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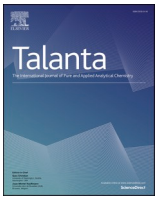

Review

# Recent advances in detection technologies for COVID-19

Tingting Han [a], Hailin Cong [a,b], Youqing Shen [a], Bing Yu [a,b,*]

[a] Institute of Biomedical Materials and Engineering, College of Chemistry and Chemical Engineering, College of Materials Science and Engineering, Qingdao University, Qingdao, 266071, China
[b] State Key Laboratory of Bio-Fibers and Eco-Textiles, Qingdao University, Qingdao, 266071, China

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ABSTRACT

Corona Virus Disease 2019 (COVID-19) is a highly infectious respiratory illness that was caused by the SARS-CoV-2. It spread around the world in just a few months and became a worldwide pandemic. Quick and accurate diagnosis of infected patients is very important for controlling transmission. In addition to the commonly used Real-time reverse-transcription polymerase chain reaction (RT-PCR) detection techniques, other diagnostic techniques are also emerging endlessly. This article reviews the current diagnostic methods for COVID-19 and discusses their advantages and disadvantages. It provides an important reference for the diagnosis of COVID-19.

## 1. Introduction

As of Feb 12, 2021, the cumulative quantity of confirmed cases of COVID-19 which is given rise to by the SARS-CoV-2 infection has reached 108.2 million worldwide, and the number of deaths from infection has increased to 2.4 million， which has become a global one. On January 31, 2020, WHO proclaimed that COVID-19 was regarded as a Public Health Emergency of International Concern, which means that it might produce a risk to a mass of countries and needs a synergetic response by the international community [1].

WHO has announced that the mortality rate of Severe Acute Respiratory Syndrome (SARS) is 9.6%, and the current mortality rate of Middle East Respiratory Syndrome (MERS) is 34.4%. So far, the mortality rate of COVID-19 is estimated to be between 3% and 5%, which is lower than the previous two [2,3]. However, the number of infections and deaths is much higher, and they are on a growing trend [4,5]. COVID-19 is no longer a regional disease, but a pandemic that has spread globally, which has greatly hindered global development [6,7]. In comparison with SARS and MERS, COVID-19 patients also have clinical manifestations such as fever and cough [8,9]. And it is often accompanied by lower respiratory tract diseases, especially those who are elderly and those with poor health are most vulnerable to infection [10]. Also, sectional patients experience gastrointestinal symptoms as well, such as diarrhea, vomiting, and abdominal pain [11], and even mild to moderate taste and smell disturbances [12]. Thrombosis is also considered a possible complication [13], and even the nervous system will have related signs of abnormality [14].

SARS-CoV-2 is a positive-stranded RNA virus [15], is also the seventh known coronavirus that can infect humans [16]. SARS-CoV-2 pertains to the identical type of coronavirus as the coronavirus which caused SARS in 2003 (SARS-CoV) and the coronavirus that caused MERS in 2012 (MERS-CoV) and is closely related [17]. But it is more transmissible [18], and there are asymptomatic infections [19,20]. The genomic information of SARS-CoV-2 has approximately 80% autoploidy with SARS-CoV. The virus belongs to the Sarbecovirus subgenus of the β coronavirus (β-CoV) genus [21,22]. Before that, β-CoV has infected humans and animals many times [23–26]. Sequencing the viral genome of patients with pneumonia revealed that an anteriorly undiscovered β-CoV strain was present in the whole patients tested [27]. This new-found β-CoV has 88% sequence homology with two bat-derived coronaviruses [28].

Given the contagious nature of SARS-CoV-2 and the wide scope of its impact, seeking valid treatments is the world's top priority [29]. Although some vaccines have been put into use, the uncertainty is still unpredictable [30–34]. Given this, the early diagnosis of SARS-CoV-2 is an effective precondition for curbing the spread and timely treatment, which allows doctors to intervene in time to hold back further spread and deterioration of the disease. This article summarizes the detection methods of SARS-CoV-2 based on nucleic acid, serology, and imaging-assisted diagnosis, which provides a valuable reference for its effective diagnosis.

* Corresponding author. Institute of Biomedical Materials and Engineering, Building D, Science park, Qingdao University, Qingdao, 266071, China.
*E-mail address:* yubing198@qdu.edu.cn (B. Yu).

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## 2. Nucleic acid-based detection methods

The nucleic acid detection process includes multiple steps such as specimen processing, nucleic acid extraction, and PCR detection. The average detection time takes 2–3 h [35,36]. Because it directly detects the viral nucleic acid in the specimens we collect, it has strong specificity and relatively high sensitivity, and it is currently the main detection method [37,38]. Detection of SARS-CoV-2 RNA can identify infected persons in the acute phase of infection [39]. The characteristics of several common nucleic acid-based detection technologies are shown in Table 1.

### 2.1. Real-time reverse-transcription polymerase chain reaction ( RT-PCR )

According to the requirements of the WHO, the golden standard for detection of COVID-19 is the RT-PCR. The PCR means has high sensitivity, specificity, and has always been a routine method for detecting coronavirus [40–42]. Generally irritating upper respiratory tract samples as test substances [43]. Related research pointed out that sputum is the best test substance, followed by nasal test [44]. The detection method uses specific primers and probes for SARS-CoV-2 RdRp, envelope, and nucleocapsid genes, and RdRp analysis has the highest analytical sensitivity [45,46]. For patients diagnosed with COVID-19, RT-PCR test results can be used as the standard for isolation and discharge [37,47,48].

The principle of detection is: RNA in the SARS-CoV-2 genome is transformed into complementary DNA (cDNA). DNA was modified by DNA polymerase through a cDNA template [49] (Fig. 1). The RT-PCR reaction was monitored by using the fluorescent dye or TaqMan DNA probe [50]. The detection steps of RT-PCR include sample collection, RNA extraction, polymerase chain reaction, and real-time analysis [49].

Cao et al. [51] released the clinical data of the first batch of 41 patients with SARS-CoV infection. Using next-generation sequencing or RT-PCR methods, the respiratory tract, blood, and stool samples of the infected were detected. The results of the detection showed that patients aged 25–49 accounted for the highest proportion of 49%, and they were mainly male.

However, the RT-PCR test results cannot completely exclude false negatives. Mismatches between primers and probes and the target sequence, as well as sampling procedures, will give rise to decreased detection performance and false-negative results [37,52,53]. Arevalo-Rodriguez et al. [54]summarized the proportion of false negatives in RT-PCR testing and found that up to 54% of patients may have false negatives from the initial RT-PCR test. Therefore, when necessary, it is necessary to carry out repeated detection and combine it with other detection technologies to comprehensively view.

**Table 1**
Summary of the characteristics of common nucleic acid detection-based technologies.

| | Detection time | Advantages | Disadvantages |
|---|---|---|---|
| RT-PCR | 2–3 h | Wide application range; high sensitivity; strong specificity | False-negative |
| Digital-PCR | 3–4 h | High accuracy, high sensitivity; stable system; excellent repeatability | High cost; complicated operation; limited detection throughput; susceptible to false positives due to external contamination |
| mNGS | 0.5–3 date | It is of great significance for the sequencing and genetic analysis of new pathogens in the respiratory tract | Short read length; uneven genome coverage; vulnerable to host genome contamination; higher cost |
| RT-LAMP | 0.5–1 h | Easy to operate; simple and fast to operate; high sensitivity and specificity; | Vulnerable to contamination to produce false positives; low viral load to produce false negatives |
| CRISPR-based assays | 30–40min | High specificity, high precision, high efficiency, simple and quick operation | The supporting closed detection system has not been established, which limits its wide application |

### 2.2. Digital polymerase chain reaction (dPCR)

dPCR can directly measure the number of nucleic acid molecules in the initial sample, quantify the absolute value of nucleic acid concentration, and is an epoch-making nucleic acid detection technology [55]. Compared with traditional RT-PCR, the core advantages of dPCR are reflected in high detection accuracy, high sensitivity, stable system, and excellent repeatability [56,57]. dPCR divides nucleic acid molecules into several reaction units, and each unit performs independent PCR amplification (The reaction principle is shown in Fig. 2).

Jiang et al. [59] made a contrast of the detection performance of digital PCR and traditional RT-PCR technology and found that digital polymerase chain reaction showed higher sensitivity than traditional reverse transcription-polymerase chain reaction. This indicates that it may be a useful clinical SARS-CoV-2 detection method. Lu et al. [60] also did research in this area and found that compared with traditional RT-PCR testing, the false-negative and false-positive results of dPCR test results are less, especially for the detection of trace samples.

Alter et al. [55] evaluated the performance of a droplet digital PCR-based (ddPCR) detection method. This method uses internal ddPCR testing to quantify the SARS-CoV-2 titer in suspected cases of new coronary pneumonia with negative RT-PCR results. This technology enables timely and precise diagnosis of SARS-CoV-2 with negative respiratory tract RT-PCR.

However, the shortcomings of digital PCR are also obvious, such as high technical cost, complicated operation, limited detection throughput, and difficulty in popularizing and applying in epidemic areas and primary medical units [61].

### 2.3. Metagenomics next-generation sequencing (mNGS)

For an emerging infectious disease, genetic sequencing of the pathogen is the most accurate identification method [62–64]. In the study of the COVID-19 genome, scientists have used a high-throughput detection

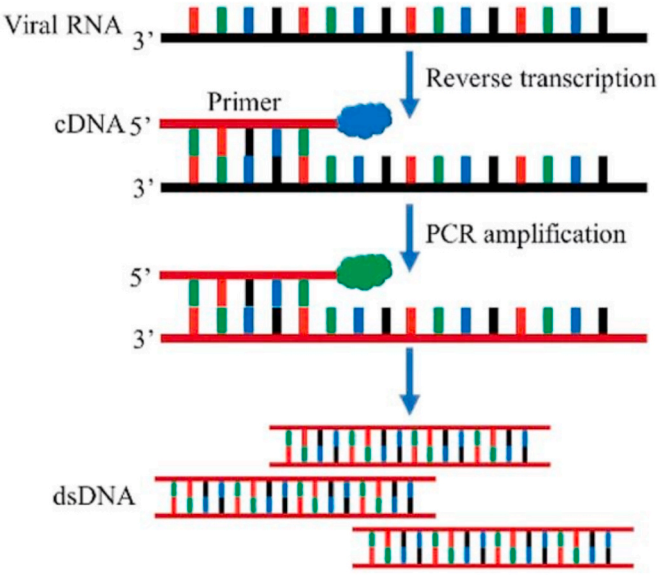


**Fig. 1.** Schematic diagram of RT-PCR detection of COVID-19 [49].

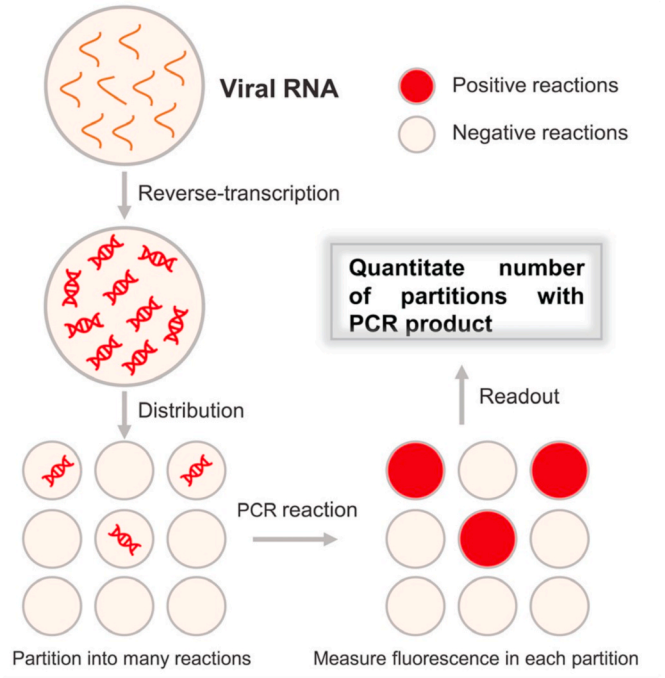


**Fig. 2.** Schematic diagram of dPCR detection principle [58].

platform to obtain first-hand information on the viral genome in a very short time [65,66]. The basic process is to extract viral RNA from the lower respiratory tract secretions of the patient, construct a genetic information database of the virus, then perform high-throughput sequencing, and identify whether the genome sequence is homologous to SARS-CoV-2 through database comparison analysis [67].

Sauter et al. [68] extracted SARS-CoV-2 viral RNA from autopsy sections, performed NGS to detect the virus, and combined immunohistochemistry to explore the pathogenic mechanism. Through mNGS technology, Antonin et al. [69] found that COVID-19 patients in many European countries have deletions in nsp2 amino acids (Asp268Del). Moore et al. [70]used amplicon and mNGS-based MinION sequencing to quickly determine the genome of SARA-CoV-2, and experiments proved the feasibility of amplicon-based sequencing.

However, mNGS detection technology also has its limitations: such as short read length, uneven genome coverage, susceptibility to host genome contamination, and high cost [71]. Therefore, it is too early to use high-throughput sequencing as a census tool at this stage, but it is of great significance for sequencing and genetic analysis of new respiratory pathogens.

### *2.4. Reverse-transcription loop-mediated isothermal amplification (RT-LAMP)*

RT-LAMP is a one-step nucleic acid amplification method that combines loop-mediated isothermal amplification (LAMP) and reverses transcription [72]. The detection principle of RT-LAMP is shown in Fig. 3. This new method is similar to traditional polymerase chain reaction detection, except that nucleic acid amplification is performed at the same temperature [73].

Compared with qRT-PCR, RT-LAMP has obvious advantages. For example, certain mandatory equipment for polymerase chain reaction is no longer needed, and it has the advantages of easy operation, simple use, rapidness, high sensitivity, and specificity [75]. It enables rapid screening, greatly shortening the detection time. However, due to the high sensitivity of RT-LAMP, it is highly susceptible to contamination and produces false-positive results [76], so operation contamination must be strictly prevented. Also, when the viral load is lower than the RT-LAMP test offline, it may cause false-negative results.

Jiang et al. [77] developed a precise RT-LAMP technology that can process samples twice as fast as RT-PCR and can achieve high-throughput screening in critical situations (Fig. 4). Moreover, this detection does not require a cold chain and can be transported at room temperature, but it has the disadvantage of low sensitivity.

Yu et al. [78] optimized the RT-LAMP method and developed a detection method called iLACO (isothermal LAMP-based method for COVID-19). The researchers selected ORF1ab fragments as the target region and compared the target sequence with other viral genomes to ensure primer specificity. Verification of RNA samples extracted from

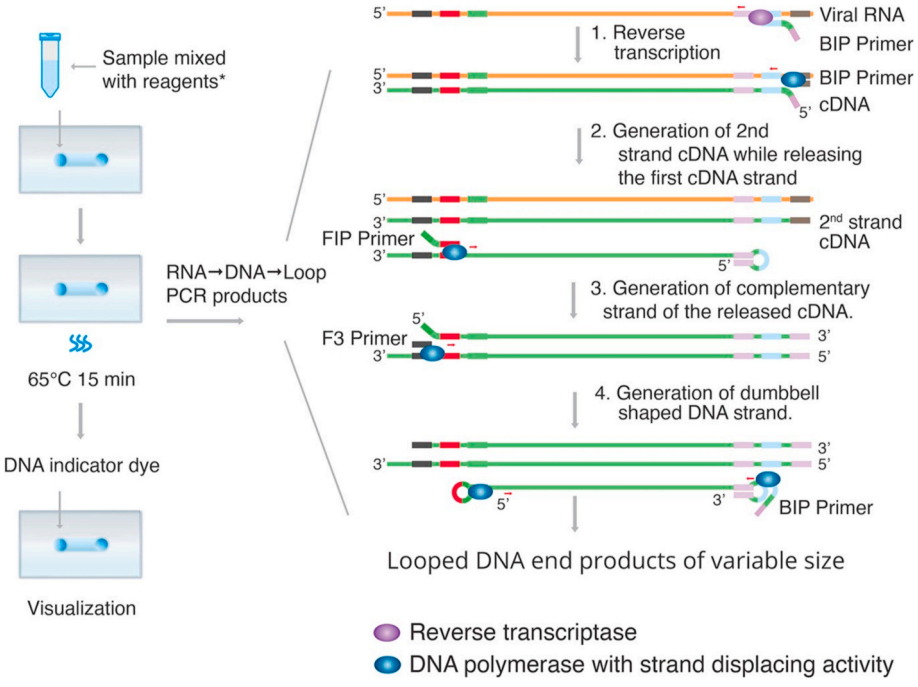


**Fig. 3.** Schematic diagram of RT-LAMP detection principle [74].

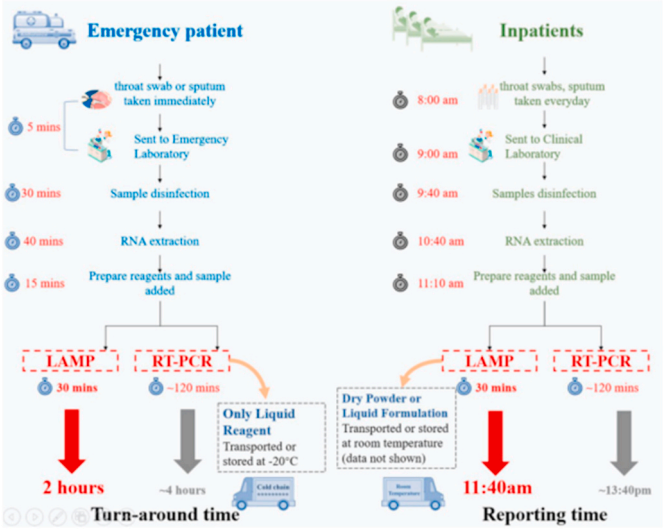


**Fig. 4.** Comparison of the detection time of RT-PCR and RT-LAMP between emergency patients and inpatients [77].

SARS-CoV-2 (verified by RT-qPCR) positive patients proved the effectiveness of the method (Fig. 5).

### 2.5. CRISPR-based assays

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and CRISPR-associated proteins (CRISPR/Cas) constitute an acquired immune system. The CRISPR/Cas system first produces an RNA sequence that is complementary to the target sequence and can be targeted to bind to the DNA of the virus or plasmid. Cas ribonucleic acid is used for double-strand cleavage targeting complementary sequences [79]. Studies in recent years have shown that it can be used for the detection of viral nucleic acids with high sensitivity, simplicity, and reliability of results [80].

Ding et al. [81] proposed a multifunctional, dual-CRISPR-Cas12a (AIOD-CRISPR) detection method with high sensitivity. By targeting SARS-COV-2 nuclear protein genes, two CRISPR RNAs without the restriction of the protospacer adjacent motif (PAM) sites were introduced, thus establishing an AIOD-CRISPR detection method. This analysis was validated using COVID-19 clinical swab samples and results were in accord with reverse transcription-polymerase chain reaction analysis. Broughton et al. [82] reported a method based on CRISPR-Cas12This study provides an intuitive, rapid alternative with 95% positive predictive accuracy and 100% negative predictive accuracy (Fig. 6).

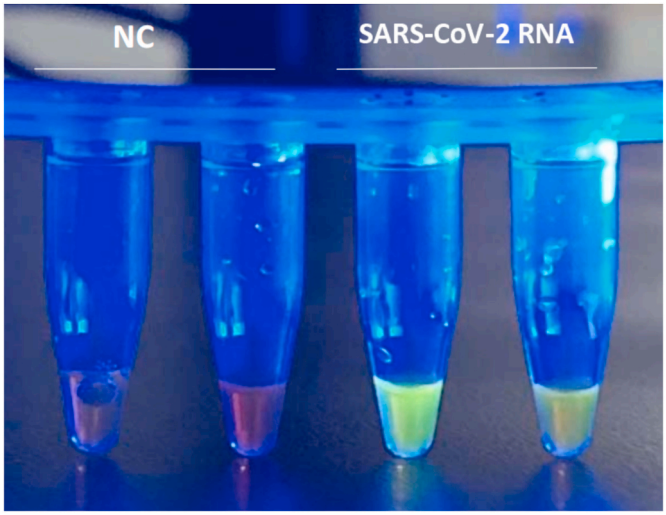


**Fig. 5.** Schematic diagram of the fluorescence results detected by iLACO. NC refers to the negative control, and the obvious fluorescent signal appears in the SARS-CoV-2 positive control [78].

Based on the CRISPR method, Zhang et al. developed a technology called SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing). The method can continuously detect the target sequence within 20–200 aM, and mainly includes three steps of constant temperature amplification, detection of pre-amplified sequence, and result detection. The detection time is within 1 h. To enable SHERLOCK to be used in a POC environment, the research team has developed a reagent called STOP (SHERLOCK test in a pot). This chemical reagent can be processed by a fluid at a temperature Steps and simple visual readings for operation [83] (Fig. 7).

## 3. Serology-based detection methods

The detection of specific antibodies in the serum is also a feasible option to confirm SARS-CoV-2 infection [84–87]. In the acute stage of infection, regardless of whether the infected person has clinical symptoms, the level of IgM in the blood will increase [88–90]. Therefore, the development of an *anti*-SARS-CoV-2 IgM detection method will provide a valuable reference.

In the early stage of infection of the disease, antibodies may not be produced in the human body, so there is a window for detection [91,92]. Therefore, antibody detection can be used to assist in the diagnosis of cases with negative nucleic acid tests, and can also be used to screen and screen cases, but it cannot replace nucleic acid detection methods.

The rapid diagnostic test strip has many advantages, such as simple operation, low cost, and fast detection speed [93]. This detection method has been widely used in many point-of-care testings (POCT) applications [94,95]. There are various signal reporters used, including colloidal gold nanoparticles [96], magnetic nanoparticles [97], quantum dots [98], and so on. The characteristics of several common serology-based detection technologies are shown in Table 2.

### 3.1. Colloidal gold immunochromatographic assay (GICA)

The colloidal gold method is to coat the SARS-CoV-2 antigen on a nitrocellulose membrane and capture the IgM/IgG antibody of SARS CoV-2 in human serum based on the principle of lateral immunochromatography [99]. The mouse anti-human IgM/IgG antibody labeled with colloidal gold is used. The IgG antibody forms an antigen-antibody complex, causing the mobile phase to gather at the detection line as a red reaction line [100]. The samples detected by the colloidal gold method are derived from the patient's fingertip blood or venous blood, and the results can be visually observed after only 10–15 min of an immune response. The detection principle of GICA is shown in Fig. 8.

Colloidal gold nanoparticles have the advantages of strong stability, easy to read detection results, and simple operation compared with other reporter markers. Also, colloidal gold nanoparticles have extremely low biological toxicity and good biocompatibility [102]. Therefore, the serological immunochromatography technology based on colloidal gold nanoparticles is very effective for rapid on-site detection.

Liu et al. [101] reported a test kit based on GICA technology, which only takes 10–15 min to get the test results. The kit has no special requirements for equipment and personnel and shows great potential for rapid and large-scale screening. Although it cannot completely replace RT-PCR technology, it can be used as an important supplementary technology.

In response to the problem of false negatives in the detection of nucleic acids by RT-PCR, Pan et al. [99] proposed a gold-based immunochromatographic (ICG) band targeting viral IgM or IgG antibodies (Fig. 9), which is in comparison with RT-PCR. The combined detection method of IgM and IgG has excellent sensitivity for the detection of

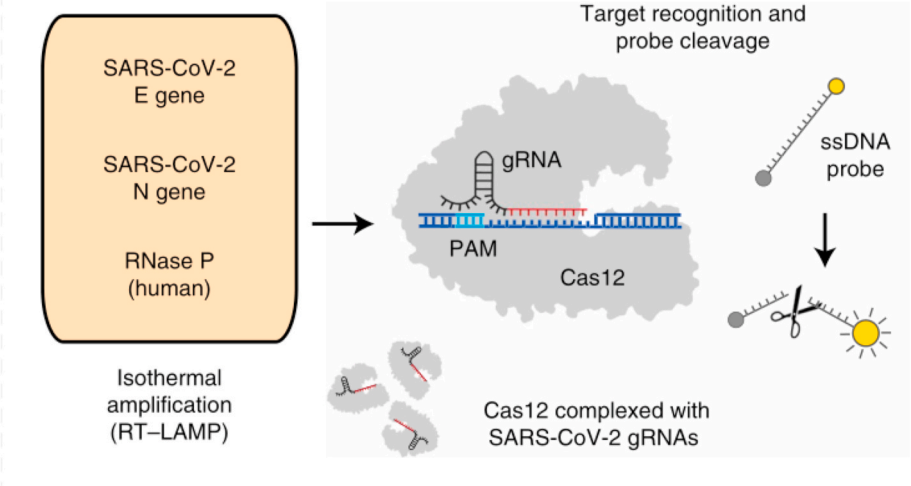


**Fig. 6.** Schematic of SARS-CoV-2 detection workflow of CRISPR-based assays [82].

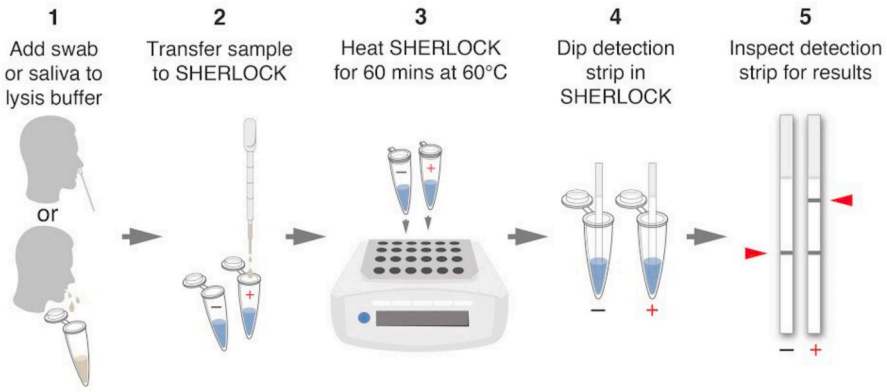


**Fig. 7.** Schematic of the one-step STOPCovid test [83].

**Table 2**
Summary of the characteristics of common serology detection-based technologies.

| | Detection time | Advantage | Disadvantage |
|---|---|---|---|
| ICG | 10–15 min | Strong stability; easy to read test results; simple operation; extremely low biotoxicity and good biocompatibility | High false-positive rate |
| CLIA | 30–60 min | Good accuracy; high sensitivity and specificity | High false-positive rate; difficult reagent transportation |
| ELISA | 1–5 h | High sensitivity and specificity, simple operation method, low instrument configuration requirements | Prone to cross-contamination |
| LFIA | 10–30 min | Low cost, simple operation, no need for matching instruments | Low detection sensitivity |

intermediate and advanced patients. The results of the study show that the serum ICG band means is eligible in diagnosing SARS-CoV-2 infection and is a good auxiliary method for clinical application.

Huang et al. [103] established a colloidal gold nanoparticle-based lateral-flow (AuNP-LF) assay and realized timely diagnosis and on-site detection of IgM antibody to SARS-CoV-2. SARS-CoV-2 nucleoprotein was coated on the analytical membrane for sample acquisition, and the

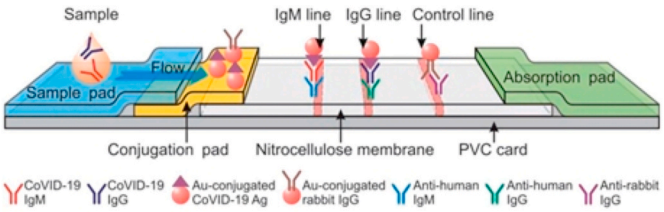


**Fig. 8.** Schematic diagram of GICA detection principle [101].

anti-human IgM antibody was integrated to produce a detection result. By changing the pH of the solution and the amount of human immunoglobulin, the immunofluorescence assay was optimized. The sensitivity and specificity were 100% and 93.3% respectively. The results of the AuNP-LF test can be obtained within 15 min, and only 10–20 μL serum is needed for each detection, which has good detection specificity and operational stability.

Shun et al. [104] made a clinical evaluation on the detection of IgM/IgG antibodies of SARS-CoV-2 in the Japanese population by colloidal gold immunochromatography. The results revealed that the sensitivity and specificity of the method were 79.7%/86.1% and 100% respectively. Also, the report points out that IgM/IgG antibody detection method is still effective in the middle and late stages of the disease, which indicates that it can be used as a supplementary diagnostic

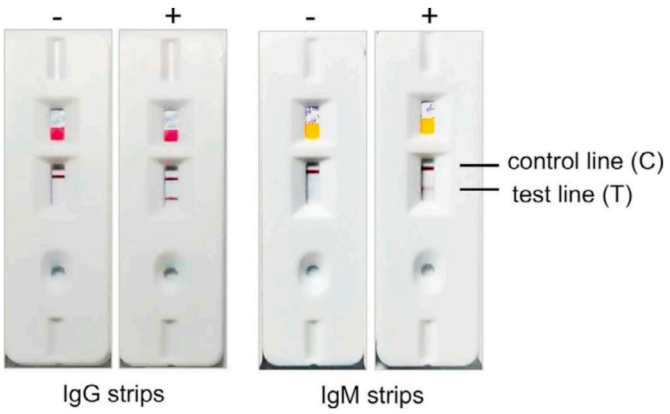


**Fig. 9.** Typical performance of *anti*-SARS-CoV-2 IgG (A) and IgM (B) antibody ICG test paper [99].

method for nucleic acid detection of COVID-19.

However, the IgM/IgG antibody colloidal gold method as serological evidence cannot replace the status of RT-PCR as pathogenic evidence. The test results may be influenced by factors such as sample hemolysis, fibrin, or the patient's autoantibodies, contributing to a high false-positive rate [105]. Also, the detection window of IgM/IgG antibodies is longer than RT-PCR [106]. Therefore, in the future, the combination of RT-PCR and IgM/IgG antibody detection can further increase the positive rate of detection and effectively eliminate false-negative or false-positive test results.

### 3.2. Chemiluminescence enzyme immunoassay (CLIA)

CLIA is a highly sensitive immunoassay, which combines highly sensitive chemiluminescence assay technology with a highly specific immune response [107]. Infantino et al. [108] used the CLIA analyzer to detect SARA-CoV-2 antibodies in COVID-19 patients and normal controls. The results confirmed that high-precision results can be achieved when the antibody concentration reaches a critical value. Soleimani et al. [109] evaluated the performance of fully automated CLIA, and the results showed that its specificity and sensitivity reached a high level. The combination of CLIA technology and nucleic acid detection can greatly improve the accuracy of detection. Padona et al. [110] studied the analytical performance and antibody kinetics of the CLIA technology to detect SARS-CoV-2, and the results revealed that the inaccuracy and repeatability were within a reasonable range.

Magnetic chemiluminescence enzyme antibody immunoassay is based on chemiluminescence detection, adding magnetic nanoparticles, so that the detection has higher sensitivity and faster detection speed. Gong et al. [111] combined flow cytometry and magnetic chemiluminescence enzyme antibody immunoassay to comprehensively analyze the peripheral $CD4^+$ cells of COVID-19 patients and verified the close connection between them and the patient's antibodies.

However, the magnetic particle chemiluminescence method has poor selectivity and will respond to a series of compounds instead of a specific compound. Therefore, the accuracy is relatively insufficient. Moreover, the environment has a relatively large influence on the detection, which is easy to cause errors.

### 3.3. Enzyme-linked immunosorbent assay (ELISA)

The ELISA method is to fix the SARS-CoV-2 antigen to the carrier, which is used to capture the SARS-CoV-2 IgM/IgG antibody [112]. Enzyme-labeled *anti*-IgM/IgG antibody is used as the secondary diagnostic antibody to construct an indirect detection system for IgM/IgG antibody, and finally, quantitatively detect the IgM/IgG antibody in the sample through enzymatic color reaction [113].

The detection sensitivity and specificity of the ELISA method are high, the operation method is simple, and the equipment configuration requirements are low [114]. However, the manual operation of the ELISA method may bring unnecessary operational errors and cross-contamination, and there is a window period for IgM/IgG antibody detection, which makes it difficult to obtain a positive test result at the initial stage of infection [115].

Compared with the colloidal gold method, its advantage is that it can quantitatively detect IgM/IgG antibodies, can judge the dynamic process of IgM antibody turning negative, IgG antibody rising, and assist in monitoring the patient's condition changes. Vermeersch et al. [116] tested the sensitivity of ELISA to diagnose SARS-CoV-2, and the result was 89.2%. Kovac et al. [117] have also done a similar study, and the results confirmed that ELISA as a diagnostic technique for COVID-19 is accurate and feasible.

### 3.4. Lateral flow immunochromatographic assay (LFIA)

The detection principle of LFIA is: antigen is fixed on the detection strip. The test sample and the labeled antibody move along the strip. If the SARA-CoV-2 antibody is present in the sample, it will combine with the labeled antibody and antigen to form a complex, and then a band will appear [58,118] (Fig. 10). This detection technology has a low cost,

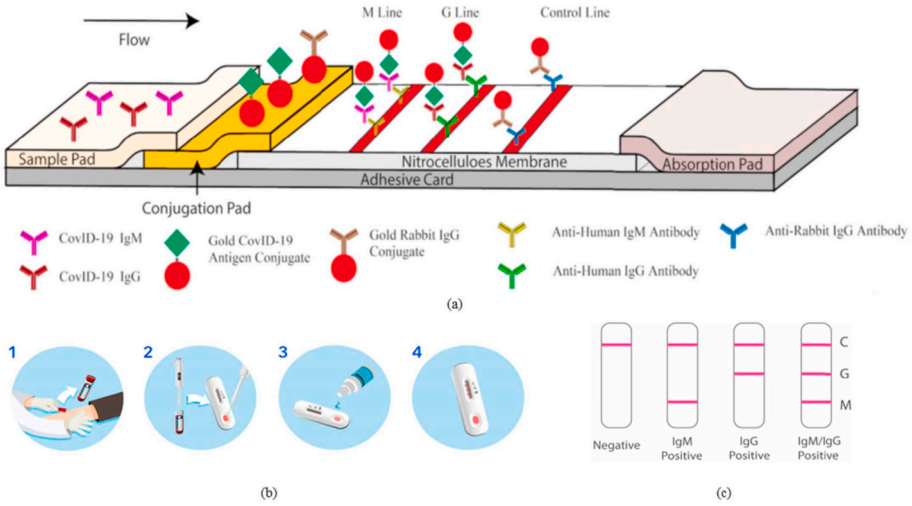


**Fig. 10.** Schematic diagram of LFIA detection principle [118].

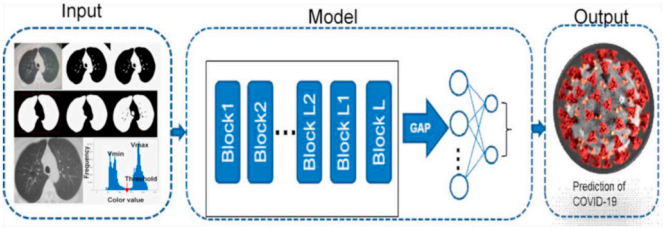


**Fig. 11.** Algorithm framework [123].

for detection, other diagnostic techniques are also meaningful. Their combined results can exclude false negative and false positive results as much as possible. Here, we discussed a variety of COVID-19 detection technologies and discussed their advantages and disadvantages in depth. Various detection technologies are in rapid development, and the main goals of development are mainly rapid diagnosis and on-site diagnosis. Diagnosis kits should be developed in the direction of being separated from the equipment and shortening the waiting time.

To prevent the large-scale spread of the virus, extensive population screening is very necessary. The rapid diagnosis and isolation of asymptomatic infections are essential. In the general direction of nucleic

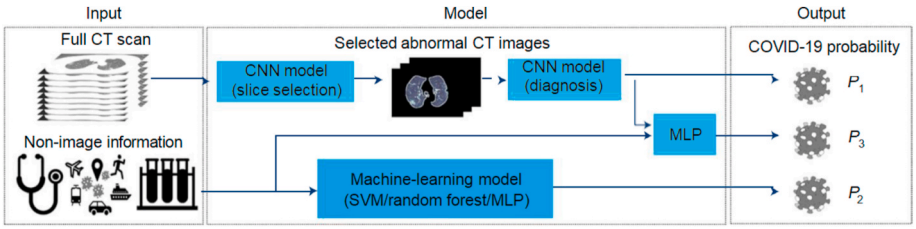


**Fig. 12.** Modeling framework [124].

simple operation, and does not require matching instruments. However, the detection sensitivity cannot reach the level of CLIA and ELISA, and the detection results need to be carefully considered [119].

## 4. CT imaging assisted diagnosis

Many characteristics of viral pathogens can be identified based on imaging patterns. These characteristics correspond to specific pathogenic mechanisms. The main characteristics of COVID-19 are early shadows and frosted glass-like shadow distribution [120]. Nucleic acid detection is currently the main detection method, but it is time-consuming and has false-positive interference. CT imaging is a good auxiliary diagnosis method [121,122].

Based on the above considerations, Xu et al. [123] developed an artificial intelligence model that uses CT images to assist in the analysis of COVID-19. The researchers collected CT images of pathologically confirmed and previously diagnosed cases of representative viral pneumonia. Modify the initial transfer model to an algorithm, and then conduct internal and external verification. Finally, the overall accuracy rate of the internal verification is 89.5%, and the external is 79.3%. It also has high specificity and sensitivity. The algorithm framework is shown in Fig. 11. The system includes 3 main processes: 1) Image preprocessing. 2) Feature extraction and training of ROI images. 3) Classification and prediction.

Yang et al. [124] also researched in this area. Because the chest CT appearance of the early infected person is normal, the researchers combined artificial intelligence algorithms with CT appearance, clinical symptoms，and laboratory tests to quickly diagnose COVID-19 patients. The ACU of the system is 0.92, and its sensitivity is no less than that of a senior radiologist. The framework of this method is shown in Fig. 12. The first part is a chest CT scan. The next part is to classify with clinical information. The last part is to generate classification results.

Although the results of chest CT may not be as precise as nucleic acid detection, it can be used as a valuable tool and reference. Given the current lack of nucleic acid detection kits and the long detection time, the advantages of the intelligent detection system are obvious.

## 5. Summary and outlook

Since the outbreak of COVID-19, various testing kits have emerged one after another. Although RT-PCR has always been the gold standard acid detection as the mainstay and serum detection as the supplement, the sensitivity and accuracy of detection should be improved as much as possible. With the development of global cooperation, there will be greater and faster breakthroughs in the diagnosis of COVID-19.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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