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Associations between severe pulmonary function and residual CT abnormalities in rehabilitating COVID-19 patients

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Abstract. – OBJECTIVE: Coronavirus disease 2019 (COVID-19) spread around the world in 2020. Abnormal pulmonary function and residual CT abnormalities were observed in COVID-19 patients during recovery. Appropriate rehabilitation training is around the corner. The correlation between spirometric impairment and residual CT abnormality remains largely unknown.

PATIENTS AND METHODS: A cross-sectional study conducted on the pulmonary function of 101 convalescent COVID-19 patients before discharge. Multivariate analysis was used to establish a scoring system to evaluate the spirometric abnormality based on residual chest CT.

RESULTS: Lung consolidation area >25% and severe-type COVID-19 were two independent risk factors for severe pulmonary dysfunction. Besides, a scoring system was established. People scoring more than 12 points have more chances (17 times) to get severe pulmonary function impairment before discharge.

CONCLUSIONS: For the first time, a chest CT characteristics-based grading system was suggested to predict the pulmonary dysfunction of COVID-19 patients during convalescence in this study. This study may provide suggestions for pulmonary rehabilitation.

Key Words:
COVID-19, Pulmonary rehabilitation, Spirometric abnormality, CT index, Scoring system.

Abbreviations

COVID-19, coronavirus disease 2019; CT, computed tomography; AUC, area under curve; WHO, World Health Organization; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS, severe acute respiratory syndrome; STARD, standards for reporting of diagnostic accuracy; FEV_1, forced expiratory volume in the first second; ATS/ERS, American Thoracic Society/European Respiratory Society; FVC, forced vital capacity; TLC, total lung capacity;PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; GGO, ground glass opacity; PFT, pulmonary function test; PEF: peak expiratory flow FVC, forced vital capacity; FEV_1/ FVC, the ratio of expiratory volume to vital capacity in 1 second; SD, standard deviation; ROC, receiver operating characteristics curve; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; OR, odds ratio; MERS, middle east respiratory syndrome coronavirus; COPD, chronic obstructive pul-

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monary disease; SpO_2, pulse oxygen saturation; HFOT, high flow oxygen therapy; NIV, non- invasive ventilation; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; Pred, prediction; BMI, body mass index; PPE, personal protective equipment; DLCO, carbon monoxide diffusing capacity.

Introduction

People around the world suffered very much from COVID-19 throughout 2020. On January 30, 2020, the World Health Organization (WHO) declared COVID-19 pandemic to be a public health emergency[1]. At the end of the year, a high-spreading mutant virus was found in some European countries. Luckly, due to the isolation policy, the epidemic spread has been decelerated for a while[2,3].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) mainly damages lung, like SARS[4-6]. Patients discharged from the hospital still have varying degrees of pulmonary impairment[7]. Therefore, a scoring system was needed for the "recovered" patients in the follow-up care and rehabilitation. Pulmonary function testing is not recommended due to high infectiousness. During the outbreak of COVID-19, chest CT has become the most popular diagnostic method[8,9]. At present, few articles focusing on the pulmonary dysfunction of COVID-19 patients after discharge have been reported. It remains unknown whether the residual CT characteristics could imply the possibility of pulmonary disorder.

In this study, a cross-sectional study was conducted to explore between residual CT features and spirometric parameters. A scoring system was established to evaluate the ventilatory severity of patients during recovery. This study aims to provide useful suggestions for the rehabilitation and further exercise of patients[10,11].

Patients and Methods

Research Object

In this retrospective study, a total of 101 COVID-19 patients from Wuhan Guanggu Central Hospital were included and confirmed by the SARS-CoV-2 nucleic acid test. The discharge time is from March 21, 2020, to April 5, 2020. The exclusion criteria were: 1) inability to cooperate with pulmonary function testing and 2) serious underlying cardiopulmonary diseases. This study expanded the use of the scoring system. Therefore, patients with lung malignancies, lobectomy, tuberculosis, or atelectasis were not excluded. According to international standards, our Institutional Review Board approved this retrospective study. Following the STARD guidelines, this study got approval from the Ethics Committee of Naval Hospital of Eastern Theater of PLA following the Declaration of Helsinki. In this study, lung function was allocated into non-severe and severe according to the percentage of FEV_1% to the expected value.

Grading Standards for Spirometric Abnormality

According to ATS/ERS guidelines, FEV_1/FVC <70% and TLC >80% are obstructive abnormalities; FEV_1/FVC >70% and TLC <80% are restrictive abnormalities; FEV_1/FVC <70% and TLC <80% are mixed abnormalities. A method to categorize the severity of ventilatory impairment based on the FEV_1% pred is: FEV_1% pred >70% is mild, FEV_1% pred 60%-69% is moderate, FEV_1% pred 50%-59% is moderately severe, FEV_1% pred 35%-49% is severe, and FEV_1% pred <35% is extremely severe.

New Coronavirus Disease Classification Standard

According to the "New Coronavirus Pneumonia Diagnosis and Treatment Plan (8^{th} Edition)" recommended by the National Health Commission of China in August 2020, COVID-19 patients are classified as mild, normal, severe, and critical. Severe COVID-19 patients should meet any of the following conditions: (1) Respiratory distress, RR≥30 beats/min; (2) resting blood oxygen saturation≤93%; and (3) arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2)≤300 mmHg. Critical COVID-19 patients should meet one of the following conditions: (1) respiratory failure, requiring mechanical; (2) shock; and (3) other organ failures requiring ICU monitoring and treatment.

Standards for Semi-Quantitative Assessment of Lung Involvement in Chest CT Images

Chest CT images were evaluated according to peer-reviewed literature on viral pneumonia and the Fleischner Society vocabulary for the following characteristics: ground glass opacity (GGO), crazy paving, consolidation, pleural thickening or adhesion, fibrosis, nodules, pleural effusion, and

bronchiectasis. A semi-quantitative scoring system was used to quantitatively assess the degree of lung involvement. The scores of the five lung lobes of the abnormally affected areas were as follows: 0 (no abnormal involvement), 1 (1%-25% abnormal involvement), 2 (26%-49% abnormal involvement), 3 (50%-75% abnormal involvement), and 4 (76%-100% abnormal involvement).

Collection of CT Characteristics

Chest CT imaging was performed on a 64-row, 128-slice CT scanner (United Imaging Uct 760). All patients were examined supine. CT images were acquired during breath-holding, with the scan ranging from the lung tip to the intercostal angle. The CT scan parameters were as follows: X-ray tube parameters-120 KVp, 263 mAs; rotation time-0.5 seconds; spacing-1.0; and section thickness-5 mm; slice thickness (0.625 mm) was used for other reconstructions. At the end of inhalation, a CT scan was performed from the lung tip to the lung base with 0.625 mm collimation at 10 mm intervals. The image was reconstructed using a high spatial frequency algorithm and photographed on the lung window (window width; 1,200H, horizontal; -600H). Two experienced thoracic radiologists (with 6 and 10 years of experience, respectively), knew nothing about the clinical, pulmonary function or pathological data independently analyzed the CT images.

Spirometry

All testers are trained to appropriately use the personal protective equipment (PPE) and follow risk assessment and standard precautions. Unless PFT was performed, COVID-19 patients should wear surgical masks or tightly fixed N95 respirators to ensure adequate sealing all the time. PPE includes headgear, goggles, N95 gas masks or FFP2 respirators, disposable protective clothing, and exercise without wrist exposure. Spirometry was performed under the supervision of a certified lung technician in a specialized lung function laboratory. PFT indexes were measured using a portable spirometer (U breath Spirometer system PF680, e-Link Care Meditech Co., Ltd., Hangzhou, China). The calculation formula used is the latest "Expected Value of Pulmonary Function Measurement for Chinese People Aged 4-80". The calculation formula of this estimated value is specifically designed for the Chinese population. Spirometry was performed by trained and certified pulmonary experts according to the ATS/ERS. The subjects are required to complete at least three repeatable operations, and the test results are displayed following ATS/ERS standards. Spirometric parameters include forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), FEF 25%-75% (MMEF), and the ratio of FEV_1/FVC. The spirometry parameters were measured as a percentage of the predicted value, including FVC, FEV_1, and FEV_1/FVC.

Statistical Analysis

Continuous data were expressed as mean±-standard deviation (SD). The frequency of demographic and clinical characteristics of populations was expressed as the number (percentage) of occurrences. Single comparisons were analyzed using the Chi-square test, Fisher's exact test, and Mann-Whitney U test. Multivariate regression analysis was performed for all statistically significant variables in univariate analysis to identify independent predictors of severe pulmonary abnormality in COVID-19 patients. Bootstrap estimates were based on 1000 bootstrap samples respectively[12,13]. Logistic regression was performed to calculate the odds ratio (OR). Receiver operating characteristics (ROC) curve analysis was used to calculate the area under the ROC curve (AUC), cut-off value, sensitivity, and specificity. Positive predictive value (PPV) and negative predictive value (NPV) were calculated to assess the diagnostic accuracy of models or predictors. Correlation between the scoring system and FEV_1% pred was determined using Spearman's correlation test. A *p*-value less than 0.05 is indicative of a statistically significant test. SPSS statistical software (SPSS 26, IBM, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Prism7, La Jolla, CA, USA) were used for statistical analyses.

Results

Basic Characteristics of the COVID-19 Patients

A total of 101 patients [(41 males (40.59%) and 60 females (59.41%)] with an average age of 57.490±12.996 years were enrolled in the experiment (Table I). The Body Mass Index (BMI) was 23.341±3.992, and the main comorbidities are hypertension (32 cases, 31.68%) and diabetes (16 cases, 15.84%). Since few patients have been diagnosed as mild and critical types, we allocated them into the mild+normal group (85

Table I. Baseline characteristics of patients with different COVID-19 pneumonia types.

	Total n = 101	Mild+normal n = 85	Severe+critical n = 16	*p*-value
Age	57 (50,68)	56 (49.5,66.5)	62 (55,73.75)	0.340
BMI	23.51 (20.97,25.47)	23.56 (20.97,25.87)	22.95 (20.79,24.29)	0.945
Gender, No. (%)				0.024*
Male	41 (40.59%)	30 (35.29%)	11 (68.75%)	
Female	60(59.41%)	55 (64.70%)	5 (31.25%)	
Comorbidities, No. (%)				
Hypertension	32 (31.68%)	24 (28.24%)	8 (50.00%)	0.140
Diabetes	16 (15.84%)	14 (16.47%)	2 (12.50%)	1.000
Coronary artery disease	7 (6.93%)	6 (7.06%)	1 (6.25%)	1.000
Respiratory system disease	7 (6.93%)	4 (4.71%)	3 (18.75%)	0.077
Chronic liver disease	3 (2.97%)	2 (2.35%)	1 (6.25%)	0.407
Types of ventilatory defects, No. (%)				
Restriction	62 (61.39%)	49 (57.65%)	13 (81.25%)	0.096
Obstruction	8 (7.92%)	8 (9.41%)	0 (0.00%)	0.350
Mixed defect	6 (5.94%)	3 (3.53%)	3 (18.75%)	0.049*
Normal	25 (24.75%)	25 (29.41%)	0 (0.00%)	0.010**
Severity classification, No. (%)				
Mild	41 (40.59%)	37 (43.53%)	4 (25.00%)	0.267
Moderate	21 (20.79%)	19 (22.35%)	2 (12.50%)	0.512
Severe	9 (8.91%)	2 (2.35%)	7 (43.75%)	0.000***
Critical	5 (4.95%)	2 (2.35%)	3 (18.75%)	0.027**
Spirometry, No. (%)				
FVC% pred < 80% pred	68 (67.33%)	52 (61.18%)	16 (100.00%)	0.001***
FEV_1% pred < 80% pred	62 (61.39%)	47 (55.29%)	15 (93.75%)	0.004**
FEV_1/FVC% < 92%	14 (13.86%)	11 (12.94%)	3 (18.75%)	0.692
MMEF% pred < 65% pred	22 (21.78%)	15 (17.65%)	7 (43.75%)	0.042*
FVC% pred < 80% pred+ FEV_1/FVC% < 92%	6 (5.94%)	3 (3.53%)	3 (18.75%)	0.049*

Notes: Data was shown as mean ± SD, or No. (%). *p*-values comparing different COVID-19 types are from Chi-square test, Fisher's exact test, or Mann-Whitney U test. **p*-value less than 0.05; ***p*-value less than 0.01; ****p*-value less than 0.001. BMI, body mass index; COVID-19, coronavirus disease 2019; FVC, forced vital capacity; FEV_1: forced expiratory volume in the first second; MMEF, maximal mid-expiratory flow.

cases, 84.16%) and severe+critical group (16 cases, 16.83%), respectively. There was no statistical difference in the baseline indicators among the groups except gender.

Ventilatory Defects of COVID-19 Patients During Rehabilitation

A total of 25 patients (24.75%) possessed normal ventilatory function during rehabilitation. The ventilatory abnormality caused by COVID-19 was mainly restricted disorder (Table I): 62 cases (61.39%) for restriction, 8 cases (7.92%) for obstruction, and 6 cases for mixed defect (5.94%). Specifically, all COVID-19 patients in the severe+critical group developed ventilatory abnormality of restriction or mixed defects, while 29.41% of patients in the mild+normal group were normal in ventilation, which indicated that severe/critical patients were more prone to pulmonary dysfunction.

According to the ATS/ERS international standard, the severity of spirometric abnormality was divided based on FEV_1% pred in our study. Accordingly, in terms of severity classification, there were 41 mild cases (40.59%), 21 moderate cases (20.79%), 9 severe cases (8.91%), and 5 critical cases (4.95%). Although the pulmonary disorder before discharge was mainly mild, severe/critical COVID-19 patients were more likely to develop severe pulmonary dysfunction before discharge. Moreover, mild/normal COVID-19 patients could also develop severe dysfunction (2.35%), though at a relatively low possibility. Hence, it is necessary to discriminate against patients with severe pulmonary abnormality and carry out rehabilitation training as soon as possible.

Specifically, there are 68 cases (67.33%) with FVC <80%, 14 cases (13.86%) with FEV_1/FVC <92%, 6 cases (5.94%) with both abnormal

FVC and FEV_1/FVC, and 22 cases (21.78%) with MMEF <65% (Table I). In severe/critical COVID-19 patients, almost all developed abnormal FVC (100%) and FEV_1 (93.75%), which was significantly different from mild/normal patients for abnormal FVC (61.18%) and FEV_1 (55.29%). Severe/critical COVID-19 patients also had more MMEF <65% abnormality (43.75%) compared with the mild/normal cases (17.65%). However, no significantly difference was observed in the FEV_1/FVC% between normal/mild (12.94%) and severe COVID-19 patients (18.75%), indicating less obstructive pulmonary abnormalities in COVID-19. From all above, these data suggested that COVID-19 pneumonia mainly caused the restricted disorder, and severe COVID-19 patients may develop more severe restriction at discharge.

Characteristics of Patients with Different Pulmonary Dysfunction

Subsequently, we tried to identify the characteristics of patients with severe or non-severe pulmonary dysfunction. No difference was found among the age, gender, BMI, and smoking habits of patients (Table II). Moreover, pulmonary coexisting disorders (such as chronic bronchi-

Table II. Characteristics of patients with non-severe and severe pulmonary function defects[§].

	Total n = 101	Non-severe n = 87	Severe and critical n = 14	*p*-value
Smoker, No. (%)	5/101 (4.95%)	5/87 (5.75%)	0	1.000
Drinker, No. (%)	5/101 (4.95%)	5/87 (5.75%)	0	1.000
Gender, No. (%)				0.242
Male	41/101 (40.59%)	33/87 (37.93%)	8/14 (57.14%)	
Female	60/101 (59.41%)	54/87 (62.07%)	6/14 (42.86%)	
Age	57.490 ± 12.996	56.78 ± 12.951	61.86 ± 12.871	0.340
BMI	23.341 ± 3.992	23.367 ± 4.165	23.18 1 ± 2.791	0.945
Respiratory symptoms, No. (%)				
Cough	51/101 (50.50%)	46/87 (52.87%)	5/14 (35.71%)	0.263
Expectoration	6/101 (5.94%)	4/87 (4.60%)	2/14 (14.29%)	0.193
Wheezing	17/101 (16.83%)	13/87 (14.94%)	4/14 (28.57%)	0.247
Dyspnea	4/101 (3.96%)	3/87 (3.45%)	1/14 (7.14%)	0.455
Underlying disease, No. (%)				
Hypertension	32/101 (31.68%)	25/87 (28.74%)	7/14 (50.00%)	0.130
Diabetes	16/101 (15.84%)	12/87 (13.79%)	4/14 (28.57%)	0.229
Coronary artery disease	7/101 (6.93%)	5/87 (5.75%)	2/14 (14.29%)	0.249
Respiratory system disease	7/101 (6.93%)	5/87 (5.75%)	2/14 (14.29%)	0.249
Chronic liver disease	3/101 (2.97%)	2/87 (2.30%)	1/14 (7.14%)	0.364
Underlying disease of respiratory system, No. (%)				
Chronic bronchitis	4/101 (3.96%)	3/87 (3.45%)	1/14 (7.14%)	0.455
Emphysema	1/101 (0.99%)	1/87 (1.15%)	0	1.000
Pulmonary tuberculosis	1/101 (0.99%)	1/87 (1.15%)	0	1.000
Cough and asthma	1/101 (0.99%)	1/87 (1.15%)	0	1.000
Rhinitis	1/101 (0.99%)	1/87 (1.15%)	0	1.000
Asthma	1/101 (0.99%)	0	1/14 (7.14%)	0.139
Oxygen therapy, No. (%)				
Low flow oxygen therapy	70/101 (69.31%)	58/87 (66.67%)	12/14 (85.71%)	0.216
High flow oxygen therapy	2/101 (1.98%)	0	2/14 (14.29%)	0.018*
Non-invasive	1/101 (0.99%)	0	1/14 (7.14%)	0.069
The lowest SpO_2 90%-93%	6/101 (5.94%)	3/87(3.45%)	3/14 (21.43%)	0.034*
The lowest SpO_2 < 90%	5/101 (4.95%)	0	5/14 (35.71%)	0.000***
COVID-19 classification, No. (%)				
Mild	3/101 (2.97%)	3/87 (3.45%)	0	1.000
Normal	82/101 (81.19%)	78/87 (89.66%)	4/14 (28.57%)	0.000***
Severe+critical	16/101(15.84%)	6/87 (6.90%)	10/14 (71.43%)	0.000***

Notes: Data was shown as mean ± SD or No.(%). *p*-values comparing different pulmonary function severity are from Chi-square test, Fisher's exact test, or Mann-Whitney U test. **p*-value less than 0.05; ***p*-value less than 0.01; ****p*-value less than 0.001. BMI, body mass index; SpO_2, pulse oxygen saturation; CT, computed tomography; COVID-19, coronavirus disease 2019. [§]The severe group in Table II was based on spirometry parameters.

tis, emphysema, tuberculosis, and asthma) and respiratory symptoms (such as cough, dyspnea, wheezing, and expectoration) were also not significantly different between COVID-19 patients with severe and non-severe pulmonary dysfunction. Among 101 cases, patients with non-severe pulmonary dysfunction were mainly normal-type COVID-19 (78/87, 89.66%), while patients with severe pulmonary dysfunction were mainly with severe COVID-19 (10/14, 71.43%) (Table II). Patients who had high-flow oxygen therapy during the disease or who had the lowest blood SpO_2 of less than 90%, indicated more severe COVID-19 diseases, and all developed severe pulmonary dysfunction at discharge. However, 28.57% of patients with severe pulmonary dysfunction developed from normal COVID-19 patients, who should be paid more attention during the rehabilitation period.

Residual CT Features of COVID-19 Patients with Pulmonary Dysfunction

Most of the patients underwent radiographic tests within 3 days before or after the pulmonary function test. Next, their radiographic characteristics were analyzed. The correlation of radiographic characteristics with the pulmonary function was explored (Table III). Consistent with previous reports, GGO was the main abnormality in COVID-19 patients (64.36%), and most of the abnormalities were bilateral (77.23%).

According to the results, 11 indicators statistically different between non-severe and severe pulmonary dysfunction patients were as follows: (1) consolidation area >25%; (2) thickening bronchial tube wall; (3) thickening bronchial vascular bundle; (4) interstitial pneumonia; (5) pleural thickening; (6) bilateral lesions; (7) total area of lung lesions >75%; (8) central area >50%; (9) anterior area >50%; (10) lung lobes lesions >5 lobes; and (11) lung segment lesions >16 segments (Table III). Consolidation area >25% in lung was significantly different between non-severe and severe groups.

Logistic Regression Equation to Predict Pulmonary Dysfunction

Through univariable analysis, the variables with a *p*-value less than 0.05 were used for binary logistic regression analysis with the forward step (likelihood ratio) method (Table IV). Finally, only two factors (consolidation area >25% and severe-type COVID-19) were enriched after multivariate logistic regression. Patients with consolidation area >25% were 11.2 times more likely to develop severe pulmonary dysfunction, and those with severe COVID-19 had 26.6 times the possibility to develop severe pulmonary dysfunction compared with mild/normal COVID-19 patients.

Bootstrap self-service sampling was used to obtain the equation as follows: ln[severe pulmonary dysfunction] = -3.452+2.418* [consolidation area >25%] +3.281* [COVID-19 in severe state]. According to *p*-values in Omnibus Tests of Model Coefficients test (0.000 <0.01) and Hosmer-Lemeshow test (0.551 >0.05), the model proved to be useful. The model (AUC 0.862, 95% CI 0.728-0.997), combing consolidation area >25%+severe COVID-19 may discriminate patients with latent severe pulmonary dysfunction from patients with mild dysfunction, with 78.57% sensitivity and 87.36% specificity (Table V and Figure 1).

The two variables in the equation do have good independent predictive effects. However, the total prediction rate was 87/101 (86.14%), and the PPV was 50%, which was relatively low (Table VI). The prediction coefficiency between predicted and measured lung function was also low. Hence, this equation exhibited an unsatisfactory predictive effect on patients with severe lung dysfunction.

Pulmonary Dysfunction Scoring System Based on Residual CT Features

To increase the PPV of the scoring standard, all the other clinically significant variables excluded in the equation were selected for scoring system construction, and the corresponding OR of each variable was assigned (Table VII and Figure 2). ORs were obtained from the univariate model. Scores ranged from 0 to 26 points. Patients who scored ≥12 points predicted severe lung dysfunction.

The correct percentage of prediction rose (Table VI and Table VII): non-severe 83/87(95.40%), severe and extremely severe 11/14 (78.57%), overall percentage 94/101 (93.07%). The PPV of the improved scoring system (11/15, 73.33%) was higher than that of the binary logistic equation (11/22, 50.00%). The specialty (from 87.36% to 95.40%) and total prediction rate (from 86.14% to 93.07%) have also rose. Therefore, the scoring system is more predictive than the logistic equation to evaluate the pulmonary dysfunction of the COVID-19 patients at discharge.

Table III. Univariate analysis of pulmonary CT characteristics in non-severe and severe pulmonary dysfunctional patients.

	Total n = 101	Non-severe n = 87	Severe and critical n = 14	*p*-value
Lesions area, No. (%)				
GGO < 50%	65 (64.36%)	55 (63.22%)	10 (71.43%)	0.765
GGO > 50%	24 (23.76%)	20 (22.99%)	4 (28.57%)	0.736
Consolidation < 25%	36 (35.64%)	32 (36.78%)	4 (28.57%)	0.765
Consolidation > 25%	12 (11.88%)	5 (5.75%)	7 (50.00%)	0.000***
Irregular interstitial lesions < 25%	33 (32.67%)	26 (29.89%)	7 (50.00%)	0.217
Irregular interstitial lesions > 25%	8 (7.92%)	6 (6.90%)	2 (14.29%)	0.306
Crazy-paving pattern < 50%	32 (31.68%)	26 (29.89%)	6 (42.86%)	0.363
Crazy-paving pattern > 50%	10 (9.90%)	7 (8.05%)	3(21.43%)	0.141
Fibrosis	47 (46.53%)	38 (43.68%)	9 (64.29%)	0.248
Thickening bronchial wall	14 (13.86%)	9 (10.34%)	5 (35.71%)	0.024*
Thickening bronchial vascular bundle	14 (13.86%)	9 (10.34%)	5 (35.71%)	0.024*
Underlying disease of lung, No. (%)				
Emphysema	38 (37.62%)	34 (39.08%)	4 (28.57%)	0.560
Tuberculosis	12 (11.88%)	10 (11.49%)	2 (14.29%)	0.671
Bronchiectasis	13 (12.87%)	10 (11.49%)	3 (21.43%)	0.383
Interstitial pneumonia	29 (28.71%)	20 (22.99%)	9 (64.29%)	0.003**
Pleural thickening	20 (19.8%)	13 (14.94%)	7 (50.00%)	0.006**
Nodules	23 (22.77%)	22 (25.29%)	1 (7.14%)	0.180
Location, No. (%)				
Unilateral	14 (13.86%)	14 (16.09%)	0 (0.00%)	0.207
Bilateral	78 (77.23%)	64 (73.56%)	14 (100.00%)	0.035*
Total area of lung lesions, No. (%)				
None	9 (8.91%)	9 (10.34%)	0 (0.00%)	0.354
< 25%	34 (33.66%)	31 (35.63%)	3 (21.43%)	0.373
25%~50%	27 (26.73%)	23 (26.44%)	4 (28.57%)	1.000
50%~75%	21 (20.79%)	18 (20.69%)	3 (21.43%)	1.000
> 75%	10 (9.90%)	6 (6.90%)	4 (28.57%)	0.031*
Predominant distribution, No.(%)				
Peripheral area < 50%	48 (47.52%)	41 (47.13%)	7 (50.00%)	1.000
Peripheral area > 50%	39 (38.61%)	32 (36.78%)	7 (50.00%)	0.385
Central area < 50%	60 (59.41%)	52 (59.77%)	8 (57.14%)	1.000
Central area > 50%	13 (12.87%)	8 (9.20%)	5 (35.71%)	0.017*
Anterior area < 50%	60 (59.41%)	51 (58.62%)	9 (64.29%)	0.776
Anterior area > 50%	11 (10.89%)	7 (8.05%)	4 (28.57%)	0.044*
Posterior area < 50%	56 (55.45%)	48 (55.17%)	8 (57.14%)	1.000
Posterior area > 50%	34 (33.66%)	28 (32.18%)	6 (42.86%)	0.544
Lung lobes lesions, No.(%)				
Lung lobes lesions > 5 lobes	59 (58.42%)	47 (54.02%)	12 (85.71%)	0.039*
Lung segments lesions, No.(%)				
Lung segments lesions > 16 segments	42 (41.58%)	32 (36.78%)	10 (71.43%)	0.020*

Notes: Data was shown as No. (%). *p*-values comparing different pulmonary CT characteristics are from Chi-square test, Fisher's exact test, or Mann-Whitney U test. **p*-value less than 0.05; ***p*-value less than 0.01; ****p*-value less than 0.001. CT, computed tomography; GGO, ground glass opacity.

Table IV. Multivariate analysis of patients with non-severe and severe pulmonary dysfunction defects.

	B	SE	Wald	*p*-value	Exp(B)	Exp(B) 95% CI
Consolidation area > 25%	2.418	4.123	7.052	0.001	11.221	3.142~19.304
Severe	3.281	5.426	16.859	0.001	26.602	15.967~37.237

Notes: B, Partial regression coefficient; SE, Standard error; Wald, Wald test statistic; Exp(B), odds ratio; 95% CI, 95% confidence interval. Omnibus Tests of Model Coefficients test, $p = 0.000 < 0.001$; Hosmer and Lemeshow Test, $p = 0.551 > 0.05$. Self-sampling results were based on 1000 self-sampling samples.

Table V. Cut-off values of predictive factor analysis of patients with non-severe and severe pulmonary dysfunction defects.

	AUROC	Cut-off value	Sensitivity	Specificity	95% CI
Consolidation area > 25%	0.721	0.500	50.00%	94.30%	0.551~0.892
Severe	0.823	0.500	71.40%	93.10%	0.678~0.968
Consolidation > 25% + Severe (Equation)	0.862	0.150	78.57%	87.36%	0.728~0.997
Scoring system	0.879	11.500	78.57%	95.40%	0.759~1.000

Notes: ROC, receiver operating characteristic curve; AUC, area under receiver operating characteristics curve; 95% CI, 95% confidence interval.

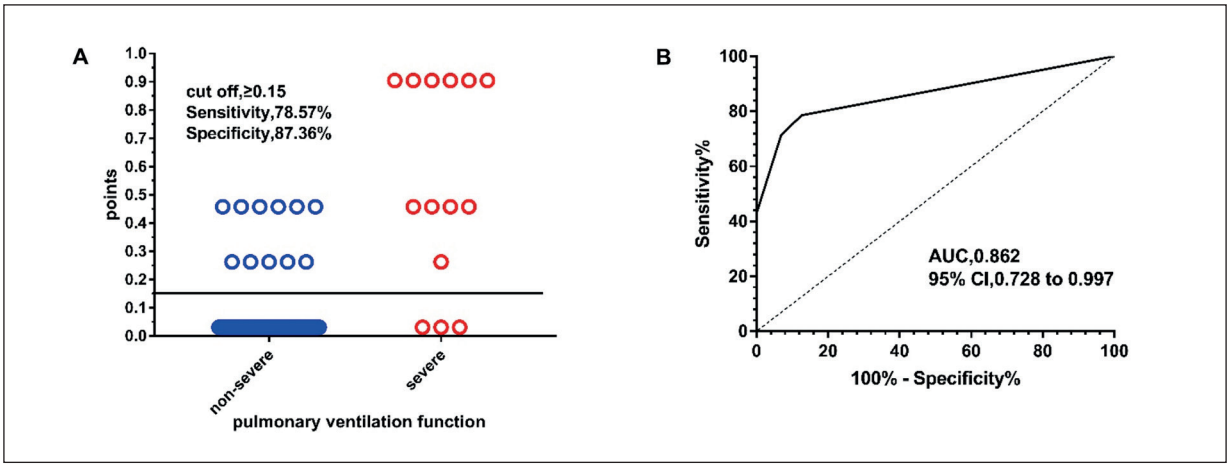

Figure 1. Scatter plot and ROC curve of binary logic equation. **A,** Scatter plot of binary logic equation. Non-severe group was shown *in blue*. Severe group was shown *in blue*. Patients score more than 0.15 is predicted to be severe. **B,** The area under curve (AUC) of binary logical regression equation for patients with severe PFTs.

Discussion

A recent study[14] has shown that restrictive deficiency is the most common spirometric abnormality associated with disease severity among discharged survivors of new coronavirus pneumonia, and patients recovered from coronavirus pneumonia may develop lung damage. Consistently, the diseased lung showed pathological changes (such as alveolar epithelial diffusely destruction, capillary endothelial damage/hemorrhage, hyaline membrane formation, alveolar

Table VI. Cut-off values of predictive factor analysis of patients with non-severe and severe pulmonary dysfunction defects.

	Equation	Scoring system
AUROC	0.862	0.879
Cut-off	0.150	11.500
Sensitivity	11/14 (78.57%)	11/14 (78.57%)
Specificity	76/87 (87.36%)	83/87 (95.40%)
Positive predictive value (PPV)	11/22 (50.00%)	11/15 (73.33%)
Negative predictive value (NPV)	76/79 (96.20%)	83/86 (96.51%)
Positive likelihood ratio (PLR)	6.214	17.089
Negative likelihood ratio (NLR)	0.245	0.225
Spearman's Correlation Coefficient between predicted and measured lung function	0.552**	0.719**
Kappa coefficient between predicted and measured lung function	0.532**	0.718**
Pearson Correlation Coefficient between scores and FEV_1% pred	0.600**	0.597**
Total prediction rate	87/101 (86.14%)	94/101 (93.07%)

Notes: Comparison between equation and scoring system **p-value less than 0.01.

Table VII. Scoring system.

	OR	Points
Clinical type:		
Severe	33.750	10
Oxygen therapy:		
High flow oxygen therapy	NA	1
The lowest SpO_2 is 90%~93%	7.636	1
The lowest SpO_2 < 90%	NA	1
Chest CT lesions patterns:		
Consolidation area > 25%	16.400	3
Underlying disease of lung:		
Thickening bronchial wall	4.815	1
Thickening broncho vascular bundles	4.815	1
Interstitial pneumonia	6.030	1
Thickening pleura	5.692	1
Location:		
Bilateral	NA	1
Total area of lung lesions:		
> 75%	5.400	1
Predominant distribution:		
Central area > 50%	5.486	1
Anterior area > 50%	4.571	1
Lung lobes lesions:		
Lung lobes lesions > 5 lobes	5.106	1
Lung segments lesions:		
Lung segments lesions > 16 segments	4.297	1

Notes: Comparison between equation and scoring system. OR, odds ratio; SpO_2, pulse oxygen saturation; NA, not applicable.

septal fibrous hyperplasia, and lung consolidation)[15,16], indicating a correlation between residual CT abnormalities and pulmonary dysfunction. As evidenced by previous follow-up studies[17,18], SARS patients still have lung function impairment, which may last for months or even years. MERS patients still have lung dysfunction after discharge[19]. Our research results on pulmonary function are consistent with that of Zhong's team[20], which further revealed the correlation between CT and pulmonary function parameters during the rehabilitation period of patients.

The abnormalities seen in chest CT changed in varying degrees with the progression[21]. The typical pattern of CT images in subclinical patients is unilateral multifocal, mainly GGO. Next, the lesion rapidly develops into bilateral diffuse disease, and the most common is bilateral peripheral GGO, which is mostly distributed in the back and peripheral of the lungs[22-24]. Consistently, the results of most of the published lung CT literature revealed this feature. In the middle and late stages of the disease, the frequency of GGO is relatively gradually reduced and transited to consolidation and mixed-mode development. Therefore, the consolidation areas will appear in the late stage of the clinical course, and the affected areas develop from outside to inside and from back to front[25-27]. Bronchial tube wall thickening, bronchial vascular bundles thickening, and interstitial changes in the lungs indicate gap changes[28]. Although no clear natural history of COVID-19 pneumonia is available, it can still indicate the progression of fibrosis[29]. Moreover, bronchiectasis, adjacent pleura thickening, and pleural effusion also appeared during this period[30]. Previous literature[31] has suggested that pleural thickening and pleural effusion may indicate a severe degree in disease progression. Most disease lung have two or more lung lobes involved, suggesting a wide involvement scope and diffuse lesion distribution. These CT findings that vary with the disease can mon-

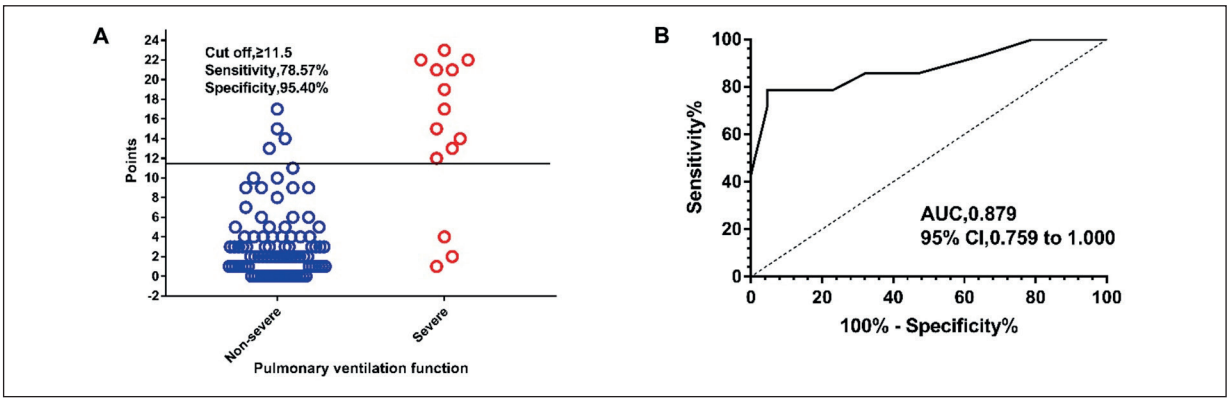

Figure 2. Scatter plot and ROC curve of scoring system. **A,** Scatter plot of scoring system for the diagnosis of patients with severe PFTs. Non-severe group was shown *in blue*. Severe group was shown *in blue*. By using a cut-off value of 11.5 points, the CT scoring system shows high specificity for the differential diagnosis of pulmonary dysfunction comparing to logical regression equation (95.40% to 87.36%). **B,** The area under curve (AUC) also shows a higher diagnostic performance of the CT scoring system (0.879 to 0.862).

itor the treatment effect, and the radiographic deterioration also seems to be related to poor prognosis.

Consistent with the different CT findings of COVID-19 pneumonia in different clinical stages in previous studies, the CT results change with the disease progression, and the CT changes of patients with different severity are different[32]. For patients in severe+critical group, the number of patients with crazy paving and consolidation was gradually increased, while the number with GGO was decreased. It has been shown[33] that with the further changes of the disease, the incidence of pleural thickening or adhesions gradually reaches the peak. This study further proved that the lung function changes, and CT are also related, and the CT of patients with severe and critical lung dysfunction showed more extensive and serious involvement. The predicted results of some patients are inconsistent with the actual pulmonary function, which may be caused by advanced age or complications with extrapulmonary diseases (such as hypertension, diabetes, and heart diseases)[34].

In addition to CT findings related to pulmonary dysfunction, we also found that severe COVID-19 diseases and oxygen therapy measures should also be highly concerned. Severe COVID-19 patients are characterized by progressive respiratory failure due to lung infection with SARS-CoV-2. Most patients develop impaired respiratory function or other system diseases. Dyspnea is the only symptom that can predict serious illness and ICU admission. COPD is the strongest predictive comorbidity for serious diseases and ICU admission, followed by cardiovascular disease, hypertension, and diabetes[35-37]. Pre-existing diabetes (mostly type 2 diabetes) is associated with a 2-3 times higher risk of serious/critical illness and intrinsic diseases[38,39]. Hypercoagulability and cytokine inflammatory response storm can also help to explain the progression of the clinical course in severe COVID-19 patients[40]. As has been previously evidenced, lymphocyte count can be used to identify patients who may develop severe COVID-19[41].

The rational use of different techniques by well-trained pulmonologists helps to prevent clinical exacerbation and reduce the risk of ICU admission, especially when resources are limited or invasive is not available. Regardless of the choice of oxygen therapy, patient comfort and reducing the risk of the nursing staff should be given priority[42].

For patients with severe COVID-19 pneumonia, oxygen therapy should be used as soon as SpO_2 <92%. Severe patients treated with nasal high flow oxygen therapy (HFOT) or non-invasive ventilation (NIV) should be closely monitored because they have a higher risk of treatment failure and then clinical deterioration[43]. Tracheal intubation should be considered if the patient's condition deteriorates acutely or show no eviednt improvement after a short-term trial. We have experienced a similar case of disease deterioration. Patient A (male, 48 years old) showed the main clinical manifestations of dry cough, muscle aches, fever, wheezing, and chest distress. The spontaneous breathing blood oxygen saturation was less than 70%; and lung CT showed large shadow patches in both sides with progressively growing. Hence, the patient was determined as critical. During the treatment process, in the case of HFOT by mask, the finger pulse oxygen saturation was still about 80%, accompanied by breath shortness (35 beats/min), raised heart rate (140 beats/min), and decreased blood pressure (90/60 mmHg). Considering hypoxemia caused by exacerbation of lung disease, non-invasive ventilation (NIV) was immediately performed (CPAP mode, FiO_2 80%, PEEP 5 cmH_2O, Pressure support 8 cmH_2O). At the same time, hormonal sedation and other drugs were given to reduce oxygen consumption. After that, SpO_2 rose to about 95%.

Limitations

This study also has some limitations. Firstly, the sample size is relatively small, especially in the severe group. It is necessary to conduct further research on more patients to obtain a clear answer. Secondly, the quantitative and semi-quantitative measurements of lung disease may be subjective, which can only partially reflect the severity. In future studies, an accurate quantitative analysis should be performed to identify the changes in clinical and imaging characteristics. Thirdly, there was no external verification. Due to national and hospital policies, more new patient data could not be obtained in the subsequent period. Finally, diffuse dysfunction is the most common lung function abnormality among survivors of COVID-19 discharged from the hospital, followed by restrictive defects. Limited by the testing equipment, the related indicators could not be measured, such as TLC or carbon monoxide diffusing capacity (DLCO). In the future, for some recovered survivors, especially

those critically ill patients, lung function tests including diffusion function should be taken into consideration during routine clinical follow-up. The relationship between lung diffusion function and CT, as well as other clinical indicators, needs to be further studied.

Conclusions

In summary, lung CT images and other indicators were firstly used to evaluate lung function in our study. The correlation between lung CT images and lung function parameters was analyzed. Therefore, a grading scale based on the lung CT scoring system was obtained to infer the pulmonary function of COVID-19 patients during the recovery period. Pulmonary function during the recovery period is especially helpful in predicting patients with poor prognoses that cannot be identified only by nucleic acid and antibody testing. These findings may help to improve the quality of life of COVID-19 patients, including early and timely lung function rehabilitation training before discharge.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Naval Hospital of Eastern Theater of PLA. All data were anonymized to comply with the provisions of personal data protection legislation. Due to the retrospective nature of this study and due the fact that only historical medical data were collected, written informed consent was not required.

Availability of Data and Materials

The data set used for this manuscript will be available from the corresponding author upon reasonable request.

Authors' Contribution

YC, HXY, ZC, YFF, LB, LY, LY, SLJ, TL, LQ, HYC, HHY, CMY, and ZZ were involved in data collection. YC, HXY, YFF, and ZZ were involved in analysis of the data. YC, HXY, and ZZ wrote the manuscript. All authors contributed to the revision and approved the final version of the manuscript. ZZ takes responsibility for the integrity of the work as a whole, from inception to published article.

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