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REVIEW

# Challenges in COVID-19 diagnosis

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**ABSTRACT**

OBJECTIVE: In this narrative review, our aim was to clarify the roles of diagnostic methods used in COVID-19 disease.

BACKGROUND: Coronavirus disease 2019 (COVID-19) caused by coronavirusis emerged as the major healthcare challenge globally. The mainstay approach to limit this virus spread is an early and accurate diagnosis of the viral infection and appropriate quarantine of patients with coronavirus infection.

RESULTS: Real time polymerase chain reaction (PCR) offers a quick detection of the disease in either symptomatic or asymptomatic patients. In literature, there are numerous studies that underline the importance of CT as the first-step diagnostic tool in COVID-19 diagnosis. Even in asymptomatic patients, COVID-19 pneumonia may manifest with chest CT imaging abnormalities.

CONCLUSION: There is a need for an algorithm, which involves a combination of PCR and CT in diagnosis of COVID-19 *(Ref. 85)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, polymerase chain reaction, computed tomography, diagnosis.

## Introduction

In December 2019, a series of pneumonia cases of unknown origin were identified in Wuhan, China. Lately, the etiological agent was defined as the 2019 novel coronavirus (2019-nCoV), and the disease was recently declared by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) (1). After epidemiological investigations carried out by the Wuhan Center for Disease Control and Prevention, it was understood that the patients worked at a local indoor seafood market. In this marketplace, besides fish and shellfish, hedgehogs, badgers, snakes, birds (turtledoves), animal carcasses and animal meat were available before the outbreak began (2).

According to WHO, Coronaviruses belong to the family *Coronaviridae* and the order *Nidovarales*, a family that includes viruses that cause diseases ranging from the common cold to severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (3). It is also known that Coronaviruses are enveloped non-segmented positive-sense RNA viruses broadly distributed in humans and other mammals (4).

Among its signs and symptoms, the most prominent ones are: fever, cough and shortness of breath. These symptoms may appear 2–14 days after an exposure (5). The disease has a high infectivity and is transmitted from person to person in hospital and family settings (6). Limiting human-to-human transmission in order to reduce secondary infections among close contacts and healthcare workers is essential. Based on previous experience of management of MERS and SARS infections, the WHO also recommends avoiding close contact with people suffering from acute respiratory infections, frequent hand-washing especially after a direct contact with ill people or their environment, and avoiding unprotected contact with farm or wild animals. Moreover, people with symptoms of acute respiratory infection should practice cough etiquette, which is to maintain distance, cover coughs and sneezes with disposable tissues or clothing, and wash hands, and enhanced standard infection prevention and control practices are recommended in hospitals, especially in emergency departments (EDs) (7). In this review, we aimed to clarify and compare diagnostic values of CT and PCR in COVID-19.

## Materials and methods

A systematic literature search of PubMed and Embase (Elsevier) databases was performed using the keywords "coronavirus", "nCoV", "computed tomography", "2019-nCoV" and "COVID-19". Furthermore, the WHO database of publications on novel coronavirus was screened for potentially relevant publications. One of the reviewers with an experience in database searches designed the search strategy, which was subsequently revised by other reviewers. With consideration to the date of the earliest confirmed reports of COVID-19, the searches were limited to articles published in 2019 and 2020. A total of 85 articles, reviews and case reports were involved into the study. If the full text of the article was not available and the researchers failed to retrieve it, then the article has been excluded if the abstracts were non-explanatory.

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*Signs, symptoms and laboratory analyses*

The most common symptoms in COVID-19 are related to respiratory system (8). The signs and symptoms of COVID-19 pneumonia are similar to other pneumonias (9). The majority of the patients with COVID-19 are admitted to EDs with mild, influenza-like symptoms. In older patients and those with co-morbidities, the disease may progress to interstitial pneumonia, acute respiratory distress syndrome (ARDS) and death. Death occurs in 2–5 % of the patients (10).

Zhao et al found that angiotensin-converting enzyme 2 (ACE2) was the receptor of COVID-19. In normal lung tissue, ACE2 is mainly expressed by type I and type II alveolar epithelial cells. It was reported that 83 % of alveolar cells expressed ACE2. Therefore, COVID-19 infection seems to show its effects by causing damage to most II type alveolar cells (11).

Extrapulmonary site for virus replication may be digestive system since a high concentration of viral RNA in anal swabs was determined (12). In a study, interestingly, 13.3 % patients had diarrhoea, while no patients had dyspnoea (13).

When laboratory findings of the disease were investigated, white blood cell (WBC) count was usually normal or might be decreased. Besides, lymphocyte count might decrease and hypersensitive C reactive protein (CRP) might be increased. In the study, it was reported that serum lactate dehydrogenase (LDH) was significantly increased, while albumin was decreased. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Tbil), serum creatinine (Scr) and other items showed no significant changes (8, 14–16).

In the study with 85 patients; fever, cough and expectoration were found to be the most common symptoms, 14 patients had a decreased oxygen saturation, 33 had leukopenia, 53 had lymphopenia, and 82 had elevated CRP (17).

It was also reported that the CRP, erythrocyte sedimentation rate and LDH showed a significantly positive correlation with the severity of COVID-19 pneumonia (18). Additionally, an increased expression of IL-2R and IL-6 in serum was shown to be related to the severity of the COVID-19 pneumonia and the prognosis of the patients (8).

Even though the most common symptom was fever, body temperature screening might not be an adequate screening as it can potentially miss travellers incubating the disease or travellers concealing fever during travel and might contribute to the importation of the virus to the countries of destination since patients having the virus in incubation period of the disease might be missed. Therefore, travel restrictions and 14-day quarantine of people who visited areas with a high risk are recommended to prevent spreading of the disease (15, 19). In the study, the median time from exposure to onset of illness was found to be 4 days (20). Patients might also be totally non-symptomatic (21). The virus may transmit from human to human even in non-symptomatic phase and during incubation by patients with brief and non-specific illness. The severity of the disease is known to be milder in children and more likely to infect elderly people with chronic comorbidities (22, 23). There is a lack of evidence about transmission to neonates during labour (4).

*PCR testing in COVID-19*

In such pandemics that we experience, it is essential to reduce anxiety through a rapid diagnosis in order to improve decision making and crisis management (25). Real time PCR is accepted to be a reliable and quick test in detecting both symptomatic and asymptomatic patients (19, 23, 26). It is obtained from swabs, sputum, secretions from the lower respiratory tract, or blood (27). As an advantage, laboratory-developed tests can be adapted for fully automated PCR platforms (28).

However, a negative Real Time PCR test result does not completely rule out COVID-19. It is not rational to use it as a single factor for the management of patients. Experiences indicate that re-testing should be considered in consultation with public health authorities (29, 30). This method also has some disadvantages since it is time-consuming, expensive and it depends upon technical expertise. It is dangerous since the virus must be contained. Also, the presence of viral RNA or DNA does not always reflect an acute disease and contribution of positive PCR results to disease severity is not always explicitly exhibited (31).

The success of this method depends on the presence of viral genome in sufficient amounts at the site of the sample collection that can be amplified (32). For high quality nasopharyngeal specimen collection procedure, the swab must be inserted into the nostril parallel to the palate. The swab must be maintained in place for a few seconds in order to enable secretion absorption and then, the swab must be quickly placed in a sterile tube, containing 2–3 mL of viral transport media. The procedure for collecting oropharyngeal (e.g. throat) specimens entails swabbing the posterior pharynx, avoiding the tongue, and immediate placement of the swab into another separate sterile tube, also containing 2–3 mL of viral transport media (23).

Since viral pneumonias may not be identified in the production of purulent sputum, a nasopharyngeal swab is usually the collection method used to obtain a specimen for testing. Besides, nasopharyngeal specimens, either, may miss some infections. When a deeper specimen is needed, bronchoscopy might be necessary (33). During sampling, professionals must wear personal protective clothing including eye protection (goggles), a filtering facepiece respirator (N95), a surgical cap, gloves, a fluid-resistant gown, and shoe covers (34).

The nasopharyngeal swabs using the real-time PCR method, besides coronavirus, rhinovirus and influenza might also be isolated (35).

As was done in Singapore, in order to win the war in pandemics, it seems vital to increase the number of tests of all suspected individuals and enhanced the surveillance for all the patients with pneumonia and a tracing of contacts of the confirmed cases within their clusters (36).

*Chest computed tomography findings in COVID-19*

In typical COVID-19 pneumonia cases, single or multiple patchy ground glass shadows accompanied by a septal thickening are common. As the disease progresses, the lesion grows, and the ground glass shadow coexists with the solid shadow or the stripe shadow (8). Unenhanced chest CT findings reveal multiple bilateral and peripheral ground-glass opacities (GGOs) in the superior segments of both lower, peripheral lobes without sparing the subpleural regions (37–51).

It was reported that GGOs might be seen in the central area of the lung lobe as round nodular-like lesions, which is different from the common imaging manifestations that are patchy-like lesion in subpleural region in the early stage of the disease (52). It was also reported that CT findings might include bilateral pleural effusions (21). Patchy consolidation and ground-glass opacities observed in chest CT may be distributed along the bronchial bundles or subpleural regions in both lungs (53).

In patients with COVID-19 pneumonia, early-stage lung CT scans mostly show multiple, small patch-like shadows, and interstitial changes, which were more obvious in the extrapulmonary region. These shadows subsequently progressed to multiple ground-glass opacities in both lungs, along with infiltration shadows with a "large white lung" observed in more severe cases. (54).

In the study by Wu J et al, it was reported that the majority of the lesions were multiple and were detected in subpleural region bilaterally. Single GGOs and a combination of GGOs and consolidation were the most common lesions. Pleural parallel sign, intralobular septal thickening, halo sign, reversed-halo sign, pleural effusion and pneumatocele were also determined (55).

Pan F et al classified the abnormalities in chest CT in 4 categories as follows: Early stage (0–4 days after onset of the initial symptom): In this stage, GGO distributed subpleurally in the lower lobes unilaterally or bilaterally. Progressive stage (5–8 days after the onset of the initial symptom): In this stage, the infection rapidly aggravates and extends to a bilateral multi-lobe distribution with a diffuse GGO, crazy-paving pattern and consolidation. Peak stage (9–13 days after the onset of the initial symptom): In this stage, the involved area of the lungs slowly increase to the peak involvement and dense consolidation became more prevalent. The findings included a diffuse GGO, crazy-paving pattern, consolidation and residual parenchymal bands. Absorption stage (≥ 14 days after the onset of the initial symptom): GGOs may be observed due to consolidation absorption. Crazy-paving pattern is not observed (56). Even in asymptomatic patients, COVID-19 pneumonia may manifest with chest CT imaging abnormalities (38).

There are also some atypical presentations seen in chest CT in COVID-19 pneumonia patients. Consolidative opacities superimposed on GGO may be found in a small number of cases, mainly in the elderly population. In the later stages of the disease, septal thickening, bronchiectasis, pleural thickening, and subpleural involvement might be seen. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax are uncommon, but may be seen with a disease progression (16, 49, 57). Also, airway changes, pleural changes, fibrosis, nodules, etc., were demonstrated in COVID-19 patients (58). In the report, pneumothorax was also observed (59).

Pneumonia related to COVID-19 more likely affects multiple lobes and the size of the lesions vary from 1 cm to more than 3 cm (16, 60).

It is also suggested to perform repetitive chest CTs in order to determine the prognosis of the disease. It is known that GGOs may evolve to consolidation as the disease progresses (58, 61, 62). On the follow-up CTs, progressive opacifications, consolidation, interstitial thickening, fibrous strips and air bronchograms may be found compared to initial CT (18).

In the intermediate stage of the disease, an increase in the number and size of GGOs and progressive transformation of GGOs into multifocal consolidative opacities, septal thickening, and development of a crazy paving pattern might be observed. After about 2 weeks, consolidative opacities gradually resolve and the number of lesions and involved lobes decrease (57).

In the follow-up CT scan, the pulmonary vessels enlargement in areas, where new lung infiltrates develop, can be an early radiological sign of lung impairment (63). In the case report, CT showed fibrous lesions after a recovery (64). Small amounts of patchy ground-glass opacities and fibrous stripes in bilateral lungs may also persist (41).

As seen in SARS and MERS pneumonias, CT is recommended in COVID-19 for follow-up in individuals, who are recovering from COVID-19 to evaluate the long-term or permanent lung damage including fibrosis (65).

*Role of computed tomography in COVID-19 pneumonia*

Timely diagnosis of COVID-19 pneumonia is the mainstay of rapid management and treatment of the disease. Definitive diagnosis of the disease is based on PCR test, however, radiological findings have indispensable value in diagnosis. Given the fact that the most frequent imaging finding is GGO, careful interpretation of the chest radiographs is needed as GGOs may look very faint. CT scans are recommended in patients with suspicious lung abnormality (44, 53, 66, 67). However, it must be kept in mind that even though CT provide an early diagnosis and stratification of the disease, it may be totally normal in some patients (68).

In the study with 80 patients, 55 (68.75 %) showed abnormal chest CT images (69). In another study, 56 % of early patients had a normal CT. It was concluded that chest CT had a limited sensitivity and negative predictive value early after symptom onset. CT imaging cannot be used as a reliable standalone tool to rule out COVID-19 infection (70). Chung et al revealed that 14 % of the patients with COVID -19 had entirely normal chest CT examinations at presentation without GGOs or consolidation (71). In the study, two of 5 children with confirmed COVID-19 infection had no sign of abnormality at chest CT (72). CT abnormality was not determined in 17.9 % with non-severe disease and in 2.9 % with severe disease (67). In another study with 15 patients, the first nasal or pharyngeal swab samples in all 15 cases were positive, while 6 patients had no lesions in CT (73). In the report, 8 of 101 patients with COVID-19 had no abnormal findings in CT (50). Wei Xia et al reported that normal CT findings in COVID-19 was 20 % (74). Another report revealed that 9 mild patients among 50 patients were negative in CT imaging (15). Among 149 PCR positive patients, 17 patients had normal CT at the time of admission (17).

The evidence revealed that a normal chest CT scan does not exclude the diagnosis of 2019-nCoV infection (75).

Another disadvantage of CT use as a sole diagnostic tool in COVID-19 pneumonia is that the CT manifestations of COVID-19 pneumonia are similar to those of SARS, which are usually fast changing, multiple, and migratory, but the distribution of lesions is mainly in the middle and peripheral zones of the lung (1, 8, 76). Similarities can be found in pneumonias related to MERS, H7N9 pneumonia, H1N1 virus infection, SARS, coronavirus infection, and avian influenza A (H5N1) (64, 71, 77). The CT findings of COVID-19 also overlaps with the CT findings of adenovirus infection (78). This fact can be problematic in paediatric patients since coinfection is common in this group (74).

*Chest computed tomography vs PCR tests*

There is an ongoing debate on the diagnostic role of chest CT in COVID-19 pneumonia. Chest CT has a high sensitivity for diagnosis of COVID-19. Even though there are studies suggesting chest CT as the primary tool for the current COVID-19 detection in epidemic areas (8, 79, 80), nucleic acid tests are recommended for a prompt diagnosis and treatment (12, 64, 81).

However, the positive ratio of PCR detection for COVID-19 may be only 47.4 % in the suspect patients, according to the study (82). Additionally, in the report, five out of 167 patients, whose PCR tests were negative, were diagnosed as COVID-19 pneumonia according to chest CT findings (83). While the rate of positivity in chest CT was found to be 88 %, the rate of positivity in PCR was found to be 59 % of the patients (23). This result may be associated with similar CT findings observed in other viral pneumonias, but it is difficult to rely on nucleic acid detection alone (84). It was also reported that follow-up chest CTs improve earlier that RT-PCT results turns negative (79). This finding emphasizes the role of chest CT in determining a disease progression. Dasheng et al. recommends CT as the first and immediate reference for doctors to screen the highly suspected cases and to take necessary actions while PCR serves as a confirmation tool, the results of which could be utilized later to decide (85). Nevertheless, a combination of CT imaging and nucleic acid tests is more likely to have a superior diagnostic value, when compared to each parameter alone (84).

## Conclusion

PCR testing for COVID-19 diagnosis has some disadvantages: it relies on the presence of adequate viral genome in the sample site, probability of missing the period of viral replication and incorrect sampling method (32). CT imaging, as an alternative, also has some disadvantages. The radiation exposure and a weak diagnostic value, when the infection is limited to upper respiratory system or performed in the early stage, can be given as examples. Also, CT is problematic in differential diagnosis of various viral pneumonias. In conclusion, an algorithm, which involves a combination of PCR and CT must be determined in order to maintain an accurate and timely diagnosis of COVID-19.

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