates the location of the 8 LUS zones. Six second clips were recorded for each zone. All LUS clips were analyzed off-line using EchoPAC version 203 (GE, Vingmed Ultrasound AS) by an experienced investigator blinded to clinical information. The following findings were recorded from the LUS clips: 1) the maximum number of B-lines in a single frame during the entire clip of each zone, 2) confluent B-lines, 3) subpleural consolidations, and 4) lobar consolidations.

A LUS score was constructed to integrate the above LUS findings in a single parameter, similar to the aeration score previously reported [5,10,32,33]. The LUS score has been described in detail previously [15]. Briefly, $\geq$3 B-lines in a single zone corresponded to a score of 1, confluent B-lines to a score of 2 and subpleural or lobar consolidation to a score of 3. The total LUS score ranged from 0 to 24. The total number of B-lines was calculated as the sum of the maximum number of B-lines in a single frame in each of the 8 zones. Confluent B-lines were counted as 7 B-lines (the highest number of B-lines in a single zone in this dataset) for the parameter total number of B-lines. The mean intra-operator total B-line difference across all 8 zones from the baseline measurements was −1.6 (95% limits of agreement −6,3 to 3.1) in 15 randomly selected patients(15).

2.3. Statistical analysis

Continuous variables were summarized with mean and standard deviation or median and interquartile range for normally and non-normally distributed variables, respectively. Categorical variables were listed as frequencies with percentages. For comparison between groups (ARDS vs. no ARDS during hospitalization), continuous variables were compared using Student's t-test or Wilcoxon rank sum test as

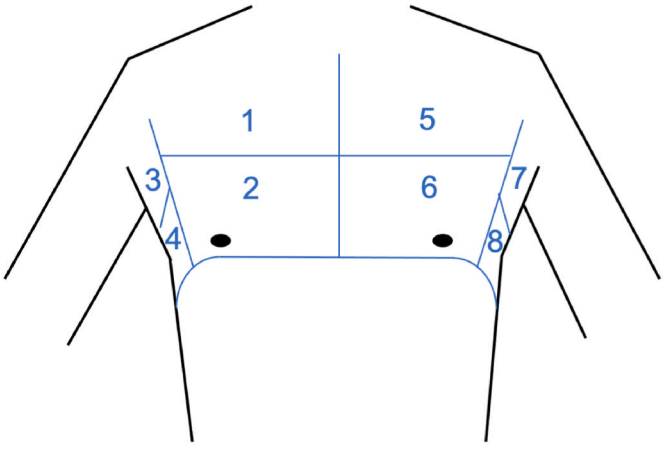

Fig. 1. Overview of the 8 LUS zones.
This schematic depicts the location of the 8 LUS zones with 2 anterior and 2 lateral zones on each hemithorax.

appropriate, and categorical variables were compared using Fischer's exact test. The paired *t*-test was used to compare the paired continuous variables measured at hospitalization and at follow-up for normally distributed variables, whereas Wilcoxon signed rank test was used to compare the paired continuous variables for non-normally distributed variables. McNemar's test was used to compare paired categorical data from hospitalization to follow-up. In a sensitivity analysis, we investigated the difference between baseline and follow-up LUS findings using imputed data for the missing LUS zones. We imputed data from anatomically adjacent zones (LUS 1: n = 39, LUS 2: n = 19): zone 1 and 2, zone 3 and 4, zone 5 and 6, zone 7 and 8 in patients with missing LUS data in ≤2 out of the 8 zones as previously described in patients with heart failure [26]. For the sensitivity analysis with imputed data, we only included those with 0 missing zones after imputation at the baseline and follow-up LUS.

A two-sided p-value of <0.05 was considered statistically significant. STATA, version 14.1, (StataCorp, College Station, TX, USA) was used for all statistical analyses.

3. Results

3.1. Baseline characteristics and complications during hospitalization

Initially, 215 hospitalized patients with COVID-19 were included in the study. Among 171 surviving participants invited for a follow-up examination, 91 participants completed the follow-up examination, and 20 of these had ≥1 missing or uninterpretable zone on the LUS at hospitalization or at follow-up and were thus excluded. Therefore, ultimately 71 participants were included in this study of follow-up LUS findings in patients hospitalized for COVID-19. Fig. 2 illustrates the inclusion and exclusion process. Baseline characteristics of patients who participated in the follow-up examination and those who did not have been published previously [30]. The initial LUS examination was performed a median of 3 days (IQR 2–6) after hospital admission, and the follow-up LUS was performed a median of 72 days (IQR 72–92) after the initial LUS.

The baseline characteristics of the study sample and complications during the hospitalization are outlined in Table 1. Overall, 61% of participants were male with a mean age of 64 years, 46% had hypertension and 19% had diabetes. The median length of stay in the hospital was 6 days (IQR 4–16). During the baseline hospitalization, 47% received supplemental oxygen at the day of LUS examination. Moreover, 19 (27%) patients developed respiratory failure (defined by the need for high flow oxygen >15 L/min and/or non-invasive ventilation), 17 (24%) developed ARDS, 7 (10%) developed a venous thromboembolic event and 12 (17%) were admitted to the ICU. These complications include events during the entire hospitalization; both before and after the LUS. Those who developed ARDS during the hospitalization (n = 17) were older and treated with higher oxygen levels compared to those who did not develop ARDS during the hospitalization (n = 54). Moreover,

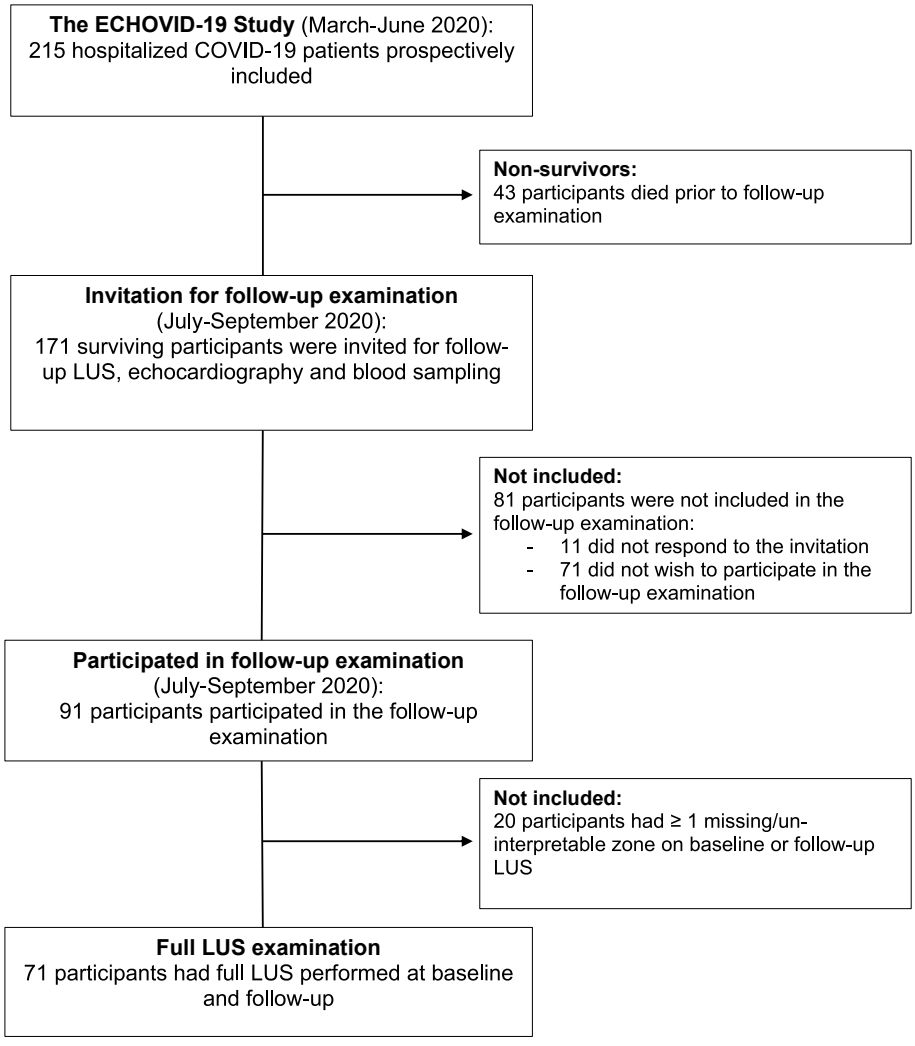

Fig. 2. Consort Diagram of the inclusion of patients.

Table 1
Baseline characteristics of patients included in the follow-up LUS study (n = 71).

	N	All patients included in follow-up LUS study (n = 71)	Those without ARDS during hospitalization (n = 54)	Those with ARDS during hospitalization (n = 17)	P
Baseline characteristics					
Male, n (%)	71	43 (61%)	32 (59%)	11 (65%)	0.78
Age, years (SD)	71	64 (12)	61 (12)	71 (9)	0.004
BMI, kg/m^2 (IQR)	71	26 (23, 29)	26 (24, 30)	24 (22, 27)	0.12
Smoking status, n (%)	65				0.025
Current		2 (3%)	1 (2%)	1 (7%)	
Former		27 (42%)	25 (50%)	2 (13%)	
Never		36 (55%)	24 (48%)	12 (80%)	
Pack-years, (IQR)	32	18 (6, 25)	19 (8, 25)	14 (3, 27)	0.8
Hypertension, n (%)	71	33 (46%)	22 (41%)	11 (65%)	0.10
Diabetes, n (%)	70	13 (19%)	9 (17%)	4 (24%)	0.72
Hypercholesterolemia, n (%)	71	21 (30%)	16 (30%)	5 (29%)	1.00
Previous ischemic heart disease, n (%)	71	6 (8%)	4 (7%)	2 (12%)	0.63
Prevalent heart failure, n (%)	71	3 (4%)	2 (4%)	1 (6%)	0.57
Asthma, n (%)	71	15 (21%)	11 (20%)	4 (24%)	0.75
Chronic obstructive pulmonary disease, n (%)	71	4 (6%)	3 (6%)	1 (6%)	1.00
Other lung disease[a], n (%)	70	2 (3%)	1 (2%)	1 (6%)	0.41
Vital signs upon inclusion					
Systolic blood pressure, mmHg (SD)	71	123 (7)	123 (17)	124 (16)	0.97
Diastolic blood pressure, mmHg (SD)	71	72 (10)	71 (10)	73 (11)	0.54
Heart rate, beats/minute (IQR)	63	76 (66, 85)	72 (65, 81)	80 (77, 98)	<0.001
Respiratory rate, breaths/minute (IQR)	71	18 (17,20)	18 (17, 20)	18 (18, 20)	0.76
Oxygen saturation, % (SD)	71	95 (2)	96 (2)	94 (1)	0.002
Oxygen therapy, n (%)	70	33 (47%)	23 (43%)	10 (63%)	0.25
Level of oxygen therapy, L/min (IQR)	33	3.0 (1.5, 5.0)	2.0 (1.0, 4.0)	7.0 (3.0, 12.0)	0.014
COVID-19 complications during hospitalization					
Length of hospitalization, days (IQR)	71	6 (4, 16)	5 (3, 7)	27 (20, 30)	<0.001
Respiratory failure[b], n (%)	71	19 (27%)	2 (4%)	17 (100%)	<0.001
Acute respiratory distress syndrome, n (%)	71	17 (24%)	0 (0%)	17 (100%)	
Venous thromboembolic events, n (%)	70	7 (10%)	1 (2%)	6 (38%)	<0.001
Admission to intensive care unit, n (%)	71	12 (17%)	1 (2%)	11 (65%)	<0.001

[a] Other lung disease includes lung fibrosis, sarcoidosis, cystic fibrosis, lung cancer, lung transplant, etc.
[b] Respiratory failure defined by the need for high flow oxygen therapy (>15 L/min) and/or non-invasive ventilation.

those with ARDS were more often admitted to the ICU, had higher rate of in-hospital venous thromboembolic events, and had a longer length of stay in the hospital. In the Supplemental Material, Table 1, we have outlined the difference in baseline characteristics stratified by the development of respiratory failure.

3.2. Differences in LUS and laboratory findings from baseline to follow-up

Overall, LUS findings improved significantly from baseline to follow-up (Table 2). The proportion of patients with at least one zone with a pathologic finding (e.g. ≥3 B-lines, confluent B-lines or subpleural consolidation) decreased from 87% at baseline to 30% at follow up ($p < 0.001$). Similarly, the proportion of patients with confluent B-lines in at least one zone decreased from 25% at baseline to none at follow-up ($p < 0.001$). On the initial LUS, 23% had ≥3 B-lines in ≥2 bilateral zones on LUS, whereas at follow-up none of the patients had this finding ($p < 0.001$). The LUS score and total number of B-lines also decreased significantly from hospitalization to follow-up (median 4 vs. 0, $p < 0.001$ and 17 vs. 4, $p < 0.001$, respectively). Figs. 3 and 4 depict the change in the total number of B-lines and LUS score from baseline to follow-up, respectively. None of the participants with ≤ 1 zone with a pathological finding on the initial LUS (n = 22) had more than 1 zone with a pathologic finding on the follow-up LUS. However, two participants without any pathologic findings on the initial LUS, both had 1 zone with a pathologic finding on the follow-up LUS (with ≥3 B-lines). In a sensitivity analysis with imputed LUS data for the missing zones (n = 75), the difference between baseline and follow-up LUS findings remained similar (Supplemental Material, Table 1).

Laboratory findings also differed significantly from hospitalization to follow-up. CRP-levels, NT-proBNP-levels and the neutrophil counts were significantly higher at baseline compared to follow-up, whereas lymphocyte counts were significantly lower at baseline compared to follow-up (Table 2).

3.3. LUS findings in patients with and without ARDS during the hospitalization

LUS findings at baseline and follow-up in patients who developed ARDS during the hospitalization (both before and after the LUS examination) and those who did not are listed in Table 3. Patients who developed ARDS during the hospitalization had a higher LUS score (median 6 vs. 3, $p = 0.034$) and more frequently presented with subpleural or lobar consolidations on the initial LUS. At follow-up, there were no statistically significant differences in LUS findings between those with ARDS during the hospitalization and those without, although the total number of B-lines (median 5 vs. 3) and the number of patients with at least one zone with ≥3 B-lines (47% vs. 22%) were numerically higher.

4. Discussion

Among COVID-19 survivors, pathologic LUS findings were common during a hospitalization for COVID-19 and improved within ~72 days after the in-hospital LUS. The total number of B-lines and LUS score

Table 2
Baseline and follow-up LUS and laboratory findings in patients included in the follow-up LUS study (n = 71).

	N	Baseline	Follow-up	P-value
LUS findings				
≥1 zone with pathologic LUS findings[a]	71	62 (87%)	21 (30%)	<0.001
≥1 zone with ≥3 B-lines, n (%)	71	61 (86%)	20 (28%)	<0.001
≥1 zone with confluent B-lines, n (%)	71	18 (25%)	0 (0%)	<0.001
≥1 zone with subpleural or lobar consolidation, n (%)	71	13 (18%)	1 (1%)	0.002
≥3 B-lines in ≥2 bilateral zones, n (%)	71	16 (23%)	0 (0%)	<0.001
LUS score, (IQR)	71	4 (1, 6)	0 (0, 1)	<0.001
Total number of B-lines, (IQR)	71	17 (10, 24)	4 (2, 7)	<0.001
Laboratory findings				
Creatinine, μmol/L (IQR)	63	70 (58, 89)	65 (58, 80)	0.06
Leucocytes, $x10^9$/L (IQR)	63	6.0 (4.5, 8.0)	6.2 (5.3, 7.2)	0.85
Neutrophils, $x10^9$/L (IQR)	64	4.0 (3.0, 5.8)	3.7 (3.0, 4.1)	0.04
Lymphocytes, $x10^9$/L (IQR)	64	1.2 (0.8, 1.6)	1.8 (1.4, 2.2)	<0.001
CRP, mg/L (IQR)	63	56 (21, 93)	0 (0, 0)	<0.001
NT-proBNP, ng/L (IQR)	35	170.8 (93.0, 380.6)	11.6 (5.7, 23.9)	<0.001

LUS: lung ultrasound, IQR: interquartile range, CRP: C-reactive protein, NT-proBNP: N-terminal pro B-type natriuretic peptide.
[a] Pathologic LUS findings correspond to ≥3 B-lines, confluent B-lines, subpleural or lobar consolidations.

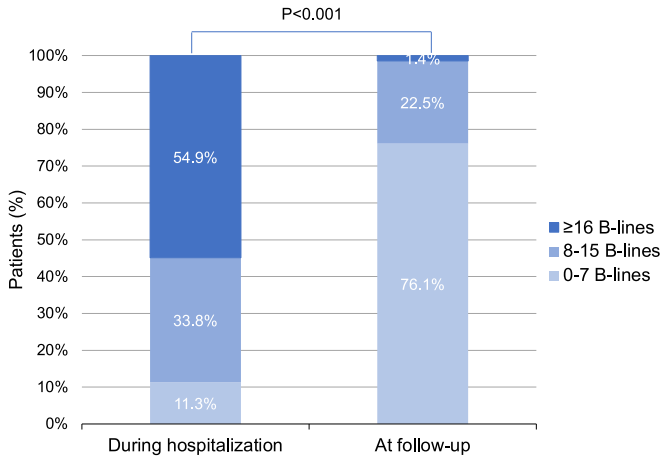

Fig. 3. Change in B-lines on LUS from hospitalization for COVID-19 to follow-up (n = 71).
Change in the total number of B-lines on 8-zone LUS from hospitalization for COVID-19 to follow-up LUS examination. The total number of B-lines is divided in tertiles of 0–7, 8–15 and ≥ 16 B-lines.

decreased significantly from baseline to follow-up. Moreover, at follow-up none of the participants had confluent B-lines or sonographic evidence of interstitial syndrome on LUS. However, the presence of multiple B-lines (≥3 B-lines) in at least one zone persisted in more than a quarter of all included participants at follow-up and in almost half of participants with ARDS during the hospitalization. LUS seems to be a useful method to detect and monitor changes in lung density from hospitalization for COVID-19 to resolution of the infection after discharge.

A prior study demonstrated the ability of LUS to detect chest CT-confirmed interstitial lung disease in 38 COVID-19 survivors three months after discharge from the ICU [34], thereby underscoring the correlation between LUS findings and chest CT findings for detecting

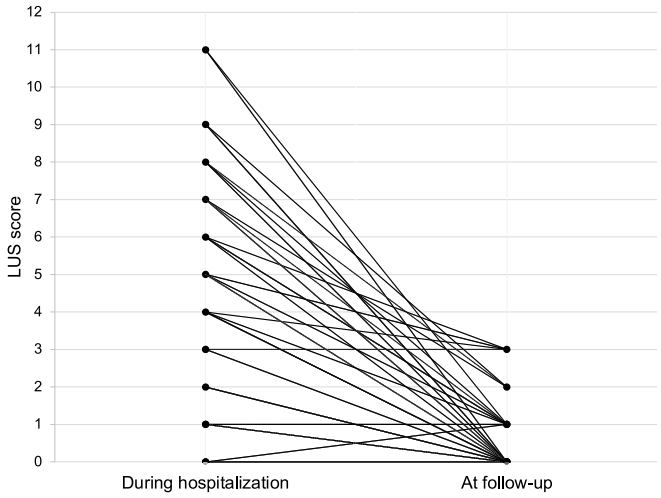

Fig. 4. LUS scores during hospitalization for COVID-19 and at follow-up (n = 71).
LUS-scores on 8-zone LUS at hospitalization for COVID-19 to the follow-up LUS examination. The solid lines track the changes in LUS score from hospitalization to follow-up.

residual lung injury. LUS may therefore be useful as a non-invasive screening tool to monitor changes and improvement in lung density after discharge in patients hospitalized for COVID-19. As such LUS could be used to identify subjects with residual lung injury requiring additional follow-up.

In this cohort, 87% of patients hospitalized for COVID-19 had at least one zone with a pathologic LUS finding, and this number decreased significantly to 30% at follow-up. In particular, consolidations and confluent and bilateral B-lines resolved at follow-up, whereas the presence of multiple B-lines in at least one zone on LUS persisted in more than a quarter of patients after 2–3 months. None of the participants still had confluent B-lines or sonographic evidence of interstitial syndrome (≥3 B-lines in ≥2 bilateral zones) at follow-up. Consolidations, confluent B-lines and multiple bilateral B-lines could thus represent acute findings on LUS due to COVID-19 infection that gradually resolve over time following resolution of the infection. The persistent presence of multiple B-lines in at least one zone could reflect prolonged effects or fibrotic changes after COVID-19 pneumonia. Prior studies investigating chest CT findings in patients after a COVID-19 hospitalization have demonstrated that ground-glass opacities and fibrotic changes are common findings in patients several months after a COVID-19 hospitalization [21,22,24].

Interestingly, in those with ARDS during the hospitalization, the presence of at least one zone with ≥3 B-lines persisted in almost half of the patients (47%) at follow-up. Therefore, the degree of lung involvement resulting from the COVID-19 induced ARDS may have caused longer-term effects on the lungs as visualized by a higher degree of persistent multiple B-lines on LUS at follow-up. Our study may have been underpowered to detect a statistically significant difference between the follow-up LUS findings in patients with and without ARDS during the hospitalization. A prior study in hospitalized COVID-19 patients found that the improvement in LUS score at follow-up post-discharge was greater for those who did not have ARDS during the hospitalization compared to those who had varying degrees of ARDS during the hospitalization [35]. Thus, patients who have had ARDS may develop more persistent lung changes detectable on LUS at least 2–3 months after discharge. This in accordance with chest CT-findings 4 months after a hospitalization for COVID-19 in which fibrotic changes were more frequent in patients with ARDS during the hospitalization [24].

Although the presence of at least one zone with ≥3 B-lines persisted

Table 3
Baseline and follow-up LUS findings in patients with and without ARDS during hospitalization for COVID-19 (n = 71).

	Baseline			Follow-up		
LUS findings	No ARDS during hospitalization (n = 54)	ARDS during hospitalization (n = 17)	P-value	No ARDS during hospitalization (n = 54)	ARDS during hospitalization (n = 17)	P-value
≥1 zone with pathologic LUS findings[a]	46 (85.2%)	16 (94.1%)	0.68	13 (24.1%)	8 (47.1%)	0.13
≥1 zone with ≥3 B-lines, n (%)	45 (83.3%)	16 (94.1%)	0.43	12 (22.2%)	8 (47.1%)	0.07
≥1 zone with confluent B-lines, n (%)	14 (25.9%)	4 (23.5%)	1.00	0 (0%)	0 (0%)	–
≥1 zone with subpleural or lobar consolidation, n (%)	5 (9.3%)	8 (47.1%)	0.001	1(1.9%)	0 (0%)	1.00
≥3 B-lines in ≥2 bilateral zones, n (%)	10 (18.5%)	6 (35.3%)	0.19	0 (0%)	0 (0%)	–
LUS score, (IQR)	3 (1, 5)	6 (3, 8)	0.034	0 (0, 0)	0 (0, 1)	0.15
Total number of B-lines, (IQR)	14 (9, 24)	18 (16, 22)	0.31	3 (2, 6)	5 (4, 9)	0.06

LUS: lung ultrasound, ARDS: acute respiratory distress syndrome, IQR: interquartile range.
[a] Pathologic LUS findings correspond to ≥3 B-lines, confluent B-lines, subpleural or lobar consolidations.

in substantial number of patients, none of the patients at follow-up had a number of B-lines on LUS that would meet the cut-off for a diagnosis of AHF based on the degree of pulmonary congestion [36]. Therefore, based on the findings of our study, the same LUS cut-off values as established prior to the pandemic may still be used in patients with a history of prior COVID-19 infection as part of the diagnostic work-up of patients presenting with symptoms of AHF. This is an important finding, as LUS is part of the most recent guidelines from the European Society of Cardiology as part of the diagnostic workup of patients with AHF to detect pulmonary congestion [37].

Prior prospective studies investigating the serial changes in LUS findings during and after a COVID-19 infection, have reported similar findings regarding the gradual decrease in pathologic LUS findings from hospitalization to follow-up 1–4 months after discharge [35,38]. However, the proportion of patients with pathologic LUS findings post-discharge was higher in these serial LUS studies [35,38] as well as in another non-serial LUS study among COVID-19 survivors [34] compared to ours. This could in part be explained by the fact that these studies employed a more extensive LUS protocol with 12–13 zones including the posterior lung areas, whereas we used a simplified 8-zone LUS protocol including only the anterior and lateral zones. Lastly, in two studies [34,38], all enrolled patients had been admitted to the ICU with severe COVID-19 infection, whereas only a subset of patients had been admitted to the ICU during the hospitalization in our study. In comparison, our study was a multicentre, prospective study investigating serial LUS examinations in patients hospitalized for COVID-19 independent of the severity of COVID-19 infection.

Although LUS is useful for monitoring changes in lung density after discharge in patients hospitalized for COVID-19, the long-term evolution in lung density as well as the association with pulmonary function and symptoms should be investigated further in future longitudinal follow-up studies. LUS could potentially be implemented in a strategy to characterize the longer-term effects of COVID-19 infection on lung density.

4.1. Limitations

The results of this study should be interpreted in the context of its limitations. First, the initial LUS was performed a median of 3 days from admission (IQR 2–6), which may affect the prevalence of abnormal findings on the baseline LUS as patients may be in different stages of their disease at the time of the LUS. Moreover, we investigated a simplified 8-zone LUS protocol scanning only the anterior and lateral lung zones for both the initial and follow-up LUS, which may have led to an underestimation of the prevalence of pathologic LUS findings as the posterior lung areas are often affected in patients with COVID-19 pneumonia [39]. However, a simplified 8-zone LUS may be easier and faster to perform in a busy clinical setting. Only a subset of patients participated in the follow-up examination, which led to a small sample size and may affect the generalizability of the results. Nonetheless, the repeated LUS examinations and blood sampling in the same group of patients allowed for direct comparison of findings at baseline and follow-up. However, as only a subset of the patients had a CT scan performed at baseline and none at follow-up, we could not compare the LUS findings with the CT findings. Moreover, B-lines are dynamic artefacts reliant on several technical aspects related to both LUS technique and the type of equipment used, including the transducer type. As more than one operator performed the LUS at baseline and discharge, it is possible that this aspect may have affected the observed change in the number of B-lines from the baseline hospitalization to follow-up. Although B-lines on LUS are nonspecific findings related to reduced lung aeration, B-lines can be used as a semi-quantitative measure of extravascular lung water [40] including pulmonary congestion in patients with heart failure [41]. However, the quality and therefore also interpretation of the LUS exam is dependent on the operator's expertise and the equipment used. Moreover, LUS may not allow for detection of centrally located pulmonary involvement [42]. Although only a subset of patients had NT-proBNP measurements at baseline and follow-up, we have previously shown that NT-proBNP and the total number of B-lines and LUS score were not correlated in this cohort(15). Finally, although the follow-up period was relatively short, most participants demonstrated resolution of pathologic LUS findings at follow-up.

5. Conclusion

Among survivors following a hospitalization for COVID-19, LUS findings improved significantly from baseline to follow-up, including the total number of B-lines and LUS score. However, multiple B-lines in at least one zone on LUS were a frequent finding at follow-up, especially among those who had ARDS during the hospitalization. LUS seems to be a promising method to monitor changes in lung density after a COVID-19 hospitalization.

Sources of funding

TBS, together with KGS and MHL, received a research grant from the Novo Nordisk Foundation to conduct the study. Europcar Denmark provided cars for KGS and MHL to transport the equipment from hospital to hospital. TBS received funds from Herlev and Gentofte Hospital and the Lundbeck foundation while conducting this study. The research salary of PS was sponsored by Herlev and Gentofte Hospital. The sponsors had no role in the design and interpretation of the data.

CRediT authorship contribution statement

Caroline Espersen: Conceptualization, Methodology, Formal analysis, Interpretation, Investigation, Writing – original draft, Writing – review & editing. **Elke Platz:** Conceptualization, Methodology, Formal analysis, Interpretation, Writing – review & editing, Supervision. **Alia Saed Alhakak:** Interpretation, Investigation, Writing – review & editing. **Morten Sengeløv:** Interpretation, Investigation, Writing – review & editing. **Jakob Øystein Simonsen:** Interpretation, Investigation, Writing – review & editing. **Niklas Dyrby Johansen:** Interpretation, Investigation, Writing – review & editing. **Filip Søskov Davidovski:** Interpretation, Investigation, Writing – review & editing. **Jacob Christensen:** Interpretation, Investigation, Writing – review & editing. **Henning Bundgaard:** Interpretation, Resources, Writing – review & editing. **Christian Hassager:** Interpretation, Resources, Writing – review & editing. **Reza Jabbari:** Interpretation, Resources, Writing – review & editing. **Jørn Carlsen:** Interpretation, Resources, Writing – review & editing. **Ole Kirk:** Interpretation, Resources, Writing – review & editing. **Matias Greve Lindholm:** Interpretation, Resources, Writing – review & editing. **Ole Peter Kristiansen:** Interpretation, Resources, Writing – review & editing. **Olav Wendelboe Nielsen:** Interpretation, Resources, Writing – review & editing. **Klaus Nielsen Jeschke:** Interpretation, Resources, Writing – review & editing. **Charlotte Suppli Ulrik:** Interpretation, Resources, Writing – review & editing. **Pradeesh Sivapalan:** Interpretation, Resources, Writing – review & editing. **Kasper Iversen:** Interpretation, Resources, Writing – review & editing. **Jens Ulrik Stæhr Jensen:** Interpretation, Resources, Writing – review & editing. **Morten Schou:** Interpretation, Resources, Writing – review & editing. **Søren Helbo Skaarup:** Interpretation, Resources, Writing – review & editing. **Mats Christian Højbjerg Lassen:** Conceptualization, Methodology, Formal analysis, Interpretation, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Kristoffer Grundtvig Skaarup:** Conceptualization, Methodology, Formal analysis, Interpretation, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Tor Biering-Sørensen:** Conceptualization, Methodology, Formal analysis, Interpretation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

TBS reports receiving research grants from Sanofi Pasteur and GE Healthcare, is a Steering Committee member of the Amgen financed GALACTIC-HF trial, on advisory boards for Sanofi Pasteur and Amgen, and has received speaker honorariums from Novartis and Sanofi Pasteur.

EP has received research support from the NIH, and consulting fees from scPharmaceuticals outside the submitted work. Her employer has received support from Novartis for consulting work outside the submitted work.

The remaining authors have nothing to disclose in relation to the present project.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.106826.

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