Abnormal pulmonary function in COVID-19 patients at time of hospital discharge

To the Editor:

On 11 March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a pandemic. As of 22 April, more than 2.4 million cases have been confirmed worldwide [1]. In light of the widely documented lung injuries related to COVID-19 [2, 3], concerns have been raised regarding the assessment of lung injury for discharged patients. A recent report portrayed that discharged patients with COVID-19 pneumonia still have residual abnormalities in chest computed tomography (CT) scans, with ground-glass opacity as the most common pattern [4]. Persistent impairment of pulmonary function and exercise capacity have been known to last for months or even years [5–8] in the recovered survivors from other coronavirus pneumonia (severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)). However, until now, there is no report in regard to pulmonary function in discharged COVID-19 survivors. This article aims to describe the characteristics of pulmonary function in these subjects.

We recruited laboratory-confirmed noncritical COVID-19 cases, from 5 February to 17 March 2020, from admitted patients. According to the WHO interim guidance [9] and the guidance from China [10], disease severity was categorised as mild illness (mild symptoms without radiographic appearance of pneumonia), pneumonia (having symptoms and the radiographic evidence of pneumonia, with no requirement for supplemental oxygen), severe pneumonia (having pneumonia, including one of the following: respiratory rate >30 breaths·min^{-1}; severe respiratory distress; or oxygen saturation measured by pulse oximetry (S_{pO_2}) ⩽93% on room air at rest), and critical cases (*e.g.* respiratory failure requiring mechanical ventilation, septic shock, other organ failure occurrence or admission into the intensive care unit). Critical cases were excluded from our study. Spirometry and pulmonary diffusion capacity tests (Quark PFT; Cosmed, Rome, Italy) were performed following the American Thoracic Society/European Respiratory Society guidelines on the day of or 1 day before discharge. To minimise cross-infections, diffusing capacity of the lung for carbon monoxide (D_{LCO}) was measured by the single-breath method. Written informed consent was obtained from all patients, and the study was approved by the ethics committee of The Guangzhou Eighth People's Hospital.

110 discharged cases were recruited, which included 24 cases of mild illness, 67 cases of pneumonia and 19 cases of severe pneumonia (table 1). The mean age of these cases was 49.1 years and 55 of them were females. 44 patients (40%) had at least one underlying comorbidity, of which 23.6% had hypertension and 8.2% had diabetes. Only three patients (2.7%) were reported as having chronic respiratory diseases (one patient with asthma, one with chronic bronchitis and one with bronchiectasis). No significant differences were found among the three groups of cases in relation to sex, smoking status, underlying disease and body mass index. The mean±SD duration from onset of disease to pulmonary function test was 20±6 days in cases with mild illness, 29±8 days in cases with pneumonia and 34±7 days in cases that presented severe pneumonia. On the day of discharge, the S_{pO_2} on room air at rest was normal in all subjects and no significant difference was found among the different groups (all $p>0.05$).

Spirometry was uneventfully completed in all patients, except for two failed diffusion capacity tests. Anomalies were noted in D_{LCO} % predicted in 51 cases (47.2%), total lung capacity (TLC) % pred in 27 (25.0%), forced expiratory volume in 1 s (FEV_1) % pred in 15 (13.6%), forced vital capacity (FVC) % pred in 10 (9.1%), FEV_1/FVC in five (4.5%), and small airway function in eight (7.3%). Table 1 shows a significant difference in impaired diffusing capacity among the different groups of severity, which accounted for 30.4% in mild illness, 42.4% in pneumonia and 84.2% in severe pneumonia, respectively ($p<0.05$).

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In discharged survivors with COVID-19, impairment of diffusion capacity is the most common abnormality of lung function, followed by restrictive ventilatory defects, which are both associated with the severity of the disease https://bit.ly/2yUaBaT

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TABLE 1 Demographics and pulmonary function characteristics of discharged patients with COVID-19

	Total	Mild illness	Pneumonia	Severe pneumonia	p-value
Patients	110	24	67	19	
Age years	49.1±14.0	46.8±15.6	47.9±13.7	56.5±11.0*,#	0.04
Female	55 (50.0)	13 (54.2)	36 (53.7)	6 (31.6)	0.21
Smoker	13 (11.8)	4 (16.7)	7 (10.4)	2 (10.5)	0.707
BMI kg·m^{-2}	23.5±3.0	23.1±2.8	23.6±3.2	23.5±2.7	0.794
Duration from onset to discharge days	27±9	20±6	29±8**	34±7**,#	<0.001
Underlying disease	44 (40.0)	10 (41.7)	25 (37.3)	9 (47.4)	0.719
Lung disease	3 (2.7)	0 (0)	3 (4.5)	0 (0)	1
Heart disease	3 (2.7)	1 (4.2)	2 (3.0)	0 (0)	1
Hypertension	26 (23.6)	6 (25.0)	15 (22.4)	5 (26.3)	0.924
Cerebrovascular disease	3 (2.7)	0 (0)	2 (3.0)	1 (5.3)	0.532
Diabetes	9 (8.2)	1 (4.2)	6 (9.0)	2 (10.5)	0.702
Liver disease	6 (5.5)	2 (8.3)	3 (4.5)	1 (5.3)	0.837
Kidney disease	2 (1.8)	1 (4.2)	1 (1.5)	0 (0)	0.631
Solid tumour	1 (0.9)	0 (0)	0 (0)	1 (5.3)	0.173
S_{pO_2} on discharge %	98.7±1.0	98.6±1.2	98.7±1.0	98.5±1.0	0.73
Spirometry					
FVC % pred	93.59±12.25	94.06±10.48	94.12±12.31	91.12±14.30	0.632
FVC <80% pred	10 (9.09)	3 (12.50)	5 (7.46)	2 (10.53)	0.644
FEV_1 % pred	92.70±11.57	94.26±11.00	92.59±11.87	91.12±11.58	0.676
FEV_1 <80% pred	15 (13.64)	4 (16.67)	9 (13.43)	2 (10.53)	0.857
FEV_1/FVC %	80.70±5.81	81.84±5.48	80.39±6.12	80.19±5.15	0.509
FEV_1/FVC <70%	5 (4.55)	0 (0)	5 (7.46)	0 (0)	0.349
MMEF % pred	97.40±26.23	99.77±28.17	96.59±26.51	96.14±23.82	0.879
MMEF <65% pred¶	7 (6.42)	1 (4.17)	6 (9.09)	0 (0)	0.551
$FEF_{50\%}$ % pred	94.74±26.11	97.47±25.48	94.09±26.80	93.53±25.56	0.845
$FEF_{50\%}$ <65% pred¶	12 (11.01)	2 (8.33)	8 (12.12)	2 (10.53)	1
$FEF_{75\%}$ % pred	96.10±32.56	102.23±40.20	95.02±30.89	92.08±27.92	0.549
$FEF_{75\%}$ <65% pred¶	12 (11.01)	3 (12.50)	4 (6.06)	5 (26.32)#	0.035
Diffusion capacity					
D_{LCO} % pred	78.18±14.29	84.70±13.88	79.76±11.99	64.79±14.35**,##	<0.001
D_{LCO} <80% pred	51 (47.22)	7 (30.43)	28 (42.42)	16 (84.21)**,##	0.001
D_{LCO}/V_A % pred	92.09±16.68	99.35±18.25	92.30±15.70	82.58±13.91**,#	0.004
D_{LCO}/V_A <80% pred	29 (26.85)	3 (13.04)	18 (27.27)	8 (42.11)	0.09
Lung volume					
TLC % pred	86.32±11.32	87.13±10.43	88.11±10.72	79.16±12.13*,##	0.008
TLC <80% pred	27 (25.00)	4 (17.39)	14 (21.21)	9 (47.37)*,#	0.049
RV % pred	86.83±19.37	87.17±16.88	89.79±19.21	76.16±19.96##	0.024
RV <65% pred	10 (9.26)	2 (8.70)	3 (4.55)	5 (26.32)#	0.021
RV/TLC % pred	96.99±16.72	98.00±14.93	98.53±17.55	90.42±14.86	0.168

Data are presented as n, mean±SD or n (%), unless otherwise stated. Comparisons between continuous variables were performed with one-way ANOVA. Chi-squared test and Fisher's exact test were applied to categorical variables as appropriate. BMI: body mass index; S_{pO_2}: oxygen saturation measured by pulse oximetry; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MMEF: maximal mid-expiratory flow; $FEF_{50\%}$: forced expiratory flow at 50% of FVC; $FEF_{75\%}$: forced expiratory flow at 75% of FVC; D_{LCO}: diffusing capacity of the lung for carbon monoxide; D_{LCO}/V_A: D_{LCO} corrected for alveolar volume; TLC: total lung capacity; RV: residual volume. *: p<0.05 *versus* mild illness; **: p<0.01 *versus* mild illness; #: p<0.05 *versus* pneumonia; ##: p<0.01 *versus* pneumonia; ¶: at least two of these <65% pred defined patients with small airway function anomalies.

This trend of the gradual decrease in level of D_{LCO} among patients was identical with the varying degree of severity. For about half (25 out of 51) of the D_{LCO}-impaired patients, the D_{LCO} corrected for alveolar volume (D_{LCO}/V_A) was still within the normal range, which might indicate that the D_{LCO} decrease was more than the D_{LCO}/V_A decrease, in recovered subjects. The value of TLC % pred in severe pneumonia cases was much less than that of pneumonia or mild illness cases, suggesting higher impairment of lung volume in severe cases. There was no significant difference among the discharged survivors with different severity in regard to other ventilatory defects (*e.g.* FEV_1, FVC, FEV_1/FVC).

Recent studies reveal that the lung is the organ most affected by COVID-19 [2, 3], with pathologies that include diffuse alveolar epithelium destruction, capillary damage/bleeding, hyaline membrane formation, alveolar septal fibrous proliferation, and pulmonary consolidation. Previous studies have demonstrated that recovered patients with coronavirus pneumonia can be left with damaged lungs. Impaired lung function was common and could last for months or even years. In the follow-up studies lasting 0.5–2 years in rehabilitating SARS patients [5–7], impaired D_{LCO} was the most common abnormality, ranging from 15.5% to 43.6%, followed by defective TLC, ranging from 5.2% to 10.9%. PARK *et al.* [8] showed that 37% of MERS survivors still presented with an impairment of D_{LCO}, but normal TLC, at 12 months. Our study seems to be more consistent with the findings in SARS. Interestingly, in our study, the greater decline in D_{LCO} *versus* D_{LCO}/V_A suggests that the diffusion membrane may be more causative of the pulmonary dysfunction compared to lowered lung volume. The low proportion and severity of small airway dysfunction in our cohort also suggests that COVID-19 is more likely associated with diffuse lung epithelial damage and small airway congestion. when evaluating lung fibrotic changes in SARS, the dynamic D_{LCO} scores were found to be more sensitive than high-resolution CT [11]. Whether survivors of COVID-19 with impairment of D_{LCO} or residual abnormalities on chest CT will develop pulmonary fibrosis requires further investigation.

There are limitations in our study. First, the lack of baseline pulmonary function test results prior to the illness make it difficult to make a comparison with the results after the illness. There were only a minority of patients with chronic respiratory disease, so it should be acceptable to speculate that the basic lung function in the majority of patients would be normal. The interpretation regarding the impact of COVID-19 on lung function remains valid. Secondly, the association between CT images and the lung function parameters was not analysed in our study. Finally, this cross-sectional analysis only provides a short follow-up, and the long-term dynamic variation of lung function after hospital discharge still requires further investigation.

In conclusion, our study reveals that, in discharged survivors with COVID-19, impairment of diffusion capacity is the most common abnormality of lung function, followed by restrictive ventilatory defects, which are both associated with the severity of the disease. Pulmonary function tests (not only spirometry but also diffusion capacity) should be considered in routine clinical follow-up for certain recovered survivors, especially in severe cases. Subsequent pulmonary rehabilitation might be considered as an optional strategy. Long-term studies are needed to address whether these deficits are persistent.

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