

Time correlation between serial RT-PCR results and serial chest CT imaging and serial CT changes of Coronavirus 2019 (COVID-19) Pneumonia: 155 cases study from China

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Abstract

Objective: To determine the CT role in the early detection of COVID-19 infection and serial CT changes in disease course in the patients with COVID-19 pneumonia.

Methods: From January 21 to February 18, 2020, all the patients who were suspected of novel coronavirus infection and verified by RT-PCR test were retrospectively enrolled in our study. All the patients underwent serial RT-PCR tests and serial CT imaging. The time correlation between serial RT-PCR results (negative conversion to positive, positive to negative) and serial CT imaging was investigated, and serial CT changes were evaluated.

Results: One hundred and fifty-five patients with confirmed COVID-19 pneumonia were evaluated. The time of chest CT detection of COVID-19 pneumonia was 2.61 days earlier than RT-PCR test ($p=0.000$). The time of lung CT improvement was significantly shorter than that of RT-PCR conversion to negative ($p=0.000$). Three stages were identified from the onset of the initial symptoms: Stage 1 (0-3 days); Stage 2 (4-7 days); and stage 3 (8-14 days and later). Ground glass opacity (GGO) was predominant on stage 1, then consolidation and crazy paving sign were dramatically increased on stage 2. On stage 3, fibrotic lesion was growing largely. There was significant difference for the main CT features ($p=0.000$), the number of involved lobes ($p=0.001$), and lesion distribution ($p=0.000$) among different stages.

Conclusion: Chest CT was earlier to detect COVID-19 pneumonia compared to RT-PCR results and monitor disease course. Combined imaging features with epidemiology history and clinical information could facilitate early diagnosis of COVID-19 pneumonia.

Key Points

1. The time of chest CT detection of COVID-19 pneumonia was 2.61 days earlier than that of initial RT-PCR positive result ($t=-7.31$, $p=0.000$).
2. The time of lung CT improvement was significantly shorter than that of RT-PCR conversion to negative ($t=-4.72$, $p=0.000$).
3. At the early stage (0-3 days), CT features of COVID-19 are predominantly GGO and small vessel thickening; At stage 2 (4-7 days), GGO evolves to consolidation and crazy paving sign. At stage 3 (8-14 days and later), fibrotic lesions was significantly increased, accompanying consolidation, GGO and crazy paving sign.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan Hubei province, China in December, 2019 (1). In the following weeks, infections spread rapidly across China and other countries around the world (2). Study showed COVID-19 had the feature of strong human-to-human transmission (2). China government has taken strict quarantine measures to contain the contagion and has acquired obvious effect. However, COVID-19 was rapidly spreading worldwide. On March 27, 2020, WHO reported more than half a million confirmed cases of COVID-19 and more than 20,000 deaths (3).

In order to spike extension of the disease, early identification of COVID-19 infection and immediately isolation of the patients is essential. Real time reverse transcription polymerase chain reaction (RT-PCR) was the reference standard to make a definite diagnosis of COVID-19 infection according to the guideline of Diagnosis and Treatment of Pneumonia caused by COVID-19 (trial third version) published by the National Health Commission of People's Republic of China (NHCPRC) (4), which is the key indicator for hospitalization. However, the high false negative rate (5) and lack of RT-PCR assay in the early stage of outbreak limited the prompt diagnosis of infected patients, which implied many COVID-19 patients were not detected and isolated timely. These patients were bound to become infection source to infect a large population due to the highly contagious nature of the virus.

Chest CT is a non-invasive imaging diagnostic tool of pneumonia, which is relatively easy to perform and can make fast diagnosis. This indicates chest CT plays a vital role in the early diagnosis of COVID-19 pneumonia. There are some literatures reporting the imaging features, including GGO (ground glass opacity), patchy consolidation, crazy paving sign (6-8). However, few literatures report the time difference in RT-PCR results and CT abnormality, and few literatures focus on the dynamic CT changes of COVID-19 pneumonia. In order to better understand the early diagnostic value of chest CT and the course of the disease, we investigated time correlation between serial RT-PCR results and serial CT imaging and serial CT changes in the patients with COVID-19 pneumonia.

Materials And Methods

Patient population and clinical arrangement

The institutional review board of our hospital approved this retrospective study and informed consent was waived. From January 21 to February 18, 2020, all the patients who were suspected of novel coronavirus infection and verified were retrospectively enrolled in our study. All the patients were confirmed by laboratory virus nucleic acid test (real-time fluorescence polymerase chain reaction revealed positive detection of COVID-19, RT-PCR assay with throat swab samples) according to the guideline of Diagnosis and Treatment of Pneumonia caused by COVID-19 (trial third version) published by the China government (4). COVID-19 infection was diagnosed as soon as any one of the nucleic acid test results was positive. Meanwhile the test, the chest CT imaging was performed to find whether pneumonia was present or not. After admitted to the hospital, all the patients underwent serial RT-PCR assays and serial chest CT imaging to provide evidences for treatment to the disease. The RT-PCR test was repeated every three to five days to monitor dynamic conversion of RT-PCR results (negative to positive, positive to negative). The RT-PCR results were reviewed in our hospital information system (HIS). We compared the differences of time point of both methods in suggesting the diagnosis of COVID-19 infection.

The RT-PCR assays were performed by using TaqMan One-step RT-PCR kits from Shanghai Huirui biotechnology CO., Ltd, which was approved by the China Food and Drug Administration (CFDA).

The chest CT protocol

The chest CT was carried out every 2 to 7 days to confirm the presence of pneumonia and monitor the changes of lung appearance according to the guideline of Diagnosis and Treatment of Pneumonia caused by COVID-19 (trial third version) published by the China government (4). All the images were acquired on 2 CT scanners (Brilliance iCT; Philips Healthcare, Cleveland, OH, USA and Aquilion 64, Toshiba, Japan) using the following parameters: tube voltage, 120 kVp; automatic tube current modulation, pitch, 0.76-1.22; matrix=512x512, field of view=400x400mm, and slice thickness, 5.0 mm. All the images were reconstructed with slice thickness of 1.0 mm with the same increment. Lung window and mediastinum window were simultaneously reconstructed.

Image interpretation and analysis

Chest imaging was analyzed by two radiologists, blinded to RT-PCR results. The epidemiological history and clinical symptoms were obtained when they reviewed the images. The time point of the first positive lung CT (after onset of the initial symptoms) and the serial CT features and changes subsequently were recorded.

The CT features of new coronavirus infected pneumonitis included ground-glass opacity (GGO), consolidation, crazy paving pattern (inter- or intra-lobular septal thickening superimposed on GGO), fibrotic lesion, air bronchogram sign, small vessel thickening and pleural effusion according to expert recommendation from the Chinese Society of Radiology (9). We divided CT findings into main features (GGO, consolidation, crazy paving pattern, fibrotic lesion) and secondary features (air bronchogram sign, small vessel thickening, pleural effusion). The number of involved lung lobes and the distribution of lung abnormality were also evaluated. The lesion distribution was classified into sub-pleural areas (predominantly the peripheral one-third of the lung involved), central areas, and sub-pleural plus central areas.

CT imaging progression presents as increasing number, size, extent and density of GGO, consolidation and crazy-paving pattern, or GGO evolving to consolidation and crazy-paving pattern (6,10,11). The smaller size, number, extent and density of these signs predict the COVID-19 pneumonia improvement (11-14). The relationship between RT-PCR results with chest imaging changes was analyzed.

Based on degree of lung involvement and CT findings, three stages were identified from the onset of the initial symptoms: Stage 1 (0-3 days); Stage 2 (4-7 days); and stage 3 (8-14 days and later).

Discharge criteria

The nucleic acid test and CT imaging were following-up to the time of discharge. According to the guideline of Diagnosis and Treatment of Pneumonia caused by COVID-19 (trial third version) published by the China government (4), the criteria of hospital discharge include follows: 1) body temperature returned to normal for at least 3 days; 2) Respiratory symptoms has been markedly improved; 3) Chest imaging has been distinctly improved; 4) Continuous RT-PCR assay with sputum, nasopharyngeal or throat swab samples converted to negative for 2 times interval at least 24 hours.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation and categorical variables were expressed as frequencies and percentages. T test was used to determine the difference in the time of RT-PCR first positive result and chest CT first positive findings (after onset of the initial symptoms), the time of RT-PCR conversion to negative and CT finding improvement (after onset of the initial symptoms). Chi-square test and Fisher's exact test were performed to compare the changes of CT features, number of involved lung lobes and lesion distribution on serial CT images. A two-tailed p value < 0.05 was considered statistically significant. All statistical analyses were conducted by SPSS version 21.0 (SPSS Inc. Chicago, IL)

Results

Study population

From January 21 to February 18, 2020, 155 consecutive patients confirmed COVID-19 pneumonia (87 males and 68 females aged from 9 months to 82 years, mean age 42.97 ± 14.85 years) were included in this study. All the patients had history of Wuhan exposure or close contact with the patients confirmed or highly suspected COVID-19 infection within two weeks before the onset of illness. The initial symptoms included fever, cough, chest distress, shortness of breath, fatigue and diarrhea. The initial laboratory examinations showed decreased Lymphocyte percentage and increased C-reactive protein and Erythrocyte sedimentation rate. The clinical data were summarized in Table 1. All the patients discharged due to reaching the discharged criteria and quarantined home continuously after a hospitalized period of 17.27 ± 5.68 days (range, 10-30 days).

The time comparison between serial RT-PCR results and chest CT findings

All the patients underwent 3 to 7 times of RT-PCR assays with time-interval of 3 to 5 days (average 4.5 days), and 4 to 6 times of chest CT scan with time-interval of 2 to 7 days (average 4.7 days). The interval between the initial RT-PCR and initial chest CT imaging was less than 1 day.

The initial time of nucleic acid test and lung CT scan, the initial time of RT-PCR positive result and lung CT abnormality, the time of RT-PCR conversion to negative and CT finding improvement (after onset of initial symptoms) were summarized in Table 2. There was no significant difference between the time of initial nucleic test and that of initial lung CT scan ($p > 0.05$). By comparing the time point of the first RT-PCR positive result and the time of positive imaging, the result showed significant difference between the two methods in detection of COVID-19 infection ($t = -7.31$, $p = 0.000$) with CT 2.61 days earlier than nucleic acid test. The time of lung CT improvement was significantly shorter than that of RT-PCR conversion to negative ($t = -4.72$, $p = 0.000$).

Serial chest CT images evaluation

Typical course of COVID-19 pneumonia was demonstrated on serial chest CT images (Fig1-3). The CT characteristics were summarized in Table 3. For the main CT features, GGO was predominant on stage 1, then consolidation and crazy paving sign were dramatically increased on stage 2. On stage 3, a stark change lied in fibrotic lesion growing largely, accompanying with existing consolidation and crazy paving sign (Fig4). There was significant difference for the main CT features among different stages ($\chi^2 = 219.00$, $p = 0.000$). For the comparison among groups, there was also significant difference between stage 1 and stage 2 ($\chi^2 = 155.98$, $p = 0.000$); stage1 and stage 3 ($\chi^2 = 186.45$, $p = 0.000$); stage 2 and stage 3 ($\chi^2 = 16.99$, $p = 0.001$).

For the secondary CT features, small vessel thickening was dominating on stage 1. Air bronchogram sign was gradually increased on stage 2 and 3. Pleural effusion was rare in the process of the disease (Fig5). There was significant difference for the secondary CT features among different stages ($\chi^2 = 48.58$, $p = 0.000$). For the comparison among groups, there was also significant difference between stage 1 and stage 2 ($\chi^2 = 23.87$, $p = 0.000$); stage1 and stage 3 ($\chi^2 = 48.10$, $p = 0.000$); but no difference between stage 2 and stage 3 ($\chi^2 = 3.70$, $p = 0.157$).

The changes of number involved lung lobes on serial CT scans were demonstrated in Fig6. For the number of involved lung lobes, there was significantly statistic difference among different stages ($\chi^2 = 29.30$, $p = 0.001$). For the comparison among groups, there was significantly statistic difference between stage 1 and stage 3 ($\chi^2 = 25.55$, $p = 0.000$), but no difference between stage 1 and stage 2 ($\chi^2 = 9.29$, $p = 0.098$), and between stage 2 and stage 3 ($\chi^2 = 8.55$, $p = 0.129$).

There was significantly statistic difference among different stages in lesion distribution ($\chi^2 = 50.99$, $p = 0.000$). For the comparison among groups, there was significant difference between stage 1 and stage 2 ($p = 0.000$), and between stage 1 and stage 3 ($p = 0.000$), but no difference between stage 2 and stage 3 ($\chi^2 = 0.841$, $p = 0.359$).

Discussion

In the present study, we evaluated the time correlation between serial RT-PCR results and serial chest CT findings and investigated lung imaging changes of COVID-19 pneumonia by the time. The major findings of the study were twofold: first, the time of initial chest CT abnormality was significantly shorter than that of initial RT-PCR positive result, the time of lung CT improvement shorter than that of RT-PCR conversion to negative; second, chest CT is a reliable, non-invasive, rapid tool to monitor the occurrence, deterioration and improvement of COVID-19 pneumonia.

The confirmation of COVID-19 infection was dependent on viral nucleic acid test by RT-PCR assay, which determined the patient hospitalization or quarantine home. But RT-PCR test had its distinct limitations due to its low sensitivity, insufficient stability, and relatively long processing time to get the results. Some scholars reported the positive rate of RT-PCR assay for throat swab samples was 30-60% (15, 16). A lot of factors can affect the RT-PCR results, including sampling operations, specimens source (upper or lower respiratory tract), sampling timing, and performance of detection kits (16). The recent study showed salivary viral load was highest during the first week after symptom onset (17), which could account for the fast spreading nature of this pandemic at the early stage. Those patients without timely isolation and therapy due to initial negative RT-PCR results, would definitely promote COVID-19 to spread.

Chest CT is a non-invasive, rapid, convenient imaging diagnostic tool and can detect mild lung abnormality at the early stage of COVID-19 pneumonia. Our study showed the time of initial chest CT abnormality (3.23 ± 3.04 days) was significantly shorter than that of initial RT-PCR positive result (5.84 ± 3.23 days). Therefore, CT plays a vital role in the early detection of COVID-19 pneumonia, especially for the patient with initial negative RT-PCR results. Of course, the specificity of CT in diagnosing COVID-19 pneumonia is low in spite of its high sensitivity. T.A et al (15) reported the sensitivity and specificity of chest CT in indicating COVID-19 infection were 97% and 25%, respectively. Although RT-PCR test is the gold standard for the diagnosis of COVID-19 infection, chest CT examination is essential for the early identification of the potential patients and helps determine the next measure. The COVID-19 infection has been currently upgraded from epidemic to pandemic disease by the World Health Organization (WHO) (18), chest CT will certainly play a crucial role in the early detection of the disease and contain the pandemic spread.

Our study also found the time of lung CT improvement (11.58 ± 4.59 days) was significantly shorter than that of RT-PCR conversion to negative (14.38 ± 5.78 days). This indicates CT is very useful to monitor the course of COVID-19 pneumonia and direct the clinician to adjust the therapeutic strategy.

In our study, dynamic serial chest CT examination (4-6 times) with relatively big patient population provided us reliable data to observe the disease course. We divided the disease into 3 stages according to the time since the onset of the initial symptoms. At the early stage, CT features of COVID-19 are predominantly GGO and small vessel thickening. GGO is the main CT feature, and small vessel thickening is the secondary feature. With the disease progression, GGO evolves to consolidation. In the process of progression, crazy paving sign is also markedly enhanced. At stage 2, air bronchogram sign is also dramatically increased as secondary sign of consolidation. Small vessel thickening is still abundant as the secondary sign of GGO and consolidation. We also noticed fibrotic lesions were gradually added, which represents reparative process. At stage 3, a prominent feature lay in fibrotic lesions significantly increased, accompanying more consolidation, GGO and crazy paving sign. This indicates reparative and progressive process of COVID-19 pneumonia simultaneously and various CT features coexist at stage 3. Our study demonstrated the time of lung improvement was 11.58 ± 4.59 days. The lung CT appearance may be consistent with the pathology. The autopsy and histological examination of COVID-19 pneumonia showed bilateral diffuse alveolar damage with proteinaceous exudate, cellular fibromyxoid exudate, pulmonary edema, reactive hyperplasia of pneumocytes, desquamation of pneumocyte, hyaline membrane formation, fibroblastic plugs in airspaces and interstitial mononuclear inflammatory infiltration (19, 20), which may be accord with the appearance of GGO, consolidation and crazy paving sign. Tian et al pointed out patchy pneumocyte hyperplasia and interstitial thickening indicating an ongoing reparative process at the early stage of COVID-19 pneumonia (20). Notably, when the patients met the discharge criteria, there was still patchy consolidation left in the lung. Could this explain that RT-PCR test converted to positive again for the individual cases after leaving hospital? A larger-scale investigation is required for a full validation. Anyway, this phenomenon suggests that the arrangement is reasonable for patients quarantining home for another period (two weeks in China) after discharge.

Our study also showed typical COVID-19 pneumonia started as unilateral or bilateral sub-pleural GGO, then evolved to consolidation, which involved sub-pleural and central areas. Our study also found 12.9% patients showed normal chest CT images at the early stage. Then the number of involved lung lobes was increased at the stage 2. However, the number of involved lung lobes was still more at the stage 3 and had no significant difference compared to that of stage 2. Residual GGO, scattered consolidation and sub-pleural parenchymal bands still existed at the stage 3. So the patients still need to be followed up after hospital discharge.

There are several limitations in the present study. First, this is a retrospective study in a short time, and long term radiological follow up is needed to supervise the pulmonary outcome due to the novel coronavirus infection. Second, this study lacks of more severe COVID-19 pneumonia patients (including respiratory failure needing mechanical ventilation, shock, multiple organ failure needing ICU care) (4), so for those patients the changes of CT findings need to be investigated in next study. Third, the radiation dose of CT scans was not evaluated, but it is more important to detect the infected patients, understand the disease course, manage the patients and contain the pandemic.

In conclusion, chest CT is playing a vital role in the early detection of COVID-19 pneumonia, monitoring lesion progression and improvement. It is earlier to show lung abnormality than the time of initial positive nucleic acid test with RT-PCR in the detection of COVID-19 infection. It is also earlier to demonstrate lung improvement than the time of RT-PCR conversion to negative. Chest CT should be considered as a screening of COVID-19, especially under circumstance of pandemic worldwide.

Abbreviations

1. RT-PCR: reverse transcription polymerase chain reaction
2. COVID-19: Coronavirus disease 2019
3. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
4. GGO: Ground glass opacity

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Tables

Table 1 Clinical characteristics of the patients with COVID-19 infection (n=155)

characteristics	results
Initial symptoms	
fever	121 (78.06%)
cough	87 (56.13%)
Chest distress and shortness of breath	25 (16.13%)
fatigue	83 (53.55%)
diarrhea	15 (9.68%)
Laboratory examination	
White blood cell count (G/L)	5.34±1.99 (3.34-7.29)
Neutrophil Count (G/L)	3.58±1.53 (1.72-5.41)
Neutrophil percentage (%)	67.7±8.55 (58.3-78.2)
Lymphocyte Count (G/L)	1.41±0.30 (0.84-2.38)
Lymphocyte percentage (%)	19.18±7.86 (8.5-30.8)
C-reactive protein (mg/L)	25.78±25.04 (1.3-76.3)
Erythrocyte sedimentation rate (s)	22.58±21.5 (3-65)

Table 2 Time comparison between serial RT-PCR results and serial lung CT findings (after onset of initial symptoms)

	Time (days)	t	p
Initial RT-PCR test	2.63±1.28	-0.90	0.38
Initial chest CT	2.29±1.30		
Initial RT-PCR positive	5.84±3.23	-7.31	0.000
Initial chest CT abnormality	3.23±3.04		
RT-PCR conversion to negative	14.38±5.78	-4.72	0.000
lung CT improvement	11.58±4.59		

Table 3 Changes of CT features, involved lung lobes and lesion distribution of different stages

CT features	Stage 1 (0-3days, n=155)	Stage 2 (4-7days, n=155)	Stage 3 (8-14days and later, n=155)
Main signs			
GGO	98[63.2%]	50[32.3%]	70[45.2%]
Consolidation	3[1.9%]	109[70.3%]	122[78.7%]
Crazy paving pattern	10[6.5%]	50[32.3%]	94[60.6%]
Fibrotic lesion	3[1.9%]	35[22.6%]	98[63.2%]
Secondary signs			
Air bronchogram sign	10[6.5%]	43[27.7%]	81[52.3%]
Small vessel thickening	90[58.1%]	70[45.2%]	83[53.5%]
Pleural effusion	3[1.9%]	3[1.9%]	3[1.9%]
Number of involved lobes			
0	20[12.9%]	8[5.2%]	5[3.2%]
1	8[5.2%]	5[3.2%]	5[3.2%]
2	17[11.0%]	12[7.7%]	6[3.9%]
3	28[18.1%]	30[19.4%]	18[11.6%]
4	39[25.2%]	42[27.1%]	58[37.4%]
5	43[27.7%]	58[37.4%]	63[40.6%]
Distribution of abnormality			
Sub-pleural areas	135[87.1%]	120[77.4%]	116[74.8%]
Sub-pleural and central areas	0	27 (17.4%)	34[21.9%]
Central areas	0	0	0

Figures

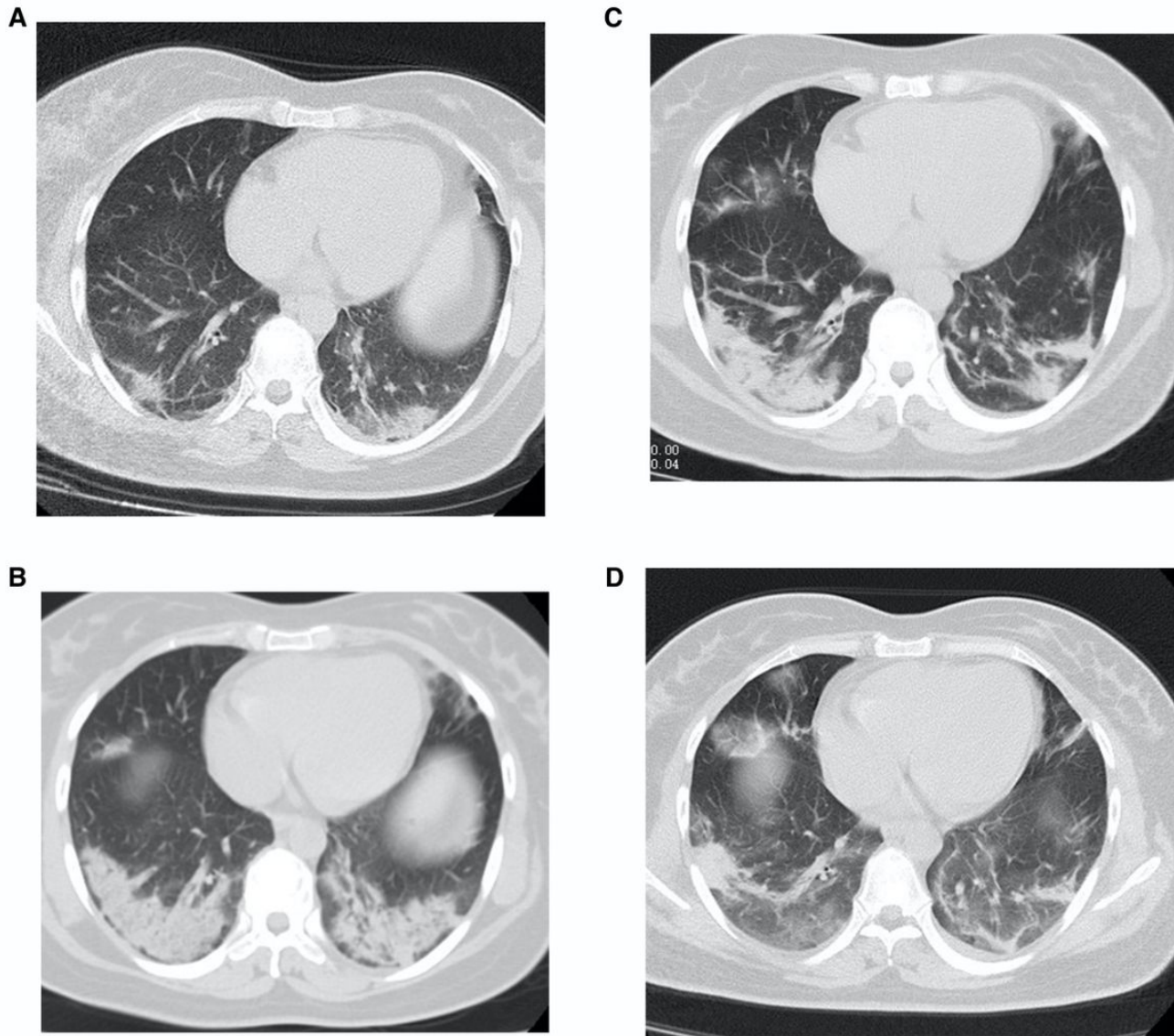


Figure 1

A 42 year-old female patient presented with fever for 2 days. (A) The baseline CT scan (2 days after initial symptom), obtained 2 days before the first positive RT-PCR test, showed discrete GGO and consolidation in bilateral lower lobes. (B) The follow-up CT 2 days later (day 4) showed enlarged patchy consolidation in bilateral lower lobes, accompanying with air bronchogram sign. New GGO was detected in right middle lobe and left lingular segment. (C) The follow-up CT 5 days later (day 9) obtained, 2 days before RT-PCR converting to negative, showed the size of consolidation decreased. (D) Another 3 days later (day 12) CT scan demonstrated lesions were further reduced in size and fibrotic lesions were predominant.

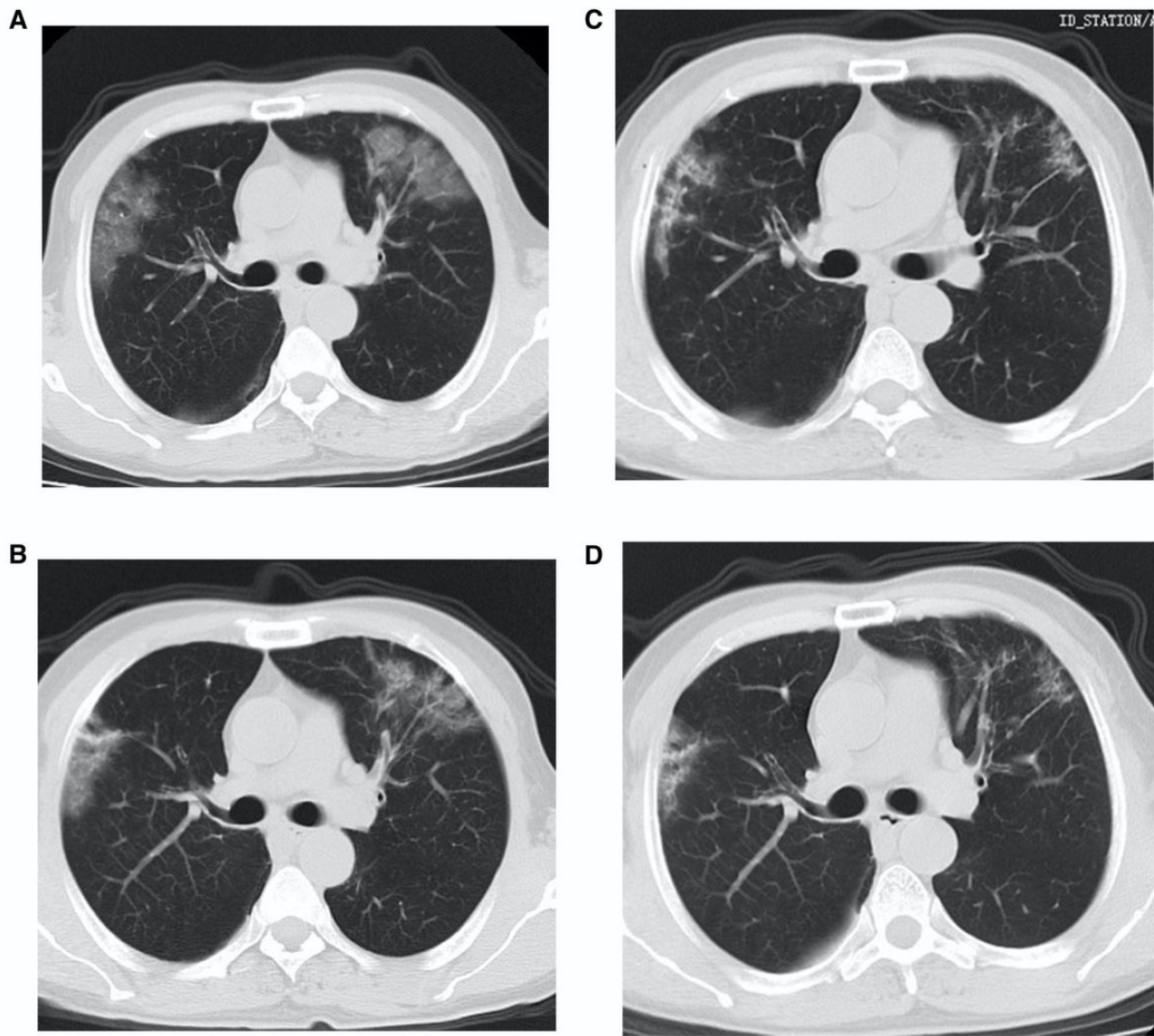


Figure 2

A 56 year-old male patient presented with fever and cough for 2 days. (A) The baseline CT scan (day 2) obtained 5 days before the first positive RT-PCR test showed discrete GGO in bilateral upper lobes and right lower lobe. Small vessel thickening was detected in the lesion of left upper lobe. (B) The follow-up CT 3 days later (day 5) showed the size of GGO was slightly reduced in bilateral upper lobes. (C) The follow-up CT 4 days later (day 9) obtained, 2 days before RT-PCR converting to negative, showed the size of lesion further decreased. (D) Another 4 days later (day 13) CT scan demonstrated lesions were further improved and fibrotic lesion was predominant.

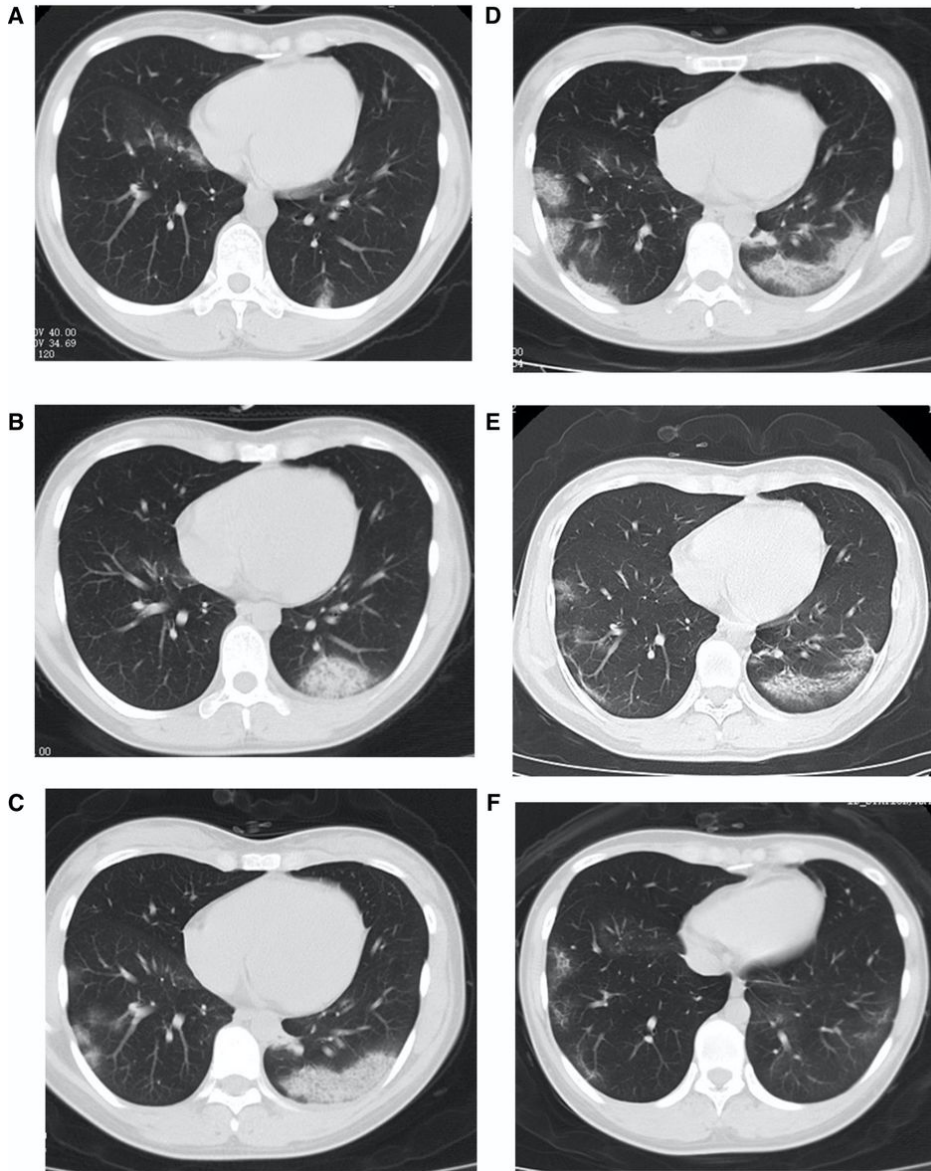


Figure 3

A 26 year-old female patient presented with fever for 1 day. (A) The baseline CT scan (day 1) obtained 3 days before the first positive RT-PCR test showed discrete GGO in bilateral lower lobes. (B) The follow-up CT 2 days later (day 3) showed the size of GGO was markedly enlarged in the left lower lobe, accompanying with small vessel thickening. (C) The follow-up CT 3 days later (day 6) obtained showed the lesions were progressive to consolidation in the left lower lobes and new GGO was identified in the right lower lobe. Crazy paving sign was detected in the left lower lobe. (D) Another 3 days later (day 9) the CT scan showed lesion progression in the right lower lobe, accompanying with crazy paving sign. (E) The follow-up CT scan 3 days later (day 12), 3 days before RT-PCR converting to negative, showed the size of lesion decreased, fibrotic lesion was predominant in the right lower lobe and crazy paving sign dominant in the left lower lesion. (F) Another 3 days later (day 15) CT scan demonstrated lesions were further improved and fibrotic lesion left.

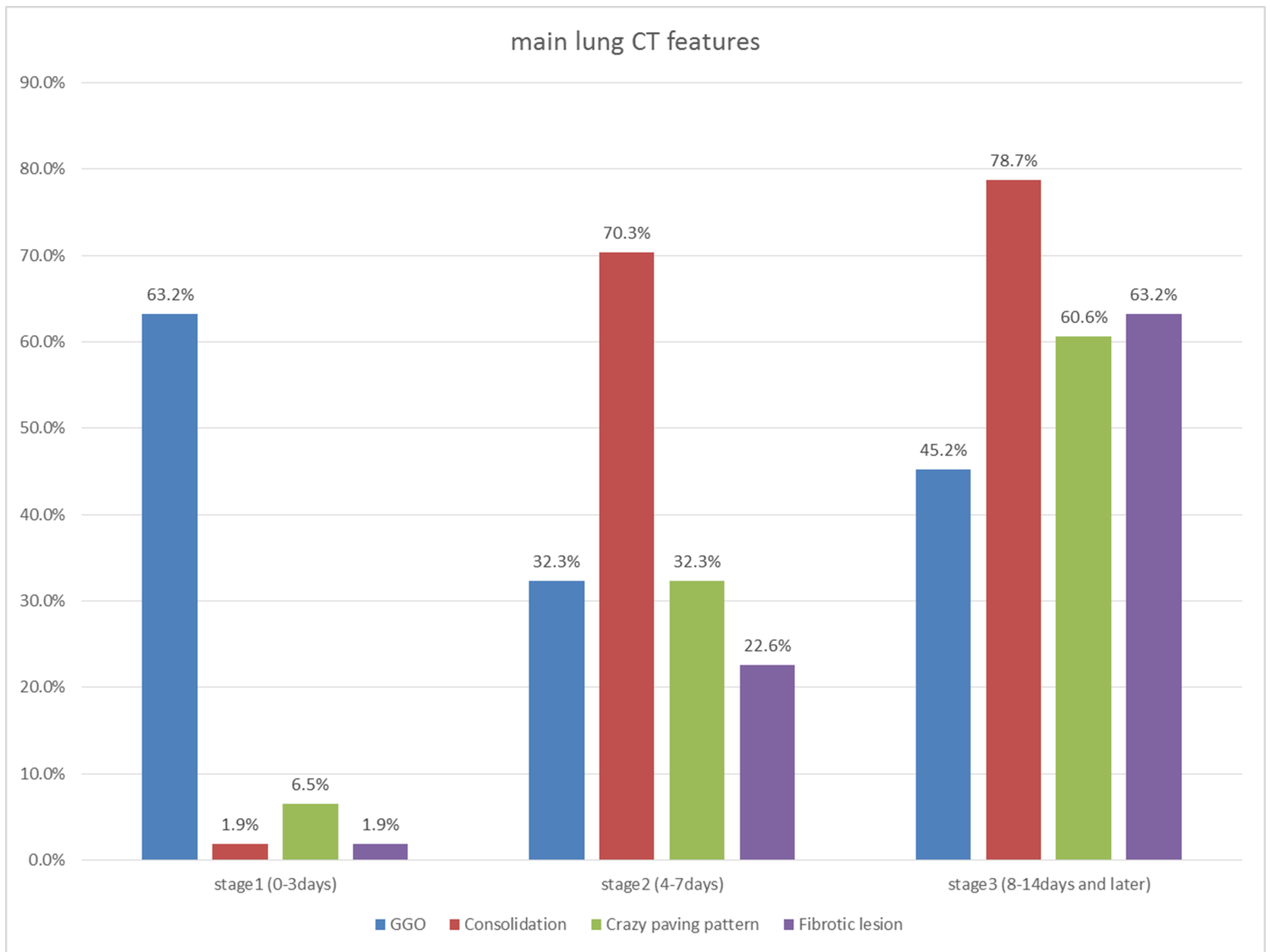


Figure 4

main lung image features changes on serial CT scans

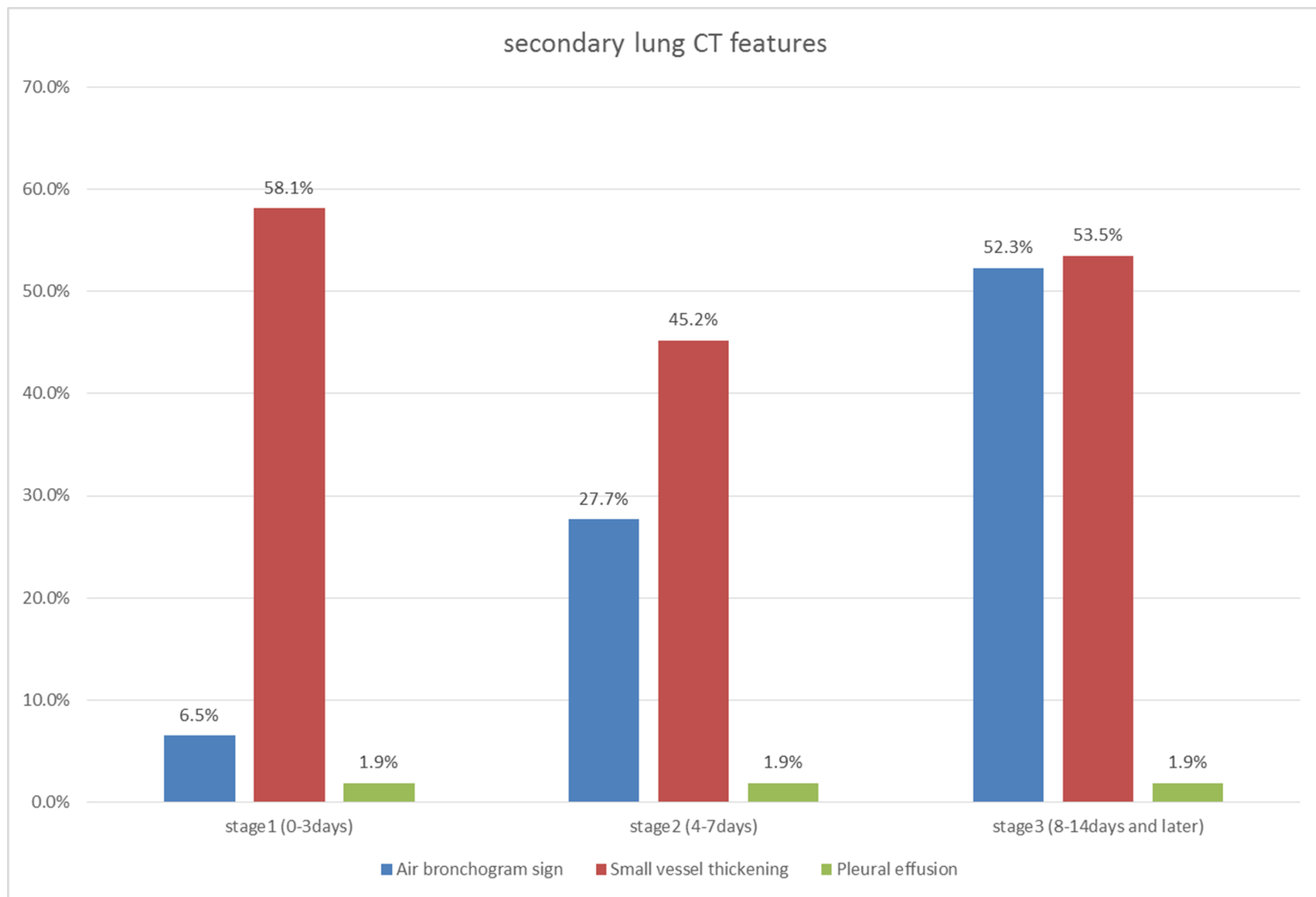


Figure 5

secondary lung image features changes on serial CT scans

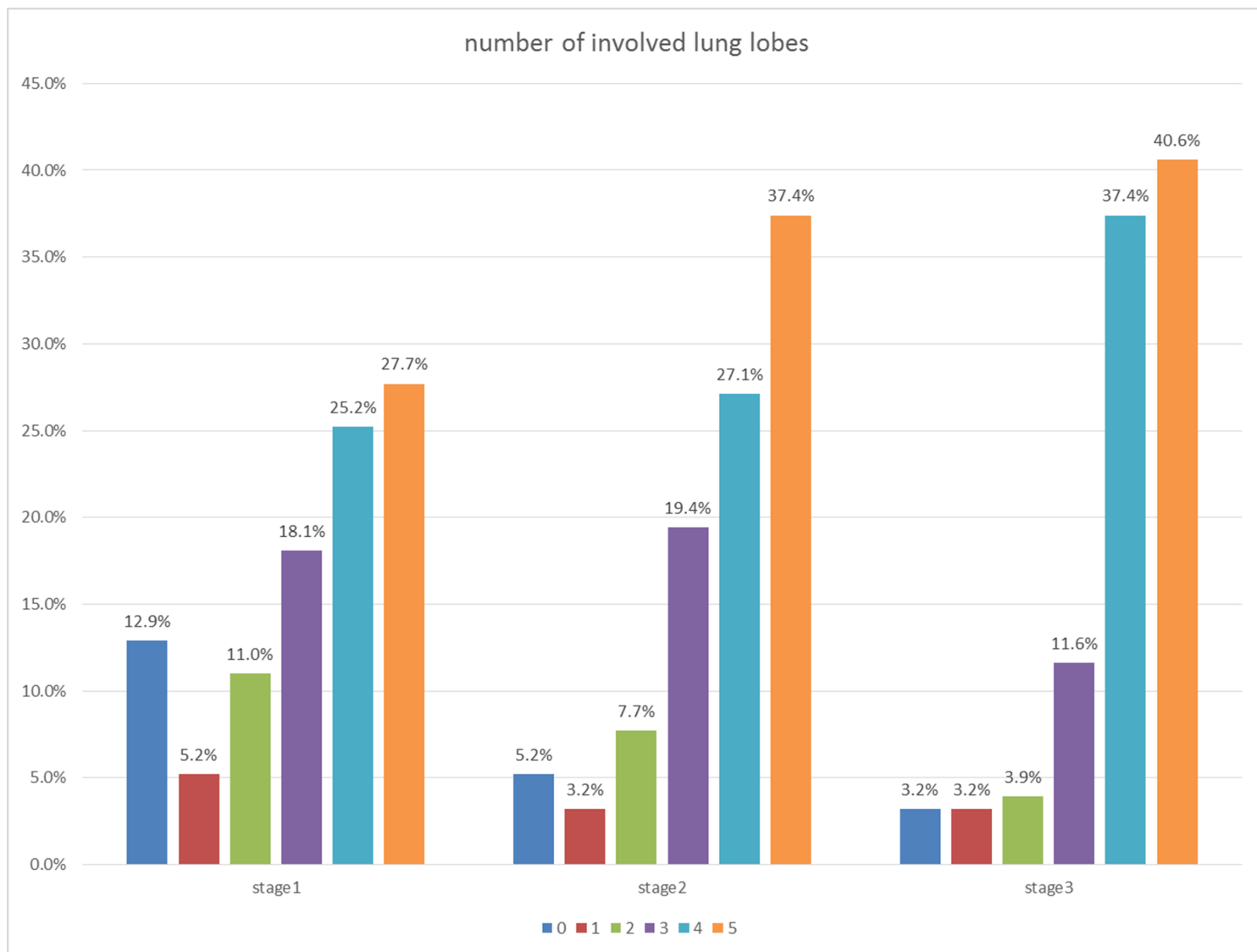


Figure 6

number of involved lung lobes at different stages