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The time course of chest CT lung changes in COVID-19 patients from onset to discharge

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ABSTRACT

Background & Aims: Computed tomography (CT) is widely used to evaluate the severity of COVID-19 infection and track disease progression. We described the changes in chest CT to enable better understanding of the progression of COVID-19 during hospitalization.
Methods: Consecutively hospitalized COVID-19 patients admitted from January 11, 2020 to February 16, 2020 and followed until March 26, 2020 at the Third People's Hospital of Shenzhen, China were included. Semi-quantitative analysis was used to assess the shape, distribution, and range of lung lesions. For each image, the lungs were divided into six regions. The total CT score was the sum of individual region scores.
Results: 305 patients underwent a total of 1442 chest CT scans with a mean interval of 5 days (interquartile range (IQR) = 3−6 days). All patients were discharged after an average hospitalization of 25 days (IQR = 20−33 days). From the onset of initial symptoms, the total CT score peaked at an earlier date in the non-severe than the severe cases (13 days versus 15 days). Typical CT image of non-severe cases mainly presented as ground-glass opacities (GGO), whilst GGO mixed with consolidation was more seen in severe cases. In addition, severe versus non-severe cases had higher prevalence of fibrosis and air bronchogram in CT scans (P from <0.001 to 0.05, P = 0.001, respectively). The proportion of patients with fibrosis and air bronchogram appeared to decrease from the fourth (20 days from onset, IQR = 16–24) and the third pulmonary CT scan (15 days from onset, IQR = 12–19), respectively.
Conclusion: COVID-19 pneumonia demonstrated progressions in early stage, with the greatest pulmonary damage on CT occurred at approximately 13 days after initial onset of symptoms. Worse bilateral pulmonary infiltrates were found in severe cases, indicating continuous health care for pulmonary rehabilitation and consecutive follow-up to monitor irreversible fibrosis and consolidation are necessary.

1. Introduction

Coronavirus disease 2019 (COVID-19), a novel disease caused by the strain of coronavirus recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has quickly spread globally [1]. As of 31 July 2020, 18 million individuals diagnosed with COVID-19, and more than 540,000 have died from this disease. The number of deaths due to COVID-19 is expected to increase [2]. The SARS-CoV-2 virus has been known to enter the respiratory tract, damage the lungs and cause pneumonia, resulting in the acute respiratory distress syndrome (ARDS) and severe hypoxemia [3,4]

. Using chest computed tomography (CT) to evaluate the severity of COVID-19 and track the disease progression has been shown to be accurate and practical [5,6].

Some previous studies reported the radiological features of CT in hospitalized COVID-19 patients, showing clear destruction of the

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pulmonary parenchyma including interstitial inflammation and extensive consolidation [7,8]. A recent study described the changes in chest CT imaging on COVID-19 patients from initial diagnosis to recovery [9]. The greatest severity of lung abnormalities on chest CT was observed approximately 10 days after initial onset of symptoms. However, this study was limited to a small number of patients with mild COVID-19 pneumonia (n = 21). Larger studies with comprehensive periodic CT examinations are warranted.

Hence, we described the changes in chest CT systematically using a larger sample of COVID-19 patients, aiming at providing a better understanding of COVID-19 disease progression during hospitalization. All patients were recruited from the only referral hospital in Shenzhen, one of the largest cities in China. Results of our study may enable more accurate evaluation of disease severity and facilitate targeted therapies and holistic care models to combat this global pandemic.

2. Methods

2.1. Study design and participant criteria

In the current study, data were collected from all consecutively hospitalized patients from January 11, 2020 to February 21, 2020 at the Third People's Hospital of Shenzhen, the only referral hospital authorized to admit COVID-19 patients by the government in Shenzhen City. COVID-19 cases were confirmed based on the WHO interim guidance [10]. All patients were followed after discharge until March 26, 2020. Data were analyzed on the basis of epidemiological and clinical data, laboratory tests, radiological findings, and progression and treatment information collected by nurses, physicians, or other professionals from electronic medical records. This study was approved by the Ethics Committee of The Third People's Hospital of Shenzhen (IRB No. 2020 108). All subjects have signed the informed consent. It was impossible to involve patients or the public in any research stage of this study.

2.2. Confirmation of COVID-19

The real-Time Reverse Transcription Polymerase Chain Reaction method was conducted to detect the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [11]. Two pairs of primers targeting the open reading frame 1ab (ORF1ab) and the nucleocapsid protein (N) were amplified and then examined. The corresponding sequences for ORF1ab were 5′−CCCTGTGGGTTTTACACTTAA-3′ (F), 5′-ACGATTGTGCATCAGCTGA-3′ (R), and 5′-CY3−CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1−3′ (probe), while for N were 5′-GGGGAACTTCTCCTGCTAGAAT-3′(F), 5′-CAGACATTTTGCTCTCAAGCTG-3′(R), and 5′-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3′(probe). Each sample was run in triplicate with both positive and negative control sets. The diagnostic criteria were in accordance with the National Centers for Disease Control and Prevention of China (China CDC) recommendations. Samples that identified as positive for COVID-19 were reconfirmed by the key laboratory of the Shenzhen CDC.

2.3. Outcome assessment

We checked the severity of disease progression as observation outcome. According to the national guidelines for community-acquired pneumonia and the diagnosis and treatment plan for new coronavirus in China [12,13], patients were categorized with mild or severe form based on chest radiography, clinical tests as well as symptoms. The non-severe group included mild cases (with the upper respiratory tract symptoms such as fever, cough and expectoration), and those without abnormalities or with mild changes on chest CT. A mild change in chest CT referred to multiple, small patchy shadows and interstitial changes, mainly involved the outer zone of the lung and under the pleura. Patients were classified into the severe group by the following conditions: 1) a significant increase in respiration rate (RR): RR $\geq$ 30 times/minute; 2) hypoxia: oxygen saturation (resting state) $\leq$ 93 %; 3) blood gas analysis: ratio of partial pressure of arterial oxygen and fraction of inspired oxygen (PaO_2 /FiO_2)$\leq$300 mmHg(millimeters of Mercury); or 4) the occurrence of respiratory or other organ failure requiring intensive care unit (ICU) monitoring and treatment, or shock.

Besides, nasal swab samples were collected every three days in COVID-19 patients and evaluated by the qPCR assay. The duration of positive viral test results was defined from the day of disease onset to the day of virus clearance, and the clearance of COVID-19 was defined as two consecutive negative results in qPCR detection at an interval of 24 h. The clearance day was considered to be the first of these consecutive days. Patients were discharged from hospital after the viral clearance.

2.4. CT data acquisition

After the RT-PCR swabs, all patients underwent chest CT to determine the absence or presence of viral pneumonia. All patients underwent a chest CT scan in supine posture when holding breath after a deep breath. The CT scan was taken from the entrance of the chest cavity to the lower edge of the diaphragm, and was repeated once every 3–6 days. All CT was performed on a 16-slice spiral CT scanner (Emotion 16 VC20B, Siemens Healthcare GmbH, Erlangen, Germany) by following the protocol: a tube voltage of 120 kV; smart mA tube current modulation; slice thickness of 1.5 mm; reconstruction matrix of 512*512; detector width of 1.5 mm; and breath hold at full inspiration. The reconstruction was performed with a thickness of 1 mm.

Semi- quantitative analysis was used to assess the shape, distribution and range of lung lesions, as well as the degree of lung involvement objectively. Each lung was divided into three regions: the upper, middle, and lower regions. The upper region refers to region above the tracheal carina, the middle between the tracheal carina and the inferior pulmonary vein, and the lower below the inferior pulmonary vein. The severity of lesions in each of the six regions was graded 0 to 5: no lung involvement = 0; lung involvement <25 % = 1, 25 %–50 % = 2, 50 %–75 % = 3, >75 % = 4. The total CT lung score was summed up by individual region scores.

2.5. Statistical analysis

Data analysis were done by R version 4.0.2 software (R Core Team, Vienna, Austria). Frequency and percentages were used to describe the qualitative variables. For quantitative variables, those normally distributed were described as mean and standard deviation and analyzed by independent group t-tests, otherwise were described as median and interquartile range (IQR) and analyzed by the Mann-Whitney test. Qualitative data were compared using the $\chi 2$ test or the Fisher exact test, if the counts were small. A 2-sided α of less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

305 COVID-19 patients admitted to the Third People's Hospital of Shenzhen from January 11, 2020 to February 16, 2020 and followed until June 13, 2020 were included. Patients who were older, male, and with pre-existing diseases (i.e. cardiovascular disease, cancer), and with initial symptoms of fever, were tended to develop severe COVID-19 (P from <0.001 to 0.03) (Table 1). Patients with severe disease tended to have lower levels of platelet (PLT) ($P < 0.001$) but higher levels of gamma-glutamyl transferase (GGT) and aspartate transaminase (AST) ($P < 0.001$, $P < 0.001$). Compared to non-severe patients, severe cases had longer duration from onset to discharge (median (IQR) = 23 (19−31) versus 32 (24.5−39.5) days) and performed more CT examinations (median (IQR) = 4 (4−5) versus 6 (4−6) scans).

Table 1
Characteristics of 305 patients with SARS-CoV-2/COVID-19 by status of progression to severe COVID-19.

Characteristics	Disease type			
	Non-severe	Severe	Total	P value
N (%)	238 (78.03)	67 (21.97)	305	
Age, year, Median (IQR)	43 (33–57)	57 (48–63)	49 (36–59)	<0.001
Male, N (%)	108 (45.38)	41(61.19)	149 (48.85)	0.03
Personal disease history, N (%)				
Hypertension	33 (13.87)	8 (11.94)	41 (13.44)	0.84
Cardiovascular diseases	14 (5.88)	10 (14.93)	24 (7.87)	0.03
Liver disease	21 (8.82)	10 (14.93)	31 (10.16)	0.17
Cancer	1 (0.42)	3 (4.48)	4 (1.31)	0.03
Initial symptoms, N (%)				
Fever	150 (63.03)	58 (86.57)	208 (68.2)	<0.001
Cough	82 (34.45)	32 (47.76)	114 (37.38)	0.06
Headache	7 (2.94)	0 (0)	7 (2.3)	0.35
Diarrhea	5 (2.1)	2 (2.99)	7 (2.3)	0.65
Sore throat	3 (1.26)	0 (0)	3 (0.98)	1.00
Nasal congestion	3 (1.26)	1 (1.49)	4 (1.31)	1.00
Laboratory investigations				
Red blood cell count, 10^12/L	4.67 (4.41–5.08)	4.58 (4.3–4.92)	4.66 (4.44–5)	0.24
Hemoglobin, g/L	137 (126.2–146.8)	138 (128–151)	137 (127–147)	0.52
White blood cell count,10^9/L	4.53 (3.59–5.64)	4.43 (3.68–5.63)	4.51 (3.6–5.64)	0.96
Platelet count,10^9/L	193 (157.2–237.5)	153 (130–185)	186 (150–226)	<0.001
Aspartate aminotransferase, U/L	26 (20–33)	31.2 (25.5–45.65)	27 (21–35)	<0.001
Gamma-glutamyl transpeptidase, U/L	22 (15–33)	33 (24.7–57.4)	24 (16–37)	<0.001
Alkaline phosphatase, U/L	62 (51.75–74)	58 (50–70)	61 (51–73)	0.19
Total bilirubin, μmol/L	11 (8.35–15.95)	10.7 (8.35–16.4)	10.9 (8.33–16)	0.82
Disease progression, days, Median (IQR)				
From onset to the first scan	5 (3–8)	5 (4–8)	5 (3–8)	0.35
Numbers of scans	4 (4–5)	6 (4–6)	5 (4–6)	<0.001
From onset to hospitalization	3 (1–6)	3 (2–5.5)	3 (1–6)	0.15
From onset to discharge	23 (19–31)	32 (24.5–39.5)	25 (20–33)	<0.001

IQR, interquartile range.

3.2. Pulmonary CT evaluation

A total of 1414 pulmonary CT images were obtained. Each non-severe patient had a mean of five (IQR, 4–6) CT scans, with an average of 5 days (IQR, 3–6 days). Each patient underwent at least five pulmonary CT scans, i.e., on the 5th day (IQR, 3–8 days), 10th day (IQR, 8–13 days), 15th day (IQR, 12–19 days), 20th day (IQR, 16–24 days) and 24th day (IQR, 21–29 days) after the onset of symptoms (Fig. 1).

The Transverse serial CT scans of COVID-19 patients were shown in supplement Fig. 1 and supplement Fig. 2. Based on total CT score detected at different time points, the trend of changes on total CT score from disease onset to hospital discharge in non-severe and severe

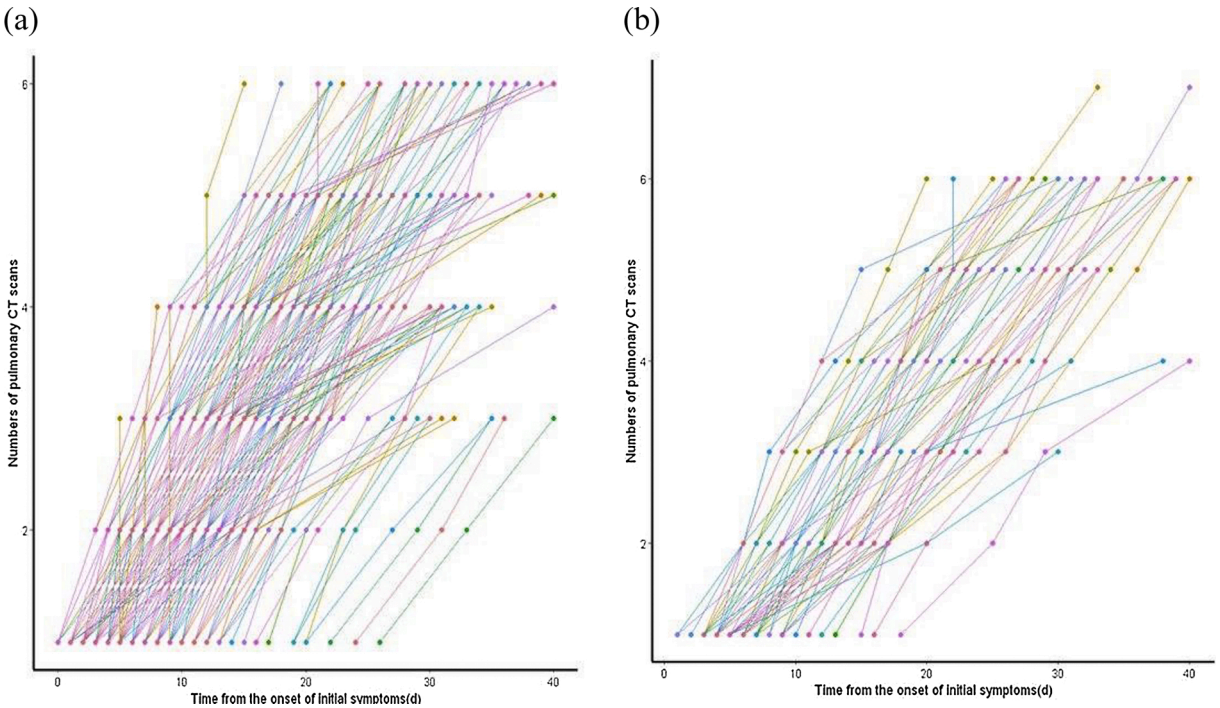

Fig. 1. Timeline of the pulmonary CT scans (a, non-severe patients; b, severe patients).

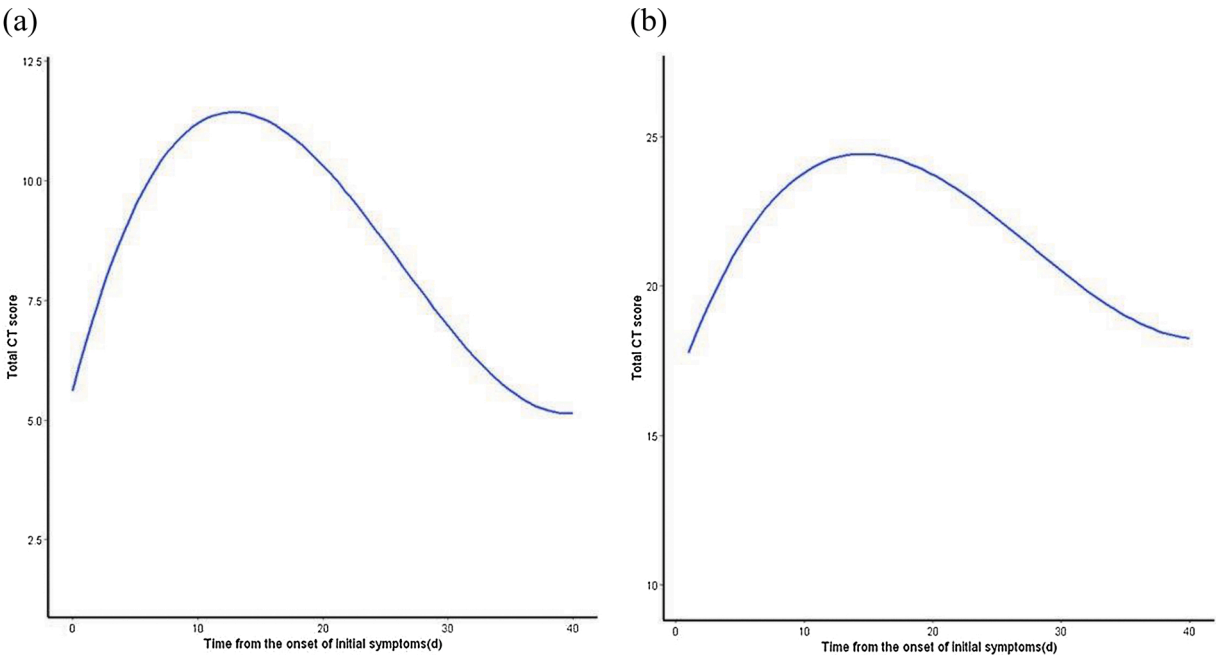

Fig. 2. Change in lung involvement on chest CT from time of onset of initial symptoms (a, non-severe patients; b, severe patients).

patients was described by fitting polynomial regression curves respectively. The total CT score peaked at approximately 13 days in non-severe patients and 15 days in severe patients from the onset of initial symptoms. After that there was a short plateau phase that followed a gradual decrease in abnormalities. The curve fitting equation of the total CT score for non-severe patients was as follows: $y = 0.0006*x^3-0.052*x^2+1.01x+5.62$, in which x refers to the time from the onset of the initial symptoms, while y refers to the total CT score of the pulmonary involvement; curve fitting equation for patients with severe COVID was: $y = 0.0006*x^3-0.056*x^2+1.22x+16.61$ (Fig. 2).

Table 2 shows that patients with severe disease had higher total scores in every CT scan and scores in each lobe than non-severe patients. More lung lobes were involved in severe patients ($P < 0.001$).Total CT scores for different CT scans were significantly higher in severe than non-severe patients ($P = 0.001$). A further pairwise comparison found that the total CT score of the second CT scan was significantly higher than that of the first one ($P = 0.03$). However, the CT score in each lobe showed no significant difference across the five scans (Table 2).

3.3. Imaging manifestation

For imaging manifestations, GGO was the most common characteristic among non-severe patients, while combined GGO and consolidation were typical in severe cases. Significant differences in imaging manifestation between these two groups were found (P from 0.001 to 0.003). The proportion of non-severe patients with combined GGO and

Table 2
The CT score of the pulmonary involvement in in four CT scans.

	Disease severity	Total CT score	Number of involved lobes	CT score in each lobe					
				Left upper lobe	Left middle lobe	Left lower lobe	Right upper lobe	Right middle lobe	Right lower lobe
The first scan (n = 305)	Non-severe	9 (4–14)	3 (1–4)	0 (0–2)	2 (0–2)	2 (0–3)	0 (0–2)	2 (0–2)	2 (0–4)
	Severe	18 (12–27)	5 (4–5)	2 (2–3.5)	2 (2–5)	3 (2–5)	2 (2–5)	3 (2–6)	3 (2–5)
	Total	11 (4–16)	4 (2–5)	2 (0–4)	2 (0–2)	0 (0–2)	0 (0–2)	2 (0–3)	2 (2–4)
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
The second scan (n = 305)	Non-severe	10 (4.25–16)	3 (2–4)	0 (0–2)	2 (0–2)	2 (0–4)	0 (0–2)	2 (0–3)	2 (0–4)
	Severe	24 (18–33)	5 (5–5)	3 (2–5)	4 (2–6)	5 (3–6)	4 (2–6)	4 (2.5–6)	5 (3–6)
	Total	12 (6–21)	4 (2–5)	2 (0–2)	2 (0–4)	2 (2–5)	2 (0–2)	2 (0–4)	3 (2–5)
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
The third scan (n = 305)	Non-severe	8 (4–14)	3 (2–4)	0 (0–2)	2 (0–2)	2 (0–3)	0 (0–2)	2 (0–2)	2 (0–3)
	Severe	22 (16–28.5)	5 (5–5)	3 (2–5)	4 (2–5)	5 (3–6)	4 (2–5)	4 (2.5–5)	5 (3–5)
	Total	10 (6–18)	4 (2–5)	2 (0–2)	2 (0–3)	2 (0–5)	2 (0–2)	2 (0–4)	2 (2–4)
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
The fourth scan (n = 253)	Non-severe	8 (4–13)	3 (2–4)	0 (0–2)	2 (0–2)	2 (0–3)	0 (0–2)	2 (0–2)	2 (0–3)
	Severe	21(14–30)	5 (5–5)	2 (2–5)	4 (2–5)	3 (2–5)	2.5 (2–5)	4 (2–5)	4 (2–5)
	Total	10 (5–17)	4 (2–5)	2 (0–2)	2 (0–3)	2 (0–3)	2 (0–2)	2 (0–3)	2 (2–4)
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
The fifth scan (n = 158)	Non-severe	9 (6–14)	3 (2–5)	0 (0–2)	2 (0–2)	2 (0–3)	0 (0–2)	2 (0–2)	2 (2–3)
	Severe	20 (12–26)	5 (5–5)	2 (2–4)	3 (2–5)	3 (2–5)	2 (2–5)	4 (2–5)	4 (2–5)
	Total	12 (6–17)	4 (2–5)	2 (0–2)	2 (0–3)	2 (2–3)	2 (0–2)	2 (2–3)	2 (2–4)
	P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Quantitative data were presented as median (IQR);

Table 3
Imaging manifestation of the pulmonary involvement in different pulmonary CT scans by disease severity.

	The first CT scan			The second CT scan			The third CT scan			The fourth CT scan			The fifth CT scan		
	Non-severe	Severe	P value	Non-severe	Severe	P value	Non-severe	Severe	P value	Non-severe	Severe	P value	Non-severe	Severe	P value
CT manifestation															
Combined GGO and consolidation	97 (40.76)	42 (62.69)		120 (50.42)	51 (76.12)	<0.001	101 (42.44)	52 (77.61)	<0.001	66 (34.2)	49 (81.67)	<0.001	39 (35.78)	34 (69.39)	<0.001
GGO	111 (46.64)	24 (35.82)	0.003	90 (37.82)	14 (20.9)		106 (44.54)	12 (17.91)		101 (52.33)	11 (18.33)		57 (52.29)	14 (28.57)	
Consolidation	8 (3.36)	0 (0)		11 (4.62)	2 (2.99)		9 (3.78)	2 (2.99)		8 (4.15)	0 (0)		4 (3.67)	1 (2.04)	
No change sign	22 (9.24)	1 (1.49)		17 (7.14)	0 (0)		22 (9.24)	1 (1.49)		18 (9.33)	0 (0)		9 (8.26)	0 (0)	
Fibrosis	59 (24.79)	22 (32.84)	0.25	83 (34.87)	37 (55.22)	0.004	95 (39.92)	46 (68.66)	<0.001	78 (40.41)	42 (70)	<0.001	47 (43.12)	30 (61.22)	0.05
Air bronchogram	33 (13.87)	34 (50.75)	<0.001	40 (16.81)	37 (55.22)	<0.001	27 (11.34)	31 (46.27)	<0.001	18 (9.33)	22 (36.67)	<0.001	8 (7.34)	17 (34.69)	<0.001
Bronchiectasis	8 (3.36)	2 (2.99)	1.00	9 (3.78)	2 (2.99)	1.00	10 (4.2)	4 (5.97)	0.52	8 (4.15)	4 (6.67)	0.49	5 (4.59)	4 (8.16)	0.46
Pleural effusion	7 (2.95)	2 (2.99)	1.00	7 (2.94)	2 (2.99)	1.00	6 (2.52)	2 (2.99)	0.69	5 (2.59)	2 (3.33)	0.67	4 (3.67)	2 (4.08)	1.00
Pericardial effusion	4 (1.68)	2 (2.99)	0.62	4 (1.68)	2 (2.99)	0.62	4 (1.68)	2 (2.99)	0.62	2 (1.04)	1 (1.67)	0.56	0 (0)	1 (2.04)	0.32

Quantitative data were presented as n (%); GGO, ground-glass opacities.

consolidation manifestation increased as the disease progressed, i.e., up to 50.42 % at day10 from disease onset, then decreased to 35.7 % at day 25. In patients with severe COVID-19, this proportion rose from 66.25 % at disease onset to 81.67 % at approximately day 20, then decreased to 69.39 % at approximately day 25, indicating that severe cases recovered more slowly than non-severe cases. In addition, patients with severe COVID-19 had higher prevalence of fibrosis and air bronchogram than non-severe patients (P from <0.001 to 0.05, P = 0.001, respectively). The prevalence of fibrosis and air bronchogram in severe cases started to decrease from the fifth and the third pulmonary CT scan, respectively (Table 3).

4. Discussion

To our knowledge, this study is the most comprehensive study to date describing the radiological characteristics on chest CT from initial diagnosis to recovery stage in COVID-19 patients admitted to a designated hospital in Shenzhen, China. Using the dynamic radiological data obtained from multiple chest CT scans (≥3 times) of 305 COVID-19 patients, we found that the number and severity of lesions in chest CT scans increased in the first 13 days in non-severe patients and in the first 15 days in severe patients. After that there was a short plateau phase that followed a gradual decrease in abnormalities. Patients with severe COVID had significantly higher total CT scores than that of non-severe patients. Significant differences in imaging manifestations between the severe and non-severe groups were found, with the most common imaging manifestation being GGO in non-severe patients and GGO mixed with consolidation in severe patients. The CT results suggested a slower recovery of COVID-19 in severe patients. Moreover, severe COVID-19 patients showed higher prevalence of fibrosis and air bronchogram than non-severe patients. Our findings suggest that periodic chest CT scans in COVID-19 patients (i.e., at least in a five-day interval during the first 13–15 days) is necessary and may provide useful information to guide clinical practice, especially allowing for more tailored therapies and holistic care models.

In this retrospective study, we found that the total lesion score of CT in severe patients was significantly higher than non-sever patients, which was consistent with previous studies showing that severe patients had a larger lung lesion area than non-severe cases [14–16]. This might be due to more severe bilateral pulmonary infiltrates at the peak of the disease in severe cases. Even though the clinical symptoms were improved gradually, severe patients required longer recovery. In addition, we found that the number and severity of lesions increased at the early stage of disease progression. After that there was a short plateau phase that followed a gradual decrease in abnormalities, indicating the infection rapidly aggravated after the onset of the initial symptoms, and the damage to the lung continued to reach the maximum degree even after the patients started to recover. Patients recovered from pulmonary abnormality since the infection was controlled and the consolidation was gradually absorbed, the affected area of the lung begins to decrease. Moreover, consistent with previous studies, we also found that typical CT image in non-severe COVID-19 patients was GGO, whilst GGO mixed with consolidation in severe patients [17,18]. The prevalence of GGO and/or consolidation manifestation in COVID-19 patients increased as the disease progressed, with severe cases generally recovered slower than non-severe cases.

In addition, there was a higher proportion of patients with severe COVID-19 experiencing fibrosis and air bronchogram [19,20]. An increasing trend in the prevalence of fibrosis occurrence in COVID-19 patients from admission to discharge was also observed and described in our study, which provides important information demonstrating the progress of fibrosis and lung damage. Moreover, irregular line was also a manifestation of pulmonary interstitial changes [21,22]. Thus, taking advantage of the dynamic CT results, radiologists could assess the disease progression more accurately, which would enable timely risk classification and effective clinical treatment.

This study has some limitations. First, as a retrospective study, all participants were enrolled from a single large city in China. Direct application of our findings to other settings, especially to the resource-limited regions, should be cautious. However, this study has provided the best available evidence to date showing the changes in chest CT radiography associated with COVID-19 from initial diagnosis until patient recovery. The second limitation lies in the lack of histopathological support in all cases. Further studies exploring the association between CT features and histopathological manifestations are needed. Finally, no data on CT scans after discharge was available, although it may be ethically unacceptable to perform CT examinations on the discharged patients.

In conclusion, most COVID-19 patients demonstrated the greatest severity of pulmonary damage on CT at approximately day 13 after initial onset of symptoms. Severe patients had higher degree of bilateral pulmonary infiltrates than non-severe patients, indicating continuous health care for pulmonary rehabilitation and consecutive follow-up to monitor irreversible fibrosis and consolidation are necessary.

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Declaration of Competing Interest

All authors declare no competing interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejro.2020.100305.

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