

Convalescence Phase

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Objective: This study investigated the influence of Coronavirus Disease 2019 (COVID-19) on lung function in early convalescence phase.

Methods: A prospective study of COVID-19 patients at the Fifth Affiliated Hospital of Sun Yat-sen University were conducted, with serial assessments including lung volumes (TLC), spirometry (FVC, FEV1), lung diffusing capacity for carbon monoxide (DLCO), respiratory muscle strength, 6-minute walking distance (6MWD) and high resolution CT being collected at 30 days after discharged.

Results: 57 patients completed the serial assessments. There were 40 non-severe cases and 17 severe cases. Thirty-one patients (54.3%) had abnormal CT findings. Abnormalities were detected in the pulmonary function tests in 43 (75.4%) of the patients. Six (10.5%), 5(8.7%), 25(43.8%) 7(12.3%), and 30 (52.6%) patients had FVC, FEV1, FEV1/FVC ratio, TLC, and DLCO values less than 80% of predicted values, respectively. 28 (49.1%) and 13 (22.8%) patients had P_Imax and P_Emax values less than 80% of the corresponding predicted values. Compared with non-severe cases, severe patients showed higher incidence of DLCO impairment (75.6%vs42.5%, $p=0.019$), higher lung total severity score (TSS) and R20, and significantly lower percentage of predicted TLC and 6MWD. No significant correlation between TSS and pulmonary function parameters was found during follow-up visit.

Conclusion: Declining DLCO, lower respiratory muscle strength, and lung

imaging abnormalities were detected in more than half of the COVID-19 patients in early convalescence phase. Compared with non-severe cases, severe patients had a higher incidence of DLCO impairment and encountered more TLC decrease and 6MWD decline.

Key words: COVID-19, early convalescence, lung function, respiratory muscle strength.

Background

Coronavirus Disease 2019 (COVID-19) was discovered due to unexplained viral pneumonia cases in Wuhan, China, and an outbreak in China even worldwide began in December 2019[1, 2]. It is a recently recognized infectious disease caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), which presented a risk of infection from human to human [3]. From December 30, 2019 to March 20, 2020, more than two hundred thousand people had been diagnosed with COVID-19. It might progress rapidly, and some patients developed respiratory failure early in the disease. The knowledge about COVID-19, including clinical manifestations, pathogenesis, even treatment came from research and observation during the acute infection period. In China, more than two-thirds of the patients had been successfully discharged. Until now, no study have reported early prognosis in relation to the degree of lung injury and rehabilitation in patients with COVID-19. Retrospective study showed

that many patients had imaging abnormalities when discharged, a few patients even had pulmonary fibrosis. Lung function damage of patients with COVID-19 during early convalescence phase deserves attention. In order to have a more comprehensive understanding of the possible clinical outcomes of COVID-19, we conducted a prospective study involving 57 discharged but undergoing rehabilitation COVID-19 patients. Serial lung function, lung imaging examination and exercise capacity were examined at 30 days after discharged. In addition, we compared severe patients with non-severe patients by outcome parameters.

Materials and Methods

Patient selection

This is a prospective follow up study of COVID-19 patients at 30 days after discharged from our hospital. From January 17, 2020 to March 1, 2020, a total of 103 COVID-19 patients were admitted to the Fifth Affiliated Hospital of Sun Yat-sen University. The diagnosis of COVID-19 was based on the CDC criteria. All patients had laboratory-confirmed SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR) or next-generation sequencing. They all reached uniform discharge standard issued by the National Health Commission of China and had been released from the hospital over one month. In 30 days after discharged, patients were eligible to participate in the study if they were over 18 years of age.

Patients with a previous history of pulmonary resection, neurological disease, or mental illness were excluded from our study. We obtained written informed consent from the patients before pulmonary function testing. This study was approved by the institutional ethics committee of the Fifth Affiliated Hospital of Sun Yat-sen University.

Classification

We retrospectively analyzed the medical records of these patients, and divided them into non-severe and severe groups according to the severity of the disease. Patients would be defined as severe cases if satisfied any of the following criteria : shortness of breath, RR \geq 30 times per minute; blood oxygen saturation \leq 93% in resting state; partial arterial oxygen pressure (PaO₂)/ fraction of inspiration O₂ (FiO₂) \leq 300mmHg;respiratory failure requires mechanical ventilation; shock occurred or combined with other organ failure required ICU monitoring and treatment. Otherwise were mild cases.

Lung imaging acquisition and CT quantitative evaluation

All subjects underwent high resolution spiral CT (SOMATOM Definition Flash Siemens; Erlangen, Germany) scans in the supine position during end-inspiration. Images were reconstructed at 1.0 mm slice thickness, with 1 mm increment, 512 mm \times 512 mm. The images were assessed by two

radiologists, both of whom were blinded to the clinical information. We used the same method as Michael et al, to quantify pulmonary inflammation severity[4-6]. Briefly, each of the five lung lobes was assessed for degree of involvement and classified as none (0%), minimal (1% -25%), mild (26% -50%), moderate (51% -75%), or severe (76% -100%). No involvement corresponded to a lobe score of 0, minimal involvement to a lobe score of 1, mild involvement to a lobe score of 2, moderate involvement to a lobe score of 3, and severe involvement to a lobe score of 4. An overall lung “total severity score” was reached by summing the five lobe scores (range of possible scores, 0-20). All CT scores were independently performed by two respiratory doctors. Agreement was reached by consensus.

6 minute walk test

6 minute walk test (6MWT) is an exercise test that evaluates the functional status which is relevant to daily activities of patients with cardiopulmonary disease. The walking distance is closely related to gender, age and height, conventionally need a hierarchical analysis according to the above parameters. However, the sample size of our study was small which was not suitable for stratified analysis based on age, gender and height. So we estimated the walking distance of healthy people of the same gender, age and height according to reference equations for the 6MWT in healthy adults[7]. Then we calculated the ratio of measured value of the patients to

the predicted value of the healthy person in fair condition. By comparing the ratio of two groups we could see whether there was difference in 6MWD between non-severe and severe COVID-19 patients.

Pulmonary function test and respiratory muscle strength measurement

Each subject underwent a standard pulmonary function test (Master Screen, Jaeger, German). Recorded parameters include: total lung volume (TLC), forced vital capacity (FVC), residual volume (RV), forced expiratory volume in the first second (FEV1), maximum expiratory flow rate (MMEF75/25), FEV1 / FVC ratio, and diffusing capacity of the lung for carbon monoxide (DLCO). Impulse oscillation system (IOS) was used to measure airway viscosity resistance at an oscillation frequency of 5Hz (R5), and central airway resistance at an oscillation frequency of 20Hz (R20).

Mouth pressure gauges can measure the maximum static inspiratory pressure (PImax) or maximum static expiratory pressure (PEmax) through a flanged cigarette holder. All subjects used this simple method to gauge inspiratory and expiratory muscle strength. The spirometry, DLCO, and respiratory muscle strength measurements were expressed as a percentage of predicted normal values.

To protect lung function laboratory staff, lung function tests were performed in a room with negative pressure device. Staff wore personal protective equipment, including N95 respirators, protective glasses, gloves

and gowns. In addition, each patient used disposable virus and bacterial filters during the test.

Statistics

Statistical analysis was performed using Statistical Package for Social Science (SPSS) Version 13.0. Measurement data was expressed as mean \pm standard deviation. Continuous variables were compared using independent-sample t test, whereas the rank sum test was used for nonparametric data. Comparison of proportion was evaluated by Chi-square test. Spearman correlation test was used to detect the correlations between lung function and lung total severity score. All statistical tests were two tailed. Statistical significance was taken as $p < 0.05$.

Results

Characteristics of the enrolled COVID-19 patients

This study evaluated a total of 102 patients. Five patients were excluded for underage. Twenty-four patients were not included as it was less than 30 days after discharge. Three patients were excluded due to neurological or mental illness. In addition, eight patients had been out of contact. At last, 57 patients had been included and completed the serial assessments in the study (Figure1). There were 26 men and 31 women with a mean age of 46.72 ± 13.78 years (age range, 19 to 71 years), the mean body mass index

was $23.99 \pm 3.55 \text{ kg / m}^2$. Among the 57 subjects, 46 (80.7%) had a history of direct contact with Wuhan, Hubei. Nine patients (15.7%) had a history of smoking. Twenty-one patients (36.8%) had preexisting medical illness. The four most common preexisting illnesses were hypertension (eleven patients), diabetes (four patients), malignant tumor (three patients) and cardiovascular disease (three patients). All of these conditions were either healed, or stable and well controlled at the time of testing during the study.

Among all subjects, seventeen were severe cases (29.8%), forty were non-severe cases (70.2%). There were mainly male patients (70.6%) in the severe group, and the average age of patients was older compared with non-severe cases. The mean $\text{Pao}_2/\text{Fio}_2$ ratio among severe cases was significantly lower than non-severe cases ($198.47[\text{SD}, 97.04]$; $355.51[\text{SD}, 37.23]$, $P < 0.001$). Meanwhile, severe cases had higher serum lactate dehydrogenase (LDH), C-reactive protein (CRP) peaks and lower lymphocyte count compared with non-severe cases. But there was no significant difference in the values of white blood cells, creatine kinase (CK), lactic acid peaks and length of hospitalization between the two groups (Table 1).

Lung function tests and respiratory muscle strength

Table 2 presents the results of pulmonary function tests and respiratory muscle strength among COVID-19 patients. During follow-up at 1 month after hospital discharge, there were 30 individuals (52.6%) with abnormal

diffusion capacity among the 57 patients participating in our study. According to the ATS recommendations for evaluating respiratory impairment [8], twenty-six patients (86.7%) had mild impairment of DLCO, while the other four (13.3%) had moderate impairment. Compared with non-severe cases (table3), severe patients had higher incidence of DLCO impairment (75.6%vs 42.5%, $p=0.019$).

The group means of forced expiratory volume in 1 second (FEV1) , static lung volumes were within normal limits ($> 80\%$ predicted). However, several cases of abnormalities in FVC, FEV1, and FEV1/FVC ratio were detected. Five patients (8.7%) had mild impairment of FVC, one (1.8%) had moderate impairment of FVC, 5 (8.7%) had mild impairment of FEV1, and 25 (43.9%) had mild impairment of FEV1/FVC. There were 8 patients (14.0%) and 10 patients (17.5%) had increased R5 and R20 more than 150% of the predicted value, respectively. Up to 12.2% ($n=7$) of patients had reduction in parameters of lung volume at 1 month. Among them, 6 had mild impairment, one had moderate impairment. TLC declined more significantly in severe cases ($p=0.048$). There was no difference in FVC, FEV1, and FEV1/FVC between the two groups. Table 4 shows the detailed pulmonary function data of 43 patients who had pulmonary function abnormalities. The majority of the impairment in FEV1 and FVC suggests a restrictive abnormality. One patient without history of asthma had obstructive abnormality with a FEV1/FVC ratio $< 70\%$ predicted, who had significant

history of cigarette smoking. Although no complained of symptoms of asthma, one other patient had a significant bronchodilator response with increments of FEV1 > 200 ml after inhalation of salbutamol.

More than half of the subjects had impairment in respiratory muscle strength. There were 28 patients (49.1%) and 13 patients (22.8%) had Pimax and Pemax values less than 80% of the predicted value, respectively. 13 patients had moderate impairment of respiratory muscle strength, of whom 11 were non-severe cases (table 4). When grouped by the administration of steroid, no statistical significance was found in respiratory muscle strength between the glucocorticoid group and the regular group (table 5).

Chest radiographs and correlations with lung function

During follow-up at 30 days after discharge, six patients (10.5%) complained of slight cough, four (7.0%) had shortness of breath, and three (5.3%) had occasional wheezing. Follow-up CT scan at this time showed that 31 patients (54.4%) had residual abnormality, of which 16 were severe cases (94.1%) and 15 were non-severe cases (37.5%). Most of the residual imaging abnormalities was patchy ground glass opacity with periphery distribution, which had obvious absorption compared with the worst chest CT scan (Figure 2.A-B). Four patients had pulmonary fibrosis (Figure 2.C-D), all of whom were severe patients. Compared with non-severe cases, severe patients had a significantly higher CT score (3.94[SD, 2.23]; 0.83 [SD, 1.39]; $p < 0.01$). At the acute phase, lung total severity score was negatively

correlated with TLC and R20 ($P=0.049,0.044$,figure 3), but the correlation disappeared during follow-up period.

6-minute walk test

The mean 6-minute walking distance (6MWD) in all subjects was 561.97m (± 45.29 m). Severe patients had a shorter 6 minutes walking distance than non-severe patients (517.43m [SD, 44.55m]; 573.52m [SD, 38.38m], $P=0.012$). And the 6MWD of severe cases reached only 88.4% of the predicted values, which was significant lower than non-severe cases ($p =0.011$, table 2).

Discussion

Since COVID-19 broke out worldwide in the last 3 months, the mechanism, clinical characteristics, prognosis and effective treatment of the disease had not yet been adequately elucidated despite the great efforts that had been extended. Follow-up surveys in patients with COVID-19 in convalescence phase are necessary for fully understanding the degree of lung injury and evaluating the prognosis of the disease. This prospective study showed that in early convalescence, approximately three-quarters of patients with COVID-19 developed pulmonary function impairment, the most common of which was the decline in diffuse function and FEV1/FVC ratio. Most of the impairment was mild.

DLCO abnormalities occurred in more than half of the COVID-19 patients, the data indicated impaired diffusion pathways in the intra-alveolar. To date, no other follow-up data on lung function in patients with COVID-19 can be compared. S.A. MEO et al reported that severe acute respiratory syndrome (SARS) and COVID-19 had similar biological and clinical characteristics [9]. And our results were consistent with those previous follow-up studies on SARS survivors[10-15]. Autopsy on patients died from COVID-19 showed different degrees of destruction in alveolar structure, and pulmonary interstitial fibrosis were observed.[16, 17]. Pathological changes in lungs can explain the impaired DLCO to a certain extent. Compared with non-severe case, severe patients were more likely to have DLCO abnormalities. Surprisingly, a small percentage of patients with no residual imaging abnormalities also experienced a slight decrease in DLCO. We think that these patients might have abnormal tiny blood vessels or microthrombus formation. Long-term follow-up studies of SARS survivors had shown that DLCO might remain abnormal within 3 years of recovery in some patients[18]. We will continue to perform long-term follow-up on these patients to see the trend of DLCO impairment.

Our results showed that six patients (10.5%) had obstructive pulmonary dysfunction and 7 (12.3%) had restrictive ventilation dysfunction. Two severe subjects had residual combined restrictive and obstructive type of functional impairment. Series articles on SARS survivors reporting very

low rates of either obstruction or restriction, which was consistent with our research data[10, 11]. Pathological findings showed that mucous plugs were found in small airway in some severe COVID-19 patients[17], which could explain the declined ventilatory function to an extent. In addition to acute lung injury, neuromuscular weakness could also lead to decreased lung function. Certainly, a few patients suffered from lower FEV1 or FEV1/FVC ratio might due to long-term smoking or untypical airway hyperresponsiveness.

Surprisingly, during the early rehabilitation phase, lung total severity score had no significant correlation with FEV1, FVC or DLCO (Figure3), which was inconsistent with researches on SARS survivors[19]. It seems that the impairment of lung function was not necessarily agreed with the severity of illness or residual imaging changes. It was an interesting finding. We speculate that it was because most severe patients used glucocorticoid during hospitalization, suggesting that corticosteroids may improve the prognosis of patients with COVID-19. But most of the subjects in our hospital were imported cases from Hubei, and small sample size and selection bias might affect statistical outcome. Besides, our CT quantitative evaluation was not actual represented the percentage of lung parenchyma that showed evidence of abnormalities. According to the criteria, in the same lung lobe, lung inflammatory lesions area within 25% of the difference was possible to be calculated as the same score, which might influence

statistical results. In the next step, we will perform long-term follow-up study and expand the sample size to see whether similar correlation conclusions still exist.

More than half of the patients experienced a decrease in respiratory muscle strength. Approximately 29.8% of patients in our study were severe or critical, who had hypoxemia during hospitalization, requiring supplemental oxygen and bed rest, and prolonged bed rest might lead to muscle disorders. In addition, systemic use of corticosteroids might cause steroid myopathy. But when grouped by the administration of steroid, no statistical significance was found in respiratory muscle strength between the glucocorticoid group and the regular group. This result indicated that corticosteroid was not the main cause of respiratory muscle weakness. In fact, there was no difference on declining respiratory muscle strength between severe and non-severe groups. However, the direct effect of virus on respiratory muscles needs further research.

In early convalescence, the 6MWD of the severe patients was significantly shorter than that of the non-severe patients, indicating that the severe patients have poor exercise tolerance. Besides the impaired TLC and worse DLCO in severe group, we should also pay attention to cardiac function of the patients. Exercise cardiopulmonary function should be performed in further studies. Series articles on SARS survivors showed the impaired lung function existed till one year[10, 11]. Longer follow-up on

COVID-19 patients should be made to observe the characteristic and change tendency of lung function and exercise tolerance.

There are several limitations to this study. Firstly, this is a cross-sectional study with small sample size in stratified analysis. The heterogeneity of our findings is not comprehensive. Secondly, only 57 of 102 COVID-19 patients (56%) in our hospital had completed the serial assessments, and the results might not be representative of the entire group. Lastly, although full lung function tests and 6MWT were conducted in our patients, we did not perform cardiopulmonary exercise testing, as many patients complained of generalized muscle weakness on follow-up. Meanwhile, labor intensity of CPET might be too high for patients in early recovery period.

In conclusion, DLCO decline, respiratory muscle strength decrease, and lung imaging abnormalities were detected in more than half of the COVID-19 patients in early convalescence phase. Compared with non-severe cases, severe patients had a higher incidence of DLCO impairment and encountered more TLC decrease and 6MWD decline. Longer follow-up studies in COVID-19 patients should be performed to investigate the clinical outcome of recovered COVID-19 patients.

Abbreviation

BMI=body mass index; CK=creatinine kinase; CRP=C-reactive protein; WBC=white blood cell count; LDH=lactate dehydrogenase; COVID-19=

Coronavirus Disease 2019; DLCO=Diffusing capacity of the lung for carbon monoxide; FVC=Forced vital capacity; FEV1=Forced expiratory volume in 1 second; LOS=length of hospital stay; PImax=Maximum static inspiratory pressures; PEmax=Maximum static expiratory pressures; Raw=Airway resistant; R5=Airway resistance at an oscillation frequency of 5Hz; R20=Airway resistance at an oscillation frequency of 20Hz; TLC= Total lung capacity; TSS=Total severity score; 6MWD=6 minute walk distance. 6MWT=6-min walk test.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional ethics committee of the Fifth Affiliated Hospital of Sun Yat-sen University;

Consent for publication

Consent for publication is not applicable;

Availability of data and materials

All data generated or analysed during this study are included in this published article;

Competing interests

The authors declare that they have no competing interests;

Authors' contributions

LJ designed the study, WJ performed the research, TCY collected the data, HYY analysed data and wrote the paper. All authors read and approved the final manuscript;

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