Review

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The optimal diagnostic methods for COVID-19

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Abstract: As the world continues to study and understand coronavirus disease (COVID-19), existing investigations and tests have been used to try and detect the virus to slow viral transmission and its global spread. A ‘gold-standard’ investigation has not yet been identified for detection and monitoring. Initially, computed tomography (CT) was the mainstay investigation as it shows the disease severity and recovery, and its images change at different stages of the disease. However, CT has been found to have limited sensitivity and negative predictive value in the early stages of the disease, and the value of its use has come under debate due to whether its images change the treatment plan, the risk of radiation, as well as its practicality with infection control. Therefore, there has been a shift to the use of other imaging modalities and tests, such as chest X-rays and ultrasound. Furthermore, the use of nucleic acid-based testing such as reverse-transcriptase polymerase chain reaction (RT-PCR) have proven useful with direct confirmation of COVID-19 infection. In this study, we aim to review and analyse current literature to compare RT-PCR, immunological biomarkers, chest radiographs, ultrasound and chest CT scanning as methods of diagnosing COVID-19.

Keywords: biomarkers; chest radiograph; computed tomography; COVID-19.

Introduction

Several cases of coronavirus disease (COVID-19) were first identified in the city of Wuhan, China in December 2019 [1].

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Those with COVID-19 generally present with fever, dry cough and fatigue [2]. On 3rd January 2020, bronchoalveolar lavage fluid (BALF) obtained from a patient with pneumonia of unknown origin in Wuhan was used to sequence the genome of the novel coronavirus for the first time with the help of Sanger sequencing, Illumina sequence and nanopore sequencing. The virus was classified as a beta-coronavirus, which is closely related to the SARS virus [1].

The COVID-19 pandemic has posed one of the greatest challenges to healthcare systems across the globe. Its scale of spread and everchanging nature has made it crucial to identify and detect, in order to try and contain viral transmission, especially since its symptoms are non-specific and common in countless other aetiologies. As such, the WHO released laboratory testing guidelines which recommended obtaining specimens from the upper respiratory tract (URT), for COVID-19 testing by reverse-transcriptase polymerase chain reaction (RT-PCR). In the event that the test was negative for the virus, but the clinical suspicion remained high, then specimens from the lower respiratory tract (LRT), such as expectorated sputum and tracheal aspirates BALF, was recommended to be used for nucleic acid amplification tests (NAATs) [3]. However, although RT-PCR is able to detect the presence of COVID-19, it comes with several disadvantages, such as being reliant on the specimen taken which could have faults, and low viral loads depending on which part of the respiratory tract the specimen was obtained from. IgM and IgG can also be detected for the diagnosis of COVID-19 [4]. However, RT-PCR and the use of biomarkers take a longer time compared to other investigations, such as imaging. Computed tomography (CT) scan is the primary imaging modality used for the diagnosis of COVID-19 [5]. However, CT scans carry their own risks due to radiation exposure as well as contamination of the radiology suites and exposing a small group of staff and other patients to possible infection. Furthermore, it has been argued that CT images do not necessarily alter the treatment plan. Therefore, its use in evaluating the infection has come under question. In its place, other imaging modalities are being studied for detection and monitoring of COVID-19, such as chest radiography (CXR) and ultrasound. Although these

modalities have a reported lower sensitivity than CT, they are advantageous in terms of infection control. The purpose of this review is to evaluate diagnostic measures, including sensitivity, specificity and predictive values of biomarkers, swabs, sputum, BAL, CXR, ultrasound and chest CT in diagnosing COVID-19 and to discuss whether these diagnostic modalities should be used as a primary diagnostic tool.

Clinical features of COVID-19

Because of the rapidly dynamic nature of COVID-19 and its relatively recent onset, the knowledge on the virus is still progressing. As such, the clinical features are constantly being reviewed. According to the World Health Organisation (WHO) [6], the most common symptoms include a fever, non-productive cough and fatigue. A study carried out by Guan et al. involving 1,099 patients in Wuhan showed that 67.8% of all patients suffered from a cough, 43.8% of patients presented with a fever on admission, 88.7% experienced a fever during hospitalisation, and 38.1% having fatigue [7]. These figures are corroborated in a study by Huang et al., which showed that 76% of patients had a cough, while 98% had a fever [8]. The majority of these patients (44%), had a fever that was between 38.1 and 39.0 °C [8], and this is supported by the in-patient figures by Guan et al., whereby 46.9% of the patients had a fever in this range as well [7]. Although interestingly, on admission, it was reported by Guan et al. that the most common core body temperature was below 37.5 °C [7]. However, this could be because the patients on admission were in the early stages of the infection.

Other symptoms include myalgia, sore throat, conjunctivitis, headache, as well as smell and taste impairment [6]. It was found that 14.9% experienced myalgia, and 13.9, 0.8, 13.6% of patients experienced a sore throat, conjunctivitis, and headache respectively [7]. Furthermore, 18.7% of patients had shortness of breath, and 33.7% were producing sputum. A retrospective study by Mao et al. involving 214 patients, showed that 5.6% of patients experienced taste impairment and 5.1% suffered from impaired smell [9]. Therefore, only a small proportion of patients experience taste and smell impairments, hence if present, it may strengthen COVID-19 as a differential diagnosis. However, the other symptoms are very non-specific, making it difficult to differentiate COVID-19 from other infections alone without the use of further investigations. The clinical features of COVID-19 are summarised in Table 1.

Table 1: Summary of the clinical features of COVID-19.

Symptom	Frequency, %		
	Guan et al. [7]	Huang et al. [8]	Mao et al. [9]
Cough	67.8	76	50.0
Fever	On admission: 43.8 During admission: 88.7	98	61.7
Fatigue	38.1	44	
Myalgia	14.9	44	
Sore throat	13.9		
Conjunctivitis	0.8		
Headache	13.6	8	13.1
Shortness of breath	18.7		
Dyspnoea		55	70.6
Sputum production	33.7	28	
Taste impairment			5.6
Smell impairment			5.1

Nucleic amplification acid testing

Nucleic acid amplification tests (NAATs) such as RT-PCR can be used as a primary diagnostic tool to confirm COVID-19 diagnosis. NAATs including RT-PCR frequently utilise the open reading frame 1ab (ORF1ab) gene, the RNA-dependent RNA polymerase (RdRp) protein from ORF1ab, the envelope (E), nucleocapsid (N) and spike genes as targets for COVID-19 detection and various retrospective studies have evaluated the test performance of RT-PCR using different molecular targets [10]. A retrospective analysis of RT-PCR test results for 4,880 patients suspected of COVID-19 infection that utilised the ORF1ab and N protein gene fragments of COVID-19 as targets, found that 1,875 patients had a positive test result, showing a relatively low test sensitivity of 38% [11]. This study had non-specific inclusion criteria, with patients being recruited based on the presence of “typical” respiratory tract infection symptoms or recent close contact with a COVID-19 patient, meaning patients who did not have COVID-19 may have been included in the study thereby accounting for the low test sensitivity reported. More recently, Chan et al. assessed the performance of RT-PCR assays targeting the RdRp/helicase (Hel), S and N genes and compared it to an RdRp-P2 assay [12]. They reported that out of the 273 clinical specimens collected from 15 patients with laboratory-confirmed COVID-19, the RdRp/Hel assay was significantly more sensitive in detecting COVID-19 than the RdRp-P2 assay, with positive rates of

43.6% for the RdRP/Hel assay and 28.2% for the RdRP-P2 assay ($p < 0.001$). Even though RT-PCR assays are designed based on the conserved regions of the COVID-19 genome, the literature seems to suggest that the target gene or protein utilised affects assay performance with the RdRP/Hel RT-PCR showing greater sensitivity for detection of COVID-19.

In addition to the target gene/protein, the clinical sample type utilised for RT-PCR may also affect test performance. Significant differences have been noticed in the viral loads of samples depending on where in the respiratory tract they have been collected. A study by Yu et al. reported that the average viral load in sputum was 17429 ± 6920 copies/test, whereas the viral load in throat swabs (2552 ± 1965 copies/test, $p < 0.001$) and nasal swabs (651 ± 501 copies/test, $p < 0.001$) was significantly lower [13]. Similar results were seen in a study by Lin et al. comparing the detection rates of COVID-19 from sputum specimens and throat swabs. The positive rate was significantly higher in the sputum group (76.9%) compared to the throat swabs (44.2%) [14]. Lower respiratory tract samples such as BALF and sputum have been similarly shown to have greater detection rates when compared to upper respiratory tract samples, but also when compared to non-respiratory samples such as faeces, blood and urine [2]. These results indicate the superiority of lower respiratory tract samples in detecting the viral replication levels over other sample types however, the need for improved diagnostic accuracy must be weighed up against the need to minimise transmission and ensure the safety of health-care staff. Collection of lower respiratory tract samples oftentimes involves aerosol generation and poses a high risk of viral transmission to staff, thus in practise upper respiratory tract samples are more frequently used.

RT-PCR has shown high sensitivity for COVID-19 detection but there remains a need for simpler diagnostic testing within resource-limited areas where there may be a lack of PCR cyclers and highly trained technicians. Therefore, other types of NAATs have been assessed including reverse transcription recombinase-aided amplification (RT-RAA) and reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay. A multi-centre study by Wang and colleagues evaluated the performance of RT-RAA assay with ORF1ab as the target gene using 947 clinical samples and compared it to RT-PCR to see if results were consistent [15]. They reported that RT-RAA results for 926 samples (97.87%) were consistent with the results from RT-PCR, suggesting that RT-RAA has comparable sensitivity for detection of COVID-19 to RT-PCR. RT-RAA had a faster turnaround time when compared to RT-PCR, with detection being achieved within 30 min in the reported

study, and the device was portable and cheaper thus making it a viable alternative for rapid diagnosis in settings where resources to carry out RT-PCR may be lacking though more comparative literature is needed going forward. Similarly, a recent study evaluated the performance of their RT-LAMP device with ORF1ab as the target gene using 248 clinical samples from patients with RT-PCR-confirmed COVID-19 [16]. The RT-LAMP device detected COVID-19 in 223 samples demonstrating a detection level of 89.9% which while it is lower than that reported with RT-RAA, is still relatively comparable to RT-PCR thus making it a viable alternative to RT-PCR in areas lacking the facilities and equipment.

Overall, NAATs are a useful tool for primary diagnosis of COVID-19 as they have demonstrated a high specificity and sensitivity, and have a rapid turnaround time that allows for rapid viral detection. NAATs are a preferable diagnostic modality as they can provide results early in the course of the disease when compared to other diagnostic modalities, which allows early detection and subsequent isolation which is key for prevention and control of the COVID-19 pandemic given that there are no suitable anti-viral drugs or vaccines as yet.

Biomarkers

Although NAATs remain the recommended primary diagnostic method for COVID-19, there has been some work looking at the diagnostic utility of biomarkers to assess whether the sensitivity and specificity of such tests is comparable to that of nucleic acid-based methods.

The production of specific IgM in the initial stages of viral infection followed by production of IgG for long-term immunity has been found to be consistent amongst SARS patients except those that are immunocompromised, so given that COVID-19 is similar to SARS this is assumed to be the case in COVID-19 patients, making the detection of IgM and IgG antibodies against COVID-19 via immunoassay a promising area of research in COVID-19 diagnosis [17]. Liu et al. utilised N and S COVID-19 proteins as targets for an enzyme-linked immunosorbent assay (ELISA) for detecting IgM and IgG antibodies in 214 patients with COVID-19 confirmed by RT-PCR and 100 control healthy blood donors to assess the diagnostic performance of ELISA [18]. The study reported that 68.2 and 70.1% of COVID-19 patients were successfully diagnosed with the N protein-based IgM and IgG ELISAs respectively, and 77.1 and 74.3% were diagnosed using the S protein-based IgM and IgG ELISAs. Hou et al. similarly looked at detection rates of IgM and IgG in 338 COVID-19 patients classified into three groups

according to disease severity but used chemiluminescence immunoassay instead and they found that for the mild, severe and critical disease groups, the detection rates for both IgM and IgG were 79.7, 77.9 and 80% respectively [19].

To improve the test efficiency of antibody-based diagnostic testing, Xiang et al. developed a method that enabled simultaneous detection of IgG and IgM using ELISA and colloidal gold-immunochromatographic assay (GICA) [20]. They analysed 63 plasma samples using ELISA and 91 plasma sample using GICA from patients with RT-PCR-diagnosed COVID-19 and found that there was no significant difference in the combined IgM and IgG sensitivity of the two types of immunoassays, with sensitivity being reported as 87.3% for ELISA and 82.4% for GICA.

These studies demonstrate the potential value of antibody testing for confirmation of COVID-19 diagnosis as they reported test sensitivity that is comparable to that of RT-PCR, with the added advantage of being simpler to carry out and cheaper, which may prove useful for areas where resources are limited. However, unlike NAATs which allow for detection early in the disease course, levels of IgM and IgG have been found to only be detectable in patient samples from 10 days and from 20 days onwards after COVID-19 infection, respectively [21]. Thereby suggesting that antibody testing has limited utility as a primary diagnostic tool for detecting COVID-19. Nevertheless, it should be noted that IgM levels are high in the early disease stage before depleting in later stages where IgG levels begin to increase instead. Which may suggest that the use of antibody testing may be a suitable diagnostic tool for monitoring disease progression instead [22]. Overall, there is a need to identify more specific biomarkers that allow for diagnosis early in the disease course before biomarkers can be utilised in primary diagnosis.

Chest radiograph

The majority of the literature surrounding imaging for COVID-19 has focused on CT as the primary imaging modality. However, other imaging modalities such as chest radiography (CXR) and ultrasound are now also being considered. CXR has shown to be useful as a first-line investigation to screen for COVID-19 because of its practical advantages, in terms of speed and infection control.

In China and Italy, alongside RT-PCR and CT, chest X-ray has been used in the screening and monitoring of patients [23]. British hospitals have also started utilising chest X-ray as a first-line tool for triage of COVID-19 patients, owing to the long turnaround times for RT-PCR [24]. Abnormalities seen in chest radiographs of COVID-19

patients mirror those in CT, with both usually showing bilateral, peripheral consolidation and ground-glass opacities. The severity of chest radiograph abnormalities was found to peak at 10–12 days from symptom onset, similar to CT findings which peak at 6–11 days [24].

However, it has been shown that CXR has a lower sensitivity than CT. Wong et al. reported that baseline chest X-ray has a sensitivity of 69%, which is significantly lower than the reported 97–98% sensitivity of CT [24]. Similar results were seen in a study by Guan et al. which reported significantly higher sensitivity (86.2%) of CT compared to chest X-ray (59.1%) in detecting opacifications in COVID-19 patients [7].

CXR may however provide practical advantages compared to CT such as preventing cross-infection from transport of patients to contaminated CT suites, inefficiencies of subsequent decontamination of CT suites, along with unavailability of CT in many parts of the world. Additionally, in patients with obvious clinical signs diagnostic of COVID-19, a positive chest radiograph may negate the need for CT, making CXR a viable alternative in terms of cost effectiveness as well [25]. Furthermore, imaging will enable detection of any underlying cardiopulmonary abnormalities as well as establishing baseline pulmonary status. Thus, allowing physicians to assess for risk and wary of any possible secondary complications of COVID-19 such as pulmonary embolism, bacterial pneumonia or possible heart failures [26, 27].

Ultrasound

Ultrasound has also been considered as an imaging modality for COVID-19 detection. Lung ultrasound (LUS) of COVID-19 patients typically show multiple B-lines, irregular pleural line with subpleural consolidations and areas of opacifications predominantly on the anterior and posterior hemi-thorax bilaterally [28]. Lu et al. reported in a study with chest CT as the reference standard that using ultrasound in mild, moderate and severe lung lesions was found to have sensitivity of 68.8, 77.8, 100.0%, specificity 85.7, 76.2, 92.9% and diagnostic accuracy 76.7, 76.7, 93.3% respectively. The PPV was reported to be 84.6, 58.3, 50.0% and NPV 70.6, 88.9, 100.0% for mild, moderate and severe lung disease due to COVID-19 respectively [29].

In addition to LUS possessing good sensitivity and specificity, there are also several practical benefits of using LUS for COVID-19 detection such as its portability. It allows the same clinician to acquire lung images directly at the bedside thus preventing exposure of several staff to the patient, which is the case when using CT where the patient

needs to be moved to the CT suite [28]. This same clinician can then also complete other tests and evaluations required for the patient, limiting exposure further. Portable ultrasound devices are also easier to sterilise and can be used to test patients directly in their homes, thus freeing up hospital beds which run a high risk of being over-saturated amid the current pandemic. Lastly, ultrasound is radiation free and is a cheap modality, suggesting that LUS may have a role in triaging symptomatic patients in multiple settings such as in the emergency department, homes of symptomatic patients, and the intensive care unit [28, 30]. However, access to equipment of adequate quality along with the requirement of proper training in ultrasound interpretation of COVID-19 findings may be some limitations of this modality [31].

Computed tomography

CT scans have played an important part in the work up of COVID-19. There are several features that have been identified as being typical of COVID-19 in a number of studies, chiefly the appearance of ground-glass opacities (GGO) which are present in most patients with COVID-19. Other typical features include consolidation, pleural thickening, “crazy-paving pattern” and “reverse halo sign” [5]. Furthermore, it has been observed that, as the disease and infection progress, the features on the CT scan may vary in morphology, distribution and severity. Within the first 2 days of disease, CT scanning may show no lung opacities whatsoever in up to 56% of patients. This proportion is even higher for asymptomatic patients, but falls rapidly further in the disease process, beyond day 3 [32]. Opacities that are present are likely to be peripheral, lower lobe predominant, multifocal and composed purely of a GGO appearance [33]. As the disease progresses and becomes more advanced, other more diverse features become significantly more common and CT scans almost always demonstrate some type of opacity. In various studies it was noted that features such as consolidation, reticular patterns, diffuse GGO and “crazy paving patterns” became more common [34]. This suggests that CT scans may have greater sensitivity in critically ill patients, but exhibit a poor sensitivity in early disease, thus we suggest that the use of CT scans in later stages of disease would be of better significance to the management of COVID-19. A noteworthy point from several studies demonstrated a regression in the CT scan appearance during the later stages of the disease process, as the patient begins to recover. Pure GGO becomes more apparent, with other opacity patterns and features declining as the patient recovers from the illness

[35]. There are also changes in distribution, where opacities are more likely to be unilateral in these final stages, although this is still uncommon [36].

As such, the sensitivity and specificity of CT scanning in the context of COVID-19 varies over time as the disease progresses and CT features change. Due to the likelihood of a normal CT appearance in the stages of the disease, CT scanning has limited sensitivity and negative predictive value in the early stages of the disease, although this is improved with disease progression. This is suggested in retrospective studies looking at CT sensitivity, although the positive findings of CT may be down to selection bias of patients who are with a more serious or later stage of the disease [35, 37]. Although, CT has been found to have limited sensitivity and negative predictive value in the early stages of the disease, and the value of its use has come under debate due to whether its images change the treatment plan, the risk of radiation, as well as its practicality with infection control. As a result, the wide-spread deployment of CT in triaging suspected cases of COVID-19 based on overestimated sensitivity reports should raise questions about patient and staff safety during CT scans, while weighing out the benefits and risks of these outcomes.

We can see that CT scanning is an important potential indicator for disease progression. Changes in CT scan appearance demonstrate significant differences from the early to the intermediate and finally to the late stages of the disease process in a particular pattern. Whilst these changes are common in COVID-19, they are also typical of other causes of viral pneumonia, particularly SARS and MERS. These infections may also demonstrate similar pattern of progression as COVID-19 [38]. This can call into question how well we can utilise CT scanning to diagnose COVID-19 infection based on CT changes alone. Furthermore, various studies have found that the earliest stages of symptomatic disease and asymptomatic disease may not demonstrate any changes to the appearance of the lungs on CT at all [12, 33, 39]. This could indicate that CT scans have limited utility in asymptomatic patients to rule out COVID-19. Additionally, it should not be neglected that CT scans come with risks of their own, which include the overuse of hospital personal protective equipment to ensure for safety in performing a scan and increased risk of disease transmission with aggregation of affected and non-affected patients in the radiology department [40].

Reports from the US have suggested an alternative role for CT in combating COVID-19 rather than a direct diagnostic modality. Emphasising that CT imaging would not significantly affect treatment directions, as oxygen and supportive care would be given, even if symptoms are

secondary to COVID-19 [41]. This is echoed in studies that reviewed the sensitivity and specificity of CT scanning in COVID-19, however there were recurring limitations such as selection bias. To date there is limited high-quality retrospective studies that support the use of chest CT in diagnosing COVID-19, but a role to facilitate patient management by ruling out differentials would be beneficial in selected cases is recommend [35]. Hence literature to date has argued that CT should be reserved for cases that would impact patient management or used for ruling out alternative diagnosis due to lower specificity than RT-PCR and limited sensitivity to COVID-19 [42].

Future studies

During these unprecedented times of the COVID-19 pandemic, in order to gain a better understanding of the nature of this disease, more and more research is being conducted at an accelerated pace worldwide. It has been widely accepted that testing is extremely important in combating this pandemic. Due to the novelty of COVID-19, this disease is often underdiagnosed and misdiagnosed [43]. Thus, many studies have explored and examined the uses of various diagnostic tools and techniques for detecting COVID-19. More work needs to be done to develop guidelines and protocols for a full set of investigations for any query COVID-19 case. Specifically, in evaluating specific features that can indicate patient prognosis both in the short-term infective period as well as in the long term after recovery from the viral infection. Considering the nature of COVID-19, it is also important to find a way to effectively rule out infection in patients who are minimally symptomatic or totally asymptomatic. Moreover, future studies intending to investigate the specificity and selectivity of CT diagnosis in COVID-19 will need better defined criteria to how positive results of COVID-19 is obtained, as well as aiming to reduce selection bias to yield stronger scientific evidence for guidance to clinical practice.

Conclusions

Viral load plays an important role in detection of positive cases of COVID-19; imaging studies can be useful tools to assess for infection with COVID-19 and CT scan is able to assess such progress. Although CT scan can be used to diagnose those who are infected with COVID-19 but are asymptomatic. From current literature it is recommended that CT should be reserved for evaluation of cases with COVID-19

complications such as pneumonia, pulmonary embolism and possible heart failures. All current available testing methods have their own sensitivity and specificity in detecting COVID-19. Accordingly, these diagnostic modalities will have different roles to facilitate treatment against COVID-19. However, larger studies are needed to effectively establish a more accurate diagnostic method or clear diagnostic pathway to optimise detection of COVID-19.

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