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Review/Thoracic imaging

Radiology indispensable for tracking COVID-19

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ABSTRACT

With the rapid spread of COVID-19 worldwide, early detection and efficient isolation of suspected patients are especially important to prevent the transmission. Although nucleic acid testing of SARS-CoV-2 is still the gold standard for diagnosis, there are well-recognized early-detection problems including time-consuming in the diagnosis process, noticeable false-negative rate in the early stage and lacking nucleic acid testing kits in some areas. Therefore, effective and rational applications of imaging technologies are critical in aiding the screen and helping the diagnosis of suspected patients. Currently, chest computed tomography is recommended as the first-line imaging test for detecting COVID-19 pneumonia, which could allow not only early detection of the typical chest manifestations, but also timely estimation of the disease severity and therapeutic effects. In addition, other radiological methods including chest X-ray, magnetic resonance imaging, and positron emission computed tomography also show significant advantages in the detection of COVID-19 pneumonia. This review summarizes the applications of radiology and nuclear medicine in detecting and diagnosing COVID-19. It highlights the importance for these technologies to curb the rapid transmission during the pandemic, considering findings from special groups such as children and pregnant women.

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1. Introduction

Since the outbreak of novel coronavirus disease 2019 (COVID-19), researchers regardless of majors and nationality have been working to curb the spread of the disease. Like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), COVID-19 is an infectious disease transmitted from person to person via the novel coronavirus SARS-CoV-2. Since there

are no clinically proven therapies, early detection and efficient isolation of suspected cases are still the most crucial to contain the COVID-19 outbreak [1]. In addition, due to the absence of specific early symptoms of COVID-19 pneumonia, some of the patients have not been diagnosed in time. The delayed diagnosis and treatment of COVID-19 may cause irreversible progression of the disease. Therefore, rapid and timely diagnosis is the key to control potential transmission.

Although the nucleic acid testing of SARS-CoV-2 is the gold standard of the diagnosis, laboratory detections are time-consuming, requiring rigorous laboratory specifications [2]. Some suspected cases may have initial false-negative results so that their severity of COVID-19 and its progression cannot be judged. Moreover, the quality of kits from different companies awaits to be studied and improved. All the challenges may increase the risk of further spread by free flow of people with suspected infection. For these reasons, Chinese radiological specialists strongly recommend computed tomography (CT), especially high-resolution CT (HRCT) imaging, as the main method for the screen and diagnosis of COVID-19 in the current situation [3].

Abbreviations: AI, Artificial intelligence; COVID-19, Novel coronavirus disease 2019; CT, Computed tomography; ¹⁸F-FDG, β-2-[18 F]-Fluoro-2-deoxy-D-glucose; GGO, Ground-glass opacity; HRCT, High-resolution CT; MRI, Magnetic resonance imaging; PET/CT, Positron emission computed tomography; RT-PCR, Reverse transcription-polymerase chain reaction; SARS, Severe acute respiratory syndrome; UTE, Ultrashort echo-time.

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Fig. 1. Typical chest X-ray image in a woman with COVID-19 (white arrow indicates patch shadow).

As reported, CT had a low rate of missed diagnosis of COVID-19 (3.9%) and thus may be considered the first-line imaging modality and an efficient clinical diagnostic tool in highly suspected cases [2]. CT has been proven to be the choice for early detection, as well as the severity assessment and timely therapeutic effects evaluation for COVID-19 with or without laboratory confirmation. Moreover, chest CT even has potential for identifying infected people with negative results of a reverse transcription-polymerase chain reaction (RT-PCR) assay [4,5]. With the accurate diagnosis of COVID-19 pneumonia based on chest CT, suspected SARS-CoV-2 infection could be isolated and treated in time so that the management can be optimized, especially for the hospitals or communities lacking nucleic acid testing kits. In addition, several laboratory parameters, including erythrocyte sedimentation rate, C-reactive protein, and lactate dehydrogenase, showed significant and positive correlation with CT-based severity of pneumonia [6]. As a specific example, histopathologic changes in diffuse alveolar damage in the autopsy report of a COVID-19 patient who had respiratory failure were consistent with the radiographic bilateral ground-glass opacities [7].

Previous reviews mainly focused on some typical and atypical radiological manifestations of COVID-19 patients [8,9]. No comprehensive systematic review of radiology and nuclear medicine has been reported currently. This review summarizes the importance of radiology and nuclear medicine in COVID-19, including chest X-ray, CT, magnetic resonance imaging (MRI) and positron emission computed tomography (PET/CT) as well as the imaging findings of special groups such as children and pregnant women.

2. Imaging manifestations

2.1. Chest radiography (X-ray)

Although chest radiography is not recommended as the first-line imaging test for diagnosing COVID-19 pneumonia, it is also worthy for its widespread availability during the global pandemic. A retrospective chest radiography study of 64 patients infected with SARS-CoV-2 found that consolidation was the most common finding, accounting for 47% of all patients, then followed by ground-glass opacity (GGO) (33%) (Fig. 1). What's more, these GGO abnormalities distributed primarily in the peripheral area and lower lung lobes. Half of the patients had bilateral lung involvement. Pleural effusion was rarely found in these patients. However, about one third of these patients had negative chest X-ray mani-

festations on the first chest X-ray [10]. Moreover, another research showed that six of nine COVID-19 patients had no abnormalities on the first chest radiography [11]. As such, chest radiography has a quite low positive detection rate at the early stage, which may be related to the insensitivity of X-rays to the density of GGO [12].

2.2. High-resolution CT (HRCT)

Symptoms of COVID-19 patients in the prodromal phase are always non-specific including fever, dry cough, and malaise, which make the early diagnosis more difficult. Chest imaging is of great importance for the diagnosis and management of patients with COVID-19 infection. However, it is easy to miss the diagnosis of early GGO with chest X-ray. Thus, CT, especially HRCT, with 90% sensitivity and 91% specificity [13], is regarded as the best choice for the early diagnosis of COVID-19 infection. Some SARS-CoV-2 infections were identified by incidental chest CT for other reason than suspecting of having caught SARS-CoV-2 [14]. HRCT allows objective evaluation of the lung lesions, enabling us to better understand the pathogenesis of the disease. Compared with histologic examination, CT can evaluate the whole lungs whereas histology looks at only localized regions of the lungs [15].

As reported, the most typical CT imaging finding of COVID-19 patients is GGO [16], combined with reticular and/or interlobular septal thickening and consolidation [17]. Pleural effusion, pericardial effusion, lymphadenopathy are rarely noticed [18]. Regarding the distribution of lesions, our previous study analyzed high-resolution chest CT examinations of 103 COVID-19 patients and found that the involvement of the right lung was the most common. Besides, the lesions in right lung developed faster than those in the left [19]. Another study including 50 patients showed that the lower lobes were the mostly infected lobes. Bilateral multiple lobes involvement was also one of the features [20], while the unilateral involvement appeared only in the early and recovery stage of the disease [21].

The progression of disease could be divided into 4 stages according to the imaging manifestations (Fig. 2). In the early stage, about 0–4 days from the initial symptoms onset, a small proportion of COVID-19 patients showed no obvious abnormalities in chest CT imaging presentations [22]. However, unilateral or bilateral pure GGO is the key feature of this stage, which could be found in almost 98% patients with COVID-19. About one week after the onset, the progression or the second stage comes. An increased range of GGO and the involvement of multiple lung lobes are the main characteristics of this stage. The obvious crazy-paving pattern appears, defined as thickened interlobular septum with superimposition, resembling irregular paving stones [1]. In addition, “halo sign” could be also seen in nearly 20% of the patients [23]. The advanced stage of the disease usually occurs around 8–13 days following symptoms onset. In this stage, CT images mainly show the gradually reduced GGOs and obviously increased consolidation, combined with air bronchogram sign. During this period, the most severe manifestation is “white lung”, as all lobes are infected [3]. Li et al. compared the CT imaging findings of patients with severe disease with ordinary patients and found that consolidation, linear opacities, crazy-paving pattern of multiple lobes are the major characteristics of patients with severe disease [24]. Similarly, the incidence rate of pleural effusion, pericardial effusion and thickening interlobular septum is also greater in patients with severe disease [24]. Therefore, the development of pleural effusion and thickened interlobular septum might be associated with clinical worsening. After the symptomatic and supportive treatment for about 14–21 days since the onset, it comes to the dissipation or the fourth stage. In this stage, the range of lesions is largely dwindled, as both GGO and consolidation have gradually absorbed [25]. As shown in a single observation, a patient presented improved CT

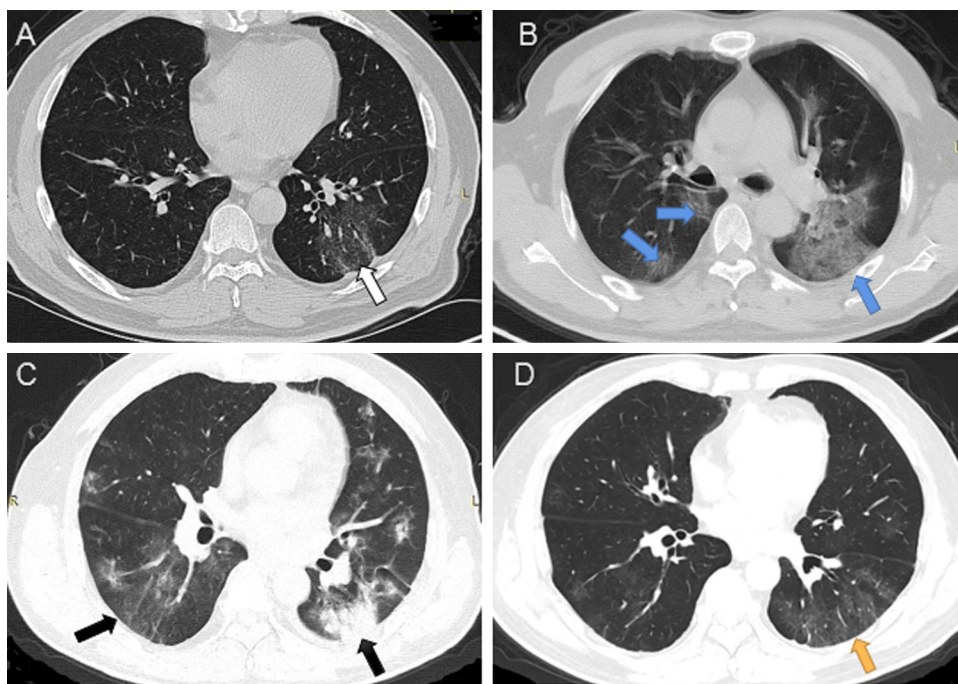


Fig. 2. Typical chest CT imaging findings at four stages of COVID-19. A. The axial CT image shows a small range of ground-glass opacity (GGO) during the early stage (white arrow). B. An increased range of GGO and the involvement of bilateral lungs during progression stage (blue arrows). C. Reduced GGO and obvious consolidation during advanced stage (black arrows). D. Bilateral lung lesions are obviously less prominent during dissipation stage (orange arrow).

manifestation after treatment with tocilizumab [26]. However, it has also been reported that in convalescent patients, symptoms disappeared and the RT-PCR results of SARS-CoV-2 nucleic acid turned negative, but the lung was not completely recovered based on the CT images. A study showed that fewer than 50% patients showed complete recovery of lungs from the last CT examination before discharge [21]. Another study analyzed the follow-up CT imaging on 32 discharged COVID-19 patients and found pulmonary fibrotic sequelae occurred in 14 of them, which was more frequent in severe patients [27]. Similarly, Huang et al. have also reported residual fibrotic damage of severe COVID-19 on follow-up CT [28]. In addition, there are some atypical CT imaging manifestations based on previously published researches. Jin et al. reported that multiple or extensive subpleural grid-like or honeycomb-like thickening interlobular septum, thickening bronchial wall and strand-like opacity could be seen in a few elderly patients [29]. A patient was reported to have mediastinal emphysema, giant bulla, and pneumothorax in his chest CT examination [30]. Another study concluded several special CT signs of COVID-19, including the Batwing sign (a large symmetrical shadow around the bilateral lung hila, which looks like butterfly wings), the Rosa roxburghii sign (semi-round GGO distributed in the peripheral area of lungs) and the Gypsum sign (consolidation with different densities appeared in the lobes) [22]. Recently, a retrospective study reported that acute adrenal infarction was frequent (23%) in severe COVID-19 patients, which is a special abdominal CT manifestation of this disease [31].

2.3. Chest CT angiography

Chest CT angiography has also shown its value in diagnosing pulmonary vascular disease associated with COVID-19, especially acute pulmonary embolism [32,33]. Current researches have mentioned that COVID-19 patients are easy to complicate with pulmonary embolism [34,35], which might be related to vascular injury caused by SARS-CoV-2 infection. In addition, hypoxia and

cytokine storm were considered as the primary mechanisms [36]. In a study, about 30% of the patients with COVID-19 were positive for acute pulmonary embolism based on CT angiography [37]. Franck et al. analyzed CT angiography in 100 COVID-19 patients and found that pulmonary embolism was more common in patients treated with mechanical ventilation and severe patients in intensive care unit than in those without [38]. However, another study in non-intensive care unit COVID-19 patients reported a high incidence (17.0%) of thrombosis in patients without severe or critical symptom [36]. Thus, we have to pay attention to a rational utilization of Chest CT angiography in COVID-19 patients.

2.4. Positron emission computed tomography (PET/CT)

Nuclear medicine may have extra potential implications on detecting asymptomatic COVID-19 patients when undergoing scans for other indications such as malignant tumor. Although PET/CT is not considered in routine diagnosis in emergency settings, it has potential clinical utility in the diagnosis of incidental cases. The use of β -2-[^{18}F]-Fluoro-2-deoxy-D-glucose (^{18}F -FDG) PET/CT detecting COVID-19 was firstly reported by Qin et al. in four patients highly suspicious for COVID-19. Besides the similar multiple GGOS and consolidative opacities findings to COVID-19, they found the lesions with high tracer uptake [39]. In this study, the increased nodal ^{18}F -FDG uptake from the ^{18}F -FDG PET/CT images, suggesting the lymph node involvement in COVID-19 infection [39]. Similarly reported, all lung lesions on CT were ^{18}F -FDG-positive in another research of seven suspected patients. This time, the patients were confirmed with SARS-CoV-2 infection by RT-PCR, further supporting the use of PET/CT in the detection of asymptomatic patients [40].

2.5. Magnetic resonance imaging (MRI)

In addition to chest CT and X-ray, MRI has also been reported to be used in screening and diagnosing COVID-19 patients. Recently, a

Table 1
Differential diagnosis of COVID-19 from other types of pneumonia.

Types of pneumonia	Pathogens	Clinical symptoms	Chest CT manifestations
COVID-19 pneumonia [44]	SARS-CoV-2	Fever, dry cough, fatigue, headache, dyspnea, diarrhea	Early stage: unilateral or bilateral pure GGOs Progressive stage: multiple GGOs, consolidation with GGO, crazy-paving pattern, halo sign in some cases Advanced stage: reduced GGOs and multiple consolidation Lobar pneumonia, bronchial pneumonia, patchy consolidations of pulmonary parenchyma, reactive pleural effusion, pulmonary cavitations
Bacterial pneumonia [45]	<i>Streptococcus pneumoniae</i> , <i>S. aureus</i> and others	Fever, chills, cough and sputum, dyspnea	Reticulonodular opacities or patchy consolidations in children, thickened centrilobular nodules and bronchial wall in adults
<i>Mycoplasma/C. pneumoniae</i> [46]	<i>Mycoplasma/Chlamydia</i>	Cough, sputum production, headache, sore throat, shortness of breath, myalgia or fatigue	Multiple GGOs along the bronchovascular bundle or subpleural area, which is very similar to COVID-19 Centrilobular nodules and tree-in-bud is the most characteristic findings
Influenza pneumonia [47]	Influenza A and B viruses	Runny noses, congestion, dry cough, sore throat	Multiple consolidations with areas of GGO, nodules, and pleural effusion, which resembles bacterial pneumonia
RSV pneumonia [48]	Respiratory syncytial virus	High fever, cough, stuffy nose	
Adenovirus pneumonia [49]	Adenovirus	Fever, cough, drowsiness	

GGO: ground glass opacities.

prospective study confirmed that ultrashort echo-time (UTE) MRI is valuable for detecting the typical pulmonary lesions including GGO, consolidation and crazy-paving pattern [41]. The results of comparative analysis suggested that UTE-MRI present a high concordance and similar image quality to CT for examining COVID-19. Furthermore, the use of UTE-MRI could avoid repeated exposures to X-rays in a short time. Another retrospective study suggested the application of brain MRI in COVID-19 patients with some neurological complications, which showed that the signal abnormalities located in the medial temporal lobe and hemorrhagic lesions were two of the most common findings [42]. In a word, MRI, with lower radiation than CT, could be a potential alternative to CT for non-invasively diagnosing COVID-19, especially for some special groups like children and pregnant women.

3. Differential diagnosis of COVID-19

Chest CT manifestations of different pneumonia caused by different pathogens may overlap, and COVID-19 pneumonia can be superimposed with pneumonia caused by other types of pathogens, presenting more challenging diagnosis. Therefore, it's crucial for radiologists to understand the differentiation.

On imaging diagnosis, it is necessary to distinguish COVID-19 from bacterial pneumonia, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* (Table 1). Bacterial pneumonia mainly invades the parenchyma of lung where bronchial or lobar pneumonia is the most common form. CT imaging findings are characterized by patchy consolidation of pulmonary segment or subsegment while GGO is not common for bacterial infection [3]. Moreover, a small amount of reactive pleural effusion could be seen occasionally. Cavitations in the consolidation frequently indicate *Staphylococcus aureus* pneumonia. *M. pneumoniae* and *C. pneumoniae* are easy to infect children and adolescents with image findings of reticulonodular opacities or patchy consolidations. In adults, major CT presentations are thickened centrilobular nodules and bronchial wall [43].

In addition, chest CT images of COVID-19 infection should be differentiated from other virus pneumonias, such as influenza virus, respiratory syncytial virus, and adenovirus. Virus pneumonia normally occurs in pulmonary interstitial which often cause alveolar wall edema. GGO is also the key feature of chest CT images, with multiple interlaced or parallel high-density fibrous streaks or reticular pattern [50]. Influenza viruses could cause grid-like changes in lungs. Influenza A virus (H1N1) and influenza B virus are the

most common infection factors. Infants and immunocompromised patients are the major infected population. Chest CT scans often present unilateral or bilateral multiple GGOs, distributed along the bronchovascular bundle or subpleural area [51], which is very similar to COVID-19. Children are more susceptible to respiratory syncytial virus. In the early stage, centrilobular nodules and tree-in-bud sign are the main characteristics of respiratory syncytial virus infection [43]. Pulmonary lesions were mostly distributed along the bronchial tree and enlarged hilar lymph nodes could be observed occasionally. Adenovirus, also known as the common cold virus, has higher density lesions on CT images, with more consolidations and fewer subpleural lesions than those of COVID-19 [52].

4. COVID-19 in children and pregnant women

Children of all ages appeared susceptible to COVID-19, and there was no significant sex difference in susceptibility [53]. Compared with adults, pediatric patients with COVID-19 have the characteristics of lower incidence. Most of them were mild with slighter clinical symptoms, shorter course of disease and better prognosis than adult patients [54]. Chest CT findings in children were similar to those in adults but more atypical, with more localized GGO extent, lower GGO attenuation, and relatively rare interlobular septal thickening. The typical imaging findings were unilateral or bilateral subpleural ground-glass opacities, and consolidations with surrounding halo sign. Consolidations with surrounding halo sign account for about a half of the cases, which should be considered as typical signs in pediatric patients.

Pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia, because they are in an immunosuppressive state, and physiologic adaptive changes during pregnancy (e.g., diaphragm elevation, increased oxygen consumption, and edema of respiratory tract mucosa) render them intolerant to hypoxia. The clinically-diagnosed cases were vulnerable to more than what? Pulmonary involvement. Physiological and mechanical changes in pregnancy increase susceptibility to infections in general, particularly when the cardiorespiratory system is affected, and encourage rapid progression to respiratory failure in the gravida [55]. The clinical symptoms of pregnant women were similar and atypical compared with the non-pregnant adults [56], which could increase the difficulty in initial diagnosis. As for the imaging findings, consolidation was more common in the pregnant groups than non-pregnant patients.

Chest CT and X-ray should be used with more caution in pediatric and pregnant patients with COVID-19 to protect the vulnerable population against risking radiation. Although the clinical manifestations of children with COVID-19 are reported generally less severe than adult patients, younger cases, and particularly infants, remain vulnerable to infection and pose a significant transmission risk [57]. In addition, although there is no direct evidence that SARS-CoV-2 undergoes intrauterine or transplacental transmission from infected pregnant women to their fetuses, special attention should be devoted to the prevention of neonatal infection in pregnant women with confirmed COVID-19. The route of delivery and delivery timing should be individualized based on obstetrical indications and maternal-fetal status.

5. Artificial intelligence (AI) and radiology

In this worldwide health crisis, the medical industry is looking for new technologies to monitor and control the spread of COVID-19 pandemic. With an urgent need to diagnose and treat numerous patients, artificial intelligence (AI) is one of such techniques those can help radiologists to identify this novel coronavirus pneumonia and segment the areas of affected lungs accurately, facilitating prompt assessment of the lesions' severity [15]. It can even predict mortality risk by adequately analyzing the previous data of the patients. Since the COVID-19 pneumonia and other viral pneumonia have overlapping imaging manifestations, AI deep learning algorithms may prove beneficial in providing new insights to the differential diagnosis such as community acquired pneumonia and other lung diseases [58].

AI can quickly analyze irregular symptoms and other 'red flags' of the infected cases at the early stage by using advanced algorithms. With the help of medical imaging technologies like CT or MRI of human body parts, it can alarm the patients and the healthcare authorities, which is fast and cost-effective. Also, AI could be used to monitor the treatment by building an intelligent platform like a neural network. It can extract the visual features of COVID-19, which would help in proper monitoring and predicting of the SARS-CoV-2 spread automatically, and then the treatment effects [59]. It has the capability of providing day-to-day updates of the patients' health conditions and then guiding further treatment.

6. Protection tips for the medical staff in radiology department

The disease caused by SARS-CoV-2 is highly contagious and transmit rapidly through respiratory droplets and contacts. A study found that droplets have the greatest risk of transmission within 91.44 cm, but they may travel up to 183 cm from their source [60]. With the increasing importance of CT or other imaging techniques in the diagnosis and follow-up of COVID-19 patients, radiographers, as the first-line health care workers, might be at a high risk by being exposed to the infection. It has already been reported that some radiologists and radiological technologists were infected when giving examinations to the confirmed patients [61]. Therefore, in order to prevent the medical staff from being infected in radiology department, some measures are needed for practical work [62,63].

Firstly, for all the medical staff themselves in radiology department, everyone should acquire proficiency in wearing and removing protective clothing. In a study of 254 medical staff members who had been exposed to SARS coronavirus, the risk for virus transmission was significantly reduced by using droplet and contact precautions [61]. There is at least one superintendent needed to be responsible for directing and supervising the disinfection and protection process. They must make a clear division and report in time to guarantee both the staff and patients avoiding infection.

Secondly, for the working environment, an independent medical imaging examination room is needed and different working areas should be strictly separated from each other in order to prevent cross-infection. In other words, a dedicated radiological examination route must be established [64].

Thirdly, as for the cleaning and disinfection of radiology equipment, including CT and MR machine gantries, noninvasive ultrasound probes, blood pressure cuffs, and image viewing station mice and keyboards, all of them need to be disinfected after every contact with suspected patients. According to the Centers for Disease Control and Prevention, the surfaces need to be either washed with soap and water or decontaminated using a low-level or intermediate-level disinfectant, such as iodophor germicidal detergent solution, ethyl alcohol, or isopropyl alcohol. Furthermore, the disposition of medical waste should also be taken seriously.

7. Conclusions

During the COVID-19 epidemic, imaging technologies, especially HRCT, are quite indispensable in the early diagnosis. For the children and pregnant women, special attention should be paid to the selection of various imaging tools to avoid radiation damage. Due to the high false-negative rate of nucleic acid test, it is crucial to make the final diagnosis accurately by referring to both clinical manifestations and imaging findings. Different radiological technologies have their respective advantages and significance. Therefore, it is of great importance to learn how to use them accurately and rationally to make the best judgments.

Human rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Jingwen Li: conceptualization, data curation, and writing – original draft preparation.

Xi Long: conceptualization, data curation, and writing – original draft preparation.

Xinyi Wang: conceptualization and data curation.

Fang Fang: visualization.
 Xuefei Lv: investigation.
 Dandan Zhang: investigation.
 Yu Sun: investigation.
 Shaoping Hu: project administration and supervision.
 Zhicheng Lin: project administration, supervision, and writing – review and editing.
 Nian Xiong: project administration, supervision and funding acquisition.

Disclosure of interest

The authors declare that they have no competing interest.

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