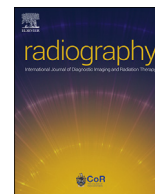




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Narrative Review

Effectiveness of COVID-19 diagnosis and management tools: A review

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ABSTRACT

Objective: To review the available literature concerning the effectiveness of the COVID-19 diagnostic tools.

Background: With the absence of specific treatment/vaccines for the coronavirus COVID-19, the most appropriate approach to control this infection is to quarantine people and isolate symptomatic people and suspected or infected cases. Although real-time reverse transcription-polymerase chain reaction (RT-PCR) assay is considered the first tool to make a definitive diagnosis of COVID-19 disease, the high false negative rate, low sensitivity, limited supplies and strict requirements for laboratory settings might delay accurate diagnosis. Computed tomography (CT) has been reported as an important tool to identify and investigate suspected patients with COVID-19 disease at early stage.

Key findings: RT-PCR shows low sensitivity (60–71%) in diagnosing patients with COVID-19 infection compared to the CT chest. Several studies reported that chest CT scans show typical imaging features in all patients with COVID-19. This high sensitivity and initial presentation in CT chest can be helpful in rectifying false negative results obtained from RT-PCR. As COVID-19 has similar manifestations to other pneumonia diseases, artificial intelligence (AI) might help radiologists to differentiate COVID-19 from other pneumonia diseases.

Conclusion: Although CT scan is a powerful tool in COVID-19 diagnosis, it is not sufficient to detect COVID-19 alone due to the low specificity (25%), and challenges that radiologists might face in differentiating COVID-19 from other viral pneumonia on chest CT scans. AI might help radiologists to differentiate COVID-19 from other pneumonia diseases.

Implication for practice: Both RT-PCR and CT tests together would increase sensitivity and improve quarantine efficacy, an impact neither could achieve alone.

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Introduction

Cases of an unidentified form of viral pneumonia were first reported in Wuhan city, Hubei province, China, in December 2019.¹ In the following weeks, this unknown virus gradually spread across the whole world.² On January 7, 2020, a scientific research institution in China announced that the viral pneumonia was a novel coronavirus (SARS-COV-2), later it was called COVID-19 by the World Health Organization (WHO).³ According to Worldometer (2020), as of August 31, 2020, there had been 25,416,807 confirmed

cases, 851,102 reported deaths and 17,724,602 recovered individuals across the world.⁴

The mortality rate of COVID-19 is lower than that of the coronavirus severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).^{5–7} However, COVID-19 is highly transmissible and rapidly spread, as it can be transmitted by respiratory droplets and contact. The common symptoms observed in patients with COVID-19 are fever, cough, severe headache, myalgia and fatigue.^{8–10} However, infection by other viruses such as influenza A or B can cause similar symptoms to COVID-19, which may make it difficult to distinguish COVID-19 from other infections, especially during flu season.¹¹ The incubation period for COVID-19 infection is typically 1–14 days and might extend up to 24 days.^{12–14} The health conditions of most COVID-19 patients are mild, but they can become severe, especially among elderly people or those with underlying diseases, such as chronic lung or cardiovascular disease.^{15–19} To date, there is no evidence of any effective treatment for patients with COVID-19.¹⁶ Due to the lack of specific

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vaccines and drugs for COVID-19, it is essential to detect and manage the disease at an early stage to immediately isolate people who are confirmed to be infected with COVID-19 from healthy people.^{19–24}

According to the guidelines for the diagnosis of COVID-19 published by the Chinese government, real-time reverse transcription-polymerase chain reaction (RT-PCR) assay is considered the first tool in COVID-19 diagnosis.²⁵ However, delayed sample collection, poor kit performance, limited supplies and strict requirements for laboratory settings might delay accurate diagnosis.^{21–26} This indicates that patients with COVID-19 may not be detected and receive appropriate treatment, which could increase the risk of spread of the infection among a larger population.²⁷ It is not about the test itself; it is often about when and how the test samples are collected from infected people, and whether these samples are prepared and transported properly.²⁸

Diagnostic imaging such as computed tomography (CT) has played an important role in the diagnosis and management of patients with COVID-19.^{29,30} CT of the chest is a routine scanning technique for pneumonia diagnosis. It can be used for the diagnosis of COVID-19, as well as to follow up the extent of lesions and track any changes in patients whose RT-PCR assays and plain radiographic images were negative.^{20,31–33} Several studies reported that a CT of the chest shows typical imaging features in nearly all patients with COVID-19.^{11,34–36} Hung et al. and Xie et al. (2020) highlight that similar imaging features were also detected in patients whose RT-PCR assays were negative.^{1,37}

Artificial intelligence (AI), an emerging technology in the field of diagnostic imaging, has contributed to improving diagnosis and prognosis of several diseases, such as pneumonia.³⁸ A research team showed the potential of AI in supporting the diagnosis of COVID-19 in patients with COVID-19 when trained on CT images, achieving a high sensitivity and specificity (90%).^{39,40} By conducting a comprehensive review of published studies and the experience of diagnosing patients with coronavirus, the aim of this article is to review the effectiveness of the available COVID-19 diagnostic tools.

RT-PCR assay and CT scans in the diagnosis of COVID-19

The standard method of COVID test is RT-PCR, and the test sample can be collected via nasopharyngeal swab or oropharyngeal swab.^{41–43} The RT-PCR is a genetic test combining reverse transcription of Ribonucleic acid (RNA) into complementary Deoxyribonucleic acid (DNA), and amplification of specific DNA targets using RT-PCR.⁴⁴ Although the RT-PCR test remains the reference standard in making a definitive diagnosis of COVID-19 infection,^{45,46} this test has rigorous laboratory specifications and takes a long time to report results.^{30,37} Several studies found that the initial RT-PCR results for patients with COVID-19 infection were false-negatives.^{1,37} These false-negative findings cannot be ignored, especially for those symptomatic people suspected to be infected with COVID-19.

CT scans of the chest are used as a routine test to diagnose pneumonia; therefore, this may be useful in diagnosing COVID-19.^{21,47} Unenhanced high resolution CT (HRCT) of the chest is acquired during a single breath-hold. CT images are then reconstructed and transmitted for subsequent interpretation and diagnosis.⁴⁸ Ai et al. (2020) conducted a study to evaluate the value and consistency of chest CT scans in the diagnosis of COVID-19 and found that the majority of patients (98%, $n = 56/57$) had initial positive chest CT scans before or within six days of the initial positive RT-PCR findings.²¹ This is in line with other studies; they found that positive diagnoses of COVID-19 were available three days earlier with chest CT scans than with RT-PCR assay.^{30–37} This

indicates that chest CT scans can play a role in rapidly detecting the infection at an early stage.

Several studies have reported that chest CT scans show typical radiographic features in all patients with COVID-19.^{1,37,49} The National Health Commission of China reported that chest CT is of a great value in diagnosing COVID-19, monitoring disease progression and evaluating treatment plans.²⁵ Lee et al. (2020) claim that most of the clinics in China currently prefer to use CT compared to other investigation tools. This preference might stem from the accessibility of CT units in China, CT's ability to diagnose patients at an early stage, concerns associated with other tests specificity and the lack of virus-testing kits.⁵⁰ However, the American College of Radiology (ACR) is against the use of chest CT as a first-line investigation tool to diagnose patients with suspected COVID-19 disease.⁵¹ This might be due to the low specificity of CT in differentiating COVID-19 from other similar illnesses. Similarly the Royal College of Radiologists (RCR) stated that CT does have a well-established role in the assessment of patients presenting with severe respiratory distress, particularly those that deteriorate clinically. However, they confirmed that CT should not be used as a diagnostic assessment of patients with suspected coronavirus infection.⁵² Further challenges related to hygiene may also be another reason for not considering CT as a sole diagnostic tool for patients with COVID-19. This includes managing ventilation, airflow, and sanitising and cleaning the scanner rooms in radiology departments.^{25,53}

Recent studies have revealed that RT-PCR has low sensitivity (60–71%) in diagnosing patients with COVID-19 infection compared to the CT chest.^{37,54,55} Fang et al. (2020) referred to the high sensitivity of CT chest (98%) compared to that of RT-PCR tests (71%).⁵⁵ This is in line with the findings of Xie et al. (2020), who evaluated 167 patients and found that 3% ($n = 5$) of the patients showed initially negative RT-PCR nasopharyngeal and/or throat swabs but simultaneously showed positive results in chest CT scans.³⁷ This finding was supported by Huang et al. (2020), who found that a laboratory test showed a normal white blood cells count with a negative RT-PCR assay; however, a chest CT scan showed multiple peripheral ground-glass opacities (GGO) in the lingual segments.¹ Such false-negative results may be attributed to the low viral load in test samples and/or laboratory errors,^{37,55} and it might be necessary to retest the patient. However, test kits are in short supply or are unavailable in some places.⁵⁴ Therefore, some hospitals have started to use chest CT scans as a primary tool to diagnose COVID-19, though the ACR advises radiographers and radiologists to apply extreme precaution in this practice.⁵¹

In a study by Xie et al. (2020), it was found that all patients presented characteristic CT image features of COVID-19 at an early stage, including GGO and/or mixed GGO and mixed consolidation, confirmed by positive RT-PCR assay during the isolation period.³⁷ Shi et al. (2020) highlighted that symptomatic patients might show changes in chest CT scans prior to obvious symptom onset.⁵⁶ Shi and colleagues indicated that following up with chest CT scans might aid the continuous monitoring of disease changes during treatment.⁵⁶ In their study, Wu et al. (2020) found that most of the patients had mild symptoms and high temperatures; however, the lung manifestations on their chest CT scans were serious. They highlighted the role of chest CT scans in evaluating the severity of COVID-19 infection.⁵⁷

In contrast, Guan et al. (2020) and Chuang et al. (2020) respectively found that 20% ($n = 230/1099$) and 14% ($n = 3/21$) of patients with clinical symptoms and positive RT-PCR findings had normal chest CT findings.^{8,20} Similar results were found by Yang et al. (2020).⁴⁶ Although chest CT scans can show higher sensitivity in COVID-19 diagnosis than RT-PCR assay, Pan et al. (2020) and Fang et al. (2020) refer to the low specificity of chest CT scans.^{55,58} This is

reinforced by Ai et al. (2020), who found that chest CT scans had low specificity (25%) in a recent study of 1,014 patients with COVID-19.²¹ This may stem from the difficulties that radiologists face in distinguishing between COVID-19 and other diseases on chest CT scans. Additionally, Li and Xia (2020) found that two patients confirmed to be infected with COVID-19 did not have CT features typical of COVID-19.^{30–37} This indicates that the differential diagnosis of COVID-19 should be considered when patients present with a fever and cough of unknown origin. It was also advised that all radiologists should familiarise themselves with the typical COVID-19 findings on chest CT scans.^{45,54} Furthermore, radiologists should pay attention while interpreting CT images and be able to differentiate the features of patients with COVID-19 from motion artefacts as some of these patients may face difficulties in following the breathing instructions during CT scans.³⁰ The above studies may suggest that chest CT imaging alone is not sufficient to exclude the diagnosis of COVID-19. Therefore, early chest CT scans combined with other investigation tools, such as RT-PCR assay, may still be required.

Features of COVID-19 in CT imaging

During the early stages of COVID-19 infection, chest x-rays may not be sensitive enough to detect these changes.^{59,60} CT on the other hand, has better sensitivity for the detection of early or mild disease.^{20,62} Focusing on the many faces of COVID-19 for better recognition and accurate diagnosis is always recommended.^{60,62} Below, typical and relatively atypical CT manifestations of COVID-19 will be reviewed to identify the potential imaging features of COVID-19.

GGO is the most common feature.^{29,49,63} It is a hazy increase in attenuation that appears in a variety of interstitial and alveolar processes with preservation of the bronchial and vascular margins.⁶⁴ Consolidation is another typical feature of COVID-19, which is an area of opacification obscuring the margins of vessels and airway walls.^{57,65} GGO with single or multiple focal lesions with or without consolidation in the posterior and peripheral lung segments that are distributed bilaterally is a common feature (Figs. 1 and 2). GGO with reticular or interlobular septal thickening in a typical 'crazy-paving' pattern is often observed, while pure consolidation is relatively less common.^{58–60,65} A recent study showed that the most frequent CT abnormalities observed in patients with COVID-19 were GGO (73/80 cases, 91%), consolidation (50/80 cases, 63%) and interlobular septal thickening (47/80, 59%). Most of the patients had multiple lesions, with an average of 12 ± 6 lung segments involved.⁵⁷

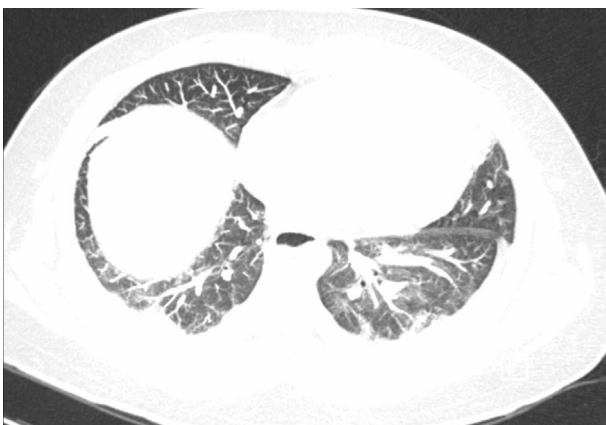


Figure 1. Lower bilateral peripheral consolidations and ground-glass opacities in keeping with the clinical diagnosis of clinical history provided of COVID-19.

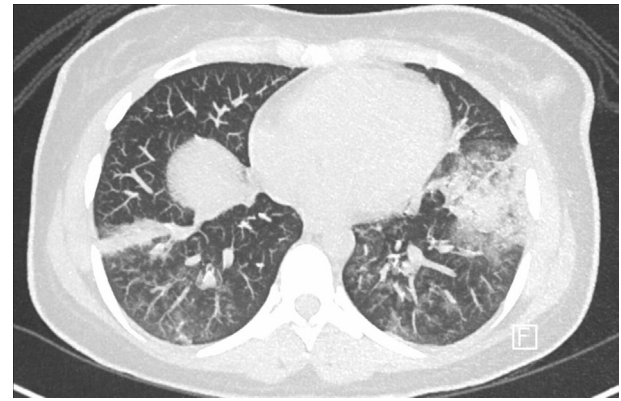


Figure 2. Bilateral mainly basilar peripheral patchy consolidative opacities associated with bilateral basilar ill-defined ground-glass opacities.

CT imaging features of COVID-19 can differ in various stages and patients.⁶⁶ In an early phase, GGO with single or multiple lesions can be found along the sub-pleural areas or bronchi.¹¹ These lesions have nodular or patchy appearance, with thickened blood vessels passing through the GGO. Thickened interlobular and interlobular septa along with halo signs are also seen.⁶⁷ As per published studies, the percentage of this finding occurrence ranges between 14 and 98% (Fig. 3).^{67,68} However, this range significantly increases in the short-term re-examination, where more denser lesions can be seen.⁵⁸ Consequently, crazy paving appearance may be noticed due to the lobular septal thickening and reflecting interstitial lesions.⁶⁷

In severe patients, bilateral multifocal consolidation can be seen, partially fused into massive consolidation with small pleural effusions and even presenting with 'white lung'.⁵⁹ Two weeks after onset, lung involvement has been shown to gradually increase to consolidation.⁶¹ Within 1–3 weeks, this GGO could progress to or co-exist with consolidations.⁵⁶ With a longer time interval, more consolidative lesions can be seen between symptom onset and the CT scan, especially in patients older than 50 years old,⁶⁵ suggesting that this feature can be used as an alert in patient management.⁶⁶ After 3–14 days of re-examination and as the disease progresses,

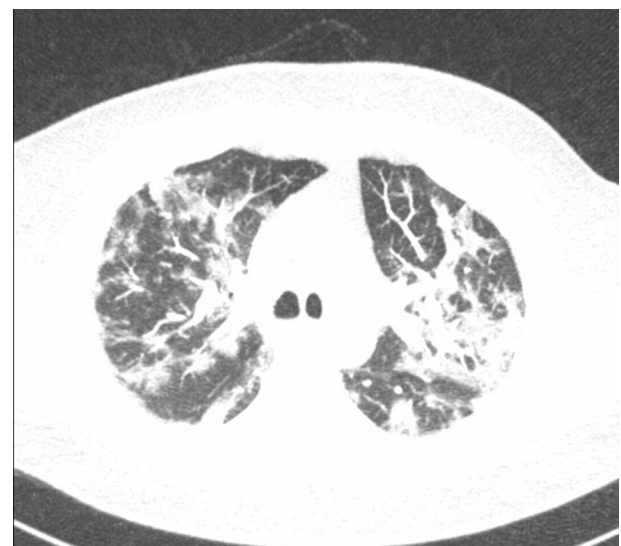


Figure 3. Upper and lower lobe coalescent patchy peribronchovascular ground-glass airspace opacities.

an increase in the range of GGO patches and consolidation can be observed (Fig. 4). The middle and lower lung regions and the posterior lung area are where this progression is mainly distributed.^{11,61} Patients may have single-lobe or multiple-lobe involvement. A study by Y. Pan et al. (2020) found that 30.2% and 44.4% of patients had only one lobe involved and all lobes involved, respectively. 'White lung' is when diffused lesions are seen in the lungs and their density increases significantly. White lung indicates that the patient's condition has worsened because it seriously affects the lung function.⁶¹

It is worth noting that several other CT imaging features can also be observed as the number of COVID-19 cases increases, including air bronchogram, airway and pleural changes, fibrosis, vascular enlargement, air bubble signs, nodules, halo signs, lymphadenopathy, and pericardial effusion.⁶⁶ The percentages of these manifestations occurrence vary widely, therefore, radiologists should be aware while interpreting the CT images for COVID-19 patients to avoid misdiagnosis with typical viral pneumonia and should always link between symptoms and CT features.

Artificial intelligence (AI) combined with CT imaging in COVID-19 diagnosis

Recently, notable advancements have been made in using AI in the diagnostic imaging field.^{69–74} Ardila et al. (2019) highlighted that AI can exceed the performance of human experts in medical imaging diagnosis.⁷⁵ A few studies in the literature have examined the use of AI in COVID-19 diagnosis, although most of them are preprint version of scientific articles that have not been peer-reviewed, thus highlighting the need for further investigation. Kermany et al. (2018) and Rajaraman et al. (2018) referred to the use of AI (deep learning) in detecting bacterial and viral pneumonia in the chest.^{76,77} Two years later, a deep learning (DL) system was developed by Shan et al. (2020), and they found that with the DL the percentage of infection (POI) of lung lobes and bronchopulmonary segments can be automatically calculated and were clinically relevant with the severity of pneumonia. They highlighted the importance of this system in quantifying the changes in the follow-up CT scans of COVID-19 patients and evaluating how the infection progresses under different forms of clinical

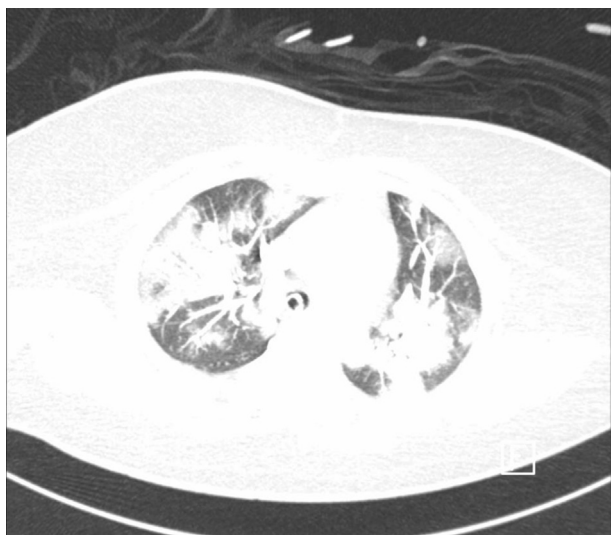


Figure 4. Multifocal bilateral airspace opacities that are more consolidation than ground glass and patchy peripheral distribution, which is related to patient's laboratory proven COVID-19.

management.⁷⁸ This was reinforced by Wang et al. (2020), who used a DL approach to extract the imaging features for COVID-19. They found that the sensitivity and specificity of this method were 74% and 67% respectively.²⁹ However, a common weakness of the above studies was the relatively low number of collected CT images from patients, which may not be representative of all COVID-19 patients. A further study was conducted by Li et al. (2020), who collected 4,536 CT images, and designed and evaluated a three-dimensional (3D) deep learning model to diagnose COVID-19 infections in chest CT scans. This model showed high sensitivity (90%) and specificity (96%) in detecting COVID-19.⁷⁹

Jin et al. (2020) conducted a large-scale study (n = 756) subjects, 496 COVID-19 positives and 260 negatives to compare the diagnostic performance of an AI system with that of five radiologists. It was found that the AI system achieved high sensitivity (94%), specificity (95.47%) and diagnostic accuracy, which was comparable to that of experienced radiologists (94.7% sensitivity).⁶⁹ This parallels with the findings of Chen et al. (2020), who found similar performance between a COVID-19 diagnosis system and an expert radiologist; however, it is important to note that the AI system in this study was validated based upon a small dataset (n = 19 confirmed COVID-19 patients) and one radiologist.⁸⁰ It was found that high classification results were achieved for coronavirus versus non-coronavirus patients with 98.2% sensitivity and 92.2% specificity.⁸¹ A similar result was reported by Xu et al. (2020); however, it is interesting to note that the diagnostic certainty of the AI system was evaluated by creating confidence scores of these forecasts.⁸² A deep learning approach can assist radiologists in diagnosing COVID-19 and can automatically extract lesions within CT images, as indicated by Song et al. (2020) and Bai et al. (2020).^{65,83–86} Bai et al. (2020) indicated that the DL tool achieved a prediction area under curve (AUC) of 0.938 by combining the clinical data and the CT data.⁸³

AI systems, especially deep learning, have been proposed to process and analyse medical imaging data such as chest CT to assist radiologists and physicians to improve diagnosis performance. The AI offers radiologists an opportunity to save time and maximise productivity especially when required to examine a lot of cases.⁸⁷ Bai et al. (2020) assessed the performance of radiologists in differentiating COVID-19 from other viral pneumonia on chest CT.⁸⁸ It was found that radiologists achieved high specificity and moderate sensitivity in distinguishing COVID-19 from other viral pneumonia on chest CT. A further interesting study was conducted by Bai et al. (2020) to assess radiologists' performance with and without AI assistance in distinguishing coronavirus versus non-coronavirus patients. The authors found that radiologists attained a higher accuracy (90%), sensitivity (88%) and specificity (91%) with AI assistance.⁸⁹ This suggests the potential role for the AI system to improve radiologists' routine workflow and diagnostic outcomes related to COVID-19. It is worth noting that all the above studies were retrospective, and prospective studies might be required to further validate AI system in real time to assist physicians' diagnosis.

As can be seen, AI systems can be used in conjunction with chest CT images and patient history (age, gender, clinical information, blood test, symptoms and possible contact with infected people) to improve the detection of the infection. The AI systems helps to segment the exact infected area of the patient's lung from the chest CT and quantify the volume with respect to the total volume of the lung.²⁸ This information might guide the physician in decision-making related to treatment options. The AI system can offer a second opinion to the physician in patients who had normal chest CT or those showing non-specific findings, in order to achieve high sensitivity, specificity and accuracy in COVID-19 diagnosis and management.

The above studies indicate that AI systems could be used to screen and diagnose quickly a great volume of patients with suspected COVID-19, which could lead to accurate discrimination between bacterial pneumonia and viral pneumonia (COVID-19) and decrease unnecessary delays. However, radiologists who are not familiar with such systems may face challenges in getting used to them, which might be problematic because COVID-19 is spreading rapidly. In addition, as most deep learning systems require experts to annotate the lesions in the CT images for disease detection, this will require time and effort from radiologists, which might be considered a big challenge due to the current radiologist shortages in some countries.⁹⁰ Naude (2020) indicate that the use of AI systems are impeded by a lack of data, and by too much data. These limitations require a careful balance between data privacy and public health, and rigorous human–AI interface. It is unlikely that these will be tackled in the current time; more diagnostic data needs to be gathered to train AI and save lives.⁴⁰ The topic of the role of AI in the diagnosis and management of COVID-19 remains open for further investigation.

Conclusion

This review of the available literature on COVID-19 provides insights into the value of CT scan in diagnosing and controlling this infection. Although in some studies chest CT scans have shown high sensitivity in diagnosing COVID-19 compared to RT-PCR tests, chest CT scans alone are not sufficient to detect COVID-19 and can be useful complement to other tools for diagnosing patients with COVID-19 and tracking their prognosis. CT scans can be used as a staging tool to assess the complications of COVID-19 on patients' lungs. The CT findings for patients with COVID-19 show that the infection has mixed and diverse features. The presence of GGO with single or multiple lesions suggests that the disease is in an early stage, while bilateral multifocal consolidation can be seen in an advanced stage. As COVID-19 has similar manifestations to other pneumonia diseases, several AI systems have been proposed and developed in order to differentiate COVID-19 from other pneumonia diseases.

Conflict of interest statement

No conflict of interest.

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