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Original article

Abnormal pulmonary function and imaging studies in critical COVID-19 survivors at 100 days after the onset of symptoms

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ABSTRACT

Background: The long-term repercussions of critical COVID-19 on pulmonary function and imaging studies remains unexplored. In this study, we investigated the pulmonary function and computed tomography (CT) findings of critical COVID-19 patients approximately 100 days after symptom onset.

Methods: We retrospectively extracted data on critical COVID-19 patients who received invasive mechanical ventilation during hospitalization from April to December 2020 and evaluated their pulmonary function, residual respiratory symptoms and radiographic abnormalities on CT.

Results: We extracted 17 patients whose median age was 63 (interquartile range [IQR], 59–67) years. The median lengths of hospitalization and mechanical ventilation were 23 (IQR, 18–38) and 9 (IQR, 6–13) days, respectively. At 100 days after symptom onset, the following pulmonary function abnormalities were noted in 8 (47%) patients: a diffusion capacity of the lung for carbon monoxide ($\%DL_{CO}$) of <80% for 6 patients (35%); a percent vital capacity (%VC) of <80% for 4 patients (24%); and a forced expiratory volume in one second/forced vital capacity ($FEV_1\%$) of <70% for 1 patient (6%) who also presented with $\%DL_{CO}$ and %VC abnormalities. Twelve (71%) patients reported residual respiratory symptoms and 16 (94%) showed abnormalities on CT.

Conclusions: Over 90% of the critical COVID-19 patients who underwent invasive mechanical ventilation continued presenting with abnormal imaging studies and 47% of the patients presented with abnormal pulmonary function 100 days after symptom onset. The extent of the residual CT findings might be associated with the degree of abnormal pulmonary function in critical COVID-19 survivors.

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1. Introduction

As the body of literature concerning the coronavirus disease 2019 (COVID-19) expands, the pathophysiology and clinical manifestations of acute COVID-19 have become relatively common knowledge. Recovery times from COVID-19 drastically differ between patients and are highly dependent on the presence or absence of various risk factors that contribute to disease severity, such as age, body mass index, and underlying comorbidities [1–3]. Although the clinical hallmarks are well-described, many symptoms are known to carry over into the recovery period, even after the acute phase has subsided. The most common persistent respiratory manifestations documented to date include cough, chest distress, and dyspnea––especially in those with severe/critical disease [4].

An emerging topic of investigation under the current pandemic is the characterization of pulmonary function in COVID-19 survivors [5–7]. A recent report showed impaired diffusion capacity of the lung for carbon monoxide (DL_{CO}) as the most common pulmonary function-related finding in COVID-19 patients on the day of discharge [5]. Another study examined the issue from a long-term perspective and found that COVID-19 patients requiring high-flow nasal oxygen therapy, non-invasive positive ventilation, or invasive mechanical ventilation had impaired DL_{CO} six months after the onset of symptoms [7].

Apart from the investigations centered around pulmonary function, some studies have examined post-recovery imaging studies. One report showed lingering radiographic and physiological abnormalities in 71% (39 out of 55 patients) of COVID-19 patients three months after discharge [8]. According to the same study, approximately half the patients presented with abnormalities spanning 1–3 lung segments, as examined via computed tomography (CT).

While informative, most of these studies excluded critical COVID-19 cases. Long-term sequelae are of particular importance among critical cases presenting with respiratory symptoms extending beyond the recovery period; however, the long-term effects on pulmonary function following critical COVID-19 remain largely unknown. Thus, the aim of the present study was to examine the pulmonary function and CT findings of patients with critical COVID-19 100 days after the onset of symptoms.

2. Patients and methods

2.1. Patient selection

We retrospectively extracted data on patients hospitalized from April 2020 to December 2020 with laboratory confirmed COVID-19. We included critical COVID-19 patients who received invasive mechanical ventilation during hospitalization and underwent a pulmonary function test and CT scan at approximately 100 days after the onset of symptoms. We excluded patients who i) expired in the hospital, ii) were transferred to other facilities and iii) were lost during the follow-up.

2.2. Patient characteristics

The patient characteristics included age, sex, smoking history, past medical history (i.e., chronic obstructive pulmonary disease, bronchial asthma, interstitial lung disease and diabetes mellitus), length of mechanical ventilation, and length of hospitalization.

2.3. Outcomes

The primary outcome was pulmonary function testing approximately 100 days after the onset of symptoms. The pulmonary function tests were performed by qualified technicians in the hospital. The assessments included the following respiratory parameters: vital capacity (VC); functional vital capacity (FVC); forced expiratory volume in one second (FEV_1); and the DL_{CO}. The DL_{CO} was measured using the single-breath test. We calculated the $\%DL_{CO}$ (DL_{CO}/predicted DL_{CO}), %VC (VC/predicted VC) and $FEV_1\%$ (FEV_1/FVC). The abnormal values were defined as $\%DL_{CO}$ <80%, %VC <80% and $FEV_1\%$ <70%.

The secondary outcomes were residual respiratory symptoms and radiographic abnormalities on CT at 100 days after the onset of symptoms. The residual respiratory symptoms were defined as cough, sputum, and dyspnea on effort and/or hoarseness and the presence or absence of these symptoms was examined at the 100-day follow-up. Dyspnea on effort was defined as a score ≥2 using the modified Medical Research Council dyspnea scale [9,10]. The abnormalities on CT were evaluated by a single radiologist and two pulmonologists, both of whom are Board Certified members of the Japanese Respiratory Society. To quantify the extent of the pulmonary abnormalities, CT scores were assigned based on the area involved for each of the five lung lobes as follows: 0, no involvement; 1, <5% involvement; 2, 5–25% involvement; 3, 26–49% involvement; 4, 50–75% involvement; and 5, >75% involvement. The total CT severity score, which ranged from 0 to 25, was calculated by summing the individual lobar scores [11].

In order to identify any potential factors contributing to an impaired $\%DL_{CO}$ value, we examined the characteristics and outcomes for patients with and without impaired $\%DL_{CO}$ values.

2.4. Ethical statement

This study was approved by the Institutional Review Board of the Tokyo Metropolitan Hiroo Hospital (approval number, J-70). Regardless of the anonymous nature of the data, informed consent was obtained from all the participants.

2.5. Statistical analyses

The continuous variables are reported as the median and interquartile range (IQR), and the categorical variables are reported as the number and percentage. The continuous variables were compared using Wilcoxon rank–sum tests, and the categorical variables were compared using the Fisher's exact test. The threshold for significance was a p-value of 0.05. All the analyses were performed using Stata MP15 (StataCorp, College Station, TX, USA).

3. Results

After application of the inclusion and exclusion criteria, we extracted 17 patients with critical COVID-19 for a follow-up examination approximately 100 days after onset of symptoms (Fig. 1). Fourteen (82%) of the patients were men and the median age of all the patients was 63 (IQR, 59–67) years. Eleven (65%) patients were current or past smokers. The median length of hospitalization was 23 (IQR, 18–38) days and the median length of mechanical ventilation was 9 (IQR, 6–13) days (Table 1).

An overview of the pulmonary function tests conducted during this study is provided in Table 2. At 100 days after the onset of symptoms, 8 (47%) patients showed abnormal pulmonary function. The median %VC, FEV_1%, and $\%DL_{CO}$ values were within the normal limits at 93.9%, 84.5% and 82.1%, respectively (Fig. 2). However, the following abnormalities were documented: a $\%DL_{CO}$ <80% for 6 patients (35%); a %VC <80% for 4 patients (24%); and an FEV_1% for 1 patient (6%) who also presented with $\%DL_{CO}$ and %VC abnormalities (Table 2). The patient who experienced the greatest reduction in the $\%DL_{CO}$ underwent a follow-up pulmonary function test 300 days after the onset of symptoms. For this patient, the % VC and $\%DL_{CO}$ values improved from 54.6% to 69.1% and 43.4%–83.1%, respectively. Another patient was placed on veno-venous extracorporeal membrane oxygenation for 28 days, underwent a tracheostomy on the 25th hospital day, was liberated from mechanical ventilation on the 55th hospital day and had the tracheal cannula removed on the 78th hospital day. Another patient underwent a tracheostomy on the 14th hospital day, was liberated from mechanical ventilation on the 22nd hospital day and had the tracheal cannula removed on the 31st hospital day. Twelve (71%) patients reported residual respiratory symptoms and 7 (41%) had dyspnea on effort.

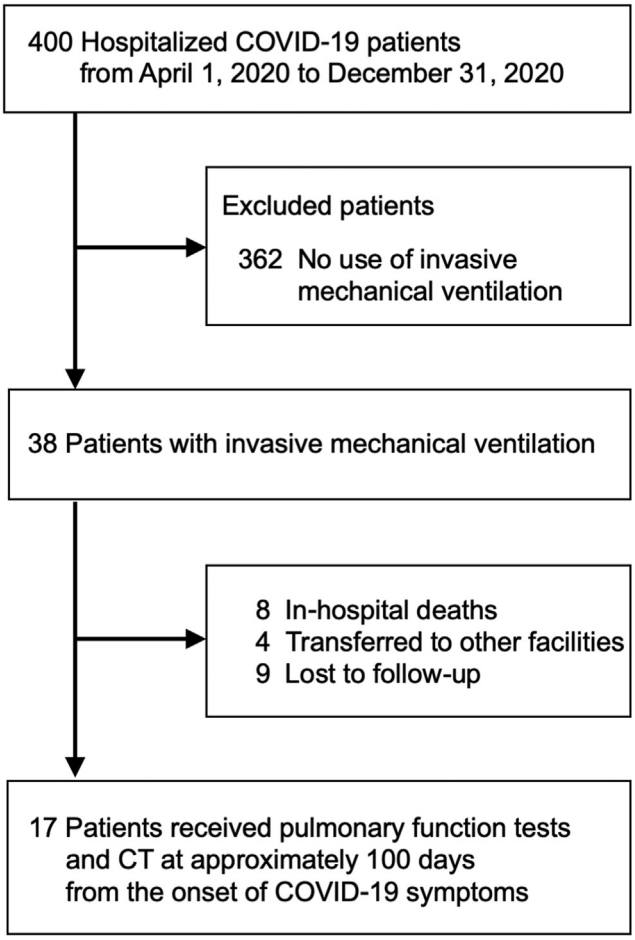

Fig. 1 – Study flow. CT, computed tomography.

A total of 16 (94%) patients had documented abnormalities on CT scans at approximately 100 days after the onset of symptoms and the median CT score was 21 (IQR, 15–25). Sixteen (94%) patients presented with ground-glass opacity (GGO) and 6 (35%) presented with consolidations. The representative imaging studies taken at admission, discharge and the 100-day follow-up are provided in Fig. 3.

Table 3 shows the outcomes for each patient at 100 days after the onset of symptoms. Four patients with %VC values < 80% had relatively high CT scores. The characteristics and outcomes for the patients with and without impaired $\%DL_{CO}$ values are provided in Table 4. Although no significant differences were observed between the patients with and without impaired $\%DL_{CO}$ values, the CT scores tended to be higher and the percentage of patients with consolidations tended to be higher in the patients with impaired $\%DL_{CO}$ values.

4. Discussion

In the present study, we investigated the pulmonary function of critical COVID-19 patients approximately 100 days after the onset of symptoms. Although the median %VC, FEV_1% and $\%DL_{CO}$ values were within the normal limits, approximately half the patients presented with abnormal pulmonary function at the 100-day follow-up. The most frequent abnormality observed in the pulmonary function tests was a reduced $\%DL_{CO}$. Residual respiratory symptoms were present in 71% of the patients and over 90% of the patients had residual CT abnormalities at 100 days after the onset of symptoms.

Spirometry, the most readily available and useful pulmonary function test, measures the volume of air exhaled at specific timepoints during a forceful and complete exhalation after a maximal inhalation [5]. The DL_{CO} i) assesses the potential of the lung for gas exchange, ii) reflects the ability of the lungs to exchange gas into the blood stream, and iii) is diminished in emphysema, interstitial lung disease, pulmonary vascular disease and anemia [12]. A decreased DL_{CO} value

Table 1 – Patient characteristics.

Case	Age	Sex	Past medical history	Smoking history (pack-years)	Length of hospitalization, days	Duration of mechanical ventilation, days	Number of days from onset to follow-up testing, days
1	68	Male	DM	Never	39	4	133
2	65	Male	None	Former (15)	19	5	116
3	65	Male	None	Former (30)	15	5	98
4	63	Male	None	Never	64[a,b]	56	187
5	59	Male	DM	Never	31	13	98
6	64	Female	None	Never	25	10	108
7	67	Male	HT	Current (47)	41	19	110
8	62	Male	DM, HT	Former (34)	18	6	98
9	43	Male	DM, HT, CKD, Dialysis	Never	23	4	107
10	52	Male	None	Former (10)	13	8	92
11	59	Male	DM, HT	Former (4)	17	7	100
12	52	Male	HT	Current (16)	20	11	91
13	54	Female	Bronchial asthma	Never	16	9	99
14	63	Female	DM, HT, DL	Former (0.15)	22	9	89
15	67	Male	Dilated cardiomyopathy, DL	Former (17)	55[b]	23	98
16	70	Male	DM, HT	Former (40)	33	12	98
17	68	Male	DM, HT, CKD, Dialysis	Former (30)	38	14	95
Median (IQR)	63 (59–67)	Male: 82%		17 (10–34)	23 (13–38)	9 (6–13)	98 (98–108)

DM, diabetes mellitus; HT, hypertension; CKD, chronic kidney disease; DL, dyslipidemia; IQR, interquartile range.
[a] Veno-venous extracorporeal membrane oxygenation.
[b] Tracheostomy during hospitalization.

Table 2 – Outcomes at 100 days after the onset of symptoms.

Outcomes	Percentage	No. of patients
Any abnormal pulmonary function[a]	47%	8/17
%VC <80%	24%	4/17
FEV_1% <70%	6%	1/17
$\%DL_{CO}$ <80%	35%	6/17
Residual respiratory symptoms	71%	12/17
CT abnormalities	94%	16/17

VC, vital capacity; FEV, forced expiratory volume; DL_{CO}, diffusion capacity of the lung for carbon monoxide; CT, computed tomography.
[a] Some patients may have multiple abnormalities.

is correlated with small airway disease in the presence of a severe expiratory airflow limitation and hyperinflation [13]. In a cohort study of 109 survivors of acute respiratory distress syndrome, the median lung volume and spirometry values were normal at 6 months after discharge from the intensive care unit; however, the DL_{CO} was persistently impaired, with a median value of 63–72% of the predicted value [14]. Virus-mediated cytokine activation of alveolar macrophages may result in lung fibrosis and damage [15]. When faced with a highly transmissible respiratory infectious agent such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), pulmonary function tests––albeit informative––are omitted

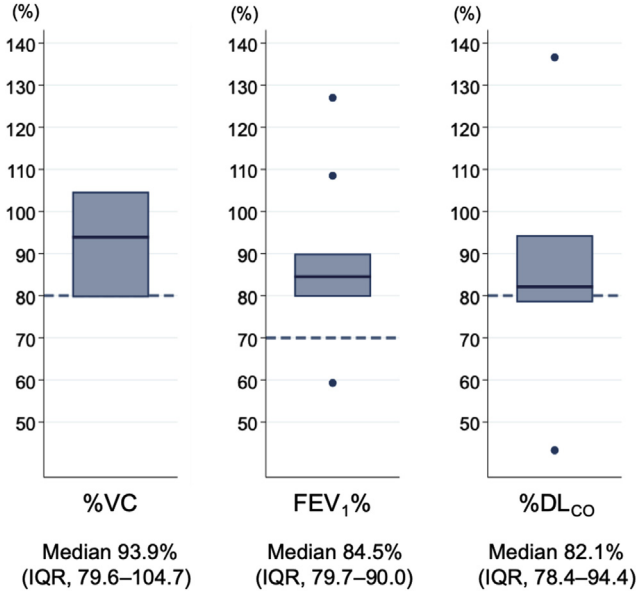

Fig. 2 – Results of the pulmonary function tests. VC, vital capacity; FEV_1, forced expiratory volume in 1 second; DLCO, diffusion capacity of the lung for carbon monoxide, IQR, interquartile range. The DLCO was measured by means of using the single-breath test. The %VC (VC/predicted VC ratio), FEV_1% (FEV_1/FVC ratio), and %DLCO (DLCO/predicted DLCO ratio) were calculated.

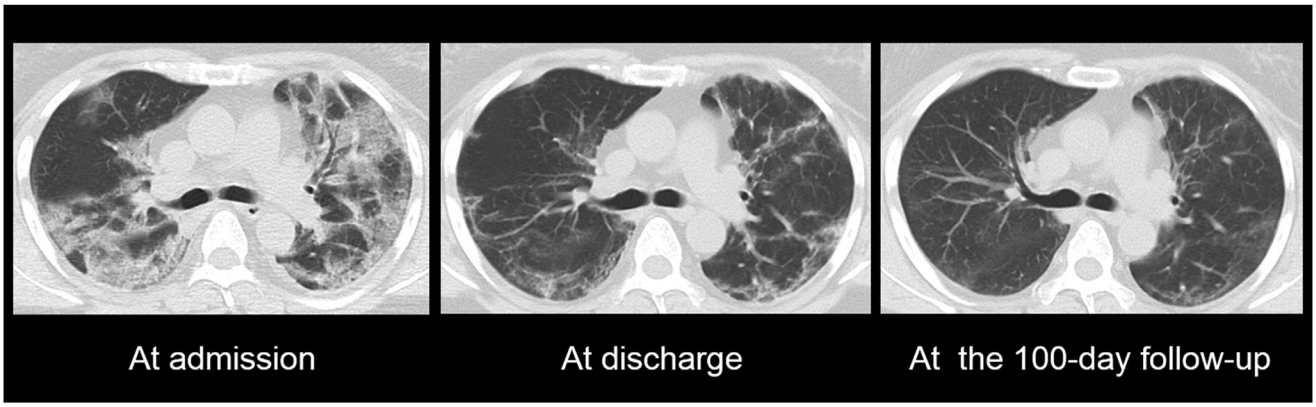

Fig. 3 – Representative computed tomography images taken at admission, discharge and 100 days after symptom onset.

from the diagnostic panel over fears of contamination. For these reasons, the long-term pulmonary function of recovered critical COVID-19 patients has remained unknown.

During the previous SARS epidemic, 16% of the infected patients were reported to have impaired DL_{CO} values at 6 months after recovery [16]. In the follow-up studies lasting 6–24 months for patients rehabilitating from SARS, impaired pulmonary function could remain for months or even years. In these long-term follow-up studies, an impaired DL_{CO} was the most common abnormality documented, ranging from 16–44% of the patients [16–18].

In the present study, approximately half the patients had abnormal pulmonary function. Consistent with the SARS studies listed above, an impaired DL_{CO} was the most common abnormality documented. Impairment of the DL_{CO} has also been reported for patients with COVID-19 [5,19]. Although the severity of the pulmonary inflammation and interstitial damage may have contributed to the impaired DL_{CO} in the previous study, it is unclear whether COVID-19 associated impairment of the DL_{CO} can be attributed to interstitial damage, pulmonary vascular disease, or both [20]. In a previous study, pulmonary function was investigated in 110 survivors of mild, moderate and severe COVID-19 approximately 20–30 days after the onset of symptoms [5]. While the patients had relatively normal spirometry values, the $\%DL_{CO}$ was reduced in 47% of the survivors. Another study (n = 50), in which the authors focused on all but critical COVID-19 patients, showed a median $\%DL_{CO}$ value of 80% (IQR, 70–92) one month after SARS-CoV-2 infection; however, this study included only one patient who underwent invasive mechanical ventilation [19]. In yet another study (n = 647), pulmonary function was evaluated in non-mechanically ventilated COVID-19 survivors within 3 months after hospital discharge and the authors found that 55% of the patients presented with abnormal DL_{CO} values [20]. Our study only included critical COVID-19 patients who required invasive mechanical ventilation and long-term outcomes (100 days) were evaluated.

In the present study, 94% of the patients had CT abnormalities at approximately 100 days after symptom onset. This percentage is higher than previous COVID-19 reports because we exclusively examined critical cases [21,22]. In one study in which patients requiring invasive mechanical ventilation were excluded, follow-up CT assessments were performed for 100 patients recovering from COVID-19 hospitalization and the authors found that 52% of the patients had abnormal CT findings at approximately 100 days after the onset of symptoms [21]. In another study, 90-day follow-up CT scans were performed for 52 patients recovering from COVID-19 (11 of the patients were in the ICU) and the authors found CT abnormalities in 58% of the patients [22]. Of note, the vast majority (94%) of the patients in the present study continued to show abnormal CTs at the 100-day follow-up; however, not all the patients (71%) presented with residual symptoms and even fewer of them (47%) showed impaired long-term pulmonary function.

For the patients with and without impaired $\%DL_{CO}$, the median CT scores, duration of mechanical ventilation and percentage of patients having consolidations may not have shown statistical significance due to the limited sample size; however, the clinical relevance of the findings are apparent. The extent and area of the residual findings on CT might be associated with the degree of the abnormal pulmonary function in critical COVID-19 patients approximately 100 days after the onset of symptoms.

There were several limitations associated with this study. First, the sample size was limited, as only 17 patients were enrolled in the study. Although a larger sample size would have been ideal, the number of surviving critical COVID-19 patients is relatively low, making recruitment for a long-term follow-up study challenging. Second, we could not assess pulmonary function prior to onset of the disease. Therefore, we could not obtain baseline pulmonary function values for comparison with pulmonary function during the follow-up period. However, initiating a pulmonary function test during the viral proliferation phase would have increased the risk of transmission. Additionally, given the lack of medical histories showing compromised baseline pulmonary function, along with the normal activity of daily living registered for all the patients included in the study, it can be assumed that the baseline pulmonary function was within normal limits. Third, only one patient whose respiratory function was impaired at 100 days was able to be followed-up at the 300-day mark. More cases need to be accumulated in the future for proper long-term analyses. Fourth, the present study might have included a selection bias, as only the patients who could independently return to the hospital to perform a follow-up pulmonary function test after 100 days from the onset of symptoms were selected for inclusion. The

Table 3 – Outcomes for each patient at 100 days after the onset of symptoms.

Case	Age (years)	Sex	%VC	%FVC	FEV_1%	$\%DL_{CO}$	Residual symptoms[a]	Dyspnea on effort[b]	CT abnormalities	CT scores[c]	GGO	Consolidations
1	68	Male	117	111.1	95.4	104.2	No	No	Yes	15	Yes	No
2	65	Male	138.4	135.0	79.7	136.6	No	No	No	0	No	No
3	65	Male	106.5	104.5	79.3	106.8	Yes	Yes	Yes	15	Yes	No
4	63	Male	79.6	81.2	86.1	94.4	Yes	No	Yes	25	Yes	No
5	59	Male	54.6	52.2	127	43.3	Yes	No	Yes	21	Yes	Yes
6	64	Female	98.8	98.8	84.5	87	No	No	Yes	2	Yes	No
7	67	Male	104.7	104.7	80.1	82.1	Yes	No	Yes	25	Yes	Yes
8	62	Male	103.4	100.3	73.6	80.7	No	No	Yes	12	Yes	No
9	43	Male	117.2	94.3	90	82.4	Yes	Yes	Yes	25	Yes	No
10	52	Male	101.5	101.5	82.8	88.6	Yes	No	Yes	15	Yes	No
11	59	Male	87.3	84.7	77	108.6	No	No	Yes	9	Yes	No
12	52	Male	74.7	74.2	59.3	62.8	Yes	No	Yes	22	Yes	Yes
13	54	Female	84	83.1	81.2	79.6	Yes	Yes	Yes	25	Yes	No
14	63	Female	93.9	92.6	85	78.4	Yes	Yes	Yes	22	Yes	Yes
15	67	Male	60.8	54.4	88.8	57.9	Yes	Yes	Yes	25	Yes	Yes
16	70	Male	70.2	68.3	93.1	81.1	Yes	Yes	Yes	21	Yes	Yes
17	68	Male	84.6	83.7	108.5	73.9	Yes	Yes	Yes	25	Yes	No
Median (IQR) or %	63 (59–67)	Male: 82%	93.9 (79.6–104.7)	94.3 (81.2–101.5)	84.5 (79.7–90.0)	82.1 (78.4–94.4)	71%	41%	94%	21 (15–25)	94%	35%

(Abbreviations) VC, vital capacity; FVC, forced vital capacity; FEV, forced expiratory volume; DL_{CO}, diffusion capacity of the lung for carbon monoxide; CT, computed tomography; IQR, interquartile range; GGO, ground-glass opacity.

[a] Including cough, sputum, dyspnea on effort and/or hoarseness.

[b] Defined as a score ≥2 using the modified Medical Research Council dyspnea scale.

[c] Adapted from Han X et al. [11].

Table 4 – Characteristics and outcomes for the patients with and without impaired %DL_{CO}.

	Normal %DL_{CO} (n = 11)	Impaired %DL_{CO}[a] (n = 6)	P-value
Age, year	64 [59–67]	61 [54–67]	0.65
Male	10 (91%)	4 (67%)	0.51
Length of hospitalization, days	23 [17–39]	26.5 [20–38]	0.69
Duration of mechanical ventilation, days	7 [5–12]	12 [9–14]	0.09
%VC	103.4 [87.3–117]	79.35 [60.8–84.6]	0.012
FEV_1%	82.8 [79.3–90]	86.9 [81.2–108.5]	0.37
D-dimer, μg/mL	1.5 [1.3–1.9]	1.75 [1.3–1.8]	0.87
Residual symptoms[b]	6 (55%)	6 (100%)	0.10
Dyspnea on effort[c]	3 (27%)	4 (67%)	0.16
CT abnormalities	10 (91%)	6 (100%)	1.00
CT scores[d]	15 [9–25]	23.5 [22–25]	0.050
GGO	10 (91%)	6 (100%)	1.00
Consolidations	2 (18%)	4 (67%)	0.11

(Abbreviations) VC, vital capacity; FEV, forced expiratory volume; DL_{CO}, diffusion capacity of the lung for carbon monoxide; CT, computed tomography; GGO, ground-glass opacity.
The data is shown as n (%) or the median [interquartile range].
[a] Diffusion capacity of the lung for carbon monoxide (%DL_{CO}) < 80%.
[b] Including cough, sputum, dyspnea on effort and/or hoarseness.
[c] Defined as a score ≥2 using the modified Medical Research Council dyspnea scale.
[d] Adapted from Han X et al. [11].

patients who had a low activity of daily living status or underlying conditions that could have impeded returning to the hospital for follow-up may have been inadvertently omitted. Lastly, the present study cannot specify which factors, such as CT findings or patient backgrounds, can influence long-term pulmonary function impairment. Given these limitations, larger scale studies that examine the long-term effects of critical COVID-19 on pulmonary function are warranted.

5. Conclusions

Over 90% of the critical COVID-19 patients who underwent invasive mechanical ventilation continued to present with abnormal CTs at the 100-day follow-up and approximately half of these patients showed impairments of long-term pulmonary function. The extent and area of the residual findings on CT might be associated with the degree of the abnormal pulmonary function observed in critical COVID-19 survivors.

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Conflict of Interest

The authors have no conflicts of interest.

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MM and MN contributed to the planning, data gathering, literature review, writing, and editing the article. RHK and HG provided professional suggestion in the conduct of the study. All authors commented on draft versions and approved the final version.

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