Respiration

Clinical Investigations

Respiration 2024;103:22–31
DOI: 10.1159/000535732

Received: August 5, 2023
Accepted: November 28, 2023
Published online: January 9, 2024

# COVID-19 after 2 Years from Hospital Discharge: A Pulmonary Function and Chest Computed Tomography Follow-Up Study

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**Keywords**
Chest computed tomography · Long COVID-19 · Spirometry

**Abstract**
***Introduction:*** Serial follow-up with pulmonary function testing (PFT) and chest computed tomography (CT) after severe COVID-19 are recommended. As a result, many longitudinal studies have been published on COVID-19 of different grade of severity up to 1-year follow-up. Therefore, we aimed at a long-term observational study throughout 2 years after severe COVID-19. ***Methods:*** Severe COVID-19 patients were consecutively recruited after hospital discharge between March and June 2020 and prospectively followed up for 24 months, with mMRC dyspnea scale and PFT at 6, 12, and 24 months. Chest CT was performed when clinically indicated. ***Results:*** One hundred one patients enrolled completed the observational study. At 24 months, those with reduced total lung capacity (TLC) were 16%, associated with fibrotic ground glass opacity (GGO) and mMRC score >1, respectively, in 75% and 69% of them. At 24 months, those with a reduced diffusing capacity of the lung for CO were 41%, associated with fibrotic GGO and mMRC score >1, respectively, in 53% and 22% of them. ***Conclusion:*** Two years after hospitalization for severe COVID-19, a non-negligible number of patients still suffer from "long COVID" due to respiratory damage.


## Introduction

Although the disease severity and mortality rate of COVID-19 have decreased [1], a new condition has emerged as "post-acute COVID-19 syndrome (PACS)" or "long COVID" defined as neurological, respiratory, or cardiovascular symptoms lasting for weeks or months [2, 3]. Daugherty et al. [4] reported in a population aged ≤65 years a percentage of 14% who developed at least one type of clinical sequelae. The persistence of respiratory symptoms, especially exertional dyspnea, appears to be common, ranging from 5 to 81% at 12 months after hospitalization [3]. Moreover, there are some concerns about pulmonary fibrosis as a sequela [5]. Impaired respiratory function after viral pneumonia has been documented in patients infected by other strains of



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the coronavirus family, such as SARS-CoV-1 (SARS) and Middle East respiratory syndrome coronavirus [6–8]. Therefore, serial follow-up with PFT and chest computed tomography (CT) after acute COVID-19 were recommended [5], resulting in many studies at 3–6 months from hospital discharge [9–13]. The first study at 6 months from hospital discharge for moderate-to-severe COVID-19 is that of Huang et al. [14]. Patients treated with oxygen ($O_2$) supplementation only or noninvasive ventilation demonstrated a reduced diffusion capacity of the lung for CO ($D_{LCO}$) and a reduced total lung capacity (TLC) in 31% and 40% and in 14% and 26% of them, respectively [14]. Recent studies at 12 months reported a percentage of survivors with impaired $D_{LCO}$ ranging from 14% [15] to 50–65% [16–18] and at 24 months up to 65% [19]. The aim of our study was to characterize the longitudinal progression of exertional dyspnea and respiratory function in COVID-19 survivors up to 2 years after acute infection and to detect the radiological sequelae.

## Methods

*Study Design and Subjects*

From March 15 up to June 15, 2020, during the first pandemic wave in Italy, we consecutively enrolled in a longitudinal cohort study patients discharged after severe COVID-19 from three hospitals (Santa Corona, Santa Maria di Misericordia, San Paolo) in North-Western Italy, serving an area of 280,000 inhabitants. Exclusion criteria were survivors who were living in a nursing or welfare home and were unable to move freely due to concomitant osteoarthropathy or immobile, or who were difficult to complete the visit due to psychotic disorder or dementia, and age <18 or >80 years. We measured exertional dyspnea with mMRC scale [20] and respiratory function at 6, 12, and 24 months after discharge. When clinically indicated, patients underwent chest CT according to the scheme proposed in August 2020 by George et al. [21].

*Pulmonary Function*

Spirometry and pulmonary diffusion capacity test were performed following the American Thoracic Society/European Respiratory Society statements [22, 23] with a Vyntus Body Plethysmograph (Vyaire Medical GmbH, Hoechberg, Germany). To minimize cross-infections, $D_{LCO}$ was measured by the single-breath method with Diffusion SB RT Module for Body Vyntus (Vyaire Medical, GmbH, Hoechberg, Germany). Abnormal results were those with a Z score >1.65 SD (< LLN, lower limit of normality or > ULN, upper limit of normality) by applying the Global Lung Function Initiative Network (GLI) reference values [24, 25]. Appropriate correction to $D_{LCO}$ for hemoglobin was considered [23].

*Chest CT Acquisition and Image Analysis*

Scans at diagnosis (t0, within 4 weeks from the first positive PCR test) and follow-up imaging studies at three timepoints (t1, t2, and t3, respectively, 3–8, 9–17, and 18–28 months after the diagnosis) have been evaluated, when available. If patients underwent multiple CT examination within a short period of time, we selected the closest study to the date of PFT.

Acquisition Protocol

CT scans have been performed on three different CT scanners (same vendor and model, GE Revolution Evo Gen 2, GE Healthcare, Milwaukee, WI, USA), according to a high-resolution CT acquisition protocol. High-resolution CT scans were acquired with the patient in supine position during a single-breath hold (free breathing for unconscious patients); tube voltage = 120–140 kVp, tube current = 100–400 mA with automatic dose modulation, pitch = 0.984:1, acquisition thickness = 1.25 mm; images were then reconstructed with two dedicated kernels (sharp and smooth). In case of clinical suspicion of pulmonary embolism, a pulmonary angiogram CT has also been performed, after the injection of 30–60 mL of non-iodine contrast medium at a flow rate of 3–5 mL/s, with a non-fixed delay based on contrast detection at the level of the pulmonary artery.

Image Interpretation

Two radiologists (S.M. and G.F.), respectively, with 9 and 7 years of experience in thoracic imaging reviewed all the scans using a dedicated virtual workstation (Advanced Workstation Server AWS, GE Healthcare). Reviewers were blinded to clinical data and laboratory test results.

*Qualitative Assessment*

Common CT features were described using internationally standard nomenclature defined by the Fleischner Society Glossary of Terms for Thoracic Imaging [26]. We considered features commonly associated with acute/subacute COVID infection such as GGO, consolidation, crazy paving, halo sign, reversed halo sign, and features of COVID resolution/sequelae such as fibrotic bands, traction bronchiectasis, fibrotic GGO, volume loss, subpleural bands. Predominant distribution of the lung alterations in lungs (unilateral vs. bilateral), lobes (upper vs. lower lobes), and axial distribution (peripheral vs. central) has been evaluated. Axial distribution of abnormalities has been defined peripheral if predominant in the outer third of the lung, central if prominent in the inner two thirds. Associated findings that could affect PFT such as pleural effusion, emphysema (only if >5% according to Fleischner Society quantification system [27]), and pulmonary fibrosis have been recorded as well.

Pulmonary fibrosis was defined according to Fleischner Society [26] and Dalpiaz criteria [28]. Apical caps have been considered as fibrotic bands, while dependent atelectasis has not been considered.

*Quantitative Assessment*

In order to evaluate the severity of pulmonary parenchymal involvement, extent of the abnormalities has been scored using three different methods:

1. Chest CT Severity Score

CT severity score (CT-SS) has been previously used to quantify parenchymal involvement in patients affected by SARS-CoV-1 [29, 30]. According to this method, lungs are divided in 20 regions of interest (ROIs): 16 ROIs correspond to anatomical pulmonary segments, whereas the posterior-apical segment of the left upper lobe is further divided into apical and posterior regions, and the antero-medial basal segment of the left lower lobe is divided into anterior and medial basal regions.

Respectively, 0, 1, and 2 points are assigned accounting for 0%, less than 50%, and equal to or more than 50% of the pulmonary parenchyma of each individual ROI; CT-SS is then determined adding all the points assigned to individual ROIs, ranging from 0 to 40.

2. Chest CT Score

Chest CT score (CCTS) has been proposed [29–31] to quantify COVID severity, demonstrating a correlation with short-term outcomes [32, 33]. It is determined assigning for each pulmonary lobe up to 5 points, based on the extent of parenchymal involvement as follows: (0) no involvement; (1) <5% involvement; (2) 5–25% involvement; (3) 26–50% involvement; (4) 51–75% involvement; and (5) >75% involvement. Chest CT score is then defined by the sum of assigned scores and ranges from 0 to 25.

3. Total Severity Score

Total severity score (TSS) has been proposed [34] to assess the extent of inflammatory abnormalities in COVID-19. For each pulmonary lobe, 0–4 points are assigned as follows: (0) = 0%, (1) = 1–25%, (2) = 26–50%, (3) = 51–75%, (4) = 76–100%. TSS is then defined by the sum of assigned points and ranges from 0 to 20.

*Statistic*

Continuous numeric variables were summarized as mean and standard deviation for normalized distributed variables and as median and interquartile range for non-normalized variables. Categorical variables were summarized in the form of percentage proportions. The differences in numeric variables were evaluated with ANOVA test for normalized distributed variables or Wilcoxon signed-rank test for non-parametric statistical analysis as appropriate. The differences in categorical variables were compared using $\chi^2$ or Fisher's exact test when appropriate. All tests were two-tailed, and a $p$ value <0.05 was determined to represent statistical significance. All statistical analyses were performed using Epi-Info 7.0 (Centers for Disease Control and Prevention, CDC, Atlanta, GA, USA). As we included in this longitudinal study all the patients discharged for COVID-19 from the three hospitals during the first pandemic wave, according to inclusion and exclusion criteria detailed in the section "Study design and subjects," the sample size was not estimated.

## Results

Of 135 enrolled subjects, all completed the follow-up at 6 months, which results were described in another manuscript [35], while 101 completed the follow-up at 12 and 24 months, and 34 declined. None of the participants died before the first visit and during the observational period, and in the lost in follow-up group, only 4 subjects reported an impaired respiratory function. The most common comorbidity was arterial hypertension (56%), followed by diabetes mellitus (17%) and chronic heart disease (15%). Asthma and COPD were reported in 1 and 2 patients, respectively. COVID-19 was complicated in 3 patients by subsegmentary pulmonary thromboembolism, in 2 patients by a pneumomediastinum, and in 1 patient by a pneumothorax.

Table 1 summarizes demographic, clinical, laboratory, and chest CT characteristics at hospitalization of the 101 enrolled subjects for severe COVID-19 (according to WHO severity classification) [36], completing the follow-up at 24 months. The mean age was 60 ± 11 years, with a BMI of 28 ± 5 kg/m$^2$ and a ratio male/female of 71/30. Former or current smokers were 17% and 19%, respectively. Subjects enrolled for severe illness ($SpO_2$ ≤93% on room sea level, or $PaO_2/FiO_2$ <300 mm Hg, respiratory rate ≥30 breaths/min, or lung infiltrates >50%) were further subdivided by the treatment for their acute respiratory failure ($PaO_2$ <60 mm Hg): (1) $O_2$ supplementation only, (2) continuous positive airway pressure (CPAP, by helmet), (3) invasive mechanical ventilation (MV).

Subjects treated with CPAP or MV were more frequently male and older than those treated with $O_2$ supplementation only, with a longer hospitalization. Generally, the more was the clinical severity, the more was the abnormality of laboratory data. Chest CT severity scores were significantly higher in the MV group, without any differences in features or predominant distribution of pulmonary involvement which was mainly bilateral and at the lower lobes (>90%) as shown in Figure 1.

At the 24-month follow-up, 16% of the enrolled subjects reported a reduced TLC (73 ± 8% of predicted), while 41% reported a reduced $D_{LCO}$ (66 ± 9% of predicted). In those with impaired $D_{LCO}$ in four cases, the transfer factor for the lung for CO ($T_{LCO}$) was also reduced, and in one case, COVID-19 was complicated by subsegmentary pulmonary thromboembolism. One patient suffered from COPD.

Table 2 summarizes data of enrolled subjects with normal (54%) or impaired respiratory function (46%) at the 24-month follow-up, subdivided in those with reduced TCL or $D_{LCO}$. Median length of hospital stay was higher in the group with impaired respiratory function ($p$ = 0.02), and those with reduced TLC were older and more frequently treated with CPAP or MV.

Table 3, 4 reports the trends of respiratory function at the timepoints of follow-up, relative to the two subgroups

**Table 1.** Subjects characteristics at hospitalization

| | Enrolled | $O_2$ | CPAP | MV | *p* value |
|---|---|---|---|---|---|
| *n* (%) | 101 | 59 (58.4) | 27 (26.7) | 15 (14.9) | |
| Male, *n* (%) | 71 (70.3) | 35 (59.3)*§ | 22 (81.5)* | 14 (93.3)§ | 0.01 |
| Age, years | 60 (54–67) | 59 (49–63)* | 64 (58–72)* | 64 (56–68) | 0.01 |
| BMI, kg/m$^2$ | 27.2 (24.4–29.7) | 26.7 (24.2–30.4) | 27.7 (25.4–29.7) | 26.4 (24.8–31.6) | 0.99 |
| Smoking | | | | | 0.12 |
| Current smokers, *n* (%) | 19 (18.8) | 42 (71.2) | 12 (44.4) | 11 (73.3) | |
| Former smokers, *n* (%) | 17 (16.8) | 9 (15.3) | 7 (25.9) | 1 (6.7) | |
| No smoking, *n* (%) | 65 (64.4) | 8 (13.5) | 8 (29.6) | 3 (20) | |
| Length of hospital stay, days | 13.5 (7–26) | 7 (5–11)*§ | 22 (15–26)* | 49 (34–64)§ | <0.001 |
| Lymphocytes, cells/μL | 1.0 (0.7–1.4) | 1.1 (0.9–1.5)*§ | 0.9 (0.5–1.4)* | 0.6 (0.3–0.9)§ | <0.001 |
| ALT, U/L | 57 (29–122) | 40 (24–101)*§ | 86 (42–121)* | 132 (77–266)§ | <0.001 |
| AST, U/L | 52 (33–86) | 37 (29–67)*§ | 56 (43–108)* | 122 (65–247)§ | <0.001 |
| LDH, U/L | 337.5 (251.5–429) | 281 (223–347)*§ | 385 (322–513)* | 639.5 (469–735)§ | <0.001 |
| D-dimer, μg/L | 883 (509–2,010) | 621 (334–969)*§ | 1,123 (767–3,420.5)* | 3,113.5 (1,425–6,089)§ | <0.001 |
| HS troponin I, ng/L | 7.9 (4.3–14) | 5.3 (2.8–8)* | 7.7 (5.9–12) | 13.7 (9.7–41.2)* | 0.03 |
| C-reactive protein, mg/L | 120 (50–219) | 76 (27–132)*§ | 170 (116–260)* | 311 (212–398)§ | <0.001 |
| IL6, pg/mL | 3.3 (1.9–6.6) | 3.2 (2.4–5.4) | 3.8 (1.7–9.2) | 3 (1.3–4.7) | 0.73 |
| Ferritin, μg/L | 577.5 (210–1,163.5) | 388 (129–803)* | 637.5 (464–999.5) | 1,313 (707–1,649)* | 0.002 |
| Chest CT, *n* (%) | 44 (43.6) | 18 (30.5)* | 13 (48.1)*§ | 13 (86.7)§ | <0.001 |
| GGO, *n* (%) | 39 (88.6) | 16 (88.9) | 11 (84.6) | 12 (92.3) | 0.99 |
| Consolidation, *n* (%) | 32 (72.7) | 10 (55.6) | 10 (76.9) | 12 (92.3) | 0.07 |
| Crazy paving, *n* (%) | 21 (47.7) | 6 (33.3) | 6 (46.2) | 9 (62.9) | 0.14 |
| Halo sign, *n* (%) | 12 (27.3) | 5 (27.8) | 3 (23.1) | 4 (30.8) | 0.99 |
| Reversal halo sign, *n* (%) | 8 (18.2) | 4 (22.2) | 3 (23.1) | 1 (7.7) | 0.62 |
| Fibrotic bands, *n* (%) | 27 (61.4) | 12 (66.7)* | 12 (92.3)§ | 3 (23.1)*§ | 0.001 |
| Traction bronchiectasis, *n* (%) | 25 (56.8) | 9 (50) | 9 (69.2) | 7 (53.8) | 0.63 |
| Fibrotic GGO, *n* (%) | 8 (18.2) | 3 (16.7) | 1 (7.7) | 4 (30.8) | 0.30 |
| Volume loss, *n* (%) | 18 (40.9) | 5 (27.8) | 5 (38.5) | 8 (61.5) | 0.16 |
| Subpleural bands, *n* (%) | 20 (45.5) | 9 (50) | 9 (62.9)* | 2 (15.4)* | 0.02 |
| Pleural effusion, *n* (%) | 7 (15.9) | 1 (5.6) | 3 (23.1) | 3 (23.1) | 0.37 |
| Emphysema (>5%), *n* (%) | 4 (9.1) | 1 (5.6) | 2 (15.4) | 1 (7.7) | 0.81 |
| Fibrosis, *n* (%) | 1 (2.3) | 1 (5.6) | 0 | 0 | 0.99 |
| TSS score | 10 (7–12) | 7.5 (5–9)* | 10 (8–11)§ | 14 (13–16)*§ | <0.001 |
| CCTS score | 14 (11–17) | 12 (6–14)*[a] | 15 (12–16)*§ | 19 (18–21)*§[a] | <0.001 |
| CT-SS score | 20 (16–28) | 16.5 (10–20)* | 20 (16–23)§ | 34 (28–35)*§ | <0.001 |

Values are reported as median and interquartile range (IQR) if not otherwise stated. For each row, identical superscript letters indicate significant differences. BMI, body mass index; GGO, ground glass opacity; TSS, total severity score; CCTS, chest CT score; CT-SS, CT severity score.

with reduced TLC or $D_{LCO}$, respectively. There was a significant improvement of exertional dyspnea (mMRC scale) during the 24 months in both groups, with a reduction of the number of subjects reporting a mMRC scale score >1 in the $D_{LCO}$ subgroup, without any change of TLC, $D_{LCO}$, or chest CT scores, apart a slight increase of fibrosis detected only in the $D_{LCO}$ subgroup. At the 24-month follow-up, the most frequent chest CT abnormalities were fibrotic bands (78%), traction bronchiectasis (39%), and fibrotic GGO (50%), with a fibrosis reported in 15% of the subjects (Fig. 2). Patients without any functional impairment at 24 months reported an mMRC score of 0.47 ± 0.66 (with an mMRC >1 in 5% of them), associated with low radiological scores, as median TSS, CCTS, and CT-SS were 2 (0–2.5), 2 (0–3), and 2 (0–4), respectively.

## Discussion

To the best of our knowledge, this is the first study reporting a 2-year follow-up of a cohort of non-Chinese severe COVID-19 survivors. In our cohort, one-third of patients still report a significant exertional dyspnea

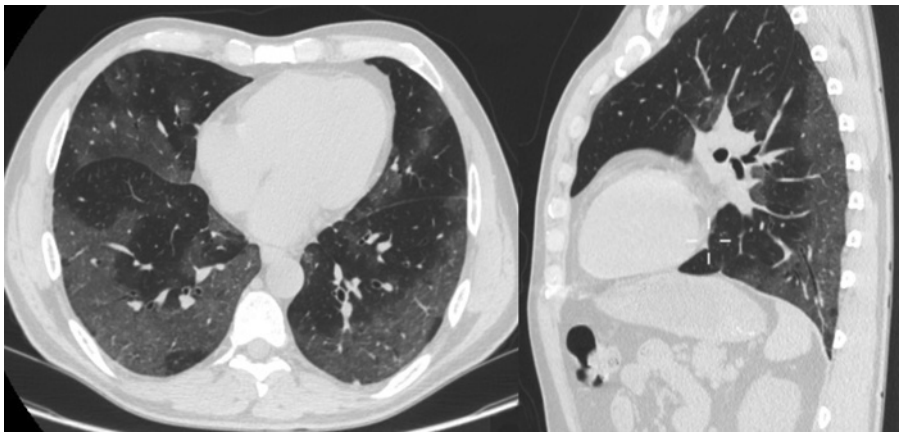

**Fig. 1.** Chest CT of acute COVID infection shows typical diffuse ground glass opacities predominant at periphery with a craniocaudal and antero-posterior gradient.

associated with an impaired respiratory function, mainly due to a reduced $D_{LCO}$ consistent with chest CT alterations. Although there was a progressive recovery after 12 months, those with impaired respiratory function at 6 months do not progress nor regress further.

*Comments on Data at Hospitalization*

Comorbidities distribution was similar as found in other studies [16, 37], as arterial hypertension, diabetes, chronic heart disease, and COPD are phenotypes of angiotensin converting enzyme 2 deficiency associated with more severe forms of COVID-19 [38]. As reported in Table 1, those who underwent CPAP or MV were characterized by more severe blood alterations (lower lymphocytes, increased CRP, D-dimer, and Troponin) and higher radiological scores [30]. However, none of the data registered at hospitalization was significantly different between subjects with or without an impaired respiratory function, apart from age (older) and severity of acute respiratory failure treatment (CPAP or MV), as found by Sanna et al. [37].

*Comments on Data at 2 Years*

We found a reduced TLC (< LLN) in 15% of the total subjects ($n$ = 101), in 7% of those requiring supplemental oxygen ($n$ = 59), and in 28% of those requiring CPAP or MV ($n$ = 42). Huang et al. [19] reported a reduced TLC (<80% of predicted) in about 25% of the total subjects ($n$ = 181), in about 12% of those requiring supplemental oxygen ($n$ = 112), and in 39% ($n$ = 69) of those requiring high-flow nasal cannula or ventilation. It is possible an overestimation by using criterium of impaired TLC based on values <80% [24, 39].

We found a reduced $D_{LCO}$ (< LLN) in 40% of the total subjects, in 35% of those requiring supplemental oxygen, and in 45% of those requiring CPAP or MV. Huang et al. [18] reported a reduced $D_{LCO}$ (<80% of predicted) in about 50% of the total subjects, in 40% of those requiring supplemental oxygen, and in 65% of those requiring high-flow nasal cannula or ventilation. Again, it is possible an overestimation by using criterium of impaired $D_{LCO}$ based on values <80% [25, 39].

Therefore, the respiratory function impairment after 2 years is similar between our study and that of Huang et al. [19] but higher than other studies at 12 months [13, 16–18, 40, 41]. Moreover, the study of Zaho et al. [13] reported a 20% of subjects with reduced $D_{LCO}$ at 1 year, but in a cohort with a mean age of 48 years and a different spectrum of COVID severity (from mild-to-severe) and in two studies restriction was inferred by forced vital capacity [16, 17] and not TLC.

When looking at chest CT abnormalities still present after 2 years, in our study, the most frequent were fibrotic bands (78%), traction bronchiectasis (39%), and fibrotic GGO (50%). Particularly, the latter was present in 75% of those with reduced TLC and in 53% of those with reduced $D_{LCO}$. Fibrosis was present in 15% of those with impaired respiratory function, more frequently (37%) in those with a reduced TLC. At 6–12 months, a meta-analysis by Lee et al. [40] reported a pooled prevalence of persistent GGO and pulmonary fibrosis of 34% and 32%, respectively. At 12 months, Zhao et al. [15] found abnormalities in chest CT, mainly GGO (40%) and nodules (30%), followed by subpleural lines (15%). At 12 months, Fortini et al. [17], on a cohort of 17 subjects, observed chest CT changes still evident in one-quarter of the patients, mainly GGOs. Finally, at 2 years, Huang et al. [19] on a cohort of

**Table 2.** Data at hospitalizations in the two groups with impaired respiratory function at the 24-month follow-up

| | Normal (*N* = 55) | TLC < LLN (*N* = 16) | $D_{LCO}$ < LLN (*N* = 40) | *p* value* | *p* value§ |
|---|---|---|---|---|---|
| Male, *n* (%) | 39 (70.9) | 15 (93.7) | 27 (67.5) | 0.12 | 0.90 |
| Age, years, median (IQR) | 59 (54–64)* | 64.5 (59.5–62)* | 62 (52.5–69.5) | 0.04 | 0.39 |
| BMI, kg/m$^2$, median (IQR) | 27.8 (24.9–30.7) | 28 (25.7–30.7) | 25.9 (32.9–29.1) | 0.22 | 0.20 |
| Smoking | | | | 0.9 | 0.42 |
| Current smokers, *n* (%) | 8 (14.5) | 2 (12.5) | 10 (25) | | |
| Former smokers, *n* (%) | 11 (20) | 2 (12.5) | 6 (15) | | |
| No smoking, *n* (%) | 36 (64.5) | 12 (75) | 24 (60) | | |
| $O_2$ supplementation only | 35 (63.6)* | 4 (25)* | 21 (52.5) | 0.01 | 0.38 |
| CPAP | 15 (27.3)* | 7 (43.7)* | 12 (30) | | |
| MV | 5 (9.1)* | 5 (31.3)* | 7 (17.5) | | |
| Length of hospital stay | 11 (6–18)*§ | 34 (22–58)* | 22 (7.5–33)§ | <0.001 | 0.01 |
| Lymphocytes, cells/μL | 0.99 (0.67–1.29) | 0.96 (0.59–1.31) | 0.96 (0.71–1.52) | 0.59 | 0.77 |
| ALT, U/L | 44 (26–107) | 52 (28–127.5) | 93.5 (38–135) | 0.69 | 0.36 |
| AST, U/L | 43 (30–73) | 47.5 (36–69.5) | 67.5 (37.5–121) | 0.80 | 0.36 |
| LDH, U/L | 322 (246–396) | 368.5 (272.5–539.5) | 342 (278–546) | 0.21 | 0.10 |
| D-dimer, μg/L | 747 (412–2,027) | 1,344 (516–4,088) | 1,086 (613–2,009) | 0.28 | 0.16 |
| HS troponin I, ng/L | 7.8 (4.2–11.3) | 12.1 (7.7–12.7) | 9.9 (4.8–19.3) | 0.36 | 0.68 |
| C-reactive protein, mg/L | 120.4 (59.5–209) | 205.8 (79.8–290.2) | 144.9 (24.5–272.2) | 0.17 | 0.44 |
| IL6, pg/mL | 2.6 (1.8–6.1) | 6 (4.7–9.2) | 4.4 (2.1–6.8) | 0.11 | 0.36 |
| Ferritin, μg/L | 481 (165–923) | 739 (351–1,446) | 744.5 (353.5–1,414.5) | 0.14 | 0.14 |
| Chest CT, *n* (%) | 23 (41.8) | 7 (43.7) | 19 (47.5) | >0.99 | 0.73 |
| GGO, *n* (%) | 19 (82.6) | 7 (100) | 18 (94.7) | 0.54 | 0.36 |
| Consolidation, *n* (%) | 16 (69.6) | 7 (100) | 15 (78.9) | 0.15 | 0.73 |
| Crazy paving, *n* (%) | 14 (60.9) | 2 (28.6) | 5 (26.3) | 0.20 | 0.05 |
| Halo sign, *n* (%) | 7 (30.4) | 2 (28.6) | 5 (26.3) | >0.99 | >0.99 |
| Reversal halo sign, *n* (%) | 6 (26.1) | 1 (14.3) | 2 (10.5) | >0.99 | 0.38 |
| Fibrotic bands, *n* (%) | 15 (65.2) | 3 (42.9) | 11 (57.9) | 0.39 | 0.87 |
| Traction bronchiectasis, *n* (%) | 12 (52.2) | 5 (71.4) | 11 (57.9) | 0.43 | 0.95 |
| Fibrotic GGO, *n* (%) | 2 (8.7) | 1 (14.3) | 5 (26.3) | >0.99 | 0.21 |
| Volume loss | 9 (39.1) | 5 (71.4) | 8 (42.1) | 0.20 | >0.99 |
| Subpleural bands, *n* (%) | 10 (43.5) | 2 (28.6) | 9 (47.4) | 0.67 | >0.99 |
| Pleural effusion, *n* (%) | 4 (17.4) | 1 (14.3) | 3 (15.8) | >0.99 | >0.99 |
| Emphysema (>5%), *n* (%) | 0 (0)* | 1 (14.3) | 4 (21.1)* | 0.23 | 0.03 |
| Fibrosis, *n* (%) | 0 (0) | 0 (0) | 1 (5.3) | NA | 0.45 |
| TSS, median (IQR) | 9 (6–12) | 11 (11–13) | 10 (9–13) | 0.09 | 0.38 |
| CCTS, median (IQR) | 13 (9–17) | 17 (16–18) | 15 (13–18) | 0.06 | 0.22 |
| CT-SS, median (IQR) | 20 (16–28) | 23 (20–34) | 22 (18–27) | 0.18 | 0.72 |

Values are reported as median and interquartile range (IQR) if not otherwise stated. For each row, identical superscript letters indicate significant differences. BMI, body mass index; CPAP, continuous positive airway pressure; GGO, ground glass opacity; TSS, total severity score; CCTS, chest CT score; CT-SS, CT severity score.

57 COVID-19 survivors with abnormal chest CT at 12 months reported GGO in 47 of them. In our study, the mean TSS improves, especially during first 6 months, with a slight decrease at 12 months without further improvement at 24 months. Probably, part of the CT abnormalities persistent at 6 months instead than "fibrotic" changes represent slowly regressive infiltrate secondary to organizing pneumonia, also seen with mild distortion mimicking actual fibrosis [42]. The longitudinal behavior of CT abnormalities mostly reflects the temporal evolution of diffuse alveolar damage and organizing pneumonia, main pathological patterns underlying COVID-19 pneumonia [43]. It is unknown if these CT abnormalities will regress after a longer follow-up; however, considering that residual lesions rarely changed after 1 year in SARS, these CT abnormalities in COVID-19 are likely permanent [6].

Finally, as in the recent manuscript of Sanna et al. [37], highlighting the importance of PFT in the long-term follow-up of patients affected by moderate to

**Table 3.** Trend of respiratory function impairment and chest CT data at different follow-ups in the subgroup with TLC < LLN at 24 months

| | Follow-up, months from discharge | | | *p* value |
|---|---|---|---|---|
| | 6 months (*N* = 21) | 12 months (*N* = 20) | 24 months (*N* = 16) | |
| Male, *n* (%) | 17 (80.9) | 17 (85) | 15 (93.7) | 0.57 |
| mMRC score, mean ± SD | 2±0.84 | 1.6±1.1 | 1.1±0.9 | 0.02 |
| mMRC >1, *n* (%) | 7 (33.3) | 11 (55) | 11 (68.7) | 0.09 |
| TLC, % pred, mean ± SD | 70±14 | 74±6 | 73±8 | 0.20 |
| $D_{LCO}$, % pred, mean ± SD | 66±20 | 67±14 | 68±16 | 0.94 |
| Chest CT, *n* (%) | 10 (47.6) | 9 (45) | 8 (50) | 0.96 |
| GGO, *n* (%) | 4 (40) | 5 (55.6) | 3 (37.5) | 0.79 |
| Consolidation, *n* (%) | 1 (10) | 2 (22.2) | 1 (12.5) | 0.81 |
| Fibrotic bands, *n* (%) | 9 (90) | 8 (88.9) | 7 (87.5) | >0.99 |
| Traction bronchiectasis, *n* (%) | 5 (50) | 5 (55.6) | 3 (37.5) | 0.80 |
| Fibrotic GGO, *n* (%) | 7 (70) | 5 (55.6) | 6 (75) | 0.77 |
| Volume loss, *n* (%) | 3 (30) | 2 (22.2) | 1 (12.5) | 0.85 |
| Subpleural lines, *n* (%) | 7 (70) | 5 (55.6) | 5 (62.5) | 0.88 |
| Fibrosis, *n* (%) | 1 (10) | 2 (22.2) | 3 (37.5) | 0.37 |
| TSS, median (IQR) | 6 (4.5–8) | 5 (2.5–7.5) | 5 (4–6) | 0.64 |
| CCTS, median (IQR) | 10 (5–12) | 8 (2.5–11) | 7.5 (5.5–10) | 0.80 |
| CT-SS, median (IQR) | 13 (8–18) | 10 (3.5–14.5) | 14 (7–17) | 0.88 |

SD, standard deviation; IQR, interquartile range; TLC, total lung capacity; GGO, ground glass opacity; TSS, total severity score; CCTS, chest CT score; CT-SS, CT severity score.

**Table 4.** Trend of respiratory function impairment and chest CT data at different follow-ups in the subgroup with $D_{LCO}$ < LLN at 24 months

| | Follow-up, months from discharge | | | *p* value |
|---|---|---|---|---|
| | 6 months (*N* = 39) | 12 months (*N* = 42) | 24 months (*N* = 40) | |
| Male, *n* (%) | 27 (69.2) | 27 (64.3) | 28 (70) | 0.83 |
| mMRC score, mean ± SD | 1.7±0.8 | 1.2±0.9 | 1.1±1 | 0.01 |
| mMRC >1, *n* (%) | 21 (53.9) | 14 (33.3) | 9 (22.5) | 0.02 |
| $D_{LCO}$, % pred, mean ± SD | 61±11 | 65±9 | 65±8 | 0.16 |
| TLC, % pred, mean ± SD | 83±17 | 87±16 | 90±18 | 0.32 |
| Chest CT, *n* (%) | 19 (48.7) | 20 (47.6) | 16 (40) | 0.69 |
| Ground glass opacity (GGO), *n* (%) | 6 (31.4) | 6 (30) | 4 (25) | 0.93 |
| Consolidation, *n* (%) | 2 (10.5) | 2 (10) | 1 (6.3) | >0.99 |
| Fibrotic bands, *n* (%) | 15 (78.9) | 14 (70) | 12 (75) | 0.92 |
| Traction bronchiectasis, *n* (%) | 8 (42.1) | 8 (40) | 6 (37.5) | 0.96 |
| Fibrotic GGO, *n* (%) | 11 (57.9) | 9 (45) | 9 (56.2) | 0.68 |
| Volume loss *n* (%) | 2 (10.5) | 4 (20) | 3 (18.7) | 0.73 |
| Subpleural lines, *n* (%) | 13 (68.4) | 10 (50) | 8 (50) | 0.42 |
| Fibrosis, *n* (%) | 0 (0) | 3 (15) | 5 (31.2) | 0.02 |
| TSS, median (IQR) | 5 (3–7.5) | 3 (2–5) | 4 (3–5.5) | 0.51 |
| CCTS, median (IQR) | 6.5 (4–12) | 3.5 (2–8) | 5.5 (3–8) | 0.41 |
| CT-SS, median (IQR) | 11 (6–17) | 5.5 (2–11.5) | 7 (4.5–16) | 0.51 |

SD, standard deviation; IQR, interquartile range; $D_{LCO}$, diffusing capacity of the lung for CO; TLC, total lung capacity; TSS, total severity score; CCTS, chest CT score; CT-SS, CT severity score.

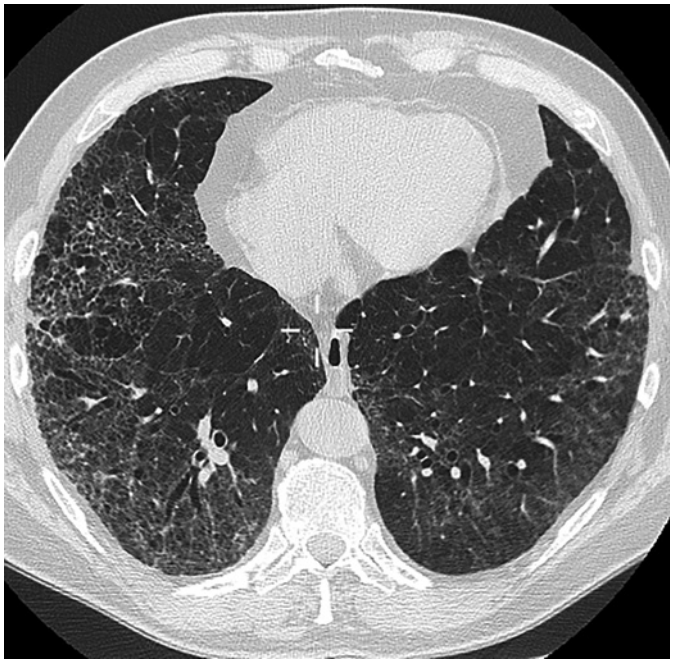

**Fig. 2.** Chest CT follow-up 2 years after COVID infection. Important fibrotic lung changes with diffuse fibrotic ground glass associated with traction bronchiectasis, volume loss, and fibrotic reticulation.

critical COVID-19, our results confirm the negative predictive value of PFT at 6 months from hospital discharge. About the group of subjects shifting from a normal $D_{LCO}$ at 6 months to an impaired at 24 months, they do not fill the criteria for progressive pulmonary fibrosis [44]; anyway, these patients have been enrolled in a further follow-up program with chest CT and PFT at 36 months.

*Limitations*

There are some limitations in our study. First, the lack of a baseline PFT before COVID-19. However, patients with known chronic respiratory disease were only 3 and former or current smokers were 17% and 19%, respectively, and none of the subjects had a history of pulmonary fibrosis. Second, chest CT was not done systematically in all patients at different timepoints, but only when clinically indicated, in 44% of the patients at hospitalization (Table 1) and in 40–50% of those with impaired respiratory function (Table 3, 4). However, this is consistent with the nature of the observational study. Third, we enrolled patients in early 2020 before the advent of the omicron and delta variant. As the SARS-CoV-2 variant types can affect the risk of PACS, more studies should be conducted to compare the severity and risk of PACS among different variants.

## Conclusions

Our study reveals that after 2 years from discharge for severe COVID-19, approximately one-third of the enrolled patients still presents an impaired respiratory function associated with variable chest CT alterations and exertional dyspnea. As in the manuscript of Sanna et al. [37], pulmonary damage due to SARS-CoV-2 (named post-COVID-19 interstitial lung disease) at 6 months is not progressive but also not reversible.


## Acknowledgments

We thank the ACOD (Assessment of Cardiac and pulmonary consequences in patients recOvered from coviD-19 infection) Group Collaborators Andrea Beltrame, Sandra Buscaglia, Gioacchino Catania, Pasqualina De Leo, Riccardo Goretti, Giovanni Riccio, Sara Grignolo, Lionello Parodi, and Bruzzone Monica, Lucio Ester, and Teleaga Gabriela for PFT data management. We thank Ilaria Pulzato for the critical review of the manuscript and English revision.


## Statement of Ethics

This study protocol (ACOD), conducted ethically in accordance with the World Medical Association Declaration of Helsinki, was reviewed and approved by Comitato Etico Regionale Liguria (CER Liguria 398/2020). Written informed consent was collected from any subject to recover data at hospitalization (clinical, laboratory, and imaging) retrospectively from electronic records (OneSys, Fenix RIS EL.CO., Italy) and to be enrolled in the follow-up program at 6, 12, and 24 months from hospital discharge comprising the mMRC dyspnea scale questionnaire, PFT, and, when indicated, a chest CT.

## Conflict of Interest Statement

Cristiano Alicino, Marco Anselmo, Giuliana Carrega, Gianluca Ficarra, Luca Garra, Paola Gnerre, Flavia Lillo, Simone Mennella, Rodolfo Tassara, and Anna Terrile report no conflicts of interest. Manlio Milanese has reported grants and attendance for advisory board from SANOFI, Glaxo Smith Kline, AstraZeneca outside the context of the current study.

## Funding Sources

No funding was received for the conduction of this study.

## Author Contributions

Manlio Milanese and Simone Mennella: study conceptualization, design of methodology, data collection, data analysis, and drafting of the manuscript. Cristiano Alicino: data collection, data analysis, and drafting of the manuscript. Marco Anselmo, Giuliana Carrega, Gianluca Ficarra, Alessandro Gastaldo, Luca Garra, Paola Gnerre, Flavia Lillo, Rodolfo Tassara, and Anna Terrile: study conceptualization, design of methodology, data collection, and critical review of the manuscript. All authors read and approved the final version of the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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