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

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\textbf{A R T I C L E   I N F O}

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\textbf{A B S T R A C T}

\textbf{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.

\textbf{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.

\textbf{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 \( \geq 227.41 \text{ U/L} \) (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.

\textbf{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.

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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 lung 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, or 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].
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 $\times$ 0.6 mm, 128 $\times$ 0.6 mm and 64 $\times$ 0.6 mm; and a matrix of 512 $\times$ 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.

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.
| Variable | 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 | – | – | – | – | – |
| Current smokers | 5 (9.6) | 1 (2.1) | 3 (7.3) | 2 (4.9) | 0.435 |
| Former smokers | 4 (7.7) | 1 (2.1) | 2 (4.9) | 1 (2.4) | 0.435 |
| Drinking history | – | 9 (17.3) | 9 (18.8) | 7 (17.1) | 0.974 |
| Current drinkers | 6 (11.5) | 7 (14.6) | 3 (7.3) | 3 (7.3) | 0.559 |
| Former drinkers | 3 (5.8) | 2 (4.2) | 4 (9.6) | 4 (9.6) | 0.547 |
| Hospital admission | – | – | – | – | – |
| Duration of in-hospital stay, days | 20.0 (14.0–26.0) | 19.0 (11.3–31.8) | 17.0 (12.0–34.8) | 17.0 (11.0–21.3) | 0.411 |
| Duration from onset of symptoms to, days | – | 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 |
| | HPNc | 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; HPNc, high-flow nasal cannula; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

1 p < 0.05 vs. Group 2.

2 p < 0.05 vs. Group 3.

3 Tuberculosis: A past history of pulmonary tuberculosis (without active tuberculosis).
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 $\geq 38^\circ$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 and lactate dehydrogenase, as-cTnl, high-sensitivity cardiac troponin I, N-terminal pro b-type natriuretic peptide; SAA, serum amyloid protein A; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

$^1$ $p < 0.05$ 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-CtNl, 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 × 10⁹/L) and neutrophil count (>6.3 × 10⁹/L)
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 (≥317 U/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).
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 stay (>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 sequelae 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

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

| Residual lung abnormalities | Univariable odds ratio (95 %CI) | p value | All COVID-19 patients with hyperglycemia | Univariable odds ratio (95 %CI) | p value |
|-----------------------------|---------------------------------|---------|-----------------------------------------|---------------------------------|---------|
| Age, years                  | 1.037                           | 0.369   | 1.013                                    | 0.738                           |         |
| Female sex (vs. Male)       | 0.974                           | 0.452   | 0.993                                    | 0.876                           |         |
| Heart rate ≥100 bpm         | 1.046                           | 0.272   | 1.005                                    | 0.965                           | 0.457   |
| Respiratory rate >20        | 1.138                           | 0.124   | 0.979                                    | 0.621                           | 0.311   |
| Oxygen saturation >95%      | 0.953                           | 0.907   | 0.545                                    | 0.087                           |         |
| Hypertension                | 0.974                           | 0.403   | 0.554                                    | 0.073                           |         |
| Cardiovascular disease      | 1.074                           | 0.403   | 1.034                                    | 0.954                           |         |
| Coronary heart disease      | 0.981                           | 0.403   | 0.921                                    | 0.738                           |         |
| Chronic pulmonary disease   | 0.974                           | 0.403   | 0.954                                    | 0.999                           |         |
| COPD ≥50 mg/dL              | 0.974                           | 0.403   | 1.034                                    | 0.954                           |         |
| Duration of in-hospital stay >20 days | 1.046 | 0.272 | 1.005 | 0.965 | 0.457 |
| ARDS ≥50 mg/dL              | 0.974                           | 0.403   | 0.921                                    | 0.738                           |         |
| Noninvasive mechanical ventilation | 0.974 | 0.403 | 0.954 | 0.999 |         |
| White blood cells, 6 × 10^9/L | 1.046 | 0.272 | 1.005 | 0.965 | 0.457 |
| Neutrophils, 10^9/L         | 0.974                           | 0.403   | 1.034                                    | 0.954                           |         |
| Lymphocytes >0.8 × 10^9/L   | 0.974                           | 0.403   | 0.921                                    | 0.738                           |         |
| Platelets ≥125 × 10^9/L     | 0.974                           | 0.403   | 0.954                                    | 0.999                           |         |
| D-dimer >1.6 mg/L           | 1.046                           | 0.272   | 1.005                                    | 0.965                           | 0.457   |
| Glucose ≥10 mg/dL           | 0.974                           | 0.403   | 0.921                                    | 0.738                           |         |
| Albumin ≥35 g/L             | 0.974                           | 0.403   | 1.034                                    | 0.954                           |         |
| ALT ≥47 U/L                 | 0.974                           | 0.403   | 0.921                                    | 0.738                           |         |
| AST ≥47 U/L                 | 0.974                           | 0.403   | 0.954                                    | 0.999                           |         |
| Creatinine ≥133 μmol/L      | 0.974                           | 0.403   | 1.034                                    | 0.954                           |         |
| Creatine kinase, U/L <38    | 1.046                           | 0.272   | 1.005                                    | 0.965                           | 0.457   |

Table 4 (continued)
Residual lung abnormalities

| Residual lung abnormalities | Univariable odds ratio (95 %CI) | p value |
|-----------------------------|---------------------------------|---------|
| All COVID-19 patients       | 0.974                           | 0.403   |

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.

1Per 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 survivors, lying 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...
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 Alwailid: 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, 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.

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