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Follow-up study of pulmonary sequelae in discharged COVID-19 patients with diabetes or secondary hyperglycemia

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ABSTRACT

Purpose: To determine chest CT changes 6 months and 12 months after the onset of coronavirus disease 2019 (COVID-19) in patients with diabetes or hyperglycemia and the risk factors for these residual lung abnormalities.
Methods: In total, 141 COVID-19 patients were assigned to group 1 (diabetes), group 2 (secondary hyperglycemia) or group 3 (controls). Initial and six- and twelve-month follow-up computed tomography (CT) scans were performed 16 days, 175 days and 351 days after symptom onset, respectively. CT findings and clinical and peak laboratory parameters were collected and compared. Univariable and multivariable logistic regression analyses were performed to identify the independent predictors for the presence of residual lung abnormalities at the 6-month follow-up exam. Seven variables (age; the presence of acute respiratory distress syndrome; the duration of hospitalization; the peak levels of lactate dehydrogenase (LDH) and C-reactive protein; and the initial total CT score) were chosen in the final multivariable models.
Results: At the six-month follow-up, abnormalities were still observed on chest CT in 77/141 (54.6%) patients. Reticular patterns (40/141, 28.4%) and ground-glass opacities (GGOs) (29/141, 20.6%) were the most common CT abnormalities on the follow-up CT scans. Patients in Groups 1 and 2 had significantly higher incidences of residual lung abnormalities than those in Group 3 (65.4% and 58.3%, respectively vs. 36.6%; $p < 0.05$). Twelve months after disease onset, the chest CT changes persisted in 13/25 (52.0%) patients. A duration of hospitalization > 20 days (OR: 5.630, 95% CI: 1.394–22.744, $p = 0.015$), an LDH level ≥ 317 U/L (OR: 7.020, 95% CI: 1.032–47.743, $p = 0.046$) and a total CT score > 15 (OR: 9.919, 95% CI: 1.378–71.415, $p = 0.023$) were independent predictors of residual pulmonary abnormalities in patients with diabetes or secondary hyperglycemia.
Conclusions: A considerable proportion of surviving COVID-19 patients with diabetes or secondary hyperglycemia had residual pulmonary abnormalities six months after disease onset, and we found evidence of persistent chest CT changes at the one-year follow-up. Residual lung abnormalities were associated with longer hospital stays, higher peak LDH levels and higher initial total CT scores.

1. Introduction

The outbreak and rapid global spread of coronavirus disease 2019 (COVID-19) have posed considerable public health threats, resulting in more than 230 million confirmed cases and 4, 724, 876 deaths worldwide as of September 24, 2021 [1]. The responsible pathogen is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The rates of developing severe COVID-19 and mortality are substantially higher in

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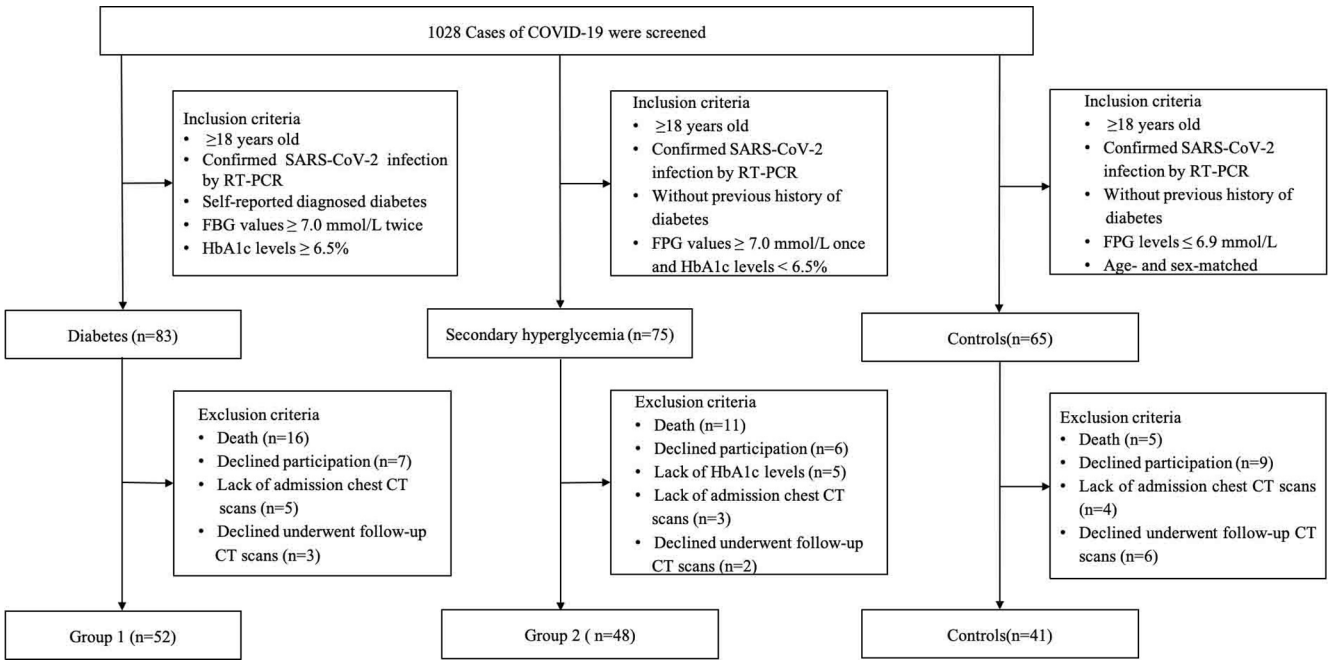

Fig. 1. Study flowchart.

elderly patients and those with concomitant conditions, including diabetes, one of the leading causes of morbidity [3]. Notably, severe acute respiratory syndrome coronavirus (SARS-CoV) has been shown to damage islet cells through its receptors and cause secondary hyperglycemia in patients who were not using any glucocorticoids and who did not have a prior history of diabetes [4]. Several recent studies have shown that hyperglycemia at admission and previously diagnosed diabetes are significant predictors of severe disease and mortality in COVID-19 patients [5–7]. Similar findings were previously observed in patients infected with SARS-CoV [8] and middle east respiratory syndrome coronavirus (MERS-CoV) [9]. However, little is known about long-term sequelae in COVID-19 survivors, especially in patients with diabetes or secondary hyperglycemia.

Computed tomography (CT) plays an important role in the diagnosis and follow-up monitoring of COVID-19 patients. Lung injury caused by SARS-CoV-2 is one of the most common clinical manifestations of the disease and directly affects patient prognosis. At discharge, many patients with COVID-19 have presented with varying degrees of residual chest CT abnormalities, with some presenting with postinflammatory pulmonary fibrosis [10,11]. Previous studies of SARS survivors revealed that 80% of patients had persistent chest CT abnormalities at the six-month follow-up after symptom presentation [12], which can remain 15 years after acute pneumonia [13]. Similarly, residual lung fibrosis in MERS survivors has been reported in 33% of patients at a median follow-up of 6 weeks after disease onset [14]. Currently, despite the many recovered COVID-19 patients, much remains unknown about the long-term consequences after discharge, especially those with underlying comorbidities.

Therefore, in this study, we analyzed the clinical and peak laboratory parameters among COVID-19 survivors with diabetes or hyperglycemia during hospitalization. We also assessed pulmonary sequelae on 6- and 12-month follow-up CT scans and further explored the risk factors for residual lung abnormalities in patients recovering from COVID-19.

2. Methods

2.1. Study design and participants

This prospective cohort study was conducted at two major tertiary hospitals in Wuhan, China (Jinyintan Hospital and Union Hospital of Tongji Medical College). The study was approved by the Ethics Committees of the two institutions. All participants signed written informed consent forms. This trial was registered with the Chinese Clinical Trial Registry, ChiCTR2000038609. All adult patients with laboratory-confirmed COVID-19 were consecutively enrolled from the hospitals between December 28, 2019, and April 30, 2020. Fig. 1 shows the flowchart of the study; over a 5-month recruitment period, 1028 consecutive patients were enrolled. COVID-19 was diagnosed according to the World Health Organization interim guidance [15]. All patients were confirmed as being infected with SARS-CoV-2 by RT-PCR, as previously described [2,16]. Patients were assigned to one of three groups based on their history of diabetes and fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) levels [5,17]. Diabetes was defined as a self-reported diagnosis of diabetes confirmed by medical records reviewed by physicians, FPG values ≥7.0 mmol/L twice or HbA1c levels ≥6.5% (Group 1). Secondary hyperglycemia was diagnosed by FPG values ≥7.0 mmol/L once and HbA1c levels <6.5% (Group 2). Patients without a previous history of diabetes who had FPG levels ≤6.9 mmol/L and HbA1c levels <6.5% were considered controls (Group 3). The exclusion criteria were as follows: (1) in-hospital mortality, (2) refusal to participate, (3) missing chest CT scans and HbA1c levels on admission, or (4) refusal to undergo follow-up imaging examination. Eventually, a total of 141 COVID-19 patients (Group 1, n = 52; Group 2, n = 48; Group 3, n = 41) who had been discharged from the hospital between December 28, 2019, and April 30, 2020 after clinical improvement and underwent follow-up chest CT examinations 6 months later were included in the present study. Patients who had residual chest CT abnormalities at discharge were all invited to undergo follow-up CT exams. The discharge criteria were in accordance with the guidelines for COVID-19 issued by the Chinese National Health Committee (version 7) [18].

Demographics, smoking (at least one cigarette each day for 3 months or longer) and drinking (consuming any alcoholic beverages at least once a week for 6 months or longer) history, onset symptoms, history of diabetes, other comorbidities, FPG and HbA1c levels on admission, the presence of acute respiratory distress syndrome (ARDS), treatments during hospitalization, and peak laboratory parameters in the acute phase were reviewed and extracted from the patient electronic medical records by three physicians. The diagnosis of ARDS was made according

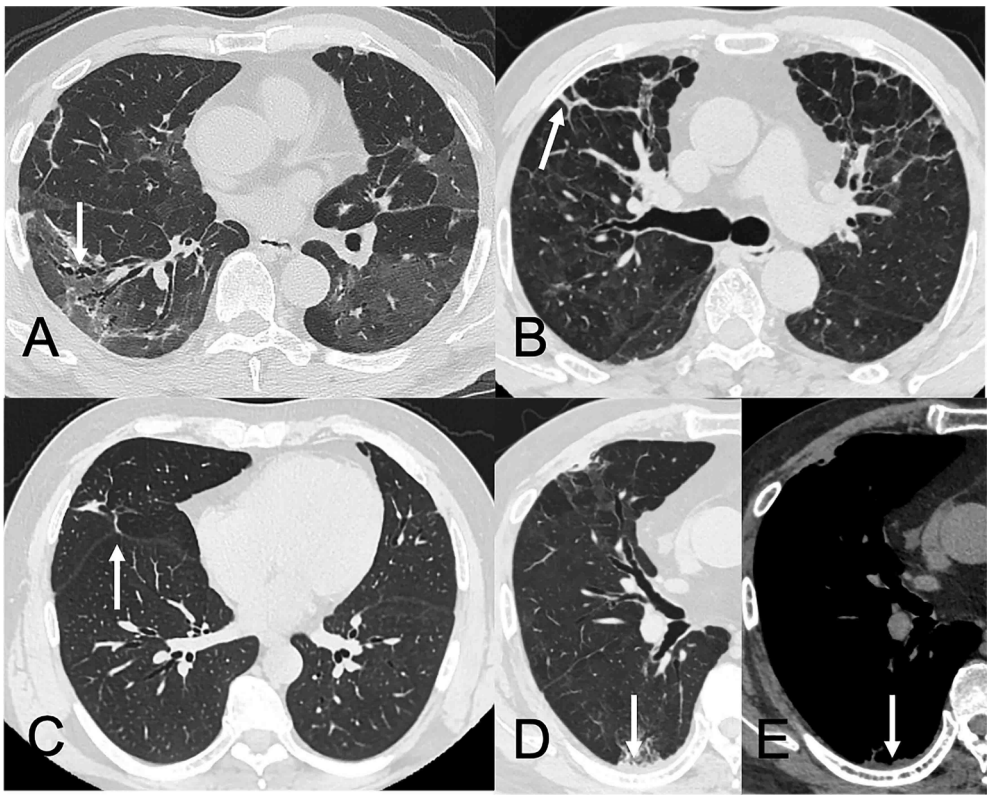

Fig. 2. Follow-up chest CT characteristics of COVID-19 pneumonia. (A) Traction bronchodilation; (B) Parenchymal bands; (C) Interlobular pleural traction; (D, E) Thickening of the adjacent pleura.

to the Berlin definition [19]. The acute phase was defined as the time between symptom onset and hospital discharge [20].

2.2. Chest CT scans and image interpretation

All initial and follow-up lung CT scans of the lungs were obtained using one of the three following CT scanners: a SOMATOM Perspective, a SOMATOM Spirit or a SOMATOM Definition AS+ (Siemens Healthineers, Forchheim, Germany). All CT acquisitions were performed without contrast medium with the following parameters: tube voltage of 120 kV with automatic tube current modulation; detector configuration of 64 × 0·6 mm, 128 × 0·6 mm and 64 × 0·6 mm; and a matrix of 512 × 512. All CT images were then reconstructed with a slice thickness of 1.0 mm with the same increment. Images were reconstructed with a pulmonary B80s kernel and a mediastinal B30s kernel (SOMATOM Perspective) or a pulmonary B70F kernel and a mediastinal B30f kernel (SOMATOM Definition AS+).

Image analysis was performed using a picture archiving and communication system (PACS). Three radiologists with over 10 years of experience in thoracic radiology reviewed all CT images, which were presented in a random order. The radiologists were blinded to the clinical data and the date of the CT scans. Any differences in opinions were resolved by discussion. CT abnormalities were described based on the Fleischner Society Nomenclature Committee recommendations [21] and previous studies on COVID-19 patients [20,22]. Chest CT abnormalities, including ground glass opacities (GGOs), consolidations, reticular patterns, thickening of the adjacent pleura, interlobar pleural traction (retraction of the interlobar pleura toward the lesions), bronchial dilatation and parenchymal bands, the presence of a nodule or mass, emphysema and pleural effusion, were recorded. Residual lung abnormalities were defined as the presence of any of the above-mentioned findings on follow-up CT scans (Fig. 2). A CT-based scoring system (ranging from 0 to 25 points) was used to quantitatively evaluate the extent of lung involvement (GGOs, consolidations and interstitial thickening). This semiquantitative scoring system had been previously used to estimate pulmonary sequelae in SARS [12] and COVID-19 [22] survivors. Each of the 5 lung lobes was assigned 0–5 points based on the extent of changes as follows: 0, no involvement; 1, <5%; 2, 5–25%; 3, 26–49%; 4, 50–75%; and 5, >75%.

2.3. Statistical analysis

Categorical variables and continuous variables are described as numbers (percentages) and medians (interquartile ranges [IQRs]), respectively. The chi-square test or Fisher's exact test was performed to compare all categorical variables. The normality of the distribution for continuous data was checked using the Kolmogorov–Smirnov test. One-way ANOVA or the independent-sample Student's t test was used to compare normally distributed variables between different groups, and Bonferroni correction was selected as the post hoc test, as appropriate. Between-group differences in nonnormally distributed variables were compared with the Kruskal-Wallis or Mann-Whitney U tests. To explore the risk factors associated with residual lung abnormalities in COVID-19 patients with diabetes and secondary hyperglycemia, univariable and multivariable logistic regression analyses were performed. We chose age; the presence of ARDS; the duration of hospitalization; the peak levels of D-dimer, lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels; and the initial total CT score as the seven variables included in the final multivariate logistic regression model. The variables included in the final models were based on the results of univariable analyses, clinical and scientific constraints, and previous findings [23–25]. The cutoff values of the selected variables were based on the medians or the normal ranges, as appropriate. The statistical analyses were performed using SPSS software version 21 (IBM, Chicago, IL, USA). A two-sided p value <0.05 was considered statistically significant.

Table 1
Demographics and clinical characteristics of COVID-19 patients.

	All patients (n = 141)	Group 1 (n = 52)	Group 2 (n = 48)	Group 3 (n = 41)	*p* value
Age, years	59.0 (51.0–66.0)	63.5 (56.3–68.5)†	56.0 (50.0–64.8)	55.0 (48.5–65.5)	0.135
Sex					
Male	89 (63.1)	37 (71.2)	31 (64.6)	21 (51.2)	0.137
Female	52 (36.9)	15 (28.8)	17 (35.4)	20 (48.8)	–
Diabetes type					
Type 2 diabetes	–	50 (96.2)	–	–	–
Type 1 diabetes	–	2 (3.8)	–		–
Diabetes duration, years	–	7.5 (4.8–11.0)	–	–	–
Smoking history	16 (11.3)	9 (17.3)	2 (4.2)	5 (12.2)	0.091
Current smokers	9 (6.4)	5 (9.6)	1 (2.1)	3 (7.3)	0.293
Former smokers	7 (5.0)	4 (7.7)	1 (2.1)	2 (4.9)	0.435
Drinking history	25 (17.7)	9 (17.3)	9 (18.8)	7 (17.1)	0.974
Current drinkers	16 (11.3)	6 (11.5)	7 (14.6)	3 (7.3)	0.559
Former drinkers	9 (6.4)	3 (5.8)	2 (4.2)	4 (9.6)	0.547
Initial signs and symptoms					
Fever	121 (85.8)	42 (80.0)	45 (93.8)	34 (82.9)	0.146
Maximum temperature, °C	38.5 (38.0–39.0)	38.5 (38.0–39.0)	38.6 (38.5–39)	38.5 (38.0–39.0)	0.084
≥38	85 (60.3)	25 (48.1)†	36 (75.0)	24 (58.5)	0.019
<38	35 (24.8)	18 (34.6)	6 (12.5)	11 (26.8)	–
Cough	99 (70.2)	37 (71.2)	38 (79.2)	24 (58.5)	0.104
Sputum	43 (30.5)	13 (25.0)	19 (39.6)	11 (26.8)	0.238
Fatigue	46 (32.6)	17 (32.7)	12 (25.0)	17 (41.5)	0.256
Dyspnea	56 (39.7)	21 (40.4)	24 (50.0)	11 (26.8)	0.083
Myalgia	11 (7.8)	3 (5.8)	4 (8.3)	4 (9.8)	0.765
Diarrhea	8 (5.7)	2 (3.8)	4 (8.3)	2 (4.9)	0.604
Anorexia	15 (10.6)	4 (7.7)	7 (14.6)	4 (9.8)	0.524
Nausea or vomiting	9 (6.4)	3 (5.8)	4 (8.3)	2 (4.9)	0.781
Heart rate, bpm	82.0 (89.0–100.0)	88.5 (82.0–99.0)	88.0 (80.0–99.8)	92.0 (84.0–106.5)	0.582
Respiratory rate	21.0 (20.0–23.0)	21.0 (20.0–22.0)	21.0 (20.0–25.8)	20.0 (20.0–22.0)	0.083
Systolic blood pressure, mmHg	130.0(120.0–140.0)	132.0 122.3–142.3)	129.0 (115.0–140.0)	130.0 (116.0–138.0)	0.586
Diastolic blood pressure, mmHg	81.0 (74.3–88.8)	81.5 (75.0–89.8)	81.0 (74.3–89.0)	81.0 (70.0–87.5)	0.372
Oxygen saturation on room air, %	95.0 (92.0–97.0)	95.0 (90.0–96.0)	95.0 (91.3–97.0)	96.0 (94.8–97.3)	0.291
Other comorbidities					
Hypertension	55 (39.0)	25 (48.1)	19 (39.6)	11 (26.8)	0.113
Cardiovascular disease	13 (9.2)	9 (17.3)‡	3 (6.3)	1 (2.4)	0.033
Coronary heart disease	12 (8.5)	8 (15.4)	3 (6.3)	1 (2.4)	0.061
Heart failure	1 (0.7)	1 (1.9)	0 (0)	0 (0)	0.422
Cerebrovascular disease	2 (1.4)	2 (1.4)	0 (0)	0 (0)	0.176
Chronic pulmonary disease	14 (9.9)	9 (17.3)	4 (8.3)	1 (2.4)	0.053
COPD	10 (7.1)	7 (13.5)	2 (4.2)	1 (2.4)	0.079
Asthma	3 (2.1)	1 (1.9)	2 (4.2)	0 (0)	0.159
*Tuberculosis	1 (0.7)	1 (1.9)	0 (0)	0 (0)	0.422
Chronic renal failure	1 (0.7)	0 (0)	0 (0)	1 (2.4)	0.293
Chronic liver disease	5 (3.5)	2 (3.8)	2 (4.2)	1 (2.4)	0.898
Chronic hepatitis	2 (1.4)	1 (1.9)	0 (0)	1 (2.4)	0.426
Cirrhosis	3 (2.1)	1 (1.9)	2 (4.2)	0 (0)	0.612
Duration from onset of symptoms to, days					
Hospital admission	10.0 (7.0–13.0)	10.0 (7.0–15.0)	8.0 (6.0–12.0)	11.0 (8.0–13.5)	0.062
Initial CT scan	16.0 (10.0–26.5)	19.0 (11.3–31.8)	13.0 (10.0–24.8)	16.0 (10.0–24.0)	0.359
Follow-up CT scan	175.0 (154.5–189.5)	170.5 (156.3–193.3)	176.0 (164.3–188.8)	170.0 (135.0–189.5)	0.411
Duration of in-hospital stay, days	20.0 (14.0–30.0)	24.5 (12.3–35.0)‡	16.5 (14.0–29.8)	20.0 (14.0–26.0)	0.023
ICU Admission	10 (7.1)	6 (11.5)	2 (4.2)	2 (4.9)	0.288
ARDS	27 (19.1)	14 (26.9)	10 (20.8)	3 (7.3)	0.050
Treatment					
Antiviral therapy	111 (78.7)	43 (82.7)	41 (85.4)	27 (65.9)	0.210
Antibiotic therapy	117 (83.0)	40 (76.9)	45 (93.8)	32 (78.0)	0.059
Glucocorticoid therapy	45 (31.9)	17 (32.7)	16 (33.3)	12 (29.3)	0.941
Traditional Chinese medicine	14 (9.9)	8 (15.4)	3 (6.3)	3 (7.3)	0.250
HFNC	22 (15.6)	10 (19.2)	8 (16.7)	4 (9.8)	0.444
Duration, days	9.0 (4.0–19.5)	11.0 (4.0–21.3)	9.5 (4.5–20.5)	7.0 (5.3–9.5)	0.832
Noninvasive mechanical ventilation	10 (7.1)	7 (13.5)‡	2 (4.2)	1 (2.4)	0.032
Duration, days	7.5 (3.8–10.5)	7.0 (4.0–15.0)	–	9.0 (9.0–9.0)	0.757
Invasive mechanical ventilation	4 (2.8)	3 (5.8)	1 (2.1)	–	0.232
Duration, days	18.0 (13.3–22.8)	–	12.0 (12.0–12.0)	–	–
CRRT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
ECMO	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–

Data are expressed as numbers (%) or medians (interquartile ranges). The *p* values reflect comparisons among groups 1, 2 and 3.
ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; HFNC, high-flow nasal cannula; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

† $p < 0.05$ vs. Group 2.

‡ $p < 0.05$ vs. Group 3.

* Tuberculosis: A past history of pulmonary tuberculosis (without active tuberculosis).

Table 2
Peak laboratory findings of COVID-19 patients.

	Normal range	All patients (n = 141)	Group 1 (n = 52)	Group 2 (n = 48)	Group 3 (n = 41)	*p* value
Hematologic, $\times 10^9$/L						
White blood cells	4.0–10.0	6.4 (4.9–9.5)	6.5 (4.2–9.9)	6.4 (4.9–10.0)	6.3 (5.4–7.6)	0.930
Neutrophils	1.8–6.3	4.4 (3.3–7.8)	4.5 (3.1–8.1)	5.4 (3.8–9.8)†	3.7 (3.2–5.3)	0.038
Lymphocytes	1.1–3.2	0.9 (0.7–1.4)	0.9 (0.5–1.3)†	0.8 (0.5–1.2)†	1.2 (0.8–1.7)	0.001
Platelets	125.0–350.0	212.0 (170.5–260.0)	204.0 (147.5–256.0)	225.5 (176.3–266.0)	212.0 (184.5–258.0)	0.311
Coagulation function						
D-dimer, mg/L	<0.5	1.0 (0.5–4.6)	1.8 (0.7–7.4)†	1.2 (0.5–4.4)	0.7 (0.4–2.0)	0.027
Prothrombin time, s	11.0–16.0	11.9 (10.6–13.1)	12.6 (10.7–13.6)	11.2 (10.6–13.1)	11.9 (10.9–12.5)	0.300
APTT, s	28.0–43.5	31.3 (24.9–36.6)	32.1 (24.1–37.7)	29.2 (21.7–35.4)	32.6 (28.7–36.1)	0.342
Thrombin time, s	14.0–21.0	16.8 (15.9–18.2)	17.5 (16.5–19.4)	17.2 (15.9–22.1)	16.5 (15.5–17.6)	0.086
Fibrinogen, g/L	2.0–4.0	4.4 (3.0–5.0)	4.7 (4.1–5.6)	4.4 (4.1–5.7)†	4.0 (2.8–4.7)	0.036
Biochemical						
Admission glucose, mmol/L	3.9–6.1	7.7 (5.6–10.4)	10.0 (8.0–13.0)†	8.4 (7.3–11.0)†	5.4 (5.1–5.8)	<0.001
Admission HbA1c, %	4.0–6.0	6.6 (5.6–7.7)	7.7 (6.7–8.1)†	6.1 (5.7–6.4)	5.6 (5.4–6.0)	0.005
Hemoglobin, g/L	110.0–150.0 (Female), 130.0–175.0 (male)	116.0 (108.0–127.0)	116.0 (106.5–125.0)	113.0 (105.0–131.0)	120.5 (108.3–129.8)	0.447
Albumin, g/L	35.0–55.0	31.9 (28.9–35.7)	31.7 (29.7–36.2)	31.3 (28.0–34.6)	32.7 (30.5–36.9)	0.212
ALT, U/L	5.0–40.0	37.5 (24.0–69.0)	50.0 (27.0–90.0)	44.0 (27.0–87.5)	32.0 (25.0–47.3)	0.055
AST, U/L	8.0–40.0	37.5 (24.0–69.0)	42.5 (25.3–69.0)†	55.0 (31.0–95.5)†	26.0 (19.0–48.8)	0.001
Creatinine, μmol/L	44.0–133.0	66.7 (54.3–83.0)	67.9 (53.2–88.5)	67.0 (53.2–88.5)	62.2 (53.9–79.4)	0.507
Creatine kinase, U/L	50.0–310.0	57.0 (35.5–120.0)	51.0 (34.0–131.0)	60.0 (32.0–99.0)	57.5 (39.0–127.3)	0.915
LDH, U/L	109.0–245.0	290.0 (204.0–408.8)	344.0 (219.3–479.5)†	295.0 (201.0–408.0)	232.0 (198.0–300.0)	0.033
hs-cTnI, ng/L	<26.2	3.7 (1.2–10.9)	7.4 (3.2–20.2)†	3.3 (0.8–9.4)	2.1 (1.1–7.0)	0.001
Nt-proBNP, pg/mL	<100.0	29.5 (10.3–68.5)	38.0 (20.0–90.2)	30.6 (10.0–59.4)	19.9 (10.0–68.5)	0.199
Infection-related indices						
Serum ferritin, ng/mL	21.0–274·7	566.4 (268.7–1250.7)	696.1 (296.4–1609.1)	565.7 (280.2–1104.3)	323.8 (97.3–811.1)	0.082
SAA, mg/L	<10.0	193.80(64.1–284.0)	245.1 (179.6–284.0)†	215.9 (64.1–284.0)†	35.9 (5.9–173.4)	<0.001
Procalcitonin, ng/mL	<0.05	0.05 (0.03–0.13)	0.05 (0.05–0.13)	0.06 (0.05–0.13)	0.05 (0.05–0.08)	0.393
ESR, mm/h	0.0–15.0	49.0 (25.2–71.4)	47.0 (24.0–72.1)	50.0 (33.3–66.4)	51.5 (21.0–78.2)	0.999
Interleukin-6, pg/mL	<7.0	8.0 (6.0–11.7)	9.8 (6.9–14.3)†	8.3 (6.0–11.7)†	6.7 (4.5–7.7)	<0.001
CRP, mg/L	<8.0	37.3 (5.5–107.1)	65.6 (9.8–150.9)†	42.1(21.7–139.9)†	9.1 (1.8–52.4)	0.001

Data are expressed as medians (interquartile ranges). The *p* values reflect comparisons among groups 1, 2 and 3.
APTT, activated partial thromboplastin time; HbA1c, glycated hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase, hs-cTnI, high-sensitivity cardiac troponin I; Nt-proBNP, N-terminal pro b-type natriuretic peptide; SAA, serum amyloid protein A; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
† $p < 0.05$ vs. Group 3.

3. Results

3.1. Demographics and baseline characteristics on admission

A total of 141 patients (89 men, 52 women; median age, 59.0 years [IQR, 51.0, 66.0] were enrolled (Table 1). The age and sex distributions were comparable among the three groups. The median diabetes duration of patients in Group 1 was 7.5 years [IQR, 4.8, 11.0]. There were no significant differences in any symptoms among the three groups. The proportion of patients with a maximum temperature ≥38 °C on admission in Group 2 was significantly higher than that in Group 1 ($p < 0.05$). The median durations of hospitalization were different among the three groups, and patients in Group 1 had significantly longer hospital stays than those in Group 3 ($p < 0.05$). The proportions of patients with ARDS in the three groups trended toward being different ($p = 0.05$) and showed a gradual decreasing trend among the groups. Regarding treatment, the proportion of patients who received noninvasive mechanical ventilation was significantly higher in Group 1 than in Group 3 (13.5% vs. 2.4%, $p < 0.05$); no significant difference was found in any other treatment among the groups.

3.2. Laboratory findings

The peak values of the laboratory test variables in all patients and the three subgroups are shown in Table 2. Regarding routine blood tests, the levels of neutrophils and lymphocytes differed among the three groups ($p < 0.05$ for both); patients in Group 2 had significantly higher neutrophil counts than those in Group 3, and the lymphocyte counts in Groups 2 and 3 were significantly lower than those in Group 1 ($p < 0.05$ for both). With regard to the coagulation indices, patients in Groups 1 and 2 had higher levels of D-dimer and fibrinogen than patients in Group 3 ($p < 0.05$ for both). Compared with Group 3, both Groups 1 and 2 had higher levels of aspartate aminotransferase (AST) ($p = 0.001$). The levels of both LDH ($p = 0.033$) and high-sensitivity cardiac troponin I (hs-cTnI, $p = 0.001$) differed among the three groups, and patients in Group 1 had the highest level. With regard to infection-related indices, patients in Groups 1 and 2 had significantly higher serum amyloid protein A (SAA), interleukin-6 (IL-6), and CRP levels than patients in Group 3 ($p < 0.05$ for both), but no significant differences were found between Groups 1 and 2.

3.3. Initial and follow-up CT features and scores

The initial, six-month and twelve-month follow-up scans were performed at 16 days [IQR, 10.0, 26.5], 175 days [IQR, 154.5, 189.5] and 351 days [IQR, 341.0, 365.5] after disease onset, respectively (Table 1; Supplemental Table S1). On the initial CT scans, the overall median total CT score was 13 [IQR, 9.0, 18.5], with no significant difference among the groups. However, the CT score for GGOs differed significantly among the groups ($p = 0.037$) and showed a gradual decreasing trend

Table 3
Initial and follow-up CT features and scores of COVID-19 patients.

	Initial CT					Follow-up CT				
	All patients (n = 141)	Group 1 (n = 52)	Group 2 (n = 48)	Group 3 (n = 41)	*p* value	All patients (n = 141)	Group 1 (n = 52)	Group 2 (n = 48)	Group 3 (n = 41)	*p* value
Residual lung abnormalities										
Yes		–	–	–	–	77 (54.6)	34 (65.4)†	28 (58.3)†	15 (36.6)	0.018
No		–	–	–	–	64 (45.4)	18 (34.6)	20 (41.7)	26 (63.4)	–
CT scores										
Total lesions	13.0 (9.0–18.5)	15.5 (10.0–20.0)	14.0 (9.3–18.8)	11.0 (8.0–16.0)	0.067	3.0 (0.0–7.5)	4.0 (0.0–8.8)†	3.0 (0.0–8.0)†	0.0 (0.0–4.0)	0.007
GGOs	10.0 (6.0–15.5)	12.5 (9.0–18.0)†	10.0 (5.0–15.8)	9.0 (5.5–12.0)	0.037	0.0 (0.0–6.0)	2.0 (0.0–8.8)†	0.5 (0.0–6.8)	0.0 (0.0–3.0)	0.023
Consolidations	4.0 (0.0–7.0)	3.0 (0.0–7.0)	4.0 (1.3–7.8)	2.0 (0.0–6.5)	0.223	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.185
Reticular patterns	4.0 (0.5–7.0)	5.0 (0.3–7.0)	3.0 (0.0–7.0)	3.0 (0.5–7.0)	0.618	0.0 (0.0–4.0)	2.0 (0.0–6.8)†	2.0 (0.0–3.8)	0.0 (0.0–2.0)	0.022
CT characteristics										
Lung involvement					0.487					0.066
Normal	0 (0)	0 (0)	0 (0)	0 (0)		64 (45.4)	18 (34.6)	20 (41.7)	26 (63.4)	
Unilateral	7 (5.0)	4 (7.7)	2 (4.2)	1 (2.4)		8 (5.7)	3 (5.8)	4 (8.3)	1 (2.4)	
Bilateral	134 (95.0)	48 (92.3)	46 (95.8)	40 (97.6)		69 (48.9)	31 (59.6)	24 (50.0)	14 (34.1)	
Predominantly CT pattern					0.687					0.153
Normal	0 (0)	0 (0)	0 (0)	0 (0)		64 (45.4)	18 (34.6)	20 (41.7)	26 (63.4)	
GGOs	90 (63.8)	34 (65.4)	32 (66.7)	24 (58.5)		29 (20.6)	14 (26.9)†	11 (22.9)	4 (9.8)	
Consolidations	25 (17.7)	6 (11.5)	9 (18.8)	10 (24.4)		8 (5.7)	4 (7.7)	3 (6.3)	1 (2.4)	
Reticular patterns	21 (14.9)	10 (19.2)	6 (12.5)	5 (12.2)		40 (28.4)	16 (30.8)	14 (29.2)	10 (24.4)	
Mix	5 (3.5)	2 (3.8)	1 (2.1)	2 (4.9)		0 (0)	0 (0)	0 (0)	0 (0)	
Thickening of the adjacent pleura	61 (43.3)	23 (44.2)	23 (47.9)	15 (36.60	0.552	39 (27.7)	19 (36.5)	12 (25.0)	8 (19.5))	0.167
Interlobar pleural traction	21 (14.9)	12 (23.1)	6 (12.5)	3 (7.3)	0.090	27 (19.1)	14 (26.9)	6 (12.5)	7 (17.1)	0.173
Bronchial dilatation	15 (10.6)	8 (15.4)	5 (10.4)	2 (4.9)	0.240	30 (21.3)	16 (30.8)	8 (16.7)	6 (14.6)	0.106
Parenchymal band	10 (7.1)	4 (7.7)	2 (4.2)	4 (9.8)	0.579	22 (15.6)	13 (25.0)	4 (8.3)	5 (12.2)	0.056
Pulmonary atelectasis	19 (13.5)	10 (19.2)	6 (12.5)	3 (7.3)	0.240	23 (16.3)	13 (25.0)	6 (12.5)	4 (9.8)	0.096
Presence of nodule or mass	19 (13.5)	9 (17.3)	3 (6.3)	7 (17.1)	0.196	26 (18.4)	12 (23.1)	10 (20.8)	4 (9.8)	0.225
Emphysema	9 (6.4)	4 (7.7)	2 (4.2)	3 (7.3)	0.739	11 (7.8)	7 (13.5)	2 (4.2)	2 (4.9)	0.158
Pleural effusion	18 (12.8)	9 (17.3)	5 (10.4)	4 (9.8)	0.464	0 (0)	0 (0)	0 (0)	0 (0)	–

Data are expressed as numbers (%) or medians (interquartile ranges). The *p* values reflect comparisons among groups 1, 2 and 3.
GGO, Ground-glass opacity.
† $p < 0.05$ vs. Group 3.

across the groups. There were no significant differences in the other CT features or scores among the three groups (all $p > 0.05$) (Table 3).

On the six-month follow-up CT scans, residual lung abnormalities were still observed on chest CT in 77 (54.6%) patients. Patients in Groups 1 (Fig. 3) and 2 (Fig. 4) had significantly higher incidences of residual lung abnormalities than patients in Group 3 (65.4% vs. 36.6%, 58.3% vs. 36.6%; $p < 0.05$ for both) (Fig. 5), but the difference between Groups 1 and 2 was not significant. The median total CT score was 3 [IQR, 0, 7.5] in all patients. The CT scores for total lesions, GGOs and reticular patterns differed among the groups; the total lesion scores in Groups 1 and 2 were higher than those in Group 3, whereas the GGOs and reticular patterns scores were both higher in Group 1 than in Group 3. Although no significant differences were found in the other CT features among the three groups (all $p > 0.05$), a gradual decreasing trend was observed across the groups. Patients in Group 1 had a trend toward a higher prevalence of parenchymal bands (Fig. 3: D) than patients in Groups 2 and 3 (25.0% vs. 8.3% vs. 12.2%, $p = 0.056$).

Of the 77 COVID-19 patients with residual lung abnormalities, 25 underwent chest CT examinations 12 months after disease onset (Supplemental Table S1). Thirteen (52.0%) patients had residual abnormalities on CT at 12 months, with reticular opacities (7, 28.0%), GGOs (6, 24.0%), adjacent pleura thickening (9, 36.0%), bronchial dilatation (6, 24.0%) (Fig. 3: H-I), parenchymal bands (5, 20.0%) (Fig. 3: G) and interlobar pleural traction (4, 16.0%) being the most common CT features found.

3.4. Comparison of baseline characteristics and peak laboratory findings of COVID-19 patients with and without residual CT abnormalities

To explore the association between residual lung abnormalities and clinical and laboratory data at 6 months, two subgroups were further designated: Subgroup 1 (COVID-19 patients with residual CT abnormalities) and Subgroup 2 (COVID-19 patients without residual CT abnormalities). Compared with Subgroup 2 (Supplemental Table S2), patients in Subgroup 1 had a higher incidence of ARDS and a greater proportion of chronic pulmonary disease, particularly chronic obstructive pulmonary disease (COPD) ($p < 0.05$ for all). The hospital stay was longer for patients in Subgroup 1 than for patients in Subgroup 2 ($p < 0.001$). Regarding treatment, patients in Subgroup 1 were more likely to receive glucocorticosteroids and humidified high flow nasal cannulas ($p < 0.05$ for both) than patients in Subgroup 2. The laboratory findings showed significantly higher peak levels of neutrophils, D-dimer, thrombin time, alanine transaminase (ALT), AST, LDH, hs-cTnI, serum ferritin, SAA and CRP in Subgroup 1 than in Subgroup 2 (all $p < 0.05$) (Supplemental Table S3).

3.5. Factors associated with residual lung abnormalities

The results of the logistic regression analysis for identifying factors associated with residual lung abnormalities in COVID-19 patients at 6 months are presented in Table 4. Univariable analysis showed that a longer duration of hospitalization (>20 days); elevated levels of white blood cell count ($>10 \times 10^9$/L) and neutrophil count ($>6.3 \times 10^9$/L)

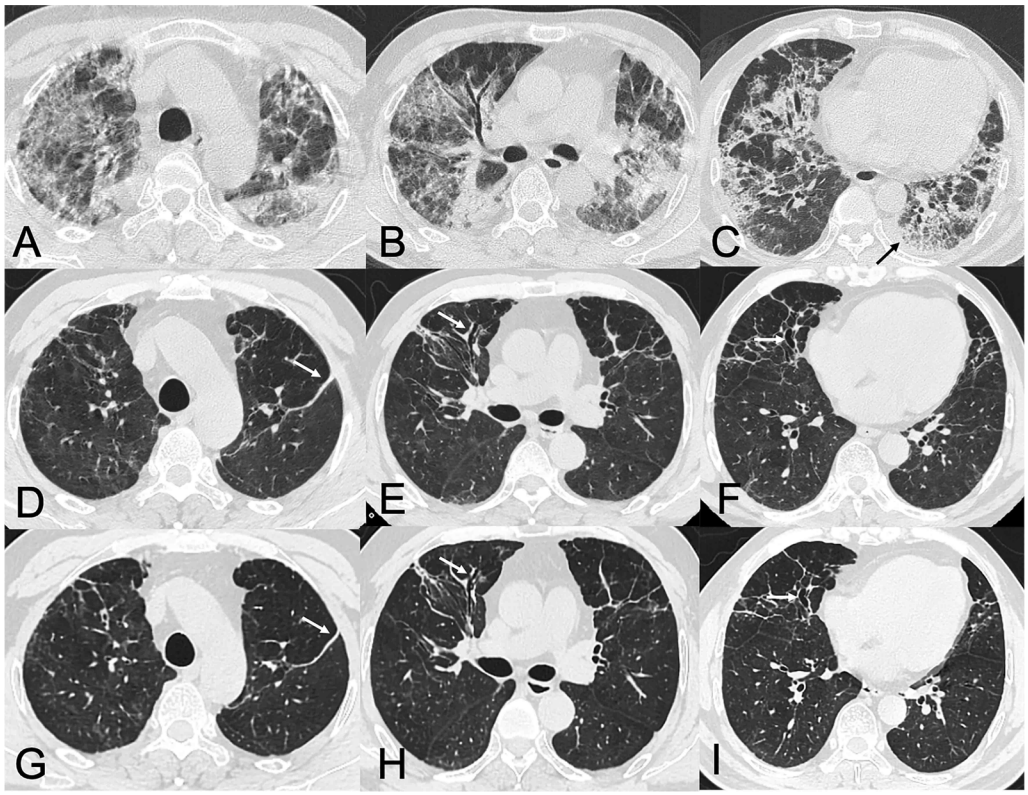

Fig. 3. Series of CT scans in a 47-year-old COVID-19 patient with a 3-year history of diabetes. (A-C) Transverse CT scan obtained 28 days after the onset of symptoms shows extensive ground-glass opacities coexisting with consolidation in both lungs, with the air bronchogram sign and a small pleural effusion on the left side (arrow in C). (D–E) Transverse thin-section CT scans obtained at 157 days showed that the previous opacifications had markedly dissipated into irregular linear opacities and that the pleural effusion had been completely resorbed, with newly emerging parenchymal bands (arrow in D) and traction bronchodilation (arrow in E and F). (G–I) Transverse thin-section CT scans obtained at 351 days shows no obvious absorption of the abnormalities, with persistent parenchymal bands (arrow in G) and traction bronchodilation (arrow in H and I).

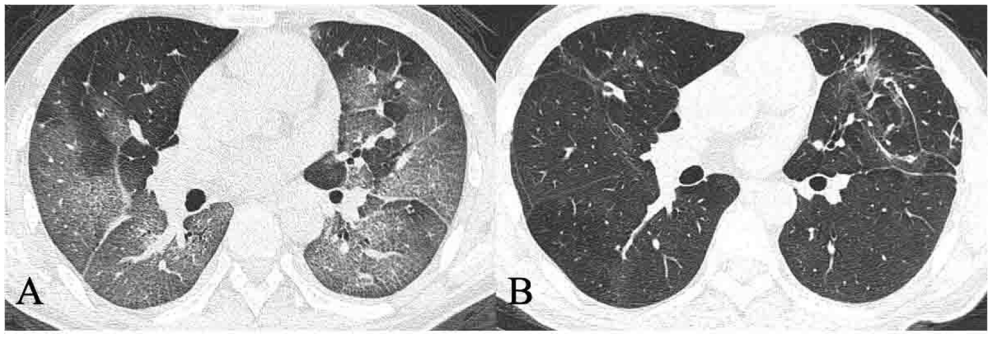

Fig. 4. Series of CT scans in a 38-year-old COVID-19 patient with secondary hyperglycemia. (A) Transverse CT scan obtained 16 days after the onset of symptoms shows diffuse ground-glass opacities with septal thickening that affected the bilateral lung parenchyma. (B) Transverse thin-section CT scans obtained at 178 days shows that the previous opacifications had been markedly absorbed, with patchy ground-glass opacities and irregular linear opacities predominantly in the left upper lobe.

and D-dimer (>1.6 mg/L), AST (≥47 U/L), ALT (≥47 U/L) and LDH levels (≥317 U/L); and a higher total CT score (>15) were factors associated with residual lung abnormalities in COVID-19 patients with diabetes or secondary hyperglycemia (all $p < 0.05$). When including the control group in the analysis, residual lung abnormalities were correlated with a longer duration of hospitalization (>20 days); elevated white blood cell count (>10 × 10^9/L) and AST (≥47 U/L) and LDH levels (≥317 U/L); and a higher total CT score (>15) (all $p < 0.05$).

Multivariable analysis showed that a longer duration of hospitalization (>20 days, OR, 5.630, $p = 0.015$), an elevated level of LDH (≥317 U/L, OR, 7.020, $p = 0.046$) and a higher total CT score (>15, OR, 9.919, $p = 0.023$) were independent predictors of residual lung abnormalities in COVID-19 patients with diabetes or secondary hyperglycemia. When including the control group in the analysis, the independent predictors of residual lung abnormalities were a longer duration of hospitalization (>20 days, OR, 3.569, $p = 0.046$) and a higher total CT score (>15, OR, 7.180, $p = 0.022$). Elevated LDH (≥317U/L) levels tended to be a significant predictor of residual lung abnormalities in all COVID-19 patients ($p = 0.066$).

3.6. Comparison of CT findings and scores between initial and follow-up scans

There were significant decreases in the total CT score ($p < 0.001$) and the CT scores for GGOs ($p < 0.001$), consolidations ($p < 0.001$) and reticular patterns ($p < 0.001$) in all patients between the initial and six-month follow-up CT scans (Supplemental Table S4). On the initial CT scans, the most frequent CT findings were GGOs (63.8%). Reticular patterns (28.4%) and GGOs (20.6%) were the most common CT characteristics on the follow-up CT scans. The incidence of thickening of the adjacent pleura (27.7% vs. 43.3%, $p = 0.006$) on the follow-up CT scans was significantly lower than that on the initial CT scans. Compared with those on the initial CT scans, the proportions of bronchial dilatation (21.3% vs. 10.6%, $p = 0.015$) (Fig. 3: E–F; Fig. 6) and parenchymal band (15.6% vs. 7.1%, $p = 0.024$) (Fig. 3: D) were significantly higher on the six-month follow-up scans, while the pleural effusions has been completely resorbed (0 vs. 12.8%, $p < 0.001$).

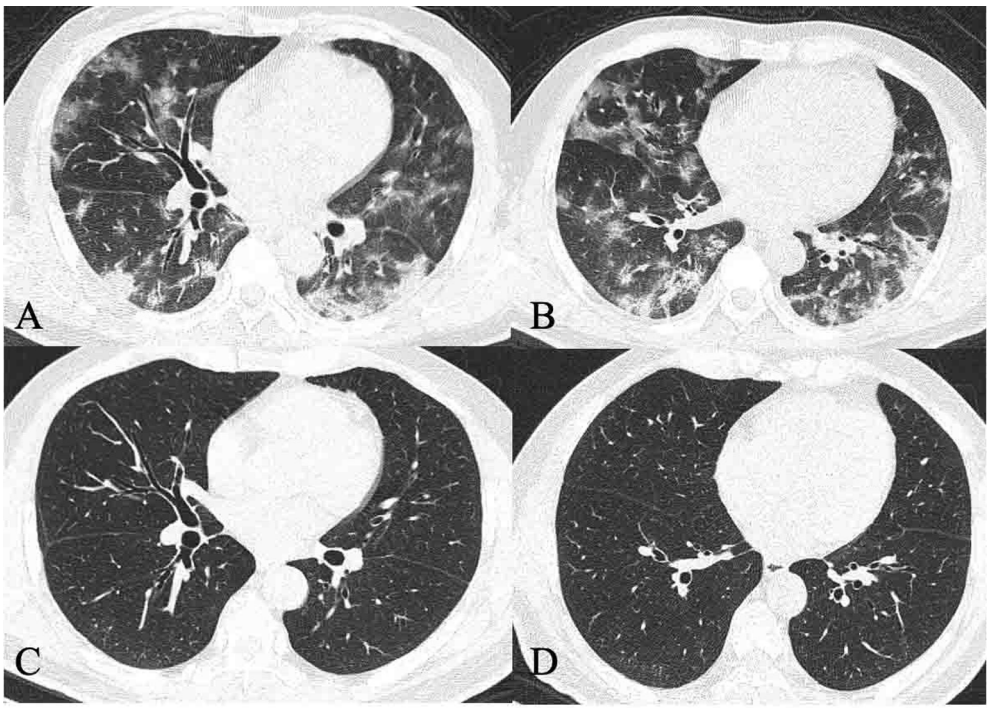

Fig. 5. Series of CT scans in a 51-year-old man with COVID-19. (A, B) Transverse CT scan obtained 14 days after the onset of symptoms shows diffuse ground-glass opacities coexisting with consolidation in both lungs. (C, D) Transverse thin-section CT scans obtained at 187 days shows the complete resolution of lung abnormalities.

3.7. Follow-up clinical characteristics

At the six-month follow-up (Supplemental Table S5), 13 (9.2%) patients were still complained of dry cough, 9 (6.4%) were still producing sputum, and 20 (14.2%) had shortness of breath after exertion. No significant differences were found in symptoms among the three groups (all $p > 0.05$). Temperature, heart rate, and oxygen saturation were within the normal ranges in all patients, and there were no differences among the three groups (all $p > 0.05$). Additionally, despite the lack of significant differences in any follow-up clinical characteristics between COVID-19 patients with or without residual lung abnormalities, patients in Subgroup 1 tended to have a higher prevalence of shortness of breath after activities than patients in Subgroup 2 (19.5% vs. 7.8%, $p = 0.055$; Supplemental Table S6).

4. Discussion

In the present study, abnormal CT findings were identified in 77 (54.6%) COVID-19 survivors six months after symptom onset, similar to previous studies on SARS and MERS [14,26]. We also found that the proportions of patients with residual lung abnormalities were significantly higher in the group with diabetes or hyperglycemia than in the control group. Previously, individuals with diabetes or secondary hyperglycemia were shown to be at a high risk of severe COVID-19 due to their impaired immunity and dysfunctional proinflammatory cytokine responses [7,27]. Thus, underlying comorbidities are associated with disease severity and, potentially, a slow recovery, which may also lead to a greater degree of residual pulmonary changes. Additionally, in this study, a few patients still experienced respiratory symptoms at the 6-month follow-up, which tended to more frequently occur in patients with residual lung changes. Consistent with our findings, in a recent study of patients recovering from COVID-19, impaired pulmonary function and respiratory symptoms could be found at 6 months after acute infection [20]. Similarly, data from SARS studies suggest that some patients will have long-term respiratory complications and symptoms [26,28]. Therefore, the impact of coronavirus infection on lung function and structure may be long-term. Moreover, we observed that a greater proportion of patients with residual lung changes had COPD. However, whether patients with symptoms after discharge were affected by underlying respiratory diseases requires further investigation.

The results of the multivariable analysis in this study showed that a prolonged hospital stays (>20 days) was an independent risk factor for residual lung abnormalities in patients with diabetes or secondary hyperglycemia. Previous data on COVID-19 showed that the duration of hospitalization was significantly longer in diabetic patients than in those without diabetes [5,25]. Understandably, lung lesions may persist in patients who have more severe disease and who experience a longer treatment period. The current study also demonstrated that elevated LDH (≥317) levels in the acute phase were associated with a higher risk of residual lung abnormalities. High levels of LDH have been regarded as a significant predictor of disease activity and severity in patients with idiopathic pulmonary fibrosis [23]. Previous data on SARS [29] and MERS [14] showed that high peak LDH levels were associated with the presence of lung fibrosis on follow-up chest CT scans or X-rays. However, when including the control group in the multivariable analysis in this study, the LDH levels were not a significant predictor of residual lung abnormalities in all COVID-19 patients ($p = 0.066$). This result might be influenced by our limited sample and the differences in baseline characteristics between the control group and the abnormal blood glucose groups. Moreover, elevated levels of D-dimer, ALT and AST were also potential factors associated with pulmonary sequalae in the univariable analyses in the present study. In critically ill patients with COVID-19 [30], coagulation activation and liver damage are common and are related to disease severity and the extent of lung injury.

We found that a higher CT score on the initial CT was an independent predictor for the presence of residual lung abnormalities on the 6-month follow-up scans. The CT score has been shown to be correlated with pathologic specimens [31]. In patients with COVID-19, the CT score is strongly related to disease severity and is a prognostic marker for mortality [32,33]. Thus, patients with more severe lung injury during treatment are more likely to have a greater extent of persistent

Table 4
Risk factors associated with residual lung abnormalities in COVID-19 patients.

	Residual lung abnormalities			
	COVID-19 patients with diabetes or secondary hyperglycemia		All COVID-19 patients	
	Univariable odds ratio (95 %CI)	*p* value	Univariable odds ratio (95 %CI)	*p* value
†Age, years	0.983 (0.949–1.019)	0.351	0.977 (0.949–1.007)	0.130
Female sex (vs. Male)	0.526 (0.212–1.305)	0.166	1.219 (0.611–2.429)	0.574
Heart rate >100 bpm	0.817 (0.320–2.082)	0.671	1.009 (0.985–1.034)	0.470
Respiratory rate >20	2.333 (0.195–27.909)	0.503	0.965 (0.879–1.060)	0.457
Oxygen saturation on room air <95%	0.795 (0.321–1.970)	0.621	1.059 (0.987–1.136)	0.111
Hypertension	0.953 (0.423–2.149)	0.907	0.545 (0.273–1.091)	0.087
Cardiovascular disease	0.571 (0.170–1.920)	0.366	1.034 (0.329–3.250)	0.954
Coronary heart disease	2.291 (0.450–11.654)	0.318	1.224 (0.375–3.998)	0.738
Chronic pulmonary disease	6.283 (0.763–51.732)	0.088	–	0.999
COPD	2.137 (0.604–7.561)	0.239	5.594 (0.735–17.572)	0.114
Duration of in-hospital stay >20 days	5.467 (2.238–13.356)	<0.001	2.383 (1.184–4.796)	0.015
ARDS	2.916 (0.986–9.627)	0.053	2.455 (0.921–6.548)	0.073
Noninvasive mechanical ventilation	5.585 (0.670–46.568)	0.112	6.078 (0.746–49.421)	0.091
White blood cells, 6.4 × 10^9/L				
>10	6.022 (1.614–22.467)	0.008	2.769 (1.030–7.439)	0.043
<4	1.290 (0.433–3.848)	0.648	0.903 (0.327–2.496)	0.844
Neutrophils, ×10^9/L				
<1.8	0.870 (0.112–6.751)	0.894	0.644 (0.086–4.833)	0.669
>6.3	3.913 (1.344–11.390)	0.012	2.336 (0.939–5.811)	0.068
Lymphocytes ≤ 0.8 × 10^9/L	2.296 (0.917–5.750)	0.076	1.560 (0.727–3.346)	0.253
Platelets < 125 × 10^9/L	2.000 (0.380–10.536)	0.414	1.704 (0.430–6.755)	0.448
D-dimer > 1.6 mg/L	2.649 (1.049–6.692)	0.039	1.650 (0.770–3.534)	0.198
Glucose ≥ 10 mmol/L	0.522 (0.227–1.201)	0.126	1.047 (0.497–2.207)	0.903
Albumin < 35 g/L	1.474 (0.590–3.682)	0.406	1.725 (0.812–3.665)	0.156
ALT ≥ 47 U/L	2.397 (1.102–5.677)	0.047	0.563 (0.274–1.154)	0.117
AST ≥ 47 U/L	3.143 (1.296–7.620)	0.011	2.872 (1.358–6.074)	0.006
Creatinine > 133 μmol/L	0.553 (0.104–2.940)	0.487	0.751 (0.160–3.526)	0.717
Creatine kinase, U/L				
<38	2.125 (0.675–6.687)	0.198	1.529 (0.592–3.951)	0.380
>174	2.267 (0.518–9.918)	0.277	2.804 (0.709–11.089)	0.142
LDH ≥ 317 U/L	7.345 (2.645–20.392)	<0.001	3.630 (1.639–8.039)	0.001
hs-cTnI > 26.2 ng/L	1.538 (0.284–8.326)	0.617	1.552 (0.295–8.160)	0.604
Serum ferritin > 585 ng/mL	2.418 (0.946–6.181)	0.065	1.540 (0.681–3.484)	0.300
SAA > 235 mg/L	2.160 (0.811–5.750)	0.123	1.676 (0.726–3.872)	0.226
ESR ≥ 50 mm/h	1.328 (0.501–3.521)	0.568	1.245 (0.543–2.856)	0.605
Procalcitonin > 0.05 g/mL	2.024 (0.765–5.355)	0.156	1.311 (0.590–2.911)	0.506
Interleukin-6 ≥ 10 pg/mL	1.098 (0.447–2.699)	0.838	1.223 (0.564–2.649)	0.610
CRP ≥ 48 mg/L	2.045 (0.833–5.020)	0.118	1.268 (0.599–2.683)	0.534
Initial total lesions CT score > 15	11.191 (3.829–32.708)	<0.001	3.996 (1.824–8.756)	0.001
	Multivariable odds ratio (95 % CI)	*p* value	Multivariable odds ratio (95 % CI)	*p* value
†Age, years	1.037 (0.958–1.124)	0.369	1.013 (0.939–1.093)	0.738
ARDS	1.204 (0.168–8.617)	0.853	1.578 (0.303–8.209)	0.588
Duration of in-hospital stay > 20 days	5.630 (1.394–22.744)	0.015	3.569 (1.023–12.458)	0.046
D-dimer > 1.6 mg/L	0.535 (0.093–3.063)	0.482	1.012 (0.233–4.404)	0.987
LDH ≥ 317 U/L	7.020 (1.032–47.743)	0.046	5.849 (0.891–38.370)	0.066
CRP ≥ 48 mg/dL	0.667 (0.137–3.249)	0.616	0.705 (0.159–3.116)	0.644
Initial total lesions CT score > 15	9.919 (1.378–71.415)	0.023	7.180 (1.334–38.637)	0.022

Data are expressed as odds ratios and 95% confidence intervals.
COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; SAA, serum amyloid protein A; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
†Per 1 unit increase.

pulmonary lesions after recovery. Additionally, we observed that the CT features of COVID-19 survivors changed from predominantly GGOs in the acute phase to predominantly reticular patterns and GGOs after six months of recovery. This trend appeared significant in the diabetic group, and the follow-up CT score was higher in individuals with diabetes than in the controls. Furthermore, compared with those on the initial CT scans, the frequencies of bronchial dilatation and parenchymal bands increased on the follow-up scans. Bronchial dilatation and parenchymal bands on CT have been identified as important signs of lung fibrosis [34,35] and may represent potentially permanent lung damage in patients who survive ARDS [34] and SARS [36]. Although the distributions of the two features did not differ significantly among the three groups in our study, the incidences of bronchial dilatation and parenchymal bands on follow-up scans were the highest in patients with diabetes. The results indicate the possibility of the presence of underlying lung fibrosis in COVID-19 survivors, especially in diabetic patients, but further investigation is needed.

Twelve months after disease onset, the chest CT changes did not resolve completely in 13/25 (52.0%) patients, and some COVID-19 survivors still presented with reticular opacities, bronchial dilatation and parenchymal bands. Although the evidence showing any definitive or progressive fibrosis revealed by the follow-up CT scans was insufficient, the burden of pulmonary fibrosis in patients recovering from COVID-19 could be substantial due to these findings and the large number of individuals affected by COVID-19 [11,37]. However, longer

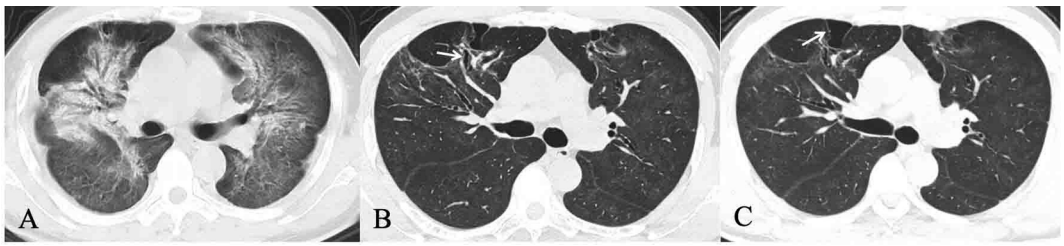

Fig. 6. Series of CT scans in a 49-year-old COVID-19 patient with a 5-year history diabetes. (A) Transverse CT scan obtained 33 days after the onset of symptoms shows extensive ground-glass opacities coexisting with consolidation in both lungs, with the air bronchogram sign. (B, C) Transverse thin-section CT scans obtained at 92 days and 165 days shows that the previous opacifications had markedly dissipated into ground-glass opacities and irregular linear opacities, with persistent traction bronchodilation (arrow in B) and localized emphysema (arrow in C).

follow-up studies in a larger sample will be required to further explore the residual lung changes in COVID-19 patients during the convalescence period.

This prospective study has several limitations. First, our findings might be limited by the small numbers in each patient subgroup. Second, the follow-up period was relatively short, and long-term follow-up monitoring is required to determine whether the identified residual lung abnormalities are progressive or reversible. Third, the mechanism underlying the greater extent of lung lesions among patients with diabetes or hyperglycemia remains largely unknown; future interventional studies are warranted. Fourth, the difference in the prevalence of GGOs among the three groups may be explained by the different timings of the baseline CT and may be unrelated to the presence or absence of diabetes or hyperglycemia, but this requires further investigation. Last, information on continuous glucose monitoring, glycemic control measures and the kinetics of the viral load and antibody titers during convalescence were not collected in the current study. Further studies will be needed to explore the effects of these factors on pulmonary sequelae.

In conclusion, a significant proportion of COVID-19 survivors with diabetes or hyperglycemia had residual lung abnormalities at the 6-month follow-up visit, which were associated with longer hospital stays, higher peak LDH levels and higher initial total CT scores. Our study suggests that patients who have severe disease during hospitalization are more likely to have severe pulmonary sequelae. Additionally, we found evidence of persistent chest CT changes even 12 months after disease onset, which highlights the significance of long-term follow-up for patients recovering from COVID-19.

CRediT authorship contribution statement

Yumin Li: Conceptualization, Data curation, Software. **Xiaoyu Han:** Conceptualization, Data curation, Software. **Jing Huang:** Conceptualization, Data curation, Software. **Osamah Alwalid:** Visualization, Investigation, Methodology. **Xi Jia:** Visualization, Investigation, Methodology. **Mei Yuan:** Visualization, Investigation, Methodology. **Yukun Cao:** Formal analysis. **Guozhu Shao:** Formal analysis. **Yue Cui:** Resources. **Jia Liu:** Resources. **Yangqing Fan:** Writing – review & editing, Validation, Supervision. **Xiangyang Xu:** Writing – review & editing, Validation, Supervision. **Heshui Shi:** Writing – review & editing, Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2021.109997.

References

[1] WHO Coronavirus Disease (COVID-19) Dashboard. Data last updated: 2021/9/24, 6:35pm CEST. https://covid19.who.int/.
[2] F. Wu, S. Zhao, B. Yu, et al., A new coronavirus associated with human respiratory disease in China, Nature 579 (7798) (2020) 265–269, https://doi.org/10.1038/s41586-020-2008-3.
[3] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a Report of 72314 cases from the Chinese Center for disease control and prevention, JAMA 323 (13) (2020) 1239–1242, https://doi.org/10.1001/jama.2020.2648.
[4] J.K. Yang, S.S. Lin, X.J. Ji, L.M. Guo, Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes, Acta Diabetol. 47 (3) (2010) 193–199, https://doi.org/10.1007/s00592-009-0109-4.
[5] Y. Zhang, H. Li, J. Zhang, et al., The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: A single-centre, retrospective, observational study in Wuhan, Diabetes Obes. Metab. 22 (8) (2019) 1443–1454, https://doi.org/10.1111/dom.14086.
[6] J. Zhang, W. Kong, P. Xia, et al., Impaired Fasting Glucose and Diabetes Are Related to Higher Risks of Complications and Mortality Among Patients With Coronavirus Disease 2019, Front. Endocrinol. (Lausanne) (2020) 00525, https://doi.org/10.3389/fendo.2020.00525.
[7] Y.H. Liao, J.Q. Zheng, C.M. Zheng, et al., Novel Molecular Evidence Related to COVID-19 in Patients with Diabetes Mellitus, J. Clin. Med. 9 (12) (2020) 3962, https://doi.org/10.3390/jcm9123962.
[8] J.K. Yang, Y. Feng, M.Y. Yuan, et al., Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS, Diabet. Med. 23 (6) (2006) 623–628, https://doi.org/10.1111/j.1464-5491.2006.01861.x.
[9] K.A. Kulcsar, C.M. Coleman, S.E. Beck, M.B. Frieman, Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection, JCI Insight 4 (20) (2019), e131774, https://doi.org/10.1172/jci.insight.131774.
[10] Y. Wang, C. Domg, Y. Hu, et al., Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study, Radiology 292 (2) (2020) E55–E64, https://doi.org/10.1148/radiol.2020200843.
[11] B. Shaw, M. Daskareh, A. Gholamrezanezhad, The lingering manifestations of COVID-19 during and after convalescence: update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19), Radiol. Med. 126 (1) (2021) 40–46, https://doi.org/10.1007/s11547-020-01295-8.
[12] Y.C. Chang, C.J. Yu, S.C. Chang, et al., Pulmonary Sequelae in Convalescent Patients after Severe Acute Respiratory Syndrome: Evaluation with Thin-Section CT, Radiology (2005) 1067–1175, https://doi.org/10.1148/radiol.2363040958.
[13] P. Zhang, L. Li, H. Liu, et al., Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study, Bone Res. 8 (34) (2020), https://doi.org/10.1038/s41413-020-0084-5.
[14] K.M. Das, E.Y. Lee, R. Singh, et al., Follow-up chest radiographic findings in patients with MERS-CoV after recovery, Indian J. Radiol. Imaging 27 (3) (2017) 342–349, https://doi.org/10.4103/ijri.IJRI-469-16.
[15] World Health Organization, Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance.

January 28, 2020. Accessed March 5, (2020) https://www.who.int/publications-detail/clinical-management-of-severeacute-respiratory-infection-when-novelcoronavirus-(ncov)-infection-is-suspected.
[16] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, The Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.
[17] D.A. American, Diagnosis and classification of diabetes mellitus, Diabetes Care 37 (Suppl 1) (2014) S81–S90, https://doi.org/10.2337/dc14-S081.
[18] NHCaNAoTC Medicine, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7), Chin. Med. J. (2020) 133.
[19] V.M. Ranieri, G.D. Rubenfeld, B.T. Thompson, et al., ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition, JAMA 307 (23) (2012) 2526–2533, https://doi.org/10.1001/jama.2012.5669.
[20] C. Huang, L. Huang, Y. Wang, et al., 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study, Lancet 397 (10270) (2021) 220–232, https://doi.org/10.1016/S0140-6736(20)32656-8.
[21] J.H. Austin, N.L. Muller, P.J. Friedman, et al., Glossary of terms for CT of the lungs: recommendations of the Nomenclature Committee of the Fleischner Society, Radiology 200 (2) (1996) 327–331, https://doi.org/10.1148/radiology.200.2.8685321.
[22] Y.M. Zhao, Y.M. Shang, W.B. Song, et al., Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery, EClinicalMedicine (2020) 100463, https://doi.org/10.1016/j.eclinm.2020.100463.
[23] T. Kishaba, H. Tamaki, Y. Shimaoka, H. Fukuyama, S. Yamashiro, Staging of Acute Exacerbation in Patients with Idiopathic Pulmonary Fibrosis, Lung 192 (1) (2013) 141–149, https://doi.org/10.1007/s00408-013-9530-0.
[24] E.K. Bajwa, U.A. Khan, J.L. Januzzi, M.N. Gong, B.T. Thompson, D.C. Christiani, Plasma C-reactive protein levels are associated with improved outcome in ARDS, Chest 136 (2) (2009) 471–480, https://doi.org/10.1378/chest.08-2413.
[25] Y. Chen, D. Yang, B. Cheng, et al., Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication, Diabetes Care 43 (7) (2020) 1399–1407, https://doi.org/10.2337/dc20-0660.
[26] L. Xie, Y. Liu, Y. Xiao, et al., Follow-up study on pulmonary function and lung radiographic changes in rehabilitating severe acute respiratory syndrome patients after discharge, Chest 127 (6) (2005) 2119–2124, https://doi.org/10.1378/chest.127.6.2119.
[27] M. Apicella, M.C. Campopiano, M. Mantuano, et al., COVID-19 in people with diabetes: understanding the reasons for worse outcomes, Lancet Diabetes Endocrinol. 8 (9) (2020) 782–792, https://doi.org/10.1016/S2213-8587(20)30238-2.
[28] J.C. Ngai, F.W. Ko, K.W. To, et al., The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status, Respirology 15 (3) (2010) 543–550, https://doi.org/10.1111/j.1440-1843.2010.01720.x.
[29] C.H. Chiang, J.F. Shih, W.J. Su, R.P. Perng, Eight-Month Prospective Study of 14 Patients With Hospital-Acquired Severe Acute Respiratory Syndrome, Mayo Clinic Proc. 79 (11) (2004) 1372–1379, https://doi.org/10.4065/79.11.1372.
[30] X. Yang, Y. Yu, J. Xu, et al., Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study, Lancet Respirat. Med. 8 (5) (2020) 475–1448, https://doi.org/10.1016/S2213-2600(20)30079-5.
[31] E.A. Kazerooni, F.J. Martinez, A. Flint, et al., Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring, Am. J. Roentgenol. 169 (4) (1997) 977–983, https://doi.org/10.2214/ajr.169.4.9308447.
[32] M. Francone, F. Iafrate, G.M. Masci, et al., Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis, Eur. Radiol. 30 (12) (2020) 6808–6817, https://doi.org/10.1007/s00330-020-07033-y.
[33] Y. Li, X. Han, O. Alwalid, et al., Baseline characteristics and risk factors for short-term outcomes in 132 COVID-19 patients with diabetes in Wuhan China: A retrospective study, Diabetes Res. Clin. Pract. 166 (2020), https://doi.org/10.1016/j.diabres.2020.108299.
[34] I.M. Nöbauer-Huhmann, K. Eibenberger, C. Schaefer-Prokop, et al., Changes in lung parenchyma after acute respiratory distress syndrome (ARDS): assessment with high-resolution computed tomography, Eur. Radiol. 11 (12) (2001) 2436–2443, https://doi.org/10.1007/s003300101103.
[35] J.L. Westcott, S.R. Cole, Traction bronchiectasis in end-stage pulmonary fibrosis, Radiology 161 (3) (1986) 665–669, https://doi.org/10.1148/radiology.161.3.3786716.
[36] G.E. Antonio, K.T. Wong, D.S. Hui, et al., Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience, Radiology 228 (3) (2003) 810–815, https://doi.org/10.1148/radiol.2283030726.
[37] P.M. George, R.G. Jenkins, Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy, Lancet Respir. Med. 8 (8) (2020) 807–815, https://doi.org/10.1016/S2213-2600(20)30225-3.