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Current challenges in COVID-19 diagnosis: a narrative review and implications for clinical practice

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ABSTRACT

Early diagnosis of coronavirus disease 2019 (COVID-19) is crucial to early treatment and quarantine measures. In this narrative review, diagnostic tools for COVID-19 diagnosis and their main critical issues were reviewed. The COVID-19 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test is considered the gold standard test for the qualitative and quantitative detection of viral nucleic acid. In contrast, tests can be used for epidemiological surveys on specific communities, including occupational cohorts, but not for clinical diagnosis as a substitute for swab tests. Computed tomography (CT) scans can be useful for the clinical diagnosis of COVID-19, especially in symptomatic cases. The imaging features of COVID-19 are diverse and depend on the stage of infection after the onset of symptoms. CT sensitivity seems to be higher in patients with positive RT−PCR. Conventional chest sensitivity shows a lower sensitivity. An important diagnostic screening tool is ultrasounds, whose specificity and sensitivity depend on disease severity, patient weight, and operator skills. Nevertheless, ultrasounds could be useful as a screening tool in combination with clinical features and molecular testing to monitor disease progression. Clinical symptoms and non-specific laboratory findings may be useful if used in combination with RT-PCR test and CT-scanning.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is an emergent public health crisis threatening the current world health establishment and, therefore, has been declared a pandemic by the World Health Organization. SARS-CoV-2 belongs to the human coronavirus (HCoV) family that targets the lower part of the respiratory tract and causes severe acute respiratory syndrome (SARS). Currently, there are no treatments for this infection. For this reason, the preventive measures established across various countries, which are social distancing, usage of a mask to prevent the entry of the virus into the respiratory tract, quarantine, and other containment measures, are capable of reducing morbidity and mortality in highly susceptible individuals.[1,2] SARS-CoV-2 is primarily transmitted by inhalation of droplets and indirectly by contact with infected fomites, and via airborne through inhalation of bioaerosols that remain suspended in the air.[3] The COVID-19 patient usually presents with fever, cough, sore throat, and breathlessness. Currently, available data indicate that most people with the disease have mild symptoms, while about 20% present with moderate-to-severe disease. About 5% of these may progress to pneumonia, acute respiratory distress syndrome, and multi-organ dysfunction.[4,5]

While several drugs have demonstrated *in vitro* activity against SARS-CoV-2 or potential clinical benefits, and current mass vaccination campaigns have just began, early recognition and appropriate treatment of immunologic complications can decrease the morbidity and mortality in COVID-19 infection.[6] For this reason, early diagnosis of COVID-19 is crucial to both

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early treatment and quarantine measures. In this narrative review, therefore, we describe the primary diagnostic methods and the current challenges concerning the COVID-19 diagnosis.

Discussion

The diagnosis of COVID-19 is based on a combination of clinical findings, epidemiological history, and exams findings of the patient, which are: chest X-ray and tomography (CT-scan) revealing the characteristic images of ground glass; serological testing; non-specific laboratory findings; and most of all, oropharyngeal swab test aimed to demonstrate SARS-CoV-2 RNA in respiratory samples, which is the gold diagnostic standard.[7]

In these months, accelerated development of molecular and serological assays across a plethora of molecular and serological assays has been developed across many platforms. There are two main tests available for COVID-19: direct tests (*i.e.*. molecular tests) that are designed for diagnosing a current infection, and indirect tests (*i.e.*, serological tests) that are designed to ascertain seroconversion upon a previous (IgG) or an early (IgM) infection. A combination of these tests, including nucleic acid amplification tests, direct viral antigen tests, and the rapidly expanding laboratory-based and point of care serological tests, may inform crucial decisions by healthcare providers and policymakers.[8]

The COVID real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test is considered the gold standard test for the qualitative and quantitative detection of viral nucleic acids. Other relevant laboratory methods include enzyme-linked immunoassays (EIA) for viral antibody and antigen detection and serum viral neutralization (SVN) assays for antibody neutralization determination. The key components of viral diagnostic tests are: i) collection of the appropriate sample (blood, nasal swab, and throat swab); ii) availability of the genetic and proteomic sequences of the novel virus for analysis; and iii) rapid and accurate laboratory testing methods. Several point-of-care molecular devices are currently being integrated for fast and accurate diagnosis of SARS-CoV-2 infections. However, diagnostic tests capable of measuring low viral loads for early detection, with low or no cross-reactivity with other viral strains, are to be developed.[9] In the event of suspected symptoms, the molecular swabs should be immediately performed to confirm the diagnosis, isolate the positive subject, and trace his/her contacts.[10,11] RT-PCR is the frontline diagnostic test for COVID-19 capable of analyzing thousands of specimens in a single day and showing a testing sensitivity of 95%.[9] It can be carried out on different types of samples (*i.e.*, nasopharyngeal swab, oropharyngeal swab, bronchoalveolar lavage, tracheal aspirates, and saliva). At present, the US Centers for Disease Control and Prevention (CDC) recommend collecting and testing a nasopharyngeal specimen as the preferred choice for swab-based SARS-CoV-2 testing. For initial diagnostic testing for SARS-CoV-2, the CDC recommends collecting and testing an upper respiratory specimen. Swabs should be placed immediately into a sterile transport tube containing 2-3 mL of either viral transport medium (VTM), amies transport medium, phosphate-buffered saline, or sterile saline unless using a test designed to analyze a specimen directly (*i.e.*, without placement in VTM), such as some point-of-care tests. Testing lower respiratory tract specimens is also an option. For patients who develop a productive cough, sputum can be collected and tested when available for SARS-CoV-2. However, the induction of sputum is not recommended. Under certain clinical circumstances (*e.g.*, those receiving invasive mechanical ventilation), a lower respiratory tract aspirate or bronchoalveolar lavage specimen should be collected and tested as a lower respiratory tract specimen.[12]

Therefore, for individuals having invasive procedures, lower respiratory tract specimens are recommended, if available.[8] The RT-PCR technique shows some analytical problems such as inadequate procedures for collection, handling, transport and storage of the swabs, manual errors, testing outside the diagnostic window, active viral recombination, and inadequately validated assays, that contribute to jeopardize the diagnostic accuracy.[13] In literature, authors reported case reports of COVID-19 patients showing a chest computed tomography (CT) picture of pneumonia and multiple negative molecular swabs.[14] Cao *et al*. found some symptomatic COVID-19 patients with positive IgM antibodies and negative nasopharyngeal swab testing.[14] Other scholars reported symptomatic patients with 2 negative nasopharyngeal swabs and a positive swab on bronchoalveolar lavage sample via bronchoscopy.[15,16] Ai *et al*. showed a prevalence of false-negative swabs as 48% in patients with a high likelihood of being infected and 33% in probable cases of infections.[17] All the authors concluded not to rely on swabs without searching for clinical and epidemiological evidence before ruling out a COVID-19 diagnosis.[18] A false negative swabs could be derived by sampling or analytical issues, low viral load, mutations in the viral genome, or active viral recombination.[13,15,17] The sensitivity of nasopharyngeal test could also depend on the timing with respect to the clinical course of the infection,[14,15,17] and viral load could depend on the number of days after the onset of the symptoms. In the first 14 days, the diagnostic reliability could be higher in nasal swabs collected by sputum, whereas oropharyngeal swabs would be less

reliable after 8 days from the onset of symptoms.[19,20] According to some scholars, the viral loads in throat swabs is most significant at the time of viral onset,[21,22] and the viral shedding may begin 2-3 days before the appearance of the first symptoms, facilitating pre-symptomatic or asymptomatic transmission.[23]

Tests for the rapid detection of SARS-CoV-2 antigens have been developed because the rapid diagnosis of COVID-19 patients is essential to reduce the disease spread. However, the sensitivity of these tests is lower than that of RT-PCR, and specificity is awaited, given the potential for cross-reaction with other human CoV.[24] Therefore, their greatest utility has been suggested for symptomatic patients, when the viral load is at its greatest level.[8] The target functional receptor of SARS and SARS-CoV-2 viruses is the angiotensin-converting enzyme 2 (ACE2).[25] Among factors contributing to the false-negative results of naso-pharyngeal and oro-pharyngeal swabs, apart from the sampling technique, the transportation process, and the limited gene(s) detection, Winichakoon suggested the nature of coronavirus itself.[15] Surface expression of ACE2 was found abundantly on both type I and type II alveolar epithelial cells but minimally on bronchial epithelial cells and negative on the nasal, oral, and nasopharynx samples.[15] Diagnostic testing suggests that simple throat swabs provide sufficient sensitivity when symptoms are still mild or in the prodromal stage.[10] Later in the disease, COVID-19 then resembles SARS in terms of replication in the lower respiratory tract, and patients with symptoms of lung affection showed a prolonged viral load in sputum.[10]

COVID-19 diagnosis is based on RT-PCR testing of respiratory samples from nasopharyngeal and oropharyngeal swabs and lower respiratory tract samples whenever possible. Bronchoalveolar lavage and sputum induction should be limited and performed only if indicated and with adequate precautions due to the risk of aerosolization and consequent exposure of healthcare professionals. Tracheal aspirate specimens appear to carry a lower risk of aerosolization and can sometimes be obtained without disconnecting the patient from the ventilator.[14] Similarly, in a study accounting for CT scan findings among suspected COVID-19 cases, 48% with negative oropharyngeal or nasal swabs were considered highly likely cases, and 33% were considered probable cases.[17]

EIA assays are diagnostic methods used to identify antibodies in patients' blood samples or nasopharyngeal swabs. Enzyme-linked immunosorbent assays (ELISAs) for antibody detection against SARS-CoV-2 measure the host humoral response. IgM is the first immunoglobulin produced in response to an antigen and is primarily detected during the early onset of disease (3-7 days). IgG is the most abundant immunoglobulin produced in response to an antigen (7-25 days) and is maintained in the body after initial exposure and may have a protective role for acquired immunity.[9] However, the overall sensitivity and specificity indicate the possibility of false negatives and false positives in this testing method.[26]

Since the risk for recurrent infection with SARS-CoV-2 is not known for COVID-19, detecting one or two antibodies (IgM and/or IgG) does not necessarily guarantee immunity against reinfection. Furthermore, negative results do not rule out SARS-CoV-2 infection, particularly in those who have been in contact with the virus, and positive results may be due to past or present infection with SARS-CoV.[27]

Several research laboratories have used the EIA platform to develop lateral flow immunoassays (LFIA) for the rapid qualitative detection of SARS-CoV. This is designed as a simple, portable diagnostic strip to measure either SARS-CoV-2 antibodies or antigens. The major advantage is that this technique delivers results in ~15 min and uses visual detection by the naked eye compared to RT-PCR (2-5 days). Finally, the SVN assay is a serological test that measures the ability of a patient's antibodies to neutralize infectivity of SARS-CoV-2 and attenuate infection. However, it is not used for routine diagnosis but is the frontline for this special indication. The specificity and sensitivity of LIFAs are comparable for antibody and antigen assays.[9]

Finally, tests that can be performed at the point-of-care by less specialized personnel are named point of care tests (POCTs). POCTs are usually rapid tests, and when rapid antigen tests are well-validated, they may be considered for the rapid diagnosis of infected patients. However, these tests tend to have lower sensitivity than RT-PCR, and therefore, even if they may be helpful during an ongoing outbreak when timely access to sensitive molecular testing is unavailable, a negative result should be interpreted by a healthcare professional with caution and based on clinical judgement.[28]

According to a recent meta-analysis on sensitivity and specificity of different serological testing [enzyme-linked immunosorbent assays (ELISAs), lateral flow immunoassays (LFIAs), or chemiluminescent immunoassays (CLIAs)] and immunoglobulin class (IgG, IgM, or both), available evidence does not support the continued use of existing point-of-care serological tests. Indeed, the pooled sensitivity of ELISAs measuring IgG or IgM was 84.3% (95% confidence interval 75.6% to 90.9%), of LFIAs was 66.0% (49.3% to 79.3%), and of CLIAs was 97.8% (46.2% to 100%). In all analyses, pooled sensitivity was lower for LFIAs, the potential point-of-care method.[29] In Italy, the Italian National Institute of Health recommends CLIA and ELISA serological tests with a specificity of at least 95% and sensitivity of at least 90%.

However, they can be used for epidemiological surveys on specific communities, including occupational cohorts, but not for clinical diagnosis as a substitute for swab tests.[30,31]

Due to the shortage of kits and false-negative rate of RT-PCR, the Hubei Province, China temporarily used CT scans as a clinical diagnosis for COVID-19.[32] The imaging features of COVID-19 are diverse and depend on the stage of infection after the onset of symptoms.[33] The most common hallmark features of COVID-19 include bilateral and peripheral ground-glass opacities (areas of hazy opacity)[34] and consolidations of the lungs (fluid or solid material in compressible lung tissue).[35,36] Typical CT manifestations of COVID-19 infection are ground-glass opacities, consolidation, reticular pattern, and crazy paving pattern. Emerging atypical CT manifestations, including airway changes, pleural changes, fibrosis, nodules, *etc*., were demonstrated in COVID-19 patients. CT manifestations may be associated with the progression and prognosis of COVID-19.[37] However, CT systems are expensive, require technical expertise, and cannot precisely diagnose COVID-19.[33] Therefore, even if CT findings are essential for both diagnosis and follow-up, they can be useful, especially for early diagnosis.[16,38-40] CT sensitivity seems to be higher in patients with positive RT-PCR (86-97% in different case studies),[41] and lower in patients with only constitutional and nonrespiratory symptoms.[42]

Although multiple studies suggest CT should be a primary diagnostic tool for coronavirus disease (COVID-19) because they reported sensitivities with CT far superior to that of reverse transcriptase-polymerase chain reaction (RT-PCR) testing, CT has limited sensitivity for COVID-19 and lower specificity than RT-PCR testing. It carries a risk of exposing providers to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Therefore, chest CT should be considered a supplemental diagnostic tool, particularly for patients who show symptoms.[43]

Conventional chest X-ray sensitivity is at around 59%.[44] A meta-analysis on chest X-ray examinations revealed that most novel coronavirus pneumonia patients presented with bilateral lung injury (72.9%), which was primarily characterized by ground-glass opacities (68.5%).[45]

Ultrasounds are a crucial diagnostic screening tool, whose sensitivity is estimated to be around 75%; however, they show very low specificity and variability depending on factors such as disease severity, patient weight, and operator skills. Nevertheless, ultrasounds could be helpful as a screening tool in combination with clinical findings and molecular testing. Furthermore, it has been suggested their use for monitoring the progression of the disease,[46] and distinguish COVID-19 by community-acquired pneumonia (CAP).[47] At present, the diagnosis of COVID-19-related pneumonia depends on a combination of laboratory testing and imaging analyses of variable diagnostic efficacy. High-resolution Computed Tomography has been associated with a higher diagnostic accuracy rate than a real-time quantitative polymerase chain reaction-based approach (P=0.0041), and chest radiography (P=0.0100).[48] Typical CT findings in individuals with COVID-19 were ground-glass opacities, particularly on the peripheral and lower lobes, and bilateral multiple lobular and subsegmental areas of consolidation, especially in ICU patients.[49] Therefore, it is essential that clinicians utilize a combination of laboratory and radiological testing when possible, to ensure that SARS-CoV-2 is reliably and quickly detected. This allows early isolation and treatment of the infected.[48]

The typical clinical features of COVID-19 are fever, fatigue, and dry cough. Atypical clinical symptoms include expectoration, headache, hemoptysis, nausea, vomiting, and diarrhea. Chemosensory dysfunction, such as loss of smell and taste, is also closely associated with COVID-19 infection but is usually recovered within 2 to 4 weeks after infection.[50,51]

Finally, non-specific laboratory findings have also been described. They include leukopenia and lymphopenia in 80% of the cases, depletion of CD4 and CD8 lymphocytes, in addition to mild thrombocytopenia, increased inflammatory markers, such as lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), aspartate aminotransferase (AST), troponin, ferritin, creatine kinase (CK) and D-dimer, in addition to the extended prothrombin time. Some studies suggest that changes in the neutrophil/lymphocyte ratio in the severe disease progression of COVID-19 patients are also suggested.[7] A meta-analysis of some research studies was conducted, and the following abnormalities in blood indicators were found: decreased albumin (75.8%), increased C-reactive protein (58.3%), increased lactate dehydrogenase (LDH) (57.0%), decreased lymphocytes (43.1%), and increased erythrocyte sedimentation rate (ESR) (41.8%).[45]

Conclusions

In accordance with the literature, although RT-PCR has been described as the gold standard for diagnosing COVID-19, several difficulties involve its use. Therefore, a positive test is highly suggestive of true COVID-19, but a negative test does not rule out the disease.[7] In this case, highly suspected patients and providers in epidemic areas should assume they have the disease and undergo early treatment. In conclusion, only a combination of clinical features, epidemi-

ological data, laboratory exams, and imaging findings may drive the physician to an appropriate diagnostic hypothesis of COVID-19 infection.

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