Acta Biomed 2020; Vol. 91, N. 3: e2020019 DOI: 10.23750/abm.v91i3.9822

The role of imaging and other diagnostic approaches in COVID-19

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Summary. As the COVID-19 pandemic develops across the globe, a large amount of literature has been written about the different ways in which we can diagnose and investigate someone suspected of being infected with the new coronavirus. Many approaches highlight the importance of using reverse transcriptase polymerase chain reaction (RT-PCR) used in conjunction with computed tomography (CT) scans. Whilst CT scans have been shown to be useful, there are multiple risks associated with them, for example radiation exposure and the transmission risk associated with repeated use of a CT suite. Therefore, it is important to analyse their diagnostic ability and limitations and to consider other methods of diagnosing COVID-19. Additionally, RT-PCR testing can have significant rates of false negatives, indicating the importance of taking a more comprehensive diagnostic approach. Here, we aim to review and analyse this literature to compare RT-PCR, serum inflammatory biomarkers, chest radiographs, ultrasound and chest CT scanning as methods of diagnosing COVID-19, particularly in asymptomatic patients. (www.actabiomedica.it)

Key words: COVID-19, Computerized tomography, Chest radiograph, Biomarkers, Ultrasound, RT-PCR

Introduction

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

Laboratory testing guidelines from WHO recommend initially taking specimens from the upper respiratory tract (URT) such as nasopharyngeal and oropharyngeal swabs for COVID-19 testing by reverse-transcriptase polymerase chain reaction (RT-PCR). If the test comes back negative, but the clinical suspicion remains high, specimens from the lower respiratory tract (LRT) such as expectorated sputum, tracheal aspirates or bronchoalveolar lavage fluid (BALF) should be used for nucleic acid amplification tests (NAATs). Repeat testing on URT and LRT specimens is recommended to indicate changes in viral load and therefore, the disease progression (3). Tests to check levels of inflammatory biomarkers such as C-reactive protein (CRP) and lymphocytes are also recommended (4). Computer tomography (CT) scan is the primary imaging modality used for the diagnosis of COVID-19. Ground-glass opacities, consolidation and pleural thickening are some of the most common features of coronavirus on CT (5).

The purpose of this review is to evaluate diagnostic measures, including sensitivity, specificity and predictive values of biomarkers, swabs, sputum, BAL,

chest x-Ray, ultrasound and chest CT in diagnosing COVID-19 and to discuss whether CT scans should be used as a primary diagnostic tool.

Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR)

NAATs such as RT-PCR are most commonly used for confirmation of COVID-19 cases (3). A study tested oropharyngeal swabs, nasopharyngeal swabs and sputum specimens to evaluate the sensitivity of RT-PCR. Between March 29 to April 6, the prevalence rate in 8 countries outside of China including Taiwan, Australia, South Korea, Germany, United States, Italy, France and the UK varied from 1.0% to 22.9% respectively. The negative predictive value (NPV) of RT-PCR in the mentioned countries ranged from 96.8-99.9%, while the NPV for CT ranged from 95.4-99.8%. For RT-PCR, the Positive predictive value (PPV) ranged from 47.3% to 96.4%, and therefore was reported to be 10 times higher than that of CT scans (1.5%-30.7%) (6), this suggests that there is a lower probability of obtaining false positives with RT-PCR compared to CT scan which makes the test highly specific in low prevalence regions. This is also evident from the pooled specificity of CT which is only 37% (6). In the longer term, this will make RT-PCR a more cost-effective diagnostic tool as there will be fewer false positives who go on to have further unnecessary testing.

Although RT-PCR has lower false positives in low prevalence regions compared to CT, a study conducted by Fang et.al reported the sensitivity of initial CT as 98% compared to 71% for initial RT-PCR ($p<.001$) (7). This shows a large number of false negative results with initial RT-PCR compared to CT scans. This could be due to several reasons, such as a faulty sample collection technique, poor quality specimen or the collection of the specimen either too late or too early in the infection (3). Another study demonstrated that 60% to 93% of the patients had positive initial CT scans consistent with COVID-19 before the initial RT-PCR came back positive and on follow-up CT scans 42% of the patients showed improvement before the RT-PCR became negative (8). These sets of results indicate that CT is more sensitive compared to RT-PCR at initial testing around day 3 as well as showing signs of recovery promptly during follow-up, so chest CT could have good potential in diagnosing COVID-19 earlier on.

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. These results may indicate the superiority of lower respiratory tract samples in detecting the viral replication levels (9). 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%) (10).

Wang et al. investigated the sensitivity of RT-PCR testing in different tissues of patients with confirmed SARS-CoV-2 in 3 different hospitals in China. The second highest positive rates were seen with sputum at 72% (n=75), then nasal swabs (63%) and pharyngeal swabs (32%). Bronchoalveolar lavage (BAL) fluid specimens were reported to show the highest positive rates at 93% (n=14) (2).

Biomarkers

Various biomarkers can be used to look at different aspects of COVID-19. Multiple organ failure (MOF) can occur in those with severe or fatal disease and this can be recognised through testing for multiple biomarkers (11). MOF can result in increased levels of cardiac biomarkers e.g. troponin, elevated liver enzymes such as alanine aminotransferase and aspartate aminotransferase, rise in renal biomarkers, namely creatinine and blood urea nitrogen and also raised levels of coagulation markers such as prothrombin time and D-dimer (12,13). As the disease advanced into later stages, lymphocytes were observed to progressively decrease while an increase during the recovery phase was also noted. Therefore, lymphocytes could be used to assess disease progression. Similarly, elevated CRP and

Interleukin-6 can indicate the development of systemic inflammatory response syndrome in those severely unwell (12). White blood cell (WBC) count, granulocyte and granulocyte/lymphocyte ratio (NLR) can also be used to form a differential diagnosis for COVID-19 as they were noted to be significantly higher in those with influenza than in patients with coronavirus (14).

A study by Tan C et. al reported remarkably raised CRP and ESR levels during the early stages in severely ill COVID-19 patients, meanwhile no major differences in CT scans were visible in between mild and severe patients (15). This implies that the patients who were deteriorating and becoming severely ill could be identified earlier using these biomarkers instead of CT. Analysis of the receiver operating characteristic curve (ROC curve) in COVID-19 patients showed that the area under the curve (AUC) for CRP to predict the severity of the disease was 0.87, which was the highest amongst all the other biomarkers including WBC count (0.51), neutrophils (0.57), lymphocytes (0.40), ESR (0.78), as well as CT (0.71) (14). This suggests that CRP has the highest probability of being able to distinguish between those with severe and non-severe disease. CRP also has one of the highest sensitivities (83%), the highest specificity (91%), with PPV of 71% and NPV of 95% (14).

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 radiographs and ultrasound are now also being considered.

In China and Italy, alongside RT-PCR and CT, chest x-ray has been used in the screening and monitoring of patients (15). 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 (16).

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 were found to peak at 10-12 days from symptom onset, similar to CT findings which peak at 6-11 days (16).

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 (16). 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 (17).

Chest x-ray 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 (18).

Ultrasound

Ultrasound has also been considered as an imaging modality for COVID-19 detection. Lung ultrasound scans 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 (19). 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 of 85.7%, 76.2%, 92.9% and diagnostic accuracy of 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 (20). The use of doppler ultrasound can be useful for diagnosis of deep venous thrombosis (DVT) as patients with COVID-19 have a severely deranged coagulation system and therefore are at a greater risk of developing this condition (21).

There are also several practical benefits of using lung ultrasound for COVID-19 detection. 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 (19).

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 (19). 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 (22).

Computerized Tomography

CT scans have been used as an important part of the workup of COVID-19. There are several features that have been identified in a number of studies as being typical of COVID-19, 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" among others (5). It has also been observed, that as the disease and infection progress, the features on CT vary in morphology, distribution and severity. Within the first 2 days of the disease, CT scanning may show no lung opacities at all 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 (23). Opacities that are present are likely to be peripheral, lower lobe predominant, multifocal and composed purely of a GGO appearance (24). 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 (25). What is also important to note, is that several studies demonstrate that in the last stages of the disease process as the patient recovers, there is a regression in the CT scan appearance. Pure GGO becomes more and more common, with other opacity patterns and features declining as the patient recovers from the illness. There are also changes in distribution, where opacities are more likely to be unilateral in these final stages, although this is still uncommon (26).

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

Table 1. Summary of efficiency of each diagnostic method of COVID-19

Diagnostic Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CT	98 (7), 86.2 (16)	37 (6)	1.5-30.7 (6)	95.4-99.8 (6)
RT-PCR (swabs, sputum)	71 (7)		47.3-96.4 (6)	96.8-99.9 (6)
RT-PCR (sputum only)	76.9 (10), 72 (2)			
RT-PCR (throat/pharyngeal swabs)	44.2 (10), 32 (2)			
RT- PCR (nasal swab)	63 (2)			
RT-PCR (BAL)	93 (2)			
Chest Radiograph	69 (15), 59.1 (16)			
Lung Ultrasound	68.8 (mild), 77.8 (moderate), 100.0 (severe) (19)	85.7 (mild), 76.2 (moderate), 92.9 (severe) (19)	84.6 (mild), 58.3(moderate), 50.0 (severe) (17)	70.6 (mild), 88.9 (moderate), 100.0 (severe) (19)

CT: computed tomography, RT-PCR: reverse-transcriptase polymerase chain reaction, BAL: bronchoalveolar lavage, PPV: positive predictive value, NPV: negative predictive value

of the disease, although this may improve with disease progression.

We can see that CT scanning is an important potential indicator for disease progression. Changes in the 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 (27, 28). 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 (23,24). This could indicate that CT scans have limited utility in asymptomatic patients to rule out COVID-19.

Future Studies

As the COVID-19 pandemic unfolds, more research is being conducted into better understanding the nature of this disease. We have seen how different studies have examined the uses of various diagnostic tools and techniques for 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, more work needs to be done to evaluate 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.

Conclusion

Viral load plays an important role in the detection of the 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. Furthermore, CT scans can be used to diagnosis those infected with COVID-19 but are symptomatic. All current available testing methods have their own sensitivity and specificity in detecting COVID-19. Larger studies are needed to effectively establish the more accurate diagnostic method of COVID-19.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 13 May 2020
Accepted: 20 May 2020
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