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CHEST

Impact of COVID-19 pneumonia on interstitial lung disease: semi-quantitative evaluation with computed tomography

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Abstract

Objectives To evaluate the CT scores and fibrotic pattern changes in interstitial lung disease (ILD) patients, with and without previous COVID-19 pneumonia.

Methods Patients with ILD (idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated ILD (CTD-ILD)) were retrospectively enrolled in the study which consisted of patients who had COVID-19 pneumonia while the control group had not. All patients had two CT scans, initial and follow-up, which were evaluated semi-quantitatively for severity, extent, and total CT scores, fibrosis patterns, and traction bronchiectasis.

Results A total of 102 patients (pneumonia group $n = 48$; control group $n = 54$) were enrolled in the study. For both groups, baseline characteristics were similar and CT scores were increased. While there was a 4.5 ± 4.6 point change in the total CT score of the COVID-19 group, there was a 1.2 ± 2.7 point change in the control group ($p < 0.001$). In the IPF subgroup, the change in total CT score was 7.0 points (95% CI: 4.1 to 9.9) in the COVID-19 group and 2.1 points (95% CI: 0.8 to 3.4) in the control group. Seven patients (14.6%) in the COVID-19 group progressed to a higher fibrosis pattern, but none in the control group.

Conclusions Semi-quantitative chest CT scores in ILD patients demonstrated a significant increase after having COVID-19 pneumonia compared to ILD patients who had not had COVID-19 pneumonia. The increase in CT scores was more prominent in the IPF subgroup. There was also a worsening in the fibrosis pattern in the COVID-19 group.

Key Points

• *The impact of COVID-19 pneumonia on existing interstitial lung diseases and fibrosis is unclear.*

• *COVID-19 pneumonia may worsen existing interstitial lung involvement with direct lung damage and indirect inflammatory effect.*

• *COVID-19 pneumonia may affect existing lung fibrosis by triggering inflammatory pathways.*

Keywords COVID-19 · Multidetector computed tomography · Fibrosis · Interstitial lung disease · Pneumonia

Abbreviations

COVID-19   Coronavirus Disease 2019
CTD-ILD   Connective tissue disease-associated ILD
GGOs   Ground-glass opacities
HU   Hounsfield units
ILD   Interstitial lung disease
IPF   Idiopathic pulmonary fibrosis
IQR   Interquartile range

PCR   Real-time fluorescence polymerase chain reaction
SD   Standard deviation
UIP   Usual interstitial pneumonia
WHO   World Health Organisation

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Introduction

Coronavirus disease 2019 (COVID-19) has become a global pandemic, and the World Health Organisation (WHO) declared it a public health emergency of international concern in January 2020 [1]. Computed tomography (CT) most commonly reveals ground-glass opacities (GGOs) or consolidations in a peripheral and subpleural distribution in the acute phase of the disease [2, 3]. The extent of lung involvement is dependent on the degree of

underlying inflammation, with greater inflammation associated with a worse outcome [4–6].

The recovery process is variable after COVID-19 pneumonia and the radiologic changes have been described in both early and late courses although the prevalence and abnormalities vary depending on the interval after infection, the severity of initial illness, comorbidities, and the study population [3, 7, 8]. The most common residual abnormalities at follow-up CT were interlobular septal thickening, focal/multifocal GGOs, subpleural parenchymal bands, and fibrotic-like changes including traction bronchiectasis, and parenchymal distortion and/or honeycombing [7, 9].

Interstitial lung disease (ILD) is a large group of diffuse lung diseases characterized by similar clinical, pathological, and radiological features. CT is a high-sensitivity imaging tool for the assessment of the severity and extent of lung changes and fibrosis. Semi-quantitative CT scoring analysis in ILD has the potential to standardize the role of imaging in ILD and correlates well with the mortality rate [10–12].

Superimposing COVID-19 pneumonia on pre-existing ILD may complicate the radiological picture. There is limited information concerning whether COVID-19 pneumonia changes the expected radiological findings during the follow-up of ILD. This is a critical but difficult issue due to the potential long-term sequelae of COVID-19 pneumonia to simulate fibrosis, secondary to ILD.

The purpose of this study was to investigate if subsequent COVID-19 pneumonia causes a change in the radiological appearance of the pre-existing ILD findings and leads to a progression in severity and extent of the ILD disease beyond the expected state.

Materials and methods

Study design

This was a cross-sectional study of retrospectively collected single-center data. All patients with previous ILD and diagnosed with definite COVID-19 pneumonia at the inpatient and outpatient clinics of a tertiary care facility between March 2020 and January 2022 were enrolled in the study. Ethical committee approval was obtained before the study started.

Study protocol

ILD patients were diagnosed according to the latest international consensus guideline and were separated into those with idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated ILD (CTD-ILD) [13, 14]. Medical records of these patients including demographic characteristics (age, gender), comorbidities, hospitalization status, need for oxygen therapy, and need for intensive care unit were evaluated.

The study cohort consists of two groups. The COVID-19 group consisted of pre-existing ILD patients with subsequent COVID-19 pneumonia, designated the study group, and the control group included ILD patients without COVID-19 pneumonia. The cases with positive real-time fluorescence polymerase chain reaction (PCR) test results according to the WHO COVID-19 case definition sheet were defined as confirmed COVID-19 cases [15]. PCR test data were identified using the local hospital and national electronic health recording system. The COVID-19 group included adult patients who had confirmed diagnoses of COVID-19 and had two serial CT scans. All patients underwent the initial CT examination within 18 months before COVID-19 pneumonia diagnosis. The duration from the onset of COVID-19 pneumonia to follow-up CT was between four months to one year. The control group included adult patients with two serial CT scans, the time between the initial and follow-up CT scans was at most three years. Patients were selected from the period before the COVID-19 pandemic. Those patients were randomly chosen from the local hospital picture archiving and communications system between 2017 and 2019 before the pandemic period.

Patients were excluded if they did not have at least two serial CT scans or if the CT scans were insufficient for interpretation.

CT technique and interpretation

Patients underwent chest CT with a 64-detector scanner (Aquillion 64; Canon Medical Systems—previously Toshiba Medical Systems) in a supine position with full inspiration. Scanning parameters were as follows: 120 kV, variable mAs according to the patient size using an automatic exposure control system, slice thickness of 1 mm, and an average $CTDI_{vol}$ 21 mGy. The images were reconstructed in a 512×512 matrix with 1 mm non-overlapping slices, applying a standard high-resolution CT reconstruction algorithm. Prone scans were obtained when there were gravitational opacities in limited patients. All images were viewed with a window level of -600 Hounsfield units (HU) and a width of 1.600 HU. Images were reconstructed with a lung parenchyma FC52 kernel and a mediastinal FC13 kernel. No iterative reconstruction techniques were applied. The CT images were interpreted independently by two thoracic radiologists, one with 15 and the other with 4 years of experience in thoracic radiology.

Both the initial and follow-up CT images in COVID-19 and control subgroups were assessed with a semi-quantitative method proposed by Warrick et al [16]. The severity score was assessed by recording five elementary lesions. These were GGOs, irregularities in the pleural margins, septal lines, honeycombing, and subpleural cysts. The basic CT terminology for elementary lesions described by the Fleischner Society glossary was used [17].

Each elementary lesion was rated from 1 to 5 and a total severity score was generated by summing the values for each lesion observed on CT images. The severity score had a possible range of 0 (no elementary lesions) to 15 (all elementary lesions present). The extent score was assessed according to the number of segments involved for each elementary lesion. Each lesion type was assigned a score from 1 to 3 where 1 indicated that the lesion was present in one to three segments, 2 indicated that the lesion was present in four to nine segments, and 3 indicated that the lesion was present in more than nine segments. The extent score had a possible range of 0–15 according to the quantification. A total Warrick score was then calculated by adding up the severity and extent scores. The total Warrick score has a range between 0 and 30. The criteria used for calculating the Warrick score are shown in Table 1.

In addition to the Warrick scoring system, we also evaluated traction bronchiectasis and fibrosis patterns. We defined the fibrosis pattern by using standard terminology to categorise the usual interstitial pneumonia (UIP) pattern in lung tissue: definite UIP, probable UIP, indeterminate for UIP, and features most likely consistent with an alternative diagnosis [18, 19].

Outcome measures

The primary outcome measure in this study was the change in the difference between the initial and follow-up total CT scores in both groups. Secondary outcome measures were the changes in individual severity and extent scores in COVID-19 and control groups and the effect of having COVID-19 in patients with IPF or without a diagnosis of IPF.

Statistical analysis

Data analysis of the current study was performed using SPSS for Windows, version 15.0. (SPSS Inc.). The Kolmogorov–Smirnov test was used to test the normal distribution of continuous variables. Continuous variables with normal distribution were tested using the Independent samples t-test for

independent variables and paired samples t-test for dependent variables. Data is presented as mean and standard deviation (SD). Non-parametric calculations for continuous data were performed using the Mann–Whitney U test and data were expressed as medians and interquartile range (IQR). Categorical variables were tested using the chi-square test. Mean differences were expressed with 95% confidence intervals (CIs). All the statistical analyses were two-sided. An alpha value of 0.05 was considered to be the nominal level of significance.

Results

Baseline characteristics

A total of 160 patients were evaluated for enrolment in the study. After the exclusion criteria were implemented, 102 patients were included, with 48 (47.1%) in the COVID-19 group and 54 (52.9%) in the control group. The COVID-19 group flowchart is shown in Fig. 1. In the COVID-19 group, 15 (31.3%) patients were diagnosed with IPF, and 33 patients (68.7%) were diagnosed with CTD-ILD. In the control group, 27 patients (50%) were diagnosed with IPF, and 27 patients (50%) were diagnosed with CTD-ILD. CTD-ILD patients included rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Sjögren's syndrome, and mixed connective tissue disease. The median interstitial disease duration from diagnosis was 60 months (IQR: 39–60) for the COVID-19 group and 48 months (IQR: 36–48) for the control group.

Table 2 depicts the characteristics of the study population in terms of age, gender, diagnosis of the patients, and their distribution according to COVID-19 status. The COVID-19 and the control groups were well balanced in terms of

Table 1 Criteria used for calculating the Warrick score

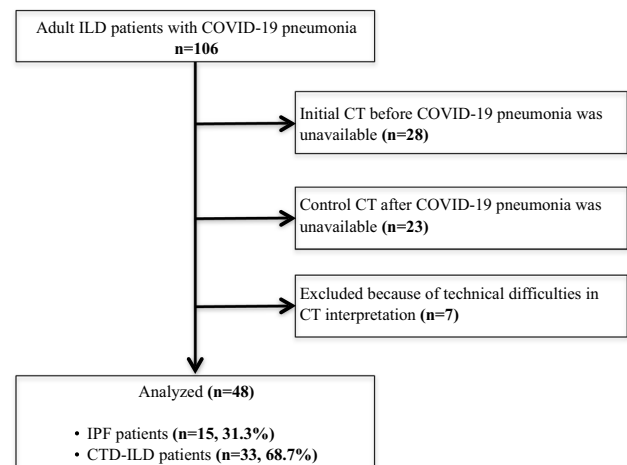| Lesions and lung segments	Score
Parenchymal abnormalities	Disease severity score
Ground-glass opacities	1
Irregularities in the pleural margins	2
Septal/subpleural lines	3
Honeycombing	4
Subpleural cysts	5
Number of lung segments	Disease extent score
1–3	1
4–9	2
>9	3

Fig. 1 Participant flow diagram for the COVID-19 group. ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; CTD-ILD, connective tissue disease-associated ILD

Table 2 Baseline characteristics and comparison of chest CT patterns of COVID-19 and the control groups

	COVID-19 group (n = 48)	Control group (n = 54)	p
Male gender, n (%)	21 (43.8%)	31 (57.4%)	0.168
Female gender, n (%)	27 (56.2%)	23 (42.6%)	0.168
Mean ± SD age (years)	63 ± 12	68 ± 9	0.022
IPF diagnosis, n (%)	15 (31.3%)	27 (50.0%)	0.055
Fibrosis pattern change, n (%)	7 (14.6%)	0 (0.0%)	0.004
Increase in GGO, n (%)	25 (52.1%)	11 (20.4%)	0.001
Increase in reticulations, n (%)	25 (52.1%)	12 (22.2%)	0.002
Increase in traction bronchiectasis, n (%)	21 (43.8%)	13 (24.1%)	0.035

Abbreviations: *GGO*, ground-glass opacity; *IPF*, idiopathic pulmonary fibrosis; *SD*, standard deviation

gender. The mean age of the control group was 68 ± 9 years, whereas the COVID-19 group was younger with a mean age of 63 ± 12 years ($p = 0.022$). GGOs, subpleural reticulations, and traction bronchiectasis were more frequently seen in patients with COVID-19 (Table 2).

A summary of comorbidities is depicted in Table 3. About 52% of all patients had comorbidities. The most prevalent comorbidity was hypertension (50%), followed by diabetes mellitus (21.5%). Analysis by stratifying patients according to their comorbidities did not reveal significant differences in any category between COVID-19 and control groups. No co-infection was detected in any of the patients in both groups.

Of the COVID-19 group, 81.2% had a history of hospitalization and 50% had oxygen therapy during hospitalization. Only two patients required non-invasive mechanical ventilation and were therefore admitted to the intensive care unit.

Comparison of CT findings and scores

The median (IQR) time interval between initial and follow-up CT scans was 17 (13–24) months for the COVID-19 group and 13 (9–22) months for the control group ($p = 0.011$). In the COVID-19 group, the patients underwent follow-up CT scans 4–9 months after positive PCR testing, with 85.4% of the CT examinations being obtained after 6 months.

The severity, extent, and total CT scores in the follow-up scans were significantly higher in both groups compared with the baseline CT scores (Table 4). There was a 4.5 ± 4.6 point change in the total CT score of the COVID-19 group and there was a 1.2 ± 2.7 point change in the control group. The difference in the increases was significant ($p < 0.001$) (Fig. 2). There was also a difference in the scores for both severity and extent between the two groups. Patients with IPF constituted 15 (31.25%) of the COVID-19 group and 27 (50%) of the control group. The change in total CT score in IPF patients in the COVID-19 group was 7.0 points (95% CI: 4.1 to 9.9), while the change in total CT score in the control group was 2.1 points (95% CI: 0.8 to 3.4). Table 5 illustrates changes in individual scores in IPF and CTD-ILD patients. Changes in the initial and follow-up total scores using COVID-19 status are shown in Fig. 3a and b.

The pattern of fibrosis changed in seven patients (14.6%) in the COVID-19 group. The indeterminate UIP pattern changed to probable UIP in 4/7 (57.1%) patients, while in the remaining three patients probable UIP pattern changed to a definite UIP pattern in 1, and normal scans changed to probable (n = 1)

**Table 3** Comorbidities of the COVID-19 and control group

	COVID-19 group (n = 48)	Control group (n = 54)	p value
Diabetes mellitus, n (%)	10 (20.8%)	12 (22.2%)	0.865
Hypertension, n (%)	26 (54.2%)	25 (46.3%)	0.427
Coroner artery disease, n (%)	5 (10.4%)	5 (9.3%)	0.844
Heart failure, n (%)	4 (8.3%)	1 (1.9%)	0.185
COPD, n (%)	3 (6.3%)	7 (13.0%)	0.255
Asthma, n (%)	2 (4.2%)	1 (1.9%)	0.600
Chronic renal disease, n (%)	2 (4.2%)	2 (3.7%)	1.000
Arrythmia, n (%)	7 (14.6%)	4 (7.4%)	0.244
Thyroid disease, n (%)	9 (18.8%)	5 (9.3%)	0.164
Hyperlipidemia, n (%)	3 (6.3%)	2 (3.7%)	0.664

Abbreviation: *COPD*, chronic obstructive pulmonary disease

Table 4 Changes between the initial and follow-up chest CT scan scores and traction bronchiectasis in the COVID-19 and the control group

	Initial CT	Follow-up CT	Mean difference (95% CI)	p
The COVID-19 group SS	5.3±3.9	7.1±4.5	1.9 (1.2 to 2.5)	<0.001
The control group SS	6.8±3.8	7.2±4.0	0.4 (0.1 to 0.7)	0.025
The COVID-19 group ES	5.5±3.7	8.2±4.5	2.7 (1.9 to 3.4)	<0.001
The control group ES	6.9±3.0	7.8±3.4	0.8 (0.3 to 1.3)	0.002
The COVID-19 group TS	10.8±7.3	15.3±8.9	4.5 (3.2 to 5.8)	<0.001
The control group TS	13.7±6.4	15.0±7.0	1.2 (0.5 to 1.9)	0.002
The COVID-19 group TB	0.6±0.5	0.7±0.5	0.1 (0.1 to 0.2)	0.044
The control group TB	0.9±0.3	0.9±0.3	0.1 (0.1 to 0.1)	0.322

Abbreviations: *SS*, severity score; *ES*, extent score; *TS*, total score; *TB*, traction bronchiectasis
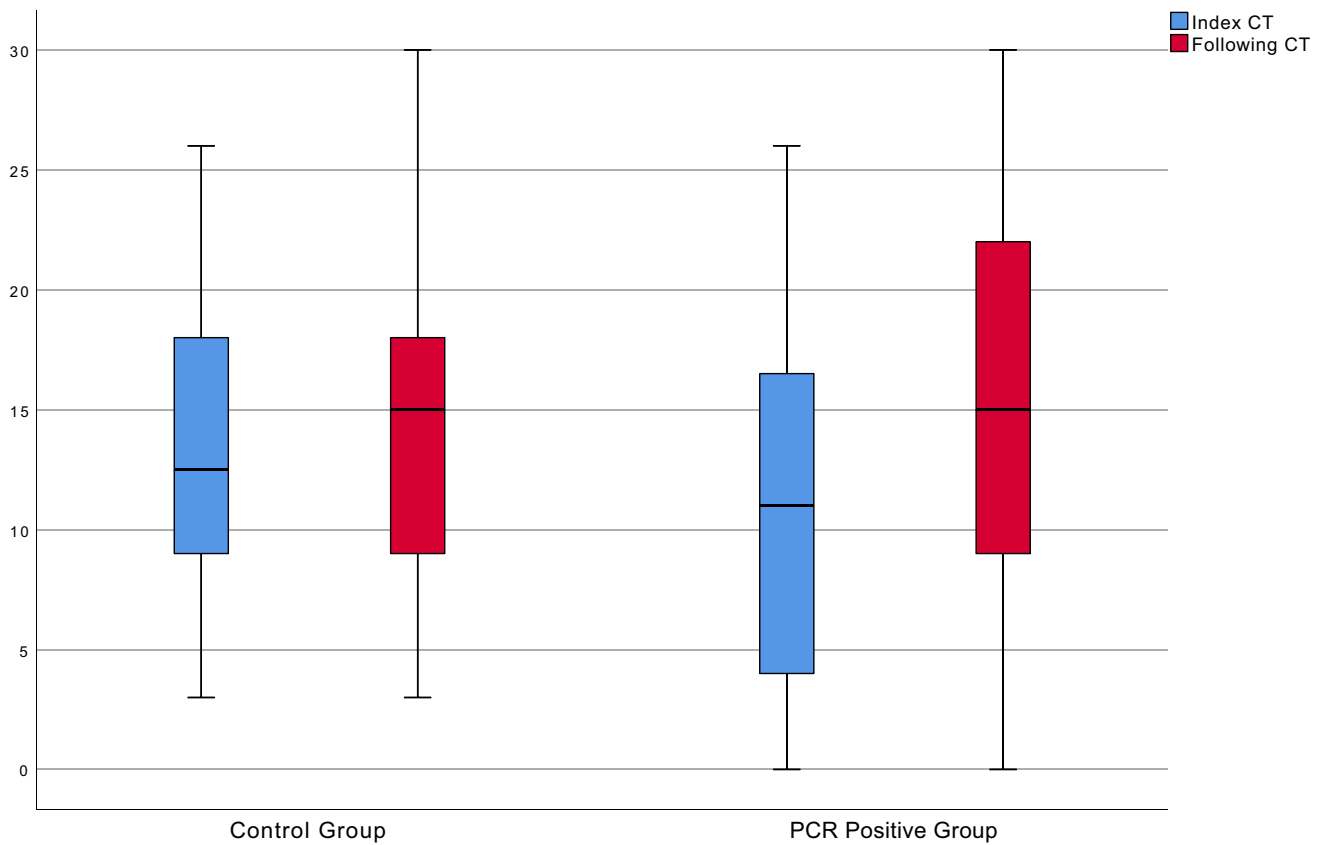
Fig. 2 Distribution of total scores of PCR positive and negative patients according to initial and follow-up CTs

Table 5 Distribution of index and follow-up CT scores between IPF and CTD-ILD patients in study groups

				Mean difference (95% CI)	p
The COVID-19 group (n=48)	IPF patients (n=15)	Initial CT Total Score	14.0±4.9	7.0 (4.1 to 9.9)	< 0.001
		Follow-up CT Total Score	21.0±6.7		
	CTD-ILD patients (n=33)	Initial CT Total Score	9.3±7.8	3.4 (2.0 to 4.7)	< 0.001
		Follow-up CT Total Score	12.7±8.6		
The control group (n=54)	IPF patients (n=27)	Initial CT Total Score	14.4±6.0	2.1 (0.8 to 3.4)	0.002
		Follow-up CT Total Score	16.6±6.5		
	CTD-ILD patients (n=27)	Initial CT Total Score	13.0±6.9	0.3 (−0.3 to 0.9)	0.327
		Follow-up CT Total Score	13.3±7.2		

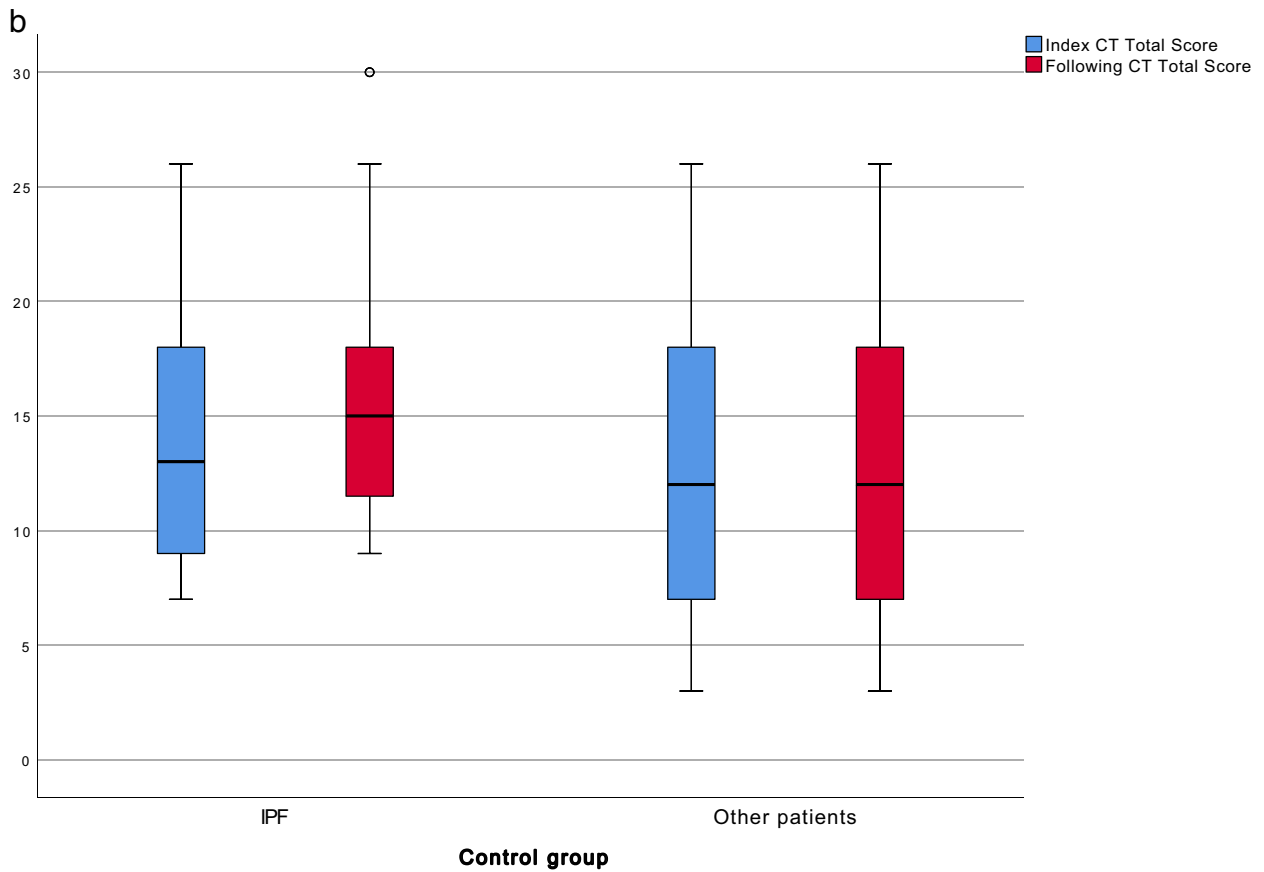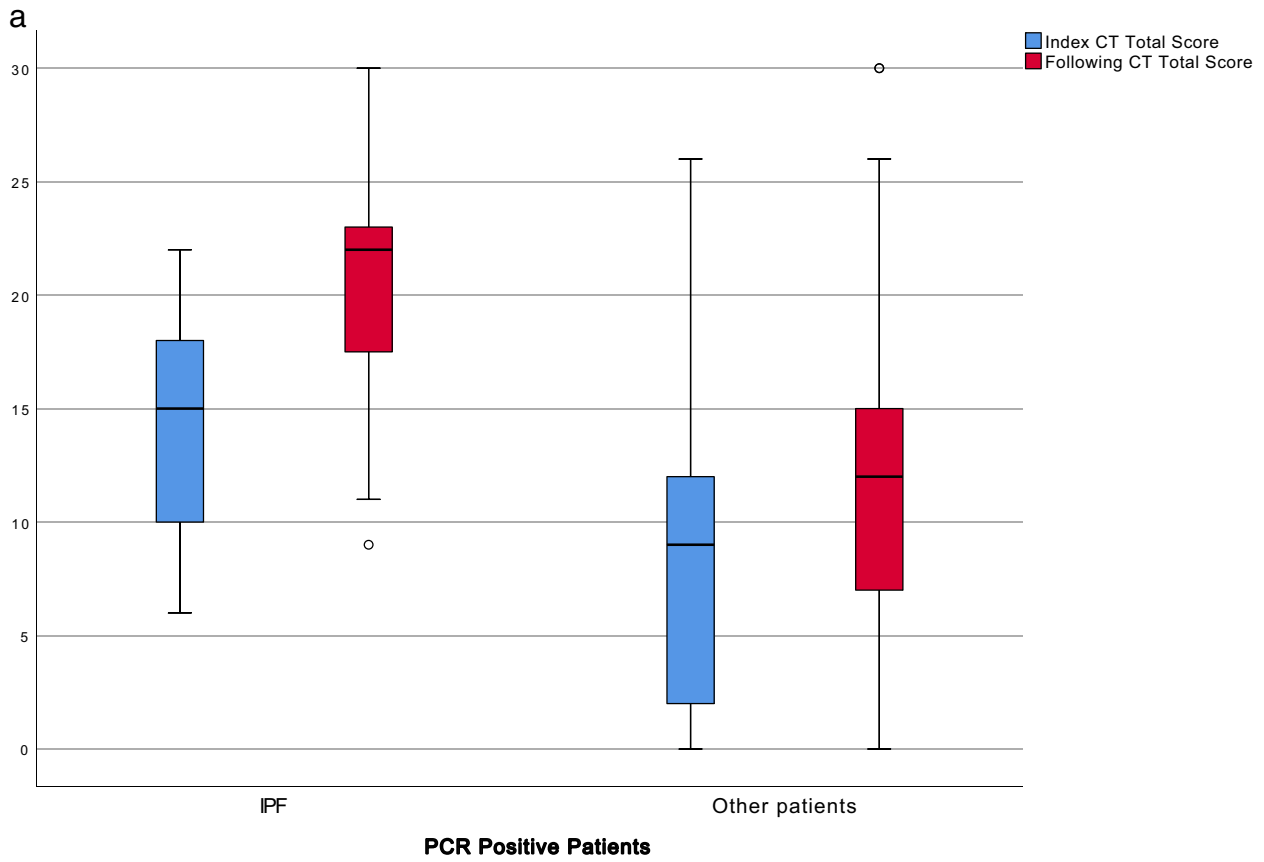Abbreviations: *IPF*, idiopathic pulmonary fibrosis; *CTD-ILD*, connective tissue disease-associated ILD

◀**Fig. 3 a** Distribution of total scores of patients according to initial and follow-up CTs in the COVID-19 group, with or without IPF. **b** Distribution of total scores of patients according to initial and follow-up CTs in the control group, with or without IPF

and indeterminate ($n = 1$) UIP patterns. The CT pattern did not change in any of the patients in the control group (Fig. 4).

Discussion

Serial CT scanning plays a key role in ILD patients for monitoring progression, during follow-up, and assessing prognosis. Semi-quantitative CT scoring analysis has been reported to be more reliable than visual qualitative assessment in this setting [11, 20]. In our study, all semi-quantitative CT scores were increased between the initial and follow-up CTs in both the COVID-19 and the control groups. However, the increase in the COVID-19 group was found to be significantly greater than in the control group. The increase in CT scores was most prominent in the group of IPF patients with a history of COVID-19 pneumonia.

The natural course of progression in ILD patients is variable [21]. It is known that viral agents can play a triggering role in autoimmune diseases and change the course [22]. Many different viral agents may play a role in the etiology and progression of pulmonary fibrosis and IPF acute exacerbation [23–27]. The interaction of COVID-19, caused by the SARS-CoV-2 virus, with pre-existing ILD, has been investigated since the beginning of the pandemic, and the virus is thought to destruct the lung tissue by creating an inflammatory response in the form of immune-mediated injury as well as by direct damage [7, 9]. It appears that ILD patients are more susceptible to contracting COVID-19, and more likely to have severe disease with fatal outcomes [28–31]. Lee et al [29] reported in their 8070 patients cohort that patients with pre-existing ILD are more prone to develop symptomatic COVID-19 disease and more likely to have worse outcomes (49.3% versus 13.1%, adjusted OR 2.32, 95% CI 1.24–4.01). Similar data were noted by Drake et al [30] that patients with pre-existing ILD but particularly those with a diagnosis of IPF rather than CTD-ILD were at very high risk of death when hospitalized with COVID-19. Although the mechanisms leading to a worse prognosis are not clearly known, reduced lung reserve, impaired gas exchange, and poor pulmonary functions in ILD patients may be the most predictable causes. The increase in SARS-CoV-2 entry genes such as angiotensin-converting enzyme-2, interleukin-6, and type 1 interferon response genes, as well as the increase of avb6 integrin levels in the alveolar epithelium, which is associated with a poor prognosis, especially in IPF patients, can be other factors of the damage in the lung parenchyma in COVID-19 patients [31]. Damaged lung parenchyma may be associated with persistent symptoms and functional impairment in patients after infection.
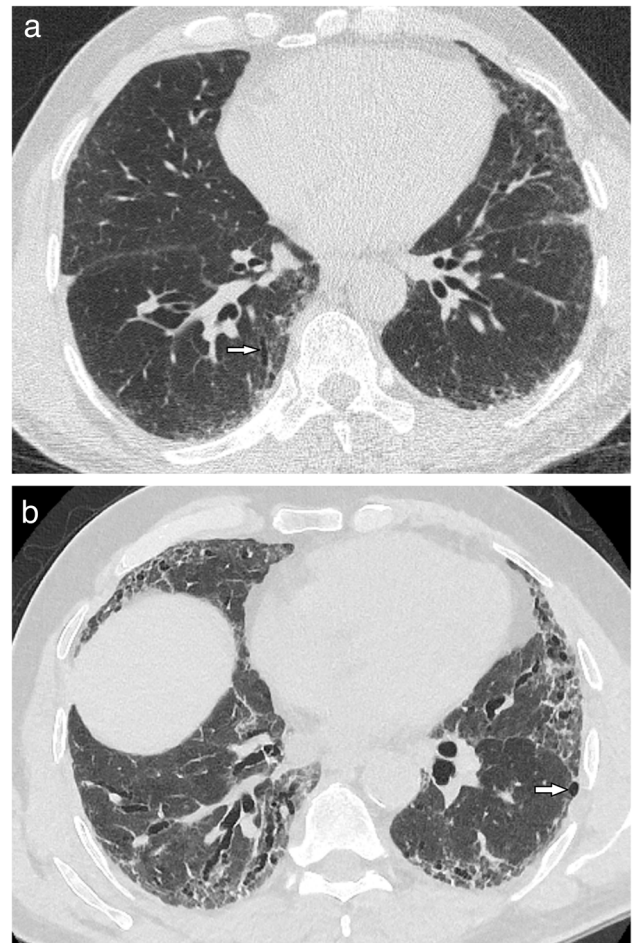

Fig. 4 A 64-year-old man with idiopathic pulmonary fibrosis (IPF) presenting with progressive dyspnea after COVID-19 pneumonia. **a** Baseline CT images obtained 2 months before COVID-19 pneumonia show peripheral reticulations and minimal traction bronchiectasis (arrow) in the lower lobes consistent with a probable UIP pattern. The Warrick CT scores were; severity score:6, extent score:9, total score: 15. **b** Follow-up CT images obtained 8 months after COVID-19 pneumonia show more prominent traction bronchiectasis and new subpleural cyst (arrow). The Warrick CT scores were progressed in the follow-up images; severity score:11, extent score:12, total score: 23

Long-term sequelae of COVID-19 pneumonia can be classified as reversible and 'fibrotic like' irreversible changes. GGOs and subpleural reticulations constitute most of the reversible changes and the incidence has been reported at different rates ranging from 7 to 92%. It may take up to one year for GGOs to disappear completely [32–34]. In our study, GGOs and subpleural reticulations were found to be increased, being more prominent in the COVID-19 group. Progression in GGOs was observed in 52% of patients in the COVID-19 group and 20% in the control group. Newly developed GGOs were not in the form of separate areas of involvement in most patients in both groups but were largely superposed to reticulations and fibrosis. It is radiologically impossible to say whether this increase

was due to COVID-19 pneumonia or to the progression of interstitial disease. To understand the cause of the increased GGOs, whether by viral pneumonia or interstitial disease, it would be helpful to compare the opacities that develop acutely during pneumonia and in the control CTs. This was not possible in our study, as CT imaging was not performed in all patients during episodes of acute pneumonia.

Irreversible sequelae changes developing after COVID-19 pneumonia are generally termed 'fibrotic-like'. The presence of parenchymal bands, reticulations, traction bronchiectasis, and/or honeycombing have been described as defining features [8, 10, 28].

In our study, we examined fibrosis pattern changes, in addition to CT scoring, to identify fibrotic changes. When fibrosis patterns were evaluated, none of the patients in the control group showed any change, whereas seven patients in the COVID-19 group showed pattern change, which may indicate a worsening of fibrosis.

'Fibrotic-like' changes are considered somewhat confusing lesions as there are not enough histopathological data yet for robust classification and the long-term outcome of the lesions is not yet known. The rates given for 'fibrotic-like' changes vary between 13 and 27% [8, 10, 35, 36]. These rates vary according to the comorbidities of the patients, the severity of COVID-19 pneumonia, and the duration of control imaging [35]. In the literature, these 'fibrotic-like' changes have been described mostly in moderate-severe COVID-19 patients who usually required intensive care unit admission [8, 10, 28]. In contrast, our COVID-19 patient group consisted of mild-to-moderate pneumonia clinically, and only two had severe COVID-19 pneumonia and needed intensive care unit admission. Thus, it seems reasonable to assign the increased fibrotic changes in our patient group to the coexistence of COVID-19 and ILD.

Traction bronchiectasis was evaluated separately because it was not considered an elementary lesion in the Warrick scoring system and is an important CT feature in the radiological definition of fibrosis. A significant progression was detected in the COVID-19 group in traction bronchiectasis in follow-up CTs.

Drake et al [30] discussed treatment differences in hospitalized COVID-19 patients with ILD. Their study showed that more patients with ILD received oral corticosteroids in the hospital than patients without ILD and there was no significant difference in outcome between those receiving corticosteroids or anti-fibrotic therapy and those who did not. We did not evaluate and compare patients' medications in terms of corticosteroids or anti-fibrotic drugs. In the future, it may be valuable to study the long-term effects of corticosteroids or anti-fibrotic therapy on fibrotic progression in ILD patients.

Our study had the following limitations. Firstly, a prospective design for the study would be more appropriate to set for more accurate time intervals in CT scanning. The control CT imaging was performed within 6 months after pneumonia in 10.4% of the COVID-19 patients. Although the number of these patients undergoing control CT within 6 months was very low, this may still be a cause of false-positive evaluation of GGO and reticulation increase. This can lead to misjudgment in pattern change. The mean time difference between initial and follow-up CTs between the two groups was 4 months. However, considering that ILD patients are often followed up with annual CTs, this time difference may not be considered long enough to explain the observed CT score increase. Secondly, the study was conducted in a single center with a limited sample size, which may limit its generalizability. Lastly, it may also be useful to support the radiological findings observed in ILD patients with detailed clinical, histopathological, and immunological data. Since we do not have complete clinical and radiological data for the period when patients had COVID-19, we could not include information on the severity of pneumonia at that time. However, considering that some patients did not have a CT scan when they had COVID-19, it can be speculated that they may have had a relatively mild disease.

In conclusion, a significant increase in CT scores was detected in a semi-quantitative analysis of follow-up CTs of ILD patients who had COVID-19 pneumonia compared to the group without pneumonia. Worsening of CT scores and fibrosis patterns was more prominent in IPF patients. Most of these patients had a mild to moderate clinical course of acute COVID-19 pneumonia. COVID-19 pneumonia may accelerate the progression of pre-existing interstitial involvement in ILD patients.

Declarations

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