Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Differential diagnosis between the coronavirus disease 2019 and *Streptococcus pneumoniae* pneumonia by thin-slice CT features

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ABSTRACT

Objective: The chest computed tomography (CT) features of coronavirus disease 2019 (COVID-19) and *Streptococcus pneumoniae* pneumonia (*S. pneumoniae* pneumonia) were compared to provide further evidence for the differential imaging diagnosis of patients with these two types of pneumonia.

Methods: Clinical information and chest CT data of 149 COVID-19 patients between January 9, 2020 and March 15, 2020 and 97 patients with *S. pneumoniae* pneumonia between January 23, 2011 and March 18, 2020 in Zhongnan Hospital of Wuhan University were retrospectively analyzed. In addition, CT features were comparatively analyzed.

Results: According to the chest CT images, the probability of lung segmental and lobar pneumonia in *S. pneumoniae* pneumonia was higher than that in COVID-19($P<0.001$); the probabilities of ground-glass opacity (GGO), the "crazy paving" sign, and abnormally thickened interlobular septa in COVID-19 were higher than those in *S. pneumoniae* pneumonia($P=0.005$, $P<0.001$, $P<0.001$, respectively); and the probabilities of consolidation lesions, bronchial wall thickening, centrilobular nodules, and pleural effusion in *S. pneumoniae* pneumonia were higher than those in COVID-19 ($P<0.001$, $P=0.001$, $P=0.003$, $P=0.001$, respectively).

Conclusion: The findings of GGO, the crazy paving sign, and abnormally thickened interlobular septa on chest CT were significantly higher in COVID-19 than *S. pneumoniae* pneumonia. The most important differential points on chest CT signs between COVID-19 and *S. pneumoniae* pneumonia were whether disease lesions were distributed in entire lung lobes and segments and whether the crazy paving sign, interlobular septal thickening, and consolidation lesions were found.

1. Introduction

The coronavirus disease 2019 (COVID-19) appeared in Wuhan, Hubei, China in December 2019 and became an outbreak in China. COVID-19 infections have also appeared in other countries worldwide. On January 30, 2020, the International Health Regulations and Emergency Committees of the World Health Organization (WHO) announced that the COVID-19 outbreak is a public health emergency of international concern. On February 11, 2020, WHO named this disease COVID-19.

The virus that causes this outbreak is a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. It is an RNA virus that shares 88% sequence homology with two coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21) found in bats, 79% homology with the SARS coronavirus (SARS-CoV), and 50% homology with the Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. Current epidemiological observation indicates that transmission routes of COVID-19 mainly include respiratory droplets and close contact. Aerosol transmission is possible only after long-term exposure to high-concentration aerosol in a relatively closed environment. It can also be transmitted through the fecal–oral route [3–5]. Extensive human-to-human transmission is obvious, and there are cluster infections within families and medical staff [5]. The main manifestations of COVID-19 are fever (83%), cough (82%), dyspnea (31%), and myalgia; less commonly runny nose, sore throat, and diarrhea; and acute respiratory distress syndrome(17%–29%) [1,4].

Streptococcus pneumoniae (*S. pneumoniae*) is an opportunistic extracellular Gram-positive bacterium that usually colonizes the mucosa of

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the human upper respiratory organs. *S. pneumoniae* can cause many diseases, including diseases that have mild symptoms but are common, such as otitis media, sinusitis, and bacterial pneumonia, as well as severe invasive pneumococcal diseases (IPD) such as bacteremia and meningitis. *S. pneumoniae* is the most common pathogen in community-acquired pneumonia (CAP) and it is also the major pathogen in nosocomial pneumonia [6,7]. Because the incidence and mortality of CAP among elderly people are both high, *S. pneumoniae* pneumonia has always been a focus of attention. The main symptoms are mostly fever and cough as well as dyspnea and shortness of breath.

Although COVID-19 and *S. pneumoniae* pneumonia are characterized by pulmonary inflammation caused by different pathogens, they have similar clinical symptoms and incidence rates. The incidence of COVID-19 seems to be higher in older men and patients with comorbidities. Particularly when the reverse transcription–polymerase chain reaction (RT-PCR) detection result is negative, there are some difficulties in distinguishing between COVID-19 and *S. pneumoniae* pneumonia. Furthermore, although COVID-19 is somewhat under control in China, the number of COVID-19 patients worldwide still shows an increasing trend. Therefore, there are many reports on chest computed tomography (CT) findings of COVID-19 [8–10]. However, there is no report on differentiation of chest CT findings between COVID-19 patients and patients with *S. pneumoniae* pneumonia. Thus, this study retrospectively analyzed chest CT findings in COVID-19 patients and compared them with chest CT findings in patients with *S. pneumoniae* pneumonia in order to describe CT features which are more common in patients with COVID-19 when compared to patients with *S. pneumoniae* pneumonia, and which may aid in differentiating these two entities clinically.

2. Materials and methods

2.1. Patient population

Clinical information and chest CT data of 151 consecutive COVID-19 patients between January 9, 2020 and March 15, 2020 and 103 consecutive patients with *S. pneumoniae* pneumonia between January 23, 2011 and March 18, 2020 in the Zhongnan Hospital of Wuhan University were collected. The inclusion criterion of COVID-19 was conformity to the *Diagnosis and Treatment of COVID-19 (revised edition of the provisional 7th edition)* which is the guideline of the National Health Commission of the People's Republic of China [11]. So we included patients having the history of contacting epidemic areas or patients, in the meanwhile, these patients had positive COVID-19 microbiology and serology and abnormal CT findings. The inclusion criteria of *S. pneumoniae* pneumonia was *S. pneumoniae* infection confirmed by blood culture or bronchoalveolar lavage (BAL), and we also found disease lesions in CT examination. Eight pneumonia patients who had poor CT image quality were excluded, including two COVID-19 patients and six patients with *S. pneumoniae* pneumonia.

This study finally enrolled 149 COVID-19 patients and 97 patients with *S. pneumoniae* pneumonia. Of them, 237 patients had fever, 197 had cough, 85 had sore throat, 216 had fatigue, 124 had dyspnea, 25 had diarrhea, and five had no symptoms. Among 149 COVID-19 patients, there were 95 men and 54 women, the age ranged from 19 to 80 years, the average age was 52.7 years old, 135 patients had low leukocytes, 14 had normal leukocytes, 130 had low lymphocyte count, and 145 had elevated C-reactive protein (CRP). Among the 97 patients with *S. pneumoniae* pneumonia, there were 58 men and 39 women, the age ranged from 18 to 87 years old, the average age was 67.9 years, 93 patients had high leukocytes, 77 had high neutrophils, and 95 had high CRP.

2.2. CT examination

The GE discovery, Philips Ingenuity, and Siemens Somatom Sensation spiral CT scanners were used. Patients took a supine position, and scanning was performed at the end of inspiration using the conventional dose. The scanning range was from the apex of the lung to the costophrenic angle, the slice thickness was 1.25 mm, the tube voltage was 120 kV, and the tube current was 100 mA.

The collected thin-slice CT images were assessed by two radiologists who had work experience in chest imaging at least 5 years together by considering the distribution features and image features of disease foci in COVID-19 and *S. pneumoniae* pneumonia.

Table 1
Chest CT findings and corresponding interpretation criteria.

CT findings	Interpretation criteria
Ground-glass opacity	Hazy increased lung opacity without obscuration of vascular markings
Crazy Paving sign	Interlobular septal thickening in a groushadownd glass background
Consolidation	Increased lung opacity with obscuration of vascular markings
Pleural effusion	Water density opacity in chest
Cavity	Gas density with walls
Centrilobular nodules	Solid or ground glass density in the center of pulmonary lobule, size below 10 mm
Lymph node enlargement	The mediastinal lymph node enlargement, short diameter greater than 10 mm
Abnormally thickened interlobular septa	Interlobular septal thicken abnormally

Table 2
Distribution of COVID-19 and *Streptococcus pneumoniae*.

Distribution	COVID-19 ($n = 149$)	*Streptococcus pneumoniae* ($n = 97$)	*P*-value
Lobe and segmental pattern	40(26.8)	61(62.9)	<0.001
Non-lobe and non-segmental pattern	109(73.2)	36(37.1)	<0.001
Bilateral lung involvement	106(71.1)	59(60.8)	0.098
Unilateral single lung involvement	31(20.8)	24(24.8)	0.532
Unilateral multilobar lung involvement	12(8.1)	14(14.4)	0.138

Data in parentheses are percentages.
COVID-19 = coronavirus disease 2019.

2.3. Image interpretation

The combination of the high-resolution algorithm and the standard algorithm and the multiplane reconstruction and the maximum-intensity-projection reconstruction methods were used for image processing. Before reviewing images, neither doctor knew the blood culture, BAL fluid, or real-time RT-PCR results. The final diagnosis was agreed upon by both doctors.

Analysis of distribution features of disease foci mainly included whether the disease foci showed distribution in entire lobes or segments and which lung lobes were involved. According to the involved lung lobes, foci were classified into bilateral lung lobe involvement, unilateral single-lobe involvement, and unilateral multilobe involvement.

Image analysis was mainly performed using the pulmonary window and the mediastinal window. The ground-glass opacity (GGO), consolidation lesions, "crazy paving" sign, bronchial wall thickening, abnormally thickened interlobular septa, centrilobular nodules, and cavitary lung lesions were analyzed using pulmonary windows. The mediastinal lymph node enlargement and pleural effusion were analyzed using mediastinal windows [12,13]. The specific image signs and analysis criteria are shown in Table 1.

Table 3
Chest CT findings for COVID-19 and Streptococcus pneumoniae.

CT findings	COVID-19 (n = 149)	Streptococcus pneumoniae (n = 97)	P-value
Ground-glass opacity	138(92.6)	78(80.4)	0.005
Crazy paving sign	40(26.8)	4(4.1)	<0.001
Consolidation	58(39.0)	80(82.4)	<0.001
Bronchial wall thickening	46(30.9)	51(52.6)	0.001
Pleural effusion	3(2.0)	13(13.8)	0.001
Cavity	0(0.0)	0(0.0)	NS
Centrilobular nodules	34(22.8)	40(41.2)	0.003
Lymphadenopathy	0(0.0)	8(8.2)	NS
Abnormally thickened interlobular septa	123(82.6)	10(10.3)	<0.001

NS, not significant.
Data in parentheses are percentages.
COVID-19 = coronavirus disease 2019.

2.4. Statistical analysis

Statistical analysis was performed with SPSS 22.0 software. Categorical data were compared using Fisher's exact test. All *P* values were from the two-sided tests. $P < 0.05$ indicated a significant difference.

3. Results

3.1. Distribution of disease foci

From the chest CT data of all 246 enrolled pneumonia patients, the distribution features of disease foci are analyzed and summarized in Table 2. The bilateral lung, unilateral single lung, and unilateral multilobar lung distributions of disease foci between COVID-19 and *S. pneumoniae* pneumonia did not have significant differences (P>0.05). *S. pneumoniae* pneumonia mainly had a segmental pneumonia, with a probability of 62.9%, which was higher than the 26.8% probability for COVID-19 (P<0.001). COVID-19 disease foci had a significantly higher probability of non-lobe and non-segment pneumonia than *S. pneumoniae* pneumonia (P<0.001).

3.2. CT features

Table 3 summarizes the chest CT features of all 246 pneumonia patients, including 149 COVID-19 patients and 97 patients with *S. pneumoniae* pneumonia. The features included GGO, consolidation lesions, bronchial wall thickening, abnormally thickened interlobular septa, centrilobular nodules, cavitary lung lesions, pleural effusion, and mediastinal lymph node enlargement.

The findings of GGO, crazy paving sign, and abnormally thickened interlobular septa on chest CT in COVID-19 were higher than those in *S. pneumoniae* pneumonia ($P = 0.005$, P<0.001, P<0.001, respectively). The findings of consolidation lesions, bronchial wall thickening, centrilobular nodules, and pleural effusion on chest CT in *S. pneumoniae* pneumonia were higher than those in COVID-19 (P<0.001, $P = 0.001$, $P = 0.003$, $P = 0.001$, respectively).

There was no patient with cavitary lung lesions on chest CT among the 246 pneumonia patients in this study. Mediastinal lymph node enlargement on chest CT was not seen in the 149 COVID-19 patients, and only 8/97 (8.2%) patients with *S. pneumoniae* pneumonia had lymph node enlargement. Therefore, the CT features of cavitary lung lesions and mediastinal lymph node enlargement did not have significant differences between the two types of pneumonia patients.

4. Discussion

Since the COVID-19 outbreak in China in December 2019, over 200 countries in the world have reported COVID-19 cases in four months. By the end of May 2020, there were more than 6 million confirmed cases worldwide. The world is in short supply of protective goods, and health care systems are under severe strain. A study of clinical symptoms of 41 COVID-19 patients showed that the major symptoms at disease onset were fever, cough, muscle soreness and fatigue [1]. Laboratory examinations usually can demonstrate normal or reduced peripheral leukocytes and lymphocytes in the early stage. Most patients have high CRP and erythrocyte sedimentation rate. The final diagnosis of COVID-19 is confirmed by nucleic acid detection. Viral nucleic acid can be detected in respiratory tract specimens (such as sputum), blood, blood swabs, and feces.

Most *S. pneumoniae* pneumonia patients have high leukocyte and neutrophil counts. Microbiological study or BAL fluid (yield ≥103 cfu/mL) sampling to analyze lung tissues may be the gold standard for the diagnosis of *S. pneumoniae* pneumonia, but they both have very high invasiveness and cannot be routinely used in clinical practice. Clinically, if *S. pneumoniae* can be isolated from the blood or pleural fluid of pneumonia patients, the diagnosis of *S. pneumoniae* pneumonia can be confirmed [14]. Positive microscopic examinations and culture of high-quality sputum specimens provide powerful evidence of *S. pneumoniae* pneumonia [15].

CT is convenient, easy, and fast imaging modality for the variable pneumonia. Chest CT examination has high value in diagnosing COVID-19 or *S. pneumoniae* pneumonia and assessing the treatment effect. Although the *Diagnosis and Treatment of COVID-19 (the provisional 7th edition)* already abolished the use of typical CT findings as independent criteria for the clinical diagnosis of suspected cases in Hubei Province, many scholars reported that abnormalities might be found in the chest CT of some patients with negative viral nucleic acid detection results [16–18]. Currently, CT examinations were performed in radiology suites, which lead to a gathering of patients and their families, increasing the risk of infection. Likewise, radiologists were at high risk of exposure to COVID-19. Imaging indications for COVID-19 were analyzed by physicians in 10 countries [19]. The first is the initial management of suspected patients with clinical symptoms of COVID-19 without detection conditions of PR-PCR. The second is the classification of patients with moderate or severe COVID-19. The third is that in regions with a large number of patients, CT examinations facilitated the triage of patients and relieved the pressure on the medical system. Therefore, chest thin-slice CT still has an important role in differential diagnosis of suspected and confirmed COVID-19 patients, monitoring the diagnosis and treatment process, and determining the prognosis.

Before this study, many studies have reported the distributions of disease foci and image presentations of COVID-19 [20–22], but there is no report on differentiation of chest CT findings between COVID-19 patients and patients with *S. pneumoniae* pneumonia. With regard to the CT findings of COVID-19, Wu et al. [20] have reported 80 COVID-19 patients, finding that the common chest CT findings of COVID-19 were GGO, consolidation and abnormally thickened interlobular septa in both lungs. Xu et al. [21] found that pleural effusion, pericardial effusion, and lymphadenopathy were uncommon findings and the probabilities of GGO, abnormally thickened interlobular septa and the crazy paving sign were basically consistent with the findings of this study. Xu et al. [22] enrolled 41 COVID-19 patients and reported the CT findings of GGO, pleural effusion, consolidation and abnormally thickened interlobular septa.

COVID-19 is one type of viral pneumonia. It mainly has lung airspace and interstitial involvement and causes bilateral lung lesions. In addition, the disease foci show a non-lobular and non-segmental distribution and mainly have a subpleural distribution. The typical image presentations are GGO, abnormally thickened interlobular septa, and the crazy paving sign. SARS-CoV-2 and SARS-CoV are highly homologous and have similar image presentations. Combining our findings with the pathology and imaging features of severe acute respiratory syndrome (SARS) and COVID-19 published by Ketai et al. and Muller et al. [23,24], we can infer the following: the GGO that develops in the early stage of COVID-19 might be mainly caused by alveolar and interstitial edema or

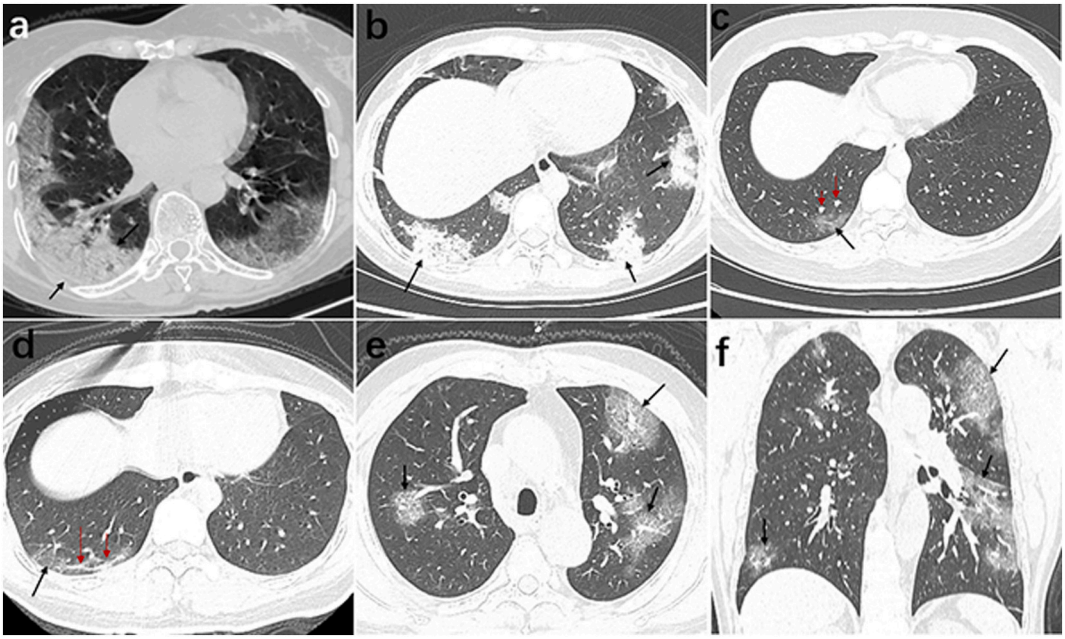

Fig. 1. Various CT features of COVID-19. (a) Axial CT image of the right lower lobe shows consolidation (arrows) along the subpleural area, and the right middle lobe and left lower lobe show GGO. (b) Axial CT image of the bilateral lower lobes show consolidation (arrows) along the subpleural area. (c) Axial CT image of the right lower lobe shows GGO (black arrow) with the surrounding blood vessels thickening (white arrows). (d) Axial CT image of the right lower lobe shows GGO (black arrow) with the subpleural curvilinear lines (white arrows). (e) Axial CT image of bilateral lung show abnormally thickened interlobular septa (arrows). (f) A coronal CT image of bilateral lung lobes show GGO in different size and crazy-paving appearance (arrows).

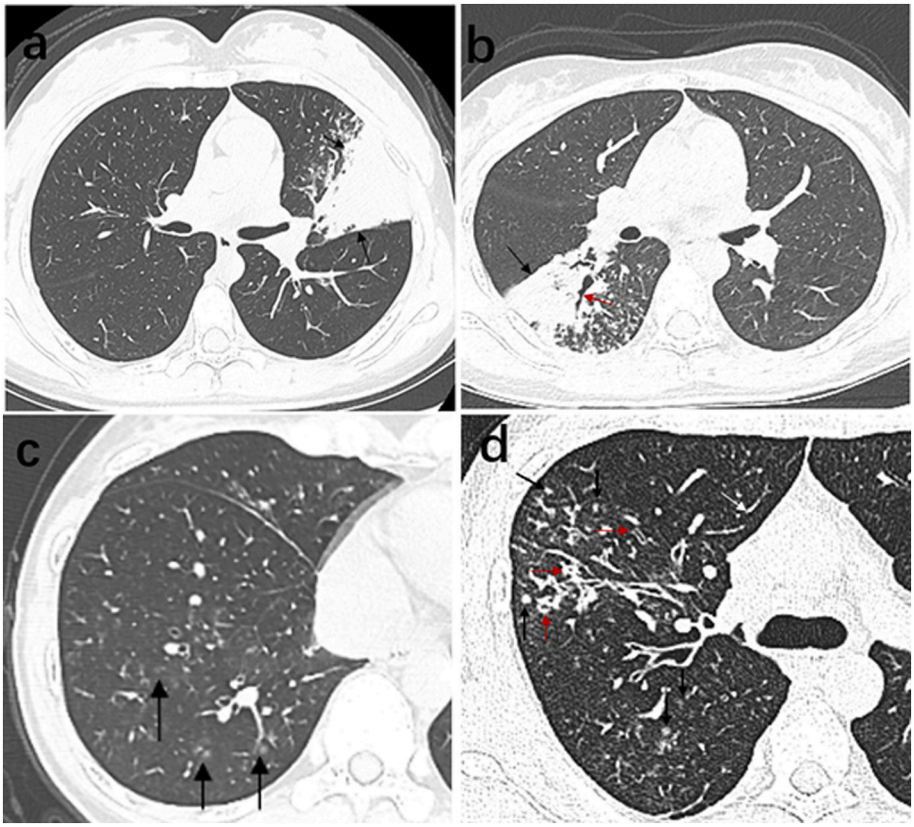

Fig. 2. Various CT features of *Streptococcus pneumoniae* pneumonia. (a) Axial CT image of right middle lobe shows wedge-shaped consolidation (arrows) (b) Axial CT image of left upper lobe shows wedge-shaped consolidation (white arrow) with air bronchogram (black arrow) in the consolidation. (c) Axial CT image of right middle and lower lobe show centrilobular ground-glass nodules and part-solid nodules distributing along the bronchovascular bundle (arrows). (d) Axial CT image of right upper lobe shows centrilobular nodules (black arrows) and bronchial wall thickening (white arrows).

alveolar hypoventilation. With the disease progression, viruses continue to spread to peripheral lung lobules and epithelium. The involved areas extend to form disease foci with a non-lobular or non-segmental distribution. In the advanced or severe stage, viruses already invade the alveolar parenchyma, and the alveolar wall collapses, leading to lung consolidation lesions (Fig. 1a, b). The GGO is the most common (Fig. 1c,

d). When GGO and abnormally thickened interlobular septa are present together, the crazy paving sign also appears (Fig. 1e, f). Mediastinal lymph node enlargement, cavitary lung lesions, and pleural effusion are rare in COVID-19.

Previous CT findings of *Streptococcus pneumoniae* pneumonia [25–27] were consistent with the findings of consolidation, bronchial wall thickening, pleural effusion and central lobular nodules in this study. *S. pneumoniae* pneumonia occurs in lung parenchyma. Most cases present lobar pneumonia, some cases present bronchopneumonia, and disease foci mainly show the lung lobe and segment distribution. Because the major presentations are consolidation lesions, centrilobular nodules, and bronchial wall thickening, there are more inflammatory secretions in the bronchus and alveolar cavity after *S. pneumoniae* infection. Therefore, the probability of consolidation lesions on chest CT is high. Consolidation lesions mainly show a lung lobular or segmental distribution (Fig. 2a, b), with inflated bronchi inside (Fig. 2b). CT images of *S. pneumoniae* pneumonia patients also show solid or ground-glass nodules that can travel along the bronchovascular bundles (Fig. 2c, d).

The pathogens of COVID-19 and *S. pneumoniae* pneumonia are SARS-CoV-2 and *S. pneumoniae*, respectively. *S. pneumoniae* is a Gram-positive bacterium, and the drugs for *S. pneumoniae* pneumonia are mainly antibiotics, such as β-lactams (penicillins and cephalosporins), quinolones, and macrocyclic lipids [28–31]. SARS-CoV-2 is a novel coronavirus for which vaccines and specific medicines have not been developed. The *Diagnosis and Treatment of COVID-19 (the provisional 6th edition)* mentioned using α-interferon combined with antiviral drugs, such as lopinavir, for treatment and avoiding blind or inappropriate use of antimicrobial agents [11,32]. Therefore, differential diagnosis of these two types of pneumonia will be significant for disease treatment and patient recovery.

Since the issuance of the *Diagnosis and Treatment of COVID-19 (first edition)* by the National Health Commission of People's Republic of China on January 15, 2020, it has been updated to the 6th edition in little more than a month, which shows the difficulty of COVID-19 diagnosis and treatment. Furthermore, the time of this writing is the season with a high incidence of respiratory diseases, and there are many CAP patients. However, whether it is *S. pneumoniae* pneumonia or COVID-19, the final diagnosis is achieved through nucleic acid detection. In some COVID-19 patients with positive CT findings, their nucleic acid detection results are not supportive, and they can even be contradictory [33]. Therefore, in the COVID-19 outbreak, familiarity with the CT signs of COVID-19 and its differential diagnosis from *S. pneumoniae* pneumonia not only can provide powerful imaging evidence for diagnosis but also can screen the patients who have symptoms but do not receive timely nucleic acid detection. Suspected patients should be isolated for treatment as soon as possible to avoid disease progression into severe illness, which is conducive to controlling the development of the disease and alleviating the shortage of medical resources.

There are some limitations in our study. Because of time and sample-size constraints, dynamic imaging data of COVID-19 and *S. pneumoniae* pneumonia after treatment were not analyzed in this study, which could be included in future studies.

In summary, the findings of GGO, the crazy paving sign, and abnormally thickened interlobular septa on chest CT were higher in COVID-19 than *S. pneumoniae* pneumonia in this study, whereas the findings of consolidation lesions, bronchial wall thickening, pleural effusion, and centrilobular nodule on chest CT were lower in COVID-19 than *S. pneumoniae* pneumonia. In addition, disease foci in *S. pneumoniae* pneumonia mainly showed a lung lobular and segmental distribution. The most important differential points were whether the disease foci had the CT features of lung lobular and segmental distribution, the crazy paving sign, abnormally thickened interlobular septa, and consolidation lesions.

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