Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Anormal pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients after discharge

To the editor,

We read with great interest an article recently published in the Journal of Infection, in which, the authors followed up the pulmonary function and chest CT changes in two critically ill patients with COVID-19. [1] The two patients' distinct outcomes that seems be related with age, the young case recovered without abnormalities on chest CT and lung function tests, while the older case had residual radiological changes and impaired lung function during the follow-up period. Recent evidences have suggested that lung is the most affected organ by COVID-19.[2] Persistent impairment of pulmonary function ranging from months to even years after discharge has been reported in other coronavirus infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[3-6] However, post-discharge imaging or lung functional data are scarce for COVID-19 survivors. Hence, we aimed to report the pulmonary function and chest CT changes in these patients with different severities.

Laboratory confirmed COVID-19 patients were enrolled from March 26 to May 1, 2020 from a designated hospital of Hubei province. According to the newest COVID-19 guidelines released by the National Health Commission of China, the disease severities were classified as mild, moderate, severe and critical illness.[7] The criteria for discharge were as follows:[7] (1) normal temperature lasting longer than three days, (2) resolved respiratory symptoms, (3) substantially improved acute exudative lesions on chest CT images, and (4) a series of two repetitive negative reverse transcription-polymerase chain reaction test results, separated by at least one day. The pulmonary function test (XEEK portable PFT X1, Xiamen, China) was performed following the American Thoracic Society/European Respiratory Society (ATS-ERS) guidelines on COVID-19 patients after discharge. The chest CT closest to the data of the pulmonary function test was reviewed independently by two cardiothoracic radiologists, who blinded to the clinical information. Final decisions were reached by consensus. This study was approved by the ethics committee of The First Affiliated Hospital of Jinan University, and written informed consent was obtained from all patients.

We performed lung function test on 18 COVID-19 patients after discharge, which included 12 cases of moderate illness, five cases of severe illness and one case of critical illness. The mean age of the patients was 50.7 ± 12.1 (range, 28–67 years) and 10 were male. Only four patients (22.2%) had one or more underlying disease, such as hypertension, diabetes, and hypothyroidism. No patients had chronic lung diseases. There were no significant differences between the non-severe and severe groups in regarding to age, sex, underlying disease and body mass index. Length of hospitalization of severe cases was significantly longer than that of non-severe cases ($P = 0.030$). The duration from hospital discharge to pulmonary function test was 40 ± 11.6 days in cases with non-severe illness, and 34.7 ± 16.5 days in cases with severe illness. On the day of discharge, the SpO_2 on room air at rest showed no significant difference between the two groups ($P = 0.465$).

Spirometry was successfully completed in all patients. Five non-severe (41.7%) and two severe (33.3%) patients had abnormal lung function, respectively. Anomalies were noted in maximum vital capacity (VCmax) in three (16.7%) cases, forced expiratory volume in the first second (FEV1) in three (16.7%), forced vital capacity (FVC) in three (16.7%), FEV1/FVC% in three (16.7%), maximal mid-expiratory flow (MMEF) in seven (38.9%), forced expired flow at 50% of forced vital capacity ($FEF_{50\%}$) in two (11.1%), and $FEF_{75\%}$ in 11 (61.1%). Among the 12 non-severe cases, three (25.0%) had obstructive ventilation impairment, one (8.3%) had restrictive ventilatory impairment, and five (41.7%) had small airway dysfunction. Among the six severe cases, two (33.3%) had restrictive ventilatory impairment and one (16.7%) had small airway dysfunction. There was no significant difference between the COVID-19 survivors after discharge with different severity regarding ventilatory and small airway function defects (Table 1). After stratified by age ($\leq$50.7 and $>$50.7 years), there was still no significant difference in the two groups (all P values $>$0.05).

After discharge, 15 patients (83.3%) still had residual CT abnormalities, including GGO plus pulmonary fibrosis in 11 cases and pulmonary fibrosis only in four cases (Table 1). The distribution of most GGO and pulmonary fibrosis were peripheral. There was no significant difference in chest CT findings between the two groups ($P = 0.882$).

The lung pathology of fatal COVID-19 was dominated by diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells.[8] The aberrant wound healing may lead to severe scaring and fibrosis. Preliminary evidence suggests impaired lung function in coronavirus pneumonia could be last for several months or even years, with the impairment of diffusing capacity (DLCO) as the most common abnormality,[3-6] followed by total lung capacity.[5, 6] Wan et al. showed that 37% of MERS-CoV survivors have impaired DLCO at one year, which was compatible with the radiological sequelae.[9] Follow-up chest radiographs obtained from the patients with MERS-CoV and SARS-CoV showed a substantial portion (around 30%) chest radiographic abnormalities, which were characterized by the presence of pulmonary fibrosis, GGO, and pleural thickening.[10] However, the lung abnormalities may be more common if detected by CT because it is more sensitive than chest radiographs. In this study, 83.3% of patients after discharge had abnormal chest CT findings, with high proportion of pulmonary fibrosis. Xie et al. showed that pulmonary fibrotic tissue and vital capacity improved with time during a one-year follow-

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Table 1
Clinical and pulmonary function characteristics of patients with COVID-19 after discharge.

Characteristics	Total ($n = 18$)	Non-severe illness ($n = 12$)	Severe illness ($n = 6$)	P-value
Age, mean (SD), years	50.7 (12.1)	51.3 (12.2)	49.7 (12.9)	0.803
Sex, n (%)				
Male	10 (55.6)	7 (58.3)	3 (50.0)	1.000
Female	8 (44.4)	5 (41.7)	3 (50.0)	
BMI, mean (SD)	26.4 (2.8)	25.8 (2.8)	27.7 (2.6)	0.182
Underlying disease, n (%)				
Hypertension	3 (16.7)	1 (8.3)	2 (33.3)	0.245
Diabetes	1 (5.6)	0	1 (16.7)	0.333
Hypothyroidism	1 (5.6)	1 (8.3)	0	1.000
Length of hospital stay, mean (SD), days	28.0 (10.3)	23.8 (8.4)	35.0 (9.9)	0.030
Days from hospital discharge to pulmonary function test, mean (SD)	38.0 (13.4)	40.0 (11.6)	34.7 (16.5)	0.459
Lung volume				
VC_{max}%pred, mean (SD)	105.1 (23.3)	108.4 (22.5)	98.6 (22.6)	0.418
VC_{max}%pred, *n* (%) <80%	3 (16.7)	1 (8.3)	2 (33.3)	0.245
TV, mean (SD), L	0.8 (0.7)	0.6 (0.4)	1.2 (1.0)	0.111
ERV, mean (SD), L	0.7 (0.9)	0.8 (0.9)	0.7 (0.9)	0.785
IRV, mean (SD), L	0.8 (0.8)	1.0 (0.9)	0.5 (0.8)	0.355
IC, mean (SD), L	1.6 (0.9)	1.5 (0.9)	1.7 (1.0)	0.699
Pulmonary ventilation function				
MVV%pred, mean (SD)	86.1 (11.9)	85.8 (14.6)	86.7 (6.6)	0.907
FVC%pred, mean (SD)	105.1 (23.3)	108.4 (22.5)	98.6 (25.6)	0.418
FVC%pred, n (%) <80%	3 (16.7)	1 (8.3)	2 (33.3)	0.245
FEV_1%pred, mean (SD)	101.0 (19.5)	102.3 (19.7)	98.6 (20.6)	0.719
FEV_1%pred, *n* (%) <80%	3 (16.7)	1 (8.3)	2 (33.3)	0.245
FEV_1/FVC%, mean (SD)	77.9 (8.1)	75.8 (8.3)	82.0 (6.1)	0.125
FEV1/FVC%, *n* (%) <70%	3 (16.7)	3 (25.0)	0	0.515
Small airway function				
MMEF%pred, mean (SD)	80.2 (33.7)	73.2 (32.4)	94.3 (34.8)	0.220
MMEF%pred, *n* (%) <65%	7 (38.9)	6 (50.0)	1 (16.7)	0.316
FEF_{50}%pred, mean (SD)	95.5 (30.9)	87.7 (30.0)	111.2 (28.8)	0.131
FEF_{50}%pred, *n* (%) <65%	2 (11.1)	2 (16.7)	0	0.529
FEF_{75}%pred, mean (SD)	67.3 (34.4)	65.1 (35.4)	71.8 (35.1)	0.706
FEF_{75}%pred, *n* (%) <65%	11 (61.1)	8 (66.7)	3 (50.0)	0.627
Ventilation impairment, *n* (%)				
Normal	12 (66.7)	8 (66.7)	4 (66.7)	0.291
Obstructive ventilation impairment	3 (16.7)	3 (25.0)	0	
Restrictive ventilatory impairment	3 (16.7)	1 (8.3)	2 (33.3)	
Small airway function impairment, *n* (%)	6 (33.3)	5 (41.7)	1 (16.7)	0.600
SaO_2, mean (SD)	95.1 (6.6)	93.4 (9.8)	96.5 (2.2)	0.465
CT changes, *n* (%)				
Normal	1 (5.6)	1 (8.3)	0	0.882
GGO plus pulmonary fibrosis	11 (61.1)	6 (50.0)	5 (83.3)	
Pulmonary fibrosis	4 (22.2)	3 (25.0)	1 (16.7)	
Not available	2 (11.1)	2 (16.7)	0	

Note: Values are presented as No. (%), or mean ± standard deviation (SD). P values were calculated by *t*-test, χ^2 test or Fisher's exact test, as appropriate. Abbreviations**:** BMI, Body Mass Index; VC, vital capacity; TV, tidal volume; ERV, expiratory reserve volume; IRV, inspiratory reserve volume; IC, inspiratory capacity; MVV, maximal voluntary ventilation; FVC, forced vital capacity; forced expiratory volume in the first second; MMEF, maximal midexpiratory flow; FEF_{50}, forced expired flow at 50% of forced vital capacity; FEF_{75}, forced expired flow at 75% of forced vital capacity; PO2, partial pressure of oxygen; SaO_2, oxygen saturation; GGO, ground-glass opacity.

up after discharge in SARS-CoV patients.[3] Hui et al. found negative correlation between residual radiographic abnormalities and parameters of lung volume and surface area for gas exchange, which might reflect the physiological effects of parenchymal inflammation and fibrosis.[5]

This study had some limitations. Firstly, we had no patients' baseline pulmonary function results before COVID-19 infection and therefore unable to compare the results after discharge. In this study, no patients having chronic lung disease, it might reasonable to presume that the basic lung function in these patients would be normal. However, the impact of COVID-19 on lung function remains to be validated in future. Secondly, we included patients without chronic lung diseases, so the findings of this study could not be generalized to these subjects. Finally, the sample size of this study was small because most patients in our institution refused lung function test or had returned to work in other places far from home.

In summary, this study indicated that, in COVID-19 survivors after discharge, restrictive ventilatory defect and small function dysfunction can be persistent, which are not associated with disease severity. Most patients still had residual abnormalities on chest CT, with GGO and pulmonary fibrosis as the most common pattern. COVID-19 survivors with residual abnormalities of chest CT will develop pulmonary fibrosis, especially in severe/critical ill patients. Impaired lung function might be related to pulmonary fibrosis but need larger studies to verify. Close follow-up of patients after COVID-19 is essential but insufficient. Long-term follow-up of lung function after discharge should be performed in clinical practice to provide a guideline for pulmonary rehabilitation. Longer term studies are needed to determine the duration of these lung deficits.

Declaration of Competing Interest

None reported.

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References

1. . Follow-up study on pulmonary function and radiological changes in critically ill patients with COVID-19. *J Infect* 2020. doi:10.1016/j.jinf.2020.05.040.
2. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020;**20**:425–34.
3. Xie L, Liu Y, Fan B, et al. Dynamic changes of serum SARS-coronavirus IgG, pulmonary function and radiography in patients recovering from SARS after hospital discharge. *Respir Res* 2005;**6**:5.
4. Xie L, Liu Y, Xiao Y, et al. Follow-up study on pulmonary function and lung radiographic changes in rehabilitating severe acute respiratory syndrome patients after discharge. *Chest* 2005;**127**:2119–24.
5. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS), on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005;**60**:401–9.
6. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest* 2005;**128**:2247–61.
7. . *Guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection*. National Health Commission of the People's Republic of China; 2020. trial version 7in ChineseMarch 04. doi:10.7661/j.cjim.20200202.064.
8. Mason RJ. Pathogenesis of COVID-19 from a cell biologic perspective. *Eur Respir J* 2020 in press. doi:10.1183/13993003.00607-2020.
9. Park WB, Jun KI, Kim G, et al. Correlation between pneumonia severity and pulmonary complications in middle east respiratory syndrome. *J Korean Med Sci* 2018;**33**:e169.
10. Das KM, Lee EY, Singh R, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. *Indian J Radiol Imaging* 2017;**27**:342–9.

Jingjing You[1], Lu Zhang[1]
Department of Radiology, The First Affiliated Hospital of Jinan University, No. 613 Huangpu West Road, Tianhe District, 510627 Guangzhou, Guangdong, China

Ma-yi-di-li Ni-jia-Ti
Department of Radiology, The First People's Hospital of Kashi area, Kashi, Xinjiang Uygur, China

Jue Zhang
Department of Radiology, The First People's Hospital of Tianmen City, Tianmen, Hubei, China

Fuyin Hu
Department of Respiratory medicine, The First People's Hospital of Tianmen City, Hubei, China

Luyan Chen
Department of Radiology, The First Affiliated Hospital of Jinan University, No. 613 Huangpu West Road, Tianhe District, 510627 Guangzhou, Guangdong, China

Yuhao Dong
Department of Catheterization Lab, Guangdong Cardiovascular Institute, Guangdong Provincial, Key Laboratory of South China Structural Heart Disease, Guangdong Provincial People's, Hospital/Guangdong academy of medical sciences, Guangzhou, Guangdong, China

Ke Yang
Department of Radiology, The First People's Hospital of Kashi area, Kashi, Xinjiang Uygur, China

Bin Zhang*, Shuixing Zhang*
Department of Radiology, The First Affiliated Hospital of Jinan University, No. 613 Huangpu West Road, Tianhe District, 510627 Guangzhou, Guangdong, China

*Corresponding authors.
E-mail addresses: xld_Jane_Eyre@126.com (B. Zhang), shui7515@126.com (S. Zhang)
[1] These authors contributed equally to this work.