Effects of acute-phase COVID-19-related indicators on pulmonary fibrosis and follow-up evaluation

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Abstract

Background

Post-COVID-19 pulmonary fibrosis is a significant long-term respiratory morbidity affecting patients' respiratory health. This study aims to investigate the incidence, clinical characteristics, and acute-phase risk factors for pulmonary fibrosis in COVID-19 patients. Additionally, it evaluates their pulmonary function and chest CT outcomes to provide clinical evidence for early intervention and prevention.

Methods

We retrospectively analyzed 595 patients hospitalized for COVID-19 from January 2022 to July 2023. Patients were divided into fibrosis and nonfibrosis groups on the basis of imaging changes. Baseline data, including demographics, disease severity, laboratory indicators, and chest imaging characteristics, were collected. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for pulmonary fibrosis. Pulmonary function and chest CT follow-ups were conducted for the fibrosis group. The data were processed via SPSS 26.0, with $P < 0.05$ considered statistically significant.

Results

The incidence of pulmonary fibrosis was 4.37%, with 2.08% in moderate cases and 8.22% in severe cases. Significant differences were found between the fibrosis and nonfibrosis groups in sex; disease severity; NLR; ALB and LDH levels; and percentages of lung reticular lesions, consolidations, and GGOs ($P < 0.05$). Multivariate analysis revealed LDH (OR = 1.004, 95% CI 1.000–1.007, P = 0.035), ALB (OR = 0.871, 95% CI 0.778–0.974, P = 0.015), lung reticular lesion volume (OR = 1.116, 95% CI 1.040–1.199, P = 0.002), and lung consolidation volume (OR = 1.131, 95% CI 1.012–1.264, P = 0.030) as independent risk factors. The follow-up results revealed significant improvements in pulmonary function, specifically in the FVC%, FEV1%, and DLCO%, but not in the FEV1/FVC. Quantitative chest CT analysis revealed significant differences in lung reticular lesions, consolidation, and GGO volumes but no significant difference in honeycomb volume.

Conclusions

The incidence of pulmonary fibrosis post-COVID-19 increases with disease severity. LDH, ALB, lung reticular lesions, and consolidation volume are independent risk factors for Patients with fibrosis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. As of 31 March 2024, over 774 million confirmed cases and more than seven million deaths have been reported globally[2]. Although COVID-19 affects multiple organs, SARS-CoV-2 primarily targets the respiratory system[3]. Accumulating evidence indicates that COVID-19 has subacute and long-term effects, which are collectively known as post-acute sequelae of SARS-CoV-2 infection (PASC) or “long COVID” [4].

One of the most significant long-term respiratory morbidities impacting patients’ respiratory health is post-COVID-19 pulmonary fibrosis[5–7]. Post-COVID-19 pulmonary fibrosis can result from acute respiratory distress syndrome (ARDS) and pneumonia during acute COVID-19 infection[8–10]. This condition leads to persistent respiratory symptoms such as fatigue, cough, and dyspnea. In severe cases, it can culminate in respiratory failure and poses a life-threatening risk [11].

Post-COVID-19 pulmonary fibrosis, as defined by Tanni et al. [12] and others in the China expert consensus, is characterized by fibrotic changes related to functional impairment. These changes are mainly manifested as radiological features[13], including reticular shadows, traction bronchiectasis, parenchymal bands, structural distortion, and honeycombing. Pulmonary fibrosis can lead to a decline in lung function and a reduced quality of life[14]. The pathogenesis of post-COVID-19 pulmonary fibrosis involves complex interactions between virus-induced lung injury, the immune response, and subsequent fibrotic processes[15]. Risk factors for developing post-COVID-19 pulmonary fibrosis include older age, preexisting comorbidities, and the severity of the initial infection, particularly the need for mechanical ventilation[16].

Recent studies have highlighted the importance of early identification and management of PC19-PF to improve patient outcomes. Imaging techniques such as high-resolution computed tomography (HRCT) play crucial roles in diagnosing and monitoring the progression of pulmonary fibrosis[17]. Additionally, pulmonary function tests (PFTs) are essential for assessing the extent of functional impairment[18].

Given the potential significant long-term health impacts of COVID-19, enhancing our understanding of post-COVID-19 pulmonary fibrosis is crucial. Therefore, this study aimed to investigate the impact of acute-phase COVID-19-related indicators on pulmonary fibrosis and identify its independent risk factors. Additionally, by conducting a follow-up chest CT scan and PFTs one year after the initial infection, we aimed to evaluate the progression of pulmonary fibrosis. This study seeks to provide clinical evidence for early intervention and prevention and to deepen our understanding of the outcomes of fibrosis.

MATERIALS AND METHODS

Study design and participants

We retrospectively analyzed the clinical data of hospitalized patients with COVID-19 who were treated at Ningbo No.2 Hospital from December 2022 to July 2023. According to the Diagnosis and Treatment Protocol for COVID-19 patients (Tentative 10th Version)[19], the diagnostic criteria are as follows: a. clinical manifestations associated with SARS-CoV-2 infection; b. positive nucleic acid test for SARS-CoV-2; and c. positive antigen test for SARS-CoV-2. Exclusion criteria: 1. Patients who did not meet the inclusion criteria; 2. Patients with preexisting pulmonary fibrosis; 3. Patients in the active phase of neurological or rheumatological disease; 4. Patients currently receiving treatment for malignant tumors; 5. Severe abnormalities in vital organ functions, such as the heart, liver, or kidney; 6. Patients with new severe trauma, surgical history, or other infectious diseases; 7. Patients who were hospitalized for less than one day; 8. Patients who died during treatment; 9. Patients who did not return for a follow-up chest HRCT after discharge. On the basis of the inclusion and exclusion criteria and by randomly selecting fibrosis group patients at a 1:5 ratio to match the nonfibrosis group, a total of 156 patients were included in this study. Among them, 26 were assigned to the fibrosis group, and 130 were assigned to the nonfibrosis group (as depicted in Fig. 1).

Insert Fig. 1

Information Sources

The following data were collected from two groups of patients diagnosed with COVID-19: 1. Basic information: Name, age, sex, BMI. 2.Disease information: Severity of COVID-19, history of underlying disease, and smoking history. 3.The laboratory indicators used were as follows: white blood cell count (WBC), red blood cell count (RBC), platelet count (PLT), neutrophil count (NE), lymphocyte count (Lym), neutrophil-to-lymphocyte ratio (NLR), serum creatinine (SCr), C-reactive protein (CRP), lactate dehydrogenase (LDH), serum albumin (ALB), fasting blood glucose (FBG), D-dimer (D-D), international normalized ratio (INR), creatine kinase (CK), alanine aminotransferase (ALT), procalcitonin (PCT), troponin (Tn), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 10 (IL-10), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ).4. Chest HRCT imaging data: All data were obtained from a 64-slice CT scanner (SOMATOM Force, Siemens) with a slice thickness of 1.25 mm. 5.Pulmonary function: Forced vital capacity (FVC % predicted), forced expiratory volume in 1 second (FEV1% predicted), FEV1/FVC % predicted, and diffusing capacity of the lungs for carbon monoxide (DLCO % predicted).

Quantitative assessment of lung texture

The chest imaging DICOM data were transferred to the image processing analysis software YZY CCIP (Yizhiyuan Health Technology Co., Ltd., Hangzhou, Zhejiang, China). YZY CCIP developed a lung

segmentation method using the U-Net deep learning architecture[20, 21] for various lung disease phenotypes[22]. In summary, the software was utilized to identify and delineate areas of normal lung tissue and lung disease phenotypes (emphysema, honeycombing, reticular structures, ground-glass opacity, consolidation) on chest CT images. This process yielded volume data and the percentage of total lung volume for these regions. The distribution of these areas was then quantified across the entire lung, left and right lungs, and individual lobes, ultimately providing volume data and percentages of total lung volume for normal lung tissue or lung disease phenotypes (as shown in Additional file 1–2).

Disease severity classification

Disease severity classification and Murray score calculation were performed as previously reported [23]. The severity of COVID-19 was graded according to the China National Health Commission Guidelines for the Diagnosis and Treatment of SARS-CoV-2 infection. Laboratory-confirmed patients with fever, respiratory manifestations and radiological findings indicative of pneumonia were considered moderate cases. Laboratory confirmed patients with any of the following conditions were considered to have severe COVID-19: (a) respiratory distress (respiration rate ≥ 30/min; (b) resting oxygen saturation ≤ 93%, and (c) arterial oxygen partial pressure (PaO2) / fraction of inspired oxygen (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa);(d) pulmonary lesions progress by more than 50% within 24–48 hours. Laboratory confirmed patients with any of the following conditions, such as (a) respiratory failure requiring mechanical ventilation, (b) shock, and (c) failure of other organs requiring intensive care unit (ICU) admission.

Statistical analysis

All the data were analyzed via SPSS statistical software version 26.0. For normally or approximately normally distributed data, the results are expressed as the means ± standard deviations, and differences between two groups were compared via independent sample t tests. For skewed data, the results are presented as M(Q1, Q3), and comparisons between two groups were made via the Mann—Whitney U test. Categorical data are expressed as cases (%), and comparisons between groups were conducted via the $\chi 2$ test. Variables with statistical significance in the univariate analysis were included in the multivariate logistic regression analysis to identify independent risk factors for post-COVID-19 pulmonary fibrosis. A P value of < 0.05 was considered to indicate statistical significance.

RESULTS

Patient Demographics and Incidence of Post-COVID-19 Pulmonary Fibrosis

Among the 1,571 hospitalized COVID-19 patients, 952 (60.6%) were male, and 619 (39.4%) were female. In terms of disease severity, there were no mild cases, 1,004 moderate cases, 511 severe cases, and 56

critical cases (as depicted in Fig. 2).

Insert Fig. 2

After applying the exclusion criteria, 595 patients remained, comprising 377 moderate cases, 201 severe cases, and 17 critical cases. Within the fibrosis group, there were 8 moderate cases, 18 severe cases, and no critical cases. The overall incidence of post-COVID-19 pulmonary fibrosis was 4.37%, with an incidence of 2.08% in moderate cases and 8.22% in severe cases.

Comparative analysis of clinical features and comorbidities

In this study, as shown in Table 1, the proportion of males in the fibrosis group was significantly greater than that in the nonfibrosis group (84.6% vs. 56.9%, P = 0.008). Additionally, the proportion of severe cases in the fibrosis group was significantly greater than that in the nonfibrosis group (69.2% vs. 26.2%, P < 0.001). However, there were no statistically significant differences between the two groups in terms of age, BMI, smoking history, length of hospital stay, diabetes, hypertension, cardiovascular and cerebrovascular diseases, renal insufficiency, or the presence of two or more underlying diseases (P > 0.05).

Insert Table 1

Comparative analysis of serological markers

As shown in Table 2, compared with patients in the nonfibrosis group, patients in the fibrosis group presented significant differences in the following serological indicators: NLR (median: 8.11% compared with 5.67%, P = 0.021) and LDH (median: 319.5 U/L compared with 235.5 U/L, P < 0.001). Additionally, the serum ALB concentration was significantly lower in the fibrosis group (median: 30.858 g/L vs. 35.177 g/L, P < 0.001). However, there were no statistically significant differences between the two groups in terms of white blood cell count, red blood cell count, platelet count, neutrophil count, C-reactive protein level, or D-dimer level (P > 0.05).

Insert Table 2

Qualitative Analysis of Chest CT Data from COVID-19 Patients

We collected chest CT scans from each patient at the onset of illness and evaluated them via YZY CCIP image analysis software. The results indicated that ground–glass opacities, pulmonary parenchymal bands, irregular interfaces, and reticular patterns were the most common CT findings in COVID-19 patients. (as depicted in Fig. 3)

Insert Fig. 3

Quantitative Chest CT Analysis: Comparison of Pulmonary Disease Phenotypes

The quantitative structured data analysis, performed via YZY CCIP image analysis software, revealed that, as indicated in Table 3, the fibrosis group presented a greater proportion of lung consolidation volume (median: 1.756% compared with 0.030%, $P < 0.001$), ground–glass opacity volume (median: 4.206% compared with 0.442%, $P = 0.006$), and reticular pattern volume (median: 6.664% compared with 1.015%, $P < 0.001$) on chest HRCT than did the nonfibrosis group. However, there was no statistically significant difference between the two groups in terms of the proportion of honeycombing volume ($P > 0.05$).

Insert Table 3

Multivariate logistic regression: Independent risk factors for post-COVID-19 pulmonary fibrosis

After the general data and clinical features of the two groups were compared, variables with statistically significant differences ($P < 0.05$) were selected as independent variables. The presence of pulmonary fibrosis was designated the dependent variable, with fibrosis coded as 1 and nonfibrosis coded as 2. The independent variables included the NLR, ALB level, LDH level, proportion of total lung reticular lesion volume, total lung consolidation volume and total lung ground-glass opacity volume.

Insert Table 4

Multivariate logistic regression analysis was conducted to identify independent risk factors for post-COVID-19 pulmonary fibrosis. As shown in Table 4 above, the total lung reticular lesion volume (OR: 1.116, 95% CI: 1.040–1.199), total lung consolidation volume (OR: 1.313, 95% CI: 1.012–1.264), and LDH level (OR: 1.004, 95% CI: 1.000–1.007) were identified as independent risk factors for post-COVID-19 pulmonary fibrosis. There was a negative correlation between post-COVID-19 pulmonary fibrosis and the serum ALB concentration (OR: 0.871, 95% CI: 0.778–0.974).

Baseline and One-Year Follow-Up: Quantitative Chest CT and Pulmonary Function Tests in Fibrosis Patients

Through a 12-month follow-up of lung function and chest CT scans in patients with post-COVID-19 pulmonary fibrosis, as shown in Table 5, we observed statistically significant improvements in FVC% (median: 78.892 vs. 80.376, P = 0.16), FEV1% (median: 80.7 vs. 81.3, P = 0.002), and DLCO% (median: 75.960 vs. 81.960, P < 0.001) compared with baseline data (1 month postonset). However, there was no statistically significant difference in FEV1/FVC %.

Quantitative analysis of chest CT images revealed significant differences in the proportion of lung consolidation volume (median: 1.850% compared with 0.061%, P < 0.001), ground-glass opacity volume (median: 4.461% compared with 1.234%, P = 0.002), and reticular pattern volume (median: 5.908% compared with 3.122%, P = 0.004) between the two groups. Conversely, the proportion of honeycomb volume did not significantly differ.

Insert Table 5

DISCUSSION

With the COVID-19 pandemic, the incidence of post-COVID-19 pulmonary fibrosis has increased, leading to persistent respiratory symptoms that significantly impact patients' quality of life and can be life-threatening in severe cases. Identifying risk factors for post-COVID-19 pulmonary fibrosis and implementing early interventions are crucial. This study retrospectively analyzed data from COVID-19 patients to explore the incidence rate, clinical characteristics, risk factors, and outcomes of post-COVID-19 pulmonary fibrosis.

The reported incidence rates of post-COVID-19 pulmonary fibrosis vary significantly among studies. Zou et al. [24] reported that 84% of COVID-19 patients had ground-glass opacities at discharge, with 30% and 36% showing reticular and honeycomb patterns, respectively. Bocchino et al. [25] followed 84 nonintubated patients with high-resolution chest CT for up to 12 months and reported 50% fibrotic-like

changes at 3 months, 42% at 6 months, and 5% at 12 months. Groff D et al. [26] reported that only 7% of COVID-19 patients developed pulmonary fibrosis. Our study revealed an incidence rate of 4.37%, with 2.08% in mild cases and 8.22% in severe cases, indicating that the incidence of pulmonary fibrosis increases with increasing COVID-19 severity. The overall low incidence rate may be due to our exclusion criteria, which included patients who were receiving treatment for malignant tumors, those in the active phase of rheumatic immune diseases, or those with a history of pulmonary fibrosis.

Research by Alrajhi [27] suggested that male sex may be a potential risk factor for post-COVID-19 pulmonary fibrosis. Studies by the Chinese Research Hospital Association's Professional Committee on Respiratory Diseases indicate that older age and disease severity are independent risk factors[28]. Our study revealed significant differences between the fibrosis and nonfibrosis groups in terms of sex and disease severity, which is consistent with previous findings. However, owing to the limited sample size, these factors were not included in the final analysis. Notably, the lack of a significant difference in age between the groups may be due to the predominance of elderly patients in both groups, which affects the age-related statistical results.

LDH is an enzyme released into the bloodstream when cells are damaged or die[29], serving as a biomarker of tissue injury[30]. In COVID-19, elevated LDH levels reflect lung tissue damage and inflammation, both of which may be associated with the progression of lung fibrosis[31, 32]. Recent studies have identified elevated LDH levels four months post-COVID-19 as an independent risk factor for residual fibrotic lesions[33]. Our study confirms that LDH is an independent risk factor for post-COVID-19 lung fibrosis, although its long-term effects require further validation due to the limited follow-up time.

Our study also revealed that the serum ALB concentration is an independent risk factor for post-COVID-19 lung fibrosis, with a negative correlation. Serum ALB has anti-inflammatory, nutritional, and hemorheological properties that prevent platelet activation and aggregation[34, 35]. Malnutrition or hypercatabolism can lead to hypoalbuminemia, whereas systemic inflammation and increased cytokine release can inhibit albumin production[36, 37]. These findings suggest that severe inflammation is correlated with lower ALB levels, although further validation is needed due to the limited sample size.

Recent studies suggest that a quantified uninvolved lung volume of ≤ 80% at admission predicts fibrotic lesions six months later[38]. Our study revealed that higher proportions of total lung reticulation and consolidation volumes at admission significantly correlate with the development of lung fibrosis. These findings align with those of previous studies and highlight these radiological parameters as potential independent factors for post-COVID-19 lung fibrosis. Increases in these parameters are associated with decreases in pulmonary function, gas exchange impairment, and reduced quality of life. However, these parameters are not absolute predictive tools, as fibrosis development is influenced by multiple factors, including baseline health status, comorbidities, treatment response, and genetic predispositions. Future research should consider a comprehensive assessment of these parameters alongside other clinical features to increase the prediction accuracy.

Our study revealed significant improvements in lung function parameters, including FVC %, FEV1%, and DLCO %, over a 12-month follow-up period in patients with post-COVID-19 pulmonary fibrosis. These findings are consistent with previous studies that reported similar trends in lung function recovery post-COVID-19. However, the lack of a significant change in FEV1/FVC% suggests that the obstructive component of lung function may not be as prominently affected in these patients. This aligns with the findings of Han et al., who reported persistent fibrotic-like changes, such as architectural distortion and traction bronchiectasis, in a subset of patients at a 2-year follow-up[39].

Quantitative analysis of chest CT images revealed significant differences in the proportions of lung consolidation volume, ground-glass opacity volume, and reticular pattern volume between the baseline and follow-up scans. These changes indicate that the inflammatory and fibrotic processes induced by COVID-19 gradually improve over time[16]. Interestingly, the proportion of honeycomb volume did not significantly differ, possibly because honeycombing typically represents irreversible fibrotic changes, which may not be as prevalent in the initial stages of post-COVID-19 pulmonary fibrosis[40].

The incidence of post-COVID-19 lung fibrosis is positively correlated with the severity of the disease during the acute phase. Studies indicate that patients with post-COVID-19 lung fibrosis are predominantly male and critically ill, exhibiting acute phase clinical manifestations such as a high NLR, elevated LDH levels, and low ALB levels. Radiologically, these patients often present with increased consolidation, ground—glass opacities, and reticular lesions. Our study identified LDH and ALB levels, as well as the percentage of total lung reticulation and consolidation volume, as independent risk factors for post-COVID-19 lung fibrosis.

These findings have significant clinical implications for the management and follow-up of COVID-19 patients. Elevated LDH levels and low ALB levels can serve as early indicators for the risk of developing pulmonary fibrosis, enabling clinicians to identify high-risk patients and implement timely interventions. Regular monitoring of these biomarkers, along with quantitative CT imaging, can facilitate the early detection and management of fibrotic changes, potentially improving patient outcomes and reducing long-term morbidity. Furthermore, understanding the role of these parameters in predicting fibrosis can aid in the development of targeted therapies and personalized treatment regimens, ultimately enhancing the quality of life for patients recovering from COVID-19.

However, this study has several limitations that need to be considered in future research. First, the relatively small sample size may limit the generalizability of the results. Future studies should expand the sample size to increase the representativeness and reliability of the findings. Second, the retrospective research design, with data collected from a short-term window postdiagnosis, may introduce temporal bias related to coronavirus infection. Therefore, prospective studies are recommended to collect more comprehensive data, further validating and deepening our findings.

CONCLUSION

The incidence of post-COVID-19 pulmonary fibrosis is positively correlated with the severity of the acute phase of the disease. Our study identified elevated LDH levels, low ALB levels, and higher proportions of total lung reticulation and consolidation volumes as independent risk factors for post-COVID-19 lung fibrosis. These findings underscore the importance of early identification and intervention in high-risk patients to mitigate long-term respiratory morbidity. Regular monitoring of these biomarkers, along with quantitative CT imaging, can facilitate early detection and management of fibrotic changes, potentially improving patient outcomes and reducing long-term morbidity. Future research should focus on expanding sample sizes and employing prospective study designs to validate and deepen these findings.

Abbreviations

COVID-19: Coronavirus disease 2019

PFTs: pulmonary function tests

WBC: white blood cell count

RBC: red blood cell count

PLT: platelet count

NE: neutrophil count

LYM: lymphocyte count

NLR: neutrophil-to-lymphocyte ratio

SCR: serum creatinine

CRP: C-reactive protein

LDH: lactate dehydrogenase

ALB: serum albumin

FBG: fasting blood glucose

D-D: D-dimer

INR: international normalized ratio

CK: creatine kinase

ALT: alanine aminotransferase

PCT: procalcitonin

TN: troponin

IL-2: interleukin 2

IL-4: interleukin 4

IL-6: interleukin 6

IL-10: interleukin 10

TNF-α: tumor necrosis factor alpha

IFN-γ: interferon gamma

Declarations

Statement of Ethics

The study protocol was reviewed and approved by the Ethical Committee of the Research and Development Department of NingBo NO.2 Hospital, reference number PJ-NBEY-KY-2024-089-01. This study has been granted an exemption from requiring informed consent by the Research and Development Department from NingBo NO.2 Hospital.

Consent for publication

All authors agreed to publish this manuscript.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Author Contributions

All the authors contributed substantially to this manuscript. All the authors read and approved the final manuscript. Qiong Wang and Ying Zhou contributed to the study concept and design, data interpretation, critical revision of the manuscript, and final approval of the manuscript. Fangxue Jing and Yingying Feng contributed to the acquisition of the data and the data analysis. Zhaoxing Dong contributed to the conception and design of the work.

Data availability statement

All the data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Tables

Table 1. Comparative analysis of clinical features and comorbidities

	fibrosis group (n=26)	nonfibrosis group (n=130)	*P* Value
Male (%)	22/26 (84.6%)	74/130 (56.9%)	0.008*
Age(years)	70.077±11.218	71.246±14.523	0.669
BMI(kg/m2)	23.3 (21.2, 24.7)	22.9 (20.8, 24.2)	0.426
Severe COVID-19 (%)	18 (69.2%)	34 (26.2%)	<0.001*
History of smoking (%)	6 (23.1%)	21 (16.2%)	0.394
Hospital Stay(days)	11.0 (7.7, 16.5)	10.0 (7.0, 14.3)	0.444
Diabetes (%)	7 (26.9%)	31 (23.8%)	0.739
Hypertension (%)	13 (50.0%)	52 (40.0%)	0.345
Cardiovascular and Cerebrovascular diseases (%)	9 (34.6%)	28 (21.5%)	0.152
Renal insufficiency (%)	6 (23.1%)	17 (13.1%)	0.189
The presence of two or more underlying diseases (%)	19 (73.1%)	105 (80.8%)	0.375

Table 2. Comparison of the features of the subjects after admission

	fibrosis group（n=26）	nonfibrosis group （n=130）	P Value
white blood cell count（×10^9/L）	6.0（3.7，8.4）	6.0（3.7，8.2）	0.971
red blood cell count（×10^{12}/L）	3.671±0.792	3.810±0.714	0.377
platelet count（×10^9/L）	200.692±89.337	195.394±90.218	0.785
neutrophil count（×10^9/L）	4.8（2.4，8.7）	6.0（3.7，7.7）	0.312
lymphocyte count（×10^9/L）	0.85（0.58，1.20）	0.70（0.40，1.10）	0.080
neutrophil to lymphocyte ratio（%）	8.11（4.47，14.4）	5.67（3.00，10.00）	0.021*
serum creatinine（μmol/L）	68.7（59.6，116.1）	65.6（49.4，89.8）	0.072
C-reactive protein（mg/L）	54.19（9.56，102.83）	29.05（4.96，81.08）	0.153
lactate dehydrogenase（U/L）	319.5（257.0，400.8）	235.5（187.8，293.5）	<0.001*
Albumin（g/L）	30.858±5.576	35.177±4.994	0.001*
fasting blood glucose（mmol/L）	7.57（5.77，11.80）	7.07（5.39，9.45）	0.163
D-dimer levels（μmol/L）	519.0（339.0，1590.5）	416.5（191.5，1008.3）	0.124
international normalized ratio（%）	1.06（0.99，1.18）	1.04（0.98，1.13）	0.392
creatine kinase（U/L）	93.00（42.75，200.75）	58.50（38.50，11.50）	0.112
alanine aminotransferase	26.5（17.3，57.3）	26.0（14.0，50.8）	0.426
Procalcitonin（U/L）	0.12（0.07，0.27）	0.09（0.06，0.18）	0.296
Troponin（μg/L）	0.016（0.006，0.027）	0.007（0.004，0.026）	0.189
Interleukin-2（pg/ml）	1.82（1.19，2.72）	1.93（1.30，2.70）	0.754
Interleukin-4（pg/ml）	0.828±0.496	0.942±0.665	0.475
Interleukin-6（pg/ml）	9.95（4.36，19.72）	10.88（6.02，23.40）	0.357
Interleukin-10（pg/ml）	4.37（2.50，4.94）	4.61（2.97，6.56）	0.284
tumor necrosis factor alpha-α （pg/ml）	1.212±0.389	1.301±0.536	0.488
Interferon-γ（pg/ml）	1.79（1.01，2.29）	1.63（1.19，2.24）	0.719

Table 3. Comparison of quantitative lung imaging results

	fibrosis group (n=26)	nonfibrosis group (n=130)	*P* Value
Proportion of lung consolidation volume (%)	1.756 (0.150, 3.485)	0.030 (0.006, 0.106)	< 0.001*
Proportion of honeycombing volume (%)	0.006 (0.002, 0.217)	0.002 (0.003, 0.246)	0.083
Proportion of ground-glass opacity volume (%)	4.206 (0.317, 14.606)	0.442 (0.460, 3.119)	0.006*
Proportion of reticular pattern volume (%)	6.664 (2.442, 12.912)	1.015 (0.174, 3.656)	< 0.001*

Table 4. Multivariate logistic regression analysis

Risk factors	*P* Value	OR-Value	95%CI
NLR	0.323	1.024	0.977-1.072
ALB	0.015	0.871	0.778-0.974
LDH	0.035	1.004	1.000-1.007
proportion of reticular pattern volume	0.002	1.116	1.040-1.199
proportion of lung consolidation volume	0.030	1.131	1.012-1.264
proportion of ground-glass opacity volume	0.511	0.983	0.934-1.034

Table 5. Baseline and one-year follow-up results

COVID-19 Patients	Follow-up time after onset		*P* Value
	One month	One year	
Pulmonary function tests			
FVC % predicted	78.892±7.300	80.376±7.536	0.16*
FEV1% predicted	80.7（73.0，82.9）	81.3（76.6，84.6）	0.002*
FEV1/FVC% predicted	77.752±8.180	77.324±8.264	0.78
DLCO % predicted	75.960±7.257	81.960±9.391	0.001*
Lung imaging quantitative analysis			
Proportion of lung consolidation volume （%）	1.850（0.175，3.922）	0.061（0.005，0.429）	0.001*
Proportion of honeycombing volume（%）	0.006（0.001，0.295）	0.045（0.001，0.209）	0.563
Proportion of ground-glass opacity volume （%）	4.461（0.313，16.577）	1.243（0.113，2.738）	0.002*
Proportion of reticular pattern volume（%）	5.908（2.393，12.012）	3.122（0.504，6.488）	0.004*

Figures

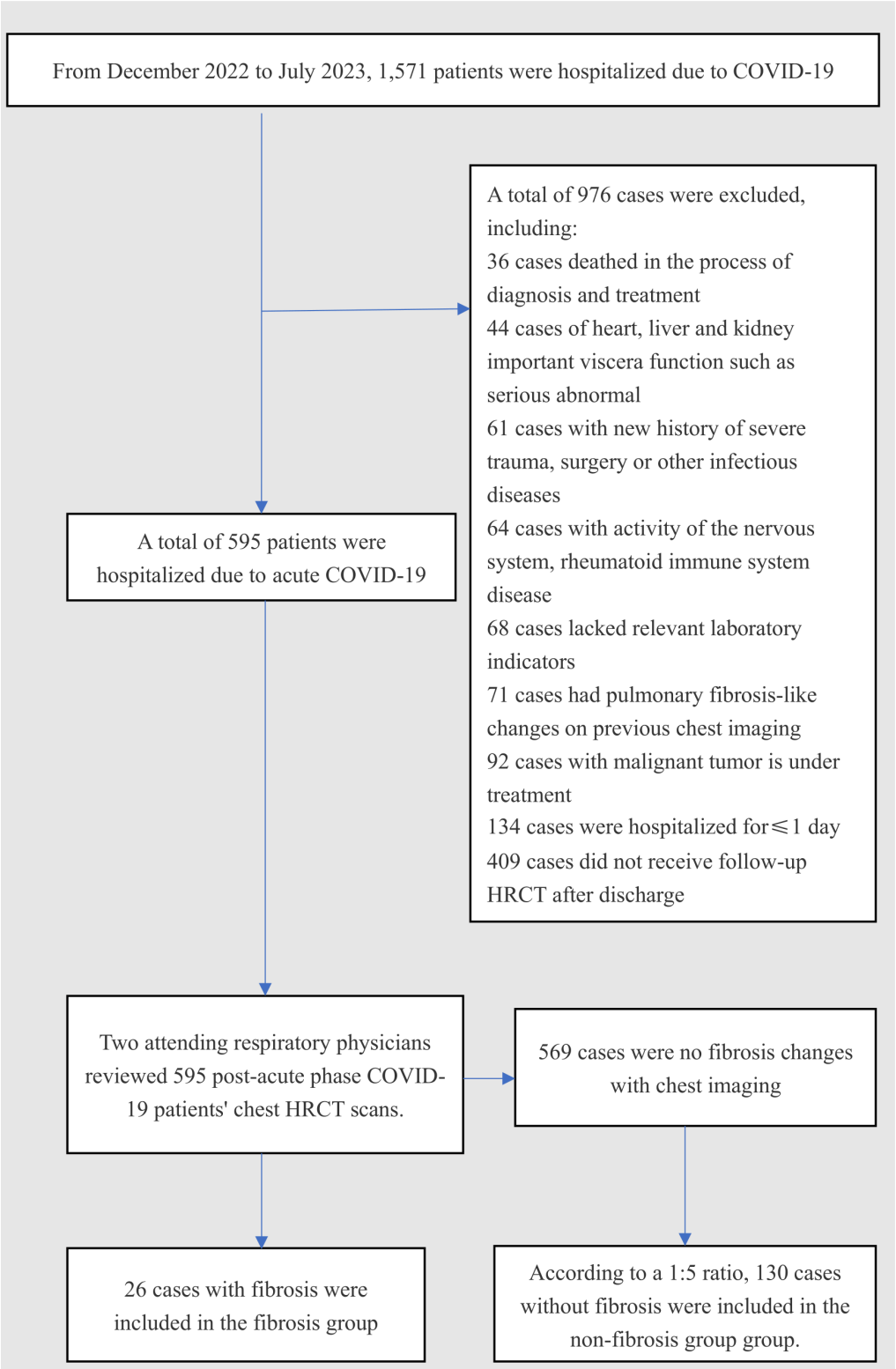

Figure 1

Flowchart for Patient Screening

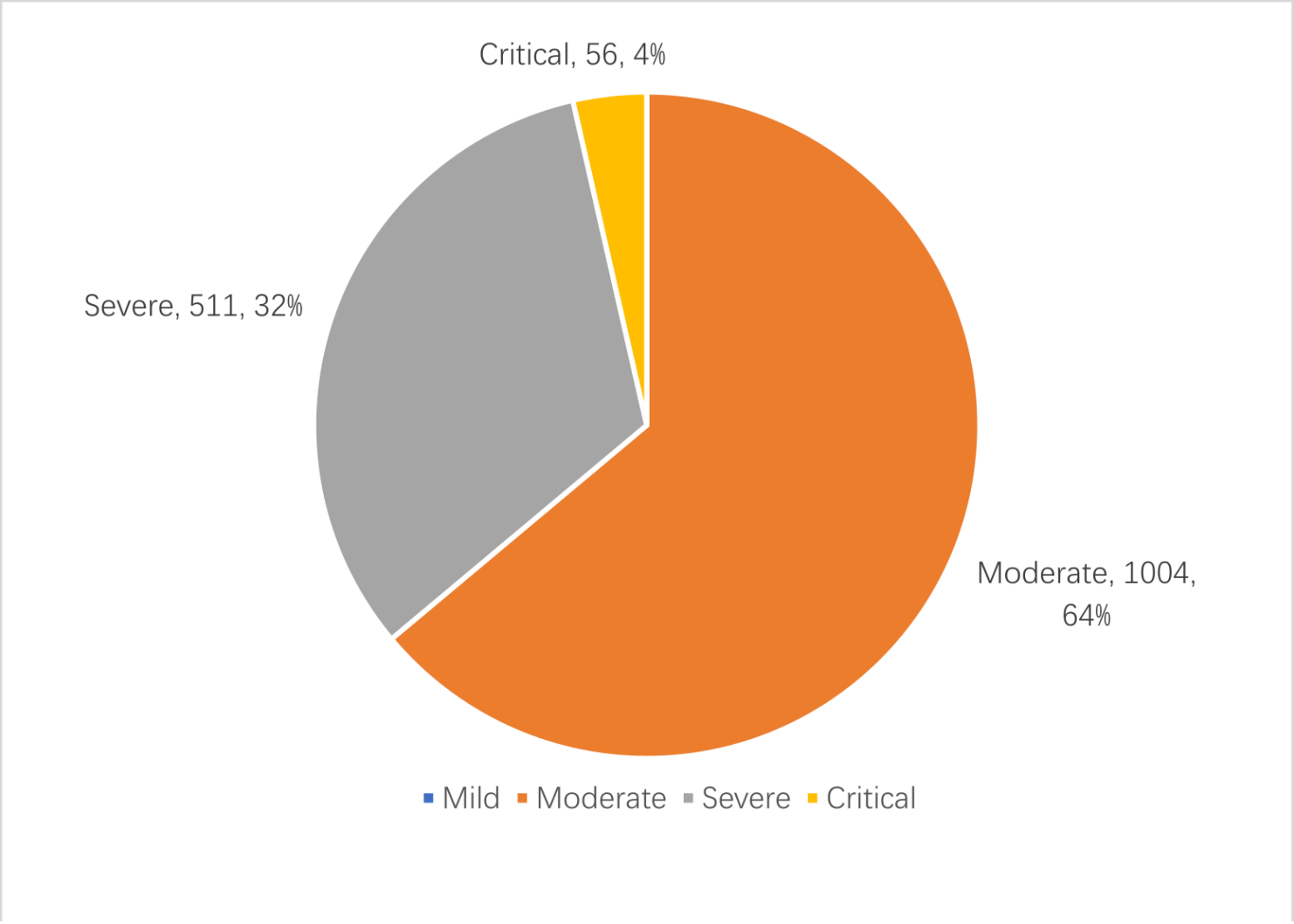

Figure 2

Distribution of disease severity among enrolled patients

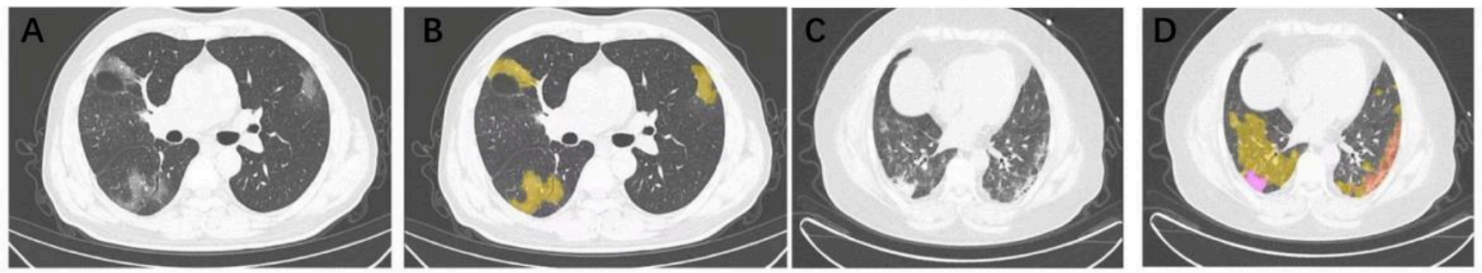

Figure 3

Qualitative comparative analysis of chest CT data. A: HRCT scans of a patient with acute COVID-19 in the nonfibrosis group. B: Qualitative analysis of the chest CT image suggested a yellow area for the pulmonary disease phenotype when the glass area was ground. C: HRCT scans of one acute COVID-19 patient in the fibrosis group. D: Qualitative analysis of the chest CT image suggested that yellow areas

are areas with a ground-glass lung disease phenotype. The pink area is the consolidation area. The orange area is the reticulate area.

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