Original Article

Long-term chest CT follow-up in COVID-19 Survivors: 102–361 days after onset

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Background: The aim of this study was to evaluate long-term longitudinal changes in chest computed tomography (CT) findings in coronavirus disease 2019 (COVID-19) survivors and their correlations with dyspnea after discharge.

Methods: A total of 337 COVID-19 survivors who underwent CT scan during hospitalization and between 102 and 361 days after onset were retrospectively included. Subjective CT findings, lesion volume, therapeutic measures and laboratory parameters were collected. The severity of the survivors' dyspnea was determined by follow-up questionnaire. The evolution of the CT findings from the peak period to discharge and throughout follow-up and the abilities of CT findings and clinical parameters to predict survival with and without dyspnea were analyzed.

Results: Ninety-one COVID-19 survivors still had dyspnea at follow-up. The age, comorbidity score, duration of hospital stays, receipt of hormone administration, receipt of immunoglobulin injections, intensive care unit (ICU) admission, receipt of mechanical ventilation, laboratory parameters, clinical classifications and parameters associated with lesion volume of the survivors with dyspnea were significantly different from those of survivors without dyspnea. Among the clinical parameters and CT parameters used to identify dyspnea, parameters associated with lesion volume showed the largest area under the curve (AUC) values, with lesion volume at discharge showing the largest AUC (0.820). Lesion volume decreased gradually from the peak period to discharge and through follow-up, with a notable decrease observed after discharge. Absorption of lesions continued 6 months after discharge.

Conclusions: Among the clinical parameters and subjective CT findings, CT findings associated with lesion volume were the best predictors of post-discharge dyspnea in COVID-19 survivors.

Keywords: Coronavirus disease 2019 (COVID-19); computed tomography (CT); dyspnea; follow-up

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Introduction

The coronavirus disease 2019 (COVID-19) outbreak has lasted more than one year. According to official World Health Organization (WHO) statistics, as of 22 March 2021, the total number of confirmed cases of COVID-19 globally was over 122.82 million, and the total number of associated deaths was 2.71 million (1).

Up to 15% of COVID-19 patients require hospital admission, of whom 98.6% can be discharged from the hospital (2). However, discharge is not the end of the disease course, and in most patients, lung lesions are not completely absorbed at the time of discharge (3-6). Up to 98.1% of all chest computed tomography (CT) scans show abnormalities more than 28 days after symptom onset (7). Some studies have shown that many discharged patients experience long-term morbidities (8,9). Therefore, it is of great significance to follow discharged COVID-19 patients.

Chest radiography is not advisable as a first-line technique for the detection of COVID-19 infection due to its limited ability to demonstrate ground-glass opacities (GGOs) (10). Point-of-care ultrasonography (POCUS) may help define the severity and progression of COVID-19 and is widely used in the evaluation of patients with dyspnea, especially in intensive care units (ICUs); however, POCUS may not provide findings as detailed or as early as CT (10). CT plays important roles in assessing the severity of COVID-19 disease and evaluating therapeutic effects (11,12). Several studies have evaluated the CT findings of COVID-19 patients in short-term follow-up (6,13-16). In one study, the CT imaging findings of COVID-19 were divided into 4 stages according to the number of days since the onset of symptoms (17). The results suggested that the early CT findings in COVID-19 patients are complex, can change rapidly, and can predict the outcome at discharge. To date, there have been few reports on the long-term changes in CT findings in COVID-19 survivors after discharge (18,19). Thus, additional longitudinal studies are needed to develop viable rehabilitation practice guidelines for survivors. This study aimed to evaluate longitudinal changes in CT findings in COVID-19 survivors from the peak period to discharge and through long-term follow-up and to determine the correlations of clinical parameters and multiperiod CT findings with dyspnea after discharge.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-1438).

Methods

Patient selection and clinical classification of severity

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Wuhan Tongji Hospital (No. TJ-IRB20210120), and individual consent for this retrospective analysis was waived. Using the Electronic Medical Record Systems and Picture Archiving and Communication Systems, we retrospectively collected data of COVID-19 patients who underwent CT examination during hospitalization between January 1 and March 31, 2020, and who underwent follow-up CT examination between 102 and 361 days after onset. All cases were confirmed by reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal swab samples. Patients in which the following criteria were met during follow-up were excluded: readmission for infection by other pathogens or extensive lung lesions due to non-COVID-19 reasons, such as pulmonary embolism or multiple lung metastases.

The diagnosis of COVID-19, the clinical classification of severity and the discharge criteria were determined according to the New Coronavirus Pneumonia Diagnosis and Treatment Plan (trial version 7) developed by the National Health Committee of the People's Republic of China (20). The clinical classification included mild, moderate, severe and critical.

Clinical information collection

Data on comorbidities, including chronic obstructive pulmonary disease (COPD), asthma, hypertension, coronary heart disease, diabetes, stroke and malignant tumor, were collected for all survivors. Some survivors had multiple comorbidities; each comorbidity received a score of 1, so the comorbidity score for each survivor ranged from 0 to 7.

Data on the main clinical treatments of COVID-19 and laboratory parameters reflecting tissue damage and inflammatory response were also collected. Treatments included hormone administration (methylprednisolone sodium succinate), immunoglobulin injection, antiviral therapy (arbidol), ICU admission, and mechanical ventilation for acute respiratory distress syndrome. Selected laboratory parameters included peak C-reactive protein (CRP), peak lactate dehydrogenase (LDH), peak D2-

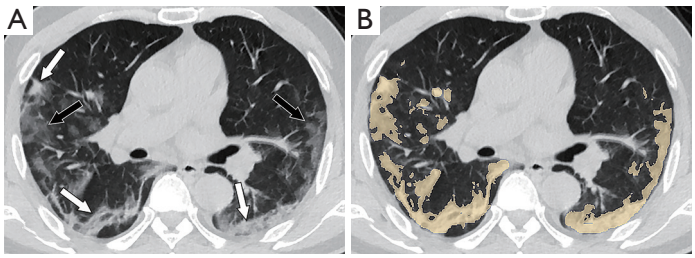

Figure 1 Thin-slice CT scan of a 57-year-old man with COVID-19 without dyspnea after discharge (obtained 9 days after onset) showing patchy consolidations (white arrows) and GGOs (black arrows) mainly in the bilateral subpleural region (A). 3D slicing was used to segment all lesions (B). CT, computed tomography; COVID-19, coronavirus disease 2019; GGOs, ground-glass opacities.

polymer, and peak calcitonin levels, peak neutrophil count, and minimum lymphocyte count.

The survivors were assessed for dyspnea with a follow-up questionnaire within one week after the follow-up CT scan. Dyspnea was scored from 1 to 4 according to the method reported by Staples *et al.* (21): 1= dyspnea with strenuous activity, such as climbing three flights of stairs or heavy housework; 2= dyspnea with mild activity, such as climbing one flight of stairs or light housework; 3= dyspnea with minimal activity, such as walking 20 to 50 feet; and 4= dyspnea at rest or while eating or talking. Dyspnea scores for the evaluation of symptoms have been validated, as they correlate well with pulmonary function parameters (22).

CT scanning protocol

All images were obtained with one of three CT systems (uCT 780, United Imaging, Shanghai, China; Optima 660, GE Healthcare, Milwaukee, WI, USA; SOMATOM Definition AS+, Siemens Healthineers, Erlangen, Germany); patients were scanned in the supine position. The main scanning parameters were as follows: tube voltage, 120 kVp; automatic tube current modulation (ATCM), 30–70 mA s; pitch, 0.99–1.22 mm; matrix, 512 ×512; field of view, 350 mm × 350 mm. All images were reconstructed with a slice thickness of 0.625–1.250 mm with the same increment. We analyzed peak CT images (CT image of the largest lesion range on multiple CT examinations during hospitalization) as well as CT images at discharge and during follow-up after discharge. Since physicians did not have a deep understanding of COVID-19 at the beginning of the epidemic and since the condition of patients in the acute phase changed rapidly, most patients received multiple CT scans during their hospitalization, with an average of 4.64±2.02.

Image interpretation

The CT images were reviewed by two radiologists (15 and 10 years of experience in cardiothoracic imaging) who were blinded to the clinical classification results and dyspnea scores. Any discrepancies were resolved by discussion until a consensus was reached. The CT findings were described using internationally standard nomenclature defined by the Fleischner Society Glossary and peer-reviewed literature on viral pneumonia. The description terms included ground-glass opacity (GGO; defined as hazy opacity that does not obscure the underlying pulmonary vessels and bronchi), crazy-paving pattern (defined as GGO with superimposed inter- and intralobular septal thickening), consolidation (defined as airspace opacity that obscures underlying parenchymal vessels and bronchi) and reticulation (defined as linear opacities) (7,17,23). The main CT findings were defined as the most prominent of the four CT findings.

Data on the presence of bronchiolectasis, pleural effusion, enlarged mediastinal lymph nodes, pleural thickening and axial lesion distribution were also collected in the study. The lung lesion volume at different periods was assessed with 3D Slicer software (version 4.10.2, https://www.slicer.org/). Image segmentation was performed manually by the above-mentioned two radiologists, with a minimum Hounsfield unit (HU) threshold of -750 and a maximum HU threshold of 80 (*Figure 1*). In addition, the residual lesion rate at discharge and at follow-up relative to the peak period was calculated according to the following formula: residual lesion rate = discharge or follow-up CT

lesion volume/peak CT lesion volume.

Statistical analysis

Statistical analyses were performed by SPSS (version 25; IBM, Chicago, IL, USA) and MedCalc version 19.1.3. Quantitative data are presented as the mean and standard deviation, and qualitative data are presented as counts and percentages of the total unless otherwise specified. Quantitative data were evaluated by *t* test if they were normally distributed or Mann-Whitney U test otherwise. Qualitative data were compared between groups using Pearson's chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curves were constructed to analyze the abilities of clinical parameters and CT parameters to predict dyspnea. $P<0.05$ was indicative of statistical significance.

Results

Patient characteristics and clinical data

A total of 337 survivors [mean age, 53.51±14.82 years; 50.45% (170/337) men] were enrolled in this study; all of these patients underwent CT at the peak period, discharge, and follow-up except for 21 survivors who did not undergo CT at discharge. The time from onset to follow-up was 203.37±52.65 days (102–361 days), and the time from discharge to follow-up was 164.13±52.04 days (57–324 days).

None of the survivors had dyspnea before onset. At the time of follow-up CT, 91 survivors still had dyspnea, of which 7 had grade 2 dyspnea and the remainder had grade 1 dyspnea; thus, we classified dyspnea only by its presence or absence. The parameters with significant differences between patient groups are presented in *Table 1*. Patients with dyspnea after discharge were older and had more comorbidities, longer hospital stays, higher peak levels of CRP, LDH, D2-polymer, calcitonin, and neutrophil counts, and lower lymphocyte counts than survivors without dyspnea after discharge. The percentages of survivors who were male, required hormone administration, immunoglobulin injection, ICU admission, mechanical ventilation and classified as having severe or critical disease were significantly higher among those with dyspnea than among those without dyspnea. Survivors whose main CT finding was reticulations at follow-up had significantly longer hospital stays than those whose main CT finding was not reticulations (33.07±14.40 and 28.44±16.10 days, respectively), with a P value of 0.003. In 67.4% of the survivors, peak D2-polymer level was higher than normal during hospitalization.

Evolution of CT findings

On follow-up CT, 55.79% of the survivors still showed residual lesions; the residual lesion rate ranged from 1% to 83%, and 15.43% of the survivors had a residual lesion rate exceeding 10%. Lesion volume during the peak period, at discharge and at follow-up was 451.55±410.86 cm^3, 298.27±365.06 cm^3 and 54.17±162.30 cm^3, respectively, indicating that lesion absorption occurred mainly after discharge (*Figure 2*).

Twenty-one survivors did not undergo CT at the time of discharge, and we excluded these patients from the comparison of images among the various timepoints. CT findings were compared between the peak period and discharge and between discharge and follow-up. The rates of most of the CT findings were significantly decreased at discharge and at follow-up; however, the rates of survivors with reticulations and reticulations as the main CT finding were significantly increased at discharge. Moreover, the rate of survivors with reticulations was significantly reduced at follow-up compared with discharge, but the rate of survivors with reticulations as the main CT finding was increased significantly at follow-up relative to discharge (*Figure 3*). Pleural effusion and enlarged mediastinal lymph nodes appeared only in the peak period, with 20 and 4 cases, respectively, so we did not include these two parameters in the analysis. The evolution patterns of the CT findings are presented in *Table 2*.

In addition, the differences in follow-up CT findings between less than 6 months (121.38±31.20 days) after discharge and more than 6 months (208.69±24.89 days) after discharge were analyzed (*Table 3*). The residual lesion rate and the rate of survivors with subpleural distribution of lung lesions were significantly reduced on follow-up CT more than 6 months after discharge compared with follow-up CT within 6 months after discharge.

Comparison of CT findings in survivors with and without dyspnea

CT findings were evaluated for significant differences between survivors with and without dyspnea. Survivors with dyspnea showed lower rates of GGO at the peak period and lower rates of subpleural distribution at the peak period and at discharge. Survivors with dyspnea had significantly

Table 1 Comparison of patient characteristics and clinical data between survivors with and without dyspnea

	All survivors (n=337)	Without dyspnea (n=246)	With dyspnea (n=91)	χ^2/t/Z	P value
Age (y)	53.51±14.82	51.60±15.47	58.68±11.47	−3.789	<0.001
Sex					
Male	170 (50.45%)	113 (45.93%)	57 (62.64%)	7.413	0.006
Female	167 (49.55%)	133 (54.07%)	34 (37.36%)		
Smokers	24 (7.12%)	16 (6.50%)	8 (8.79%)	0.525	0.469
Comorbidities	0.42±0.63	0.37±0.57	0.57±0.76	−1.975	0.048
Hospital stays	29.62±15.78	26.85±12.37	37.12±20.88	−4.399	<0.001
Time from onset to follow-up	203.37±52.65	200.67±52.07	210.67±53.79	−1.605	0.109
Treatment modalities					
Hormone administration	187 (55.49%)	118 (47.97%)	69 (75.82%)	20.870	<0.001
Immunoglobulin injection	151 (44.81%)	96 (39.02%)	55 (60.44%)	12.319	<0.001
Lianhua Qingwen capsule (Chinese medicine)	157 (46.59%)	117 (47.56%)	40 (43.96%)	0.347	0.556
Antiviral therapy (arbidol)	300 (89.02%)	217 (88.21%)	83 (91.21%)	0.611	0.435
ICU admission	12 (3.56%)	4 (1.63%)	8 (8.79%)	7.954	0.005
Mechanical ventilation	27 (8.01%)	8 (3.25%)	19 (20.88%)	28.005	<0.001
Selected laboratory parameter					
Peak CRP (mg/L)	52.71±73.33	34.57±44.63	101.76±106.42	−7.413	<0.001
Peak LDH (U/L)	294.19±112.14	267.24±84.03	367.05±142.73	−6.680	<0.001
Peak D2-polymer (ug/mL)	2.42±4.14	1.76±2.99	4.23±5.92	−5.340	<0.001
Peak calcitonin level (ng/mL)	0.28±1.33	0.12±0.27	0.72±2.47	−5.196	<0.001
Peak neutrophil count (10^9/L)	6.64±4.30	5.69±3.38	9.21±5.35	−6.445	<0.001
Minimum lymphocyte count (10^9/L)	0.95±0.47	1.05±0.47	0.68±0.37	−6.969	<0.001
Clinical classification					
Mild or moderate	294 (87.24%)	233 (94.72%)	61 (67.03%)	45.730	<0.001
Severe or critical	43 (12.76%)	13 (5.28%)	30 (32.97%)		

ICU, intensive care unit; CRP, C-reactive protein; LDH, lactate dehydrogenase.

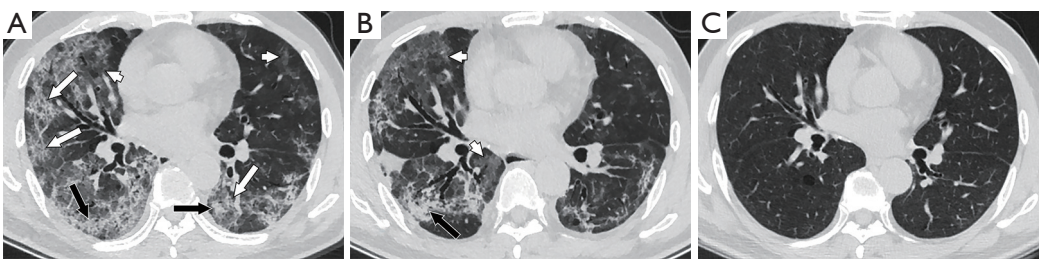

Figure 2 Thin-slice CT scan of a 48-year-old man with COVID-19 with dyspnea after discharge (A-C obtained at 35, 66 and 284 days after onset, respectively). Lesion volume was largest in the peak period, mainly manifested as crazy-paving patterns (white arrows), with some GGOs (white arrowheads) and a small amount of consolidations (black arrows) (A). At discharge, the lesion range was reduced, most of the crazy-paving patterns had disappeared, and the lesions mainly presented as GGOs (white arrowheads) and consolidations (black arrow) (B). In the follow-up CT at 284 days after discharge, almost all the lesions had been absorbed (C). CT, computed tomography; COVID-19, coronavirus disease 2019; GGOs, ground-glass opacities.

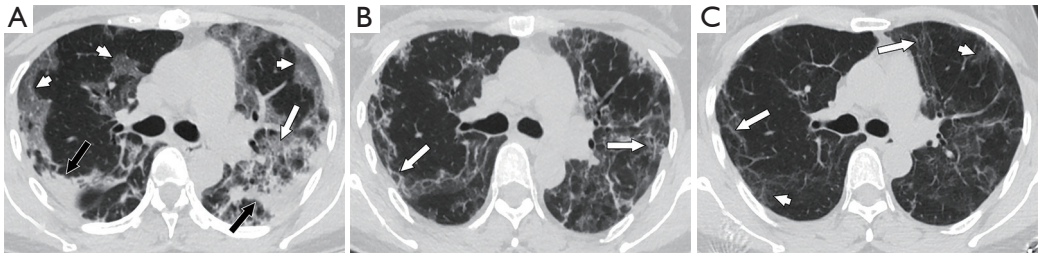

Figure 3 Thin-slice CT scan of a 40-year-old woman with COVID-19 with dyspnea after discharge (A-C obtained at 23, 70 and 254 days after onset, respectively). In the peak period, consolidation (black arrows), GGOs (white arrowheads) and crazy-paving patterns (white arrow) were observed bilaterally (A). At discharge, most areas of consolidation and the crazy-paving pattern had been absorbed, but reticulations (white arrows) had increased significantly (B). Only reticulations (white arrows) and small areas of ground-glass opacities (GGOs, white arrowheads) remained at follow-up (C). CT, computed tomography; COVID-19, coronavirus disease 2019; GGOs, ground-glass opacities.

Table 2 Evolution of CT findings

CT findings	Peak period (n=316)	Discharge (n=316)		Follow-up (n=316)	
		Value	P*	Value	P**
GGO, n (%)	281 (88.92%)	263 (83.23%)	0.039	106 (33.54%)	<0.001
Crazy-paving pattern	179 (56.65%)	128 (40.51%)	<0.001	24 (7.59%)	<0.001
Reticulation	226 (71.52%)	256 (81.01%)	0.005	146 (46.20%)	<0.001
Consolidation	176 (55.70%)	53 (16.77%)	<0.001	12 (3.80%)	<0.001
Main CT finding					
GGO	163 (51.58%)	160 (50.63%)	0.811	53 (16.77%)	<0.001
Crazy-paving pattern	58 (18.35%)	53 (16.77%)	0.601	11 (3.48%)	<0.001
Consolidation	84 (26.58%)	19 (6.01%)	<0.001	8 (2.53%)	0.030
Reticulation	11 (3.48%)	72 (22.78%)	<0.001	95 (30.06%)	0.038
Bronchiolectasis	80 (25.32%)	79 (25.00%)	0.927	43 (13.61%)	<0.001
Distribution of lesions					
Subpleural	190 (60.13%)	202 (63.92%)	0.325	139 (43.99%)	<0.001
Random	59 (18.67%)	60 (18.99%)	0.919	17 (5.38%)	<0.001
Diffuse	67 (21.20%)	42 (13.29%)	0.008	11 (3.48%)	<0.001
Pleural thickening	70 (22.15%)	50 (15.82%)	0.043	11 (3.48%)	<0.001
Lesion volume (cm^3)	451.55±410.86	298.27±365.06	<0.001	54.17±162.30	<0.001

*, the P value represents the comparison between discharge and peak period; **, the P value represents the comparison between follow-up and discharge. CT, computed tomography; GGO, ground-glass opacity.

higher rates or values of the following CT findings: (I) peak period: consolidation, bronchiolectasis, random or diffuse distribution, pleural thickening, and lesion volume; (II) at discharge: crazy-paving pattern, reticulations, reticulation as the main CT findings, bronchiolectasis, random or diffuse distribution, pleural thickening, lesion volume and residual lesion rate; and (III) follow-up: GGOs, reticulations, GGOs as the main CT finding, reticulations as the main CT findings, bronchiolectasis, random or diffuse distribution, pleural thickening, lesion volume, and residual lesion rate.

Table 3 Comparisons of follow-up CT findings between survivors at less than 4 months and more than 4 months after discharge

Follow-up CT findings	Within 6 months after discharge (n=172)	More than 6 months after discharge (n=165)	P
GGO	63 (36.63%)	51 (30.91%)	0.267
Crazy-paving pattern	16 (9.30%)	12 (7.27%)	0.500
Reticulation	83 (48.26%)	76 (46.06%)	0.687
Consolidation	4 (2.33%)	8 (4.85%)	0.212
Main CT finding			
GGO	34 (19.77%)	23 (13.94%)	0.154
Crazy-paving pattern	5 (2.91%)	6 (3.64%)	0.706
Consolidation	4 (2.33%)	6 (3.64%)	0.698
Reticulation	56 (13.37%)	42 (25.45%)	0.151
Bronchiolectasis	23 (13.37%)	24 (14.55%)	0.756
Distribution of lung lesions			
Subpleural	84 (48.84%)	60 (36.36%)	0.021
Random	8 (4.65%)	9 (5.45%)	0.736
Diffuse	7 (4.07%)	8 (4.85%)	0.729
Pleural thickening	6 (3.49%)	5 (3.03%)	0.813
Lung lesion volume (cm^3)	57.38±165.11	50.63±150.81	0.102
Residual lesion rate (%)	7.80±15.43	5.81±13.20	0.026

CT, computed tomography; GGO, ground-glass opacity.

A comparison of CT findings between survivors with and without dyspnea is shown in *Table 4*.

ROC analysis

Figure 4 and *Table 5* show the clinical parameters and CT findings with the top 10 largest areas under the curve (AUCs) that were used to identify dyspnea in survivors. Lesion volume at discharge had the largest AUC (0.820) and the highest sensitivity (0.908), and GGOs at follow-up had the highest specificity (0.799). The presence of GGOs and the presence of reticulations were analyzed as qualitative data, so cutoff values could not be obtained. The parameters of the top 10 AUCs were pairwise compared, and most of the comparisons between the first 5 parameters and the last 5 parameters showed significant differences.

Discussion

A total of 27.00% of the survivors had dyspnea at follow-up; this rate is slightly less than the rate of one-third observed among patients with severe acute respiratory syndrome (SARS) and similar to the finding of pulmonary function tests in COVID-19 survivors at 3 months after discharge, showing residual pulmonary function abnormalities in 25.4% of patients (24,25).

Survivors of COVID-19 with dyspnea after discharge were older and had more comorbidities than those without dyspnea after discharge, and male survivors were more likely than female survivors to have dyspnea after discharge. Previous SARS studies have shown that men and older survivors are more likely to develop fibrosis; similarly, our study shows that survivors with dyspnea have more reticulations, which may be the cause of dyspnea (26). Parameters that reflect disease severity, such as the duration of hospital stay, hormone administration, ICU admission, and clinical classification, showed significant differences between survivors with and without dyspnea, suggesting that more severe illness during hospitalization was associated with a higher risk of dyspnea. In addition, the hospital stays were significantly longer among survivors whose main CT finding during follow-up was reticulation,

Table 4 Comparison of CT findings between survivors with and without dyspnea

CT findings	Peak period			Discharge			Follow-up		
	Without dyspnea (n=246)	With dyspnea (n=91)	P	Without dyspnea (n=229)	With dyspnea (n=87)	P	Without dyspnea (n=246)	With dyspnea (n=91)	P
GGO	226 (91.87%)	76 (83.52%)	0.026	192 (83.84%)	71 (81.61%)	0.635	50 (20.33%)	64 (70.33%)	<0.001
Crazy-paving pattern	136 (55.28%)	51 (56.04%)	0.901	80 (34.93%)	48 (55.17%)	0.001	13 (5.28%)	15 (16.48%)	0.001
Reticulation	169 (68.70%)	66 (72.53%)	0.497	173 (75.55%)	83 (95.40%)	<0.001	83 (33.74%)	76 (83.52%)	<0.001
Consolidation	124 (50.41%)	60 (65.93%$)	0.011	34 (14.85%)	19 (21.84%)	0.137	8 (3.25%)	4 (4.40%)	0.864
Main CT finding									
GGO	127 (51.63%)	37 (40.66%)	0.074	123 (53.71%)	37 (42.53%)	0.076	31 (12.60%)	26 (28.57%)	0.001
Crazy-paving pattern	48 ((19.51%)	21 (23.08%)	0.472	40 (17.47%)	13 (14.94%)	0.592	6 (2.44%)	5 (5.49%)	0.291
Consolidation	63 (25.61%)	29 (31.87%)	0.252	13 (5.68%)	6 (6.90%)	0.684	6 (2.44%)	4 (4.40%)	0.563
Reticulation	8 (3.25%)	4 (4.40%)	0.864	41 (17.90%)	31 (35.63%)	0.001	53 (21.54%)	45 (49.45%)	<0.001
Bronchiolectasis	46 (18.70%)	38 (41.76%)	<0.001	38 (16.59%)	41 (47.13%)	<0.001	25 (10.16%)	22 (24.18%)	0.001
Distribution of lung lesions									
Subpleural	177 (71.95%)	26 (28.57%)	<0.001	165 (72.05%)	37 (42.53%)	<0.001	91 (36.99%)	53 (58.24%)	<0.001
Random	36 (14.63%)	27 (29.67%)	0.002	36 (15.72%)	24 (27.59%)	0.016	5 (2.03%)	12 (13.19%)	<0.001
Diffuse	33 (13.41%)	38 (41.76%)	<0.001	16 (6.99%)	26 (29.89%)	<0.001	0 (0.00%)	15 (16.48%)	<0.001
Pleural thickening	41 (16.67%)	29 (31.87%)	0.002	28 (12.23%)	22 (25.29%)	0.004	4 (1.63%)	7 (7.69%)	0.015
Lesion volume (cm^3)	346.70±360.0	774.12±465.42	<0.001	203.55±263.84	582.33±457.03	<0.001	27.07±79.68	158.18±281.05	<0.001
Residual lesion rate (%)	–	–	–	48.55±28.68	77.92±41.12	<0.001	4.45±10.97	17.38±22.21	0.011

CT, computed tomography; GGO, ground-glass opacity.

suggesting that the more serious the disease was, the longer hospital stay was, the more reticulation formed after discharge, and the more likely it was that dyspnea occurred. Peak CRP, peak LDH, peak D2-polymer, peak calcitonin, peak neutrophil count, and minimum lymphocyte count are laboratory parameters indicative of disease severity, inflammatory response, and tissue damage in the acute phase (27). These parameters showed significant differences between survivors with and without dyspnea, similar to results obtained in SARS survivors (22,24). D2-polymer is frequently elevated in acute venous thromboembolism (VTE) but is nonspecific, being frequently elevated in many other nonthrombotic conditions, including pregnancy, cancer and inflammation, and it has been shown to be frequently elevated in COVID-19-positive patients in the absence of VTE (28). In our study, 67.4% of the survivors had an elevated peak D2-polymer level during hospitalization, but no cases of pulmonary embolism were confirmed during hospitalization, and only 3 patients were readmitted for pulmonary embolism within 5–7 months after discharge. Since COVID-19 could not be identified as the cause of pulmonary embolism in these patients, we excluded these cases. Evidence suggests that small vessel pulmonary thrombi are more commonly involved than large pulmonary vessel thrombi in COVID-19 (29,30). The observations that COVID-19 can cause an increase in D2-polymer and small vessel embolism has a limited effect on lung function may explain why no cases of pulmonary embolism were confirmed during hospitalization.

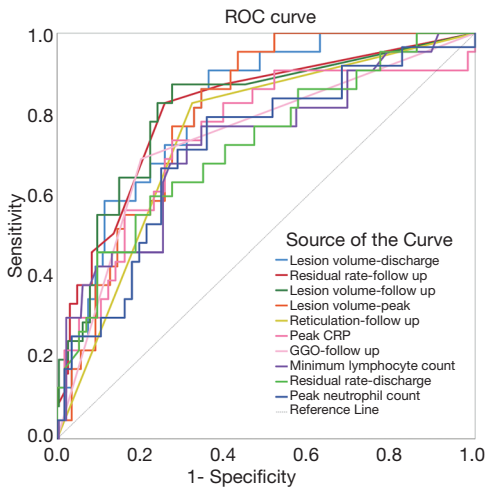

Figure 4 ROC curves for the top 10 clinical parameters and CT findings for differentiating between survivors with and without dyspnea. ROC, receiver operator characteristic; CT, computed tomography; CRP, C-reactive protein; GGO, ground-glass opacity.

CT findings, including a crazy-paving pattern, consolidation, consolidation as the main CT finding, and lesion volume, were significantly reduced at discharge compared with during the peak period, reflecting lesion absorption. The above parameters, as well as GGOs and reticulations, were further significantly reduced during follow-up compared with at discharge. A previous study showed that only 9% of COVID-19 survivors were free of residual disease after three months, but another study

Table 5 Area under the curve

Test result variable(s)	Cutoff	Sensitivity	Specificity	AUC	P	95% CI	
Lesion volume-discharge	140.171	0.908	0.638	0.820	<0.001	0.772	0.867
Residual rate-follow up	0.015	0.828	0.742	0.813	<0.001	0.759	0.868
Lesion volume-follow up	6.198	0.874	0.725	0.812	<0.001	0.757	0.867
Lesion volume-peak	286.611	0.954	0.568	0.803	<0.001	0.756	0.850
Reticulation-follow up	†	0.828	0.677	0.752	<0.001	0.693	0.811
Peak CRP	36.850	0.736	0.725	0.746	<0.001	0.681	0.811
GGO-follow up	†	0.690	0.799	0.744	<0.001	0.680	0.809
Minimum lymphocyte count	1.220	0.770	0.655	0.728	<0.001	0.663	0.793
Residual rate-discharge	0.702	0.598	0.777	0.724	<0.001	0.660	0.788
Peak neutrophil count	5.450	0.793	0.642	0.720	<0.001	0.656	0.784

†, the dichotomous variable is considered to have this CT finding as the threshold. AUC, area under the curve; CRP, C-reactive protein; GGO, ground-glass opacity.

showed that 57.7% of survivors had no lesions on follow-up CT after a three-month interval (7,15). Our results showed that 44.21% of the survivors had no lesions at follow-up and that survivors with residual lesion rates greater than 10% accounted for only 15.43% of the study population, indicating that most of the lesions had been absorbed by 3 months after disease onset. Among the main CT findings, reticulations were significantly increased at discharge and further significantly increased at follow-up. We found that the rate of survivors with reticulations was significantly reduced at follow-up, whereas that of survivors with reticulation as the main CT finding was significantly increased at follow-up. This difference may be due to the fact that other lesions are relatively easy to absorb, thus leaving only reticulations; alternatively, it may be that reticulations are representative of lesions in the late stage in some survivors. Previous short-term follow-up studies have suggested that reticulations are indicative of fibrosis (31-33). However, our results showed that nearly half of the reticulations observed on CT at discharge were absorbed during follow-up, suggesting that not all reticulations represent true fibrosis. Approximately one-quarter of survivors had bronchiolectasis during the peak period and at discharge; the frequency significantly decreased to approximately one in eight at follow-up. We observed that bronchiolectasis was most obvious at discharge and then recovered significantly during follow-up as lesion volume significantly reduced. A small number of patients showed pleural effusion and enlarged mediastinal lymph nodes, consistent with previous reports (34). *Table 3* shows that among the CT parameters, only the residual lesion rate and rate of subpleural distribution were significantly decreased at more than 6 months after discharge compared with less than 6 months after discharge. This indicates that the lesions were still being absorbed more than 6 months after discharge. Moreover, GGOs continued to be observed on CT images in 30% of the survivors more than 6 months after discharge; these lesions may be absorbed over time.

The rates of reticulation as the main CT finding at discharge and at follow-up were significantly higher among survivors with dyspnea than survivors without dyspnea, which is consistent with long-term follow-up results in SARS patients (22,26). These results may have been obtained because survivors with dyspnea have larger lesions that are incompletely absorbed at discharge and at follow-up, and chest CT showed more reticulations in these survivors. The rate of bronchiolectasis in survivors with dyspnea was significantly higher than that in survivors without dyspnea at the three time points. We found that bronchiolectasis tended to occur in patients with larger lesion volumes. Since patients with dyspnea had significantly larger lesion volumes than those without dyspnea, the incidence of bronchiolectasis was higher in the former. At follow-up, the rates of GGOs and reticulations were higher in survivors with dyspnea than in those without dyspnea. This result may be due to the fact that survivors with dyspnea have larger lesions and a higher residual lesion rate, with these incompletely absorbed lesions manifesting as GGOs and reticulations.

As shown in *Table 5* and *Figure 4*, among the parameters for identifying dyspnea, most of the top 10 parameters with the largest AUC were related to the lesion volume. The paired comparison results showed that the AUC values of the first 5 volume-related parameters were significantly larger than those of the last 5 parameters, which indicated that the parameters associated with lesion volume are the most accurate predictors of postdischarge dyspnea in COVID-19 survivors. The AUC for lesion volume at discharge was the largest (0.820), suggesting that the larger the lesion is at discharge, the more likely the persistence of dyspnea is after discharge.

This study has several limitations. First, it was a single-center retrospective study. However, there have been few long-term follow-up CT studies of COVID-19, and expert opinions on practice guidelines and rehabilitation need to be validated in sufficiently powered longitudinal studies. Second, we did not have data on the pulmonary function of survivors, but a previous study has validated dyspnea for the evaluation of symptoms based on its strong correlation with pulmonary function parameters (21). Third, some GGOs and reticulations were not completely absorbed according to the follow-up CT images; therefore, a longer time is required to observe the complete process. Fourth, the proportion of patients from the ICU setting in our sample was low. However, according to a report from *N Engl J Med*, only a small number of confirmed COVID-19 pneumonia patients (5.0%) were admitted to the ICU (2).

Conclusions

In this longitudinal study of COVID-19 patients during the peak period, at discharge, and at follow-up, the lesion volume in survivors decreased gradually over time, especially after discharge. Among the CT findings and clinical parameters, CT findings associated lesion volume were the best predictors of dyspnea in COVID-19 survivors. In the long-term management of discharged

COVID-19 survivors, extra vigilance is required regarding the persistence of dyspnea when the lesion volume remains large at discharge. Such patients need active rehabilitation after discharge to improve their long-term quality of life.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Wuhan Tongji Hospital (No. TJ-IRB20210120), and individual consent for this retrospective analysis was waived.

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