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Diagnostic value of ground-glass opacities on computed tomography combined with computed tomography re-examination in patients with suspected novel coronavirus pneumonia

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ABSTRACT

Background: This study aimed to determine the diagnostic value of ground-glass opacities on computed tomography combined with computed tomography re-examination in patients with suspected novel coronavirus pneumonia. ***Materials and Methods***: Suspected cases of novel coronavirus pneumonia were identified retrospectively between January 23 and February 18, 2020. Computed tomography examination was conducted for all patients. For all suspected cases, real-time reverse transcription-polymerase chain reaction detection of novel coronavirus nucleic acid was conducted. Computed tomography re-examination in the short term was also performed. ***Results***: Among 92 patients suspected with novel coronavirus pneumonia, 15 were diagnosed with coronavirus disease 2019. There were ground-glass opacities on chest computed tomography in 34 patients, and 8 of these patients were confirmed to have novel coronavirus pneumonia. In total, 30 patients showed no absorption on computed tomography re-examination, of which 10 (10/30) were diagnosed with novel coronavirus pneumonia. Additionally, 20 patients had non-absorption of lesions when ground-glass opacities on initial and follow-up computed tomography were combined, and 13 of these patients were confirmed to have novel coronavirus pneumonia. For ground-glass opacities on computed tomography combined with non-absorption of lesions on computed tomography re-examination, the sensitivity and specificity for the diagnosis of the novel coronavirus were 86.7% and 90.1%, respectively. ***Conclusion***: Among suspected patients with novel coronavirus pneumonia, combining ground-glass opacities on computed tomography with a computed tomography re-examination might improve the accuracy of diagnosis.

INTRODUCTION

Many cases of the COVID-19 have been diagnosed in Wuhan，China, since December 2019. With the spreading of the disease, many cases have also been diagnosed in other Chinese cities, as well as foreign countries [(1)]. By February 19, 2020, 74,280 cases of novel coronavirus pneumonia had been reported nationwide, with this number comprising 2,009 deaths.

Previous research has demonstrated that the genetic characteristics of the novel coronavirus are distinct from those of the previously discovered SARSr-CoV and MERSr-CoV [(2)]. The homology of SARS -like coronavirus in bats is > 85% [(2)]. Although the proportion of severe patients was less than in the SARSr-CoV and MERSr-CoV epidemics, more evidence of person-to-person spread and a significant increase in new cases showed that COVID-19 is more infectious than SARSr-CoV and MERSr-CoV [(1)].

The novel coronavirus mainly spreads in humans via physical contact and respirator droplets [(3)]. The incubation period is typically 3 to 7 days but can be up to 14 days. The symptoms include dry cough，weakness and fever, although some patients may also develop nasal obstruction, rhinorrhea, sore throat, muscle pain, or diarrhea. In severe cases, breathing difficulty occurs one week later, and Septic shock, acute respiratory distress syndrome, refractory metabolic acidosis, coagulation disorders [(4)], and

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multiple organ failure may also develop. Confirmation of COVID-19 requires testing for the viral nucleic acid in sputum，throat swabs, or lower respiratory secretions. The specificities of these tests are strong, although the sensitivities are poor [5].

In our experience as clinicians treating patients with COVID-19, pulmonary imaging manifestations occur before the clinical symptoms. Therefore, imaging examinations are very important for pre-clinical screening. Many studies have shown that the number of ground-glass opacities on computed tomography (CT) suggest a novel coronavirus infection [4,6]; however, ground-glass attenuation on chest images can present in many infectious and non-infectious diseases and its presence can thus can be used to confirm COVID-19 but cannot serve as a stand-alone diagnostic finding. Moreover, a recent study has reported that a follow-up CT could help diagnose novel coronavirus pneumonia [7]. However, there remains a dearth of evidence in the literature regarding the potential diagnostic value of combining the two indices mentioned above (i.e., ground-glass opacities on initial and follow-up CTs) for diagnosing COVID-19-related pneumonia. To the best of our knowledge, this study is the first to investigate the diagnostic value of this multi-part CT examination regimen. Detailed CT imaging taken at illness onset and repeated later in the disease progression could provide valuable information for clinicians seeking to better understand the physical manifestations and imaging characteristics of COVID-19-related pneumonia, which in turn could lead to improved medical treatment and patient outcomes.

MATERIALS AND METHODS

Ethics

This study was approved by the Ethics Committee of the First People's Hospital (Shuangliu District; approval number: 202000014). Informed consent was waived for this retrospective study.

Study participants

A total of 92 patients who were diagnosed as suspected COVID-19 (as described in the *Diagnostic and Treatment Regimen of Novel Coronavirus [Trial Version]*), seeking care in the fever clinic of the People's Hospital of Shuangliu District and People's Hospital of Pidu District from January 23, 2020, to February 18, 2020, were retrospectively enrolled in this study. Specifically, the inclusion criteria were as follows: 1) history of epidemiologic risk (traveled or lived in Wuhan City and the nearby cities or the communities with patients of COVID-19 within 14 days before onset, got the touch with patients of COVID-19 within 14 days before onset [persons with positive nucleic acid testing results], and got the touch with patients with fevers or cough from Wuhan City and the nearby cities or communities with patients of COVID-19 within 14 days before onset and a clustering onset), and 2) clinical symptoms (fever and/or respiratory symptoms, chest CT characteristics of COVID-19, and normal or reduced total white cell count or reduced lymphocyte count was in early-onset). Patients who conformed to any epidemiologic risk factors, any two clinical symptoms, or to three clinical symptoms without epidemiologic risk factors were regarded as suspected cases.

Patient examination

All enrolled patients had undergone routine blood testing, had data on C-reactive protein levels, and had undergone a high-resolution chest CT scan. All patients underwent two or more consecutive novel coronavirus reverse transcription-polymerase chain reaction (RT-PCR) tests (Shanghai BioGerm Medical Biotechnology Co., Shanghai, China. Ltd. Lot No. 20200304A) of throat swabs with a sampling interval of at least 24 h. The time from onset to chest CT examination was recorded, and then a chest CT re-examination was obtained in the short term; the time from onset to chest CT re-examination was recorded.

CT scanning method and interpretation

A multi-detector CT scanner (Somtom Definition AS; Siemens Healthineers, Erlangen, Germany) was used for chest CT scanning. The first chest CT scan results were divided into ground- and non-ground-glass opacities. The chest CT re-examination results consisted of absorption and non-absorption (including no change and progression of the lesion), and all the images were read by two CT diagnosticians with > 10 years of Imaging diagnosis experience. A diagnosis of COVID-19 was made if the chest CT examination showed ground-glass opacities and the follow-up re-examination CT image showed non-absorption of lesions.

Statistical methods

SPSS 19.0 software (IBM Corp., Armonk, NY, USA) was used for analysis. The measurement data are expressed as the mean ± standard deviation, and the enumeration data are represented by a proportion of the total number. The four-fold table method of diagnosis experiments was applied. Patients diagnosed with the novel coronavirus pneumonia through PCR were considered the gold standard. Patients who had ground-glass opacities on CT, non-absorption of lesions on CT re-examination, and combined ground-glass opacities on CT and non-absorption of lesions on CT re-examination were diagnosed with the novel coronavirus pneumonia. The results of these diagnoses were then compared with those of the gold standard. The sensitivity, specificity, false-positive rate, false-negative rate, positive likelihood ratio, negative likelihood ratio, diagnosis index, and Youden's index were calculated.

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RESULTS

92 patients with suspected COVID-19 were enrolled (table 1), comprising 40 men and 52 women, with a mean age of 40±14 years. Regarding symptoms, 78 had fevers, 74 had coughs, 20 experienced weakness, and one had no symptoms. The white blood cell count on routine blood testing was 5.62±1.54 × 10^9/L, the lymphocyte count was 1.06±0.51 × 10^9/L, the platelet count was 196±64 × 10^9/L, the high sensitivity C-reactive protein level was 36.7±14.5 mg/L, the number of nucleic acid testing times of respiratory tract specimens was 3±1, the time from onset-to-the first CT time was 4±2 days (range, 1–7 days), the time from onset-to-CT re-examination was 6±3 days (range, 4–10 days), and CT re-examinations occurred 2±1 times (range, 1–4 times).

Table 1. Basic information of enrolled patients.

	Number of patients (92)
Age (years)	40±14
Gender	
Male	40 (40/92)
Female	52 (52/92)
PCR results	
Positive	15(15/92)
Negative	77(77/92)
Symptoms	
Fever	78 (78/92)
Cough	74 (74/92)
Weakness	20 (20/92)
No symptoms	1 (1/92)
Lab testing	
White blood cell count (10^9/L)	5.62±1.54 (3.66-8.18)
Lymphocyte count (10^9/L)	1.06±0.51 (0.28-2.06)
Blood platelet count (10^9/L)	196±64 (107-316)
High sensitivity C-reactive protein (mg/L)	36.7±14.5 (0.6-80.8)
Time from onset-to-the first CT (days)	4±2 (1-7)
Time from onset-to-the first CT re-examination (days)	6±3 (4-10)
CT re-examination times (days)	2±1 (1-4)
Number of testing times of nucleic acid in throat swabs	3±1 (2-4)

In total, 34 patients had ground-glass opacities on CT (table 2), including eight with confirmed novel coronavirus pneumonia, 25 with bacterial pneumonia, and one with human immunodeficiency virus (HIV) infection with *Pneumocystis* pneumonia (PCP). Additionally, 58 patients had non-ground-glass opacities on CT, including seven with confirmed novel coronavirus pneumonia and 51 with bacterial pneumonia. The sensitivity of ground-glass opacities on CT to the novel coronavirus was 53.3%, the specificity was 66.2%, the false-negative rate was 46.7%, the false-positive rate was 33.8%, the positive likelihood ratio was 1.58, the negative likelihood ratio was 0.7, the diagnosis index was 119.5%, and the Youden's index was 0.195.

A total of 30 patients had non-absorption of lesions on follow-up CT (table 3), including 10 confirmed to have novel coronavirus pneumonia, 19 confirmed to have bacterial pneumonia, and one with HIV infection with PCP. Additionally, 62 patients had absorption of lesions, all of whom were confirmed to have bacterial pneumonia. The diagnosis sensitivity of non-absorption of lesions on follow-up CT to novel coronavirus pneumonia was 66.7%, the specificity was 74%, the false-negative rate was 33.3%, the false -positive rate was 26%, the positive likelihood ratio was 2.57, the negative likelihood ratio was 0.45, the diagnosis index was 140.7%, and the Youden's index was 0.407.

Table 2. Influence of CT ground-glass opacities on diagnosis of Covid-19.

Ground-glass opacities on CT	Confirmed Covid-19	Non-Covid-19	Total
Conforming	8	26	34
Non-conforming	7	51	58
Total	15	77	92

Table 3. Influence of non-absorption of lesions on CT re-examination on diagnosis of Covid-19.

Ground-glass opacities on CT	Confirmed Covid-19	Non-Covid-19	Total
Conforming	10	20	30
Non-conforming	5	57	62
Total	15	77	92

A total of 20 patients had non-absorption of lesions when ground-glass opacities on CT and CT follow-up were combined, including 13 with confirmed novel coronavirus pneumonia, one with HIV infection with PCP. Additionally, 72 patients had bacterial infection .The diagnosis sensitivity for the non-absorption of lesions when the ground-glass opacities on CT were combined with CT follow-up for the novel coronavirus was 86.7%, the specificity was 90.1%, the false-negative rate was 13.3%, the false-positive rate was 9.9%, the positive likelihood ratio was 8.7, the negative likelihood ratio was 0.15, the diagnosis index was 176.8%, and the Youden's index was 0.768.

DISCUSSION

This retrospective study investigated the diagnostic value of combining two indices—ground-glass opacities and follow-up CT—for diagnosing novel coronavirus-related pneumonia. Our results show that for ground-glass opacities on CT combined with non-absorption of lesions on CT re-examination, the sensitivity and specificity for diagnosis of novel coronavirus was 86.7% and 90.1%, respectively.

The 92 patients enrolled in this study who were diagnosed as suspected COVID-19 were mostly young and middle-aged and younger than those enrolled in other studies [6]. The main symptoms were cough, fever, and weakness. The white blood cell counts were normal and the lymphocyte counts were decreased, similar to the findings of previous studies [1, 4, 6, 8].

In total, 34 patients had ground-glass opacities on

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lung CT, including eight who were confirmed to have novel coronavirus pneumonia. Most patients had multiple small ground-glass opacities in both lungs, as shown in figure 1, and the opacities were around the lung, which was consistent with the findings of Huang [4] and Chen [9]. In this study, most patients with novel coronavirus pneumonia had ground-glass attenuation on CT [4, 6, 10]. There were 40% (34/92) of suspected patients with ground-glass opacities, while 53.3% (8/15) of the confirmed patients had ground-glass opacities, which was lower than that previously reported (85.7%) [6]. This finding might be due to a low prevalence area for the novel coronavirus. The sensitivity and specificity of pure ground-glass opacities in the diagnosis of novel coronavirus pneumonia were not very high, which might be because many diseases exhibit ground-glass opacities on chest imaging, including acute lupus pneumonia, diffuse interstitial pneumonia, pulmonary collagen vascular disease, acute eosinophilic pneumonia, atypical pathogen infection in the lungs (*Mycoplasma*; figure 2) [11-14], and bacterial pneumonia (figure 3). Among the patients enrolled in this study, there was also one case of HIV with PCP (figure 4); therefore, CT was not able to diagnose novel coronavirus pneumonia solely based on ground-glass opacities.

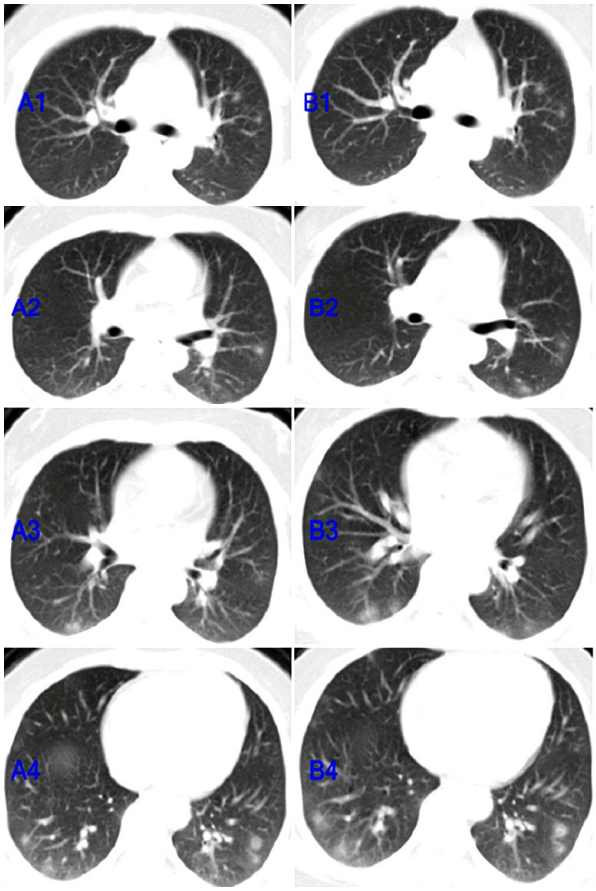

Figure 1. A1-4 shows the first chest computed tomography (CT) (no high-resolution CT) scan of a 32-year-old woman from Wuhan. The first CT scan was obtained 4 days after onset, and multiple ground-glass opacities can be observed around the lung. B1-4 shows the re-examination 2 days after anti-infective therapy with moxifloxacin. The increase in ground-glass opacities can be observed, and the nucleic acid examination of the novel coronavirus from a throat swab was positive.

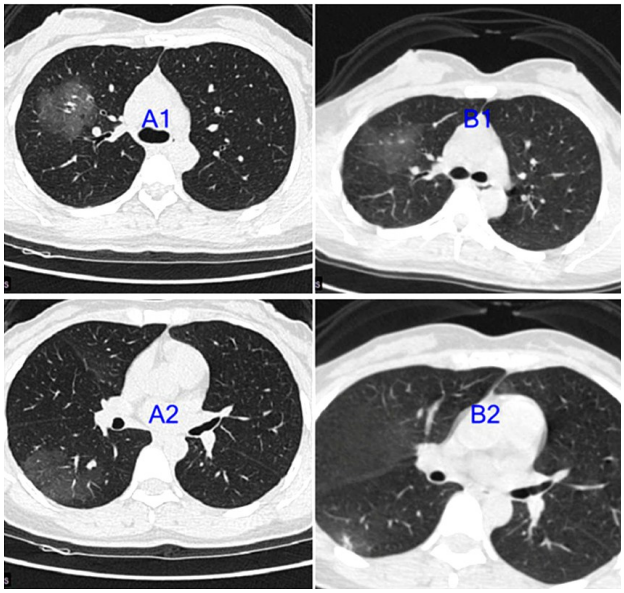

Figure 2. A local 28-year-old woman. Figure (A1-2) shows the chest computed tomography (CT) scan from another hospital 2 days after onset and indicates multiple ground-glass opacities in the right lung. Figure (B1-2) b shows the chest CT re-examination scan 2 days after treatment with moxifloxacin and indicates significant absorption of ground-glass opacities. The patient was diagnosed with Mycoplasma pneumoniae infection.

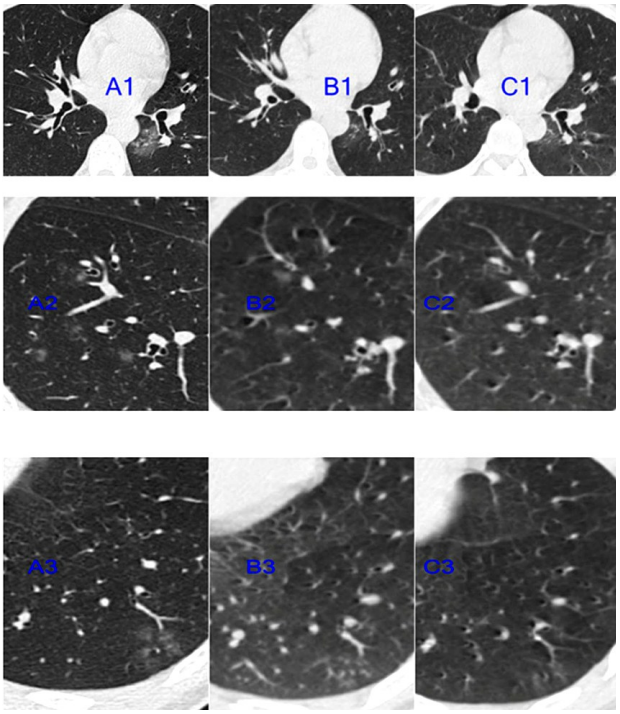

Figure 3. A local 33-year-old man. Figure (A1-3) shows a chest computed tomography (CT) scan from another hospital 2 days after onset; multiple GGOs are noted in both lungs. Figure (B1-3) shows the chest CT re-examination scan obtained in our hospital 2 days after anti-microbial therapy with moxifloxacin; some lesions are absorbed. Figure (C1-3) shows a chest CT re-examination scan in our hospital 5 days after anti-microbial therapy with moxifloxacin; most of the lesions are absorbed. The patient was diagnosed with bacterial pneumonia.

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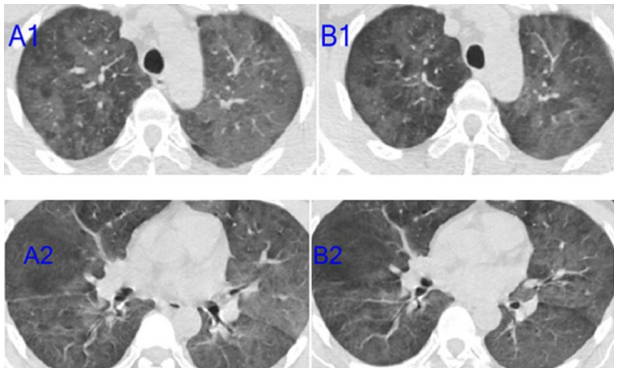

Figure 4. A local 28-year-old man. Figure (A1-2) shows a chest computed tomography (CT) scan 3 days after onset; there are diffuse GGOs in both lungs. Figure (B1-2) shows a chest CT re-examination scan 7 days after oral administration of sulfamethoxazole; there is absorption of GGOs in both lungs compared with prior imaging. The patient was diagnosed with HIV-related Pneumocystis pneumonia.

The diagnosis of COVID-19 depends on RT-PCR of the virus. Such testing was equipped with the advantages of early detection, high specificity, and ease of operation; however, it does not have high sensitivity based on current practices, which is related to many nucleic acid test factors [15]. Clinically, novel coronavirus pneumonia is different from a number of lung-related diseases, including bacterial pneumonia. Therefore, chest CT re-examination after anti-microbial therapy might be a good way to distinguish novel coronavirus pneumonia from lung-related diseases. In our study, most of the patients with absorption of lesions (56/62, 90.3%) had bacterial pneumonia, and one (1/62) had HIV infection with PCP (figure 4). The time for both cases from onset to re-examination CT was 3 and 6 days, consistent with that observed in a previous study [7]. The sensitivity was 66.7%, and the specificity was 74% only by re-examination CT. Combined with the characteristic imaging manifestations of novel coronavirus pneumonia, non-absorption of GGO on chest CT in the short term increased the diagnostic accuracy, sensitivity (86.7%), specificity (90.1%), and Youden's index (0.768). Due to the possibility of false positives in our study, 30 patients (30/92) had no absorption, and only 10 (10/30) had novel coronavirus pneumonia (figures 1 and 5). This might be because the anti-microbial pathogens did not completely treat the pathogenic bacteria completely or other types of virus pneumonia, which might have resulted in non-absorption and even aggravation or other non-infectious lung diseases. In addition, there was lower diagnostic accuracy only by the ground glass or by re-examination CT in suspected COVID-19 cases, and the bias in this study was attributed to the study hospital being in an area with a low prevalence of COVID-19, and there were few confirmed novel coronavirus infection cases.

Overall, among the suspected cases of novel coronavirus pneumonia, both the sensitivity and specificity of GGO on CT to novel coronavirus pneumonia were not high. A chest CT re-examination in the short term still has low sensitivity and poor specificity. A combination of both CT exams might improve the accuracy of diagnosis. This index might be a supplementary means for diagnosing novel coronavirus pneumonia, especially under the condition of undesirable testing accuracy of novel coronavirus nucleic acid and in a low prevalence area. However, there might also be selection bias because few confirmed and suspected cases were enrolled in this study. Thus, large-sample multi-center studies are required for further verification.

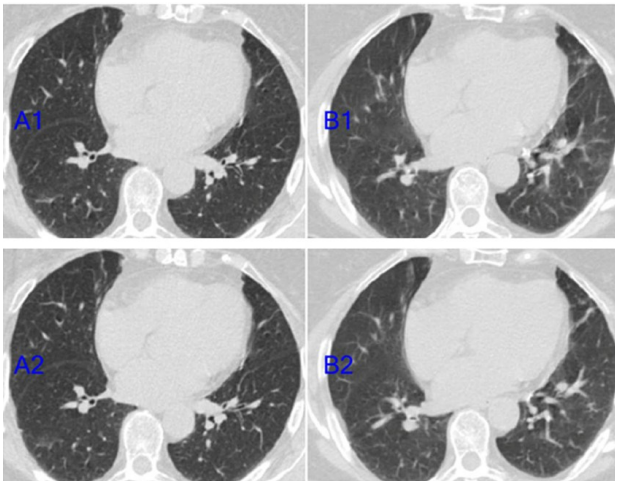

Figure 5. Chest computed tomography (CT) scan of a 76-year-old woman from Wuhan. Figure (A1-2) shows the first chest CT scan 1 day after onset; there are multiple fiber strip microcosms and small patchy shadows in both lungs. Figure (B1-2) shows the re-examination scan 2 days later; there are increased patchy shadows in the middle lobe of the right lung and increased GGOs in the lingual lobe of the left lung. The patient had positive throat swab testing results and was confirmed to have novel coronavirus pneumonia.

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Conflicts of Interest: None.

Ethical approval: This study was approved by the Ethics Committee of The First People's Hospital (Shuangliu District) in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Availability of data and material: The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contribution: TL, WH, GZ, DYC: study concepts; study design; data analysis; manuscript preparation, editing and review WH, GZ, TL: definition of intellectual content; statistical analysis WH, GZ, TL, JL, FG, ML, HY: guarantor of integrity of the entire study; literature research; clinical studies; experimental studies; data acquisition.

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