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Early View

COVID-19 after 6-months from hospital discharge: pulmonary function impairment and its heterogeneity

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COVID-19 after 6-months from hospital discharge: pulmonary function impairment and its heterogeneity.

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To the Editor:

Until now, reports about pulmonary function in previously hospitalized subjects for COVID-19 are at discharge (1) or at 3-4 months (2-4). The first study at 6 months is that of Huang et al. (5), enrolling 1733 discharged subjects, 349 of them underwent a pulmonary function study.

We consecutively enrolled from 15 March to 15 June 2020, during the first pandemic wave in Italy, 135 discharged COVID-19 patients, aged ≤80 yrs, in a follow-up study (Assessment of Cardiac and pulmonary consequences in patients recOvered from coviD-19 infection, the ACOD study) approved by the regional ethics committee (CER Liguria), aiming to collect data at 6 and 12 months after discharge from Hospitals (Santa Corona, Santa Maria di Misericordia, San Paolo) serving an area of 280.000 habitants.

The present research letter reports timely preliminary data on respiratory function at 6 months from discharge.

Written informed consent was collected from any subject. Spirometry and pulmonary diffusion capacity test were performed following the American Thoracic Society/European Respiratory Society statements (6-7) with a Vyntus Body Plethysmograph (Vyaire Medical GmbH, Hoechberg, Germany). To minimise cross-infections, diffusing capacity of the lung for carbon monoxide (D_{LCO}) was measured by the single-breath method with Diffusion SB RT Module for Body Vyntus (Vyaire Medical, GmbH, Hoechberg, Germany). Abnormal data were that with a Z score >2SD (<LLN, Lower Limit of Normality or >ULN, Upper Limit of Normality) by applying The Global Lung Function Initiative Network (GLI) reference values (8-9). Appropriate correction to D_{LCO} for haemoglobin was considered (7).

Descriptive statistics are reported as mean (± standard deviation). Differences between two groups were analysed for statistical significance by Student's t-test (unpaired) and between more than two groups by ANOVA, Kruskal-Wallis, or χ^2 where appropriate. A two-sided $p<0.05$ was considered for all comparisons.

Table I summarized demographic and pulmonary function characteristics of the 135 enrolled subjects at follow-up for moderate-to-severe COVID-19, subdivided by the treatment for their acute respiratory failure (PaO_2<60 mmHg): 1) O_2 supplementation only, 2) Continuous Positive Airway Pressure (CPAP, by helmet), 3) invasive mechanical ventilation (MV). No differences were found between the 3 groups, apart from age and gender.

At follow-up, impaired respiratory function was found 64 (47%) of the enrolled subjects, characterized by an older age (62±11 vs 55±10 yrs, $p<0.001$) and a higher mMRC dyspnea scale (1.58±0.76 vs 0.36±0.48, $p<0.01$), without any differences in the ratio Male/Female (44/20 vs 47/24) or in BMI index (28±5 vs 28±5, kg/m^2).

In 46 (34%) subjects D_{LCO} was impaired (61±14% of predicted), associated with reduced (62%) or normal (38%) or D_{LCO} corrected for alveolar volume (K_{CO}, 81±15% of predicted).

Table II reports the pathophysiologic classification (10) of the impairment found: a) pulmonary restriction (Total Lung Capacity<LLN), isolated reduction of CO diffusion capacity (D_{LCO} <LLN), airway obstruction (FEV_1/FVC<LLN), and isolated air trapping (Residual Volume >ULN). No differences were found between groups on age, M/F ratio, BMI, mMRC score. K_{CO} % of predicted was higher in the group with a restrictive pattern vs that with isolated D_{LCO} reduction (p=0.04).

At follow-up, D_{LCO} reduction was mainly associated with pulmonary restriction (53%), as expected, and less frequently with airway obstruction/airway trapping (8%), but also isolated (38%). In the latter case, subjects did not report pulmonary thromboembolism during hospitalization or indirect signs of pulmonary hypertension at follow-up.

When comparing our data with that of Huang et al. (5), in moderate-to-severe COVID-19 (n=260), the impairment of respiratory function is similar among subjects requiring supplemental oxygen and less among those requiring CPAP or MV. Specifically, based on this subdivision, D_{LCO} was impaired in 31 and 40% of subjects (vs 29 and 56%), pulmonary restriction was present in 14 and 26% of subjects (vs 10 and 35%), and FEV_1/FVC <LLN in 8 and 10% of the subjects (vs FEV_1/FVC<0.7 in 8 and 2%). It is noteworthy that Huang et al. did not use the Z score criterium, with a possible overestimation and that the mean age of those who underwent spirometry in their study was unknown. At 8 months, using the Z score criterium, Barisione et al. (10) found less subjects with impaired D_{LCO} (20%), but in mild-to-severe COVID-19 and after having carefully excluded all subjects with comorbidities (also obesity) potentially affecting D_{LCO}.

As in the study of Mo et al. (1), but at discharge, for about 29 out of 46 of the D_{LCO}-impaired patients, the K_{CO} was still within the normal range, which might indicate that the D_{LCO} decrease was more than the K_{CO} decrease, or, in other words, that lung volume is contributing to the gas exchange impairment. However, the relationship between V_A, DL_{CO} or K_{CO} is complex and any interpretation a surmise. By using D_{LNO} Barisione et al (11) suggest that a decreased alveolar membrane diffusive conductance (DM) is more frequent and persistent than the reduction of pulmonary capillary blood volume (V_C) in the recovery phase, at 8 months from discharge.

About the restrictive pattern, in the Mo et al. study (1), at discharge, it was interpreted a consequence of a critical illness (due to a transient impairment in mechanical properties of the chest wall and respiratory muscles). In our study, after 6 months, is more suggestive of a change in the elastic properties of the lung.

Airway obstruction (n=11) or isolated air trapping (n=10) was present in 15% of the subjects at follow-up. Even subtracting known (n=4) or underdiagnosed (1 current and 3 former smokers) COPD, a value of 9% of the discharged is still higher to the expected rate within a population of their age. Air trapping (an increase of RV e RV/TLC ratio) can be interpreted as an involvement of small airways not yet detected using conventional pulmonary function tests (i.e FEV_1/FVC ratio). An inflammatory process in the small airways could contribute to airway closure, by interfering with surfactant activity, by increasing the volume of intraluminal material or, more consistent in our 6-month discharged subjects, by airway remodelling (12).

Finally, Huang et al. reported data on 89 subjects not requiring supplemental oxygen (mild pneumonia). As our subjects were all affected by ARF, we have no data to compare. However, we found that on 20 subjects undergoing spirometry for exertional dyspnea after 6 months from SARS-CoV2 infection recovered at home, 12 presented an impaired respiratory function. Apart from 4

former smokers probably affected by underdiagnosed emphysema (TLC 120%±9, RV 169%±30, D_{LCO} 74%±2 of predicted) and 1 asthmatic subject (FEV_1/VC 66%, FEV_1 48% of predicted), the other 7 were non-smokers and previously healthy subjects reporting a reduced D_{LCO} (65%±9 of predicted), associated with a restrictive pattern (TLC 67%±8 of predicted) in 3 of them. These results are in line with that reported by Trinkmann et al. (13) on non-hospitalized subjects, but at 3 months (10) and after a first evaluation in emergency department.

There are some limitations in our study. First, the lack of baseline pulmonary function before COVID-19. However, patients with chronic respiratory disease, were a minority, as current or former smokers and none of the subjects had a history of pulmonary fibrosis. Secondly, the association with Computed Tomography chest images were not analysed in this preliminary report.

In conclusion, our study reveals that after 6 months from discharge for moderate-to-severe COVID-19 about half of the enrolled subjects presents an impaired respiratory function and a significant exertional dyspnea. Although is tempting to speculate on the pathophysiology of the type of impairment found, our aim is to report timely to the clinicians its entity and heterogeneity, consistent with the complex pathophysiology of COVID-19 (14). Long-term follow-up (i.e at 12 months) is required (ongoing) and research protocols with tools not yet routinely available (D_{LNO}) or for highly specialized centres (Forced Oscillatory Technique) to be developed. It is alarming the possible impact of those recovering from COVID-19 at home, still to be determined.

Take home message: After 6 months, about half of COVID-19 discharged subject presents an impaired respiratory function with exertional dyspnea, mainly due a reduced CO diffusion (34%), followed by pulmonary restriction (19%).

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Table I. Clinical characteristics and lung function by COVID-19 severity at 6 months from discharge

		O_2	CPAP	MV	
Number (%)	135	86 (64)	29 (21)	20 (15)	
Age, yrs	59±11	57±12[§]	61±11	64±7[§]	p=0.01
Male, % total	67	61[§]	70	85[§]	P=0.04
BMI, kg/m^2	28±5	27±4	29±7	29±3	NS
Current smokers, n (%)	4 (3)	2 (1.5)	2 (1.5)	0	NS
Former smokers, n (%)	25 (18)	19 (14)	5 (3)	1 (1)	NS
COPD, n (%)	4 (3)	0	1 (1.5)	1 (1.5)	NS
Asthma, n (%)	3 (2)	0	0	3 (2)	NS
mMRC dyspnea scale, score	0.93±0.84	0.90±0.89	1.07±0.75	0.85±0.75	NS
mMRC dyspnea scale, >1	27 (20)	16 (12)	7 (5)	4 (3)	NS
TLC, L	5.72±1.28	5.73±1.23	5.62±1.65	5.79±1.28	NS
TLC, %	96±33	96±17	90±18	89±13	NS
TLC<LLN	25 (19)	12 (9)	8 (6)	5 (4)	NS
RV, L	2.09±0.80	2.13±0.82	2.01±0.77	2.05±0.76	NS
RV, %	96±33	100±33	89±32	87±30	NS
RV>ULN	10 (7)	8 (6)	3 (2)	2 (2)	NS
RV/TLC	0.36±0.10	0.37±0.11	0.35±0.08	0.35±0.09	NS
RV/TLC, %	96±24	99±27	92±20	91±22	NS
FVC, L	3.61±0.65	3.56±0.92	3.72±1.09	3.71±0.72	NS
FVC, %	91±16	90±17	94±16	92±12	NS
FEV_1, L	2.92±0.96	2.91±0.74	2.94±0.86	2.91±0.69	NS
FEV_1, %	94±16	94±16	94±16	92±14	NS
FEV_1/VC	0.81±0.07	0.82±0.07	0.79±0.07	0.79±0.08	NS
FEV_1/VC, %	101±9	102±9	100±9	100±10	NS
FEV_1/VC <LLN	11 (8)	7 (5)	3 (2)	2 (1)	NS
D_{LCO}, mmol/kPa/min	7.20±2.06	7.29±2.16	7.02±1.87	7.06±1.96	NS
D_{LCO}, %	82±20	83±21	80±16	79±20	NS
D_{LCO} <LLN	46 (34)	27 (20)	11 (8)	9 (7)	NS
K_{CO}, mmol/kPa/min/L	1.37±0.26	1.38±0.27	1.36±0.27	1.35±0.22	NS
K_{CO}, %	95±18	94±18	96±19	98±19	NS
K_{CO} <LLN	17 (13)	11 (8)	4 (3)	3 (2)	NS

LLN, Lower Limit Normality; ULN, Upper Limit Normality; mMRC, modified Medical Research Council dyspnea scale (at 6 months), NS, not significant.

Table II. Respiratory Function impairment at 6-months from discharge for COVID-19.

	TLC<LLN	Is.D_{LCO}<LLN	FEV_1/FVC<LLN	Is. RV>ULN	
Number	25	18	11	10	
% of discharged	19	13	8	7	
Age, yrs	62±10	59±12	68±5	64±6	NS
M/F	20/5	10/8	8/3	5/4	NS
BMI, kg/m^2	28±5	27±4	28±5	28±4	NS
Current smokers, n	1	0	1	0	
Former smokers, n	2	1	3	2	
COPD, n	0	0	4	0	
Asthma, n	0	0	1	0	
CPAP, n/total	8/29	2/29	3/29	1/29	NS
MV, n/total	6/20	0/20	2/20	1/20	NS
mMRC dyspnea, score	1.84±0.80	1.22±0.55	1.27±0.90	1.3±0.67	NS
TLC, L	4.54±1.05	5.36±1.04	6.07±1.22	6.89±1.60	
TLC, %	69±9	90±10	106±13	114±12	
RV, L	1.45±0.48	1.99±0.67	3.28±0.86	3.44±0.62	
RV, %	63±21	92±22	138±24	155±18	
RV/TLC	$0.33±0.10^{ab}$	$0.37±0.09^{§c}$	$0.52±0.09^{§a}$	$0.51±0.99^{bc}$	P=0.01
RV/TLC, %	$82±28^{ab}$	$96±21^{§c}$	$125±21^{§a}$	$130±20^{bc}$	P=0.01
FVC, L	3.11±0.85	3.36±0.71	2.92±0.81	3.40±1.25	NS
FVC, %	76±14§	89±14§	85±19	90±19	P=0.04
FEV_1, L	2.69±0.67	2.73±0.56	1.93±0.53	2.83±0.97	NS
FEV_1, %	85±13	92±12	72±17	97±19	NS
FEV_1/VC	0.85±0.04	0.81±0.05	0.67±0.06	0.84±0.06	
FEV_1/VC, %	109±6	102±6	83±5	107±7	
D_{LCO}, mmol/kPa/min	6.16±1.97	5.36±1.09	5.67±2.02	6.95±2.19	NS
D_{LCO}, %	68±19	63±10	73±28	82±17	NS
K_{CO}, mmol/kPa/min/L	1.34±0.26	1.19±0.27	1.19±0.34	1.38±0.11§	NS
K_{CO}, %	97±21§	80±13§	85±28	98±10	P=0.04

LLN, Lower Limit Normality; ULN, Upper Limit Normality; mMRC, modified Medical Research Council dyspnea scale.