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# Residual respiratory impairment after COVID-19 pneumonia

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# Abstract

**Introduction:** The novel coronavirus SARS-Cov-2 can infect the respiratory tract causing a spectrum of disease varying from mild to fatal pneumonia, and known as COVID-19. Ongoing clinical research is assessing the potential for long-term respiratory sequelae in these patients. We assessed the respiratory function in a cohort of patients after recovering from SARS-Cov-2 infection, stratified according to PaO<sub>2</sub>/FiO<sub>2</sub> (p/F) values.

**Method:** Approximately one month after hospital discharge, 86 COVID-19 patients underwent physical examination, arterial blood gas (ABG) analysis, pulmonary function tests (PFTs), and six-minute walk test (6MWT). Patients were also asked to quantify the severity of dyspnoea and cough before, during, and after hospitalization using a visual analogic scale (VAS). Seventy-six subjects with ABG during hospitalization were stratified in three groups according to their worst p/F values: above 300 (n = 38), between 200 and 300 (n = 30) and below 200 (n = 20).

**Results:** On PFTs, lung volumes were overall preserved yet, mean percent predicted residual volume was slightly reduced (74.8  $\pm$  18.1%). Percent predicted diffusing capacity for carbon monoxide (DLCO) was also mildly reduced (77.2  $\pm$  16.5%). Patients reported residual breathlessness at the time of the visit (VAS 19.8, p < 0.001). Patients with p/F below 200 during hospitalization had lower percent predicted forced vital capacity (p = 0.005), lower percent predicted total lung capacity (p = 0.012), lower DLCO (p < 0.001) and shorter 6MWT distance (p = 0.004) than patients with higher p/F.

**Conclusion:** Approximately one month after hospital discharge, patients with COVID-19 can have residual respiratory impairment, including lower exercise tolerance. The extent of this impairment seems to correlate with the severity of respiratory failure during hospitalization.

**Keywords:** COVID, dyspnoea, cough, ABG, PFT, 6MWT

#### Introduction

In December 2019, a novel coronavirus (SARS-CoV-2) able to infect the respiratory tract in humans emerged in Wuhan (China), causing a disease known as COVID-19. A possible complication of SARS-CoV-2 infection is

a severe acute respiratory syndrome (SARS) due to interstitial pneumonia [1]. On March 11, 2020, the WHO declared COVID-19 a global pandemic. As of June, 2021 more than 175 million people have been infected by SARS-CoV-2 worldwide and 3.8 have died [2].

Several studies reported a range of clinical and laboratory features among hospitalized COVID-19 patients, including increased levels of inflammatory markers [3]. The frequency of respiratory and functional impairment after COVID-19 is still debated but several studies found

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reduced lung volumes, reduced diffusing capacity of the lung for carbon monoxide (DLCO) and reduced exercise tolerance following hospital discharge [4–7]. A comprehensive follow-up strategy for COVID-19 patients after clinical recovery has been advocated [8]. We performed a study to investigate the prevalence of respiratory impairment in a cohort of COVID-19 patients after hospital discharge and to determine the relationship between the severity of pulmonary involvement during hospitalization and the extent of residual clinical and functional abnormalities.

#### **Material and methods**

# Study population and subgroups

In the post-COVID-19 outpatient program at Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome (Italy), a multidisciplinary team evaluates patients after hospital discharge. Patients presenting between April 22nd and May 27th, 2020 were invited to participate in the study. Inclusion criteria were: previous hospitalization for COVID-19; radiological evidence of interstitial pneumonia at the time of hospital admission; nasopharyngeal swab negative for SARS-Cov-2 in the 48–72 h before study enrolment.

Based on arterial blood gas (ABG) analysis values during hospitalizzation, three subgroups were defined using the worst  $PaO_2/FiO_2$  value (p/F): mild (p/F  $\geq$  300), moderate ( $\leq$  200 p/F < 300), and severe (p/F < 200). Such values, derived from the Berlin Criteria for ARDS, have been used in clinical practice to stratify severity of respiratory failure [9]. Written informed consent was obtained from each participant. The study protocol was approved by the Institutional Review Board of the Università Cattolica del Sacro Cuore (Rome, Italy) (approval number 0024185/20). Clinical evaluations, exams, and procedures were performed in accordance with the Declaration of Helsinki.

# Study design and assessments

In this cross-sectional study, all patients underwent physical examination, resting ABG, pulmonary function tests (PFT) with DLCO, and 6MWT at the time of the study visit. ABG was analyzed using the ABL90FLEX radiometer (A. de Mori Spa Milano, Italy). The Biomedin Spirometer (software Baires version 5.1 revision 3, Biomedin SRL, Padova, Italy) was used to perform PFT and DL $_{\rm CO}$  with the single breath-hold method (software Baires version 5.1 revision 3, Biomedin SRL, Padova, Italy). Lung function tests were performed according to current international guidelines [10, 11]. The 6MWT was used to assess the sub-maximal level of functional capacity. After 6 min of rest, the patient was instructed to walk along a 50 m corridor as fast as possible for 6 min

wearing a finger/forehead pulse oximeter (Nonin 3100 Wristox pulse oximeter with nVISION software; Nonin Medical Inc, Plymouth, MN, USA) to record percutaneous oxygen saturation (SpO<sub>2</sub>) and heart rate (HR). At the end of the 6 min (or before, if the patient was unable to walk any further for fatigue, dyspnoea, or chest pain, or if saturation dropped below 80%) the distance covered was recorded and the patient was invited to sit and rest for 6 min. A drop in oxygen saturation≥4% from baseline was considered to be clinically relevant During the study visit, a visual analog scale (VAS) score was used to measure the levels of dyspnoea and cough. Using a 100 mm linear scale, where 0 mm represents absence and 100 mm represents the worst dyspnoea and cough, patients were asked to report the levels of these two symptoms at the onset of the disease (i.e. immediately before hospital admission), during hospitalization, and at the moment of the study visit [12]. Retrospective data collected for this study included chest imaging findings, pharmacological treatments, p/F values, the type of respiratory support, and duration of hospitalization.

# Statistical analysis

Descriptive statistics such as means with standard deviations or medians with interquartile ranges were used for continuous variables after checking for normal distribution of data. Frequencies or percentages were used to describe categorical variables. Dyspnea and cough VAS scores collected from the same patient were compared using analysis of variance (ANOVA) for repeated measures. Between-group comparisons of demographics and clinical data were performed using one-way analysis of covariance (ANCOVA) for continuous variables and the chi-square test for categorical variables. Estimated means of physiological variables across study groups were reported after adjustment by age, included as covariate in the ANCOVA model due to a significant age difference between study groups. P-values less than 0.05 were considered statistically significant. SPSS (version 24, IBM, New York, NY, USA) was used to perform statistical analyses.

# **Results**

# Characteristics of the study population

One hundred and fifty-seven patients included in the post-Covid follow-up program were screened for inclusion in the study. Twenty-six patients were excluded due to positivity at the nasopharyngeal SARS-Cov-2 swab; eighteen patients were excluded due to lack of radiological evidence of COVID-19 pneumonia at the time of hospitalization; twenty-seven patients were excluded because they had not been hospitalized (discharged from

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the Emergency Department). Eighty-six patients were included in the analyses.

The characteristics of the study population are reported in Table 1. Study visit occurred 35 (SD: $\pm$ 21) days after hospital discharge. At the time of hospital admission, chest imaging (i.e., chest X-ray or chest CT scan) revealed bilateral ground-glass opacities (GGO) with or without consolidations in 70 patients (81%). Sixteen patients (19%) had unilateral lung involvement. During hospitalization, 56 (65%) patients required supplemental oxygen and 15 patients (17%) were admitted to the intensive care unit.

Pulmonary function testing (Fig. 1) showed overall preserved lung volumes, with mean percent predicted total lung capacity (TLC) of 89.6% ( $\pm$ 14.6%) and mean percent predicted forced vital capacity (FVC) of 104.6% ( $\pm$ 18.5%). Mean percent predicted forced expiratory volume in one second (FEV $_1$ ) was 102.8% ( $\pm$ 16.0%). Mean percent predicted residual volume (RV) was the only respiratory volume reduced under the 5th percentile (74.8 $\pm$ 18.1%). Percent predicted DLco was also mildly reduced (77.2 $\pm$ 16.5%).

Mean partial pressure of oxygen (pO<sub>2</sub>) was 91.4 mmHg ( $\pm$ 8.0) and mean alveolar-arterial oxygen gradient (d(A-a)) was 13.0 mmHg ( $\pm$ 7.5). Approximately one month after hospital discharge, patients reported more dyspnoea than pre-admission values (VAS score estimated mean difference: 15.3 mm; p < 0.001) (Fig. 2; Table 2).

# Comparison of study groups by p/F ratio

Most patients (n=76, 88%) had an ABG performed during the hospitalization and were therefore included in this analysis. Among excluded patients, 8 patients had no ABG and 2 patients had an ABG performed with unknown oxygen inhaled fraction.

Gender, smoking status and comorbidities were not different across groups. Six patients (21%) in the mild hypoxemia group had a history of asthma. Patients in the severe hypoxemia group were older (63.1 years, p = 0.014 vs other groups), had a longer hospitalization time (23.0 days,  $p < 0.001 \ vs$  other groups) and were treated with anti-IL-6 drugs and enoxaparin more frequently (respectively 81% and 95%,  $p < 0.001 \ vs$  other groups).

Lung volumes were generally lower in the severe hypoxemia group, including lower percent of predicted FVC (p=0.005), lower percent of predicted FEV1 (p=0.009) and lower percent of predicted TLC (p=0.012) (Table 3). In the severe hypoxemia group mean percent predicted TLC was 80.4% ( $\pm 3.1$ ), indicating a residual restrictive impairment after 35 days from hospital discharge. DLco was also more reduced (64.9 $\pm 3.2\%$  predicted) in the severe hypoxemia group than in the other two groups (p<0.001).

**Table 1** Characteristics of patients during the hospitalization for Covid-19

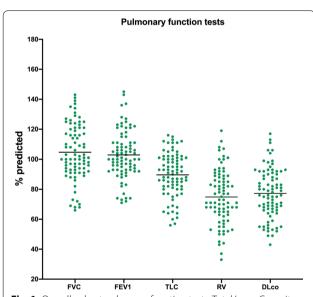
	Available observations	N=87
Age, years		58 (13)
Male, n (%)		58 (67)
BMI (kg/m <sup>2</sup> )		26.7 (4.4)
p/F worst	76	281 (150)*
Hospitalization time (days)	86	13 (10)*
Day from discharge (days)	85	35 (21)*
Smoking history, n (%)	85	
Never smoker		33 (39)
Smoker		4 (5)
Former smoker		48 (56)
Pulmonary disease history, n (%)	86	
COPD		3 (4)
Asthma		9 (11)
Radiology (chest XR or CT), n (%)	86	
Chest CT performed		51 (59)
Unilateral involvement		16 (19)
Bilateral involvement		70 (81)
Antiviral therapy, n (%)	86	
Lopinavir/Ritonavir		37 (43)
Darunavir/Ritonavir		53 (62)
Anti-IL-6, n (%)	86	31 (36)
Enoxaparin, n (%)	86	42 (49)
Azithromycin, n (%)	86	41 (48)
Hydroxychloroquine, n (%)	86	81 (94)
Corticosteroids, n (%)	86	6 (7)
Respiratory support, n (%)	86	. ,
Ventimask		56 (65)
HFNC		9 (11)
NIV or CPAP		13 (15)
Orotracheal Intubation		6 (7)
ICU admission, n (%)	86	15 (17)
FVC	83	,
Litres		3.9 (1.1)
% predicted		104.6 (18.5)
FEV-1	83	,
Litres		3.1 (0.9)
% predicted		102.8 (16.0)
FEV-1/FVC	83	
% predicted		79.6 (5.8)
TLC	82	7 3.0 (3.0)
Litres	02	5.7 (1.3)
% predicted		89.6 (14.6)
DLco	83	33.0 (11.0)
Litres	00	21.2 (6.8)
% predicted		77.2 (16.5)
RV	82	, , .2 (10.3)
Litres	UZ	1.58 (0.47)*
% predicted		74.8 (18.1)
70 predicted		/4.0 (10.1)

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Table 1 (continued)

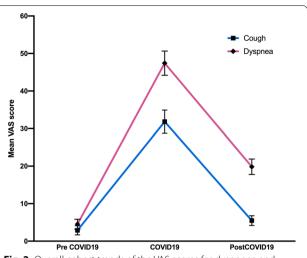
	Available observations	N=87
RC/TLC	82	
Ratio		30 (10)*
% predicted		79.0 (13.0)
ABG	84	
pO2 (mmHg)		91.4 (8.0)
pCO2 (mmHg)		38.8 (3.1)
рН		7.42 (0.02)*
d(A-a) (mmHg)		13.0 (7.5)
6MWT	82	
SpO2 basal		97 (2)*
SpO2 nadir		95 (4)*
Meters		500 (88)*

Categorical data are presented as counts (%). Continuous data are presented as means with standard deviation (SD) or medians with interquartile range (IQR) for non-normally distributed variables (indicated with \*). BMI: Body Mass Index; ICU: Intensive Care Unit; COPD: Chronic Obstructive Pulmonary Disease; IL-6: Interleukin; HFNC: High Flow Nasal Cannula; NIV: Non-Invasive Ventilation; CPAP: Continue Positive Airway Pressure



**Fig. 1** Overall cohort pulmonay function tests. Total Lung Capacity (TLC), Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV-1), Residual Volume (RV) Diffusion Lung capacity for carbon monoxide (DLco)

As expected, the alveolar-arterial oxygen gradient increased progressively across study groups, ranging from 10.1 mmHg ( $\pm$ 1.4) in the mild hypoxemia group to 16.6 mmHg ( $\pm$ 1.6) in the severe hypoxemia group (p=0.011). Compared to patients in the severe hypoxemia group, patients in the mild hypoxemia group



**Fig. 2** Overall cohort trends of the VAS scores for dyspnoea and cough before hospitalization, during hospitalization, and at follow-up

**Table 2** Dyspnoea and cough in overall population in three-time points: before hospitalization, during the hospitalization, and at study visit-time; VAS: Visual Analogic Scale

	Before hospitalization	During Covid-19 hospitalization	Visit- time	<i>p</i> value
Dyspnoea VAS	4.5 (1.3)	47.4 (3.2) °#	19.8 (2.1) #	< 0.001
Cough VAS	2.9 (1.2)	31.8 (3.1) °#	5.5 (1.3)	< 0.001

Data are reported as estimated means (Standard Error) after adjustment for age used as covariate in the ANOVA model.  $^{\circ}$  p value < 0.05 vs "before hospitalization".  $^{\sharp}$  p value < 0.05 vs "visit-time"

demonstrated greater exercise tolerance (+80.0 m in 6MWD;  $p\!=\!0.004$ ) and higher nadir in SpO2 (+2.5%;  $p\!=\!0.005$ ). Dyspnoea and cough levels at the time of study visit were similar across groups.

# **Discussion**

The findings of this study suggest that respiratory abnormalities persist over time in COVID-19 patients who experienced a more severe form of disease during hospitalization. Several studies already reported a reduction in lung volumes and DLco levels as well as reduced exercise tolerance following hospital discharge [4–7]. Our study expands these findings in a larger Italian cohort. To our knowledge, this is the first study establishing the relationships between the severity of acute respiratory failure (as measured by the p/F ratio) and a wide range of blood gas and physiological parameters.

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**Table 3** Characteristics of patients stratified by p/F during hospitalization

NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC*         73         Eitres         4.23 (0.18)         3.77 (0.18)         3.68 (0.21)           % predicted         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)°           FEV <sub>1</sub> *         73         Eitres         3.36 (0.14)         3.00 (0.14)         2.98 (0.16)           % predicted         107.8 (3.0)         103.0 (3.1)         92.6 (3.6)°           FEV <sub>1</sub> /FVC*         73         *** FEV <sub>1</sub> /FVC*         73         *** FEV <sub>1</sub> /FVC*         73         *** FEV <sub>1</sub> /FVC*         **		N available observations	$p/F \ge 300 \ (N = 28)$	$p/F < 300 \ge 200 \ (n = 27)$	p/F < 200 (n = 21)	<i>p</i> value
Male         19 (68)         17 (63)         16 (76)           Female         9 (32)         10 (37)         \$ (24)           Molt ((sg/m²))         75         \$2.57 (51)         27.3 (3.9)         \$2.0 (43)           p/F worst         76         \$49.0 (55.8)*         \$75.0 (54.0)*         \$35.0 (92.5)*           Hospitalization time (days)         76         \$9.6 (60)*         \$13.0 (90)*         \$25.0 (40)*           Hour admission         76         \$0.00         \$1 (4)         \$13.62)           Smoking history         75         ***         ***         ***           Smoker         \$1 (3)         \$2 (8)         \$0 (9)           Smoker         \$1 (3)         \$2 (8)         \$0 (9)           Smoker         \$1 (61)         \$1 (69)         \$10 (50)           Pullmonary disease history         ***         ***         ***           COPD         76         \$0 (9)         \$2 (7)         \$0 (10)           Asthman         76         \$6 (21)         \$1 (4)         \$0 (9)           Cortical Criperformed         76         \$6 (21)         \$1 (4)         \$0 (9)           Balacity Chest Xikor Crip         76         \$1 (3)         \$3 (11)         \$0 (9)	Age (years)	76	52.3 (14.0)	59.2 (12.2)	63.1 (11.9)	0.014
Female         9 (32)         10 (37)         5 (24)           BM (Rg/m²)         75         25.7 (5.1)         27.3 (3.9)         28.0 (4.3)           p² (worst)         76         349.0 (55.8)*         276.0 (64.0)*         135.0 (90.5)*           Hospitalization time (days)         76         9.5 (6.0)*         13.0 (9.0)*         23.0 (14.0)*           ICU admission         76         0.00         1 (4)         13 (62)           Never smoker         10 (30)         9 (33)         10 (50)           Never smoker         17 (61)         16 (59)         10 (50)           Former smoker         17 (61)         16 (59)         10 (50)           Pulmonary disease history         17 (61)         16 (59)         10 (50)           COPD         76         0 (0)         2 (7)         0 (0)           Asthma         76         6 (21)         1 (4)         0 (0)           Chest CT performed         76         6 (21)         1 (4)         0 (0)           Asthma         76         6 (21)         1 (4)         0 (0)           Asthma (bull and involvement)         11 (39)         3 (11)         0 (0)           Bilaceral Involvement         11 (39)         3 (11)         0 (0) </td <td>Sex</td> <td>76</td> <td></td> <td></td> <td></td> <td>0.618</td>	Sex	76				0.618
BMI (kg/m²)         75         25.7 (S.1)         27.3 (3.9)         28.0 (4.3)           p/r worst         76         349.0 (55.8)*         275.0 (54.0)*         135.0 (92.5)*           ICU admission         76         9.5 (6.0)*         13.0 (90.0)*         23.0 (14.0)*           ICU admission         76         0.00         1.49         13.62)           Smoking history         75         8         8         0.00         9.933         10.60           Smoker         1.03         2.80         0.00         2.07         0.00           Smoker smoker         1.7 (61)         16.699         10.50         10.50           Pullmonary disease history         COPD         76         0.00         2.77         0.00           Asthma         76         6.21)         1.40         0.00           Asthma         76         6.21)         1.40         0.00           Chest CT performed         76         6.21)         1.40         0.00           Malidated involvement         1.17 (61)         24.899         21.1000           Millateral involvement         1.7 (61)         24.899         21.1000           Antillateral involvement         75         1.2 (43)         9.35	Male		19 (68)	17 (63)	16 (76)	
p/F worst         76         3490 (55.8)*         2760 (54.0)*         135.0 (92.5)*           Hospitalization time (days)         76         95 (6.0)*         130 (9.0)*         230 (14.0)*           Club admission         76         0 (0)         1 (4)         13 (62)*           Smoking history         75         The sear moker         10 (30)         9 (33)         10 (50)           Smoker         1 (3)         2 (8)         0 (0)         10 (50)         10 (50)           Former smoker         1 (3)         2 (8)         0 (0)         2 (7)         0 (0)           Asthma         76         0 (0)         2 (7)         0 (0)         0 (0)         Asthma         76         6 (21)         1 (4)         0 (0)         0 (0)         Cortect performed         76         6 (21)         1 (4)         0 (0)         0 (0)         Cortect performed         76         6 (21)         1 (4)         0 (0)         0 (0)         Cortect performed         76         6 (21)         1 (4)         0 (0)         0 (0)         Cortect performed         76         6 (21)         1 (4)         0 (0)         0 (0)         0 (0)         0 (0)         0 (0)         0 (0)         0 (0)         0 (0)         0 (0)         0 (0)         0	Female		9 (32)	10 (37)	5 (24)	
Foliabilization time (days)   76	BMI (Kg/m <sup>2</sup> )	75	25.7 (5.1)	27.3 (3.9)	28.0 (4.3)	0.181
ICU admission	p/F worst	76	349.0 (55.8)*	276.0 (54.0)*	135.0 (92.5)*	< 0.001
Smoking history         75           Never smoker         10 (36)         9 (33)         10 (50)           Smoker         1 (3)         2 (8)         0 (0)           Former smoker         17 (61)         10 (59)         10 (50)           Pulmonary disease history         COPD         76         0 (0)         2 (7)         0 (0)           Asthma         76         6 (21)         1 (4)         0 (0)           Chest CT performed         76         15 (54)         17 (63)         13 (62)           Radiclogy (chest XR or CT)         76         11 (39)         3 (11)         0 (0)           Linitateral involvement         11 (39)         3 (11)         0 (0)           Bilateral involvement         17 (61)         24 (89)         21 (100)           Anti Life         75         12 (43)         9 (35)         13 (62)           Darunavir/Ritonavir         75         12 (43)         9 (35)         13 (62)           Anti Life         76         8 (29)         11 (41)         20 (95)           Actibromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         8 (29)         25 (93)         21 (100)	Hospitalization time (days)	76	9.5 (6.0)*	13.0 (9.0)*	23.0 (14.0)*	< 0.001
Never smoker         10 (36)         9 (33)         10 (50)           Smoker         1 (3)         2 (8)         0 (0)           Former smoker         17 (61)         16 (59)         10 (50)           Pulmonary disease history         76         0 (0)         2 (7)         0 (0)           Asshma         76         15 (4)         17 (63)         13 (62)           Ascillor performed         76         15 (54)         17 (63)         13 (62)           Badiology (chest XR or CT)         76         11 (39)         3 (11)         0 (0)           Billateral involvement         17 (61)         24 (89)         21 (100)           Antiliard therapy         12 (33)         9 (35)         13 (62)           Apriliary/Ritonavir         76         14 (50)         9 (35)         13 (62)           Antil Li-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         4 (50)         19 (70)         12 (57)           Hydroxychloroquine         76         2 (7)         10 (37)         12 (100)           Actitionycine         76         2 (20)         2 (3)         21 (100)           Altiproxychloroquine         76         2 (20)         2	ICU admission	76	0 (0)	1 (4)	13 (62)	< 0.001
Smoker         1 (3)         2 (8)         0 (0)           Former smoker         17 (61)         16 (59)         10 (50)           Pulmonary disease history         76         0 (0)         2 (7)         0 (0)           Asthma         76         6 (21)         11 (4)         0 (0)           Chest CT performed         76         15 (54)         17 (63)         13 (62)           Baldiology (chest XR or CT)         76         11 (39)         3 (11)         0 (0)           Unilateral involvement         11 (39)         3 (11)         0 (0)           Bilateral involvement         17 (61)         24 (89)         21 (100)           Antiviral therapy         4         14 (50)         19 (35)         13 (62)           Antiviral therapy         5         12 (43)         9 (35)         13 (62)           Darunawir/Ritonavir         76         14 (50)         19 (70)         13 (62)           Anti Il-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         21 (100)           Respiratory support         Ventinask	Smoking history	75				0.595
Former smoker   17 (61)   16 (59)   10 (50)   Pulmonary disease history	Never smoker		10 (36)	9 (33)	10 (50)	
Former smoker   17 (61)   16 (59)   10 (50)   Pulmonary disease history	Smoker		1 (3)			
Pulmonary disease history         COPO         76         0 (0)         2 (7)         0 (0)           Asthma         76         6 (21)         1 (4)         0 (0)           Chest CT performed         76         15 (54)         17 (63)         13 (62)           Badiology (chest XR or CT)         76         76         11 (39)         3 (11)         0 (0)           Billateral involvement         11 (39)         3 (11)         0 (0)           Billateral involvement         11 (39)         3 (11)         0 (0)           Antiviral therapy         1         24 (89)         21 (100)           Lopinavir/Ritonavir         75         12 (43)         9 (35)         13 (62)           Antil IL-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         111 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         2 (79)         25 (93)         21 (100)           Hydroxychloroquine         76         8 (28)         25 (93)         21 (100)           HSP Veritinask         76         8 (28)         25 (93)         21 (100)      <	Former smoker					
COPD         76         0 (0)         2 (7)         0 (0)           Asthma         76         6 (21)         1 (4)         0 (0)           Chest CT performed         76         6 (21)         1 (3)         13 (62)           Addiology (chest XR or CT)         76         Verification         Verification           Unilateral involvement         11 (39)         3 (11)         0 (0)           Bilateral involvement         17 (61)         24 (89)         21 (100)           Antiviral therapy         Verification         Verification         Verification           Lopinavir/Ritonavir         75         12 (43)         9 (35)         13 (62)           Darunavir/Ritonavir         76         14 (50)         19 (70)         13 (62)           Antil L6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (57)           Hydroxychloroquine         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         1 (4)         8 (38)           Hydroxychloroquine         75	Pulmonary disease history					
Asthma         76         6 (21)         1 (4)         0 (0)           Chest C performed         76         15 (54)         17 (63)         13 (62)           Radiology (chest XR or CT)         76         76           Unilateral involvement         11 (39)         3 (11)         0 (0)           Bilateral involvement         17 (61)         24 (89)         21 (100)           Antiviral therapy         Upoinavir/Ritonavir         75         12 (43)         9 (35)         13 (62)           Darunavir/Ritonavir         76         14 (50)         19 (70)         13 (62)           Anti IL-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         1 (4)         8 (38)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         0 (0)         1 (1)         8 (38) <td></td> <td>76</td> <td>0 (0)</td> <td>2 (7)</td> <td>0 (0)</td> <td>0.155</td>		76	0 (0)	2 (7)	0 (0)	0.155
Chest CT performed         76         15 (54)         17 (63)         13 (62)           Radiology (chest XR or CT)         76         Unilateral involvement         11 (39)         3 (11)         0 (0)           Bilateral involvement         17 (61)         24 (89)         21 (100)           Antiviral therapy         Lopinavir/Ritonavir         75         12 (43)         9 (35)         13 (62)           Darunavir/Ritonavir         76         14 (50)         19 (70)         13 (62)           Antil IL-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         5 (25)           FVC*         73         111 (50)         3 (70)         3 (8)           Litres	Asthma	76				0.017
Radiology (chest XR or CT)         76           Unilateral involvement         11 (39)         3 (11)         0 (0)           Bilateral involvement         17 (61)         24 (89)         21 (100)           Antiviral therapy         Validation of the properties of the pr	Chest CT performed	76				0.745
Unilateral involvement         11 (39)         3 (11)         0 (0)           Bilateral involvement         17 (61)         24 (89)         21 (100)           Antiviral therapy         3 (11)         9 (35)         13 (62)           Lopinavir/Ritonavir         76         14 (50)         19 (70)         13 (62)           Anti IL-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         8 (28)         25 (33)         21 (100)           Corticosteroids         74         0 (0)         3 (11)         2 (11)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         1 (52)           Orotracheal Intubation		76	,	. ,	, ,	0.001
Bilateral involvement         17 (61)         24 (89)         21 (100)           Antivial therapy           Lopinavir/Ritonavir         75         12 (43)         9 (35)         13 (62)           Darunavir/Ritonavir         76         12 (43)         19 (70)         13 (62)           Antil IL-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         3 (11)         2 (11)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (52)           FVC <sup>5</sup> 73         11 (52)         10 (53)         10 (53)         10 (53)         10 (53)         10 (53)         10 (53)	= -		11 (39)	3 (11)	0 (0)	
Antiviral therapy  Lopinavir/Ritonavir 75 12 (43) 9 (35) 13 (62)  Darunavir/Ritonavir 76 14 (50) 19 (70) 13 (62)  Anti IL-6 76 2 (7) 10 (37) 17 (81)  Enoxaparin 76 8 (29) 11 (41) 20 (95)  Azithromycin 75 12 (43) 13 (50) 12 (57)  Hydroxychloroquine 76 27 (96) 25 (93) 21 (100)  Corticosteroids 74 0 (0) 3 (11) 2 (11)  Respiratory support  Ventimask 76 8 (28) 25 (93) 21 (100)  HFNC 75 0 (0) 1 (4) 8 (38)  NIV or CPAP 75 0 (0) 10 (0) 11 (52)  Orotracheal Intubation 68 0 (0) 0 (0) 11 (52)  Orotracheal Intubation 68 75 (25)  FVC 5 73  Litres 4 4.23 (0.18) 3.77 (0.18) 3.68 (0.21)  % predicted 119.6 (3.3) 104.5 (3.4) 2.98 (0.16)  % predicted 2 119.6 (3.3) 103.0 (3.1) 2.98 (0.16)  % predicted 3 8.00 (1.0) 79.3 (1.0) 81.1 (1.2)  TLC 5 72  Litres 8 80.0 (1.0) 79.3 (1.0) 81.1 (1.2)  TLC 5 72  Litres 9.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 5 72  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 7 2  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 7 2  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 7 2  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 7 2  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 7 2  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 7 2  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 7 2  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 8.2,7 (2.7) 80.6 (2.8) 64.9 (3.2)* *	Bilateral involvement					
Lopinavir/Ritonavir         75         12 (43)         9 (35)         13 (62)           Darunavir/Ritonavir         76         14 (50)         19 (70)         13 (62)           Anti IL-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         3 (11)         2 (110)           Respiratory support         Vertimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC <sup>5</sup> 73         119.6 (3.3)         104.5 (3.4)         32.0 (3.9)*           FEV <sub>1</sub> <sup>5</sup> 73         119.6 (3.3)         104.5 (3.4)         2.0 (3.9)*           FEV <sub>1</sub> <sup>5</sup> 73         107.8 (3.0)         10.0 (3.1)			(-1)	_ · (/	_: (:::)	
Darunavir/Ritonavir         76         14 (50)         19 (70)         13 (62)           Anti IL-6         76         2 (7)         10 (37)         17 (81)           Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         3 (11)         2 (11)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Or otracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC <sup>5</sup> 73         11 (52)         3 (30)         3 (30)         3 (30)         3 (30)         3 (30)         9 (20)         3 (30)         9 (20)         3 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)         9 (30)<		75	12 (43)	9 (35)	13 (62)	0.165
Anti IL-6 76 2 (7) 10 (37) 17 (81)  Enoxaparin 76 8 (29) 11 (41) 20 (95)  Azithromycin 75 12 (43) 13 (50) 12 (57)  Hydroxychloroquine 76 27 (96) 25 (93) 21 (100)  Corticosteroids 74 0 (0) 3 (11) 2 (11)  Respiratory support  Ventimask 76 8 (28) 25 (93) 21 (100)  HFNC 75 0 (0) 1 (4) 8 (38)  NIV or CPAP 75 0 (0) 1 (4) 8 (38)  NIV or CPAP 75 0 (0) 0 (0) 11 (52)  Orotracheal Intubation 68 0 (0) 0 (0) 5 (25)  FVC <sup>6</sup> 73  Litres 4,23 (0.18) 3,77 (0.18) 3.68 (0.21)  % predicted 1 19 (3.3) 10.45 (3.4) 92.0 (3.9)  FEV <sub>1</sub> <sup>6</sup> 73  Litres 3,36 (0.14) 3.00 (0.14) 2.98 (0.16)  % predicted 1 107.8 (3.0) 103.0 (3.1) 92.6 (3.6)  FEV <sub>1</sub> /FVC <sup>6</sup> 73  Litres 3,36 (0.14) 3.00 (0.14) 2.98 (0.16)  % predicted 107.8 (3.0) 103.0 (3.1) 92.6 (3.6)  FEV <sub>1</sub> /FVC <sup>6</sup> 73  Litres 3,55 (0.24) 5.53 (0.24) 5.53 (0.26)  % predicted 92.6 (2.7) 9.0.7 (2.8) 80.4 (3.1)  Litres 92.6 (2.7) 9.0.7 (2.8) 80.4 (3.1)  Litres 92.3 (3.9)  Litres 92.3 (3.97) 2.1.05 (1.00) 18.69 (1.15)  % predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)  ***Interest**  ***Int						0.300
Enoxaparin         76         8 (29)         11 (41)         20 (95)           Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         3 (11)         2 (11)           Respiratory support         25 (93)         21 (100)           Wentimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC <sup>6</sup> 73         3         3.77 (0.18)         3.68 (0.21)           % predicted         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)°           FEV <sub>1</sub> <sup>5</sup> 73         3.30 (0.14)         3.00 (0.14)         2.98 (0.16)           % predicted         107.8 (3.0)         103.0 (3.1)         92.6 (3.6)°           FEV <sub>1</sub> /FVC <sup>6</sup> 73         3         3.10 (2.10)         3.11 (1.2)           ILC <sup>6</sup> 2         5.95 (0.23)         <						< 0.001
Azithromycin         75         12 (43)         13 (50)         12 (57)           Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         3 (11)         2 (11)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC*         73         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)*           FEV,**         73         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)*           FEV,**         73         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)*           FEV,**FVC**         73         107.8 (3.0)         103.0 (3.1)         2.98 (0.16)           % predicted         107.8 (3.0)         103.0 (3.1)         92.6 (3.6)*           FEV,**FVC**         73         80.0 (1.0)         79.3 (1.0)         81.1 (1.2)           Lic**         5.95 (0.23)         5.53 (0.24)         5.31 (0.26)						< 0.001
Hydroxychloroquine         76         27 (96)         25 (93)         21 (100)           Corticosteroids         74         0 (0)         3 (11)         2 (11)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC <sup>5</sup> 73         Litres         4.23 (0.18)         3.77 (0.18)         3.68 (0.21)           % predicted         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)°           FEV <sub>1</sub> <sup>5</sup> 73         Litres         3.36 (0.14)         3.00 (0.14)         2.98 (0.16)           % predicted         107.8 (3.0)         103.0 (3.1)         92.6 (3.6)°           FEV <sub>1</sub> /FVC <sup>6</sup> 73         **           **         8.00 (1.0)         79.3 (1.0)         81.1 (1.2)           TLC <sup>5</sup> 72         Litres         5.95 (0.23)         5.53 (0.24)         5.31 (0.26)           % predicted         92.6 (2.7)         90.7 (2	·					0.611
Corticosteroids         74         0 (0)         3 (11)         2 (11)           Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC <sup>5</sup> 73         4.23 (0.18)         3.77 (0.18)         3.68 (0.21)           % predicted         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)°           FEV <sub>1</sub> <sup>5</sup> 73         100.0 (0.14)         2.98 (0.16)           % predicted         107.8 (3.0)         103.0 (3.1)         92.6 (3.6)°           FEV <sub>1</sub> /FVC <sup>5</sup> 73         80.0 (1.0)         79.3 (1.0)         81.1 (1.2)           TLC <sup>5</sup> 72         80.0 (1.0)         79.3 (1.0)         81.1 (1.2)           TLC <sup>5</sup> 72         100.0 (2.8)         80.4 (3.1)° *           Litres         5.95 (0.23)         5.53 (0.24)         5.31 (0.26)           % predicted         92.6 (2.7)         90.7 (2.8)         80.4 (3.1)° *           Litres         23.23 (0.97)	*					0.422
Respiratory support         Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC*         73						0.195
Ventimask         76         8 (28)         25 (93)         21 (100)           HFNC         75         0 (0)         1 (4)         8 (38)           NIV or CPAP         75         0 (0)         0 (0)         11 (52)           Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC5         73			- (-)	- ()	_ ()	
HFNC 75 0 (0) 1 (4) 8 (38)  NIV or CPAP 75 0 (0) 0 (0) 11 (52)  Orotracheal Intubation 68 0 (0) 0 (0) 5 (25)  FVC\$ 73  Litres 4.23 (0.18) 3.77 (0.18) 3.68 (0.21)  % predicted 119.6 (3.3) 104.5 (3.4) 92.0 (3.9)°  FEV_1\$ 73  Litres 3.36 (0.14) 3.00 (0.14) 2.98 (0.16)  % predicted 107.8 (3.0) 103.0 (3.1) 92.6 (3.6)°  FEV_1/FVC\$ 73  % 80.0 (1.0) 79.3 (1.0) 81.1 (1.2)  TLC\$ 72  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26)  % predicted 92.6 (2.7) 90.7 (2.8) 80.4 (3.1)° *  DLC_0\$ 73  Litres 23.23 (0.97) 21.05 (1.00) 18.69 (1.15)°  % predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)° *		76	8 (28)	25 (93)	21 (100)	< 0.001
NIV or CPAP 75 0 (0) 0 (0) 11 (52) Orotracheal Intubation 68 0 (0) 0 (0) 5 (25) FVC <sup>5</sup> 73 Litres 4.23 (0.18) 3.77 (0.18) 3.68 (0.21) % predicted 119.6 (3.3) 104.5 (3.4) 92.0 (3.9)° FEV <sub>1</sub> <sup>\$</sup> 73 Litres 3.36 (0.14) 3.00 (0.14) 2.98 (0.16) % predicted 107.8 (3.0) 103.0 (3.1) 92.6 (3.6)° FEV <sub>1</sub> /FVC <sup>\$</sup> 73 % 80.0 (1.0) 79.3 (1.0) 81.1 (1.2) TLC <sup>\$\$</sup> 72 Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26) % predicted 92.6 (2.7) 90.7 (2.8) 80.4 (3.1)° # DL <sub>CO</sub> <sup>\$\$</sup> 73 Litres 23.23 (0.97) 21.05 (1.00) 18.69 (1.15)° % predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)° #						< 0.001
Orotracheal Intubation         68         0 (0)         0 (0)         5 (25)           FVC <sup>5</sup> 73           Litres         4.23 (0.18)         3.77 (0.18)         3.68 (0.21)           % predicted         119.6 (3.3)         104.5 (3.4)         92.0 (3.9)°           FEV <sub>1</sub> <sup>5</sup> 73						< 0.001
FVC <sup>§</sup> 73         Litres       4.23 (0.18)       3.77 (0.18)       3.68 (0.21)         % predicted       119.6 (3.3)       104.5 (3.4)       92.0 (3.9)°         FEV <sub>1</sub> <sup>§</sup> 73       73       73       74       74       74       74       75						0.002
Litres 4.23 (0.18) 3.77 (0.18) 3.68 (0.21) % predicted 119.6 (3.3) 104.5 (3.4) 92.0 (3.9)°  FEV <sub>1</sub> § 73  Litres 3.36 (0.14) 3.00 (0.14) 2.98 (0.16) % predicted 107.8 (3.0) 103.0 (3.1) 92.6 (3.6)°  FEV <sub>1</sub> /FVC§ 73  % 80.0 (1.0) 79.3 (1.0) 81.1 (1.2)  TLC§ 72  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26) % predicted 92.6 (2.7) 90.7 (2.8) 80.4 (3.1)° #  DL <sub>CO</sub> § 73  Litres 23.23 (0.97) 21.05 (1.00) 18.69 (1.15)° % predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)° #			5 (5)	o (e)	3 (23)	0.002
% predicted       119.6 (3.3)       104.5 (3.4)       92.0 (3.9)°         FEV <sub>1</sub> §       73           Litres       3.36 (0.14)       3.00 (0.14)       2.98 (0.16)         % predicted       107.8 (3.0)       103.0 (3.1)       92.6 (3.6)°         FEV <sub>1</sub> /FVC§       73           % (3.0)       79.3 (1.0)       81.1 (1.2)         TLC§       72           Litres       5.95 (0.23)       5.53 (0.24)       5.31 (0.26)         % predicted       92.6 (2.7)       90.7 (2.8)       80.4 (3.1)° *         DL <sub>CO</sub> §       73           Litres       23.23 (0.97)       21.05 (1.00)       18.69 (1.15)°         % predicted       82.7 (2.7)       80.6 (2.8)       64.9 (3.2)° *		, 3	4 23 (0 18)	3 77 (0 18)	3.68 (0.21)	0.099
FEV <sub>1</sub> §       73         Litres       3.36 (0.14)       3.00 (0.14)       2.98 (0.16)         % predicted       107.8 (3.0)       103.0 (3.1)       92.6 (3.6)°         FEV <sub>1</sub> /FVC§       73       72       80.0 (1.0)       79.3 (1.0)       81.1 (1.2)         TLC§       72       10.26						0.005
Litres 3.36 (0.14) 3.00 (0.14) 2.98 (0.16) % predicted 107.8 (3.0) 103.0 (3.1) 92.6 (3.6)°  FEV <sub>1</sub> /FVC <sup>§</sup> 73 % 80.0 (1.0) 79.3 (1.0) 81.1 (1.2)  TLC <sup>§</sup> 72 Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26) % predicted 92.6 (2.7) 90.7 (2.8) 80.4 (3.1)° #  DL <sub>CO</sub> <sup>§</sup> 73 Litres 23.23 (0.97) 21.05 (1.00) 18.69 (1.15)° % predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)° #		73	113.0 (3.3)	101.5 (5.1)	32.0 (3.3)	0.003
% predicted       107.8 (3.0)       103.0 (3.1)       92.6 (3.6)°         FEV <sub>1</sub> /FVC <sup>§</sup> 73       80.0 (1.0)       79.3 (1.0)       81.1 (1.2)         TLC <sup>§</sup> 72       72       72       72       73.1 (0.26)       90.7 (2.8)       5.31 (0.26)       80.4 (3.1)° #         % predicted       92.6 (2.7)       90.7 (2.8)       80.4 (3.1)° #       90.7 (2.8)       80.4 (3.1)° #         DL <sub>CO</sub> <sup>§</sup> 73       73       73       73       73       74       7		73	3 36 (0 14)	3 00 (0 14)	2 98 (0 16)	0.110
FEV1/FVC <sup>§</sup> 73         %       80.0 (1.0)       79.3 (1.0)       81.1 (1.2)         TLC <sup>§</sup> 72         Litres       5.95 (0.23)       5.53 (0.24)       5.31 (0.26)         % predicted       92.6 (2.7)       90.7 (2.8)       80.4 (3.1)° *         DL <sub>CO</sub> <sup>§</sup> 73         Litres       23.23 (0.97)       21.05 (1.00)       18.69 (1.15)°         % predicted       82.7 (2.7)       80.6 (2.8)       64.9 (3.2)° *						0.009
%     80.0 (1.0)     79.3 (1.0)     81.1 (1.2)       TLC <sup>5</sup> 72       Litres     5.95 (0.23)     5.53 (0.24)     5.31 (0.26)       % predicted     92.6 (2.7)     90.7 (2.8)     80.4 (3.1)° #       DL <sub>CO</sub> <sup>5</sup> 73       Litres     23.23 (0.97)     21.05 (1.00)     18.69 (1.15)°       % predicted     82.7 (2.7)     80.6 (2.8)     64.9 (3.2)° #		73	107.0 (5.0)	103.0 (3.1)	J2.0 (J.0)	0.000
TLC <sup>§</sup> 72  Litres 5.95 (0.23) 5.53 (0.24) 5.31 (0.26) % predicted 92.6 (2.7) 90.7 (2.8) 80.4 (3.1)° #  DL <sub>CO</sub> <sup>§</sup> 73  Litres 23.23 (0.97) 21.05 (1.00) 18.69 (1.15)° % predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)° #	,	73	80.0 (1.0)	70 3 (1 0)	81 1 (1 2)	0.536
Litres     5.95 (0.23)     5.53 (0.24)     5.31 (0.26)       % predicted     92.6 (2.7)     90.7 (2.8)     80.4 (3.1)° #       DL <sub>CO</sub> <sup>§</sup> 73       Litres     23.23 (0.97)     21.05 (1.00)     18.69 (1.15)°       % predicted     82.7 (2.7)     80.6 (2.8)     64.9 (3.2)° #		72	00.0 (1.0)	7 7.5 (1.0)	01.1 (1.2)	0.550
% predicted     92.6 (2.7)     90.7 (2.8)     80.4 (3.1)° #       DL <sub>CO</sub> §     73       Litres     23.23 (0.97)     21.05 (1.00)     18.69 (1.15)°       % predicted     82.7 (2.7)     80.6 (2.8)     64.9 (3.2)° #		72	5.05 (0.23)	5 53 (0 24)	5 31 (0 26)	0.191
DL <sub>CO</sub> §     73       Litres     23.23 (0.97)     21.05 (1.00)     18.69 (1.15)°       % predicted     82.7 (2.7)     80.6 (2.8)     64.9 (3.2)° #						0.191
Litres 23.23 (0.97) 21.05 (1.00) 18.69 (1.15)° % predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)° <sup>#</sup>		73	JZ.U (Z./)	JU.1 (Z.U)	υυ. <del>¬</del> (υ.1)	0.012
% predicted 82.7 (2.7) 80.6 (2.8) 64.9 (3.2)° <sup>#</sup>		13	23 23 (0.07)	21.05 (1.00)	18 60 (1 15\0	0.017
						< 0.0017
	% predicted RV <sup>§</sup>	72	UZ./ (Z./)	00.0 (2.0)	U+.7 (J.Z)	< 0.001
Litres 1.58 (0.48)* 1.58 (0.44)* 1.48 (0.71)*		12	1 50 (0 40)*	1 50 (0 44)*	1 40 (0 71)*	0.362

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Table 3 (continued)

	N available observations	$p/F \ge 300 \ (N = 28)$	$p/F < 300 \ge 200 \ (n = 27)$	p/F < 200 (n = 21)	<i>p</i> value
% predicted		77.6 (3.6)	73.8 (3.8)	70.8 (4.2)	0.498
ABG <sup>§</sup>	74				
pO <sub>2</sub> (mmHg)		93.3 (1.6)	92.7 (1.5)	87.8 (1.8)	0.053
pCO <sub>2</sub> (mmHg)		39.2 (0.6)	38.3 (0.6)	38.9 (0.7)	0.467
рН		7.41 (0.03)*	7.41 (0.04)*	7.42 (0.03)*	0.995
d(A-a) (mmHg)		10.1 (1.4)	12.3 (1.3)	16.6 (1.6)°	0.011
6MWT <sup>§</sup>	72				
SpO <sub>2</sub> basal		98.0 (1.0)*	97.0 (2.0)*	97.0 (2.0)*	0.121
SpO <sub>2</sub> nadir		96.5 (3.0)*	95.0 (3.0)*	94.0 (4.0)*°	0.005
Meters		560 (130)*	500 (95)*°	480 (140)*°	0.004
Dyspnoea VAS (mm) <sup>§</sup>					
Before	75	3.5 (2.1)	6.1 (2.1)	1.5 (2.5)	0.359
During	75	44.1 (5.4)	45.1 (5.5)	60.0 (6.4)	0.128
Follow-up	75	14.1 (3.5)	22.5 (3.6)	25.9 (4.1)	0.077
Cough VAS (mm)§					
Before	75	0.4 (1.3)	4.8 (1.4)	1.1 (1.6)	0.055
During	75	37.0 (5.8)	35.1 (5.9)	31.5 (6.9)	0.830
Follow-up	75	2.9 (2.3)	8.8 (2.3)	7.7 (2.7)	0.171

Data are presented as counts (%) or means (SD) or medians with interquartile range (IQR) for non-normally distributed variables (indicated with \*). BMI: Body Mass Index; ICU: Intensive Care Unit; COPD: Chronic Obstructive Pulmonary Disease; IL-6: Interleukin; HFNC: High Flow Nasal Cannula; NIV: Non-Invasive Ventilation; CPAP: Continue Positive Airway Pressure; VAS: Visual Analogic Scale.  $^{5}$ Pulmonary Function, ABG, 6MWT parameters, Dyspnoea Visual Anlogic Scale (VAS) and Cough VAS are reported as estimated means (Standard Error) after adjustment for age used as covariate in the ANOVA model.  $^{\circ}$ p value < 0.05 versus p/F  $\geq$  300 group.  $^{\#}$ p value < 0.05 versus p/F  $\geq$  300 group

We identified a persistence of dyspnoea in the overall study population, a finding consistent with a study by Wong and coworkers, which reported dyspnoea in half of 78 COVID-19 patients after hospital discharge [13].

In order to explore the impact of disease severity on residual respiratory abnormalities, patients were stratified into three groups, according to levels of respiratory failure during hospitalization. No significant differences were observed regarding therapies, except for enoxaparin and anti-IL-6 drugs, administered more frequently in the severe group. The limited use of corticosteroids was likely due to the fact that evidence for dexamethasone use appeared towards the end of study completion [14]. We cannot exclude that a more extensive use of corticosteroids would have changed our findings.

Patients with mild and moderate disease had normal lung volumes. In contrast, a mild reduction in RV was found in the severe hypoxemia group. Whether this finding results by altered lung compliance in this group [15] remain to be determined. Moreover, TLC was at the lower limit of normal in the severe group: this finding suggests a link between severity of COVID-19 pneumonia and reduction in lung volumes. Whether such abnormalities were due to the presence of fibrotic sequelae after acute interstitial pneumonia could not be determined, since our cohort did not undergo a chest CT scan

at the time of the study visit. Moreover, we identified normal DLco values in the mild and the moderate hypoxemia groups and reduced values in the severe hypoxemia group. This could reflect the degree of microvascular and epithelial damage, likely to be more consistent in the severe cases [16]. Patients recovering from ARDS from any cause may have persistent functional impairment one year after hospital discharge [17]. Therefore, these findings might not be COVID-19-specific.

Our study had several limitations. CT imaging was not available at the time of study visit: as such, the relationships between functional impairment and residual fibrotic changes remain unknown. The follow-up time in this study is short, and further studies are warranted to clarify whether respiratory abnormalities persist in the longer term. The use of p/F ratio to classify COVID-19 severity is not ideal as it may not be reliable in non-intubated patients [18]. Finally, the levels of dyspnoea and cough before and during hospitalization were collected at the time of the follow-up clinical evaluation: they may therefore not measure accurately the severity of symptoms at those timepoints.

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# **Conclusion**

Severe COVID-19 pneumonia may result in respiratory abnormalities and a reduction in exercise tolerance, which can be present at least one month after hospital discharge. Moreover, a low p/F ratio during the acute phase of the infection seems to correlate with a residual reduction of lung volumes, and residual reduction in DLCO. Further follow up is required to determine the degree of pulmonary and exercise impairment following hospitalization for COVID-19 pneumonia.

#### **Abbreviations**

SARS: Severe acute respiratory syndrome; CRP: C-reactive protein; ARDS: Acute distress respiratory syndrome; ICU: Intensive Care Unit; 6MWD: Six-minute walk distance; 6MWT: Six-minute walk test; p/F:  $PaO_2/FiO_2$  ratio; ABG: Arterial blood gas analysis; PFT: Pulmonary function tests; DLco: Diffusing capacity of the lung for carbon monoxide;  $SpO_2$ : Percutaneous oxygen saturation; HR: Heart rate; VAS: Visual Analog Scale; COPD: Chronic Obstructive Pulmonary Disease; NIV: Non-Invasive Ventilation; CPAP: Continuous Positive Airway Pressure; TLC: Total lung capacity; FVC: Forced vital capacity; FEV-1: Forced expiratory in the first second; RV: Residual volume;  $pO_2$ : Partial pressure of oxygen; d(A-a): Alveolar-arteriosus oxygen gradient.

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# Authors' contributions

Conceptualisation of the study: FL, AC, GS, LR. Data collection: FL, AC, CP, ML. Statistical Analysis: GS. Writing of study manuscript: FL, AC, GS, LR. Review of study manuscript: BI, FV, LR, GS. Study supervision: LR, GS. All authors read and approved the final manuscript.

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#### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

# **Declarations**

# Ethics approval and consent to participate

The study was reviewed and received approval by the ethics committee of Fondazione Policlinico Universitario "A. Gemelli" IRCCS (Approval Number 0024185/20).

#### Consent for publication

Written informed consent was obtained from all participants. The study protocol was approved by the Institutional Review Board of the Università Cattolica del Sacro Cuore (Rome, Italy) (Approval Number 0024185/20).

#### Competing interests

Dr. Lombardi has nothing to disclose; Dr. Calabrese has nothing to disclose; Dr. lovene reports personal fees from Boehringer Ingelheim, Menarini, outside the submitted work; Dr. Pierandrei has nothing to disclose; Dr. Lerede has nothing to disclose; Dr. Varone reports personal fees from Boehringer Ingelheim, Roche, outside the submitted work; Dr. Richeldi reports personal fees from FibroGen, Boehringer Ingelheim, Roche, Biogen, Veracyte, Promedior, outside the submitted work; Dr. Sgalla reports personal fees from Boehringer Ingelheim, outside the submitted work.

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