REVIEW

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Current laboratory diagnosis of coronavirus disease 2019

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Coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, China; it has since caused a pandemic, with more than 10,000 confirmed cases (> 800,000 tests) in Korea as of May 2020. Real-time reverse transcription polymerase chain reaction (RT-PCR) is currently the most commonly used method for the diagnosis of COVID-19 worldwide. The Korean Society for Laboratory Medicine and Korea Centers for Disease Prevention and Control regularly update the guidelines for COVID-19 diagnosis. Emergency use authorization for some laboratory diagnostic kits has been granted, enabling the timely diagnosis and treatment of COVID-19, and the isolation of infected patients. Due to the collective efforts of the government, medical professionals, local authorities, and the public, Korea's response to the COVID-19 outbreak has been accepted widely as a model. Here, we summarize the currently available laboratory tests for COVID-19 diagnosis. Although RT-PCR tests are used widely to confirm COVID-19, antibody tests could provide information about immune responses to the virus.

Keywords: COVID-19; Diagnosis; Real-time reverse transcription polymerase chain reaction; Coronavirus; Serology

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), is a large, enveloped, single-strand ribonucleic acid (RNA) genome virus consisting of four structural proteins: nucleocapsid, spike, envelope, and membrane proteins. The receptor-binding domain of the spike protein binds to human and bat angiotensin-converting enzyme 2 receptors, mediating virus entry into host cells [1]. The World Health Organization (WHO) named the novel respiratory disease caused by SARS-CoV-2 to COVID-19 on February 11, 2020; it declared that this disease had caused a public health emergency of international concern on January 30, 2020, and finally, it was a pandemic on March 11, 2020.

Based on previous experience with Middle East Respiratory Syndrome, Korea responded promptly to the COVID-19 outbreak. The Korea Centers for Disease Control and Prevention (KCDC) and the Ministry of Food and Drug Safety (MFDS) of Korea developed diagnostic kits for COVID-19, and emergency use authorization (EUA) for these kits was granted. The timely distribution of these diagnostic tests to medical institutions enabled early detection and self-isolation of confirmed COVID-19 cases. Based on cooperation among the government, local authorities, and the public, effective contact tracing and quarantine policies were established in the early stage of the disease outbreak.

Clinical laboratories and *in vitro* diagnostic tests played crucial roles in this health crisis, providing for large-scale patient screening, diagnosis and monitoring, as well as epidemiological surveillance (Table 1) [2]. In this article, we provide an overview of laboratory tests used for COVID-19 diagnosis and summarize current practices for laboratory data interpretation.

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Table 1. The laboratory tests used most commonly to monitor patients with coronavirus disease 2019

Role	Tests
Diagnosis	RT-PCR (gold standard), serologic tests
Staging, prognostication, therapeutic monitoring	Various in vitro diagnostic tests (↑WBC, ↑neutrophil counts, ↓lymphocytes count, ↓platelet count, ↓albumin, ↑LDH, ↑AST & ALT, ↑total bilirubin, ↑urea & creatinine, ↑cardiac troponin, ↑D-dimer & prothrombin time, ↑procalcitonin & CRP, ↑ferritin, ↑cytokines
Epidemiological surveillance	SARS-CoV-2 antibodies

↑, increased; ↓, decreased.
RT-PCR, real-time reverse transcription polymerase chain reaction; WBC, white blood cell; LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Coronavirus disease 2019 case classification in Korea and the United States

	Korea (KCDC)	United States (CDC)
Diagnostic test	Nucleic acid (RT-PCR)	Nucleic acid or antigen
Case definition	Suspected case Cases with clinical symptom of COVID-19 (major symptoms: fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, loss of smell or taste or pneumonia, etc.) within 14 days of being in close contact with a confirmed case.	High priority Hospitalized patients with symptoms Healthcare facility workers, workers in congregate living settings, and first responders with symptoms Residents in long-term care facilities or other congregate living settings, including prisons and shelters, with symptoms
	PUI (patient under investigation) Cases suspected of having a symptom of COVID-19 based on a physician's opinion (e.g., pneumonia of unknown origin). Cases with history of visiting overseas and having a symptom of COVID-19 within 14 days after return to homeland Cases showing epidemiological correlation with the domestic mass outbreak of COVID-19 and exhibiting a symptom of COVID-19 within 14 days.	Priority Persons with symptoms of potential COVID-19 infection, including: fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat. Persons without symptoms who are prioritized by health departments or clinicians, for any reason, including but not limited to: public health monitoring, sentinel surveillance, or screening of other asymptomatic individuals according to state and local plans.

KCDC, Korea Centers for Disease Control and Prevention; CDC, Centers for Disease Control and Prevention; RT-PCR, real-time reverse transcription polymerase chain reaction; COVID-19, coronavirus disease 2019.

CASE CLASSIFICATION FOR LABORATORY TESTING

In Korea, COVID-19 case definition is currently based on the 8th (May 15, 2020) edition of the KCDC's Guidelines on Response to Coronavirus Disease 2019. According to these guidelines, cases are classified as confirmed, suspected, and patient under investigation (PUI). The definitions of suspected and PUI cases are revised regularly based on the incidence of confirmed cases, results of epidemiological studies, and extent of the epidemic [3,4]. In the United States, according to the Centers for Disease Control and Prevention guidelines, cases are classified as high priority and priority (Table 2) [5].

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SPECIMENS USED FOR TESTING

Specimen types

For real-time reverse transcription polymerase chain reaction (RT-PCR) tests, upper respiratory specimens (including nasopharyngeal and oropharyngeal swabs) and lower respiratory specimens (including sputum, bronchoalveolar lavage [BAL] specimens, and tracheal aspirates) are used. The use of induced sputum specimens for RT-PCR testing is not recommended. When necessary, additional specimens, such as blood, urine, and feces, may be collected; however, the diagnostic value of these specimens remains unclear. For serological tests, whole blood and serum samples are used.

Specimen selection according to patient status

For asymptomatic individuals and those with mild symptoms, both nasopharyngeal and oropharyngeal swabs are recommended. When collecting only one specimen, a nasopharyngeal swab is recommended first. Although sputum can also be collected for examination, sputum induction is not recommended for these patients. For patients with severe symptoms, productive cough, and intubation, lower respiratory specimens, such as sputum, BAL specimens, and tracheal aspirates, are collected. When possible, nasopharyngeal and oropharyngeal swabs should also be tested. For patients referred for additional testing, including those with pneumonia whose nasopharyngeal and/or oropharyngeal swab tests yielded negative results, lower respiratory specimens, such as sputum, BAL specimens, and tracheal aspirates, should be collected.

CONFIRMATORY TESTING BY RT-PCR

RT-PCR procedures

For SARS-CoV-2 detection using RT-PCR, the following steps are required: sample collection, sample preparation, nucleic acid extraction, reverse transcription, and PCR using real-time fluorescence signal detection. Currently, RT-PCR is the gold-standard laboratory test for COVID-19 confirmation in suspected cases. RT-PCR detects the nucleic acid of the virus with high specificity and sensitivity.

Sometimes it can be used to quantify the target gene amount. It is a similar method to PCR, but the ampli-

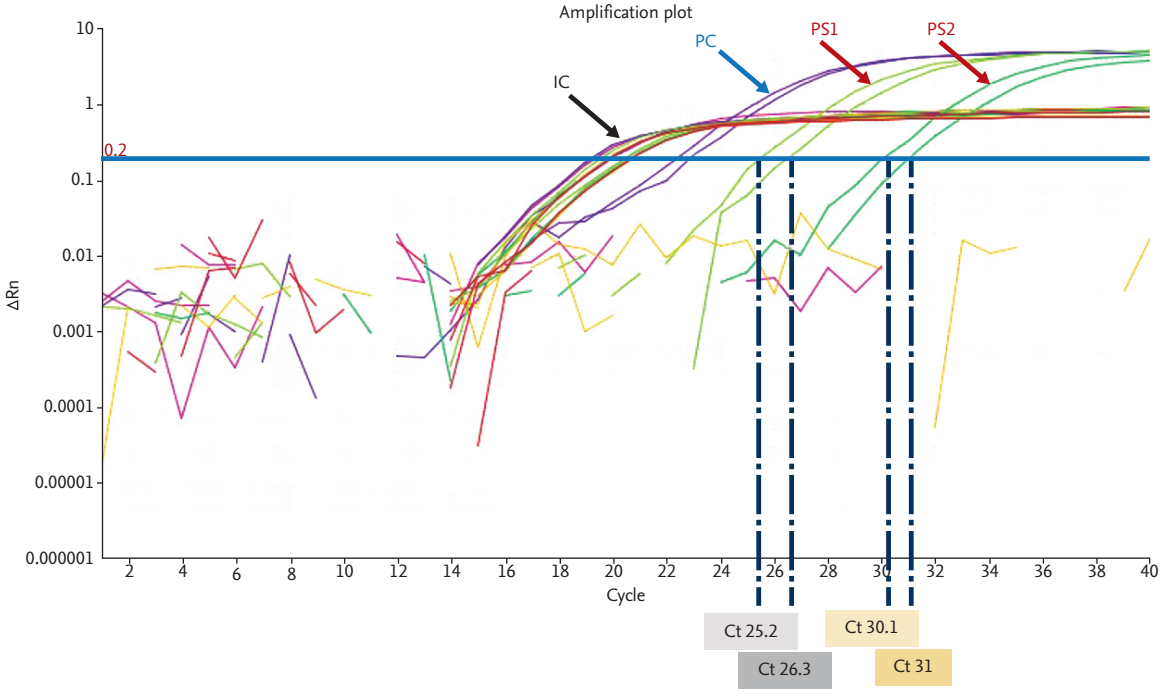

Figure 1. Coronavirus disease 2019 diagnosis using real-time reverse transcription polymerase chain reaction. IC, internal control; PC, positive control; PS, positive specimen; Rn, normalized reporter (normalized fluorescence signal of reporter dye); Ct, cycle threshold.

Table 3. Target genes of seven RT-PCR kits currently used for SARS-CoV-2 detection in Korea (as of May 29, 2020)

Approval date	Kit name (manufacturer)	Target genes
Feb 4, 2020	PowerCheck 2019-nCoV real-time PCR kit (Kogene biotech)	RdRp, E
Feb 12, 2020	Allplex 2019-nCoV Assay (Seegene)	RdRp, E, N
Feb 27, 2020	DiaPlexQ Novel Coronavirus (2019-nCoV) Detection Kit (Solgent)	ORF1a, N
	STANDARD M n-CoV Real-Time Detection Kit (SD biosensors)	RdRp, E
Mar 13, 2020	Real-Q 2019-nCoV Detection Kit (BioSewoom)	RdRp, E
May 11, 2020	BioCore 2019-nCoV Real Time PCR Kit (BioCore)	RdRp, N
May 29, 2020	careGENE N-CoV RT-PCR Kit (Wells Bio)	RdRp, E

RT-PCR, real-time reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

fied nucleic acid is measured by real-time monitoring fluorescence signal RT-PCR yields cycle threshold (Ct) values, which are inversely proportional to the amounts of the target nucleic acid in samples (Fig. 1). RT-PCR tests should comply with the standard operating procedures of each laboratory and the manufacturers' instructions. Currently, clinical laboratories in Korea are using various nucleic acid extraction methods and reagents for RT-PCR with EUA for COVID-19 diagnosis (Table 3).

Interpretation of RT-PCR results

For RT-PCR–based viral nucleic acid detection methods, Ct values of the target genes below the cut-off Ct value indicate positivity and Ct values above the cut-off Ct value indicate negativity. Positive and negative controls are included in each reaction to assess method performance and the presence of contaminants (Fig. 1). In specimens with low viral loads, Ct values can be close to the cut-off and may yield false-negative or false-positive results. Thus, RT-PCR results should be interpreted carefully, with consideration of patients' histories and clinical symptoms. In some cases, retesting should be performed using residual or newly collected specimens. All EUA kits currently available in Korea can detect two or three viral genes (Table 3). It is recommended that samples are considered to be positive only when all target genes are detected. When only one gene is detected, retesting or consultation with the reference laboratory is recommended.

The optimal timing of viral genome detection in COVID-19 cases remains unknown. COVID-19 cannot be ruled out safely based on one negative result from the testing of upper respiratory specimens alone. Thus, highly suspicious COVID-19 cases with negative results from single upper respiratory specimens, should be retested using additional upper respiratory specimens or lower respiratory specimens. False-negative results could be obtained for samples with low viral loads and those collected too early or too late during the clinical course of the disease. Mutations in the viral genome, the presence of PCR inhibitors, the receipt of antiviral therapy prior to testing, and poor specimen quality could also lead to false-negative results. Thus, for patients with negative results from upper respiratory specimens, lower respiratory specimens should be tested. Positive and negative control samples should be tested simultaneously with patient specimens, and internal controls should be included in all reactions to monitor the performance of PCR. For highly suspicious cases that repeatedly yield negative test results, specimens should be submitted to a reference laboratory for further confirmatory testing.

Concerns regarding RT-PCR testing

To ensure infection control during a COVID-19 outbreak, a strict sample transportation protocol should be implemented. All specimens must be considered to be potentially infectious, and appropriate personal protective equipment must be used during specimen collection [6]. The molecular diagnosis of COVID-19 typically begins with the collection of a nasopharyngeal or an oropharyngeal swab and its transport to a laboratory in a universal/viral transport medium. According to a recent report on the SARS-CoV-2 detection rate in 1,070 clinical specimens collected from 205 patients with COVID-19,

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the positivity rate is highest for BAL fluid (14 of 15; 93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fibrobronchoscope brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%). None of the 72 urine specimens was found to be positive [7]. The exact sensitivity and specificity of RT-PCR tests for COVID-19 are unknown, but a positive test result appears to be strongly suggestive of true COVID-19 whereas a negative result does not rule out COVID-19 [8]. Hence, multiple specimens should be tested in highly suspicious cases.

Potential RT-PCR test pitfalls include pre-analytical errors, such as inappropriate identification, collection, handling, transport, and storage of samples, as well as the collection of inappropriate or inadequate material. Additionally, the presence of interfering substances, manual errors, sample contamination, and patients' receipt of antiretroviral therapies can further interfere with the accuracy of RT-PCT tests [9]. Furthermore, most RT-PCR tests have relatively long turnaround times, ranging from 4 to 6 hours from specimen preparation to RT-PCR; thus, further improvement is required such as shorten TAT for testing in the current COVID-19 outbreak [10].

In Korea, as of May 15, 2020, 447 (approximately 4.5%) cases reported reactivated or positive result after recovered COVID-19. It has been implementing measures equivalent to confirmed patients since April 14, but an epidemiological investigation into the case of reactivated case has not confirmed the evidence that the cases of positive result after recovery are infectious. Current guidelines regarding hospital discharge and the discontinuation of quarantine may need to be reevaluated [11]. Although the presence of residual viral nucleic acid after recovery is likely, more research is needed because it shows various progress in COVID-19 patients.

ALTERNATIVE TESTS FOR COVID-19

Antibody detection using serological tests

The urgent needs for the standard of procedures of sampling from different anatomic sites, sample transportation, optimization of RT-PCR, serology diagnosis/screening for SARS-CoV-2 infection, and distinct diagnosis from other respiratory diseases such as influenza infections as well [12]. A wide range of immunoassays for the detection of SARS-CoV-2 proteins and antibodies in serum and plasma has been developed. Using chemiluminescent immunoassay (CLIA), manual enzyme-linked immunosorbent assay (ELISA), and fast lateral flow immunoassay (LFIA) complementing molecular diagnosis using RT-PCR [13].

Antibodies against SARS-CoV-2 can be detected in the middle and late stages of the disease [14]. Immunoglobulin M (IgM) and IgA antibodies were detected 3 to 6 days (median 5 days) after the onset of symptoms, whereas IgG antibodies were detected 10 to 18 days (median 14 days) after symptom development, with positivity rates of 85.4%, (IgM and IgA 92.7%, and IgG 77.9%, respectively) [15]. IgG and IgM seroconversion occurred simultaneously or sequentially, with the plateauing of titers within 6 days thereafter [16,17]. Neutralizing antibodies (NAbs) play essential roles in protection against viral diseases and viral clearance. Virus-specific NAbs, induced through natural infection or vaccination, can block viral infection. The efficacy of passive antibody therapy is associated with the NAb concentration in the plasma of recovered donors. As the COVID-19 pandemic proceeds, the transfusion of convalescent plasma or serum from recovered patients has been considered as a promising approach to prevent infection and treat the disease [18].

The Food and Drug Administration has granted EUA for a serological test that is intended for use by clinical laboratories. This test might aid determination of whether individuals have immunity to the virus and identify those who could donate plasma for the treatment of seriously ill patients with COVID-19 [19]. Test results can be obtained in 15 to 20 minutes [20,21]. Numerous LFIA-based rapid point-of-care (POC) tests have been developed by several companies; they enable the detection of IgM and IgG antibodies produced in response to SARS-COV-2 infection. Updates on the Foundation for Innovative New Diagnostics (FIND) independent evaluation of SARS-CoV-2 immunoassays are provided regularly; five currently available antigen-detection rapid diagnostic tests (RDTs), 26 serological-antibody-detection RDTs, and eight serological ELISA/automated immunoassays are currently available [22].

Although the usefulness of serological tests remains under debate, these can clearly aid the identification of

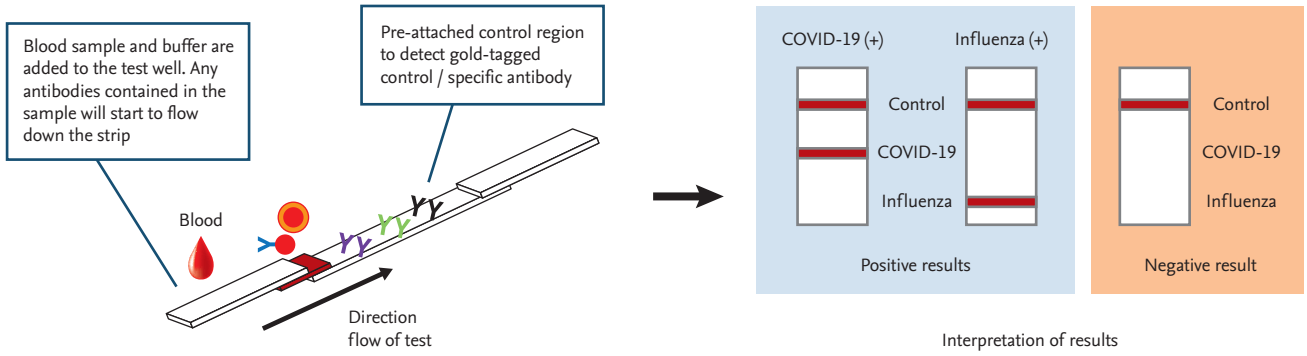

Figure 2. Diagram of a proposed point-of-care testing procedure for coronavirus disease 2019 (COVID-19) and influenza diagnosis.

asymptomatic patients with COVID-19 who may transmit the virus. They can also be used to determine the seroprevalence in different populations, assess previous exposure, and contact trace. Moreover, serology can be used to diagnose COVID-19 in the late stages of the disease, even in viral RNA-negative patients. Serological RDTs could be used to complement currently used IVD assays, improving COVID-19 diagnosis and providing additional information about immune status in suspected cases [23]. However, a recent study showed that IgM and IgG could be detected only about 2 weeks after the onset of infection [24], and the overall testing sensitivity and specificity have been found to be 88.66% and 90.63%, respectively [23]. Although the rapid acquisition of results could reduce the lengths of emergency department stays, test performance should not be compromised to achieve this goal [25]. Current WHO guidelines recommend the use of new POC immunodiagnostic tests only in research settings until evidence supporting their clinical use becomes available [26]. Although RT-PCR testing of respiratory samples is currently the gold standard for COVID-19 diagnosis, molecular testing is time consuming and requires experienced professionals, increasing the need for the development of novel rapid diagnostics. Rapid LFIA and automated CLIA tests for IgM and IgG are believed to be promising emerging methods; however, their clinical performance needs to be evaluated thoroughly [27].

As the COVID-19 outbreak begins to subside, serological testing will enable the identification of individuals with immunity against SARS-CoV-2, who thus might be able to return to work [28].

Antigen detection

RDTs detect the presence of viral proteins (antigens) in respiratory specimens. The accurate detection of SARS-CoV-2 is essential to curb the global spread of COVID-19. Nevertheless, currently available RT-PCR–based diagnostic assays are not robust as they are still missing several infected cases [6,8,9]. Additionally, they are not widely available in developing countries and remote locations, which lack well-equipped laboratories and experienced professionals. The MFDS of Korea has approved the export of rapid IVD tests; however, their use is strictly regulated.

Nasopharyngeal and oropharyngeal swabs are commonly used for RDTs. However, the collection of these specimens requires close contact with patients, which entails the risk of virus transmission to healthcare workers. In contrast, saliva specimens can be obtained easily and noninvasively as sputum samples, minimizing the risk of SARS-CoV-2 exposure for healthcare workers. Hence, saliva is considered to be a promising, noninvasively collected specimen type for COVID-19 diagnosis, monitoring, and infection control [29].

Other tests for the monitoring of patients with COVID-19

SARS-CoV-2 infection can cause mild to severe respiratory, enteric, cardiovascular, and neurological symptoms. The laboratory tests used most commonly to

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monitor patients with COVID-19 are listed in Table 1. The serum levels of certain markers can be used to predict the course of the disease and patient prognosis [30-32]. Careful monitoring of the myocardial enzyme profiles is of great importance in reducing the complications and mortality in patients with COVID-19 [33].

CONCLUSIONS

RT-PCR testing has played a vital role in COVID-19 diagnosis and infection control. New, more accurate, and rapid RT-PCR tests are expected to become the gold standard for SARS-CoV-2 detection in the near future. Furthermore, serological tests could complement currently used RT-PCR tests, and can be used to identify individuals who have developed immunity against SARS-CoV-2. As the need for rapid testing is increasing continuously, and with consideration of the possibility that COVID-19 may become seasonal, similar to influenza, diagnostic kits that can differentiate the two diseases are urgently needed (Fig. 2).

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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