Can Chest CT Features Distinguish Patients With Negative From Those With Positive Initial RT-PCR Results for Coronavirus Disease (COVID-19)?

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OBJECTIVE. The purpose of this study was to explore the value of CT in the diagnosis of coronavirus disease (COVID-19) pneumonia, especially for patients who have negative initial results of reverse transcription–polymerase chain reaction (RT-PCR) testing.

MATERIALS AND METHODS. Patients with COVID-19 pneumonia from January 19, 2020, to February 20, 2020, were included. All patients underwent chest CT and swab RT-PCR tests within 3 days. Patients were divided into groups with negative (seven patients) and positive (14 patients) initial RT-PCR results. The imaging findings in both groups were recorded and compared.

RESULTS. Twenty-one patients with symptoms (nine men, 12 women; age range, 26–90 years) were evaluated. Most of the COVID-19 lesions were located in multiple lobes (67%) in both lungs (72%) in our study. The main CT features were ground-glass opacity (95%) and consolidation (72%) with a subpleural distribution (100%). Otherwise, 33% of patients had other lesions around the bronchovascular bundle. The other CT features included air bronchogram (57%), vascular enlargement (67%), interlobular septal thickening (62%), and pleural effusions (19%). Compared with that in the group with positive initial RT-PCR results, CT of the group with negative initial RT-PCR results was less likely to show pulmonary consolidation ($p < 0.05$).

CONCLUSION. The less pulmonary consolidation found at CT, the greater is the possibility of negative initial RT-PCR results. Chest CT is important in the screening of patients in whom disease is clinically suspected, especially those who have negative initial RT-PCR results.

Keywords: coronavirus disease, COVID-19, CT, pneumonia, reverse transcription–polymerase chain reaction, RT-PCR

doi.org/10.2214/AJR.20.23012

Received February 26, 2020; accepted after revision April 3, 2020.

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AJR 2020; 215:1–5

ISSN-L 0361–803X/20/2155–1

On December 31, 2019, the World Health Organization (WHO) was alerted to several cases of a respiratory illness of unknown causation emerging from Wuhan, China, and rapidly spreading elsewhere in China and abroad. As of March 25, 2020, there were more than 81,000 confirmed cases and more than 3200 deaths attributed to this illness in China. Analysis of bronchoalveolar lavage fluid samples and electron microscopy revealed the culprit to be a coronavirus, a virus with a characteristic crownlike shape due to the presence of viral spike peplomers emanating from the viral envelope. On January 12, 2020, WHO temporarily named the virus 2019 novel coronavirus (2019-n-CoV) [1]. On February 10, 2020, the International Committee on Taxonomy of Viruses and WHO officially named the new coronavirus and the resulting illness severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19) [2, 3].

COVID-19 pneumonia is a new disease outbreak with potentially far-reaching public health ramifications first found in Wuhan, China, on December 30, 2019, by the Wuhan Municipal Health Commission [4]. According to current diagnostic criteria, laboratory examinations, such as swab tests, have become a standard and formative assessment for the diagnosis of SARS-CoV-2 infection [5]. Some patients with suspected COVID-19 pneumonia may have the virus detected by means of reverse transcription–polymerase chain reaction (RT-PCR) testing of the respiratory tract. However, RT-PCR is subject to false-negative results because it can easily be affected by multiple factors, such as insufficient cellular material for detection and improper extraction of nucleic acids from clinical materials. On February 8, 2020, the China National Health Commission released the guidance Diagnosis and Treatment of Pneumonitis Caused by New Coronavirus (trial version 5, revision) [6], which defined the clinical diagnostic criteria for Hubei Province as imaging characteristics of pneumonia. The commission also noted that high-resolution CT is an important element in the diagnosis of COVID-19 pneumonia. After this guidance was instituted, the number of new cases in Hubei had increased by 14,840 on February 13, 2020, which indicated that CT had a higher detection rate in patients with disease in the incubation period, especially for those with negative initial RT-PCR results. This finding showed that CT is helpful for early diagnosis, timely isolation, and treatment of COVID-19 pneumonia.

The primary purpose of this study was to describe CT in a group of 21 patients with SARS-CoV-2 infection in Guangzhou, China, especially those with negative initial RT-PCR results with highly suspected COVID-19 pneumonia.

Materials and Methods

Study Population

This retrospective study received institutional review board approval, and the requirement for informed consent was waived. To avert any potential breaches of confidentiality, no link between the patients and the researchers was made available. From January 19, 2020, to February 20, 2020, the admission data of 21 patients with confirmed COVID-19 pneumonia from five nonspecialized infectious disease hospitals in Guangzhou, China, were obtained. The five hospitals are located in four districts of Guangzhou (13 cases in Huadu, four cases in Baiyun, three cases in Yuexiu, and one case in Nansha). All 21 patients had positive final RT-PCR results for SARS-CoV-2 in laboratory testing of respiratory secretions obtained by nasopharyngeal or oropharyngeal swab. On the basis of the initial RT-PCR results, these patients were divided into two groups: seven patients with negative initial results (who were found to have positive results after a second RT-PCR test 2 days later) and 14 patients with initial positive results.

The 21 patients' clinical and laboratory data were collected retrospectively, specifically including clinical symptoms, WBC counts, lymphocyte counts, C-reactive protein level, and erythrocyte sedimentation rate. An epidemiologic history of being in Wuhan or exposure to a person with the infection was also recorded.

CT Image Data Acquisition

All 21 patients underwent CT on the same day that the initial mouth swab tests were performed. Chest CT was performed with the patients in the supine position during end-inspiration without IV contrast administration. Nine patients were evaluated with a Somatom Definition AS CT scanner (Siemens Healthineers) at 1.5-mm slice thickness, 120-kV tube voltage, and 100- to 200-mAs tube current–exposure time product. Four patients underwent 16-MDCT (Somatom Emotion scanner, Siemens Healthineers) at 1-mm slice thickness, 120 kV, and 100–200 mAs. Four patients underwent CT with an Optima CT 520 Pro scanner (GE Healthcare) at 1-mm slice thickness, 120 kV, and 200–300 mAs. Three patients underwent 16-MDCT (Aquilion scanner, Toshiba) at 2-mm slice thickness, 120 kV, and 100–300 mAs. The last patient underwent CT with a Brilliance 64-MDCT scanner (Philips Healthcare) at 1-mm slice thickness, 120 kV, and 100–200 mAs.

CT Image Evaluation

Two experienced thoracic radiologists (5 years of experience) blinded to the clinical data and RT-PCR results reviewed the CT images independently at a PACS workstation. The final decisions were reached by consensus of the two radiologists. If there was disagreement between them, a third fellowship-trained thoracic radiologist with 10 years of experience adjudicated the final decision. All of the unenhanced CT images were evaluated in preset standard pulmonary (width, 1500–2000 HU; level, –450 to 600 HU) and mediastinal (width, 400 HU; level, 60 HU) windows. The following CT characteristics of the lesions were evaluated: distribution (left or right lung, single or multiple lobes, subpleural or peribronchial), attenuation (ground-glass opacities, consolidation), air bronchogram, vascular enlargement, interlobular septal thickening, mediastinal lymph adenopathy (defined as lymph node size ≥ 10 mm in short-axis dimension), pleural effusion, and pulmonary fibrosis.

Statistical Analysis

Statistical analyses were performed with SPSS software (version 21.0, IBM). The categoric variables of CT characteristics were expressed as cases and compared by Pearson chi-square test between the group with negative initial RT-PCR results and the group with positive initial RT-PCR results. A value of $p < 0.05$ was considered significant.

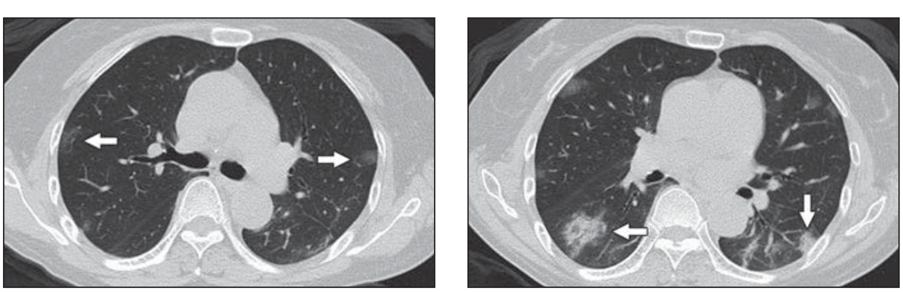
Results

Patient Characteristics

This study included 21 patients (nine men, 12 women; mean age, 49.7 ± 15.7 [SD] years; range, 26–90 years). Nineteen (90%) patients had a history of exposure to a person with SARS-CoV-2 infection or had been to Wuhan. The mechanism of exposure of the other two patients was unknown. Blood counts at admission showed that 10 of the 21 (48%) patients had leukopenia (WBC count, $< 4 \times 10^9$/L) and four patients (19%) had lymphopenia (lymphocyte count, $< 1.0 \times 10^9$/L). C-reactive protein levels were above the normal range in 14 (67%) and erythrocyte sedimentation rates were elevated in six (29%) patients. Common symptoms were fever (13 patients [62%]), cough (eight patients [38%]), and headache (five patients [24%]).

Chest CT Features

The 21 chest CT examinations showed that lesions were bilateral in 15 (71%) patients, in the left lung in three (14%) patients, and in the right lung in three (14%) patients. Most of the lesions (14 [67%]) were located in multiple lobes, and the other seven (33%) in a single lobe, with the lower lobe being involved most often (17 [81%]). Twenty patients (95%) had ground-glass opacities (Fig. 1), and 15 (71%) had consolidation (Fig. 2). All 21 patients (100%) had lesions in the subpleural area, and seven (33%) also had lesions around the bronchovascular bundle (Figs. 2A, 3C, and 4A). Other CT findings included air bronchogram



A B

Fig. 1—63-year-old woman who had traveled to Wuhan and had positive initial reverse transcription–polymerase chain reaction result.
A, Axial thin-section unenhanced CT scan shows bilateral multifocal lesions with ground-glass opacities (*arrows*) in subpleural region of upper lobes.
B, Axial thin-section unenhanced CT scan shows multiple bilateral areas of ground-glass opacities and consolidation (*arrows*) within subpleural distribution.

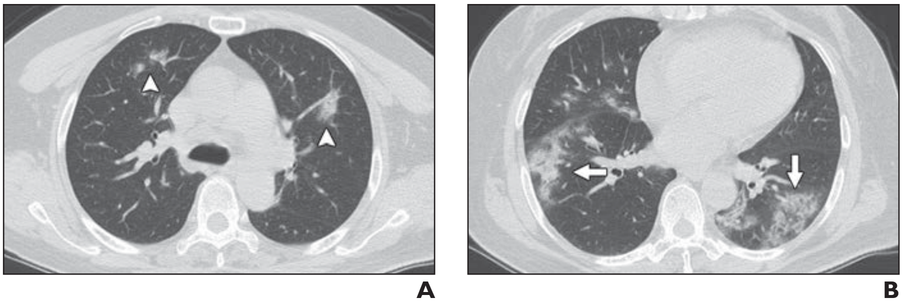


Fig. 2—66-year-old woman without epidemiologic history with positive initial reverse transcription–polymerase chain reaction result.
A, Axial unenhanced thin-section CT scan shows bilateral multifocal consolidations (*arrowheads*) around bronchovascular bundle in upper lobes.
B, Axial unenhanced thin-section CT scan shows multiple bilateral consolidations (*arrows*) with ground-glass opacities in subpleural region of lower lobes.

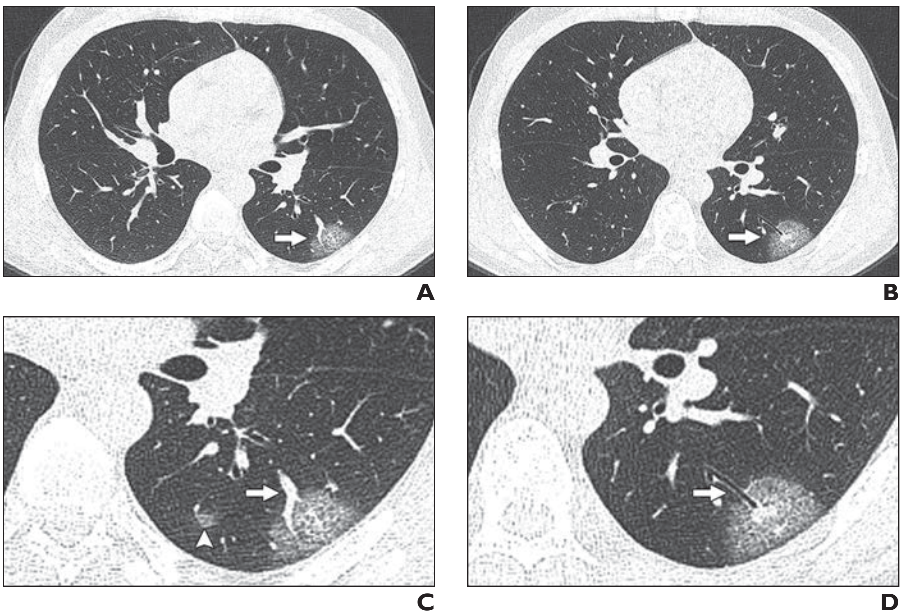


Fig. 3—28-year-old man who had worked in Wuhan and had negative initial reverse transcription–polymerase chain reaction results.
A, Axial unenhanced thin-section CT scan shows ground-glass opacities with subpleural distribution in lower lobes of left lung and thickened interlobular septa, presenting as typical crazy paving pattern. Enlarged vessel extends into lesion (*arrow*).
B, Axial unenhanced thin-section CT scan shows air-filled bronchus extending into lesion (*arrow*).
C, Enlarged view of lesion in **A** shows clear signs of vascular enlargement (*arrow*) and crazy paving pattern. Another small lesion appears as ground-glass opacity (*arrowhead*) around bronchus.
D, Enlarged view of lesion in **B** clearly shows air bronchogram (*arrow*).

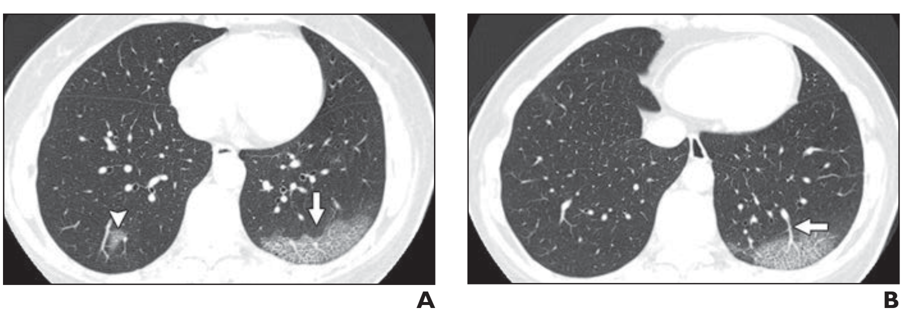


Fig. 4—55-year-old woman who had been in Wuhan and had negative initial reverse transcription–polymerase chain reaction results.
A, Axial unenhanced thin-section CT scan shows lesion (*arrow*) in subpleural region of left lower lung with attenuation of ground-glass opacities, with thickened interlobular septa presenting as typical crazy paving pattern. Ground-glass opacities in right lower lung indicate another small lesion (*arrowhead*) around bronchus.
B, Axial unenhanced thin-section CT scan shows vascular enlargement. (*arrow*).

($n = 12$, 57%) (Figs. 3B and 3D), vascular enlargement ($n = 14$, 67%) (Figs. 3A, 3C, and 4B), and interlobular septal thickening ($n = 13$, 62%) (Figs. 3A, 3C, and 4A). Only four (19%) patients had pleural effusion. No patient had lymphadenopathy or pulmonary fibrosis.

Identification Value of CT Features Between Negative and Positive Initial RT-PCR Result Groups

Seven (33%) patients had negative RT-PCR results at the first test but positive results at the second testing; the other 14 (67%) patients had positive initial RT-PCR results. The CT scans of the group with positive initial RT-PCR results had more consolidation lesions than did those in the group with negative initial RT-PCR results ($p = 0.04$). The unilateral versus bilateral distribution patterns of lesions in the lungs and involvement of single versus multiple lobes were not significantly different between the two groups, nor were the other CT findings—ground-glass opacities, air bronchogram, vascular enlargement, and interlobular septal thickening (Table 1).

Discussion

The RT-PCR test is considered the standard for the diagnosis of COVID-19, but in some cases it can have false-negative results in the early stages of the disease. CT findings have confirmed the diagnosis in a number of patients with an initial false-negative RT-PCR result [7]. In these cases, chest CT may be considered a primary tool for detection of current COVID-19 in epidemic areas [8]. In this study, we found differences in CT features between the group with negative and that with positive initial RT-PCR results.

In our cohort of 21 patients, the disease had a high likelihood of bilateral multifocal involvement of the lower lobe of the lung, similar to the findings reported by Chung et al. [9]. However, a small number of patients

TABLE 1: Comparison of CT Features Between Groups With Negative and Positive Initial Reverse Transcription–Polymerase Chain Reaction (RT-PCR) Results

Index	Initial RT-PCR Result		p
	Negative ($n = 7$)	Positive ($n = 14$)	
Left or right lung	2	4	1.000
Left and right lung	5	10	
Single lobe	2	5	0.743
Multiple lobes	5	9	
Ground-glass opacities present	7	13	0.469
Consolidation present	3	12	0.040[a]
Air bronchogram present	6	6	0.061
Vascular enlargement present	5	9	0.743
Interlobular septal thickening present	5	8	0.525

[a]The difference was statistically significant in comparison of the two groups ($p < 0.05$).

had involvement of only a single lobe. Han et al. [10] reported that the single lobe usually was the right lower lobe, possibly because its thick and short anatomic features make it easy for the virus to invade. We also found the disease likely to have a subpleural distribution, possibly because the target cells are located in the lower airway [11]. In addition, some lesions were located around the bronchovascular bundle, which may indicate that the pneumonia can spread along the pulmonary intralobular interstitium and induce an inflammatory reaction. It has been supposed [12] that the lesions start by invading the bronchioles and alveolar epithelium of the cortical lung tissues and extend gradually from the periphery to the center.

Patients with COVID-19 pneumonia usually had ground-glass opacities (95%) and consolidation (72%). That ground-glass opacities were more common is similar to findings in previous studies [9, 13]. Because of the highly homologous sequences between the genomes of SARS-CoV-2 and SARS-CoV [14], it has been speculated that the ground-glass opacities are caused by serous inflammatory exudation from the pulmonary alveoli and that the consolidation is caused by the increased inflammatory exudation. It has also been reported [15] that patients admitted to an ICU are more likely to have large areas of bilateral consolidation on CT scans, whereas patients not needing admission and presenting with milder forms of the illness are more likely to have ground-glass opacities and small areas of consolidation. That is, the disease usually manifests ground-glass opacities in the early stage and then the area of consolidation increases after the disease progresses, which may be predictive of severe complications, such as acute respiratory disease.

Other CT features included air bronchogram, vascular enlargement, and interlobular septal thickening. With superimposed ground-glass opacification, the interlobular septal thickening can form the crazy paving pattern. Four patients (19%) had pleural effusions, and three of them had underlying diseases, such as hypertension and diabetes mellitus. Whether pleural effusion is related to the underlying diseases remains to be further studied.

We found that compared with the findings in patients with positive initial RT-PCR results, the area of consolidation lesions in the patients with negative initial RT-PCR results was smaller. In the group with negative initial RT-PCR results, most of the lesions appeared as ground-glass opacities or opacities mixed with a small area of consolidation, which indicated that the disease was in its early stage. A recent study [16] had a similar result: all five of the patients in the study had ground-glass opacification, and only two had mixed consolidation. It has been reported [15] that the presence of consolidation lesions suggests an organizing pneumonia pattern of lung injury. A small area of consolidation indicates that the injury to lung tissue is mild, increasing the possibility of negative initial RT-PCR results. In contrast, when the area of consolidation is large, the possibility of negative initial RT-PCR results decreases.

Our study had limitations. First, it was retrospective and included a small number of patients. Second, RT-PCR detection is affected by many factors, such as laboratory reagents, test method used, and subjective operability. However, the multicenter nature of this study should have theoretically reduced interference by these factors. Third, no follow-up CT was performed to observe dynamic changes resulting from treatment.

Conclusion

Apart from the typical CT findings of bilateral ground-glass opacities and consolidation, subpleural distribution was observed. The less pulmonary consolidation found at CT, the greater was the possibility of initial negative RT-PCR results. Although CT is not the final standard for the diagnosis of COVID-19 pneumonia, it nevertheless plays an irreplaceable role. When patients with suspected COVID-19 pneumonia who have an epidemiologic history and typical CT features have negative initial RT-PCR results, repeated RT-PCR tests and patient isolation should be considered.

Acknowledgments

We thank the emergency services, nurses, and physicians for their efforts in combating the COVID-19 outbreak.

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