REVIEW ARTICLE

Comparison of PCR Test Accuracy with Laboratory Data and CT SCAN in COVID-19: A Systematic Review

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Abstract

Background: Given the novelty of COVID-19, reviewing diagnostic methods can be of great help to community health policymakers. Considering the importance of diagnosing COVID-19 and the need for reducing the number of false positive and false negative cases that appear to be different in various diagnostic methods, this systematic review aimed at comparison of PCR test accuracy with laboratory data and CT SCAN in COVID-19.

Methods: In this systematic review, EMBASE (Elsevier, 2018), MEDLINE (National Library of Medicine, 2018), Scopus, ProQuest, Web of Science (Clarivate Analytics, 2018b), and Google Scholar data bases were searched for the studies published prior to 3 April 2020. Based on the inclusion criteria, 20 out of 859 primarily screened studies were finally assessed.

Results: The results indicated that the laboratory diagnosis of viral nucleic acid could have false-negative results, and serological testing of virus-specific IgG and IgM antibodies should be used as an option for diagnosis. Moreover, chest Computerized Tomography (CT) was found to be more sensitive in comparison to Reverse Transcription Polymerase Chain Reaction (RT-PCR) (98% vs. 71%). Hence, the articles offered the combined use of chest CT, SARS-CoV-2 RT-PCR, and multiplex PCR.

Conclusion: Follow-up RT-PCR and chest CT are necessary in COVID-19. In addition, serological testing of virus-specific IgG and IgM antibodies along with laboratory diagnosis of viral nucleic acid can lead to the highly sensitive and accurate diagnosis. Moreover, Enzyme-Linked Immunosorbent Assay (ELISA) is one of the cost-effective methods in epidemic conditions in low- and middle-income countries.

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Keywords: COVID-19, Diagnostic test, Accuracy, Systematic review

Introduction

Since the beginning of December 2019, an explosion has been reported in the number of new cases of an acute respiratory illness caused by a new coronavirus in the city of Wuhan in central China.[1] Genomic sequence analysis of respiratory samples showed that this was a new type of beta-coronavirus,[2] and 203 countries reported a positive pattern for Coronavirus disease (COVID-19) on 2nd of April.[4]

Today, Real-Time Polymerase Chain Reaction (RT-PCR) techniques are being increasingly used to

detect viral Respiratory Tract Infections (RTI). High sensitivity and short analysis time with the ability to diagnose the pathogens in a single sample compared to serology, viral culture, and antigen detection are some of the advantages of this technique.[5-7] PCR measurement may increase the detection rate of respiratory pathogens by at least 50% compared to traditional diagnostic methods by identifying viruses such as human rhinoviruses, human coronaviruses, and human metapenomoviruses, for which there are no common methods.[8-10] Diagnosis of viral agents in the respiratory tract samples using RT-PCR is fast and highly sensitive, and this method will be most likely replaced for traditional diagnostic methods. Nonetheless, the clinical significance of the results of high-sensitivity molecular methods should be assessed carefully.[11, 12]

In addition to laboratory testing, Computerized Tomography (CT) scan has played an important role in screening and diagnosing COVID-19. Experts have divided the CT demonstration into early, progressive, and severe stages depending on the extent and characteristics of pulmonary abnormalities. However, the relationship between inflammation and the clinical incidence of the disease has not been established.[2]

Given the novelty of COVID-19, reviewing diagnostic methods can be of great help to community health policymakers. Given the importance of diagnosing COVID-19 disease and the need for reducing the number of false positive and false negative cases that appear to be different in various diagnostic methods, this systematic review aimed at examining the accuracy of COVID-19 diagnostic tests.

Methods

Search Strategy and Study Selection

This systematic review was conducted by searching EMBASE (Elsevier, 2018), MEDLINE (National Library of Medicine, 2018), Scopus, ProQuest, Web of Science (Clarivate Analytics, 2018b), and Google Scholar databases for the studies on the consequences of coronavirus among health workers published prior to 3rd of April 2020, using the search strategy presented in Supplement 1. The selected keywords for international databases included "Novel coronavirus pneumonia", "Leukocyte count", "Neutrophil count", "Lymphocyte count", "Platelet count", "Prothrombin time", "Partial thromboplastin time", "Creatinine kinase", "L-lactate dehydrogenase", "Alanine aminotransferase", "Aspartate aminotransferases", "Bilirubin", "Blood urea nitrogen", "Creatinine", "Troponin I", "Procalcitonin", "Real-time polymerase chain reaction", "Real-time PCR", "CT scan", and "Laboratories". The collected data were entered into the EndNote X7 software and duplicate articles were automatically deleted.

Data Extraction

The search and data extraction were conducted by two authors (MV and FG) and no publication date restrictions were imposed. Discrepancies and doubts about the relevance of the sources were resolved via consultation with the corresponding author (HGh). The corresponding PRISMA flowchart is presented in Figure 1.

Eligibility Criteria

Records were excluded in case they met the following criteria established prior to the search: opinion pieces or reviews reporting no new data, studies investigating a single aspect of COVID-19, and the studies that were not available in English. The full text of all articles included in the study was available. The remaining studies were categorized as longitudinal or cross-sectional for qualitative synthesis (Table 1). It should be noted that the systematic review protocol was not registered due to the urgency of the issue and because limited available evidence on the topic was anticipated.

Quality Assessment

To check and control the quality of the articles, the Newcastle-Ottawa checklist was used. This tool consisted of three different parts, including selection (four questions), comparability (one question), and outcome (three questions). Accordingly, the final scores were divided into three categories of good (three or four stars in the selection domain, one or two stars in the comparability domain, and two or three stars in the outcome/exposure domain), fair (two stars in the selection domain, one or two stars in the comparability domain, and two or three stars in the outcome/exposure domain), and poor (zero or one star in the selection domain, zero stars in the comparability domain, or zero or one star in the outcome/exposure domain).[13] The results of quality assessment are presented in Table 1.

Results

Study Selection

A total of 859 studies were searched; of them, 589 were reviewed, and 270 duplicate studies were removed. After title and abstract screening, 373 articles were excluded. Also, in the second screening, 196 articles were excluded for various reasons. There were different reasons for excluding the articles; 105 articles did not report PCR test accuracy, laboratory data, and CT SCAN in COVID-19; 31 articles were review; 21 articles reported PCR test accuracy, laboratory data and CT SCAN on similar diseases COVID-19; and 39 articles did not present comparison data. On the other hand, four studies were included

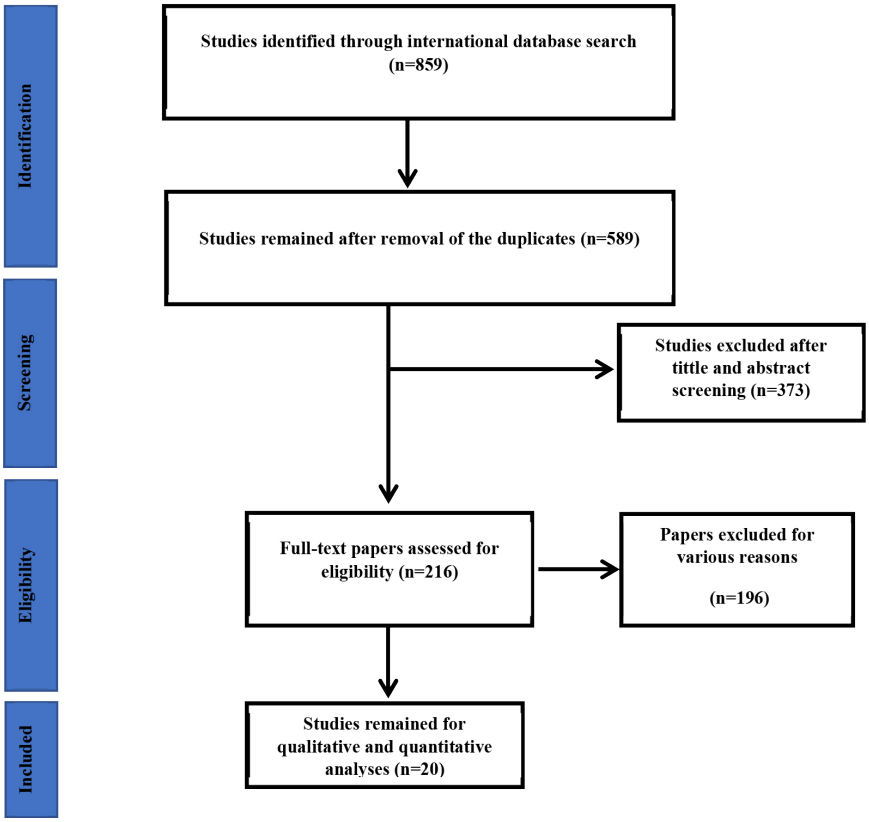

Figure 1: The process of deleting the articles obtained from the search in scientific bases and selecting the 20 articles in question

Table 1: Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Author (year)	Selection	Comparability	Outcome	Total	Quality
Jing-Wen Ai1, 2020	3	1	2	6	Good
Yicheng Fang, Feb 19 2020	3	1	2	6	Good
Peng An, 2020	2	1	2	5	Fair
Damiano Caruso, Apr 3 2020	3	1	2	6	Good
Xiang Dong, 19 March 2020	3	1	2	6	Good
Hang Fu, 2020	3	1	2	6	Good
Lei Gao, 03 March 2020	3	1	2	6	Good
Yong Gao, 13 March 2020	3	1	2	6	Good
Xingwang Jia, 2020	3	1	2	6	Good
Dasheng Li, Feb 25, 2020	3	1	2	6	Good
Kunwei Li, 16 March 2020	3	1	2	6	Good
Chunqin Long, 11 March 2020	2	1	2	5	Fair
Xiaomin Luo, 2020	2	1	2	5	Fair
Cong-Ying Song, 2020	2	1	2	5	Fair
K. Wang, 4 March 2020	2	1	2	5	Fair
Jin Zhang, 2020	3	1	2	6	Good
Juanjuan Zhao, 28 March 2020	3	1	2	6	Good
Hao Feng, 28 March 2020	3	1	2	6	Good
Wanbing Liu, 30 March 2020	3	1	2	6	Good
Tao Ai, Feb 26 2020	3	1	2	6	Good

via a manual search, which left a total of 20 studies for analysis (Figure 1).

This study examined the diagnostic methods for COVID-19 disease. The outcomes were divided into three groups, including laboratory data, CT scan and RT-PCR, and combination of several diagnostic methods, based on the final diagnostic method proposed by the articles. All included studies are listed in details in Table 2, and their results were compared in order to find the most qualified studies.

Laboratory Data

The results indicated that the laboratory diagnosis of viral nucleic acid could have false-negative results, and serological testing of virus-specific IgG and IgM antibodies should be used as an option for diagnosis.

Table 2: The list of the characteristics of articles the obtained

Number	Authors	Year	Country	Type of test	Study duration	Aim of study	Findings	Population	Type of study
1	Jing-Wen Ai1	2020	China	Laboratory assessments, and computed tomographic (CT) scans and Pathogen screen were performed including RT-PCR, multiplex PCR, rapid flu antigen tests and mNGS	January 22nd to February 9th, 2020	Effective and feasible strategy in precision diagnosing novel coronavirus pneumonia (NCP)	Our study discovered that a combination of chest CT, SARS-CoV-2 RT-PCR and multiplex PCR is recommended in regions outside Hubei province.	53 suspected NCP patients	Multicenter prospective study
2	Yicheng Fang	Feb 19 2020	China	Chest CT and RT-PCR	January 19, 2020 to February 4, 2020.	Compare the sensitivity of chest CT and viral nucleic acid assay at initial patient presentation.	In our series, the sensitivity of chest CT was greater than that of RT-PCR (98% vs 71%, respectively, p<.001).	51 patients (29 men and 22 women)	Retrospective study
3	Peng An	2020	China	Chest CT and RT-PCR	2020	Define the chest computed tomography findings of 2019-novel coronavirus associated with pneumonia and its successful resolution after treatment	Chest computed tomography offers fast and convenient evaluation of patients with suspected 2019-novel coronavirus pneumonia.	A fifty-year-old female patient	Case Report
4	Damiano Caruso	Apr 3 2020	Italy	Chest CT and RT-PCR	March 4, 2020, until March 19, 2020	To investigate CT features of patients with COVID-19 in Rome, Italy, and to compare the accuracy of CT with RT-PCR	In this prospective study of patients in Rome, Italy, the sensitivity, specificity, and accuracy of CT for COVID-19 were 97%, 56%, and 72%, respectively, using RT-PCR as standard of reference.	158 consecutive study participants (83 male and 75 female)	prospective study
5	Xiang Dong	19 March 2020	China	Laboratory detection and IgG and IgM antibodies	2020	describe the various clinical presentations of this disease by examining eleven cases	Laboratory detection of the viral nucleic acid can yield false-negative results, and serological testing of virus-specific IgG and IgM antibodies should be used as an alternative for diagnosis.	11 patients with COVID-19	Case series
6	Hang Fu	2020	China	Clinical, laboratory and CT characteristics and RT-PCR r	2020	the association between clinical, laboratory and CT characteristics and RT-PCR r	Heterogeneity between CT features and RT-PCR results was found in COVID-19, especially in some recovered patients with negative RT-PCR results. Our study highlights that both RT-PCR and chest CT should be considered as the key determinants for the diagnosis and management of COVID-19 patients.	52 admitted COVID-19 patients	Cohort study
7	Lei Gao	03 March 2020	China	NT-proBNP	2020	Prognostic value of NT-proBNP in patients with severe COVID-19	The best cut-off value of NT-proBNP for predicting in-hospital death was 88.64pg/mL with the sensitivity for 100% and the specificity for 66.67%. NT-proBNP might be an independent risk factor for in-hospital death in patients with severe COVID-19.	54 patients	Clinical trial (not Random)

Number	Authors	Year	Country	Type of test	Study duration	Aim of study	Findings	Population	Type of study
8	Yong Gao	13 March 2020	China	IL-6 and D-D	January 23, 2020 to February 2, 2020	Look for the warning index in severe COVID-19 patients.	The optimal threshold and area under the receiver operator characteristic curve (ROC) of IL-6 were 24.3 and 0.795μg/L, respectively, while those of D-D were 0.28 and 0.750μg/L, respectively. The area under the ROC curve of IL -6 combined with D-D was 0.840. The specificity of predicting the severity of COVID-19 during IL-6 andD-D tandem testing was up to 93.3%, while the sensitivity of IL-6 andD-D by parallel test in the severe COVID-19 was 96.4%. IL-6 andD-D combined detection had the highest specificity and sensitivity for early prediction of the severity of COVID-19 patients.	43 adult patients with COVID-19	retrospective study
9	Xingwang Jia	2020	China	IgM and IgG test	2020	Clinical significance of IgM and IgG test for diagnosis of highly suspected COVID-19 infection	The positive rate of COVID-19 nucleic acid was 42.10%. The positive detection rate of combination of IgM and IgG for patients with COVID-19 negative and positive nucleic acid test was 72.73% and 87.50%. The results were significantly higher than the nucleic acid or IgM, IgG single detection.	57 suspected COVID-19 infection patients	retrospective study
10	Dasheng Li	Feb 25, 2020	China	Real-Time ReverseTranscriptase Polymerase Chain Reaction and CT Diagnosis	2020	False-Negative Results of Real-Time ReverseTranscriptase Polymerase Chain Reaction for Severe Acute Respiratory Syndrome Coronavirus 2: Role of Deep-Learning-Based CT Diagnosis and Insights from Two Case	We reported two false-negative results of rRT-PCR for SARS-CoV-2 infection and mentioned the possible tandem approaches for clinical practices to ensure an early and accurate diagnosis of COVID-19. In addition, the potential role of laboratory examination results in differentiating the infection status was revealed as well.	two representative false-negative cases	Case Report
11	Kunwei Li	16 March 2020	China	CT image	Jan. 18, 2020 to Feb. 7, 2020	To explore the relationship between the imaging manifestations and clinical classification of COVID-19	The ICC value of the two observers was 0.976 (95% CI 0.962–0.985). ROC analysis showed the area under the curve (AUC) of TSS for diagnosing severe-critical type was 0.918. The TSS cutoff of 7.5 had 82.6% sensitivity and 100% specificity. The proportion of clinical mild-type patients withCOVID-19 was relatively high;CT was not suitable for independent screening tool.	78 patients ,38males and 40 females	retrospective, single-center study
12	Chunqin Long	11 March 2020	China	rRT-PCR and CT	January 20th, 2019 to February 8th, 2020	To evaluate the diagnostic value of computed tomography (CT) and real-time reverse-trans criptase polymerase chain reaction (rRT-PCR) for COVID-19 pneumonia.	CT sensitivity was 97.2%, whereas the sensitivity of initial rRT-PCR was only 83.3%. rRT-PCR may produce initial false negative results.We suggest that patients with typical CT findings but negativerRT-PCR results should be isolated,and rRT-PCR should be repeated to avoid misdiagnosis.	204 patients suspected for COVID-19	retrospective study

Number	Authors	Year	Country	Type of test	Study duration	Aim of study	Findings	Population	Type of study
13	Xiaomin Luo	2020	China	C-reactive protein(CRP)	Jan 30 to Feb 20, 2020	Elevated serum C-reactive protein (CRP) level was observed in most patients with COVID-19.	With a cut-off value of 41.4, CRP exhibited sensitivity 90.5%, specificity 77.6%, positive predictive value 61.3%, and negative predictive value 95.4%.	298 patients with COVID-19	retrospective study
14	Cong-Ying Song	2020	China	CT score and laboratory data	January 20th to February 19th,	develop a diagnostic model that allows for the quick screening of highly suspected patients using easy-to-get variables.	CT score was, Sensitivity=0.95 and Specificity =0.94 , AUROC=0.98 and Cut-off Value =8.5.	1,311 patients receiving severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	retrospective study
15	K. Wang	4 March 2020	China	Spiral CT and nucleic acid detection	25 January 2020, to 9 February 2020	To report the epidemiological, clinical, and radiological characteristics of patients with COVID-19 in Xiaogan, Hubei, China.	Spiral CT is a sensitive examination method, which can be applied to make anearly diagnosis and for evaluation of progression, with a diagnostic sensitivity and accuracybetter than that of nucleic acid detection.	114 confirmed COVID-19 patients	retrospective study
16	Jin Zhang	2020	China	serum IgM and IgG antibodies	January 21, 2020 to February 16, 2020	Serological detection of 2019-nCoV respond to the epidemic is a useful complement to nucleic acid testing	The areas under the ROC curves of IgM and IgG were 0.988 and 1.000, respectively. Specific antibody detection has good sensitivity and specificity. Detection of specific antibodies in patients with fever can be a good distinction between COVID-19 and other diseases, so as to be a complement to nucleic acid diagnosis to early diagnosis of suspected cases.	228 suspected COVID-19 cases	retrospective study
17	Juanjuan Zhao	28 March 2020	China	RNA and antibody detections	Jan 11 and Feb 9, 2020	Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019	Combining RNA and antibody detections significantly improved the sensitivity of pathogenic diagnosis for COVID-19 , even in early phase of 1-week since onset. Moreover, a higher titer of Ab was independently associated with a worse clinical classification.	173 patients with SARS-CoV-2 infection	retrospective study
18	Hao Feng	28 March 2020	China	CT and RT-PCR tests	2020	A case report of COVID-19 with false negative RT-PCR test: necessity of chest CT	It is difcult to distinguish COVID-19 pneumonia from other viral pneumonia on CT fndings alone; however, we emphasize the utility of chest CT to detect early change of COVID-19 in cases which RT-PCR tests show negative results.	a case of 34-year-old man	Case report

Number	Authors	Year	Country	Type of test	Study duration	Aim of study	Findings	Population	Type of study
19	Wanbing Liu	30 March 2020	China	rN-based IgM and IgG ELISAs	January 18 and February 26, 2020	Evaluation of Nucleocapsid and Spike Protein-based ELISAs for detecting antibodies against SARS-CoV-2	The positive rates of the rN-based and rS-based ELISAs for antibody (IgM and/or IgG) detection were 80.4% and 82.2%, respectively. The sensitivity of the rS-based ELISA for IgM detection was significantly higher than that of the rN-based ELISA. ELISA has a high sensitivity, especially for the detection of serum samples from patients after 10 d.p.o, it can be an important supplementary method for COVID-19 diagnosis.	214 confirmed COVID-19 patients	Retrospective study
20	Tao Ai	Feb 26 2020	China	RT-PCR and chest CT imaging	January 6 to February 6, 2020	To investigate the diagnostic value and consistency of chest CT as compared with comparison to RT-PCR assay in COVID-19.	The positive rates of RT-PCR assay and chest CT imaging in our cohort were 59% (601/1014), and 88% (888/1014) for the diagnosis of suspected patients with COVID-19, respectively. 2. With RT-PCR as a reference, the sensitivity of chest CT imaging for COVID-19 was 97% (580/601). In patients with negative RT-PCR results but positive chest CT scans (n=308 patients), 48% (147/308) of patients were re-considered as highly likely cases, with 33% (103/308) as probable cases by a comprehensive evaluation. 3. 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. 42% of patients showed improvement of follow-up chest CT scans before the RT-PCR results turning negative.	1014 patients in Wuhan, China	Report Cases

Therefore, all different clinical features of COVID-19 should be taken into consideration in order to identify the patients who need to be strictly quarantined to control the epidemic effectively.[14] Another study indicated that the rate of positive diagnosis of IgM and IgG was 72.73% and 87.50% in patients with negative and positive COVID-19 nucleic acid tests, respectively. These results were significantly higher than nucleic acid or IgM, IgG single diagnosis.[15] Similarly, Jin Zhang et al. reported that the areas below the Receiver Operating Characteristics (ROC) curves of IgM and IgG were equal to 0.988 and 1,000, respectively. They believed that the specific diagnosis of antibodies had good sensitivity and specificity. Moreover, diagnosis of specific antibodies in patients with fever could make a good distinction between COVID-19 and other diseases, causing it to be considered as a supplement to the diagnosis of nucleic acid for early detection of the suspected cases.[15] Furthermore, N-Terminal pro B-type Natriuretic Peptide (NT-proBNP), which might be an independent risk factor for hospital death in patients with severe COVID-19, had a sensitivity of 100% and a specificity of 66.67%. Based on the results, the patients with high NT-proBNP values (>88.64 pg/ml) had a significantly higher risk of death during the follow-up compared to low-value individuals (88.64 pg/ml).[16]

Other laboratory diagnostic methods included the use of IL-6 and D-D. According to the results, the optimum threshold and area below the ROC curve of IL-6 were 24.3 and 0.795 µg/L, respectively. These measures were respectively equal to 0.28 and 0.750 µg/L for the D-D level. Additionally, the area below the IL-6 ROC curve was 0.840 with D-D. The specificity of Tandem IL-6 and D-D experiments in predicting the severity of COVID-19 was 93.3, while the sensitivity of IL-6 and D-D with parallel experiments was 96.4 in severe COVID-19. The combined diagnosis of IL-6 and D-D showed the highest specificity and sensitivity for the initial prognosis of patients with severe COVID-19.[16]

Xiaomin Luo et al. reported a cut-off value of 41.4%, CRP sensitivity of 90.5%, specificity of 77.6%, positive predictive value of 61.3%, and negative predictive value of 95.4% in coronavirus diagnosis. As a result, PCR was one of the recommended diagnostic methods for COVID-19 with a relatively high sensitivity.[17] ELISA was the next suggested method for diagnosing coronavirus. Positive rN-based and rS-based ELISAs for antibody detection (IgM and/or IgG) were 80.4% and 82.2%, respectively. The rS-based ELISA sensitivity for IgM detection was significantly higher compared to the rN-based ELISA. Overall, ELISA was highly sensitive, especially for the detection of serum samples from patients after 10 DPO and could consequently be an important complementary method for the diagnosis of COVID-19.[17]

CT Scan and RT-PCR

Yicheng Fang et al. reported that the sensitivity of chest CT was higher than that of RT-PCR (98% vs. 71%). The reasons for the decrease in the efficiency of viral nucleic acid might include 1) the immature development of nucleic acid detection technology, 2) changes in the rate of diagnosis from different manufacturers, 3) low viral load of the patient, or 4) incorrect clinical sampling. Thus, CT scan was suggested to be used for COVD-19 screening among the patients with consistent clinical and epidemiological features with COVID-19 infection, especially when the RT-PCR test result was negative.[18] In another study on 204 patients suspected of coronavirus, the sensitivity of CT was 97.2%, while the initial sensitivity of RT-PCR was only 83.3%. RT-PCR might produce false negative results. Hence, patients with normal CT findings but negative RT-PCR results were recommended to be isolated and RT-PCR was suggested to be repeated to prevent misdiagnosis.[19] In another investigation, the sensitivity and specificity of CT were 0.95 and 0.94, respectively (area under the ROC curve=0.98 and cut-off=8.5).[20] Hao Feng et al. also believed in the difficulty of distinguishing between COVID-19 and other viral pneumonias using CT alone. However, they emphasized the use of chest CT for early detection of COVID-19 in cases where the RT-PCR test showed negative results.[21] In another study, chest CT was considered as the diagnostic method for rapid and comfortable evaluation of the patients suspected of COVID-19.[22]

In the research performed by Damiano Caruso et al., with RT-PCR as the reference, the sensitivity, specificity, and accuracy of CT for detecting COVID-19 were reported as 97%, 56%, and 72%, respectively. Moreover, Ground-Glass Opacities (GGO) technique confirmed RT-PCR in 100% of the patients with COVID-19. Additionally, 93% of the patients had multifaceted and posterior lung involvement and 91% had pneumonia. Besides, enlargement of the secondary vessels (more than three mm in diameter) in the areas of pulmonary opacity for unknown reasons was observed in 89% of the patients with COVID-19 pneumonia.[23] In the study by Tao Ai et al., with RT-PCR as the reference, the sensitivity of chest CT imaging for COVID-19 was 97% (580/601).[22] Nonetheless, a study found that in the case of a large number of patients with a mild clinical type of COVID-19, CT would not be appropriate as an independent screening tool.[24] K. Wang et al. also recommend spiral CT, which is a sensitive examination method that can be used for early diagnosis and evaluation of disease progress with higher diagnostic sensitivity and accuracy compared to nucleic acid diagnosis.[20]

Combining Several Diagnostic Methods

In their study, Jing-Wen Ai et al. suggested the

combined use of chest CT, SARS-CoV-2 RT-PCR, and multi-plex PCR. In eastern China, pathogens other than SARS-COV-2 still account for approximately 60% of the suspicious individuals. Therefore, chest CT alone cannot be used as a diagnostic criterion for SARSCOV-2 infections. A combination of CT and other diagnostic methods is essential to reduce the likelihood of misdiagnosis in the areas outside China.[25]

In another study, due to the discrepancy between CT characteristics and RT-PCR results in COVID-19, especially in some patients who improved with negative RT-PCR results, both RT-PCR and CT were recommended to be performed. In addition, long-term follow-up studies in COVID-19 patients were found to be essential after obtaining negative RT-PCR results, especially in patients with stable abnormal indicators and progression of CT chest manifestations.[24] Another recommended diagnostic method included the mixture of RNA and antibody detection, which significantly improved the sensitivity of pathogenic diagnosis of COVID-19, even within one week from the onset. Moreover, a headline above Ab was independently related to worse clinical classifications.[26]

Comparison of the sensitivity and specificity of COVID-19 diagnostic testing in the present study and other studies conducted on the issue is shown in Figures 2 and 3.

Discussion

Several methods, including laboratory data, CT scan, and RT-PCR, and combination of several diagnostic methods are used to diagnose COVID-19. The present review was conducted to evaluate COVID-19 diagnostic tests.

Studies have shown that the laboratory diagnosis of viral nucleic acid might have false negative results. Therefore, the combined use of serological testing of virus-specific IgG and IgM antibodies and laboratory diagnosis of viral nucleic acid can be extremely useful. The findings of the research by Juanjuan Zhao et al. were consistent with those of the present investigation,

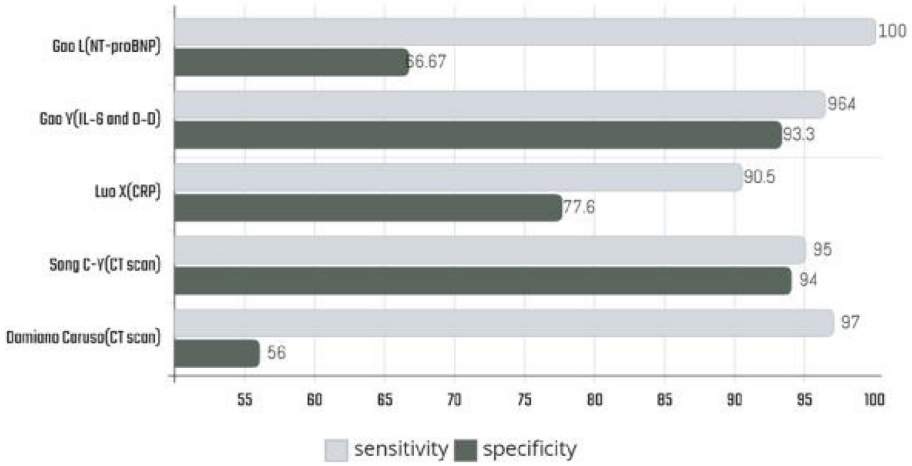

Figure 2: Comparison of the extracted articles regarding the sensitivity and specificity of diagnostic tests for COVID-19 (%)

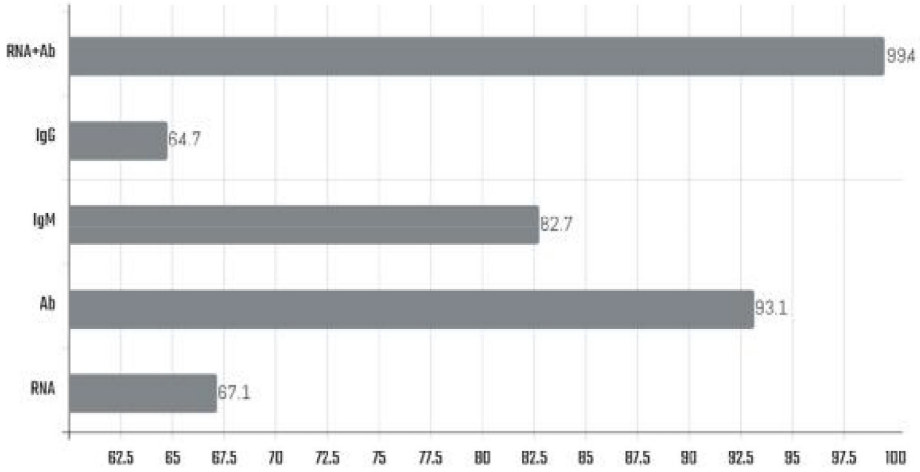

Figure 3: Comparison of the sensitivity of COVID-19 diagnostic tests (%) in the research by Juanjuan Zhao

indicating that IgG and IgM serological tests were often vital for diagnosis and management of COVID-19.[18] Because the serological testing of virus-specific IgG and IgM antibodies has a high sensitivity and specificity, this method can differentiate between COVID-19 and other diseases in suspected cases with clinical symptoms such as fever.[1-3,18]

In the study carried out by Yicheng Fang et al., CT scan was shown to be more sensitive than RT-PCR for a variety of reasons. In addition, RT-PCR might produce false-negative results. Therefore, the majority of studies used the combination of CT scan and RT-PCR, which led to a faster and more accurate diagnosis of the suspected cases of COVID-19.[8-10]

According to the current study results, the use of a combination of CT scan and RT-PCR is emphasized to prevent false negative results.[11, 12, 14] Consistently, Hang Fu et al. reported that both RT-PCR and chest CT should be used as a key determinant for diagnosis and management of COVID-19.[17] In the same line, Jing-Wen Ai et al. concluded that a combination of chest CT, SARS-CoV-2, RT-PCR, and multi-plex PCR should be utilized in the areas outside Hubei province.[16] Furthermore, the combination of IL-6 and D-D diagnostic methods was found to have the highest sensitivity and specificity for the initial prognosis of patients with COVID-19.[5] Besides, the use of CPR as one of the diagnostic methods was sensitive, but ELISA was most sensitive to serum samples from patients after 10 DPO.[7] This method, with its high sensitivity and accuracy and low cost, was regarded a simple way to diagnose COVID-19, which could be effective in epidemic conditions in low- and middle-income countries.[7]

The present study had a number of limitations. Firstly, heterogeneity among the referenced studies, including settings, methods, and outcome measures, might have influenced the findings. Secondly, another limitation of our study was the non-English language of some articles, which of course were few in number, and we tried to reduce this limitation by examining the English abstract. Another limitation of our study was the inclusion of different types of studies, which according to the strengths and weaknesses of each type of study, can affect the outcome of the work, which is inevitable.

Recommendations for Future Research

Considering the simpler and cheaper use of ELISA, further research is required to be done on this diagnostic method as it can be extremely helpful in low-income and economically weaker countries.

Conclusion

The results of this systematic review showed that the majority of the studies used a combination of CT and PCR techniques. Thus, follow-up RT-PCR and chest CT were reported to be necessary in COVID-19. Moreover, the utilization of serological testing of virus-specific IgG and IgM antibodies along with laboratory diagnosis of viral nucleic acid could provide a diagnosis with higher sensitivity and accuracy. Furthermore, ELISA was found to be one of the cost-effective methods in epidemic conditions in low- and middle-income countries.

Abbreviations

COVID-19: Coronavirus Disease 2019
PCR: Polymerase chain reaction
CT scan: computed tomography scan
IgG: Immunoglobulin G
IgM: Immunoglobulin M
SARS: Severe Acute Respiratory Syndrome
ELISA: Enzyme-Linked Immunosorbent Assay
RTI: Respiratory Tract Infections

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and material

All data is available upon request.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HGh was the leading author and guarantor. MV, AA, ZM and FG planned the study and led the drafting and revising of the manuscript. MV, ZM, AM contributed to interpretation of the data, and drafting and revising the manuscript. All authors approved the submitted version of the manuscript.

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