

Role of radiology in RT-PCR negative COVID-19 pneumonia: Review and recommendations

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ABSTRACT

Currently, RT-PCR is the gold standard for diagnosing SARS-CoV-2 infection. However, due to the time-consuming laboratory tests and the low positivity rate of RT-PCR, it cannot be an ideal screening tool for infected population. In this review article, we have reviewed studies related to RT-PCR and CT chest and we would like to give our recommendations. Depending upon the patient's clinical symptoms and radiology imaging typical of viral pneumonia compatible with COVID-19 infection, clinicians need to consider isolation of these patients early even if the RT-PCR test is negative.

Keywords: COVID-19, CT, negative, RT-PCR

Introduction

The first case of coronavirus infection was documented in November 2019 in Wuhan in China. Following that, a Pandora's box unfurled with a continuous rise in the number of cases that led WHO to declare it as a "Health emergency of international concern" in January 2020 and subsequently as a pandemic in March 2020.^[1] The first case in India was diagnosed in January 2020 with an upsurge in cases in March 2020. The number of cases continues to increase phenomenally reached approximately 7 million in India in October 2020.^[2] The corona virus infectious disease was named as COVID-19. The various tests are used including reverse transcriptase-polymerase chain

reaction (RT-PCR) and rapid antigen test for assessment of current infection and antibody tests for assessment of remote infections.

The respiratory system is predominantly affected by the virus leading to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing significant mortality and morbidity burden for the health system.^[3] The various imaging modalities like Radiographs, Computed tomography (CT) scans, etc., has also being used with variable specificity and sensitivity. Imaging contributes to the patient management and monitoring of the disease progression apart from the initial diagnostic dilemmas.

RT-PCR test

The RT-PCR with virus RNA extraction is a type of nucleic acid amplification tests which is used to detect coronavirus in various body secretions, including the nasopharyngeal and oropharyngeal secretions. RT-PCR test, although, remains the gold standard for the diagnosis, it has an estimated sensitivity of 65-75% and specificity of 99%.^[4] Results of the RT-PCR tests depend upon

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the day of illness, sample collection site, and type of testing kit with the sensitivity of bronchoalveolar lavage fluid markedly more than nasal and pharyngeal swab.

RT-PCR false-negative rates are 65-68% when sample were taken within 4 days of infection, reduces to approximately 35-38% at 5-6 days of infection and approximately 20% on the 8th day of infection.^[5] Many factors have been attributed to false negativity of RT-PCR including improper swab collection techniques and early testing if done before 5 days. Another fallacy of RT-PCR is that it is designed for a specific prevalent strain that may undergo mutations over time leading to false-negative results. False-positive results of RT-PCR have been very rarely documented with cross-contamination being the primary reason for the same.^[5,6]

Rapid antigen test

These are immunoassays which detect the presence of specific viral antigen, performed on nasopharyngeal or nasal swabs. Antigen tests comprise immunoassays that detect a specific viral antigen to test for acute viral infection. These are specimens derived from the nasopharyngeal or nasal swab and are placed directly into the extraction buffer or reagent. The advantage of rapid antigen testing is they can be used in point of care settings, are relatively inexpensive, and give rapid results within 15 minutes of testing. The efficacy of rapid antigen tests primarily depends upon its use in the appropriate clinical scenarios and have increased efficacy in early stages of infection, have a role in screening of high-risk congregate settings. However, the biggest drawback is the sensitivity ranging from 30% to 80% which is drastically lower than RT-PCR.^[7]

Antibody test

These are based upon the detection of IgG and IgM antibodies in the blood against the coronavirus. The presence of antibodies suggest possibility of remote infection and not useful for the diagnosis of current infection.

Radiological investigation

The coronavirus enter through the respiration and enters the lung and primarily affect the lungs and leading to COVID-19 pneumonia. The lung parenchymal changes can be utilized for the primary diagnosis as well as to assess the progression of disease in the patients. The lung parenchymal changes are seen using various imaging modalities including radiograph, ultrasound and CT scan.

Imaging evaluation using chest radiograph and chest CT at the time of presentation have a sensitivity of 69% and 97% for the diagnosis of COVID-19 pneumonia, respectively. The multinational consensus statement given by the Fleischner Society in April 2020, proposed to avoid imaging in suspected cases having only mild symptoms except in cases where there are risks for disease worsening and has recommended imaging evaluation only for triaging of the suspected cases of COVID-19 who have moderate to severe clinical symptoms with a high pre-test probability of disease.^[8]

Imaging of pulmonary involvement by COVID-19 has been overwhelmingly evaluated and documented in the scientific literature, most of the literature reviews are mainly focused on the CT findings. As the disease is widely spreading and roping in the remote areas, which are lacking healthcare infrastructure, radiographs can aid physicians in early identification and adequate management and referral.^[9] Patient mobilization for CT Thorax is required which predisposes to increased risk of cross-infection, if necessary precautions are not undertaken. In contrast, portable chest X-ray units can be installed in the COVID-19 wards as well as in the intensive care units optimizing the logistics and reducing the risk of cross infections. Keeping this in mind, new studies are coming up with the increased usage of bedside ultrasound and the portable chest radiographs for the COVID-19 assessment.^[10]

Chest radiographs

Chest radiograph is useful early investigation in case of COVID-19 pneumonia. The chest radiograph can be utilized for early isolation of suspected cases in areas where there is a lack of resources with a very high number of cases and having long-awaited PCR turnaround times.^[11]

The various abnormal imaging manifestation of the chest radiograph in COVID-19 cases includes multifocal ground-glass opacities in peripheral distribution, consolidations, reticular opacities predominantly in the bilateral lower lobes as the commonest features. Apart from these other radiographic patterns like peribronchial consolidations, nodule or mass-like opacities, mid-upper zone opacities, and extensive diffuse airspace opacities giving ARDS picture also have been described.^[12]

HRCT (high resolution computed tomography)

The HRCT is very sensitive in detecting small changes which usually not seen on chest radiograph. The characteristic changes seen are multifocal ground glass opacity, consolidation, reticular opacity, fibrosis, etc. Presence of nodules, pleural effusion, pneumothorax, lymphadenopathy is uncommonly seen. The characteristic involvement is bilateral multifocal subpleural, peripheral ground glass opacity typically involving bilateral lower lobes of lung. The various signs have been described on HRCT including parallel pleura sign, vascular dilatation sign, paving stone sign, halo sign, reverse halo sign, target sign, etc.^[13] These signs are although non-specific but helpful in diagnosis.

The various changes seen on HRCT can be divided into exudative, organizing and recovering phase. The exudative phase shows multifocal ground glass opacity as predominant finding along with consolidation and reticular opacity with in bilateral lungs typically peripheral and subpleural location. The organizing phase shows more florid and contiguous involvement of large area of consolidation as predominant finding along with ground glass and reticular opacity. The involvement is predominantly involve peripheral lung but can also involve central lung in severe cases. The recovering phase showing predominantly reticular and fibrotic opacity along with consolidation.

The severity of lung involvement by COVID-19 has been described using various scoring system.

In most widely used scoring system a score of 1 to 5 was given for each of the lobes of the lung. The score was given 1 for <5%, 2 for 5-25%, 3 for 25-50%, 4 for 50-75% and 5 for >75% involvement of each lobes. The minimum total score is 0 and maximum is 25. The mild category having score of 1-8, moderate having score of 9-15 and severe having score of 16-25.^[14]

The Dutch society has given the CO-RADS score (COVID-19 Reporting and data system) similar to the BI-RADS (Breast imaging reporting and data system) system, used universally to describe various breast lesions. The CO-RADS score predict the chances of lung lesions having the COVID-19. CO-RADS score was given from 0-6 as described in Table 1.^[15]

With the increase use of HRCT chest in patient having RT-PCR negative with high clinical suspicion, it was realized that HRCT may be more sensitive in comparison to RT-PCR test. Many of these patients tested positive on repeat second and third RT-PCR tests. Hence it was extensively discussed about the RT-PCR vs HRCT in diagnosis of COVID-19.^[16,17]

Although the HRCT is more sensitive in comparison to RT-PCR, the disadvantage is low specificity, with similar changes can be seen in lung by Non-COVID-19. The other disadvantage of radiation exposure, issue with sanitization of CT scanner, risk of cross infection of health care worker/other patients and delaying the CT scan to the patients with other indications. So ideally

CT should be performed in patient with RT-PCR negative but high index of clinical suspicion, in patient with moderate and severe symptoms who developed respiratory or nonrespiratory complications.

Chest CT or RT-PCR for diagnosis of COVID-19?

Any test recommended for screening should have high sensitivity whereas test recommended for treatment should have high specificity. Parallel testing with simultaneous RT-PCR and CT imaging at the same time can increase the sensitivity of tests for the diagnosis of COVID-19. Serial testing, i.e., chest CT followed by RT-PCR can increase the specificity and help in starting early treatment.^[18] Primary care physicians should use a holistic approach in diagnosing, isolating and treating patients with COVID-19 infection. Combined approach with exposure history, epidemiological features and clinical symptomatology in patients with initial negative RT-PCR tests, CT chest may be used to identify COVID-19 when the index of suspicion is very high.

There may be overlap in CT imaging features between COVID-19 pneumonia and other viral pneumonias, but some false-positive cases may be acceptable in reality in order to isolate probable cases early considering the rapid spread of this pandemic disease. Due to lack of sensitivity of RT-PCR, these false positive cases on CT may be actually true positives as RT-PCR may be an imperfect gold standard test for the diagnosis of COVID-19.^[19] CT chest has higher sensitivity (86-98%) but lower specificity (25%).^[20] Few relevant studies published recently have been highlighted in Table 2 below.

Table 1: Categories and Level of Suspicion for Pulmonary Involvement in COVID-19

CO-RADS Category	Level of Suspicion	Summary
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very low	Normal or non-infectious
2	Low	Typical for other infection but not COVID-19
3	Equivocal/unsure	Features compatible with COVID-19 but also other diseases
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

Table 2: Literature review

Study	Date	Conclusion of the study
Fang et al. ^[17]	February 2020	In a series of 51 patients with chest CT and RT-PCR assay performed within 3 days, the sensitivity of CT for COVID-19 infection was 98% compared to RT-PCR sensitivity of 71% (p<0.001)
Feng et al. ^[21]	April 2020	Chest CT is more sensitive than RT-PCR to detect early change of COVID-19 in cases which RT-PCR tests show negative results. In this case, fifth RT-PCR test was positive with initial positive CT and subsequent four negative RT-PCR tests.
Long C, et al. ^[4]	May 2020	RT-PCR may produce initial false negative results. The authors suggest that patients with typical CT findings but negative RT-PCR results should be isolated, and RT-PCR should be repeated to avoid misdiagnosis
Ai T, et al. ^[19]	August 2020	The positive rates of RT-PCR assay and chest CT imaging in study cohort were 59% and 88% respectively. With RT-PCR as a reference, the sensitivity of chest CT imaging for COVID-19 was 97%. With analysis of serial RT-PCR assays and CT scans, 60% to 93% of patients had initial positive chest CT consistent with COVID-19 before the initial positive RT-PCR results.
Xie X, et al. ^[22]	August 2020	A combination of repeated swab tests and CT scanning may be helpful when for individuals with high clinical suspicion of nCoV infection but negative RT-PCR screening

Key Points

- CT chest should not be used as the first line modality to diagnose COVID-19.
- Holistic approach considering clinical features, history, epidemiological factors combined with imaging may be done if the index of suspicion is very high.
- Concept of parallel and serial testing may be applied in the field when the infection rate is very high.

Conclusion

In patients with initial negative RT-PCR tests, combined approach with exposure history, epidemiological features, and clinical symptomatology along with CT chest may be used to identify COVID-19.

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Conflicts of interest

There are no conflicts of interest.

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