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Early View

Research letter

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

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To the editors:

On the 11th of March 2020, the World Health Organization (WHO) declared the 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 with COVID-19[2-3], concerns are raised regarding the assessment of the lung injury for discharged patients. A recent report portrayed that discharged patients with COVID-19 pneumonia are still having residual abnormalities in chest 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 with 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. Our manuscript aims to describe the characteristics of pulmonary function in these subjects.

We recruited laboratory confirmed non-critical COVID-19 cases, from February 5th to March 17th from admitted patients. According to the WHO interim guidance[9] and the guidance from china[10], disease severity were categorized 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/minute; severe respiratory distress; or SpO2 ≤ 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 ICU). Critical cases were excluded from our study. Spirometry and pulmonary diffusion capacity test (Cosmed PFT Quark, Rome, Italy) were performed following the ATS-ERS guidelines on the day of or one day before discharge. To

minimize cross infections, carbon monoxide diffusion capacity (DLCO) 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.

One-hundred and ten 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 fifty-five of them were females. Forty-four (40%) patients had at least one underlying comorbidity, of which 23.6% had hypertension and 8.2% had diabetes. Only 3 patients (2.7%) were reported 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 the relation to gender, smoking status, underlying disease and the BMI value. The 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 SpO2% 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 DLCO% in 51 cases (47.2%), total lung capacity (TLC)% in 27 (25.0%), forced expiratory volume in the first second (FEV_1)% in 15 (13.6%), forced vital capacity (FVC) % in 10 (9.1%), FEV_1/FVC in 5 (4.5%), and small airway function in 8 (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($p<0.05$). This trend of the gradual decrease in level of DLCO among patients was identical with the varying degree of severity. For about half (25/51) of the DLCO-impaired patients, the DLCO corrected for alveolar

volume (DLCO/VA) was still within the normal range, which might indicate that DLCO decrease was more than the DLCO/VA in recovered subjects. The value of TLC % predicted in severe pneumonia cases was much less than that of pneumonia or mild illness, 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 most affected organ 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 the 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 from half a year to two years in the rehabilitating SARS patients[5-7], impaired DLCO was the most common abnormality, ranging from 15.5% to 43.6%, followed by defected TLC, ranging from 5.2% to 10.9%. Wan et.al showed that 37% of MERS survivors still presented with an impairment of DLCO, but normal TLC at 12 months[8]. Our study seems to be more consistent with the findings in SARS. Interestingly, in our study, the greater decline in DLCO vs DLCO/VA suggests that 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 DLCO scores were found more sensitive than HRCT[11]. Whether survivors of COVID-19 with impairment of DLCO or residual abnormalities of chest CT will develop pulmonary fibrosis requires further investigation.

There are limitations in our study. Firstly, the lack of the baseline PFT results prior to the illness make it difficult to make a comparison with the results after the illness. there are only a minority of patients having chronic respiratory disease, it should be acceptable to speculate that the basic lung function in majority of patients would be normal. The interpretation regarding to the impact of the COVID-19 on lung function remain valid. Secondly, the association between CT image and the lung function parameter wasn't analyzed in our study. Finally, this cross-sectional analysis only provides a short follow-up, the long-term dynamic variation of the lung function after hospital discharge still require further investigation.

In conclusion, our study firstly reveals that, in discharged survivors with COVID-19, impairment of diffusion capacity is the most common abnormality of lung function followed by restrictive ventilatory defect, which are both associated with the severity of the disease. Pulmonary function test (not only spirometry, but also diffusion capacity) should be considered to performed 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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Table 1. Demography and pulmonary function characteristics of discharged patients with COVID-19

	Total (n=110)	Mild illness (n=24)	Pneumonia (n=67)	Severe Pneumonia (n=19)	*p* value
Age, years	49.1 ± 14.0	46.8 ± 15.6	47.9 ± 13.7	56.5 ± 11.0[a,b]	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	23.5 ± 3.0	23.1 ± 2.8	23.6 ± 3.2	23.5 ± 2.7	0.794
Duration (onset to discharge)	27±9	20±6	29±8 [a']	34±7 [a',b]	<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 tumor	1 (0.9%)	0 (0%)	0 (0%)	1 (5.3%)	0.173
Oxygen saturation % 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
<80% pred, No.(%)	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
<80% pred, No.(%)	15 (13.64)	4 (16.67)	9 (13.43)	2 (10.53)	0.857
FEV1/FVC%	80.70 ± 5.81	81.84 ± 5.48	80.39 ± 6.12	80.19 ± 5.15	0.509
<70%, No.(%)	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
<65% pred, No.(%)	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
<65%pred, No.(%)	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
<65%pred , No.(%)	12 (11.01)	3 (12.50)	4(6.06)	5 (26.32)[b]	0.035

Diffusion capacity					
DLCO%pred	78.18 ± 14.29	84.70 ± 13.88	79.76 ± 11.99	64.79 ± 14.35[a',b']	<0.001
<80%pred, No.(%)	51 (47.22)	7 (30.43)	28 (42.42)	16(84.21)[a',b']	0.001
DLCO/VA%pred	92.09 ± 16.68	99.35 ± 18.25	92.30 ± 15.70	82.58 ± 13.91[a',b]	0.004
<80%pred, No.(%)	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[a,b']	0.008
<80%pred, No.(%)	27 (25.00)	4 (17.39)	14 (21.21)	9 (47.37)[a,b]	0.049
RV%pred	86.83 ± 19.37	87.17 ± 16.88	89.79 ± 19.21	76.16 ± 19.96[b']	0.024
<65%pred, No.(%)	10 (9.26)	2 (8.70)	3 (4.55)	5 (26.32)[b]	0.021
RV/TLC%pred	96.99 ± 16.72	98.00 ± 14.93	98.53 ± 17.55	90.42 ± 14.86	0.168

Values are presented as No. (%), or mean±SD. Comparisons between continuous variables were performed with one-way ANOVA. Chi-square test and Fisher's exact test were applied to categorical variables as appropriate.

[a]p <0.05 versus Mild illness, [a']p <0.01 versus Mild illness

[b]p <0.05 versus Pneumonia, [b']p <0.01 versus Pneumonia

Abbreviation: FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; MMEF: maximal mid-expiratory flow. FEF_{50}: forced expired flow at 50% of FVC; FEF_{75}: forced expired flow at 75% of FVC; BMI: body mass index; DLCO: carbon monoxide diffusing-capacity; DLCO/VA: carbon monoxide diffusing-capacity corrected for alveolar volume; TLC: total lung capacity; RV: residual volume.