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

To the Editor:

Until now, reports about pulmonary function in previously hospitalised subjects for coronavirus disease 2019 (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], which enrolled 1733 discharged subjects, 349 of whom 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 years, 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.

This letter reports timely preliminary data on respiratory function at 6 months from discharge.

Written informed consent was collected from all subjects. Spirometry and pulmonary diffusion capacity tests 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 using the Diffusion SB RT Module for Body Vyntus (Vyaire Medical, GmbH). Abnormal data were that with a Z score >2SD (less than lower limit of normality (<LLN) or greater than upper limit of normality (>ULN)) 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±SD. Differences between two groups were analysed for statistical significance by t-test (unpaired) and between more than two groups by ANOVA, Kruskal-Wallis or Chi-squared test, where appropriate. A two-sided p<0.05 was considered significant for all comparisons.

Table 1 summarises 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 (arterial oxygen tension <60 mmHg): 1) oxygen supplementation only, 2) continuous positive airway pressure (CPAP, by helmet), and 3) invasive mechanical ventilation (MV). No differences were found between the three groups, apart from age and gender.

At follow-up, impaired respiratory function was found in 64 (47%) of the enrolled subjects, characterised by an older age (62±11 *versus* 55±10 years; p<0.001) and a higher modified Medical Research Council (mMRC) dyspnoea scale (1.58±0.76 *versus* 0.36±0.48; p<0.01), without any differences in the ratio of males/females (44/20 *versus* 47/24) or in body mass index (BMI) index (28±5 *versus* 28±5 kg·m^{-2}).

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

Shareable abstract (@ERSpublications)

After 6 months, about half of #COVID19 discharged subjects present impaired respiratory function with exertional dyspnoea, mainly due a reduced CO diffusion (34%), followed by pulmonary restriction (19%) https://bit.ly/3vcnbdR

TABLE 1 Clinical characteristics and lung function by COVID-19 severity at 6 months from discharge					
	Whole cohort	Oxygen supplementation	CPAP	MV	p-value
Subjects n (%)	135	86 (64)	29 (21)	20 (15)	
Age, years	59±11	57±12[#]	61±11	64±7[#]	0.01
Males % total	67	61[#]	70	85[#]	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 score	0.93±0.84	0.90±0.89	1.07±0.75	0.85±0.75	NS
mMRC score >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, % predicted	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, % predicted	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, % predicted	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, % predicted	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$_1$, % predicted	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, % predicted	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^{-1}·min^{-1}	7.20±2.06	7.29±2.16	7.02±1.87	7.06±1.96	NS
D_{LCO}, % predicted	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^{-1}·min^{-1}·L^{-1}	1.37±0.26	1.38±0.27	1.36±0.27	1.35±0.22	NS
K_{CO}, % predicted	95±18	94±18	96±19	98±19	NS
K_{CO} <LLN	17 (13)	11 (8)	4 (3)	3 (2)	NS

Data are presented as mean±SD, unless otherwise stated. All percentages are calculated as % of total number of enrolled subjects (n=135). CPAP: continuous positive airway pressure; MV: mechanical ventilation; BMI: body mass index; mMRC: modified Medical Research Council dyspnoea scale (at 6 months); TLC: total lung capacity; LLN: lower limit of normality; RV: residual volume; ULN: upper limit of normality; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 s; VC: vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide (D_{LCO} corrected for alveolar volume); NS: nonsignificant. [#]: within each row, identical superscripts indicate significant difference.

Table 2 reports the pathophysiological classification [10] of the impairment found: pulmonary restriction (total lung capacity <LLN), isolated reduction of diffusing capacity of the lung for carbon monoxide (D_{LCO} <LLN), airway obstruction (forced expiratory volume in 1 s (FEV$_1$)/forced vital capacity (FVC) <LLN), and isolated air trapping (residual volume >ULN). No differences were found between groups in terms of age, male/female ratio, BMI or mMRC score. K_{CO} % of predicted was higher in the group with a restrictive pattern *versus* 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 hospitalisation 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 (*versus* 29 and 56%), pulmonary restriction was present in 14 and 26% of subjects (*versus* 10 and 35%), and FEV$_1$/FVC <LLN in 8 and 10% of the subjects (*versus* FEV$_1$/FVC <0.7 in 8 and 2%). It is noteworthy that HUANG *et al.* [5] 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

TABLE 2 Respiratory function impairment at 6 months from discharge for COVID-19

	TLC <LLN	D_{LCO} <LLN	FEV_1/FVC <LLN	RV >ULN	p-value
Subjects n	25	18	11	10	
% of discharged subjects	19	13	8	7	
Age, years	62±10	59±12	68±5	64±6	NS
Males/females n/n	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 dyspnoea, 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, % predicted	63±21	92±22	138±24	155±18	
RV/TLC	0.33±0.10$^{\#,\P}$	0.37±0.09$^{\S,+}$	0.52±0.09$^{\#,\S}$	0.51±0.99$^{\P,+}$	0.01
RV/TLC, % predicted	82±28$^{\#,\P}$	96±21$^{\S,+}$	125±21$^{\#,\S}$	130±20$^{\P,+}$	0.01
FVC, L	3.11±0.85	3.36±0.71	2.92±0.81	3.40±1.25	NS
FVC, % predicted	76±14§	89±14§	85±19	90±19	0.04
FEV_1, L	2.69±0.67	2.73±0.56	1.93±0.53	2.83±0.97	NS
FEV_1, % predicted	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, % predicted	109±6	102±6	83±5	107±7	
D_{LCO}, mmol·kPa^{-1}·min^{-1}	6.16±1.97	5.36±1.09	5.67±2.02	6.95±2.19	NS
D_{LCO}, % predicted	68±19	63±10	73±28	82±17	NS
K_{CO}, mmol·kPa^{-1}·min^{-1}·L^{-1}	1.34±0.26	1.19±0.27	1.19±0.34	1.38±0.11§	NS
K_{CO}, % predicted	97±21§	80±13§	85±28	98±10	0.04

Data are presented as mean±SD, unless otherwise stated. TLC: total lung capacity; LLN: lower limit of normality; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; ULN: upper limit of normality; BMI: body mass index; CPAP: continuous positive airway pressure; MV: mechanical ventilation; mMRC: modified Medical Research Council dyspnoea scale (at 6 months); VC: vital capacity; K_{CO}: transfer coefficient of the lung for carbon monoxide (D_{LCO} corrected for alveolar volume); NS: nonsignificant. $^{\#,\P,+,\S}$: within each row, identical superscripts indicate significant difference.

Z score criterium, BARISIONE *et al.* [11] found fewer subjects with impaired D_{LCO} (20%), but in mild-to-severe COVID-19 and after having carefully excluded all subjects with comorbidities (including obesity) potentially affecting D_{LCO}.

As in the study of MO *et al.* [1], which was carried out at hospital discharge, for about 29 out of 46 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 alveolar volume (V_A), D_{LCO} or K_{CO} is complex and any interpretation a surmise. By using diffusing capacity of the lung for nitric oxide (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.

Regarding the restrictive pattern, in the study of MO *et al.* [1], at discharge, it was interpreted as 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 (one current and three former smokers) COPD, a value of 9% among the discharged is still higher to the expected rate within a population of their age. Air trapping (an increase of residual volume (RV) and 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 months after discharge subjects, by airway remodelling [12].

Finally, HUANG *et al.* [5] reported data on 89 subjects not requiring supplemental oxygen (mild pneumonia). As our subjects were all affected by acute respiratory failure, we have no data to compare. However, we found that among 20 subjects undergoing spirometry for exertional dyspnoea 6 months after SARS-CoV-2 infection recovered from at home, 12 presented an impaired respiratory function. Apart from four former smokers probably affected by underdiagnosed emphysema (TLC 120±9%, RV 169±30%, D_{LCO} 74%±2 of predicted) and one asthmatic subject (FEV_1/vital capacity 66%, FEV_1 48% of predicted), the other seven were nonsmokers and previously healthy subjects reporting a reduced D_{LCO} (65±9% of predicted), associated with a restrictive pattern (TLC 67±8% of predicted) in three of them. These results are in line with those reported by TRINKMANN *et al.* [13] on nonhospitalised subjects, but at 3 months [10] and after a first evaluation in the emergency department.

There are some limitations in our study. First, the lack of baseline pulmonary function data before COVID-19. However, patients with chronic respiratory disease were a minority, as were 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 presented an impaired respiratory function and a significant exertional dyspnoea. Although it is tempting to speculate on the pathophysiology of the type of impairment found, our aim is to report timely to 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 specialised centres (forced oscillatory technique) to be developed.

Manlio Milanese[1], Marco Anselmo[1], Sandra Buscaglia[1], Luca Garra[2], Riccardo Goretti[1], Lionello Parodi[1], Giovanni Riccio[3], Rodolfo Tassara[1] and Paola Gnerre[1] on behalf of the ACOD Group

[1]Dipartimento Medico, ASL 2 Savonese, Savona, Italy. [2]Direzione Sanitaria, ASL 2 Savonese, Savona, Italy. [3]Struttura Complessa Malattie Infettive Osteoarticolari, ASL 2 Savonese, Albenga (SV), Italy.

Corresponding author: Manlio Milanese (m.milanese@asl2.liguria.it)

References

1   Mo X, Jian W, Su Z, *et al.* Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020; 55: 2001217.

2   Lerum TV, Aaløkken TM, Brønstad E, *et al.* Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19. *Eur Respir J* 2021; 57: 2003448.

3   Guler A, Ebner L, Beigelman C, *et al.* Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J* 2021; 57: 2003690.

4   Bellan M, Soddu D, Balbo PE, *et al.* Respiratory and psychophysical sequelae among patients with COVID-19 four months after hospital discharge. *JAMA Netw Open* 2021; 4: e2036142.

5   Huang C, Huang L, Wang Y, *et al.* 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; 397: 220–232.

6   Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019; 200: e70-e88.

7   Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017; 49: 1600016.

8   Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur J Respir 2012; 40: 1324–1343.

9   Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J 2017; 50: 1700010.

10 Pellegrino R, Brusasco V, Viegi G, et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26: 948–968.

11 Barisione G, Brusasco V. Lung diffusing capacity for nitric oxide and carbon monoxide following mild-to-severe COVID-19. Physiol Rep 2021; 9: e14748.

12 Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. Am J Respir Crit Care Med 2003; 168: 1277–1292.

13 Trinkmann F, Müller M, Reif A, et al. Residual symptoms and lower lung function in patients recovering from SARS-CoV-2 infection. Eur Respir J 2021; 57: 2003002.

14 Ackermann M, Vereleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis and angiogenesis in COVID-19. N Engl J Med 2020; 383: 120–128.