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MINIREVIEWS

Molecular and serology methods in the diagnosis of COVID-19: An overview

Marcel Silva Luz, Ronaldo Teixeira da Silva Júnior, Gabriella Almeida Santos de Santana, Gabriela Santos Rodrigues, Henrique de Lima Crivellaro, Mariana Santos Calmon, Clara Faria Souza Mendes dos Santos, Luis Guilherme de Oliveira Silva, Qesya Rodrigues Ferreira, Guilherme Rabelo Mota, Heloísa Heim, Filipe Antônio França da Silva, Breno Bittencourt de Brito, Fabrício Freire de Melo

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Abstract

Coronavirus disease-19 (COVID-19) has become a pandemic, being a global health concern since December 2019 when the first cases were reported. Severe acute respiratory syndrome coronavirus 2, the COVID-19 causal agent, is a β-coronavirus that has on its surface the spike protein, which helps in its virulence and pathogenicity towards the host. Thus, effective and applicable diagnostic methods to this disease come as an important tool for the management of the patients. The use of the molecular technique PCR, which allows the detection of the viral RNA through nasopharyngeal swabs, is considered the gold standard test for the diagnosis of COVID-19. Moreover, serological methods, such as enzyme-linked immunosorbent assays and rapid tests, are able to detect severe acute respiratory syndrome coronavirus 2-specific immunoglobulin A, immunoglobulin M, and immunoglobulin G in positive patients, being important alternative techniques for the diagnostic establishment and epidemiological surveillance. On the other hand, reverse transcription loop-mediated isothermal amplification also proved to be a useful diagnostic method for the infection, mainly because it does not require a sophisticated laboratory apparatus and has similar specificity and sensitivity to PCR. Complementarily, imaging exams provide findings of typical pneumonia, such as the ground-glass opacity

radiological pattern on chest computed tomography scanning, which along with laboratory tests assist in the diagnosis of COVID-19.

Key Words: COVID-19; Pandemic; Diagnosis; Polymerase chain reaction; Molecular biology; Serology

Core Tip: Severe acute respiratory syndrome coronavirus 2 is primarily detected by PCR, which is the gold standard diagnostic method to detect viral RNA. On the other hand, techniques such as serology with detection of immunoglobulin M and immunoglobulin G antibodies, imaging, and laboratory tests also assist in the diagnosis of severe acute respiratory syndrome coronavirus 2 infection. Moreover, the reverse transcription loop-mediated isothermal amplification has similar specificity and sensitivity to PCR. In this review, we discuss the main diagnostic methods and their uses in the current pandemic.

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INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as responsible for severe cases of pneumonia in Wuhan, China, which culminated in the description of a new disease: coronavirus disease-19 (COVID-19)[1]. As a result of the large number of affected countries and high potential of viral infection, the World Health Organization declared COVID-19 as a pandemic in March 2020. Up to December 2020, 66243918 cases and 1528984 global deaths were officially confirmed[2]. SARS-CoV-2 is a single-stranded RNA, enveloped virus, which has the ability to attach to the angiotensin-converting enzyme 2 cell receptor due to the expression of the spike (S) protein on the viral envelope and then enter the host tissues[3]. The *Coronaviridae* family is made up of viruses historically known to cause diseases in animals and humans. The SARS and Middle East Respiratory Syndrome outbreak in 2002 and 2012, respectively, granted them wider visibility in the scientific community[4]. Furthermore, the dissemination potential of SARS-COV-2 is far higher than the others, due to structural differences in the S protein[5].

The most common signs and symptoms of COVID-19 include fever, dry cough, shortness of breath, myalgia, ageusia, anosmia, headache, rhinorrhea, nausea, vomiting, and diarrhea[6], and most patients showing severe symptoms are often affected by chronic disease. In addition, disturbed immune status, increased age, and obesity are strongly correlated to higher mortality rates[7]. Reverse transcription (RT)-PCR is considered the gold standard test for the diagnosis of COVID-19, due to its highly widespread and reliable technique performed in laboratories worldwide[8]. In addition, immunoenzymatic and immunochromatographic assays as well as reverse transcription loop-mediated isothermal amplification (RT-LAMP) are other diagnostic methods that have been applied in this field. Of note, clinical and epidemiological analysis, chest radiography and tomography, and laboratorial findings are crucial tools for an accurate diagnosis and appropriate evaluation of patients[9]. This article aimed to review the main aspects of COVID-19 diagnostic methods, providing updated information with an emphasis on molecular biology techniques and serology tests used in the detection of SARS-CoV-2 infection.

RT-PCR

RT-PCR is considered as the gold standard method in COVID-19 diagnosis, due to rapid detection with an average of 3-4 h and high sensibility and specificity[10]. The sample is usually taken through nasopharyngeal swab[11]. However, a systematic review and meta-analysis with 7 studies showed that bronchoalveolar lavage fluid had a higher positivity rate in the detection of SARS-CoV-2[12].

The test analysis usually starts from a sample collected from nasal and oropharyngeal swabs[13]. It is then divided in several steps that occur in different preset temperatures in order to provide RT and nucleic acid amplification[14]. The result is thus analyzed through probes marked with fluorescent dyes that enhance the sensitivity of the test[15]. The analysis of fecal samples, especially in children[16], may

be used as well, as the virus can remain viable for approximately 5 wk after patient respiratory samples are negative for SARS-CoV-2 RNA[17].

RT-PCR is considered the actual main method as a result of its fastness, reproducibility, and mitigation of false-positive results[18]. The test shows good sensitivity and specificity, such as 94% and 100%, respectively (Table 1)[19-28]. Studies have also pointed to a level of detection that can vary from 3.8 to 23.0 copies/mL of viral RNA and showed no cross-reactivity with circulating respiratory viruses [20].

However, in a study with 610 patients from Wuhan, China, 18 patients had a positive RT-PCR result after two consecutive negative results, which might be owing to insufficient viral material, test handling error, or incorrect collection processing[21]. This is an alert to the need for a pattern in sampling procedures and alignment between the test and the patient's clinical manifestation in order to achieve a higher diagnostic accuracy[22].

RT-LAMP

LAMP is a DNA amplification technique under isothermal conditions in a sample with 4 or 6 primers, which in contrast to RT-qPCR does not require a sophisticated laboratory apparatus, although it has similar specificity and sensitivity rates[29]. The visualization through pH-sensitive dyes, without the need of expensive instrumentation is also an advantage of this test[30]. As SARS-CoV-2 is an RNA virus, the test is therefore called RT-LAMP, due to the need for RTase to amplify RNA sequences[29].

The RT-LAMP is a fast test, providing results within 30 min[31]; moreover, unpurified samples can be directly used[32]. Studies also show that when the template has more than 200 copies of viral RNA, amplification curves appear within 15 min[33], which means an even quicker diagnosis. In addition, studies describe a level of detection of 2 copies of viral RNA in a 25 μL reaction[34], sensitivity rates that varies from 80%[26] to 97.5%[27], concomitantly with no cross-reactivity with other respiratory pathogens (high specificity)[33,35] and lower cost, all of which endorses that the diagnosis of COVID-19 through LAMP needs to be considered[36,37].

However, a meta-analysis including 138 articles showed that RT-LAMP sensitivity (86.3%) is lower than that of RT-PCR (96.2%)[38]. Furthermore, carry-over contamination, which can lead to false positive results, are common in LAMP reactions, probably as a consequence of aerosol formed from the products of the test[34]. This phenomenon highlights the need of laboratories with good practice of molecular biology and separate spaces to deal with the components of the test as well as more studies about the efficacy of all types of genes and primers used in this test.

SEROLOGICAL TESTS

Serological tests have become even more available during the COVID-19 pandemic. Consequently, research on their role as auxiliary diagnostic methods for SARS-CoV-2 infection has experienced exponential growth[39]. Thereby, these tests may support the COVID-19 diagnosis, especially when there is a longer period of symptoms with negative RT-PCR assays in a patient with a suspected infection by SARS-CoV-2[40]. Moreover, its use allied to RT-PCR greatly increases the diagnostic sensitivity[41].

Among the serological tests commonly used for diagnosis of COVID-19, the ELISA, the chemiluminescence immunoassay (CLIA), and the lateral flow immunochromatographic assay (LFA) stand out. The ease, agility, and point-of-care testing are great advantages associated with the use of these tests[42]. However, they may often show low sensitivity, require specialized equipment[39,42], or have cross-reactivity with other pathogens, such as SARS-CoV-1[43]. A study also showed a cross-reactivity of 26% in serological tests for COVID-19 during acute Zika virus infection[44].

The sensitivity of the test is strictly related to the elapsed time from the beginning of symptoms, being more useful 15 d after the onset of clinical manifestations, especially regarding the detection of isolated immunoglobulin (Ig) G[45]. In that context, a meta-analysis including 40 studies evaluated the presence of anti-SARS-CoV-2 IgG during the first symptomatic week, and the rates of false-negative diagnoses ranged from 44% to 87%[46]. Therefore, simultaneous analysis of IgM and IgG antibodies, as they have different emergence times, may increase the serological test sensitivity[39,47]. Although some studies compare IgG with other antibodies, such as IgA, to analyze any increase in the effectiveness of serological surveillance, the results are not promising[48].

The overall specificity for all types of antibodies was higher than 98%. The average sensitivity for IgG detection ranges from 80% to 85%, with CLIA being the most sensitive, followed by ELISA, and with much lower performance the LFA test[42,45]. IgM evaluation showed a sensitivity of 80.9% for CLIA, 84.5% for ELISA, and 51.4% with LFA. This study also demonstrated that in the use of combined IgM/IgG tests, the CLIA performance was higher than ELISA and LFA, with results of 97.3%, 90.5% and 85.8%, respectively[45].

Table 1 Coronavirus disease 2019 main diagnostic methods characteristics

Ref.	Diagnostic method	Sensitivity	Specificity	Time to result
Liu *et al*[23]	ELISA (IgM/IgG)	57.9%-90.7%	No cross-reactivity observed	About 100 min
Cai *et al*[24]	CLIA (IgM/IgG/IgM and IgG)	57.2%-81.5%	No cross-reactivity observed	ND
Montesinos *et al*[25]	LFA (IgM/IgG/IgM and IgG)	~70.0%	95.8%-100%	About 10 min
Scohy *et al*[52]	Antigen detection	30.2%	100%	About 15 min
Porte *et al*[54]	Antigen detection	93.9%	100%	About 15 min
Suo *et al*[19]	RT-PCR	94.0%	100%	ND
Österdahl *et al*[26]	RT-LAMP	80.0%	73%–100%	About 25 min
Dao Thi *et al*[27]	RT-LAMP	97.5%	99.7%	About 30 min
Ai *et al*[28]	Chest CT	97.0%	25%	ND

ELISA: Enzyme-linked immunosorbent assay; IgA: Immunoglobulin A; IgM: Immunoglobulin M; IgG: Immunoglobulin G; LFA: Lateral flow assay; CLIA: Chemiluminescence immunoassay; RT-PCR: Reverse transcription-polymerase chain reaction; RT-LAMP: Reverse transcription loop-mediated isothermal amplification; CT: Computed tomography; ND: Not described.

Sensitivity and specificity differences according to the viral protein analyzed are also documented: S protein is more specific, but the nucleocapsid and receptor-binding domain proteins are more sensitive in patients with mild infection[47,49]. Therefore, research on antibodies against different antigens may be useful in order to improve diagnostic methods, avoid false-negatives, and reach a higher diagnostic accuracy.

ANTIGEN DETECTION METHODS

Viral antigen is a molecule with immunogenic potential that can be targeted by diagnostic tests through a reaction with monoclonal antibodies. Several antigen detection tests have been developed as alternatives for the rapid diagnosis of the COVID-19[50,51]. The results of the test with nasopharyngeal secretions are ready within 15 min[52], and it can be performed either through immunochromatography, with rapid detection, or ELISA with better sensitivity[50].

The average sensitivity of antigen detection tests is around 50%–70%, and they are 100% specific[51,53]. Of note, the performance of those tests may be influenced by higher or lower viral loads as well as by the specific antigen used. In that context, studies have shown different results when this method was evaluated, and the sensitivity values varied from 30.2%[52] to 93.9%[54] Overall, higher rates of accurate diagnosis in antigen tests were greatly correlated with early infection, when the viral load of the upper respiratory tract is higher[55].

Therefore, although the COVID-19 diagnosis through antigen detection has a high specificity and is faster and cheaper than RT-PCR, the precise time of usage of this test is crucial for proper detection of the virus antigens[52]. That said, the current gold standard diagnostic test for COVID-19 is still more reliable because its use is associated with lower rates of false negative results[56]. Nevertheless, utilization of antigen detection tests, with additional research, could turn into a viable option in the current pandemic context.

COMPLEMENTARY DIAGNOSTIC METHODS

Chest computed tomography findings

Chest computed tomography (CT) has been used as an alternative and complementary method for COVID-19 diagnosis since CTs can detect pulmonary abnormalities even when RT-PCR results turn negative[57] for highly suspect cases with clinical symptoms[58] in the early days of infection[59].

The chest CT diagnosis works through analysis of the variation in imaging findings that occur according to the disease progression and severity[60]. The pulmonary imaging abnormalities start to appear around 4 d after the first symptoms, and their findings are more visible following the second week of clinical manifestations[58].

Accordingly, the most predominant COVID-19 pneumonia imaging changes are ground-glass opacity lesions with or without consolidations, peripheral and bilateral lung distribution of the disease, and multilobar lung involvement, predominantly in the lower lobes[61,62]. Some less common CT manifest-

ations are the crazy-paving pattern, ground-glass opacity with consolidation, interlobular septal thickening, and pleural effusion[63]. Chest CT scans are highly sensitive to COVID-19 lung abnormalities[64], mainly in high-risk symptomatic cases[65].

However, these imaging findings have low specificity[63]. A study performed with 1014 patients showed an average specificity of 25%[28], probably due to other viral pneumonias leading to similar imaging alterations, a fact that limits the use of this method in areas with high prevalence of other respiratory tract infections[64]. Moreover, chest CT exams can detect no abnormalities in some asymptomatic or mild symptomatic cases[63], making CT scans more of a complementary diagnostic test than a definitive one. Table 1 summarizes the sensitivity, specificity, time to result, and limitations of the diagnostic methods discussed in this review so far.

Laboratory findings

Patient reports from Wuhan showed recurrent cases of lymphocytopenia since the beginning of the infections in China[66]. Besides that, studies also show a relevant frequency of patients with leukocytosis during SARS-CoV-2 infection[67]. A meta-analysis showed that non-surviving patients had an expressive increase in leukocyte count, total bilirubin, serum ferritin, and interleukin 6 as well as a reduced lymphocyte count[68]. Thus, leukocyte series elevation can represent worse prognostic and high risk of unfavorable outcomes.

Increases in the levels of lactate dehydrogenase and C-reactive protein were also highlighted and associated with pulmonary and myocardial lesions, especially in severe patients[69]. Low serum albumin rates and high levels of alanine aminotransferase and aspartate aminotransferase points to possible liver complications, which is very common in acute phases of the disease in patients with a severe infection[70,71]. Furthermore, the association of these points with elevation in renal biomarkers (for example, creatinine), coagulation measures, and heart and muscle injury scores suggest potential progression to multiple organ failure in severe patients[68]. Thereby, elevated levels of D-dimer, fibrin degradation products, and fibrinogen can be observed during the course of the disease, with the D-dimer alterations being the most common[72]. A study related that levels of these coagulation parameters were observed in severe patients with worse prognosis, while mild disease or early stage patients had normal ranges[73,74]. In addition, thrombocytopenia is also a possible laboratory finding in COVID-19. A meta-analysis reported that platelet count was minor in severe disease and even smaller in non-surviving patients[74]. These findings might be indicative of disease progression and coagulation disorders, which means that the tracking of these signs is very important while managing patients[74,75].

Moreover, possible coinfections of SARS-CoV-2 and bacterial infections might cause neutrophilia and leukocytosis, associated with lymphocytopenia, without increasing inflammatory factors, such as D-dimer and C-reactive protein[76]. Therefore, laboratory findings have proven to be a helpful option as a complementary diagnosis. It is also suitable in the visualization of possible comorbidities in patients with COVID-19 and as an indicator of disease severity.

Several studies are being carried out to test the efficacy of drugs, foods, and mineral supplements against COVID-19. Lymecycline and famotidine, for example, are being studied as a potential treatment for COVID-19[77,78], due to a possible ability to bind some SARS-CoV-2 structures (M^{pro}, S protein, RdRp, and furin) and have an anti-inflammatory action[79], respectively. However, there is, up to this moment, not enough evidence and controlled clinical trials to affirm its efficacy against the disease. In addition, mineral supplements such as zinc apparently have some antiviral properties that could be used against SARS-CoV-2 infection, such as a capability of modulating the host's immune response and attenuating the cytokine storm caused by COVID-19[80]. However, a randomized clinical trial of 214 patients showed that zinc supplementation had no significant benefits[81].

CONCLUSION

Notably, the use of serology and antigen detection tests have important limitations since false negative results are common. Nonetheless, in a pandemic context, these methods are crucial for epidemiological surveillance. RT-PCR remains the gold standard test and should be preferred to diagnose COVID-19. However, the high potential of RT-LAMP, given that it is a fast and affordable test, should be considered in diagnostic propedeutics. In addition, the laboratory and imaging findings play important roles as complementary diagnostic tools aiding in patient management.

FOOTNOTES

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