ORIGINAL ARTICLE

The role of ventilatory support for long-term outcomes after critical infection with COVID-19: A prospective cohort study

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Abstract

Objectives: The full range of long-term health consequences in intensive care unit (ICU) survivors with COVID-19 is unclear. This study aims to investigate the role of ventilatory support for long-term pulmonary impairment in critically ill patients and further to identify risk factors for prolonged radiological recovery.

Methods: A prospective observational study from a single general hospital, including all with COVID-19 admitted to ICU between March and August 2020, investigating the association between ventilatory support and the extent of residual parenchymal changes on chest computed tomography (CT) scan and measurement of lung volumes at follow-up comparing high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) with invasive ventilation. A semi-quantitative score (CT involvement score) based on lobar involvement and a total score for all five lobes was used to estimate residual parenchymal changes. The association was calculated with logistic regression and adjusted for age, sex, smoking, and severity of illness.

Results: Among the 187 eligible, 86 had a chest CT scan and 76 a pulmonary function test at the follow-up with a median time of 6 months after ICU discharge. Residual lung changes were seen in 74%. The extent of pulmonary

changes was similar regardless of ventilatory support, but patients with invasive ventilation had a lower total lung capacity 84% versus 92% of predicted ($p < 0.001$).

Conclusions: The majority of ICU-treated patients with COVID-19 had residual lung changes at 6 months of follow-up regardless of ventilator support or not, but the total lung capacity was lower in those treated with invasive ventilation.

KEYWORDS
COVID-19, CT, follow-up study

1 | INTRODUCTION

COVID-19 is the disease caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), which developed into a pandemic in 2020. Symptoms associated with the disease vary widely, and 80% of the cases are described to be asymptomatic and mild, whereas 14% have had more severe symptoms, such as dyspnea and hypoxia with >50% of the lungs engaged; critical illness with acute respiratory distress syndrome (ARDS) has been reported in 5% of the affected patients.[1] Clinical and laboratory findings such as male sex and elevated C-reactive protein (CRP) and lymphocytopenia have all been described as associated factors to severe disease of COVID-19 with extensive pulmonary involvement.[2] In regard to treatments, several antiviral drugs have been used without convincing results in improving the outcomes.[3] Corticosteroids have become standard treatment in those with severe COVID-19, and the evidence of corticosteroids point toward a more favorable outcome in the short run.[4] Yet, reports concerning the effect on the long-term outcomes are still warranted to be able to formulate a clear strategy for cure and relief.[5] Studies of chest imaging findings in COVID-19 patients in the acute phase have so far indicated that the majority of patients have some lung changes, where ground-glass opacities (GGO), reticular interstitial pattern, and consolidation are the most common findings.[6] Among the most severely ill, all appeared to have computed tomography (CT) findings, and the findings seem to increase in proportion to the disease severity.[7] For those admitted to the hospital, the natural evolution of the disease involved a progression from GGO to consolidation.[7] Radiological abnormalities were still found in a considerable proportion of cases 3 months after hospital discharge, where GGO, reticular interstitial thickening, and a mixture of these findings were the most common.[8] Among intensive care unit (ICU) survivors with COVID-19, the majority reported impaired health quality of life 5 months from ICU discharge and where outcomes were similar regardless of ventilatory support.[9] Furthermore, earlier reports concerning long-term follow-up after previous outbreaks of other coronaviruses, such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), demonstrated that lung function impairment may persist beyond 6 months.[10] Additional data and more knowledge are needed to understand which parameters influence the long-term outcome in COVID-19. Therefore, this study aims to investigate the association between ventilator support because of COVID-19 and pulmonary impairment at follow-up and further to identify risk factors for prolonged pulmonary recovery.

2 | METHODS

2.1 | Study design and participants

This prospective observational cohort study involved survivors of a severe COVID-19 infection admitted to two ICUs at Södersjukhuset, a general hospital in Stockholm, Sweden, between March 25 and August 13, 2020. During the acute phase of COVID-19, standard treatment with oxygen, thromboembolic prophylaxis, and antibiotics in cases of suspected superinfection were given. At the end of the study period, corticosteroids became standard treatment at the ICU.

All critically ill patients with a positive polymerase chain reaction (PCR) for COVID-19 and treated for respiratory failure with mechanical ventilation, high-flow treatment with oxygen (high-flow nasal oxygen [HFNO]), or non-invasive treatment (non-invasive ventilation [NIV]) in the ICU were eligible for inclusion. Patients were excluded if they did not attend a follow-up appointment and if no chest CT scan was performed at the follow-up.

Ethical approval was obtained by the Ethics Review Authority in Sweden (DNR2020-03760). Oral and written

informed consent was obtained from all participants before study inclusion. All procedures performed in the study involving human participants were made in accordance with the ethical standards of the institutional and/or national research committee as well as with the 1964 Helsinki declaration and its later amendments or comparable applicable ethical standards.

2.2 | Data collection

Patients who survived ICU treatment were invited for a hospital-based follow-up visit between 2 and 7 months after ICU discharge. Clinical variables retrieved from each participant's medical record were age; sex; body mass index (BMI) at time point for follow-up; comorbidities such as diabetes, hypertension, cardiovascular disease, and chronic lung disease; if ever smoker; corticosteroid treatment; mechanical ventilation or non-invasive ventilation such as HFNO or NIV; highest CRP during the acute phase (CRP max); length of stay in the ICU; and Simplified Acute Physiology Score III (SAPS 3), which is a scoring system used to predict mortality risk in the ICU. A higher score at ICU admission indicates higher mortality risk.[11]

2.3 | CT protocol and image analysis

All patients were examined in a Siemens Somatom Drive using a standard 120-kV CT thorax protocol in a supine position during end inspiration without intravenous contrast material. Images were reconstructed at 0.75-mm slice thickness and 0.5-mm increment. Axial, coronal, and sagittal 2/2-mm multiplanar reconstructions (MPR) were available in all cases.

International standard thoracic radiological terminology from Fleischner Society[12] was implemented to identify the parenchymal changes related to SARS-CoV-2 infection.[13] The CT anomalies scored were GGO, subpleural bands, reticular pattern, and bronchiectasis, where typical chest CT changes identified are presented in Figure 1A–D. Atypical SARS-CoV-2 CT changes, such as pleural effusion, lymphadenopathy, and preexisting chest CT changes (for those patients with previous CT scan) were excluded from the score, a procedure in line with previous research.[13]

A semi-quantitative CT score (CT involvement score) was estimated based on lobar involvement and then calculated as a total score for all five lobes: 0: 0%, 1: <5%, 2: 5%–25%, 3: 26%–50%, 4: 51%–75%, 5: >75%, yielding a score ranging from 0 to 5 in each lobe and a global score of 0–25. This scoring system has earlier

been adopted for estimating lung involvement in COVID-19.[7]

Every CT was reviewed independently and countersigned by one medical resident in radiology with 3 years of experience (G.H.) and one experienced thoracic radiologist with either 12 (J.M.) or 3 (S.B.) years of experience as a consultant. All images were reviewed and countersigned by a senior/attending radiologist (i.e., all images were thus reviewed by a senior radiologist). In cases of disagreement, a third thoracic radiologist was consulted, and all three radiologists obtained a decision in consensus. A sample of 15/86 CT images was collected to calculate inter-reader variability using Cohen's kappa for each pair, 0.86 (GH/JM), 0.49 (GH/SB), and Krippendorff's alpha (0.71) for a total score of inter-reader agreement. Fleischner kappa could not be calculated as there was no cross-evaluation between all reviewers.

2.4 | Pulmonary function testing

Lung volumes were measured according to standard procedures, where total lung capacity (TLC) was examined with whole-body plethysmography.[14–16] Diffusion capacity for carbon monoxide (DLCO) (uncorrected value) was measured according to standard methods.[17] Outcomes were expressed according to reference values (Hedenström).[18,19] TLC ≥ 80% was set as normal.

2.5 | Statistical analysis

Descriptive statistics were presented as counts (n), proportions (%), means ± standard deviations, and medians (interquartile range [IQR]), according to type and distribution of data. Differences between groups were analyzed by Fisher's exact test, χ^2, or Mann–Whitney U-test where appropriate. Logistic regression analysis was used to investigate associations between type of respiratory support (HFNO/NIV vs. invasive ventilation) and extent of residual pulmonary changes (CT score > 0) as well as pulmonary function (TLC). An adjustment was made for sex, age (<50, 50–65, and >65), smoker (ever/never), and severity of disease with SAPS 3 (≤34/>34). Multivariable ordinal regression analysis was used to investigate the associations between preexisting risk factors for lung injury such as chronic lung disease (yes/no) and smoking as well as age and sex for remaining abnormalities on chest CT scans (0, 1–5, 6–10, and 11–15). An adjustment was made for sex and age. Results were presented as odds ratio (OR) with 95% confidence intervals (CIs). Statistical
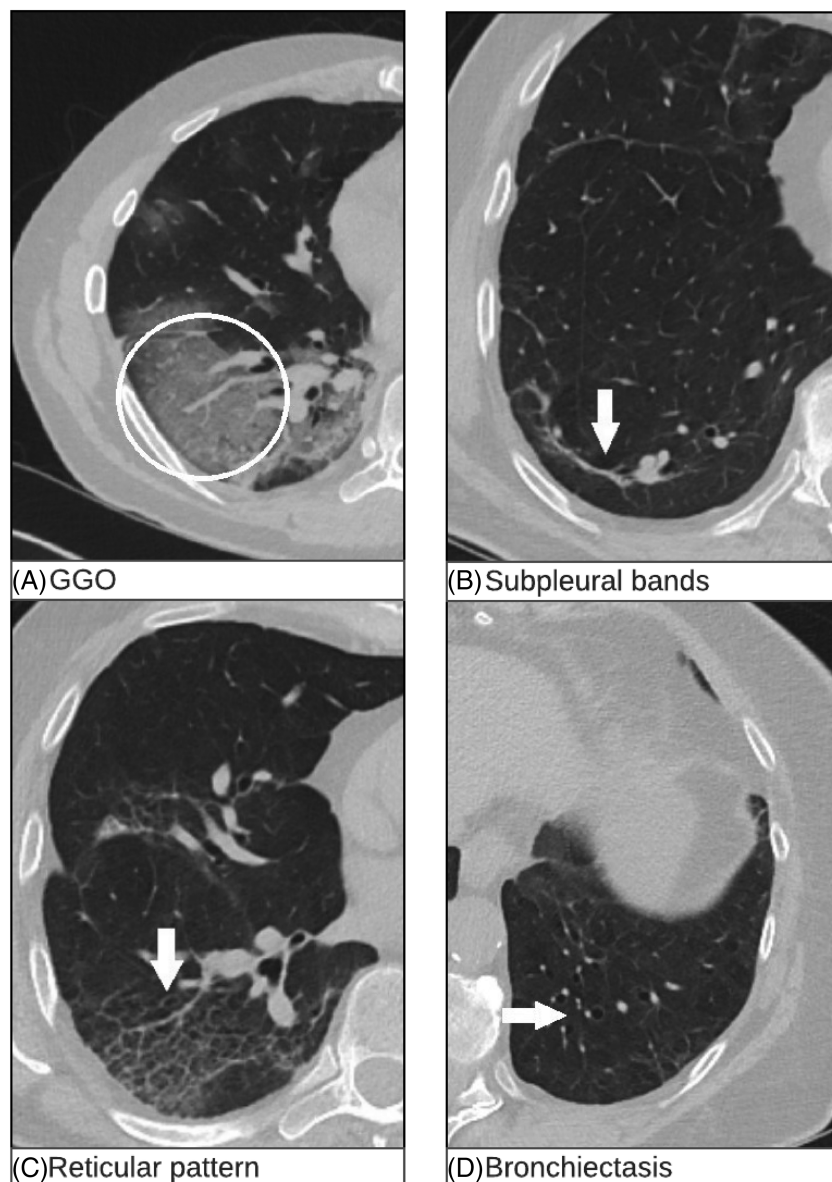
FIGURE 1 From top left to bottom right: (A) Ground-glass opacity (GGO), (B) subpleural band, (C) reticular pattern, and (D) bronchiectasis

analyses were performed with GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA) and R Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was regarded as statistically significant.
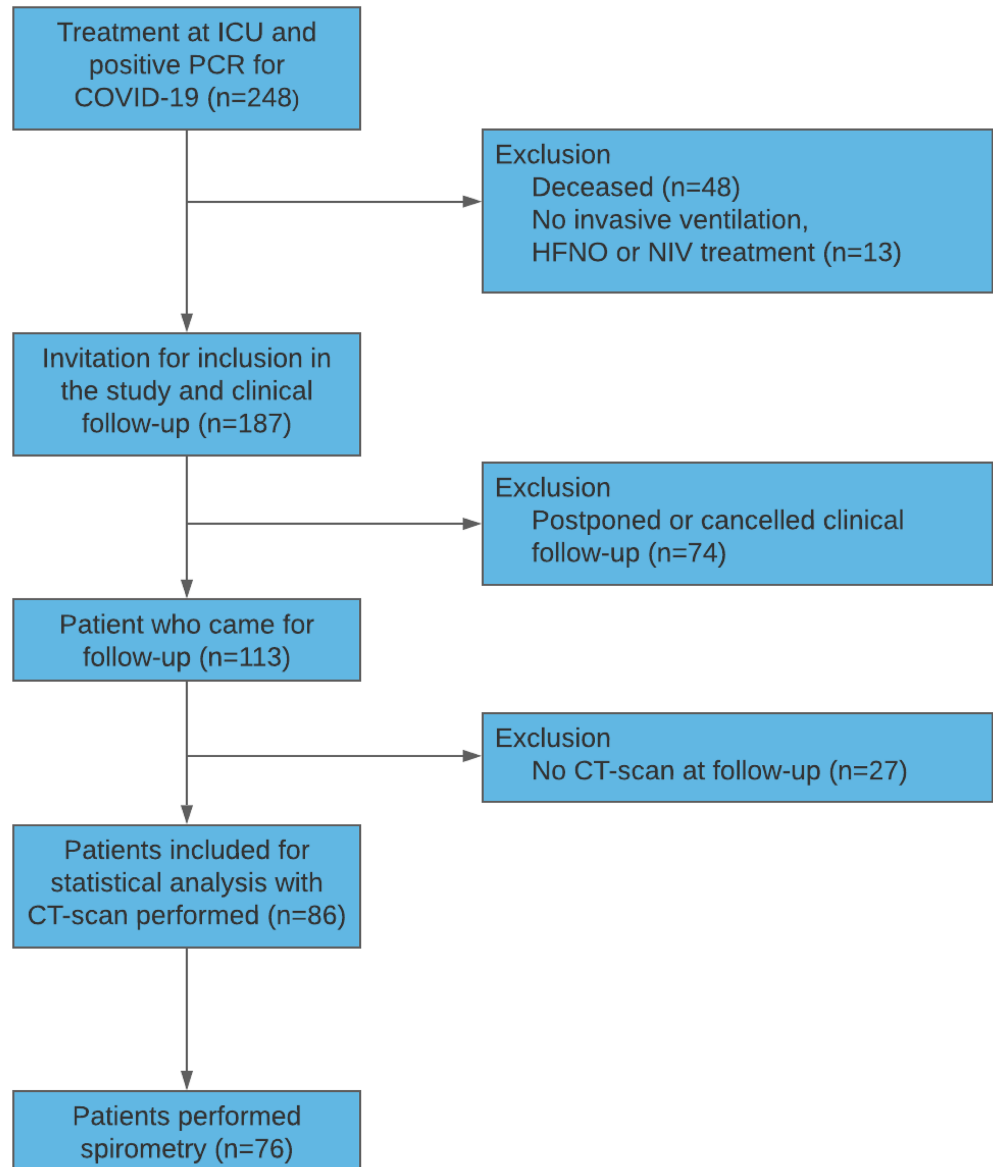
3 | RESULTS

3.1 | Demographics and patients' characteristics

During the study period, 248 cases with severe COVID-19 were admitted to the ICU. Two hundred (81%) survived and were discharged from the ICU. Among them, 187 (94%) had been treated for respiratory failure and

were eligible for this study (Figure 2). Several of those who canceled their appointment already had a follow-up in another hospital to which they had been moved due to lack of beds in the ICU. Out of those who came for follow-up, 86 performed a chest CT scan and 76/86 performed a pulmonary function test (PFT). The median time for follow-up with CT scan was 6 months (IQR 5–7) after discharge from ICU (PFT 6 months [IQR 6–7]). Patient characteristics were similar between those who attended the follow-up examination with chest CT scan and those who did not, except that younger participants were less likely to undergo chest CT scan (Table S1). The majority of the survivors were men (74%) with a slight overweight (mean BMI 28 kg/m^2). The median age was 59 years (IQR 52–66), almost two thirds (60%) had been on mechanical ventilation, and

Treatment at ICU and positive PCR for COVID-19 (n=248)

Exclusion
Deceased (n=48)
No invasive ventilation, HFNO or NIV treatment (n=13)

Invitation for inclusion in the study and clinical follow-up (n=187)

Exclusion
Postponed or cancelled clinical follow-up (n=74)

Patient who came for follow-up (n=113)

Exclusion
No CT-scan at follow-up (n=27)

Patients included for statistical analysis with CT-scan performed (n=86)

Patients performed spirometry (n=76)

the median length of stay in the ICU was 16 days (IQR 4–24) (Table 1).

3.2 | Ventilator support and pulmonary impairment at follow-up

In 22/86 (26%) cases, there was a complete regression observed on the chest CT scan, that is, a CT score of 0. However, 64/86 (74%) had remaining abnormalities on chest CT scan, with a median score of 7 (IQR 4–10). No participant in the cohort had CT score > 15 at follow-up (Table 2). Participants with complete regression on chest CT scans were younger (median age 52 years old, IQR 48–58) compared with patients with residual lung parenchymal changes (median age 62 years old, IQR 55–68) ($p < 0.0001$). In patients with residual abnormalities on

chest CT scan who had performed PFTs ($n = 56$), 17 (30%) had a reduced lung function (TLC < 80% of predicted). Further, those treated with invasive ventilation had a lower TLC 84% versus 92% of expected ($p < 0.001$), but no significant differences in gas exchange (DLCO) were seen between groups (Table S2). Further, there was no significant association between invasive ventilation and abnormalities on chest CT scan either in the crude analysis (OR 2.5, 95% CI: 0.9–6.6) or after adjustments for age, sex, smoking, and SAPS 3 (Table 3). However, patients with invasive ventilation were more likely to have impaired pulmonary function (TLC < 80% of predicted) compared with participants treated with HFNO or NIV (OR 4.1, 95% CI: 1.2–18.9). There was a trend toward an increased risk also after adjustments for potential confounders (OR 3.6, 95% CI: 1.0–17.3) (Table 3).

T A B L E 1 Clinical characteristics of ICU survivors

	All participants ($n = 86$)	HFNO or NIV ($n = 33$)	Invasive ventilator treatment ($n = 53$)
Male	64 (74)	23 (70)	41 (77)*
Age, years	59 (52–66)	56 (48–62)	62 (54–67)
BMI, kg/m^2	28 (25–31)	29 (26–31)	28 (24–31)
Diabetes	15 (17)	4 (12)	11 (33)
Hypertension	38 (44)	12 (36)	26 (49)
Cardiovascular disease	5 (6)	2 (6)	3 (6)
Chronic lung disease	16 (19)	7 (21)	9 (17)
Ever smoker	34 (40)	11 (33)	23 (44)
Corticosteroid treatment	32 (37)	8 (24)	24 (45)
CRP max, mg/L	322 (214–358)	226 (140–316)	343 (271–400)***
Length of ICU stay (days)	16 (4–24)	4 (3–8)	21 (16–30)***
SAPS 3	54 (50–60)	52 (49–56)	57 (53–61)**

Note: Values presented as n (%) or median (interquartile range).
Abbreviations: BMI, body mass index; CRP, C-reactive protein; HFNO, high-flow nasal oxygen; ICU, intensive care unit; NIV, non-invasive ventilation; SAPS, Simplified Acute Physiology Score.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

T A B L E 2 Results from chest CT scan with CT scores

	CT score 0	CT score 1–5	CT score 6–10	CT score 11–15	
	n (%)	n (%)	n (%)	n (%)	p-value
All patients	22	23	26	15	
Male	14 (64)	21 (91)	19 (73)	10 (67)	0.12
Age					
<50	8 (36)	5 (22)	2 (8)	1 (7)	0.0012*
50–65	13 (59)	14 (61)	12 (46)	5 (33)	
>65	1 (5)	4 (17)	12 (46)	9 (60)	
BMI					
<25	3 (14)	5 (22)	9 (35)	6 (40)	0.53
25–30	9 (41)	10 (43)	7 (27)	4 (27)	
>30	10 (45)	8 (35)	10 (38)	5 (33)	
Diabetes	3 (14)	3 (13)	6(23)	3 (20)	0.78
Hypertension	7 (32)	10 (43)	11 (42)	10 (67)	0.23
Cardiovascular disease	0 (0)	0 (0)	3 (12)	2 (13)	0.093
Chronic lung disease	7 (32)	3 (13)	5 (19)	1 (7)	0.26
Ever smokers	12 (55)	8 (35)	10 (38)	4 (27)	0.37
CRP ≥ 300 mg/L	8 (36)	15 (65)	17 (65)	8 (53)	0.16
Invasive ventilation	10 (45)	15 (65)	18 (69)	10(67)	0.36

Note: None of the patients had CT score 16–25.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; CT, computed tomography.
*Statistically significant value.

TABLE 3 CT score ($n = 86$) and total lung capacity ($n = 76$) and associations with invasive ventilation (HFNO or NIV as reference) in COVID-19 patients with adjustment for, age, sex, smoking, and Simplified Acute Physiology Score 3, presented as odds ratios with 95% confidence intervals

	All participants	HFNO or NIV	Invasive ventilator treatment		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
CT score (IQR)	5 (0–9)	4 (0–7)	6 (1–10)	CT score > 0	2.5 (0.9–6.6)	2.0 (0.6–6.6)
TLC < 80%, n/N (%)	18/76 (24)	3/29 (10)	15/47 (32)	TLC < 80%	4.1 (1.2–18.9)*	3.6 (1.0–17.3)

Abbreviations: CI, confidence interval; CT, computed tomography; HFNO, high-flow nasal oxygen; IQR, interquartile range; NIV, non-invasive ventilation; OR, odds ratio; TLC, total lung capacity.
*Statistically significant value ($p < 0.05$).

TABLE 4 Associations between computed tomography scores and the following risk factors presented as odds ratio with 95% confidence intervals ($n = 86$) with adjustment for age and sex

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Male	1.0 (0.4–2.4)	1.4 (0.5–3.7)
Age, 50–65 years	2.5 (0.9–4.2)	3.1 (1.0–9.7)
Age, >65 years	14.3 (7.8–52.5)*	27.0 (6.7–110)*
Chronic lung disease	0.4 (0.2–1.2)	0.7 (0.2–2.0)
Ever smokers	0.5 (0.2–1.2)	0.2 (0.1–0.6)*

Abbreviations: CI, confidence interval; OR, odds ratio.
*Significant value $p < 0.05$, cardiovascular disease excluded because of few individuals.

3.3 | Factors associated with radiologic recovery

Age was of importance for radiologic recovery as shown in Table 2. In the subgroup analysis including sex, age, chronic lung disease, and smoking, higher age, that is, >65 years (OR 27.0, 95% CI: 6.7–110), was independently associated with remaining abnormalities on chest CT scans, while the opposite was seen for smokers (OR 0.2, 95% CI: 0.1–0.6) (Table 4).

4 | DISCUSSION

This study suggests that approximately three out of four treated in the ICU because of COVID-19 have residual lung changes 6 months after ICU discharge. The extent of remaining abnormalities on chest imaging was independent of whether treated with invasive or non-invasive ventilator support, but those who had been mechanically ventilated had lower TLC. Further, the majority of participants appeared to have a normal lung function with TLC ≥ 80%, 6 months after discharge from the ICU, but where those treated with invasive ventilation had lower lung volumes on average. For participants treated because of respiratory failure in the ICU, high age was associated with an increased proportion of remaining abnormalities on chest CT scan. As of the point of this study's completion, few studies have reported the long-term outcomes in those critically ill with COVID-19 and where it is necessary to gain a deeper understanding of this area to better predict disease outcomes.

Clinically manifest symptoms of COVID-19 have been shown to increase with age as well as severity of disease.[20] In our study, higher age was a risk factor for residual abnormalities on chest CT scan following COVID-19 requiring respiratory support in the ICU. Our findings are supported by a 12-month follow-up study where residual CT opacities also increased with age.[21] This might be explained not only by severity of disease but also by a slower healing process where a previous study has shown that increasing age was associated with a slower decline in CT score between initial chest CT scan and chest CT scan at follow-up.[22]

It has been shown that men have a higher risk for severe COVID-19[23] and this was reflected in our cohort where the majority were men. In a Swedish nationwide case–control study of those requiring invasive mechanical ventilation matched for age and sex, several comorbidities such as obesity, diabetes, and hypertension were identified as important risk factors for critical disease.[24] These comorbidities were common in our cohort as well. In our analysis, smokers had a better radiologic outcome compared with non-smokers after adjustment for confounders, and this may be due to respiratory failure not only because of COVID-19 but also in combination with previous smoking-related lung damage. In general, participants who had received invasive ventilation had a lower pulmonary function (TLC) at follow-up. In addition, the predictors for the severity of the disease may not necessarily be the same predictors used to

foresee remaining residual parenchymal pulmonary changes and remaining symptoms after COVID-19 requiring ICU care.

Based on the finding of this study, we suggest to further investigate if the residual lung changes at 12 months will remain as scars, and what impact it will have on the lung function. In a 15-year follow-up study of health care workers who survived SARS infection, the extent of pulmonary injury gradually decreased, but the findings were not completely resolved.[25] Also, in those with early complete resolution, the pulmonary function took years to return to normal.

Our cohort received treatment at a general hospital in a Stockholm area with a heterogenic population, and there is no reason to believe they would differ from others ICU treated in similar settings. The knowledge from the study may be used to identify risk groups for slower recovery and/or need for tailored follow-up based on the patient's needs.

The prospective design is one of the strengths of the study, where all surviving patients admitted to the ICU treated with invasive ventilation, HFNO, and NIV were eligible for inclusion, minimizing selection bias. Moreover, all chest CT scans were conducted on the same Siemens machine, and inter-reader agreement between the three radiologists from the sample was good. The radiologists were blinded for all clinical data except age and diagnosis. Further, the scoring system to estimate the lung involvement in COVID-19 with CT involvement score 0–25 has been used by several other study groups.[7,13,22,26] The results were adjusted for concerning confounders that could affect the outcome. The study also holds limitations. Firstly, this is a single-center study and 53% of eligible patients did not come for follow-up with chest CT scan. Out of those eligible who came for a clinical follow-up visit (60%), younger individuals were at a less degree examined with chest CT scan. Whether they were judged by the physician or by themselves to be fully recovered or did not have the strength to come was not investigated but may constitute a risk of selection bias in the study. Secondly, the CT examination was performed months after ICU discharge and not controlled by the number of months since the debut of symptoms, which can have an implication on the end CT score. Further, the lack of baseline data is a major limitation of the study, because we do not know what lung function the patients had before ICU admission. However, the majority had no known pulmonary disease.

A weakness with CT score is that it does not describe the type of involvement, that is, GGO, consolidation, or reticulation. In the majority of participants, there was no CT performed prior to COVID-19 infection, and therefore, we can only assume that the changes seen in the study were associated with severe infection. This may suggest the necessity for other data points, as the existence of chest CT scans prior to infection in all studied patients cannot be guaranteed in a study such as the one performed by the authors. Finally, the wide CIs indicate that a larger sample size would likely have improved the precision of the results as well as the generalizability of the results.

In conclusion, the majority of ICU-treated patients with COVID-19 had residual lung changes at 6 months of follow-up regardless of ventilator support or not. Higher age was associated with more residual chest imaging manifestations, and participants treated with invasive ventilation were more likely to have a lower TLC 3–8 months after ICU discharge.

AUTHOR CONTRIBUTIONS
Gabriel Hanna: Conceptualization, methodology, investigation, writing—original draft. **Sara Bankler**: Conceptualization, methodology, investigation, writing—review and editing. **Anna Schandl**: Conceptualization, methodology, writing—review and editing. **Mari Roël, Patrik Lyngå, Anne Geborek, Eva Joelsson-Alm, Mårten Söderberg**: Conceptualization, writing—review and editing. **Anders Hedman**: Conceptualization, investigation, writing—review and editing. **Mikael Andersson Franko**: Formal analysis, writing—review and editing. **Hans Friberg**: Methodology, writing—review and editing. **Pernilla Darlington**: Conceptualization, methodology, investigation, formal analysis, writing—review and editing. All authors read and approved the final manuscript.

CONFLICT OF INTERESTS
The authors declare that they have no competing interests.

ETHICS STATEMENT
All included patients had signed a written consent form, and approval was granted from the regional ethical review board in Stockholm.

DATA AVAILABILITY STATEMENT
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.