Radiological and Laboratory Modalities for Diagnosis of COVID-19: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

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ABSTRACT

The world has witnessed the dreadful COVID-19 pandemic and the rapid rate of its spread across countries. The key measures in pandemic control includes early detection of cases, isolation of cases to prevent spread and appropriate management of confirmed cases. The present diagnostic criteria for COVID-19 in India is based on RT-PCR. This technique has its own limitations. There are ongoing debates to the cost, time taken and type of diagnostic sensitivity and predictive values of RT-PCR. Researchers across globe have been exploring alternative methods to enhance the mainstay of protocols for identifying suspected cases of COVID-19. With media news of too many

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asymptomatic positive results from community in New Delhi, Ahmedabad and other places in India, along with prompt withdrawal of antibody based tests by ICMR after questions on validity, such test raises concerns and urgent need for exploring the need for rethinking the diagnostic algorithm. This is a systematic review to explore possibility of novel diagnostic approaches for a suspected case of COVID-19 with an objective to early detection of case and using appropriate methods to halt the chain of transmission.

1. INTRODUCTION

SARS-COV2 (Severe Acute Respiratory Syndrome- Corona Virus 2) is a novel coronavirus that belongs to the same family as MERS-COV (Middle East Respiratory syndrome-Corona Virus) and SARS-COV [1]. On March 11 2020, World Health Organization declared COVID-19 as pandemic and as of 22nd April 2020, COVID-19 has spread across more than 210 Countries and Territories around the world have reported a total of 2,555,737 confirmed cases of the coronavirus, COVID-19 that originated from Wuhan, China, and a death toll of 177,459 deaths [2]. In India, first case of COVID-19 infection was reported on 30th January and after that the pandemic wave had badly affected almost all the states of India. On April 25rd, India has 26,250 confirmed cases of COVID-19 with 811 reported deaths. In the month of January 2020, genetic sequencing identified the virus among the initial cluster of cases as novel SARS-COV2 [3]. COVID-19 diagnostic testing is essential for tracking the virus, understanding its epidemiology, advising case treatment, and preventing its spread. Various strategies were developed by the World Health Organization (WHO) and adapted locally for the strategic use of diagnostic testing in different transmission scenarios of the COVID-19 outbreak [4,5]. Over time countries are making essential amendments keeping in view of epidemiological transition of COVID-19, from, no cases to community transmission, including directives on how testing might be rationalized when lack of reagents or testing capacity necessitates prioritization of testing in certain populations or individuals or even for surveillance [6].

Corona virus is an RNA virus with a positive sense [7]. The COVID diagnostic algorithm is based on the most commonly prescribed laboratory tests, which include direct evidence of virus or antigens, detection of specific antibodies against SARS-COV2, and molecular testing to detect viral nucleic acid [6]. In today's world, real-time reverse transcriptase PCR (RT-PCR) is commonly used to detect viral nucleic acids. There are multiple genomic sites which code for specific structural and non-structural proteins of the virus. Different countries or the research bodies have aimed at targeting at least two proteins to increase the sensitivity and specificity of the testing protocol [8].

There are ongoing debates to the cost, time taken and type of diagnostic sensitivity and predictive values of RT-PCR. Researchers across globe have been exploring alternative methods to enhance the mainstay of protocols for identifying suspected cases of COVID-19, but it should be appreciated that, RT-PCR was identified under the extra ordinary circumstances using the available research and development and intellectual property frameworks, which were not designed to address a pandemic of this scale and hence can pose its own challenge [9]. Presently, diagnostic algorithm used in India is based on RT-PCR only [6].

One of the most common argument, against sole use of RTC-PCR being used as a gold standard diagnostic tool for detection of COVID-19 is the risk of eliciting false-negative and false-positive results [10]. It is reported that many 'suspected' cases with typical clinical characteristics of COVID-19, RT-PCR has reported various sensitivities [11, 12]. This sensitivity might reduce further due to issues related to sample collection and transportation, more specifically when samples are taken from field, which is becoming more common with aggressive contact tracing. The availability of accredited laboratory is also another issue in execution of RT-PCR as mainstay for diagnosis. Due to limited laboratories that can carry out this testing, there is considerable delay between samples collection and reports received. Different laboratory practise standards, as well as individual employee ability in the appropriate technical and safety procedures, may result in variable outcomes. Because of the ongoing discussion about RT-PCR, the Centers for Disease Control and Prevention (CDC) has developed a SARS-COV2 Real-Time RT-PCR Diagnostic Panel to

reduce the risk of false-positive results [13].

Experts in Radiological imaging who too have witnessed the COVID-19 pandemic unfold, are wondering if and how Chest imaging could also be useful for diagnosis. The assumption is based on fact that perhaps imaging could aid in screening or accelerate the speed of diagnosis, especially with shortages of RT-PCR and debates strong pivotal role of radiological scans during such crisis [14,15]. As the COVID-19 pandemic and its clinical mystery has started getting unfolded, there are now evidences that pneumonia in COVID-19 patient do manifests with chest CT imaging abnormalities, even in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progressed to or co-existed with consolidations within 1-3 weeks [15]. In The Lancet Infectious Diseases, Heshui Shi and colleagues in the largest cohort thus far reported, discussed the CT findings and temporal changes of COVID-19 pneumonia with reference to the time of onset of symptoms [15]. The predominant CT findings included ground-glass opacification, consolidation, bilateral involvement, and peripheral and diffuse distribution. This possibly can generate a recommendation of combining assessment of imaging features with clinical and laboratory findings that could facilitate early diagnosis of COVID-19 pneumonia. Researchers have also been exploring the use of chest x-ray as an aid to diagnostic algorithm of COVID [16]. More so, in last recent years, advances in artificial intelligence (AI) technology and methods have also led to major progression in automated image recognition by computers. AI has been applied to the analysis of radiologic images to identify abnormalities—referred to as computer-aided detection, or CAD—and that has given a directive to overcome the personnel shortage makes it a potential candidate for inclusion in the tree of diagnostic algorithm [17].

With media news of too many asymptomatic positive results from community in New Delhi, Ahmedabad and other places in India, along with prompt withdrawal of antibody based tests by ICMR after questions on validity, such test raises concerns and urgent need for exploring the need for rethinking the diagnostic algorithm [18,19]. Presented here is a systematic review to explore possibility of novel diagnostic approaches for a suspected case of COVID-19 with an objective to early detection of case and using appropriate methods to halt the chain of transmission.

2. METHODOLOGY

Criteria for considering studies for this review: We included studies observational studies such as case series, cohort studies, case-control studies, time series, and interrupted time series, and excluded short abstracts, case reports, animal studies, and diagnostic efficacy studies of various models or algorithms in this rapid review. We included studies on suspected or confirmed cases of COVID-19 irrespective of age, gender, ethnicity, or presence of comorbid conditions. The studies were included if they reported data on sensitivity, specificity or accuracy of either CT scan, chest x-ray or RT-PCR or studies that compared Radiological scans with RT-PCR. Studies published in languages other than English or Chinese were excluded. We included Chinese studies only if summaries were available in English.

2.1 Search Methods for Identification of Studies

Trained Researchers (NK & BM) undertook a literature search for studies published between November 2020 to 25 April 2020 in MEDLINE through PubMed and CENTRAL. The detailed search strategies are given. Additionally; we searched WHO and UNICEF database. One reviewer (KS) screened the reference lists of included studies and related systematic reviews for identifying potentially relevant studies and another reviewer.

2.2 Selection of Studies

Studies identified during database searches were exported to Excel file and one reviewer (KS) screened the titles and abstracts of the all the studies on the basis of inclusion criteria and the other reviewers (DS, AG) checked 30% of all the excluded studies. One reviewer (KS) then retrieved and screened the full texts of all the studies for inclusion and other reviewer (AG) checked all the excluded studies. Disagreements amongst the reviewers were resolved by consensus and critical care expert in team (DSh). The details of the screening process were recorded in PRISMA flow diagram.

2.3 Data Extraction and Management

One reviewer (KS) extracted data from included studies into predesigned data extraction form and other reviewers (NK, AG & BM) cross-checked the data. Following data was extracted from included studies: Study ID, country, study

design, details of participants, details of the diagnostic test, outcomes reported, and findings of the study.

2.4 Data Synthesis

We synthesized results narratively and in tabular form Tables 1, 2 and 3).

2.4.1 Medline via PubMed

Search (((((((((coronavirus[Title/Abstract]) OR nCoV[Title/Abstract]) OR SARS-CoV-2[Title/Abstract]) OR "corona virus"[Title/Abstract]) OR Covid*[Title/Abstract]) OR "Coronavirus Infections"[Mesh]) OR ("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]))) AND (((((((((CT-scan[Title/Abstract]) OR "CT scan"[Title/Abstract]) OR "computed tomography"[Title/Abstract]) OR "CAT scan"[Title/Abstract]) OR "Tomography, X-Ray Computed"[Mesh]) OR PCR[Title/Abstract]) OR "Polymerase Chain Reaction"[Title/Abstract]) OR ("Polymerase Chain Reaction"[Mesh] OR "Real-Time Polymerase Chain Reaction"[Mesh] OR "Reverse Transcriptase Polymerase Chain Reaction"[Mesh] OR "Multiplex Polymerase Chain Reaction"[Mesh])) OR radiolog*[Title/Abstract]) OR ("Radiography"[Mesh] OR "diagnostic imaging" [Subheading]))) AND (((((sensitivity[Title/Abstract]) OR specificity[Title/Abstract]) OR "diagnostic tool"[Title/Abstract]) OR diagnos*[Title/Abstract]) OR "predictive value"[Title/Abstract]) Filters: Publication date from 2019/10/01 to 2020/04/14; Humans

2.4.2 Central

Last Saved: 17/04/2020 20:00:11

ID   Search

#1 : coronavirus*
#2 : "corona virus"
#3 : nCoV*
#4 : 2019nCoV
#5 : SARS-CoV-2
#6 : MeSH descriptor: [Coronavirus] explode all trees
#7 : COVID*
#8 : #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 : CT-scan
#10 : "CT scan"
#11 : "CAT scan"
#12 : "computed tomography"
#13 : MeSH descriptor: [Cone-Beam Computed Tomography] explode all trees
#14 : PCR
#15 : "Polymerase Chain Reaction"
#16 : MeSH descriptor: [Polymerase Chain Reaction] explode all trees
#17 : radiograph*
#18 : radiolog*
#19 : #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 : #8 AND #19

3. OBSERVATIONS

The systematic search yielded 39 studies that used and compared various diagnostic tests [14,16, 20-57]. We included studies using RT-PCR, CT or Chest x-ray only, studies exclusively using biomarkers for ruling out the disease were excluded from the evidence synthesis. The key characteristics of the included studies were summarized and are presented as Table 1. As expected, majority of the studies were reported from China (60%), followed by USA and other parts of world. Thirteen studies reported cases from adult population and only two studies exclusively involved reports from children and infants. The sample size ranged from 2 patients to cohort of 3322 patients, with majority of the studies using retrospective data (40.5%) sets only. Popular choice of diagnostic test was CT as 78% of the studies used it as a diagnostic tool. Chest CT was compared with various diagnostic tools such as RT-PCR, conventional versus machine learning/artificial intelligence supported CT, chest x-ray and biomarkers as well.

The brief description of findings of each study is summarized in Table 2. It was found that there is substantial heterogeneity among the recommendations and findings with 7% of the reports remaining inconclusive. Though relatively large number of studies supported use of CT as screening and early identification of COVID-19, algorithm based CT also fairs better when compared to conventional CT. Few studies also reported that though CT may provide some critical information regarding the pathophysiological changes, but RT-PCR still remains the gold standard for confirmation of the disease. The actual indicators of diagnostic

Table 1. Summary features of included studies

Sr. No	Authors	Title	Country	Population	Sample	Study design	Diagnostic test used
1	Ai et al., [14]	Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases	China	All	1014	Retrospective	RT-PCR, CT
2	Al-Tawfiq and Memish, [19]	Diagnosis of SARS-CoV-2 Infection based on CT scan vs. RT-PCR: Reflecting on Experience from MERS-CoV	USA			Opinion	RT-PCR, CT
3	Araujo- [20]	COVID-19 pneumonia: what is the role of imaging in diagnosis?	Brazil, USA			Review	RT-PCR, CT scan, Chest x-ray
4	Barstugan et al., [21]	Coronavirus (COVID-19) Classification using CT Images by Machine Learning Methods	Turkey	Adult	53	Retrospective	CT with machine learning
5	Chen et al., [22]	Deep learning-based model for detecting 2019 novel coronavirus pneumonia on high-resolution computed tomography: a prospective study.	China	Adult	51	Prospective	CT with machine learning
6	Chen et al., (a) [23]	Analysis of Clinical Features of 29 Patients With 2019 Novel Coronavirus Pneumonia	China		29	Cross-sectional	CT, Biochemical markers
7	Chua et al., [24]	The role of CT in case ascertainment and management of COVID-19 pneumonia in the UK: insights from high-incidence regions	UK			Commentary	RT-PCR, CT
8	Fang et al., [25]	Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR	China	Adult	51	Retrospective	Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR
9	Feng et al., [26]	CT image features analysis of 15 cases of novel coronavirus infection in children	China	Children	15	Retrospective	CT
10	Gao et al., [27]	Pulmonary High-Resolution Computed Tomography (HRCT) Findings of Patients With Early-Stage Coronavirus Disease 2019 (COVID-19) in Hangzhou, China	China	Not mentioned	6	Retrospective	High-resolution computed tomography (HRCT)
11	Gozes et al., [28]	Rapid AI development cycle for the coronavirus (covid-19) pandemic: initial results for automated detection & patient monitoring using deep learning CT image analysis.	Multicentre databases	All	Multicentre databases	Retrospective	CT with machine learning
12	Guan et al., [29]	Clinical Characteristics of Coronavirus Disease 2019 in China	China	All	1099	Retrospective	RT-PCR, CT
13	Hope et al., [30]	Chest Computed Tomography for Detection of Coronavirus Disease 2019 (COVID-19): Don't Rush the Science	San Francisco			Opinion	RT-PCR, CT
14	Jacobi et al., [31]	Portable chest x-ray in coronavirus disease-19 (COVID-19): A pictorial review	USA	All		Review	RT-PCR, Chest X ray
15	Jin et al., [32]	Development and Evaluation of an AI System for COVID-19 Diagnosis	China	Adult	1255	Observational	CT with AI

Sr. No	Authors	Title	Country	Population	Sample	Study design	Diagnostic test used
16	Jin et al., (a)[33]	AI-assisted CT imaging analysis for COVID-19 screening: Building and deploying a medical AI system in four weeks	China	Not mentioned	1136	Observational	CT with AI
17	Kanne et al., [34]	Essentials for Radiologists on COVID-19: An Update—Radiology Scientific Expert Panel	USA			Expert panel report	RT-PCR, CT scan
18	Konrad et al., [35]	Rapid establishment of laboratory diagnostics for the novel coronavirus SARS-CoV-2 in Bavaria, Germany, February 2020	Germany			Prospective	Types of PCR
19	Li et al., [36]	Artificial Intelligence Distinguishes COVID-19 from Community Acquired Pneumonia on Chest CT	China	Adult	3322	Retrospective	CT with machine learning
20	Li et al., (a) [37]	CT imaging changes of corona virus disease 2019(COVID-19): a multi-center study in Southwest China	China	Adult	131	Retrospective	RT-PCR and CT
21	Li et al., (b) [38]	False-Negative Results of Real-Time Reverse-Transcriptase Polymerase Chain Reaction for Severe Acute Respiratory Syndrome Coronavirus 2: Role of Deep-Learning-Based CT Diagnosis and Insights From Two Cases	China	Adult	2	Retrospective	RT-PCR, CT with deep learning
22	Long et al., [39]	Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT?	China	Adult		Retrospective	RT-PCR, CT
23	Majidi [40]	Chest CT in patients suspected of COVID-19 infection: A reliable alternative for RT-PCR	Review	All		Opinion	RT-PCR, Chest X ray
24	Ming-Yen et al., [41]	Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review	China	All	21	Literature review	CT and Chest x-ray
25	Patel et al., [42]	Report from the American Society for Microbiology COVID-19 International Summit, 23 March 2020: Value of Diagnostic Testing for SARS–CoV-2/COVID-19	USA			Expert panel report	RT-PCR, Antibody test
26	Shi et al., [43]	Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study	China	Adult	81	Descriptive study	RT-PCR, CT
27	Song et al., [44]	Deep learning Enables Accurate Diagnosis of Novel Coronavirus (COVID-19) with CT images	China	Not mentioned	275	Experimental study	CT with machine learning
28	Thomas-Rüddel et al., [45]	Coronavirus disease 2019 (COVID-19): update for anesthesiologists and intensivists March 2020	Germany			Expert report - Update	RT-PCR, CT
29	Udugama et al., [46]	Diagnosing COVID-19: The Disease and Tools for Detection	Canada	All		Review	RT-PCR, Chest X ray
30	Wang et al., [47]	A deep learning algorithm using CT images to screen for Corona Virus Disease (COVID-19)	China	Adult	259	Retrospective	CT with machine learning
31	Wang et al., (a)[48]	Imaging manifestations and diagnostic value of chest CT of coronavirus disease 2019 (COVID-19) in the Xiaogan area	China		114	Retrospective	RT-PCR, CT

Sr. No	Authors	Title	Country	Population	Sample	Study design	Diagnostic test used
32	Wong et al., [49]	Frequency and Distribution of Chest Radiographic Findings in COVID-19 Positive Patients	Hong Kong	Adult	64	Retrospective	RT-PCR, Chest X ray
33	Xie et al., 2020[50]	Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing	China	Adult	5	Observational	RT-PCR, Chest CT
34	Xu et al., [51]	Deep Learning System to Screen Coronavirus Disease 2019 Pneumonia	China	Adult	618	Retrospective	CT with machine learning
35	Zhou et al., [52]	Clinical features and chest CT findings of coronavirus disease 2019 in infants and young children	China	Infants, young children	9	Retrospective	RT-PCR, CT
36	Zhang et al., [53]	[Clinical Features of 2019 Novel Coronavirus Pneumonia in the Early Stage From a Fever Clinic in Beijing]	China	All	9		Chest radiograph, HRCT
37	Zheng et al., [54]	Deep Learning-based Detection for COVID-19 from Chest CT using Weak Label	China	All	540	Retrospective	CT with machine learning
38	Ye et al., [55]	Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review	China			Review	RT-PCR, CT
39	Zu et al., [56]	Coronavirus Disease 2019 (COVID-19): A Perspective from China	China	Not applicable		Perspective	RT-PCR, CT scan, Chest x-ray

Table 2. Descriptive key findings of studies comparing various diagnostic techniques

Sr No	Authors	Diagnostic test used	Findings
1	Al-Tawfiq and Memish, [21]	RT-PCR, CT	CT should not be used for COVID-19 screening in asymptomatic patients, but may be considered in hospitalized patients, symptomatic cases, or in specific clinical situations. RT-PCR should be used for final diagnosis.
2	Araujo-Filho [20]	RT-PCR, CT scan, Chest x-ray	Recommended algorithm-based combination of RT-PCR and CT for diagnosis of COVID
3	Chen et al., 2020 (a) [23]	CT, Biochemical markers	CT findings may provide useful information about COVID diagnosis when coupled with inflammatory biomarkers
4	Chua et al., [26]	RT-PCR, CT	Inconclusive. Highlighted need for more data for evaluation of diagnostic efficacy of CT
5	Feng et al., [28]	RT-PCR, CT	Identified need for further evaluation of both nucleic acid based and CT based tools for diagnosis of COVID in children.
6	Gao et al., [29]	High-resolution computed tomography (HRCT)	Advocated use of HRCT for early screening and diagnosis
7	Guan et al., [31]	RT-PCR, CT	Observed lack of abnormal radiographic findings in subgroup of COVID patients
8	Hope et al., [30]	RT-PCR, CT	Inconclusive
9	Jacobi et al., [31]	RT-PCR, Chest X ray	Patterns of COVID infections can be identified by Chest x-ray and CT and can be used effectively under clinical settings
10	Konrad et al., [35]	Types of PCR	Identified need for further data for validation of the sensitivity and specificity of the new kit.

Sr No	Authors	Diagnostic test used	Findings
11	Li et al., [37] (a)	RT-PCR and CT	Changes in CT can serve as important diagnostic tool for COVID-19
12	Li et al.,[37] (b)	RT-PCR, CT with deep learning	Inconclusive
13	Patel et al., [42]	RT-PCR, Antibody test	Indicated usefulness of both the test in identifying COVID cases, however did not prove superiority of any of the technology
14	Thomas-Rüddel et al., [45]	RT-PCR, CT	CT diagnostics seem to be sensitive; however, due to the unspecific findings, neither imaging nor laboratory diagnostic seem to be suitable for diagnosis or exclusion diagnostics.
15	Xie et al., [50]	RT-PCR, Chest CT	Advocated repeated swab and CT evaluation in cases with high clinical suspicion but negative RT-PCR.
16	Yun et al., 2020	RT-PCR, CT	Infants and young children with COVID-19 tend to have mild clinical symptoms and imaging findings not as typical as those of adults, and therefore, the diagnosis of COVID-19 should be made based on imaging findings along with epidemiological history and nucleic acid detection. Chest CT has guiding significance for the early diagnosis of asymptomatic children.
17	Zhang et al., [53]	Chest radiographs, HRCT	Inconclusive
18	Zheng et al., 2020 [54]	RT-PCR, CT	In diagnosis, chest computed tomography (CT) manifestations can supplement parts of limitations of real-time reverse transcription polymerase chain reaction (RT-PCR) assay.
19	Zu et al.,[56]	RT-PCR, CT scan, Chest x-ray	Though clinical features of CT provides valuable insights for COVID infection, RT-PCR remains standard reference.

Table 3. Comparison of the diagnostic efficacy of the methods

Sr No	Authors	Diagnostic test used	Sensitivity	Specificity	AUC	Accuracy	Findings
1	Ai et al., 2020	RT-PCR, CT	97	25		68	Chest CT is superior diagnostic tool with higher sensitivity and can be considered as primary tool for diagnosis of COVID-19.
2	Barstugan et al., [21]	CT with machine learning				99.68	CT findings supported through machine learning may provide better diagnostic efficacy than conventional CT
3	Chen et al., [22]	CT with machine learning	100	93.55		95.24	The deep learning model showed a comparable performance with expert radiologist, 63 and greatly improve the efficiency of radiologists in clinical practice.
4	Fang et al., [25]	Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR	98	71			Recommended chest CT for diagnosis of COVID-19, especially when RT-PCR is negative.
5	Gozes et al., [28]	CT with machine learning	98.2	92.2	0.996		Rapidly developed AI-based image analysis of CT can be used as an effective tool for COVID diagnosis.
6	Jin et al., [32]	CT with AI	94.06	95.47	0.979	94.98	The AI system is two orders of magnitude faster than radiologists in diagnosing COVID-19.
7	Jin et al., 2020 (a) [33]	CT with AI	97.4	92.2	0.991		AI based CT tool can be promising alternative to conventional techniques.

Sr No	Authors	Diagnostic test used	Sensitivity	Specificity	AUC	Accuracy	Findings
8	Kanne et al., [34]	RT-PCR, CT scan	60-70				Only 50% COVID patients will have abnormal CT changes during initial 1-2 days. RT-PCR have 60-70% sensitivity. CT can be useful in initial RT-PCR negative patients.
9	Li et al., [36]	CT with machine learning	90	96	0.96		AI supported Chest CT is an useful tool for diagnosis of COVID-19.
10	Long et al., [39]	RT-PCR, CT	CT-92.7; RT-PCR-83.3				rRT-PCR may produce initial false negative results. We suggest that patients with typical CT findings but negative rRT-PCR results should be isolated, and rRT-PCR should be repeated to avoid misdiagnosis.
11	Majidi [40]	RT-PCR, Chest X ray	80-90	82.8-96			CT can be an useful tool for early detection of COVID, however it should be confirmed by RT-PCR at later stage.
12	Ming-Yen et al., [41]	CT and Chest x-ray	Higher sensitivity and specificity of CT than X-ray				Both are useful in detecting COVID infections, but X-ray may lack sensitivity of diagnosis
13	Shi et al., [43]	RT-PCR, CT	100				Abnormal CT can be an useful feature to diagnose COVID-19 infection in asymptomatic cases
14	Song et al., [44]	CT with machine learning	93		0.99		Deep learning supported CT can provide rapid and accurate diagnosis
15	Udugama et al., [46]	RT-PCR, Chest X ray	86-98	25			CT has good sensitivity but low specificity due to overlapping of the imaging features with other viral pneumonia.
16	Wang et al.,[47]	CT with machine learning	87	88		89.5	AI-based CT can be used to extract radiological features for timely and accurate COVID-19 diagnosis.
17	Wang et al., [48] (a)	RT-PCR, CT				97.3	CT is better diagnostic tool for early and accurate diagnosis of COVID-19 as compared to nucleic acid tests.
18	Wong et al., [49]	RT-PCR, Chest X ray	69				Chest x-ray findings have a lower sensitivity than initial RT-PCR testing
19	Xu et al., [51]	CT with machine learning				86.7	Deep learning based CT are effective imaging tool for early diagnosis of COVID-19 infection
20	Zheng et al., [54]	CT with machine learning	90.7	91.1	0.975		Machine learning algorithm supported CT images are fast and effective tools for diagnosis of COVID-19 infection.

efficacy of the tests were extracted from the studies and are presented as Table 3. Twenty studies compared diagnostic value of CT, RT-PCR and chest x-ray and expressed in terms of either sensitivity, specificity, accuracy or area under curve. It was found that CT coupled with algorithm yielded fairly high sensitivity. Overall CT showed better sensitivity (>86%), though it was found to have low specificity. One study stated inferior diagnostic potency of both CT and RT-PCR and showed that only 50% and 60-70% of the cases can be diagnosed using CT and RT-PCR respectively. Although, chest x-ray showed sensitivity of 69% slightly better than or equal to RT-PCR but it was not commonly advocated as diagnostic tool alone on its own [50].

4. DISCUSSION

As guidelines given by WHO, COVID-19 detection by RT-PCR is a cornerstone in the current pandemic. The positive rate of RT-PCR assay for throat swab samples was in the range of 30-70% in different studies. RT-PCR's low sensitivity, insufficient stability, and relatively long processing time delays the diagnosis of COVID-19 disease. As there is no specific treatment for COVID-19 disease at present, only way to prevent or decrease the spread is to diagnose and put the case on isolation to break the chain of transmission. At some places, chest scan is suggested typically as the first-line imaging modality for patients with suspected COVID-19 due to its high sensitivity [16]. The global radiological fraternity in current position has not recommended use of chest x-ray and/or CT beyond 'routine clinical care', however, a modified version as suggested by British Thoracic Imaging Society incorporating on use of chest x-ray and CT Scan in algorithm for clinical diagnosis and management of COVID-19 cases is worth exploring and deliberating as a guiding policy document for enhancing testing in Indian context and similar resource constraint settings. Evidence suggest that CT chest can also be a useful modality to diagnose COVID-19 disease as its sensitivity is reaching up-to 97% and can be a useful tool to diagnose early even before it is picked by RT-PCR [14]. In resource adequate setting, the first CT test can be useful as a baseline for the treatment of the patients and follow up CT can give us information regarding disease progression or improvement. However, in resource poor settings like India, there are some limitations of this modality like infrastructure, observer variability and radiation hazard. More so, after performing the CT chest

on suspected patient, decontamination of the CT machine room has to be done before taking the next patient [58,59]. Large-scale use of CT scan might lead to an increase radiation exposure of the population, which increases the probability of uncertain biological effects on long term use [60].

Although further studies are needed, in the scenario when there is a very high clinical suspicion of COVID-19 it is conceivable that a positive chest x-ray may even obviate the need for a CT, thus reducing burden on CT units in this pandemic [16]. Because of its convenient use and decontamination, there are recommendations to include chest x-ray as an aid to diagnostic algorithm for COVID-19 [58]. Moreover, there are reports that COVID-19 viruses can survive on the non-living surfaces till 72 hours and hence disinfection of these instruments are utmost important between the patients. In case of chest x-ray, periodic cleaning and lag phase between two cleaning period can be easily managed through additionally available equipment. It is also reported that portable chest x-ray can improve the accessibility in resource limited country [61]. Due to this additional advantages of portability, chest x-ray could be an effective alternative in isolation wards for both diagnosis as well as screening of individuals with clinical suspicion of the infection, when there is limited availability of RT-PCR and CT scan. Chest radiographs may be normal in early or mild disease. In recent years, there has been increasing interest in expanding access to chest radiography in order to improve TB case detection in high-burden areas. Under National Tuberculosis Elimination Program (NTEP) in India, a diagnostic algorithm using combination of clinical evaluation with sputum microscopy and chest radiography provided high sensitivity and specificity in early detection and management of Tuberculosis [61].

In a study done by Ho Yuen Frank Wong et al of patients with COVID-19 requiring hospitalization, 69% had an abnormal chest radiograph at the initial time of admission, and 80% had radiographic abnormalities sometime during hospitalization [50]. Although the chest x-ray findings had a lower sensitivity than initial RT-PCR testing (69% versus 91%, respectively), but authors suggested that chest x-ray can play a role in the initial screening of COVID-19. One more advantage of using chest x-ray is that negative findings on chest x-ray can provide some valuable information especially in case when RT-PCR shows positive results [50]. This

may help in screening patients who are cured in whom the RT-PCR may provide false positive results and their chest x-ray may be used to rule out the disease severity status and these patients can be shifted to other wards/home isolation [50]. Moreover, it is a cost-effective and more feasible alternative due to its wide reach and can be used for screening and active follow up of the cases. So, it can be effectively used in screening and stratify the patients as per risk especially 1) at diagnoses of symptomatic patients where through evident changes on x-ray, may avoid cost-burden associated with RT-PCR, and 2) for patients who are recovered, if no changes are present in x-ray, but RT-PCR is positive, then the patients may be shifted to primary care centres/quarantine facility from tertiary care and kept under observation. This may reduce additional burden on tertiary care system. Successful policy responses to curb the pandemic necessitates cooperation at all levels from laboratories, hospitals and public health experts by regularly updating existing tools used for diagnosis and management based on available evidences.

5. CONCLUSION

With serious debate across the validity of RT-PCR, its cost and the time taken for processing, policy planers should think of strategies in resource constrained countries like India for developing alternate diagnostic algorithm like the one used under NTEP. There is a considerable scope for inclusion of chest x-ray and/or CT chest in existing diagnostic algorithm that might help in early isolation of the patients to halt the progression of COVID-19 pandemic. However, the use of chest x-ray and/or CT chest for screening and diagnosing COVID-19 with or without RT-PCR should also be evaluated against risk–benefit ratio. There is an urgent need for undertaking an operational research to develop such algorithm that can capitalize on existing health care ecosystem.

6. LIMITATION

Majority of the studies included in the review were not from Indian origin. So contextual effect of available resources, features and reach of existing health care system and availability of skilled human resources, especially for India cannot be drawn from current review. A policy directive for India should be framed considering all these factors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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