Pulmonary fibrosis and its related factors in discharged patients with new coronavirus pneumonia: A cohort study of 90-150 days follow-up after onset

Xiaohe Li
Shenzhen Third People's Hospital
Chenguang Shen
Shenzhen Third People's Hospital
Lifei Wang
Shenzhen Third People's Hospital
Sumit Majumder
Southern University of Science and Technology
Die Zhang
Shenzhen Third People's Hospital
M. Jamal Deen
Southern University of Science and Technology
Yanjie Li
Shenzhen Third People's Hospital
Ling Qing
The Third People's Hospital of Shenzhen
Ying Zhang
Shenzhen Third People's Hospital
Chuming Chen
Shenzhen Third People's Hospital
Rongrong Zou
The Third People's Hospital of Shenzhen
Jianfeng Lan
The Third People's Hospital of Shenzhen
Ling Huang
Shenzhen Third People's Hospital
Cheng Peng
Shenzhen Third People's Hospital
Lijiao Zeng
The Third People's Hospital of Shenzhen

Yanhua Liang
The Third People's Hospital of Shenzhen
Mengli Cao
The Third People's Hospital of Shenzhen
Yang Yang
The Third People's Hospital of Shenzhen
Minghui Yang
The Third People's Hospital of Shenzhen
Guoyu Tan
The Third People's Hospital of Shenzhen
Shenghong Tang
The Third People's Hospital of Shenzhen
Lei Liu
The Third People's Hospital of Shenzhen
Jing Yuan
The Third People's Hospital of Shenzhen
Yingxia Liu (34762354@qq.com)
The Third People's Hospital of Shenzhen

Research

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Abstract

Background: Thousands of the Coronavirus Disease 2019 (COVID-19) patients have been discharged from hospitals, long-term follow-up studies are required to evaluate the prevalence of post-COVID-19 fibrosis.

Methods: This study involves 462 laboratory confirmed patients with COVID-19 who were admitted to Shenzhen Third People's Hospital from January 11, 2020 to April 26, 2020. A total of 457 patients underwent thin-section chest CT scans during the hospitalization or after discharge to identify the pulmonary lesion. A total of 289 patients were followed up from 90 days to 150 days after the onset of the disease.

Results: Parenchymal bands, irregular interfaces, meshwork and traction bronchiectasis were the most common CT features in all COVID-19 patients. 86.87%, 74.40%, 79.56%, 68.12% and 62.03% patients developed with pulmonary fibrosis and 4.53%, 19.61%, 18.02%, 38.30% and 48.98% patients reversed pulmonary fibrosis during the 0-30, 31-60, 61-90, 91-120 and >120 days after onset, respectively. It was observed that Age, BMI, Fever, and Highest PCT were predictive factors for sustaining fibrosis even after 90 days from onset. A predictive model of the persistence with pulmonary fibrosis was developed based-on the Logistic Regression method with an accuracy, PPV, NPV, Sensitivity and Specificity of the model of 76%, 71%, 79%, 67%, and 82%, respectively. Only a fraction of COVID-19 patients suffered with abnormal lung function after 90 days from onset, and the ratio of abnormal lung function did not differ on a statistically significant level between the fibrotic and non-fibrotic groups.

Conclusions: Long-term pulmonary fibrosis was more likely to develop in patients with older age, high BMI, severe/critical condition, fever, long time to turn the viral RNA negative, pre-existing disease and delay to admission. Fibrosis developed in COVID-19 patients could be reversed in about a half of the patients after 120 days from onset. The pulmonary function of most of COVID-19 patients with pulmonary fibrosis could turn to normal condition after three months from onset. An effective prediction model with an average Area Under the Curve (AUC) of 0.84 was established to predict the persistence of pulmonary fibrosis in COVID-19 patients for early diagnosis.

Background

The Coronavirus Disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic [1]. As of July 14, 2020, there have been 13,070,095 confirmed cases of COVID-19, including 572,539 deaths globally, posing a serious threat to public health worldwide [2]. Infection of SARS-CoV-2 could cause atypical pneumonia with clinical presentation, mainly causing respiratory system infections in humans that can range from a minor common cold to severe diseases [1, 3]. COVID-19 causes pulmonary syndromes similar to other strains of the coronavirus family, namely severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS)

coronavirus. Previous data from the study of MERS and SARS suggested that there could be substantial fibrotic consequences following SARS-CoV-2 infection [4, 5].

Chest computed tomography (CT) plays an important role in the diagnosis and treatment of patients with COVID-19 that helps in the diagnosis by depicting lung abnormalities and in the evaluation of the progress of disease and response to treatment [6–8]. Several studies have described the imaging and clinical features of patients during hospitalization or discharged after treatment with COVID-19 using serial thin-section CT [9–14]. At present, it is not known if COVID-19 patients who survived pneumonia would be at risk of chronic sequelae. Long-term follow-up studies are required to evaluate the prevalence of post-COVID-19 fibrosis. In this study, by observing the long-term dynamic changes and the predictors of pulmonary fibrosis in discharged patients with COVID-19, we tried to identify whether the development of pulmonary fibrosis occurs in the survivor population and find early warning indicators that cause pulmonary fibrosis, with a view to develop an early intervention tool to reduce the occurrence of pulmonary fibrosis.

Methods

Study Design and Patients

This study involves 462 patients with COVID-19 who had been admitted to Shenzhen Third People's Hospital from January 11, 2020 to April 26, 2020. COVID-19 patients were diagnosed using quantitative reverse-transcription polymerase chain reaction (qRT-PCR) based on the World Health Organization's interim guidance [15]. Among them, a total of 457 patients underwent thin-section chest CT scans during the hospitalization or after discharge. These patients were discharged from the hospital between January 23, 2020 and May 21, 2020, and the discharge criteria were in line with the Chinese guideline for COVID-19 pneumonia.

After discharge, the patients were followed up every four weeks or so, and the final date of follow-up was June 20, 2020. The average observation time of these 457 patients was 80.57 days after onset, the median time was 76 days, including the shortest of 12 days and the longest of 151 days. A total of 289 patients was followed up from 90 days to 150 days after the onset of the disease. During the period of hospitalization, 457 patients underwent routine laboratory tests in every 3 to 7 days, and CT scans in every 3–5 days. In addition, lung function tests were conducted in about 3 months after the onset. Clinical data during hospitalization, and imaging and pulmonary function data after discharge of these patients were obtained from a review of the hospital computer medical system to analyze the pulmonary fibrosis status of COVID-19 patients at different stages. The effect of pulmonary fibrosis on pulmonary function was analyzed simultaneously. The risk factors affecting the persistence of pulmonary fibrosis were identified through regression analysis and a prediction model of the persistence with pulmonary fibrosis was established.

CT Imaging

Several non-contrast thin-section chest CT scans were performed for each patient using two independent medical CT machines. Equipment and scanning parameters are as follows: 1) Toshiba TSX-101A64 row spiral CT machine, tube voltage 120 kV, automatic tube current, reconstructed layer thickness 1 mm. 2) Shanghai uCT760 64-row spiral CT machine, tube voltage 120 kV, automatic tube 40 mA, reconstructed layer thickness 0.625 mm. All image data were observed in the pulmonary window, with window width and window level of 1600 HU and − 550 HU, respectively.

Judgment Of Pulmonary Fibrosis

All thin-section CT images were independently analyzed by three experienced radiologists to determine the presence of pulmonary fibrosis, and any disagreement was resolved by discussion and consensus. Pulmonary fibrosis on chest CT imaging was defined as a combination of findings including parenchymal bands, irregular interfaces, meshwork and traction bronchiectasis [5, 16, 17].

Disease Severity Classification

Disease severity classification and Murray Score calculation were evaluated as previously reported [18]. Severity of COVID-19 was graded according to China National Health Commission Guidelines for Diagnosis and Treatment of SARS-CoV-2 infection. Laboratory confirmed patients with fever, respiratory manifestations and radiological findings indicative of pneumonia were considered as the moderate cases. Laboratory confirmed patients who met any of the following were considered to have severe COVID-19: (i) respiratory distraction (respiration rate ≥ 30/min; (ii) resting oxygen saturation ≤ 93%, or (iii) arterial oxygen partial pressure (PaO2) / fraction of inspired oxygen (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa). Laboratory confirmed patients who had any of the following were considered in critical condition: (i) respiratory failure requiring mechanical ventilation, (ii) shock, or (iii) failure of other organs requiring intensive care unit (ICU).

Statistical Analysis

Continuous variables were presented as mean ± standard deviation and categorical variables were presented as *n* (%). Event frequencies were compared with Chi-squared test. The comparisons of continuous parameters between two groups were made with the one-way Analysis of Variance (ANOVA) method. ANOVA shows if the distribution of a parameter is different in different groups. That is, it provides a measure of the significant difference (*p*-value) between the averages of a parameter from two groups. A *p*-value < 0.05 was considered as significant for all statistical tests. Only statistically significant variables ($p < 0.05$) were selected to develop a simple logistic regression model–based clinical tool for early diagnosis. Variables with $p > 0.05$ were considered as irrelevant and were discarded during the parameter selection and training process. The performance of the model was validated using a five-fold cross validation and assessed with the Receiver Operating Characteristic (ROC) curve, accuracy, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Sensitivity and Specificity. The analysis was performed using a custom-written code in the MATLAB (version R2017b) environment. MATAB is a

powerful and commonly used software for mathematical analyses, modeling, classification and prediction.

Results

Demographics and baseline characteristics of 457 COVID-19 patients

Our study included all 457 confirmed COVID-19 cases admitted to the Shenzhen Third People's Hospital and followed up till June 20, 2020. For this part of the study, the patients were divided into three groups depending on their lung conditions. Group1 (G1) had 29 (6.3%) patients without pneumonia from onset to end of follow-up, Group 2 (G2) had 31 (6.8%) patients with pneumonia but no lung fibrosis from onset to end of follow-up and Group 3 (G3) had 397 (86.9%) patients with pneumonia and lung fibrosis during period. The average age of all patients was 43.8 ± 17.7 years, 227 of 457 patients (49.7%) were male, and the average length of hospital stay was 23.0 ± 9.8 days. Table 1 presents the general statistics of epidemiological and baseline clinical features of all 457 patients with CT scan.

Table 1
General Statistics of epidemiological and baseline clinical features of all patients with CT scan

	All Patients (N = 457)	Group 1 (N = 29)	Group 2 (N = 31)	Group 3 (N = 397)	P value (G2 vs G3)
Physical Characteristics					
Gender (male ratio)	50%	41%	45%	51%	0.689
Age (year)	43.81 ± 17.68	23.21 ± 10.54	31.97 ± 18.82	46.24 ± 16.67	< 0.0001
BMI (kg/m^2)	23.08 ± 3.66	20.19 ± 3.00	20.65 ± 2.90	23.48 ± 3.60	< 0.0001
Pre-existing Conditions					
Pre-existing disease (%)	29%	7%	10%	32%	0.016
DM (%)	5%	0%	0%	6%	0.356
Hypertension (%)	13%	0%	0%	15%	0.044
Coronary heart disease (%)	5%	0%	0%	6%	0.335
Respiratory disease (%)	5%	3%	3%	5%	0.986
Others					
Time from onset to virus RNA negative	19.05 ± 10.23	18.79 ± 12.84	12.74 ± 7.49	19.56 ± 10.05	0.0002
Time from onset to admission (day)	4.34 ± 4.22	4.31 ± 5.85	1.71 ± 2.16	4.55 ± 4.13	0.0002
Length of hospitalization (day)	22.95 ± 9.75	21.93 ± 8.90	18.35 ± 6.44	23.39 ± 9.95	0.006
Case type: (severe/critical ratio, %)	20%	00%	00%	23%	0.006
Symptoms					
Fever (%)	65%	48%	16%	70%	< 0.0001
Fatigue (%)	11%	10%	6%	12%	0.539
Cough (%)	15%	14%	3%	16%	0.096

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PaO_2, partial pressure of oxygen; FIO_2, fraction of inspired oxygen; WBC, white blood cells; N, neutrophils; L, lymphocyte; HB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin.

	All Patients (N = 457)	Group 1 (N = 29)	Group 2 (N = 31)	Group 3 (N = 397)	P value (G2 vs G3)
Expectoration (%)	9%	7%	6%	10%	0.799
Diarrhea (%)	4%	7%	0%	4%	0.517
Laboratory Report					
Oxygenation index (PaO_2/FiO_2)	427.28 ± 125.37	504.89 ± 127.60	472.13 ± 102.10	419.31 ± 124.83	0.030
Lactic acid (mmol/L)	1.35 ± 0.49	1.34 ± 0.44	1.35 ± 0.44	1.35 ± 0.49	0.997
WBC (10^9/L)	5.05 ± 1.89	6.16 ± 1.84	5.28 ± 1.44	4.95 ± 1.90	0.340
N (10^9/L)	3.01 ± 1.53	3.23 ± 1.41	2.80 ± 1.20	3.01 ± 1.56	0.460
L (10^9/L)	1.50 ± 0.74	2.32 ± 0.88	1.96 ± 0.68	1.41 ± 0.68	< 0.0001
HB (g/L)	138.09 ± 16.69	141.93 ± 14.26	138.26 ± 14.29	137.79 ± 17.03	0.883
PLT (10^9/L)	198.54 ± 64.83	250.86 ± 64.88	227.87 ± 57.15	192.43 ± 63.16	0.003
ALB (g/L)	43.35 ± 3.74	46.66 ± 2.96	44.00 ± 3.19	43.05 ± 3.72	0.169
ALT (U/L)	25.74 ± 19.41	20.68 ± 9.65	27.05 ± 43.04	26.00 ± 16.89	0.777
AST (U/L)	29.90 ± 15.68	27.51 ± 10.77	29.39 ± 33.30	30.12 ± 13.81	0.807
LDH (U/L)	291.37 ± 172.02	211.15 ± 115.79	226.79 ± 130.32	302.20 ± 175.97	0.024
CK (U/L)	100.96 ± 130.41	69.77 ± 23.36	74.69 ± 30.93	105.30 ± 139.26	0.328
BUN (mmol/L)	4.25 ± 3.78	3.76 ± 0.85	4.55 ± 2.10	4.26 ± 4.02	0.700
Cr (μmol/L)	65.74 ± 19.51	59.43 ± 17.95	60.24 ± 17.96	66.63 ± 19.62	0.080
ESR (mm/h)	31.07 ± 22.97	13.15 ± 10.48	15.43 ± 9.74	33.60 ± 23.34	< 0.0001

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PaO_2, partial pressure of oxygen; FIO_2, fraction of inspired oxygen; WBC, white blood cells; N, neutrophils; L, lymphocyte; HB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin.

	All Patients (N = 457)	Group 1 (N = 29)	Group 2 (N = 31)	Group 3 (N = 397)	P value (G2 vs G3)
D-Dimer (μg/mL)	0.54 ± 0.76	0.38 ± 0.29	0.31 ± 0.09	0.57 ± 0.81	0.071
CRP (mg/dL)	20.19 ± 29.94	3.04 ± 4.16	2.92 ± 6.13	22.59 ± 31.19	0.002
IL-6 (ng/L)	16.13 ± 23.11	4.07 ± 3.68	4.19 ± 4.90	17.55 ± 24.04	0.012
PCT (ng/mL)	0.12 ± 0.31	0.21 ± 0.54	0.14 ± 0.11	0.12 ± 0.30	0.653
CD4 cells (count/μL)	601.83 ± 323.69	757.39 ± 218.81	805.36 ± 262.60	574.41 ± 326.36	0.001
Highest CRP (mg/dL)	37.21 ± 48.98	5.35 ± 6.37	7.23 ± 13.75	41.82 ± 50.82	< 0.0001
Highest IL-6 (ng/L)	36.44 ± 126.14	4.18 ± 3.21	3.92 ± 2.29	40.64 ± 133.67	0.171
Highest PCT (ng/mL)	0.31 ± 0.08	0.30 ± 0.07	0.27 ± 0.08	0.31 ± 0.08	0.002
Lowest CD4 (count/μL)	543.21 ± 308.21	728.08 ± 249.35	771.07 ± 276.01	511.41 ± 302.83	< 0.0001
Highest ESR (mm/h)	43.40 ± 31.48	15.63 ± 12.85	20.82 ± 12.81	47.09 ± 31.75	< 0.0001
Highest D-Dimer (μg/mL)	1.05 ± 1.89	0.40 ± 0.28	0.36 ± 0.15	1.16 ± 2.02	0.029
Highest lactic acid (mmol/L)	2.52 ± 1.34	2.06 ± 0.85	1.84 ± 0.56	2.60 ± 1.39	0.003
Lowest oxygenation index (PaO_2/FiO_2)	311.57 ± 132.81	414.26 ± 134.18	407.17 ± 105.68	297.11 ± 128.65	< 0.0001

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PaO_2, partial pressure of oxygen; FIO_2, fraction of inspired oxygen; WBC, white blood cells; N, neutrophils; L, lymphocyte; HB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin.

CT Characteristics And Dynamic Changes In Pulmonary Fibrosis

We analyzed the three CT scans for every patient. Parenchymal bands, irregular interfaces, meshwork and traction bronchiectasis were the most common CT features in all COVID-19 patients. During hospitalization and follow-up, some patients had persistent pulmonary fibrosis (Fig. 1), while some patients had reversal of pulmonary fibrosis (Fig. 2). Typical CT imaging of a 67-year-old man showed diffuse ground glass opacities in both lungs, and visible parenchymal band in the lower lobe of left lung

on initial CT. Diffuse ground glass opacities, consolidation and irregular interfaces with a small amount of pleural effusion were observed on the first follow-up CT. For the third (88 days after symptoms onset) and latest (132 days after symptoms onset) follow-up CT after discharge, diffuse ground glass opacities, consolidation and pleural effusion were still observed in the lungs, although most lesions were absorbed (Fig. 1). Typical CT imaging findings of a 53-year-old woman showed multiple lesions, a mass of ground glass opacities, consolidation and irregular interfaces on initial CT. The lesions were absorbed obviously on the 6th day after onset, further absorbed on the 9th and 19th days after onset, and completely absorbed in both lungs on 108th day after symptoms onset (Fig. 2).

Some patients did not follow-up along with the time extension, a total of 457 patients was included during the 0–30 days after onset in this study. During the 31–60, 61–90, 91–120 and > 120 days after onset, there were 418, 279, 207 and 79 patients included, respectively, among them, 397 (86.87%), 360 (86.12%), 236 (84.59%), 171 (82.61%) and 64 (81.01%) patients developed with pulmonary fibrosis, respectively. It is interesting to see that pulmonary fibrosis developed in COVID-19 patients could be reversed. Reversal of pulmonary fibrosis were found in 18 (4.53%), 49 (13.61%), 14 (5.93%), 30 (17.54%) and 15 (7.81%) COVID-19 patients during the 0–30, 31–60, 61–90, 91–120 and > 120 days after onset, respectively (Table 2). There was a total of 126 patients who had pulmonary fibrosis reversed, and the median time of reversal of pulmonary fibrosis was 70.79 ± 37.67 days (median: 59 days, range: 8-148 days). In contrast, there were 271 patients who still had pulmonary fibrosis at the last follow-up.

Table 2
Dynamic changes of pulmonary fibrosis in 457 patients at different stages after onset of COVID-19

COVID-19 Patients	Days after onset				
	0–30	31–60	61–90	91–120	>120
Patients included in different stages	457	418	279	207	79
Patients with pneumonia	428 (93.65%)	397 (94.98%)	272 (97.49%)	202 (97.58%)	77(97.47%)
Patients with pulmonary fibrosis	397 (86.87%)	360 (86.12%)	236 (84.59%)	171 (82.61%)	64 (81.01%)
Patients with reversal of pulmonary fibrosis	18 (4.53%)	49 (13.61%)	14 (5.93%)	30 (17.54%)	15 (7.81%)

Comparison of clinical characteristics between patients with pulmonary fibrosis and with no fibrosis/reversal of pulmonary fibrosis after 90 days from onset.

In order to observe the long-term pulmonary consequences of COVID-19 patients, 289 confirmed COVID-19 patients who was followed up more than 90 days after onset were further divided into two groups

(group A and group B) according to the progression of pulmonary fibrosis. Group A (GA) had 116 (40.14%) patients who either had no lung fibrosis, or their lung fibrosis disappeared within 90 days after onset. On the other hand, 173 (59.86%) patients who still had lung fibrosis after 90 days from onset, were categorized as Group B (GB) (Table 3).

Table 3
Epidemiological and baseline clinical features of 289 patients

	Group A (N = 116)	Group B (N = 173)	P value
Physical characteristics			
Gender (male ratio, %)	44%	52%	0.2212
Age (year)	33.06 ± 17.50	50.68 ± 13.25	< 0.0001
BMI (kg/m^2)	22.10 ± 3.43	24.06 ± 3.21	< 0.0001
Pre-existing Conditions (with pre-existing disease ratio)			
Pre-existing disease (%)	19.0%	38.2%	0.0008
DM (%)	0%	7.5%	0.0063
Hypertension (%)	3.5%	19.1%	0.0002
Coronary heart disease (%)	3.5%	6.9%	0.3131
Respiratory disease (%)	3.5%	5.2%	0.6776
Others			
Case type: (severe/critical ratio, %)	4.3%	29.5%	< 0.0001
Time from onset to virus RNA negative (day)	14.72 ± 8.22	20.99 ± 9.34	< 0.0001
Time from onset to admission (day)	3.01 ± 3.03	5.22 ± 4.29	< 0.0001
Length of hospitalization (day)	19.17 ± 6.85	24.35 ± 9.70	< 0.0001
Follow-up period from onset (day)	67.78 ± 36.09	117.77 ± 14.24	< 0.0001
Symptoms			
Fever (%)	51.7%	72.8%	0.0004
Fatigue (%)	9.5%	10.4%	0.9554
Dry cough (%)	18.1%	25.4%	0.1871
Cough (%)	13.8%	18.5%	0.3724
Expectoration (%)	9.5%	6.9%	0.5739

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PaO_2, partial pressure of oxygen; FIO_2, fraction of inspired oxygen; WBC, white blood cells; N, neutrophils; L, lymphocyte; HB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin.

	Group A (N = 116)	Group B (N = 173)	P value
Diarrhea (%)	0.9%	5.8%	0.0675
Treatment			
Hormones (%)	5.17%	32.3%	< 0.0001
Acetylcysteine (100%)	41.4%	71.7%	< 0.0001
Gamma globulin (100%)	4.3%	31.8%	< 0.0001
Invasive ventilator (100%)	0%	5.2%	0.0315
Non-invasive ventilator (100%)	0.9%	14.5%	0.0002
Laboratory findings			
Oxygenation index (PaO_2/FiO_2)	463.15 ± 123.05	411.60 ± 130.24	0.0014
Lactic acid (mmol/L)	1.29 ± 0.45	1.34 ± 0.44	0.2963
WBC (10^9/L)	5.179 ± 2.04	4.82 ± 1.71	0.1174
N (10^9/L)	2.85 ± 1.47	3.00 ± 1.43	0.3689
L (10^9/L)	1.7659 ± 0.88	1.32 ± 0.59	< 0.0001
HB (g/L)	137.11 ± 15.43	138.28 ± 15.08	0.5240
PLT (10^9/L)	210.35 ± 65.32	188.19 ± 56.95	0.0025
ALB (g/L)	43.91 ± 3.18	42.64 ± 3.55	0.0021
ALT (U/L)	24.54 ± 26.74	26.32 ± 17.20	0.4918
AST (U/L)	28.34 ± 20.18	31.01 ± 13.97	0.1855
LDH (U/L)	267.37 ± 144.00	308.43 ± 191.53	0.0594
CK (U/L)	115.30 ± 194.97	103.05 ± 112.20	0.5729
BUN (mmol/L)	4.16 ± 1.41	4.09 ± 1.62	0.6789
Cr (μmol/L)	60.92 ± 17.81	68.75 ± 20.66	0.0010
ESR (mm/h)	23.01 ± 20.32	35.95 ± 23.00	< 0.0001

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PaO_2, partial pressure of oxygen; FIO_2, fraction of inspired oxygen; WBC, white blood cells; N, neutrophils; L, lymphocyte; HB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin.

	Group A (N = 116)	Group B (N = 173)	P value
D-Dimer (μg/mL)	0.42 ± 0.37	0.52 ± 0.68	0.1732
CRP (mg/dL)	12.25 ± 25.58	23.96 ± 30.38	0.0008
IL-6 (ng/L)	11.27 ± 19.57	20.68 ± 30.70	0.0112
PCT (ng/mL)	0.12 ± 0.10	0.09 ± 0.08	0.0053
CD4 cells (count/μL)	771.89 ± 419.79	535.68 ± 276.76	< 0.0001
Highest CRP (mg/dL)	19.23 ± 30.71	47.81 ± 54.94	< 0.0001
Highest IL-6 (ng/L)	8.91 ± 11.92	45.62 ± 142.25	0.0099
Highest PCT (ng/mL)	0.29 ± 0.09	0.32 ± 0.08	0.0003
Lowest CD4 cell (count/μL)	700.81 ± 383.69	471.46 ± 274.76	< 0.0001
Highest ESR (mm/h)	32.00 ± 29.07	50.29 ± 30.70	< 0.0001
Highest D-Dimer (μg/mL)	0.63 ± 0.84	1.40 ± 3.11	0.0095
Highest lactic acid (mmol/L)	2.19 ± 0.93	2.62 ± 0.85	0.0001
Lowest oxygenation index(PaO_2/FiO_2)	379.97 ± 118.46	270.93 ± 124.19	< 0.0001

Abbreviations: BMI, body mass index; DM, diabetes mellitus; PaO_2, partial pressure of oxygen; FIO_2, fraction of inspired oxygen; WBC, white blood cells; N, neutrophils; L, lymphocyte; HB, hemoglobin; PLT, platelet; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin-6; PCT, procalcitonin.

Among the physical characteristics studied, Age and BMI were found to be two significant ($p < 0.05$) risk factors between the two groups. Older patients (mean age 50.68 years vs 33.06 years) and patients with higher BMI (mean BMI 24.1 kg/m^2 vs 22.1 kg/m^2) still showed signs of lung fibrosis even after 90 days from onset. Most symptom profiles were comparable between GA and GB, while fever occurred in a significantly ($p < 0.0001$) higher proportion among the patients in GB (~ 73%) compared to those in GA (~ 52%). In addition, severe/critical COVID patients were found more likely to sustain lung fibrosis even after 90 days, and patients with pre-existing health conditions were found to be more vulnerable to sustaining lung fibrosis after 90 days (Table 3).

It can also be seen that, patients in the GB took significantly longer time (21 days vs 14.7 days, $p < 0.0001$) from onset to get virus RNA negative, required longer follow-up period from onset (117.8 days vs 67.8 days, $p < 0.0001$) and stayed in the hospital for longer period of time (24.4 days vs 19.2 days, $p < 0.0001$). These observations can be attributed to the significantly higher proportion (29.5% vs 4.3%, $p <$

0.0001) of severe/critical COVID cases in GB since critical/severe COVID patients generally require more treatment and follow-up for a longer period time. It is interesting to see that an average delay of ~ 2 days before hospital admission following the onset of the symptoms had a significant ($p < 0.0001$) detrimental effect on the patients with pneumonia, thus rendering them more vulnerable to developing and sustaining lung fibrosis for a longer period of time (Table 3).

Establishment of prediction model of the persistence of pulmonary fibrosis

A total of 56 features (Table 3) were collected from each patient. After performing the statistical significance test, a set of 35 statistically significant ($p < 0.05$) remained for developing the prediction model. However, features related to treatment measures and temporal patterns were not considered for model development since those features are determined by the physicians based on the condition of the patients and thereby are dependent variables.

Among the significant independent variables, it was observed that Age, BMI, Fever, and Highest PCT were predictive factors for sustaining fibrosis even after 90 days (Fig. 3A). Among the 289 patients, 288 patients had complete data for these four parameters that were used to develop a predictive model based-on the Logistic regression method. The performance of the model was validated by 5-fold cross validation and evaluated by the ROC, accuracy, PPV, NPV, Sensitivity and Specificity. The confusion matrix of the five-fold cross validation is presented in Fig. 4B. An average AUC (Area under the ROC Curve) of 0.84 obtained from 5-fold cross validation that affirms a good reliability of the predictive model. The accuracy, PPV, NPV, Sensitivity and Specificity of the model was 76%, 71%, 79%, 67%, and 82%, respectively (Fig. 4C).

Pulmonary function of patients with pulmonary fibrosis and with no fibrosis/reversal of pulmonary fibrosis after 90 days from onset.

33 patients from Group A (GA) and 114 patients from Group B (GB) underwent pulmonary function testing after 90 days from onset to observe the effect of pulmonary fibrosis on lung function. Six patients (18.18%) in GA and 26 patients (22.81%) in GB had a pulmonary function abnormality. Two patients (6.06%) in GA and 5 patients (4.39%) in GB were diagnosed with obstructive pulmonary disorder. Restrictive disorder was found in 1 patient (3.03%) in GA and 8 patients (7.02%) in GB. In addition, 3 patients (9.09%) in GA and 13 patients (11.40%) in GB had small airway disorder. MEF 25 decrease was found in 12 patients (36.36%) in GA and 46 patients (40.35%) patients in GB. 2 patients (6.06%) in GA and 8 patients (7.02%) in GB had a pulmonary diffusion abnormality (Table 4). It is interesting to see that the ratio of abnormal lung function, obstructive disorder, restrictive disorder, small airway disorder, MEF 25 decrease and abnormal Lung diffusion did not differ on a statistically significant level ($p > 0.05$) between the two groups.

Table 4
Pulmonary function test results for two groups of COVID-19 patients with pulmonary fibrosis.

	Group A	Group B	P value
	(N = 33)	(N = 114)	
Abnormal lung function ratio	18.18% (6/33)	22.81% (26/114)	0.7433
Obstructive disorder ratio	6.06% (2/33)	4.39% (5/114)	0.9471
Restrictive disorder ratio	3.03% (1/33)	7.02% (8/114)	0.6679
Small airway disorder ratio	9.09% (3/33)	11.40% (13/114)	0.9535
[a]MEF 25 decrease	36.36% (12/33)	40.35% (46/114)	0.8333
Abnormal lung diffusion function	6.06% (2/33)	7.02% (8/114)	0.8413

[a]MEF 25, maximal expiratory flow after 25% of the forced vital capacity has not been exhaled.

Discussion

Data from previous coronavirus infections such as SARS, as well as emerging data from the COVID-19 pandemic, suggest there could be substantial fibrotic consequences following SARS-CoV-2 infection [5, 19–22]. Given the huge numbers of individuals infected by SARS-CoV-2, it is important to identify and predict the occurrence of pulmonary fibrosis in the survivor population after discharge.

In our study, thin-section CT scans obtained in hospitalized or discharged patients have shown that fibrosis occurred in a large proportion of the COVID-19 patients, and it occurred in more than a half even for the subset of patients after 120 days from onset. Numerous similarities were found among SARS-CoV coronavirus, MERS coronavirus and SARS-CoV-2. In an early follow-up study of patients with SARS, 62% patients revealed CT evidence of pulmonary fibrosis at a mean follow-up duration of 37 days after hospital discharge [5], whereas in a follow-up study of patients with MERS, 33% had radiographic evidence of pulmonary fibrosis [4]. In view of this, the infection of SARS-CoV-2 has a high incidence of pulmonary fibrosis, which is comparable to those of SARS and MERS.

Comparison of the CT findings with clinical data has revealed significant differences between patients with CT evidence of fibrosis and those without after 90 days from onset in terms of age, BMI, pre-existing disease rate, severe/critical rate, time from onset to virus RNA negative, time from onset to admission, incidence of fever, the treatment conditions and some laboratory findings in this study. Clinically, patients with fibrosis after long term from onset were significantly older, with higher BMI and with significantly higher proportions of fever and severe/critical COVID cases than those without fibrosis. These results implied that fibrosis was likely to be more common in elderly, obese and severe/critical patients, similar to those patients with SARS [5], and COVID-19 patients with fever are more vulnerable to developing pulmonary fibrosis. In addition, patients with pulmonary fibrosis need a much longer time to turn the RNA

of SARS-CoV-2 negative in their bodies, implied that the longer the virus lived in vivo, the more damage it did to the patient's lungs. Meanwhile, it is interesting to observe that the delay to admission following the onset of the symptoms had a significant detrimental effect on the patients with pneumonia, suggested that it is important to seek medical advice in time after onset for the COVID-19 patients.

The pulmonary fibrosis of COVID-19 patients in our study was identified by reviewing the CT scans, in many previous studies, this method was also used to diagnose the lung damage resulted from viral pneumonia, such as lung fibrosis [4, 9, 14, 22, 23]. Thin-section CT scans from all the patients showed that evidence of fibrosis was found in almost a half of patients, which was consistent with the findings of some previous studies in COVID-19 patients [9, 14, 24]. We found that pulmonary fibrosis developed in COVID-19 patients could be reversed in a part of population. The pulmonary fibrosis in some patients was persistent during the follow-up period, it is necessary to follow-up on these patients for longer time to assess the long-term pulmonary consequence of them.

For the survivors from SARS, at one-year follow-up, pulmonary function testing showed a pulmonary function abnormality in a subset of patients, who suffered with poor quality of life after discharge [25]. In this study, the infection of SARS-CoV-2 has a high incidence of pulmonary fibrosis, however, it is interesting to see that only a fraction of COVID-19 patients suffered with abnormal lung function after 90 days from onset, and the ratio of abnormal lung function did not differ on a statistically significant level between the fibrotic and non-fibrotic groups. These results suggested that the pulmonary function of most of COVID-19 patients with pulmonary fibrosis could turn to normal condition after 3 months from onset. It is reassuring to see that patients with COVID-19 seem to have a better prognosis than those with severe acute respiratory syndrome coronavirus.

Significantly, we established a prediction model for the prediction of the persistence of pulmonary fibrosis in this study for early diagnosis. It was observed that Age, BMI, Fever, and Highest PCT were predictive factors for sustaining fibrosis even after 90 days. The patients with high risk to develop persistent pulmonary fibrosis deserve special attention, anti-fibrosis drugs can be considered in the early stage of treatment to prevent further damage to the lungs of such kind of patients.

This study has some limitations. First, the follow-up time for these patients is not long enough, and it is unknown whether the pulmonary fibrosis will permanently remain. Second, there is no histologic confirmation of fibrosis in any of the patients, although the signs on thin-section CT scans are convincing.

Conclusions

Long-term pulmonary fibrosis was more likely to develop in patients with older age, high BMI, severe/critical condition, fever, long time to turn the viral RNA negative in vivo, pre-existing disease and delay to admission. Pulmonary fibrosis occurred in a large proportion of the COVID-19 patients, even for the patients after 120 days from onset, the fibrosis developed in COVID-19 patients could be reversed in about a half of the patients after 120 days from onset. The pulmonary function of most of COVID-19

patients with pulmonary fibrosis could turn to normal condition after 3 months from onset. An effective prediction model with an average AUC of 0.84 was established to predict the persistence of pulmonary fibrosis in COVID-19 patients for early diagnosis. By doing this, we hope to deliver appropriate clinical care and in time design interventional trials to the patients with high risk to develop persistent pulmonary fibrosis. Future follow-up studies with a longer follow-up period would be necessary in order to confirm our findings and better determine the long-term outcomes of patients who recovered from COVID-19.

List Of Abbreviations

COVID-19: The Coronavirus Disease 2019; SARS: Severe acute respiratory syndrome; MERS: coronavirus and Middle East respiratory syndrome; CT: Chest computed tomography; qRT-PCR: quantitative reverse-transcription polymerase chain reaction; ROC: Receiver Operating Characteristic; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUC: Area under the ROC Curve.

Declarations

Ethics approval and consent to participate

This study was conducted at Shenzhen Third People's Hospital and approved by the Ethics Committees, each patient gave written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

YL, LL, JY and XL designed this study; XL, CS, LH, DZ, YL, LQ, YZ, CC, RZ, JL, CF, LZ, YL, MC, YY, MY, GT, ST collected the data; YL, XL, SM, JD, CS analyzed and interpreted the data; Predictions and discussions: XL, SM, JD, CS established the prediction model; XL, CS, SM and JD wrote the manuscript. All authors read and approved the final manuscript.

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Figures

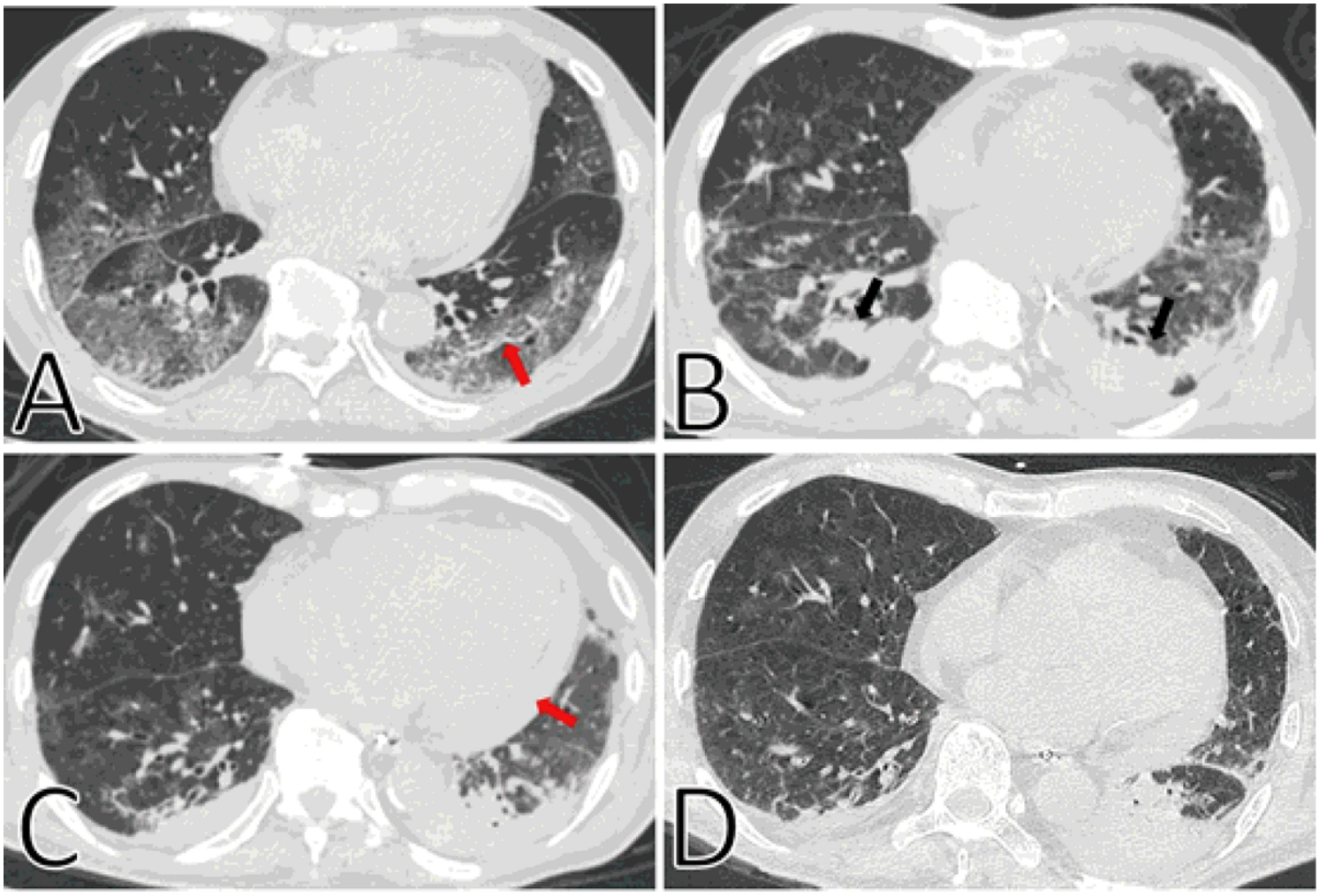


Figure 1

Typical CT imaging findings of a 67-year-old man with persistent pulmonary fibrosis. A. Thin-section chest CT scan in our hospital on January 26, 2020 (9 days after symptoms onset). Chest CT imaging showed diffuse ground glass opacities in both lungs, and visible parenchymal band in the lower lobe of left lung (red arrow). B. On March 23, 2020 (66 days after symptoms onset), diffuse ground glass

opacities were absorbed partially in both lungs and new consolidation was observed. Irregular interfaces (black arrows) with a small amount of pleural effusion were observed in the lower lobes of both lungs. C. On April 14, 2020 (88 days after symptoms onset), diffuse ground glass opacities in both lungs were further absorbed, and the consolidation in both lower lungs was also absorbed. Besides, a small amount of bilateral pleural effusion and new pericardial effusion were observed (red arrow). D. On May 28, 2020 (132 days after symptoms onset), a little ground glass opacities could still be observed in both lungs, consolidation was seen in the lower lobe of both lungs, which was obvious in the lower lobe of the left lung. Besides, there was still a small amount of pleural effusion in the left pleural cavity.

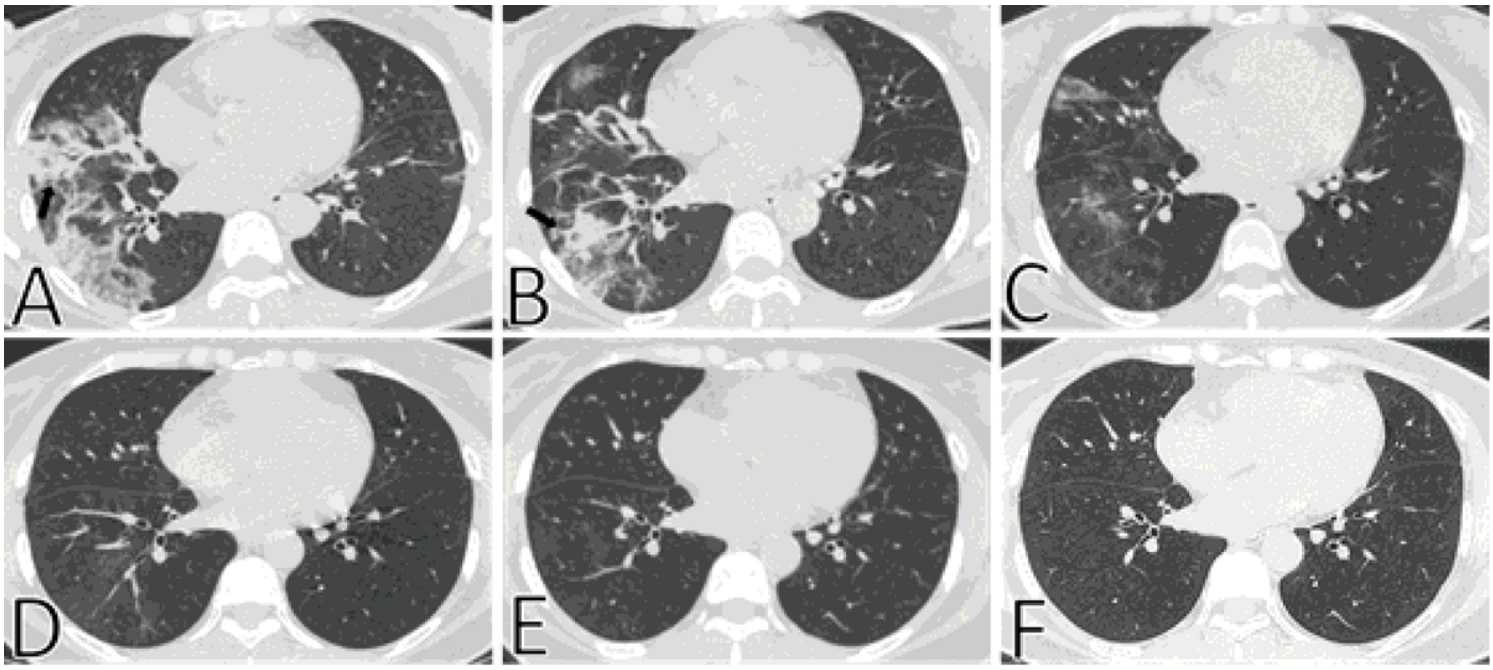


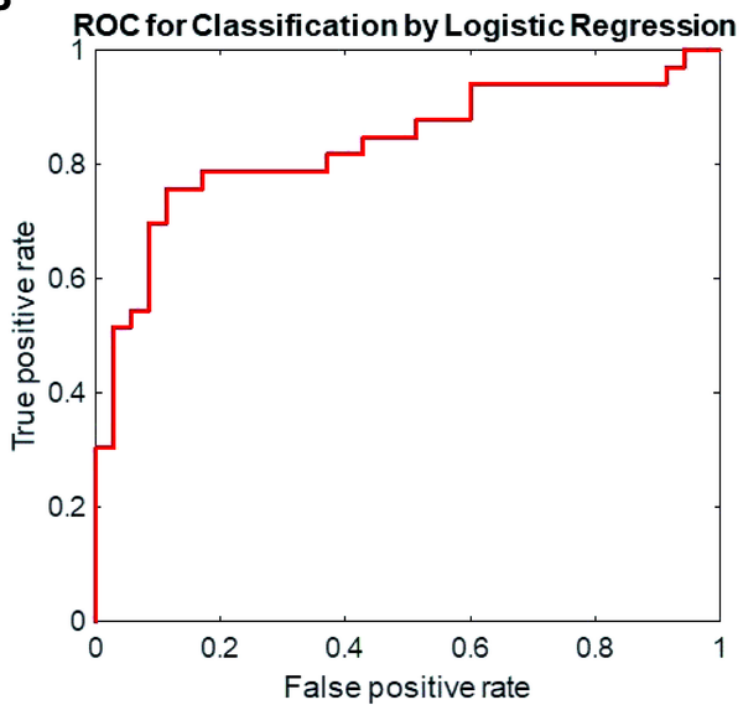
Figure 2

Typical CT imaging findings of a 53-year-old woman with absorbed pulmonary fibrosis. A. Thin-section chest CT scan in our hospital on February 7, 2020 (4 days after symptoms onset). Chest CT imaging showed multiple lesions in both lungs, a mass of ground glass opacities were observed in the middle and lower lobes of the right lung, with consolidation and irregular interfaces (black arrow). B. On February 9, 2020 (6 days after symptoms onset), the absorption of the lesion was obvious, ground glass opacities, consolidation and irregular interfaces (black arrow) were still observed. C. On February 12, 2020 (9 days after symptoms onset), the lung lesions were further absorbed, the density of consolidation decreased. D and E. On February 22, 2020 (19 days after symptoms onset) and March 14, 2020 (40 days after symptoms onset), respectively, only a little ground glass opacities were observed in the lower lobe of the right lung, with obscure boundaries. F. On May 22, 2020 (108 days after symptoms onset), the lesions in both lungs have been completely absorbed.

A

Parameters	*P*
Age	<0.00001
BMI	<0.034
Fever	0.055
Highest PCT	<0.002

B



C

		Predicted	
		GA	GB
Actual	GA	77	38
	GB	31	142

Figure 3

Prediction model of the persistence of pulmonary fibrosis. A. Identified 4 Parameters those can distinguish between two groups. B. The confusion matrix of the five-fold cross validation which was used to validate the performance of the model. C. Receiver operating characteristic curve which was used to evaluate accuracy, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Sensitivity and Specificity of the model. True positive rate = Sensitivity; True negative rate = Specificity.