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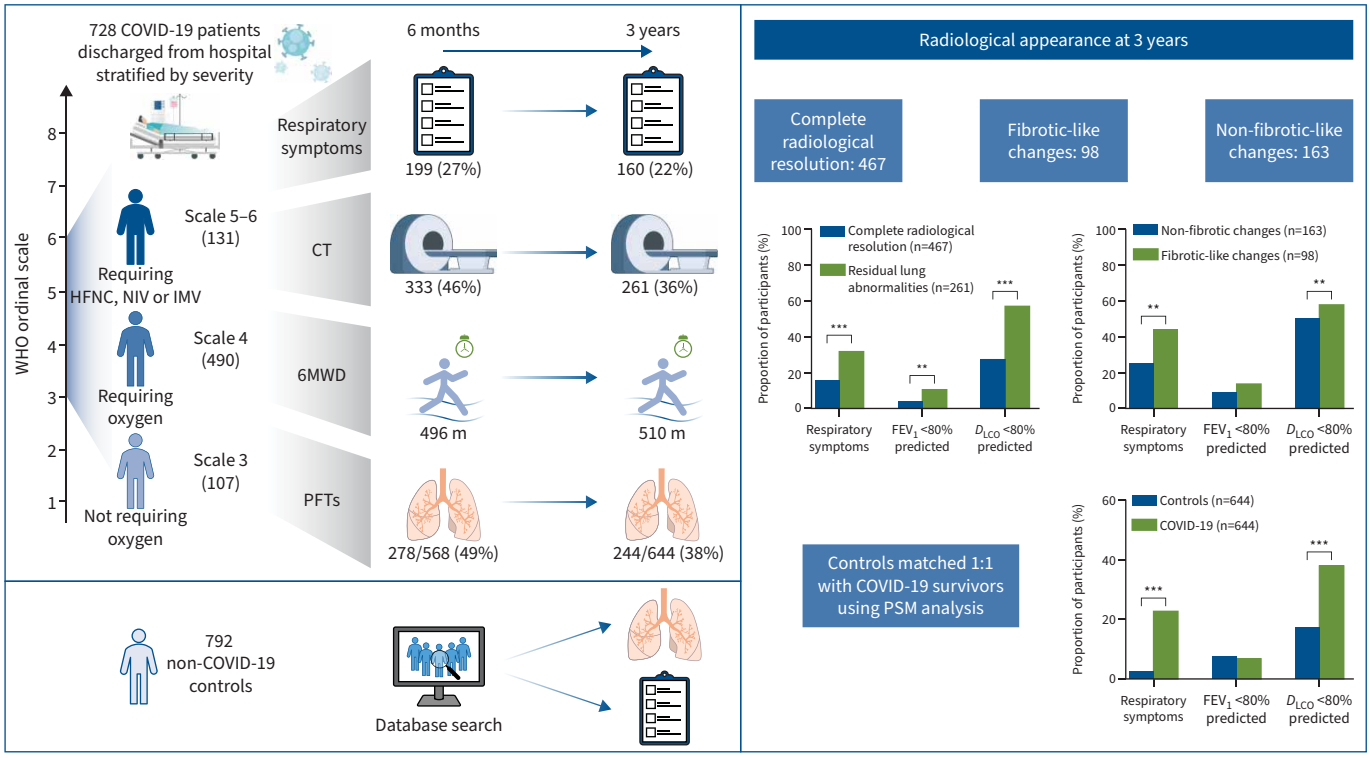

GRAPHICAL ABSTRACT Summary of the main study findings. Severity scale 3: patients not requiring supplemental oxygen. Severity scale 4: patients requiring supplemental oxygen *via* nasal cannula or mask. Severity scale 5–6: patients requiring high-flow nasal cannula (HFNC), non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV) for oxygen therapy. COVID-19: coronavirus disease 2019; WHO: World Health Organization; CT: computed tomography; 6MWD: 6-min walk distance; PFT: pulmonary function test; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; PSM: propensity score matching. **: p<0.01; ***: p<0.001.

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More than a third of patients have lung function abnormalities and residual lung abnormalities at 3 years post-COVID-19. Residual lung abnormalities, *e.g.* fibrotic-like changes on CT, should be considered in long-term management strategies for COVID-19. https://bit.ly/3uvSDZm

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Abstract

Background This study aimed to evaluate the longitudinal progression of residual lung abnormalities (ground-glass opacities, reticulation and fibrotic-like changes) and pulmonary function at 3 years following coronavirus disease 2019 (COVID-19).

Methods This prospective, longitudinal cohort study enrolled COVID-19 survivors who exhibited residual lung abnormalities upon discharge from two hospitals. Follow-up assessments were conducted at 6 months, 12 months, 2 years and 3 years post-discharge, and included pulmonary function tests, 6-min walk distance (6MWD), chest computed tomography (CT) scans and symptom questionnaires. Non-COVID-19 controls were retrospectively recruited for comparative analysis.

Results 728 COVID-19 survivors and 792 controls were included. From 6 months to 3 years, there was a gradual improvement in reduced diffusing capacity of the lung for carbon monoxide (D_{LCO} <80% predicted: 49% *versus* 38%; p=0.001), 6MWD (496 *versus* 510 m; p=0.002) and residual lung abnormalities (46% *versus* 36%; p<0.001), regardless of disease severity. Patients with residual lung abnormalities at 3 years more commonly had respiratory symptoms (32% *versus* 16%; p<0.001), lower 6MWD (494 *versus* 510 m; p=0.003) and abnormal D_{LCO} (57% *versus* 27%; p<0.001) compared with those with complete resolution. Compared with controls, the proportions of D_{LCO} impairment (38% *versus* 17%; p<0.001) and respiratory symptoms (23% *versus* 2.2%; p<0.001) were significantly higher in the matched COVID-19 survivors at the 3-year follow-up.

Conclusions Most patients exhibited improvement in radiological abnormalities and pulmonary function over time following COVID-19. However, more than a third continued to have persistent lung abnormalities at the 3-year mark, which were associated with respiratory symptoms and reduced diffusion capacity.

Introduction

On 3 May 2023, the World Health Organization (WHO) released the coronavirus disease 2019 (COVID-19) strategic preparedness and response plan for 2023–2025 that emphasises the significance of

establishing an evidence base regarding the post-COVID condition [1, 2]. Emerging data show that ∼50% of COVID-19 survivors experience long-term respiratory sequelae, such as chronic dyspnoea, cough and reduced lung function [3–5]. The causes and progression of these pulmonary sequelae are not fully understood. One hypothesis suggests that respiratory symptoms in COVID-19 survivors may be associated with pulmonary fibrosis, a condition observed in previous coronavirus [6, 7] and influenza [8] pandemics. Recent research has proven that post-COVID-19 fibrosis could result from acute respiratory distress syndrome (ARDS) [9, 10] or be triggered by COVID-19-induced auto-inflammatory and/or autoimmune mechanisms [11, 12]. Further studies are required to understand the relationship between ongoing organ impairment, symptoms and functional damage, and to develop effective therapeutic and rehabilitative strategies [13].

Chest computed tomography (CT) scan plays a crucial role in diagnosing and monitoring COVID-19 patients [14]. Follow-up studies within 2 years after infection have shown varying rates of persistent lung abnormalities (ground-glass opacities (GGOs), reticulation and fibrotic-like changes: 22–83%) [5, 15–20]. However, small sample sizes, differences in evaluation standards and variations in severity of the studied cohorts contribute to the wide range of reported proportions. In addition, limited long-term data exist on the development of irreversible lung abnormalities, such as fibrosis, in COVID-19 survivors beyond 3 years, and no large studies have investigated the association between those lung abnormalities and ongoing function impairments after COVID-19. Therefore, large-scale longitudinal cohort studies are urgently needed to understand the natural history of residual lung abnormalities and their functional implications, especially with stratification based on initial disease severity.

This study aimed to assess the longitudinal progression of radiological and pulmonary function abnormalities in COVID-19 patients with residual lung abnormalities upon discharge, considering varying initial disease severity, up to 3 years. Additionally, we explored the association between these radiological abnormalities and respiratory outcomes.

Methods

Study design and participants

This prospective, longitudinal study evaluated COVID-19 patients with residual lung abnormalities upon discharge from Wuhan Jin Yin-tan Hospital and Wuhan Union Hospital (Wuhan, People's Republic of China) between 12 January 2020 and 12 April 2020. All patients had laboratory confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using real-time reverse transcription PCR with a standard protocol following WHO interim guidance [21]. Exclusion criteria included age <18 or >80 years, lack of chest CT at admission or discharge, complete resolution of lung abnormalities at discharge and previous pulmonary diseases (figure 1a; for rationale see supplementary table S1). Participants were interviewed face-to-face at 6 months (23 June 2020–21 September 2020), 12 months (2 November 2020–2 February 2021), 2 years (19 November 2021–28 January 2022) and 3 years (23 February 2023–23 April 2023) from symptoms onset. The cohort included 120 participants previously reported in a study with 2-year follow-up data (which only included severe COVID-19 survivors from a single centre) [17]. To determine the recovery status of COVID-19 survivors at 3 years, a control population group who tested negative for COVID-19 serology were retrospectively collected in the health examination centre of Wuhan Union Hospital from 2 February 2023 to 30 July 2023, as described in the supplementary material. Subsequently, the control population was matched with COVID-19 survivors (1:1) who completed pulmonary function tests (PFTs) at the 3-year visit by age, sex, smoking history and comorbidities (figure 1b).

Ethical approval was obtained from the Ethics Commission of Wuhan Jin Yin-tan Hospital (KY-2020-04-01) and Wuhan Union Hospital (0030). All participants were anonymous and signed an informed consent. This study is registered at the Chinese Clinical Trial Registry with identifier number ChiCTR2000038609.

Data collection at the acute phase

The medical records in the acute phase of each COVID-19 survivor were reviewed by one of four physicians (Lu Chen., J. Liu, X. Han or Y. Zheng, with 10, 10, 7 and 4 years of experience in thoracic radiology, respectively). Age, sex, body mass index (BMI), underlying comorbidities, disease severity, hospital stay and treatments received by individual patients were recorded. We categorised COVID-19 patients based on the mode of oxygen inhalation during hospitalisation using the WHO seven-category scale (supplementary table S2) [22], which is commonly used in clinical trials in patients hospitalised with COVID-19 or severe influenza [9, 23]. Severity scale 3: patients not requiring supplemental oxygen. Severity scale 4: patients requiring supplemental oxygen *via* nasal cannula or mask. Severity scale 5–6: patients requiring high-flow nasal cannula, non-invasive ventilation or invasive mechanical ventilation for oxygen therapy. ARDS was diagnosed if the ratio of arterial partial pressure of oxygen to fraction of

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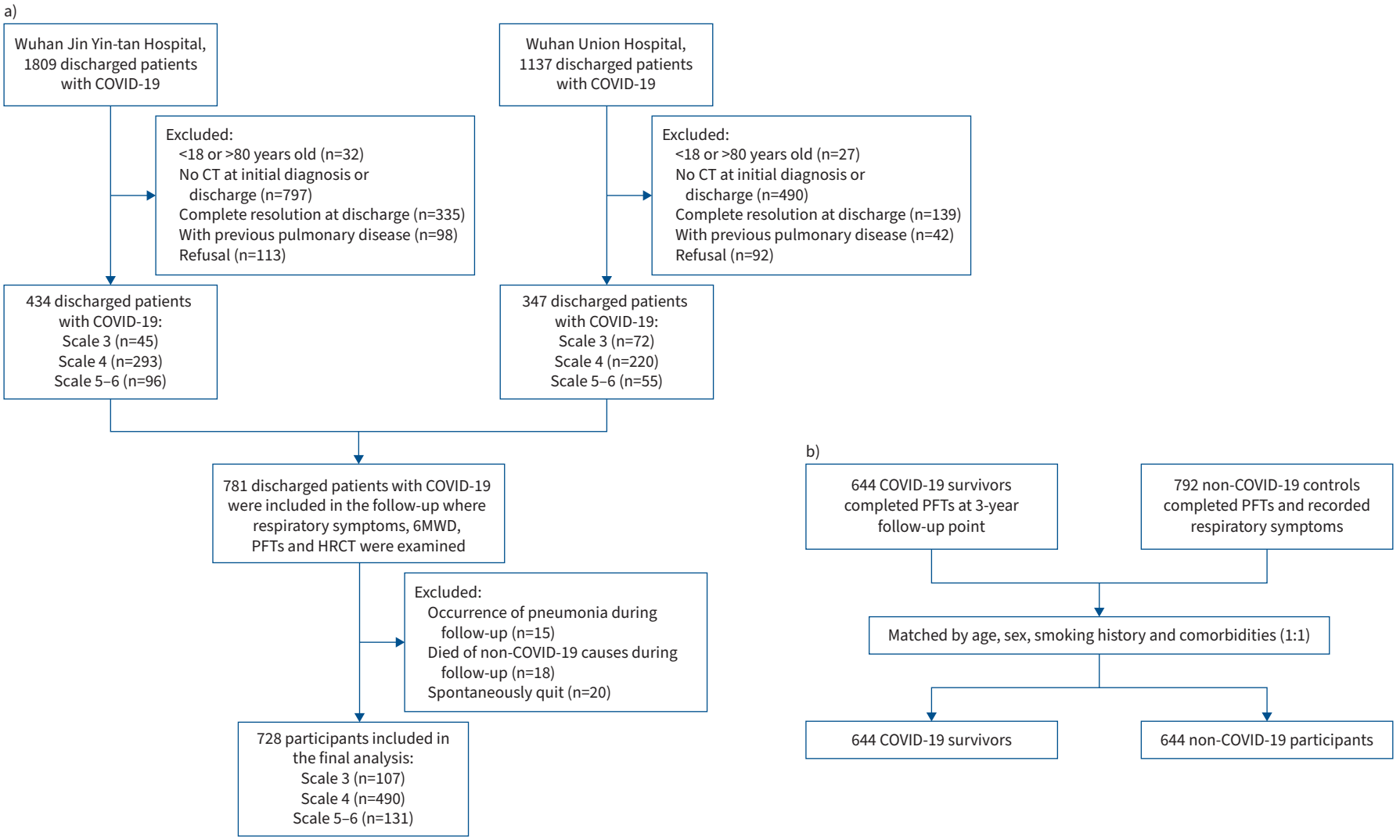

FIGURE 1 Study flowcharts. a) Flow diagram of coronavirus disease 2019 (COVID-19) patients. b) Matching process of COVID-19 survivors and non-COVID-19 participants who completed pulmonary function tests (PFTs) at the 3-year follow-up visit (1:1). Severity scale 3: patients not requiring supplemental oxygen during hospitalisation. Severity scale 4: patients requiring supplemental oxygen *via* nasal cannula or mask during hospitalisation. Severity scale 5–6: patients requiring high-flow nasal cannula, non-invasive mechanical ventilation or invasive mechanical ventilation during hospitalisation. CT: computed tomography; 6MWD: 6-min walk distance; HRCT: high-resolution CT.

inspired oxygen was ⩽300 mmHg [24]. The acute phase was defined as the time between symptoms onset and hospital discharge [5]. The history of self-reported use of respiratory medications within 1 month after discharge was also documented through telephone interviews.

Respiratory assessment at follow-up

During the follow-up visit, COVID-19 survivors underwent face-to-face interviews, PFTs, 6-min walk distance (6MWD) assessments and chest CT. PFT parameters included maximum vital capacity, forced expiratory volume in 1 s (FEV_1), forced vital capacity and diffusing capacity of the lung for carbon monoxide (D_{LCO}), all measured in a single-breath test. Abnormal pulmonary diffusion was defined as D_{LCO} <80% predicted [25]. The number of participants who underwent PFTs was 568 at 6 months, 565 at 12 months, 678 at 2 years and 644 at 3 years. Patients completed a self-reported respiratory symptoms questionnaire designed for this follow-up study assessing cough, expectoration and exertional dyspnoea (yes/no options and severity indicated in supplementary table S3). The 6MWD test was conducted following the European Respiratory Society/American Thoracic Society guidelines [26].

Patients underwent unenhanced chest CT examinations using SOMATOM Perspective or SOMATOM Spirit CT scanners (Siemens Healthineers, Erlangen, Germany). For each patient, CT features according to the Fleischner Society glossary were assessed and recorded [27], and a semiquantitative CT score was assigned according to the extent of involvement (supplementary material) [28].

Statistical analysis

Data analysis and graphing were performed using SPSS version 21.0 (IBM, Armonk, NY, USA), R version 4.3.1 (www.r-project.org) and Prism version 9.4.0 (GraphPad, Boston, MA, USA) as described in the supplementary material. Statistical significance was defined as $p<0.05$ (two-tailed).

Results

Characteristics of the study population

In this prospective study, 1809 COVID-19 patients from Wuhan Jin Yin-tan Hospital and 1137 COVID-19 patients from Wuhan Union Hospital were screened for eligibility. Among them, 2165 patients were excluded and 781 patients with residual lung abnormalities at discharge were enrolled for follow-up. During the follow-up, 15 patients developed pneumonia, 18 patients died from causes unrelated to COVID-19 and 20 patients dropped out (figure 1a). As shown in supplementary table S5, baseline characteristics of included COVID-19 survivors were compared with those not included, indicating that included patients had older age, increased requirement for supplemental oxygen during hospitalisation and higher prevalence of comorbidities, *e.g.* diabetes and hypertension.

728 participants (median (interquartile range) age 61 (51–68) years; 418 men (57%)) constituted the study population (table 1). Patients in the severity scale 5–6 (n=131) subgroup were significantly older and had a higher proportion of comorbidities compared with those in severity scale 3 (n=107) or 4 (n=490) subgroups ($p<0.05$). During hospitalisation, 499 patients (69%) received antiviral treatment and 439 patients (60%) received antibiotics; 571 patients (78%) were treated with anticoagulants. The median duration of hospital stay was 14 (10–23) days. 43 participants (5.9%) experienced ARDS and 67 patients (9.2%) were admitted to the intensive care unit (table 1).

Evolution of respiratory symptoms and lung function over 3 years

Among the 728 patients, the proportion of individuals with respiratory symptoms decreased from 27% (199/728) at 6 months to 22% (160/728) at 3 years (table 2). This trend was consistent in subgroups with severity scale 3 and 4 (supplementary tables S6 and S7). However, patients with severity scale 5–6 showed slightly worse symptoms from 12 months (49/131 (37%)) to 3 years (55/131 (42%)) (supplementary table S8). Dyspnoea and cough were the most common symptoms at 3-year follow-up. Of the 728 patients, only 32 (4.4%) had self-reported use of respiratory medications within 1 month after discharge. The 6MWD showed gradual improvement from 6 months to 3 years (496 *versus* 505 *versus* 507 *versus* 510 m; $p=0.002$). The proportion of individuals with abnormal ventilation function (FEV_1 <80% predicted) had a downward trend from 6.9% (39/568) at 6 months to 6.2% (40/644) at 3 years ($p=0.22$) (table 2). The proportion of reduced D_{LCO} decreased from 49% (278/568) at 6 months to 38% (244/644) at 3 years ($p=0.001$) (figure 2a). These improvements were observed regardless of disease severity (figure 2b–d).

Evolution of chest CT findings during 3 years

The CT scores for total lesions, GGOs, consolidations and reticulations showed a significant decrease at 6-month CT scans compared with the initial scan taken upon admission (figure 3a and supplementary table S9). This trend was observed across different severity subgroups ($p<0.001$) (supplementary tables

TABLE 1 Demographic and clinical characteristics at the acute phase in the study population

	Total (n=728)	Severity scale 3 (n=107)	Severity scale 4 (n=490)	Severity scale 5–6 (n=131)	p-value
Sex					0.27
Female	310 (43)	52 (49)	208 (42)	50 (38)	
Male	418 (57)	55 (51)	282 (58)	81 (62)	
Age, years	61 (51–68)	58 (46–68)[¶]	60 (51–68)	64 (56–68)	0.03
BMI, kg·m^{-2}	21 (19–22)	21 (18–22)	21 (19–23)	21 (19–22)	0.87
Smoking history	113 (16)	17 (16)	69 (14)	27 (21)	0.19
Drinking history	177 (24)	29 (27)	110 (22)	38 (29)	0.23
Allergy history	119 (16)	21 (20)	77 (16)	21 (16)	0.61
Comorbidities	323 (44)	31 (29)[#,¶]	230 (47)	62 (47)	0.002
Diabetes	116 (16)	10 (9.4)	88 (18)	18 (14)	0.07
Hypertension	239 (33)	22 (21)[#,¶]	167 (34)	50 (38)	0.009
Cardiovascular disease	25 (3.4)	2 (1.9)	19 (3.9)	4 (3.1)	0.57
Liver disease	27 (3.7)	8 (7.5)	15 (3.1)	4 (3.1)	0.08
Kidney disease	7 (1.0)	1 (0.9)[#,¶]	1 (0.2)[¶]	5 (3.8)	0.001
Non-lung cancer tumour	8 (1.1)	0 (0)	6 (1.2)	2 (1.5)	0.48
Hospital stay, days	14 (10–23)	14 (8–20)[¶]	14 (9–21)[¶]	17 (11–45)	<0.001
ICU admission	67 (9.2)	0 (0)[¶]	0 (0)[¶]	67 (51)	<0.001
ARDS experience	43 (5.9)	0 (0)[¶]	0 (0)[¶]	43 (33)	<0.001
Treatment					
Antivirals	499 (69)	50 (47)[#,¶]	340 (70)[¶]	109 (83)	<0.001
Antibiotics	439 (60)	45 (42)[#,¶]	300 (61)	94 (72)	<0.001
Corticosteroids	275 (38)	9 (8.4)[#,¶]	193 (39)[¶]	73 (56)	<0.001
Intravenous immunoglobulin	175 (24)	0 (0)[#,¶]	107 (22)[¶]	68 (52)	<0.001
Anticoagulation therapy	571 (78)	49 (46)[#,¶]	261 (53.3)[¶]	131 (100)	<0.001
Respiratory treatment initiated after discharge	32 (4.4)	2 (1.9)[¶]	17 (3.5)[¶]	13 (9.9)	0.002

Data are presented as n (%) or median (interquartile range), unless otherwise stated. Severity scale 3: patients not requiring supplemental oxygen during hospitalisation; severity scale 4: patients requiring supplemental oxygen *via* nasal cannula or mask during hospitalisation; severity scale 5–6: patients requiring high-flow nasal cannula, non-invasive mechanical ventilation or invasive mechanical ventilation during hospitalisation; BMI: body mass index; ICU: intensive care unit; ARDS: acute respiratory distress syndrome. [#]: statistically significant compared with moderate group (severity scale 4); [¶]: statistically significant compared with severe group (severity scale 5–6).

S10–S12). However, there was no significant decrease in scores from 6 months to 3 years in subgroups with severity scale 4–6 (supplementary tables S11 and S12, and figure 3a). The proportion of COVID-19 survivors with residual lung abnormalities on CT scans gradually decreased from 46% at 6 months to 36% at 3 years. As shown in figure 3b–d, COVID-19 survivors exhibited the highest prevalence of non-fibrotic changes 6 months after discharge, which gradually decreased over a 3-year period, regardless of initial disease severity. Meanwhile, patients with severity scale 5–6 showed the highest prevalence of fibrotic changes at 6 months, which persisted for 3 years. Specifically, among 333 COVID-19 survivors with residual lung abnormalities at 6 months, 0.9% (3/333) showed progressive fibrotic-like changes, 29% (95/333) exhibited stable fibrotic-like changes, 23% (75/333) demonstrated the usual CT progression with complete resolution of non-fibrotic changes and 48% (160/333) displayed stable non-fibrotic changes over 3 years of follow-up (figure 4a–d). However, the extent of fibrotic-like changes remained stable from 6 months to 3 years (0.83±2.3 *versus* 0.80±2.2; p>0.05), regardless of disease severity.

Comparisons between groups of patients with different radiological appearances

At the 3-year follow-up, patients with residual lung abnormalities had higher rates of respiratory symptoms (32% *versus* 16%), reduced 6MWD (496 *versus* 510 m) and more diffusion abnormalities (57% *versus* 27%) compared with those with complete resolution (p<0.05 for all) (table 3 and supplementary figure S1a). Similarly, among those with fibrotic-like changes, more respiratory symptoms (44% *versus* 25%; p=0.003) and lower D_{LCO} values (57% *versus* 50%; p=0.006) were observed compared with those with non-fibrotic changes (supplementary figure S1b). After adjusting for age, sex, BMI, smoking history, drinking history and comorbidities, the presence of fibrotic-like changes at the 3-year follow-up was associated with a higher risk of residual respiratory symptoms (OR 2.26, 95% CI 1.28–3.97) (supplementary table S13) and lung diffusion impairment (OR 1.99, 95% CI 1.07–3.68) (table 4). Respiratory treatment initiated after discharge was also linked to an increased risk of residual respiratory symptoms (OR 4.14, 95% CI 1.93–8.89) (supplementary table S13) and reduced D_{LCO} (OR 2.71, 1.05–7.02). Male sex was

TABLE 2 Comparison of clinical characteristics at the four follow-up time-points

	6 months (n=728)	12 months (n=728)	2 years (n=728)	3 years (n=728)	p-value
Respiratory symptoms	199 (27)	168 (23)	161 (22)	160 (22)	0.15
Dyspnoea	110 (15)	94 (13)	91 (13)	86 (12)	0.11
Dyspnoea severity					<0.001
Present after activity	100 (14)	82 (11)	72 (9.9)	78 (11)	
Present at rest	10 (1.4)	12 (1.7)	29 (4.0)	8 (1.1)	
Cough	103 (14)	68 (9.4)	78 (11)	88 (12)	0.02
Cough severity					0.01
Mild	100 (14)	59 (8.1)	74 (10)	84 (12)	
Moderate	3 (0.4)	9 (1.2)	4 (0.6)	4 (0.6)	
Expectoration	71 (9.8)	53 (7.3)	52 (7.1)	59 (8.1)	0.24
Expectoration severity					0.45
Mild	68 (9.3)	48 (6.6)	49 (8.3)	56 (7.7)	
Moderate	3 (0.4)	5 (0.7)	3 (0.5)	3 (0.4)	
6MWD	496 (445–540)[#,¶,+]	505 (452–550)	507 (457–554)	510 (460–554)	0.002
Pulmonary function					
VC_{max}	105±18[¶,+]	106±16	108±16	108±16	0.02
FVC	111±50	110±18	110±17	111±18	0.80
FEV_1	104±18	105±19	105±18	106±18	0.09
FEV_1 <80% predicted	39/568 (6.9)	48/565 (7.5)	33/678 (4.9)	40/644 (6.2)	0.22
MVV	94±20	96±21	96±21	95±20	0.20
RV/TLC	97±15[¶,+]	99±45[+]	99±21[+]	94±15	0.005
D_{LCO}	82±16[¶,+]	84±37	83±16[+]	84±13	0.274
D_{LCO} <80% predicted	278/568 (49)[#,¶,+]	244/565 (43)[+]	269/678 (40)	244/644 (38)	0.001

Data are presented as n (%), median (interquartile range), mean±SD or n/N (%), unless otherwise stated. Population who completed pulmonary function tests at the four time-points: 568 at 6 months, 565 at 12 months, 678 at 2 years and 644 at 3 years. 6MWD: 6-min walk distance; VC_{max}: maximum vital capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MVV: maximum ventilatory volume; RV: residual volume; TLC total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: statistically significant compared with 12-month follow-up; [¶]: statistically significant compared with 2-year follow-up; [+]: statistically significant compared with 3-year follow-up.

associated with a lower risk of lung diffusion impairment (OR 0.40, 95% CI 0.25–0.65), while a total CT score >2 at the 3-year follow-up posed higher risks of lung diffusion impairment (OR 2.08, 95% CI 1.06–4.08) (table 4).

Comparisons between matched pairs of COVID-19 survivors and controls

As shown in figure 1b, 792 controls were collected retrospectively and then 644 controls were used to match the COVID-19 survivors who underwent PFTs. There were no significant differences in age, sex or comorbidities between the two groups (supplementary table S14). At 3-year follow-up, 145/644 COVID-19 survivors (23%) had at least one respiratory symptom, significantly higher than the matched controls (14/644 (2.2%); p<0.001) (supplementary table S15), and all recorded respiratory symptoms, dyspnoea, cough and expectoration, were significantly higher in the COVID-19 survivor group than in the control group (p<0.001 for all). In addition, the proportion of D_{LCO} impairment in COVID-19 survivors was also significantly higher than in the control group (38% *versus* 17%; p<0.001) (supplementary table S15 and supplementary figure S1c).

Discussion

This is the longest follow-up study on lung abnormalities and respiratory outcomes in COVID-19 patients, lasting up to 3 years. We observed gradual improvements in symptoms, pulmonary function, 6MWD and lung abnormalities over this period for patients with residual lung abnormalities at discharge. However, a significant number of patients still experienced persistent lung dysfunctions and abnormalities. Notably, the presence of fibrotic-like changes at 3 years correlated with increased symptoms, lower 6MWD and abnormal pulmonary function. This study confirms the correlation between lung damage, symptoms and functional impairment, highlighting the need for targeted management of post-COVID-19 pulmonary sequelae.

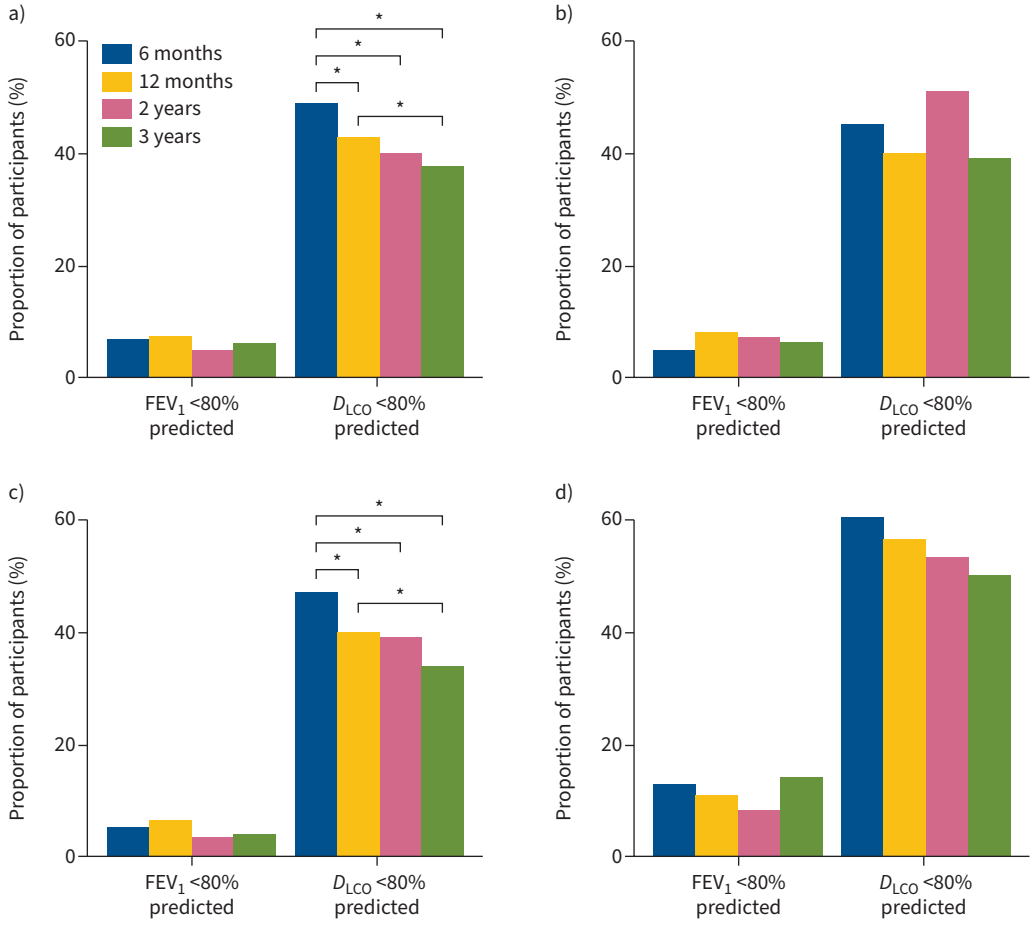

FIGURE 2 Longitudinal evolution of lung function over time. a) Evolution of lung function in all coronavirus disease 2019 (COVID-19) patients who underwent pulmonary function tests. b–d) Evolution of lung function in COVID-19 patients with different disease severity scales: b) severity scale 3 (patients not requiring supplemental oxygen during hospitalisation), c) severity scale 4 (patients requiring supplemental oxygen *via* nasal cannula or mask during hospitalisation) and d) severity scale 5–6 (patients requiring high-flow nasal cannula, non-invasive mechanical ventilation or invasive mechanical ventilation during hospitalisation). FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusion capacity for carbon monoxide. *: p<0.05 for the comparison of different time-points.

Various studies have reported varying rates (22–83%) of persistent radiological and functional abnormalities in COVID-19 survivors 2 years post-discharge [15–20, 22]. In our study, 22% of patients had respiratory symptoms, 38% had reduced D_{LCO} and 36% had radiological lung abnormalities at the 3-year follow-up, and patients with severity scale 5–6 had the highest proportion of pulmonary sequelae. Differences in study design, patient populations and methodologies could account for variations in the observed outcomes. This study only included hospitalised patients with residual lung abnormalities at discharge, which may be more representative of the more severe COVID-19 compared with other studies [16, 20]. In addition, the results of our study align with long-term studies on SARS-CoV-1, which showed a high prevalence of radiological abnormalities and functional decline even after 7 and 15 years [29, 30]. We also observed fluctuating or progressive ongoing respiratory symptoms and diffusion abnormalities at late follow-up, consistent with previous 2-year studies [22], which may be attributed to psychological and physical factors [31, 32]. Patients with persistent symptoms should consider early pulmonary rehabilitation training, including exercise rehabilitation or other effective methods used for COPD or interstitial lung disease (idiopathic pulmonary fibrosis (IPF)) [33, 34].

Furthermore, we found that patients with residual lung abnormalities had a higher incidence of respiratory symptoms compared with those with complete radiological resolution, and fibrotic-like changes at the 3-year follow-up increased the risk of residual respiratory symptoms and impaired lung diffusion.

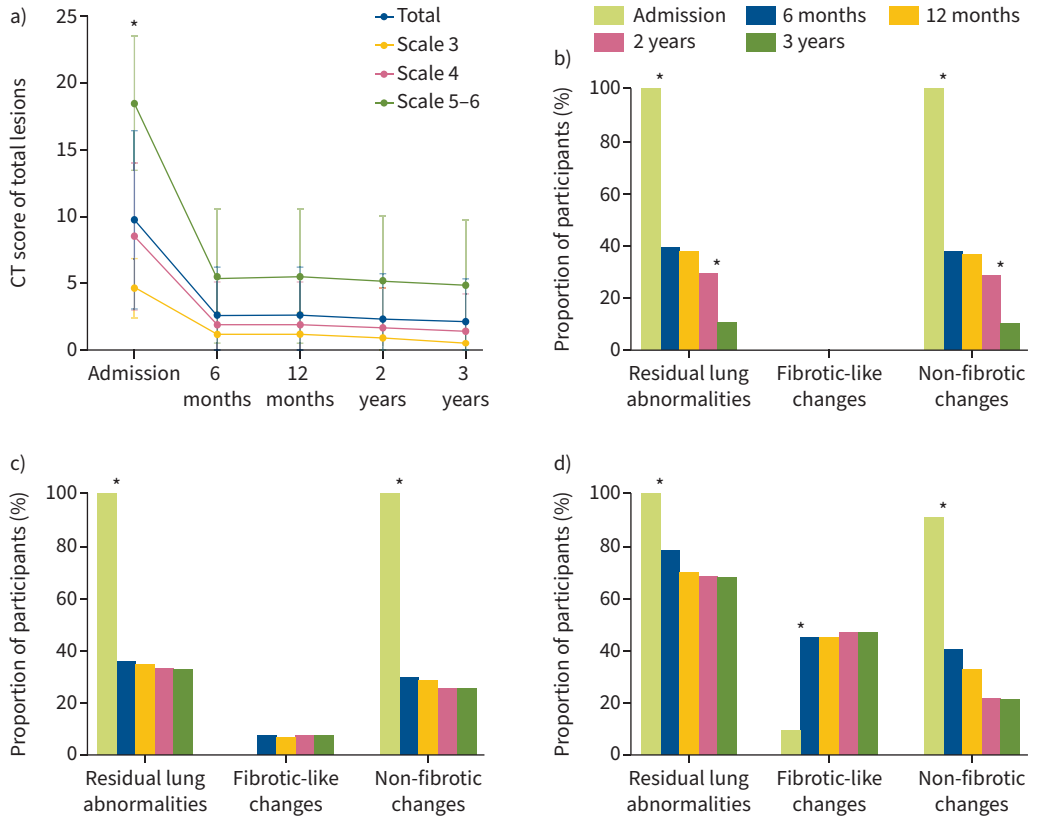

FIGURE 3 Dynamic changes observed in computed tomography (CT) scans over time. a) Mean±SD total CT score for patients stratified by different disease severity scales. b–d) The changes in the proportion of residual lung abnormalities among COVID-19 patients classified by different disease severity scales: b) severity scale 3 (patients not requiring supplemental oxygen during hospitalisation), c) severity scale 4 (patients requiring supplemental oxygen *via* nasal cannula or mask during hospitalisation) and d) severity scale 5–6 (patients requiring high-flow nasal cannula, non-invasive mechanical ventilation or invasive mechanical ventilation during hospitalisation). *: p<0.05 for the comparison of different time-points.

Therefore, radiological examinations can be utilised to identify lung abnormalities in COVID-19 survivors experiencing ongoing respiratory symptoms or reduced lung function. However, a portion of participants with normal CT still had respiratory symptoms and impaired D_{LCO}. This finding supports recent publications showing that COVID-19 causes persistent symptoms but normal CT results from thromboembolic disease or diffuse vascular disease [13, 35]. A multidisciplinary evaluation of these patients is needed to determine the possible mechanisms and optimal management [36].

Post-COVID fibrosis has been documented with similarities to IPF in macrophage profiles [9]. Various terms, such as fibrotic-like changes [15, 19], organising pneumonia [37], interstitial lung disease [38] or simply pulmonary fibrosis [39, 40], have been used to describe these changes. As the term "fibrosis" refers to an irreversible pathological condition, relying solely on CT findings for its diagnosis is improper. We adopt the term "fibrotic-like change" to describe architectural distortion, traction bronchiectasis and honeycombing on CT scans. While some studies broadly categorise various CT abnormalities as "post-COVID fibrosis", the presence of reticulation and GGOs alone, without traction bronchiectasis, could suggest resolving diffuse alveolar damage or ARDS, characterised by histopathological variability. In contrast, some studies have used the term "post-COVID fibrosis" broadly to describe various lung abnormalities observed on CT scans, including irregular bronchial dilatation, reticulation, parenchymal bands, architectural distortion and GGOs [39, 40]. Nevertheless, reticulation and GGOs alone, without the presence of traction bronchiectasis, could indicate resolving diffuse alveolar damage or ARDS, in which there is substantial histopathological heterogeneity [41]. Therefore, diagnosing lung fibrosis based solely on reticulation or GGOs may overestimate its prevalence [42]. Standardisation for diagnosis and follow-up of post-COVID fibrosis is urgently needed to guide the formulation of clinical anti-fibrosis treatment strategies.

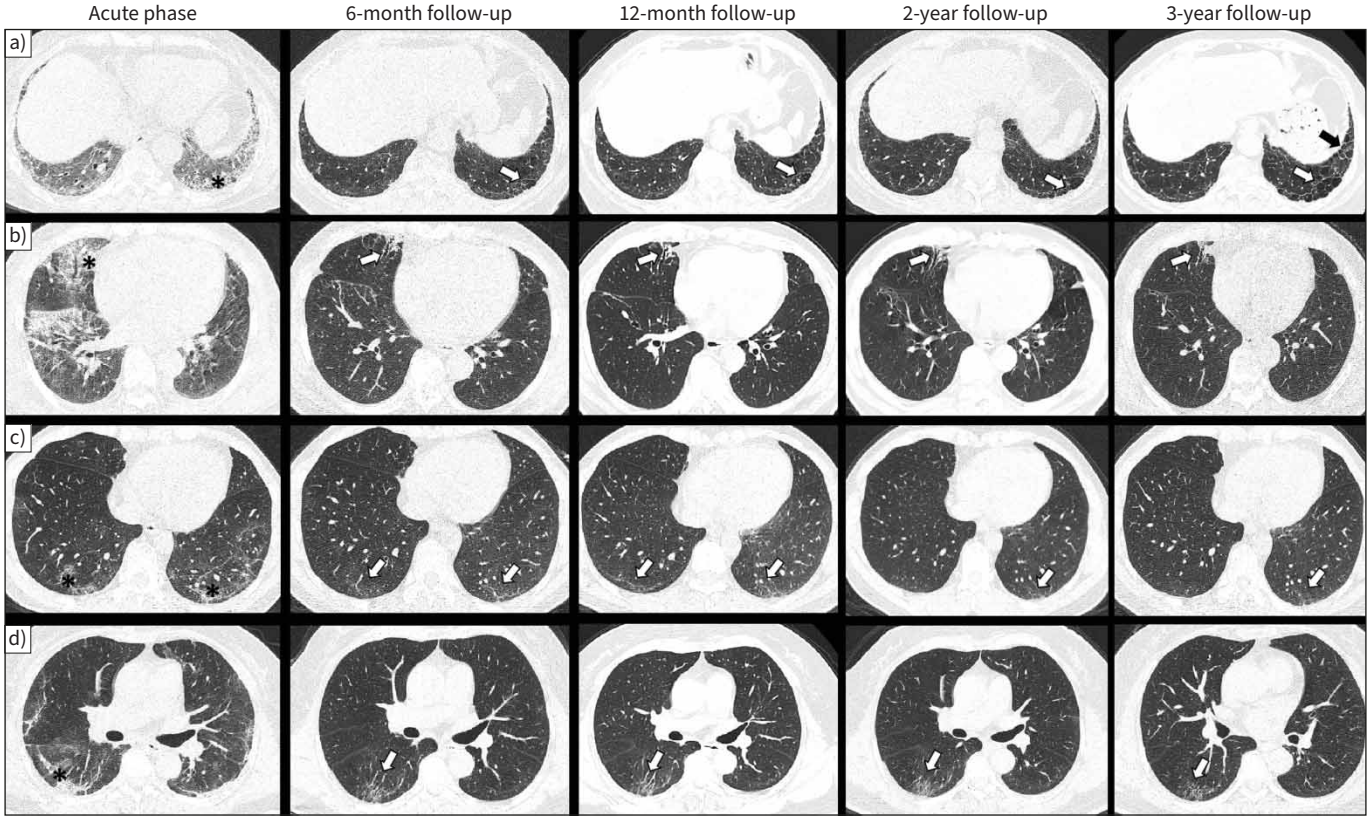

FIGURE 4 Various patterns of computed tomography (CT) evolution in residual lung abnormalities over 3 years. a) Typical findings in participants (n=3) with progressive fibrotic changes. Initial scans revealed extensive bilateral ground-glass opacities (GGOs) with septal thickening (asterisk). The 6-month follow-up displayed focal subpleural reticular lesions in the left upper lobe, evolving into parenchymal bands and cystic lesions at the 12-month follow-up. At 3 years post-symptoms onset, CT scans depicted multiple cystic airspaces and honeycombing (arrows) in the left lower lobe. b) Typical findings in participants (n=95) with stable fibrotic-like changes. Acute-phase scans exhibited diffuse GGOs and consolidation (asterisk) in the right upper and middle lobes. The 6-month follow-up showed subpleural reticular lesions with traction bronchiectasis (arrows), persisting as stable subpleural bronchiectasis in the same lung zone at 12 months and 3 years. c) Typical CT progression in participants (n=75) with complete resolution of non-fibrotic changes. Acute-phase scans displayed GGOs with linear opacities in both lower lobes (asterisks). By the 6-month follow-up, partial resorption was evident (arrows), and by the 3-year follow-up, nearly complete resolution of abnormalities was observed. d) Typical CT findings over time in participants (n=160) with stable non-fibrotic changes. Acute-phase scans revealed a mixed pattern of GGOs and consolidation in the right middle and lower lobes (asterisk). Subsequent scans at 6 months, 2 years and 3 years showed persisting subpleural localised GGOs and reticular lesions in the right lower lobe (arrows).

In this study, we observed a significant decrease in non-fibrotic changes (GGOs and reticular abnormalities) from 6 months (33%) to 3 years (22%). Studies suggest that these changes tend to gradually resolve over time [4, 43]. Additionally, we found individuals with fibrotic-like changes had more respiratory symptoms and lower D_{LCO} values compared with those with non-fibrotic changes. Therefore, non-fibrotic change might mean reversible pulmonary sequelae and less impact on symptoms and functional damage in COVID-19 survivors. However, a previous study reported that reticular abnormalities remained present on CT scans during a 7-year follow-up in survivors of SARS-CoV-1 [29]. Similarly, during the 3-year follow-up, we observed persistent reticular abnormalities and GGOs in certain patients with non-fibrotic changes. A recent study pathologically identified three clusters of radiological patterns in patients with post-acute COVID-19, revealing that persistent GGOs corresponded to organising pneumonia and fibrosing non-specific interstitial pneumonia [35]. Consequently, different patterns of CT changes require distinct clinical decision-making processes, follow-up protocols or treatment strategies for COVID-19 survivors.

This study is not without limitations. First, as the evaluated cohort consisted solely of individuals from Wuhan, a single city in China, the generalisability of the findings to populations outside of China may be limited. Second, our study focuses on unvaccinated individuals infected with the original strain of COVID-19; therefore, the findings may not apply to those with variant strains or who have received

TABLE 3 Comparison of clinical characteristics between different radiological appearances at 3-year follow-up

	Complete radiological resolution (n=467)	Residual lung abnormalities (n=261)	p-value	Non-fibrotic changes (n=163)	Fibrotic-like changes (n=98)	p-value
Respiratory symptoms	76 (16)	84 (32)	<0.001	41 (25)	43 (44)	0.003
Dyspnoea	38 (8.1)	48 (18)	<0.001	19 (12)	29 (30)	<0.001
Dyspnoea severity			<0.001			<0.001
Present after activity	32 (6.9)	46 (18)		2 (0.8)	29 (30)	
Present at rest	6 (1.3)	2 (0.8)		2 (1.2)	0 (0)	
Cough	45 (9.6)	43 (17)	0.003	22 (14)	21 (21)	0.09
Cough severity			0.020			0.19
Mild	43 (9.3)	42 (16)		22 (14)	21 (21)	
Moderate	3 (0.6)	1 (0.4)		1 (0.6)	0 (0)	
Expectoration	27 (5.8)	32 (12)	0.003	16 (9.8)	16 (16)	0.12
Expectoration severity			0.007			0.17
Mild	25 (5.4)	31 (12)		15 (9.2)	16 (16)	
Moderate	2 (0.4)	1 (0.4)		1 (0.6)	0 (0)	
6MWD	510 (462–560)	494 (449–541)	0.003	494 (451–545)	498 (443–537)	0.57
Pulmonary function						
VC_{max}	107±15	105±18	0.29	106±17	104±20	0.33
FVC	113±20	109±16	0.41	109±17	107±20	0.31
FEV_1	104±17	104±19	0.53	103±18	105±22	0.55
FEV_1 <80% predicted	16/408 (3.9)	24/236 (10)	0.002	13/148 (8.8)	11/88 (13)	0.38
MVV	95±20	92±22	0.24	91±22	96±22	0.12
RV/TLC	99±15	94±15	<0.001	96±16	91±22	0.03
D_{LCO}	87±16	82±17	0.001	85±18	78±14	0.002
D_{LCO} <80% predicted	110/408 (27)	134/236 (57)	<0.001	74/148 (50)	60/88 (57)	0.006

Data are presented as n (%), median (interquartile range), mean±SD or n/N (%), unless otherwise stated. Population who completed pulmonary function tests at the four time-points: 568 at 6 months, 565 at 12 months, 678 at 2 years and 644 at 3 years. 6MWD: 6-min walk distance; VC_{max}: maximum vital capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MVV: maximum ventilatory volume; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

vaccinations. Third, due to the retrospective collection of our control group, potential biases and confounding factors may be introduced, and the group may not fully capture the comparative risk or respiratory burden of COVID-19 compared with other respiratory infections. Fourth, the absence of pre-infection chest CT scans makes it challenging to determine whether the observed abnormalities are exclusively due to COVID-19, although we excluded patients with prior lung disease. Fifth, we were unable to examine potential links between chronic embolism and symptoms due to the lack of enhanced CT scans for assessing pulmonary vascular abnormalities [13]. Moreover, we excluded patients with normal CT at discharge. Consequently, the non-participating patients in our study likely had less severe

TABLE 4 Multivariable logistic regression analysis models for the association between decreased lung diffusion function and listed variables at 3-year follow-up (n=644)

	Coefficient±SE	z-value	p-value	OR (95% CI)
Sex	−0.91±0.24	14.31	<0.001	0.40 (0.25–0.65)
Age >61 years	0.01±0.009	1.06	0.30	1.01 (0.99–1.03)
BMI >21 kg·m^{-2}	0.04±0.21	0.03	0.86	1.04 (0.69–1.57)
Smoking history	0.60±0.32	3.52	0.06	1.83 (0.97–3.42)
Drinking history	−0.10±0.29	0.13	0.72	0.90 (0.51–1.6)
Allergies	0.43±0.25	2.83	0.09	1.53 (0.93–2.52)
Comorbidities	−0.22±0.21	1.13	0.29	0.80 (0.53–1.21)
Residual abnormalities	0.13±0.33	0.15	0.70	1.14 (0.59–2.17)
Fibrotic-like changes	0.69±0.32	4.75	0.03	1.99 (1.07–3.68)
Total CT score >2	0.73±0.34	4.54	0.03	2.08 (1.06–4.08)
Respiratory treatment initiated after discharge	1.0±0.49	4.23	0.04	2.71 (1.05–7.02)
Intercept	−1.35±0.58	5.41	0.02	0.26

BMI: body mass index; CT: computed tomography.

infections compared with those who participated, potentially leading to an overestimation of the prevalence of post-COVID-19 symptoms. Lastly, our study lacks histological correlation and the definition of pulmonary fibrosis relies solely on CT abnormalities.

In summary, this study illustrates ongoing improvement in respiratory outcomes up to 3 years after COVID-19. However, a significant proportion of patients, particularly those with severe initial infections, continue to exhibit radiological lung abnormalities and abnormal pulmonary function. Residual lung abnormalities, particularly the fibrotic-like changes on CT, are associated with persistent respiratory symptoms and abnormal pulmonary function, and should be considered in long-term management strategies for COVID-19 survivors.

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Ethics statement: This study received ethical approval from the Ethics Commission of Wuhan Jin Yin-tan Hospital (KY-2020-04-01) and Wuhan Union Hospital (0030).

Author contributions: C. Zheng, H. Shi, X. Han, Y. Fan and F. Yang conceived and designed the study. X. Han, Lu Chen, O. Alwalid, Y. Zheng and J. Liu contributed to the literature search. L. Guo, L. Wu, H. Zhao, H. Li, W. Wu, L. Zhang, Y. Bai, T. Nie, B. Sun, T. Sun, Y. Gui, Q. Luo, Lei Chen and Leqing Chen collected and verified the data. X. Han, Lu Chen and H. Zhao performed the analysis. C. Zheng, H. Shi, X. Han and Y. Fan contributed to the figures. X. Han, F. Yang and O. Alwalid contributed to the writing of the report. All authors had full access to the data in the study, critically revised the manuscript for important intellectual content and had final responsibility for the decision to submit for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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