

Review Article

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Clinical Performance of RT-PCR and Chest CT Scan for Covid-19 Diagnosis; a Systematic Review

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Abstract

Context: Due to their availability and rapid turnaround time, the supplemental role of chest computed tomography (CT) scan and real-time polymerase chain reaction (RT-PCR) is growing for early diagnosis of patients with COVID-19. However, due to the low efficiency of viral nucleic acid detection as well as low specificity of chest CT scan for detecting COVID-19 pneumonia, both methods show incomplete clinical performance for proper COVID-19 disease diagnosis. The purpose of this review was to compare the clinical performance of two methods and to evaluate the diagnostic values of chest CT scan and RT-PCR for suspected COVID-19 patients.

Evidence acquisition: We systemically searched PubMed, Cochrane, from December 2019 to the end of April 2020. Clinical research papers in goal fields that reviewed COVID-19 patients, whom chest CT scan, and PCR testing were performed together were included.

Results: In total, we found 536 studies; and finally 168 studies were shortlisted. Following title and abstract screening, we reached 83 studies based on the inclusion and exclusion criteria. Conducted screen by the full text covered 28 studies, which led to data extraction. By the full-text assessment of 28 included studies, we found 4486 assessed patients. Totally, 3164 patients had positive chest CT scans, and 3014 patients had positive PCR results. The finding showed that recent studies on the diagnostic performance of RT-PCR and chest CT scan have commonly been reported from China.

Conclusion: The results from this review indicate that the chest CT scan should be used for symptomatic and hospitalized patients. Moreover, chest CT scan should not be used as a primary screening tool for diagnosing COVID-19. Application of RT-PCR as the first line diagnosis is still recommended.

Key words: COVID-19; Diagnosis; Real-Time Polymerase Chain Reaction; Tomography, X-Ray Computed

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CONTEXT

Since December 2019, a cluster of pneumonia cases caused by a novel coronavirus named COVID-19 originating in Wuhan City, China, has spread to more than 200 countries globally, with prolonged human-to-human transmission. Subsequently, it has alarmed as a public health emergency of international concern ⁽¹⁾. The clinical spectrum of COVID-19 ranged from either asymptomatic or mild to moderate respiratory infection to severe cases who were rapidly developing acute respiratory distress syndrome (ARDS) or multi-organ failure resulting in fatal outcomes ⁽²⁻⁴⁾. Therefore, the early diagnosis for both asymptomatic and symptomatic cases is of paramount importance for the management of

patients as well as for infection control measurements to mitigate the transmission to other members of society. Currently, the gold-standard method for the diagnosis of COVID-19 is a positive polymerase chain reaction (PCR)-based viral ribonucleic acid (RNA) detection, which is also helpful for discharging patients from isolation ⁽²⁾. In addition, recent studies explored that COVID-19 pneumonia has typical chest computed tomography (CT) scan characteristics with subsequent time-course features ⁽⁵⁻⁸⁾. Therefore, chest CT scan has become a routine tool for detection, diagnosis, and monitoring of COVID-19 pneumonia in both symptomatic and asymptomatic cases. However, both diagnostic

methods have shown to suffer from some limitations. A proportion of false-negative results have been reported for Reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19⁽⁹⁻¹¹⁾. The explanation for the low efficiency of viral nucleic acid detection may include the following. Inappropriate sampling (improper clinical sampling, different levels of viral load at the time of examination, etc.), technical issues (immature development of nucleic acid detection technology for COVID-19, the risk of primer/probe mismatch due to the high mutation rate of the virus, etc.) and the lack of standardization and validation processes across different laboratories and hospitals. On the other hand, the attributable features of COVID-19 pneumonia on the chest CT scan, such as ground-glass opacity (GGO) or bilateral involvement, are nonspecific and could be observed in other viral pneumonia^(5, 12). Therefore, the diagnostic utility of chest CT scan in a clinical setting, especially where the occurrence of COVID-19 pneumonia is lower than that of other respiratory diseases, is still unidentified⁽¹³⁾. These problems can potentially contribute to the delay in the effective diagnosis and monitoring of the patients and preventive quarantine. Consequently, some experts suggest that the application of clinical, imaging and laboratory procedures is necessary for confirmation of the final diagnosis⁽¹¹⁾. We, therefore, aimed to analyze the published scientific literature concerning the comparison between the diagnostic values of chest CT scan compared with RT-PCR testing and to better understand their usefulness for proper diagnosis of COVID-19.

EVIDENCE ACQUISITION

Search strategy

We systemically searched PubMed, Cochrane, from December 2019 to the end of April 2020. Our search was restricted to original articles in the English language. In the search strategy for searching “Diagnostic Performance of Chest CT scan versus Real-Time PCR for COVID-19 patients”; we used the following keywords and medical subject headings (MeSH): “SARS-CoV-2” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS Coronavirus-2” OR “Novel Coronavirus 2019” OR “COVID-19” OR “Coronavirus disease 2019” AND “PCR” OR “Molecular detection” OR “Molecular diagnosis” OR “RT-PCR” OR “Real time-PCR” AND “CT scan” OR “Imaging techniques” OR “Chest radiology.” Two independent researchers performed the search, and results were triple checked by a third researcher.

Inclusion criteria

Clinical research papers in goal fields that reviewed COVID-19 patients, whom chest CT scan, and PCR testing were performed together were included. Articles published, in a peer-reviewed journal, articles indexed in Medline during December 2019 to the end of April 2020 included in this review.

Exclusion criteria

Articles, which reported patients who went under CT scan only or PCR testing separate, in vitro studies, literature reviews (The literature reviews were checked for relevant citations), papers published in a language other than English, and case reports articles were excluded. Personal communication and letter to the editor with relevant experts were also dismissed.

Data extraction and quality assessment

Data included author name, sample size, CT scan results, PCR results, and main finding of studies. In order to evaluate the quality of screened studies, data extraction, and study quality assessment were performed independently by two reviewers, and the third researcher resolved conflict cases.

RESULTS

In total, we found 536 studies published from December 2019 to the end of April 2020 by the advanced search strategy on PubMed and Cochrane. Finally, after the exclusion of duplicates, 168 studies were shortlisted. Following title and abstract screening, we reached 83 studies based on the inclusion and exclusion criteria. Conducted screen by the full text covered 28 studies, which led to data extraction (Figure 1). The data extraction

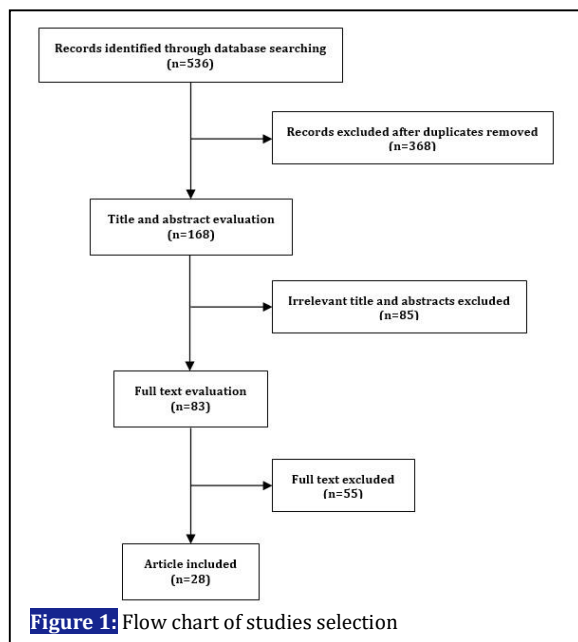


Table 1: Comparison of clinical performance of chest CT scan versus Real Time PCR from available studies

No.	Author	Sample Size	Positive Chest CT scan	Positive RT-PCR test
			n (%)	
1	Ai et al. ⁽¹⁰⁾	1014	888 (87.6)	601 (59.3)
2	Caruso et al. ⁽²⁷⁾	158	102 (64.6)	62 (39.2)
3	Chen J et al. ⁽²⁸⁾	249	163 (65.7)	248 (99.6)
4	Chen N et al. ⁽²⁹⁾	99	99 (100)	99 (100)
5	Chen Y et al. ⁽³⁰⁾	42	40 (95.2)	28 (66.7)
6	Cheng et al. ⁽³¹⁾	33	31 (93.9)	11 (33.3)
7	Fang et al. ⁽¹¹⁾	51	50 (98.0)	36 (70.5)
8	Himoto et al. ⁽¹³⁾	21	211 (100)	6 (28.5)
9	Huang C et al. ⁽³²⁾	59	41 (69.4)	41 (69.4)
10	Huang G et al. ⁽³³⁾	30	25 (83.3)	30 (100)
11	Kim et al. ⁽³⁴⁾	28	13 (46.4)	28 (100)
12	Lei et al. ⁽³⁵⁾	14	10 (71.4)	14 (100)
13	Xu et al. ⁽³⁶⁾	90	69 (76.6)	90 (100)
14	Young et al. ⁽³⁷⁾	18	6 (33.3)	18 (100)
15	To et al. ⁽³⁸⁾	23	15 (65.2)	23 (100)
16	Wang et al. ⁽³⁹⁾	1012	917 (90.6)	1012 (100)
17	Wu et al. ⁽⁴⁰⁾	80	55 (68.8)	80 (100)
18	Shi et al. ⁽⁴¹⁾	81	81 (100)	81 (100)
19	Long et al. ⁽⁴²⁾	36	35 (97.2)	30 (83.3)
20	Pan et al. ⁽⁶⁾	21	17 (80.9)	21 (100)
21	Yang et al. ⁽⁴³⁾	149	132 (88.5)	149 (100)
22	Zhao et al. ⁽⁴⁴⁾	34	19 (55.9)	19 (55.9)
23	Xie C et al. ⁽⁴⁵⁾	19	17 (89.5)	9 (47.4)
24	Su et al. ⁽⁴⁶⁾	23	14 (60.8)	23 (100)
25	Xie, X et al. ⁽⁹⁾	167	160 (95.8)	162 (97.0)
26	Sun et al. ⁽⁴⁷⁾	788	104 (13.2)	54 (6.9)
27	Albano et al. ⁽⁴⁸⁾	65	6 (9.2)	5 (7.7)
28	He et al. ⁽⁴⁹⁾	82	28 (34.1)	34 (41.5)

procedure is shown in table 1. By the full-text assessment of 28 included studies, we found 4486 assessed patients. Totally, 3164 patients had positive chest CT scans, and 3014 patients had positive PCR results. The finding showed that recent studies on the diagnostic performance of RT-PCR and chest CT scan have commonly been reported from China. Results indicated that the number of studies from China was higher than the other five countries we analyzed in this study. Our results in this review indicated that chest CT scan should be used for symptomatic and hospitalized patients. However, chest CT scan should not be used as a primary screening tool for diagnosing COVID-19. Application of RT-PCR as the first line diagnosis is still recommended.

DISCUSSION

Since the recognition of the SARS-CoV-2 virus in late December 2019, more than 4 million people are known to have been infected. SARS-CoV-2 causes COVID-19, which has been led to over 250,000 deaths worldwide so far ⁽¹⁵⁾. At the moment, in the lack of specific vaccines or therapeutic drugs against COVID-19, it is crucial to diagnose the disease at the early stage and immediately isolate infected patients from the

healthy population.

According to the latest guidelines released by the Chinese government, the key indicator for the confirmation of the diagnosis of COVID-19 is based on RT-PCR or sequencing of the gene for respiratory or blood specimens ⁽¹⁰⁾; however, there are some limitations in collection and transportation of samples and also the kit performance. Chest CT scan is a common imaging tool for pneumonia diagnosis; it is relatively easy to perform and fast ⁽¹⁶⁾. The initial diagnosis of COVID-19 is essential for infection control and treatment of disease. In the epidemic area, chest CT scan in comparison with RT-PCR, maybe a more reliable, practical, and rapid method to diagnose COVID-19 ⁽¹⁰⁾. On the other hand, in terms of RT-PCR as a gold standard method for COVID-19 diagnosis, we still believe in its application as the first line diagnosis. However, a rate of 10-40% RT-PCR false-negative results made this technique insufficient for proper detection. A major obstacle for this low efficacy might be related to sampling errors, markedly inappropriate timing of sampling, which is reflected by variations in viral load in upper versus lower respiratory tract. Wang et al. showed that SARS-CoV-2 viral load increased in sputum similar to levels in the throat and nasopharyngeal swabs in

the early stage of the disease ⁽¹⁷⁾. Recent studies also reported that testing of different types of specimens from multiple sites might reduce false-negative and improve the sensitivity test results ^(17, 19). Moreover, in late post-infection days, the viral load levels were still higher than that of upper respiratory tract specimens. These results indicated complicated viral kinetics in the respiratory tract of patients, making the choice of specimens more puzzling. In a retrospective study, Ai et al. analyzed 1014 hospitalized patients with suspected COVID-19 in Wuhan, China with patients undergoing both serial RT-PCR testing and chest CT scan; they showed that chest CT has higher sensitivity for the diagnosis of COVID-19 as compared with initial RT-PCR from pharyngeal swab samples ⁽²⁾. In a study, medical data from 1099 hospitalized patients and outpatients with laboratory-confirmed COVID-19 were analyzed. Confirmed cases of COVID-19 were defined as a positive result on real-time RT-PCR assay of nasal and pharyngeal swab specimens; however, chest CT scan findings suggested infection in 86% (n = 840) of patients. Positive CT findings included ground-glass opacity, patchy local shadowing, bilateral patchy shadowing, or interstitial abnormalities. Additionally, in 17.9% (n=157) of patients with non-severe disease and in 2.9% (n=5) of patients with severe disease did not observe radiographic or CT abnormality ⁽¹⁸⁾. A study reported that the Chest CT test is essential to avoid COVID-19 missed diagnosis due to false-negative RT-PCR ⁽²⁰⁾. Chinese guidelines recommended that suspected COVID-19 patients with negative RT-PCR tests should re-tested 24 hours later. Patients can be discharged from the hospital after two consecutive negative RT-PCR tests and with no suspicion or clinical manifestation of the disease ⁽²¹⁾.

World Health Organization (WHO) advises the lower respiratory tract samples (expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage in ventilated patients) for patients who showed negative upper respiratory sample (nasopharyngeal /oropharyngeal swabs) PCR results ⁽²²⁾. Screening and monitoring of patient conditions in Italy and China are performed by

Chest CT scan alongside RT-PCR ^(22, 23). Screening criteria including fever, chest CT scan abnormalities, reduced white cell, or lymphocyte counts for diagnosing of COVID-19; individuals with these criteria for confirmation of COVID-19 would be tested by RT-PCR ⁽²⁴⁾. WHO suggests chest CT scan for the patient with severe pneumonia ^(21, 25). American College of Radiology, American Society of Emergency Radiology and the Society of Thoracic Radiology recommended that chest CT scans are not recommended as a first-line test to diagnose COVID-19 ⁽¹⁴⁾. Kings College Hospital guidelines reported that chest CT scan has higher sensitivity in the early stage of COVID-19 disease than RT-PCR test, and chest CT scan abnormalities may appear before PCR positivity; however, some studies have not shown this pattern ⁽²⁶⁾.

CONCLUSIONS

The results from this review indicate that the chest CT scan should be used for symptomatic and hospitalized patients. Moreover, chest CT scan should not be used as a primary screening tool for diagnosing COVID-19. A proportion of COVID-19 patients show false-negative RT-PCR results. Therefore, we recommend careful respiratory tract sampling and considering the appropriate timing and correct anatomical site (in relation to viral kinetics in individual patients) to avoid false-negative detection outcomes. In brief, for moderate to severe as well as hospitalized COVID-19 patients, a synergy of both methods is recommended.

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AUTHORS' CONTRIBUTION

All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

CONFLICT OF INTEREST

None declared.

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