

# Residual Respiratory Impairment After COVID-19 Pneumonia

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## Research Article

**Keywords:** Covid-19, respiratory, patients, pneumonia

**Posted Date:** January 25th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-142958/v1>

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**Version of Record:** A version of this preprint was published at BMC Pulmonary Medicine on July 17th, 2021. See the published version at <https://doi.org/10.1186/s12890-021-01594-4>.

# Abstract

**Introduction:** the Novel Coronavirus Disease (Covid-19) can infect the respiratory tract, causing mild to deadly respiratory impairment. It is still unknown whether patients recovering from Covid-19 will develop respiratory sequelae. This study aims to evaluate the respiratory and functional condition of Covid-19 recovered patients, stratified according to their worst p/F during hospitalization for Covid-19.

**Method:** 86 Covid-19 recovered subjects performed, after 39 days on average, physical examination and arterial blood gas (ABG) examination, pulmonary function tests (PFTs) with diffusing capacity of the lung for carbon monoxide (DLco), and six-minute walk test (6MWT). Subjects also quantified their dyspnoea and cough using a visual analogic scale (VAS) at three-time points: previously than COVID infection, during COVID hospitalization, and currently. The 76 subjects with reliable ABG during the hospitalization were stratified in three groups according to their worst PaO<sub>2</sub>/FiO<sub>2</sub> ratio (p/F): "mild": p/F>300 (n = 38); "moderate": 200<p/F<300 (n = 30), "severe" p/F < 200 (n = 20).

**Results:** In this cohort, Covid-19 recovered subjects still reported significant residual dyspnoea at the visit time. The severe subjects group showed a lower Total Lung Capacity (TLC), a lower DLco, and a worse 6MWT performance.

**Conclusion:** After Covid-19, respiratory and functional impairments may persist. These impairments seem to be more severe as much as minor was the patient worst p/F during hospitalization. These patients should receive a strict follow-up.

## Introduction

In December 2019, a novel coronavirus (SARS-CoV2) able to infect the respiratory tract in humans emerged in Wuhan (China). To date, the World Health Organization still considers SARS-CoV2 pandemic diffused worldwide, with over 32 million cases and more than 991.000 deaths being confirmed (1).

The most dangerous complication of SARS-CoV2 infection is a severe acute respiratory syndrome (SARS) in susceptible patients (2). In particular, older patients with respiratory, cardiac, and/or metabolic comorbidities are likely to have a worse outcome. (3) Hypertension and diabetes mellitus seem to be the most frequent comorbidities in Wuhan Covid-19 patients (4).

Several studies pictured a range of clinical and laboratoristic features that are common among hospitalized patients, such as dry cough or high levels of C-reactive protein (CRP). Respiratory symptoms frequently emerge from two to seven days after the onset of infection and usually include a non-productive cough and dyspnoea at rest. (5) Dyspnoea is a common symptom that may be the primary manifestation of lung diseases as viral pneumonia (6) but the prevalence and the severity of this symptom during Covid-19 are still unclear.

Furthermore, there is a lack of evidence about the severity, the prevalence, and the persistence of respiratory symptoms and functional impairment in Covid-19-recovered patients (7).

Other viruses are able to induce interstitial pneumonia and acute distress respiratory syndrome (ARDS). In a 2002 study, survivors from SARS caused by Coronavirus SARS-CoV, showed a reduced exercise tolerance, without significant difference between the patients that were or not admitted to the Intensive Care Unit (ICU) (8).

In patients recovered from SARS with ARDS, a complete restoration of lung volumes and six-minute walk distance (6MWD) to normal values was observed in 3–12 months after discharge, with no significant differences between patients that underwent mechanical ventilation and those who did not, according to a prospective study (9).

A similar study on 9 patients who survived ARDS due to H1N1 Influenza A pandemic showed that pulmonary function and 6MWD improved significantly in the first 3 months and reached normal values within 6 months in all the patients (10).

As such, it is pivotal to implement a follow-up strategy for patients clinically recovered from Covid-19 (11). We therefore aimed to investigate the prevalence of signs of respiratory impairment in a cohort of Covid-19 patients after hospital discharge, and to determine the relationship between the severity of pulmonary involvement and the degree of clinical and functional abnormalities.

## **Material And Methods**

### **Study population and groups**

In the post-Covid-19 outpatient program at Fondazione Policlinico Universitario “A. Gemelli” IRCCS, Rome, Italy, a multidisciplinary team evaluates the patients after Covid-19 recovery. All evaluated patients between April 22nd and May 27th 2020 were invited to participate to the study. Eligibility criteria were a previous hospitalization for Covid-19 and nasal and pharyngeal swabs negative for SARS-Cov-2 in the 48–72 hours preceding the evaluation at the outpatient clinic. Patients who did not have evidence of pneumonia at radiological examination at the time of the hospitalization were excluded.

Three groups were defined according to the severity of pulmonary disease as defined by the worst PaO<sub>2</sub>/FiO<sub>2</sub> ratio (p/F) found at arterial blood gas analysis (ABG) performed during hospitalization: mild (p/F ≥ 300), moderate (200 ≤ p/F < 300), and severe (p/F < 200). Such values, derived from Berlin Criteria for ARDS, were used in clinical practice to stratify the severity of the respiratory failure. (12)

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). All the clinical evaluations, exams, and procedures were performed in accordance with the Declaration of Helsinki

# Study assessments

All patients underwent physical examination, resting ABG, pulmonary function tests (PFT) with diffusing capacity of the lung for carbon monoxide (DLco), and 6MWT as part of the clinical follow-up program. 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 DLCO with the single breath-hold method (software Baires version 5.1 revision 3, Biomedin SRL, Padova, Italy). All lung function tests were performed according to the ATS/ERS guidelines (13, 14). The 6MWT was used to assess the sub-maximal level of functional capacity. After 6 minutes of rest, the subject was invited to walk along a 50 mt corridor as fast as possible for 6 minutes 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 minutes (or before, if the subject 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 subject was invited to sit and rest for 6 minutes. A drop in oxygen saturation equal or above 4% from baseline was considered as clinically significant.

A Visual Analog Scale (VAS) score was used to assess the impact of dyspnoea and cough at three different time points: the subjects were asked to indicate the severity of symptoms before hospital admission, during the hospital stay and at the moment of the clinical evaluation using a 100-mm linear scale where 0 mm represents absence and 100 mm represents the worst dyspnoea and cough ever. (15)

## Statistical analysis

Descriptive statistics such as means with standard deviations and frequencies or percentages were used for continuous and categorical variables. Dyspnea and cough VAS scores collected from the same patients were compared using ANOVA for repeated measures. Between-group comparisons of demographics and clinical data were performed using one-way ANOVA for continuous variables and the chi-square test for categorical variables. Estimated means of physiological variables were reported after adjustment by age, used as covariate in the ANOVA model. P-values less than 0.05 were considered statistically significant. SPSS (version 24, IBM, New York, NY, USA) was used to perform all statistical analyses.

## Results

### Characteristics of the study population

One hundred and fifty-seven patients 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 Covid-19 swab; eighteen were excluded due to the absence of radiological manifestations of Covid-19 pneumonia at the time of the hospitalization; finally, twenty-seven patients were excluded because they were therefore not

hospitalized, being directly discharged from the Emergency Department. As such, 86 patients were included in the analysis.

The characteristics of the study population are reported in Table 1. The post-Covid-19 clinical evaluation averagely occurred 36 (SD 11) days after discharge from the hospital. The mean hospitalization time was 15 (SD 9) days. Fifty-eight subjects (67%) were male and the mean age was 58 (SD 13) years. With regards to pulmonary comorbidities, 3 (4%) subjects had a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) and 9 (11%) had a diagnosis of asthma. Four (5%) subjects were current smokers at the time of hospital admission, 54 (56%) were former smokers and 33 (39) were non-smokers. Seventy patients (81%) had bilateral abnormalities on the chest X-ray or chest CT scan as defined by the presence of bilateral ground-glass opacities (GGO) with or without consolidated appearance, while 16 (19%) patients showed monolateral lung involvement. During hospital admission, 56 (65%) patients required supplemental oxygen therapy. Thirteen patients (15%) were treated with positive pressure devices (either Non-Invasive Ventilation-NIV or Continuous Positive Airway Pressure-CPAP) and 6 (7%) underwent orotracheal intubation. Overall, 15 patients (17%) were admitted to the intensive care unit .

Table 1

Characteristics of patients during the hospitalization for Covid-19. Data are presented as counts (%) or means (SD). 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;

	<b>N</b>	<b>N (%)</b>	<b>Mean (SD)</b>
Age (years)			58 (13)
Male		58 (67)	
BMI (Kg/m <sup>2</sup> )			26.7 (4.4)
P/F worst	76		260 (101)
Hospitalization time (days)	86		15 (9)
ICU time (days)	15		6 (5)
Day from discharge (days)	85		36 (11)
Smoking history	85	33 (39)	
Never smoker		4 (5)	
Smoker		48 (56)	
Former smoker			
Pulmonary disease history	86	3 (4)	
COPD		9 (11)	
Asthma			
Radiology (chest XR or CT)	86	51 (59)	
Chest CT performed		16 (19)	
Unilateral involvement		70 (81)	
Bilateral involvement			
Antiviral therapy	86	37 (43)	
Lopinavir/Ritonavir		53 (62)	
Darunavir/Ritonavir			
Anti-IL-6	86	31 (36)	
Enoxaparin	86	42 (49)	
Azithromycin	86	41 (48)	

	<b>N</b>	<b>N (%)</b>	<b>Mean (SD)</b>
Hydroxychloroquine	86	81 (94)	
Corticosteroids	86	6 (7)	
Respiratory support	86	56 (65)	
Ventimask	86	9 (11)	
HFNC	86	13 (15)	
NIV or CPAP	86	6 (7)	
Orotracheal Intubation			
ICU admission	86	15 (17)	
FVC	83		3.9 (1.1)
Litres	83		104.6 (18.5)
% predicted			
FEV-1	83		3.1 (0.9)
Litres	83		102.8 (16.0)
% predicted			
FEV-1/FVC	83		79.6 (5.8)
% predicted			
TLC	82		5.7 (1.3)
Litres	82		89.6 (14.6)
% predicted			
DLco	83		21.2 (6.8)
Litres	83		77.2 (16.5)
% predicted			
RV	82		1.7 (0.7)
Litres	82		74.8 (18.1)
% predicted			
RC/TLC	82		30 (11)
Ratio	82		79.0 (13.0)
% predicted			

	N	N (%)	Mean (SD)
ABG	84		91.4 (8.0)
pO <sub>2</sub> (mmHg)	84		38.8 (3.1)
pCO <sub>2</sub> (mmHg)	84		7.42 (0.02)
pH	84		13.0 (7.5)
d(A-a) (mmHg)			
6MWT	82		97 (1)
SpO <sub>2</sub> basal	82		95 (3)
SpO <sub>2</sub> nadir	82		517 (85)
Meters			

At pulmonary function testing (Fig. 1), our cohort showed overall preserved lung volumes, with a mean predicted total lung capacity (TLC) of 89.6% (SD 14.6) and a mean predicted forced vital capacity (FVC) of 104.6% (SD 18.5). The mean predicted volume during the forced expiratory in the first second (FEV-1) was 102.8% (SD 16.0). The mean predicted residual volume (RV) was the only respiratory volume reduced under the 5th percentile and was 74.8% (SD 18.1). Predicted DLco was mildly reduced (77.2%, SD 16.5).

At the ABG examination, the mean partial pressure of oxygen (pO<sub>2</sub>) was 91.4 mmHg (SD 8.0) and the mean alveolar-arteriosus oxygen gradient (d(A-a)) was 13.0 mmHg (SD 7.5).

The analysis of the trends of the VAS scores for respiratory symptoms experienced before, during, and after the hospitalization (Table 2, Fig. 2) showed that some degree of breathlessness persisted after Covid-19 recovery, as the levels of dyspnea were significantly higher if compared with baseline ( $p < 0.001$ ). On the other hand, patients did not report significant cough at the follow up.

Table 2

– Dyspnoea and cough in overall population in three-time points: previous, during the hospitalization, and at visit-time; VAS: Visual Analogic Scale. Data are reported as estimated means (Standard Error) after adjustment for age used as covariate in the ANOVA model. ° p value < 0.05 versus “previous”. # p value < 0.05 “Time visit”.

	Previous	During Covid-19 hospitalization	Time visit	p value
Dyspnoea VAS*	4.51 (1.31)	47.43 (3.24) °#	19.83 (2.07) #	< 0.001
Cough VAS*	2.88 (1.22)	31.83 (3.09) °#	5.49 (1.29)	< 0.001

## Comparison of study groups by p/F ratio

To further explore residual respiratory impairment after hospital discharge, the study population was divided into three groups based on the worst p/F values collected during the hospital stay: twenty-eight subjects (37%) were considered having “mild” disease for having  $p/F \geq 300$  (mean  $p/F = 359$ , SD: 43), twenty-seven (35%) had a “moderate” disease for having  $p/F < 300$  and  $\geq 200$  (mean  $p/F = 260$ , SD: 29) and twenty (28%) had a “severe” disease for having  $p/F < 200$  (mean  $p/F = 127$ , SD: 45). Seventy-six subjects (88%) had reliable data of ABG performed during the hospitalization and were therefore included in this analysis. Eight subjects did not perform any ABG, while 2 subjects had ABG performed but with unknown oxygen inhaled fraction and were therefore excluded.

The male prevalence, the smoking status and the history of COPD were not significantly different across the groups. 6 subjects (21%) of the “mild” group had a history of asthma that is statistically more frequent than in other groups ( $p = 0.017$ ). The “severe” group was significantly older (63.1 years,  $p = 0.014$ ) showed a longer hospitalization time (25.5 days,  $p < 0.001$ ), and received anti-IL-6 and enoxaparin therapy more frequently (respectively 81% and 95% of the “severe” group,  $p < 0.001$ ).

Estimated means of several parameters of pulmonary function were significantly lower in the “severe” patients as compared to the other groups, including percent predicted forced vital capacity (FVC) ( $p = 0.005$ ), forced expiratory volume in the first second (FEV-1) ( $p = 0.009$ ) and total lung capacity (TLC) ( $p = 0.012$ ) (Table 3). In particular, the “severe” group showed an estimated mean TLC of 80% (SE 3), indicating a mild restrictive impairment of pulmonary function after hospital discharge. DLco was also significantly reduced (65% of predicted, SE: 3) in the lower p/F group as compared to the other groups ( $p < 0.001$ ).

Table 3

Characteristics of patients stratified by pO<sub>2</sub>/FiO<sub>2</sub> during the hospitalization for Covid-19. Data are presented as counts (%) or means (SD). 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.\*Pulmonary Function, ABG, 6MWT parameters, Dyspnoea Visual Analogic Scale (VAS) and Cough VAS are reported as estimated means (Standard Error) after adjustment for age used as covariate in the ANOVA model. ° p value < 0.05 versus P/F ≥ 300 group. # p value < 0.05 versus 300 < P/F ≤ 200 group.

	N available observations	P/F ≥ 300 (N = 28)	300 < P/F ≤ 200 (n = 27)	P/F < 200 (n = 21)	p value
Age (years)	76	52.3 (14.0)	59.2 (12.2)	63.1 (11.9)	0.014
Sex	76	19 (68)	17 (63)	16 (76)	0.618
Male		9 (32)	10 (37)	5 (24)	
Female					
BMI (Kg/m <sup>2</sup> )	75	25.7 (5.1)	27.3 (3.9)	28.0 (4.3)	0.181
P/F worst	76	359 (43)	260 (29)	127 (45)	< 0.001
Hospitalization time (days)	76	10.5 (4.0)	15.4 (7.9)	25.5 (9.2)	< 0.001
ICU admission	76	0 (0)	1 (4)	13 (62)	< 0.001
ICU time (days)	14	0 (0)	4 (0)	6 (6)	0.681
Smoking history	75	10 (36)	9 (33)	10 (50)	0.595
Never smoker		1 (3)	2 (8)	0 (0)	
Smoker		17 (61)	16 (59)	10 (50)	
Former smoker					
Pulmonary disease history	76	0 (0)	2 (7)	0 (0)	0.155
COPD	76	6 (21)	1 (4)	0 (0)	0.017
Asthma					
Chest CT performed	76	15 (54)	17 (63)	13 (62)	0.745
Radiology (chest XR or CT)	76	11 (39)	3 (11)	0 (0)	0.001
Monolateral involvement		17 (61)	24 (89)	21 (100)	
Bilateral involvement					

	<b>N available observations</b>	<b>P/F ≥ 300 (N = 28)</b>	<b>300 &lt; P/F ≤ 200 (n = 27)</b>	<b>P/F &lt; 200 (n = 21)</b>	<b><i>p</i> value</b>
Antiviral therapy	75	12 (43)	9 (35)	13 (62)	0.165
Lopinavir/Ritonavir	76	14 (50)	19 (70)	13 (62)	0.300
Darunavir/Ritonavir					
Anti IL-6	76	2 (7)	10 (37)	17 (81)	< 0.001
Enoxaparin	76	8 (29)	11 (41)	20 (95)	< 0.001
Azithromycin	75	12 (43)	13 (50)	12 (57)	0.611
Hydroxychloroquine	76	27 (96)	25 (93)	21 (100)	0.422
Corticosteroids	74	0 (0)	3 (11)	2 (11)	0.195
Respiratory support	76	8 (28)	25 (93)	21 (100)	< 0.001
Ventimask	75	0 (0)	1 (4)	8 (38)	< 0.001
HFNC	75	0 (0)	0 (0)	11 (52)	< 0.001
NIV or CPAP	68	0 (0)	0 (0)	5 (25)	< 0.001
Orotracheal Intubation					0.002
FVC*	73	4.23 (0.18)	3.77 (0.18)	3.68 (0.21)	0.099
Litres		119.6 (3.3)	104.5 (3.4)	92.0 (3.9) <sup>°</sup>	0.005
% predicted					
FEV-1*	73	3.36 (0.14)	3.00 (0.14)	2.98 (0.16)	0.110
Litres		107.8 (3.0)	103.0 (3.1)	92.6 (3.6) <sup>°</sup>	0.009
% predicted					
FEV-1/FVC*	73	80.0 (1.0)	79.3 (1.0)	81.1 (1.2)	0.536
%					
TLC*	72	5.95 (0.23)	5.53 (0.24)	5.31 (0.26)	0.191
Litres		92.6 (2.7)	90.7 (2.8)	80.4 (3.1) <sup>° #</sup>	0.012
% predicted					

	<b>N available observations</b>	<b>P/F ≥ 300 (N = 28)</b>	<b>300 &lt; P/F ≤ 200 (n = 27)</b>	<b>P/F &lt; 200 (n = 21)</b>	<b>p value</b>
DLCO*	73	23.23 (0.97)	21.05 (1.00)	18.69 (1.15) <sup>°</sup>	0.017
Litres		82.7 (2.7)	80.6 (2.8)	64.9 (3.2) <sup>° #</sup>	< 0.001
% predicted					
RV*	72	1.86 (0.15)	1.59 (0.15)	1.58 (0.17)	0.362
Litres		77.6 (3.6)	73.8 (3.8)	70.8 (4.2)	0.498
% predicted					
ABG*	74	93.3 (1.6)	92.7 (1.5)	87.8 (1.8)	0.053
pO2 (mmHg)	74	39.2 (0.6)	38.3 (0.6)	38.9 (0.7)	0.467
pCO2 (mmHg)	74	7.42 (0.01)	7.42 (0.01)	7.42 (0.01)	0.995
pH	74	10.1 (1.4)	12.3 (1.3)	16.6 (1.6) <sup>°</sup>	0.011
d(A-a) (mmHg)					
6MWT*	72	97.3 (0.2)	96.7 (0.2)	96.7 (0.3)	0.121
SpO2 basal		96.0 (0.4)	94.6 (0.4)	93.8 (0.5) <sup>°</sup>	0.005
SpO2 nadir		552 (13)	491 (14) <sup>°</sup>	497 (16) <sup>°</sup>	0.004
Meters					
Dyspnoea VAS*	75	3.5 (2.1)	6.1 (2.1)	1.5 (2.5)	0.359
Before Covid-19 (mm)	75	44.1 (5.4)	45.1 (5.5)	60.0 (6.4)	0.128
During Covid-19 (mm)	75	14.1 (3.5)	22.5 (3.6)	25.9 (4.1)	0.077
Visit Time (mm)					
Cough VAS*	75	0.4 (1.3)	4.8 (1.4)	1.1 (1.6)	0.055
Before Covid-19 (mm)	75	37.0 (5.8)	35.1 (5.9)	31.5 (6.9)	0.830
During Covid-19 (mm)	75	2.9 (2.3)	8.8 (2.3)	7.7 (2.7)	0.171
Visit Time (mm)					

The estimated mean difference between alveolar and arterial oxygen pressure at the ABG examination increased progressively across study groups, ranging from 10.1 mmHg (SE 1.4) in the “mild” group and 16.6 mmHg (SE 1.6) in the “severe” group (p = 0.011).

The “mild” group showed a higher tolerance to exercise as compared to the other groups. In particular, there was a significant estimated mean difference in 6MWD (+ 55 meters compared to the “severe” group,  $p = 0.004$ ) and in SpO<sub>2</sub> nadir (+ 2.2% compared to the “severe” group,  $p = 0.005$ ).

There are not significant differences about dyspnoea and cough among the three group.

## Discussion

In this study we investigated, we believe for the first time in a European cohort, a wide range of respiratory parameters in patients who were followed up after recovering from Covid-19 Pneumonia. Our findings suggest that respiratory abnormalities may persist over time in those who experienced a more severe disease during hospitalization.

Patients with Covid – 19 may present with varying clinical severity, ranging from asymptomatic infection to severe respiratory failure. In hospitalised patients, a common radiological feature is represented by monolateral or bilateral interstitial pneumonia (16). While the spectrum of clinical manifestations of the acute phase of Covid-19 pneumonia has been elucidated (7), whether patients recovering from the disease may develop lasting respiratory abnormalities is still largely unknown. Mo and colleagues s (17) studied the lung volumes and the DLco in a Chinese cohort of 110 patients at the time of hospital discharge. In this study, patients were stratified according to clinical criteria, such as the oxygen therapy need and radiological features. ICU admission or ventilatory support represented exclusion criteria. Our study expands Mo’s findings showing that some degree of residual functional impairment persists at the short-term follow up, especially in those patients who experienced more severe respiratory involvement during the hospital stay. Notably, we also investigated tolerance to exercise demonstrating that it can be also significantly affected after recovery from Covid-19.

The first important finding of our study is that in the overall study population, there was a significant persistence of dyspnoea after recovering. This data agrees with a study by Wong and a colleagues that found dyspnoea in 50% of Covid-19 patients performing questionnaires after clinical recovery (18). On the other hand, dry cough - that was reported as significant during the hospitalization decreased after discharge to a level comparable with baseline.

In the overall study population, we did not find any lung function abnormalities except for a mild reduction of DLco (77.2% of predicted). Also, the average results from ABG examination and 6MWT were within normal value ranges. .

In order to explore the impact of disease severity on residual respiratory abnormalities, patients were stratified according to the severity of respiratory failure experienced during hospitalization.

No significant differences were observed with regards to the therapy administered to the three groups, except for enoxaparin and Anti-IL6 drugs, more frequently used in the “severe” patients. The use of enoxaparin could be explained by the need for anticoagulant prophylaxis in the more severe patients with

reduced mobility during hospitalization. The unfrequent administration of steroids could be due to the evidence of the dexamethasone effectiveness for the treatment of Covid-19 is later than our enrolling time. (19)

Mild and moderate subjects had normal lung volumes but a mild reduction of RV was found also in the severe group. This is a common abnormality of unknown clinical relevance that could be explained by higher lung compliance described by Gattinoni and coworkers (20). Despite forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV-1) were still within normal value ranges in the severe group,, they were significantly lower as compared to the other groups. Notably, TLC was at the lower limit of normality (80% of predicted). Such findings suggest a link between the severity of Covid-19 pneumonia and a lasting reduction in pulmonary 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 CT scan of the chest at the time of the follow-up evaluation. Moreover, we found a barely normal DLco in mild and moderate groups and a mild-to-moderate reduction in the severe group. We hypothesize that this could reflect the degree of microvascular and epithelial damage, that may be more consistent in severe cases. Clarifying the relative contribution of interstitial and microvascular involvement in future studies could be pivotal to better understand the course of Covid infection. .

The difference between alveolar and arterial partial pressure of oxygen at the follow up ABG examination progressively increased in patients with history of more severe disease, who also performed worse during the 6MWT, showing a lower resting SpO<sub>2</sub>, a lower nadir SpO<sub>2</sub>, and a shorter walked distance. These findings together further suggest that severe Covid-19 may produce persistent respiratory abnormalities, including a significant reduction in exercise tolerance. Moreover, the worst p/F during the acute phase of the infection seems able to predict a reduction of lung volume, DLCO, and worse respiratory performance status.

Indeed, based on the short follow up of our cohort it is still not possible to foresee if these abnormalities will last in the longer term or a “restitution ad integrum” will occur at some point. Nevertheless, our findings suggest that patients with a more aggressive disease should be strictly followed up for recognizing any persistent respiratory impairment that should be properly managed.

Our findings on DLco impairment and the slight reduction in lung volumes data in the first months after recovery are consistent with those reported on other ARDS-inducing respiratory infections such as SARS. (21). Patients recovering from ARDS from any cause showed persistent functional impairment during a one year follow up after hospital discharge, primarily concerning DLco and 6MWT (22). Similar to previous ARDS experiences, the ARDS Covid-19 patients may present long term lung sequelae. That could be a common evolution of a viral pneumonia and not a specific complication of Covid-19.

The first and most important limitation of our study is the lack of CT imaging at the time of the follow-up, as such the relationships between functional impairment and residual fibrotic alterations in the lungs of these patients remain unclear. Second, the follow-up time was relatively short, and it is unclear whether respiratory abnormalities may persist in the longer term. Third, we are not aware of the pulmonary

function of these patients before hospitalization for Covid-19, As such it is not possible to know if there were previous respiratory abnormalities. However, due to the low prevalence of chronic respiratory conditions in our cohort, it seems reasonable to suppose that most patients are unlikely to present previous respiratory impairment. Finally, the levels of dyspnoea and cough before and during hospitalization were collected at the time of the follow-up clinical evaluation, as such, they may not reflect the actual severity of symptoms of the patients at that time.

## Conclusion

In conclusion, in our study we demonstrated that Covid-19 can cause respiratory abnormalities, including reduction of lung volumes and impairment of gas exchange and exercise tolerance, that may persist up to a month after hospital discharge. In particular, such abnormalities are more evident in patients with a lower p/F ratio during the acute phase of Covid-19, indicating a link between disease severity and the likelihood of residual pulmonary impairment. Further research is warranted to determine whether this functional impairment may be long-lasting or even progressive as a result of residual lung fibrosis, as well as to clarify whether any treatment should be considered in these patients.

## List Of 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<sub>2</sub>/FiO<sub>2</sub> ratio

ABG: arterial blood gas analysis

PFT: pulmonary function tests

DLco: diffusing capacity of the lung for carbon monoxide

SpO<sub>2</sub>: 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<sub>2</sub>: partial pressure of oxygen

d(A-a): alveolar-arteriosus oxygen gradient

## Declarations

### **Ethics approval and consent to participate:**

The study was reviewed and received approval by the local ethics committee of Fondazione Policlinico Universitario "A. Gemelli" IRCCS in Rome.

### **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).

### **Availability of data and materials:**

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

### **Availability of data and materials:**

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

### **Funding:**

No external funding was provided for the conduction of this study.

### **Authors' contributions**

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

## Acknowledgments

Gemelli Against COVID-19 Post-Acute Care Study Group is composed by: Francesco Landi, Elisa Gremese, Roberto Bernabei, Massimo Fantoni, Antonio Gasbarrini, Carlo Romano Settanni, Francesca Benvenuto, Giulia Bramato, Angelo Carfi, Francesca Ciciarello, Maria Rita Lo Monaco, Anna Maria Martone, Emanuele Marzetti, Carmen Napolitano, Francesco Pagano, Sara Rocchi, Elisabetta Rota, Andrea Salerno, Matteo Tosato, Marcello Tritto, Riccardo Calvani, Lucio Catalano, Anna Picca, Giulia Savera, Enrica Tamburrini, Alberto Borghetti, Simona Di Gianbenedetto, Rita Murri, Antonella Cingolani, Giulio Ventura, Eleonora Taddei, Davide Moschese, Arturo Ciccullo, Leonardo Stella, Giovanni Addolorato, Francesco Franceschi, Gertrude Mingrone, Maria Assunta Zocco, Maurizio Sanguinetti, Paola Cattani, Simona Marchetti, Alessandro Bizzarro, Alessandra Lauria, Stanislao Rizzo, Maria Cristina Savastano, Gloria Gambini, Maria Grazia Cozzupoli, Carola Culiarsi, Giulio Cesare Passali, Gaetano Paludetti, Jacopo Galli, Fabrizio Crudo, Giovanni Di Cintio, Ylenia Longobardi, Laura Tricarico, Mariaconsiglia Santantonio, Danilo Buonsenso, Piero Valentini, Davide Pata, Davide Sinatti, Cristina. De Rose, Luca Richeldi, Francesco Lombardi, Aangelo Calabrese, Gabriele Sani, Delfina Janiri, Giulia Giuseppin, Marzia Molinaro, Marco Modica, Luigi Natale, Anna Rita Larici, Riccardo Marano, Annamaria Paglionico, Luca Petricca, Laura Gigante, Gerlando Natalello, Anna Laura. Fedele, Marco Maria Lizzio, Angelo Santoliquido, Luca Santoro, Antonio Nesci & Valentina Popolla

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# Figures

## Pulmonary function tests

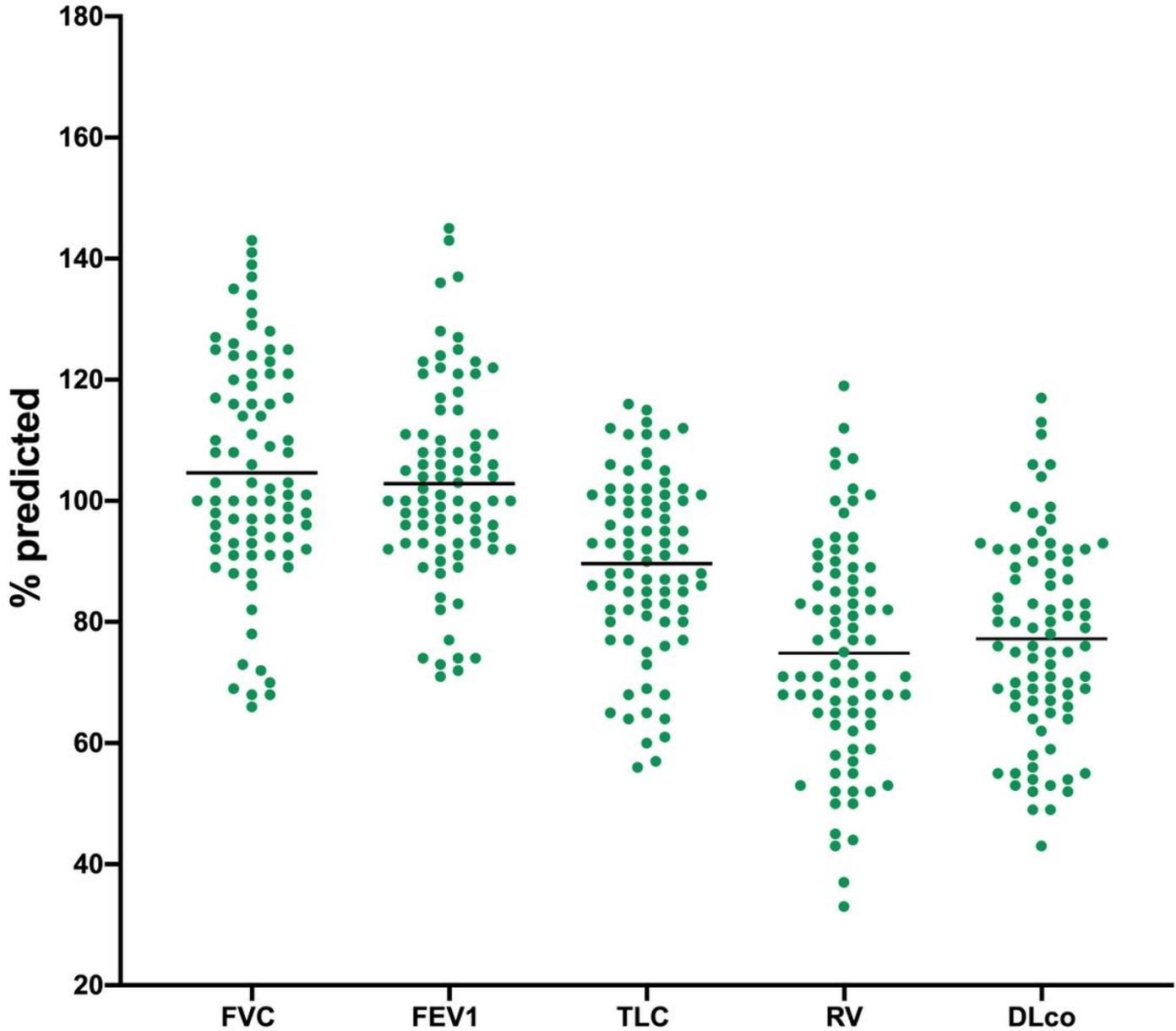


Figure 1

Overall cohort pulmonary 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)

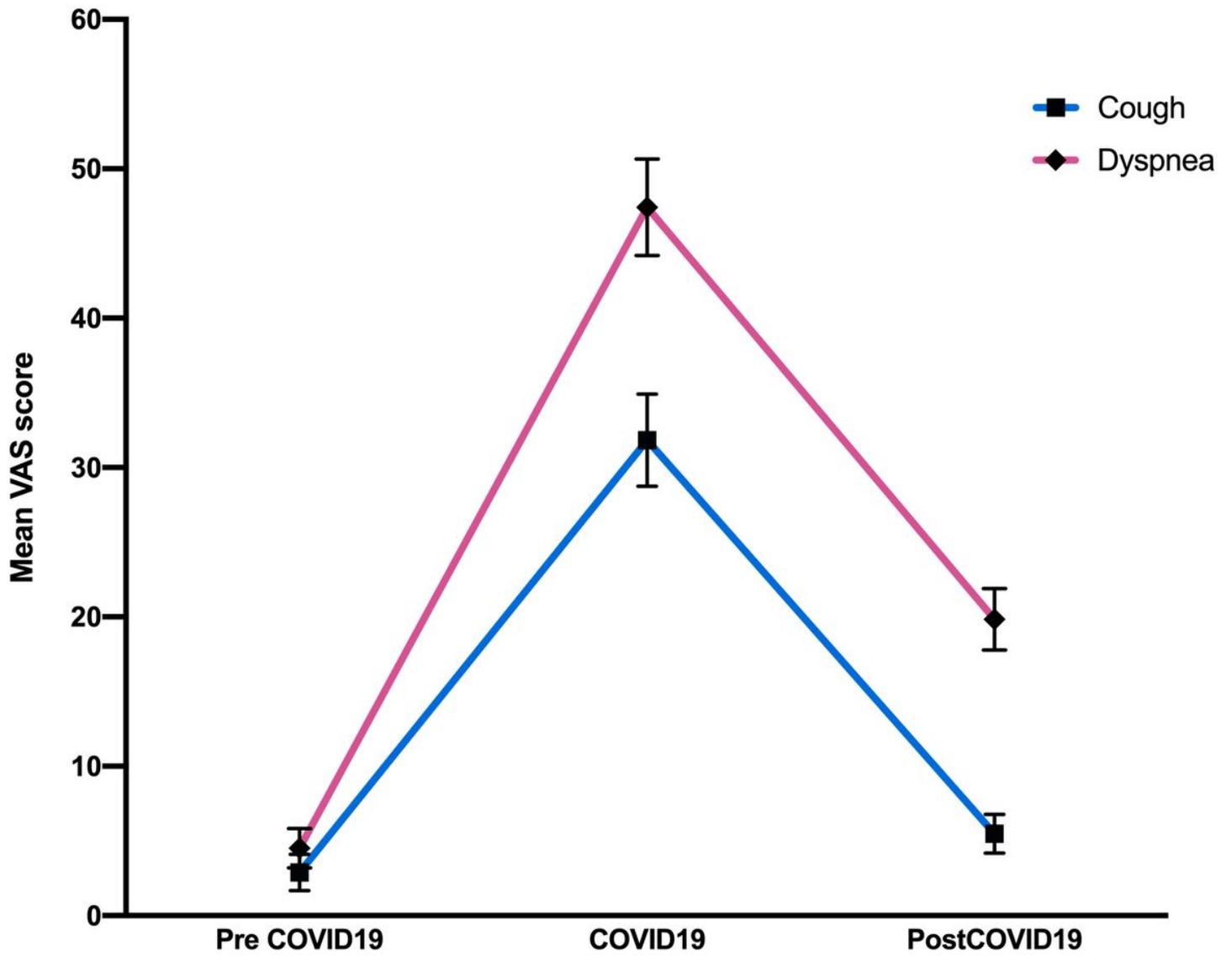


Figure 2

Overall cohort trends of the VAS scores for dyspnoea and cough before Covid-19, during the hospitalization, and at visit time.