



Nanobiotechnology as a platform for the diagnosis of COVID-19: a review

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Abstract

A sensitive method for diagnosing coronavirus disease 2019 (COVID-19) is highly required to fight the current and future global health threats due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2). However, most of the current methods exhibited high false-negative rates, resulting in patient misdiagnosis and impeding early treatment. Nanoparticles show promising performance and great potential to serve as a platform for diagnosing viral infection in a short time and with high sensitivity. This review highlighted the potential of nanoparticles as platforms for the diagnosis of COVID-19. Nanoparticles such as gold nanoparticles, magnetic nanoparticles, and graphene (G) were applied to detect SARS-CoV 2. They have been used for molecular-based diagnosis methods and serological methods. Nanoparticles improved specificity and shorten the time required for the diagnosis. They may be implemented into small devices that facilitate the self-diagnosis at home or in places such as airports and shops. Nanoparticles-based methods can be used for the analysis of virus-contaminated samples from a patient, surface, and air. The advantages and challenges were discussed to introduce useful information for designing a sensitive, fast, and low-cost diagnostic method. This review aims to present a helpful survey for the lesson learned from handling this outbreak to prepare ourself for future pandemic.

Keywords COVID-19 · Nanoparticles · Sensors · Nucleic acid tests · Antibody · Antigen · Quantitative analysis

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) is associated with a pandemic of the acute respiratory disease called coronavirus disease 2019 (COVID-19) [1–7]. To date (March 2021), there are more than 118 million reported infections and over 2.6 million deaths. Most countries faced mandatory quarantines and lockdowns fighting this threat, leading to an economic crisis [8]. An infected person suffers from fever or chills, dry cough, sore throat, diarrhea, headache, nausea or vomiting, fatigue, and breathing difficulty. All these symptoms or some of them can be observed. The infection of SARS-COV was also related to the cardiovascular system (CVS) [9], central nervous system

(CNS), gastrointestinal tract (GIT) [10], and female reproductive strategies [11]. To date, there is no medicine/drug that has been proved to be effective in treating COVID-19. The only hope now is in the success of the emergency-approved vaccines [12, 13]. The early diagnosis of COVID-19 may help control the spread of the pandemic [14–16].

Nanotechnology describes the technology for using particles (nanoparticles) with at least one dimension in the nanometer range ($1 \text{ nm} = 10^{-9} \text{ m}$, Fig. 1). Nanoparticles exhibit distinct properties such as large surfaces, many active sites, and high adsorption capacities compared to bulk materials. Thus, they have been applied for several applications such as analytical chemistry [17–26], proteomics [27], sensing/biosensing [28–35], biotechnology [36–45], nanomedicine [46–53], drug delivery [54–56], gene transfer [57–60], wound healing [61], energy-based applications [62–67], and environmental applications [68–75]. Nanoparticles improved these applications by showing high performance [76–84] with a great potential for implementation into a miniaturized device, including wearable electronics [85–87]. Thus, they exhibit the great potential to improve the quality of life via controlling the viral spread through early detection

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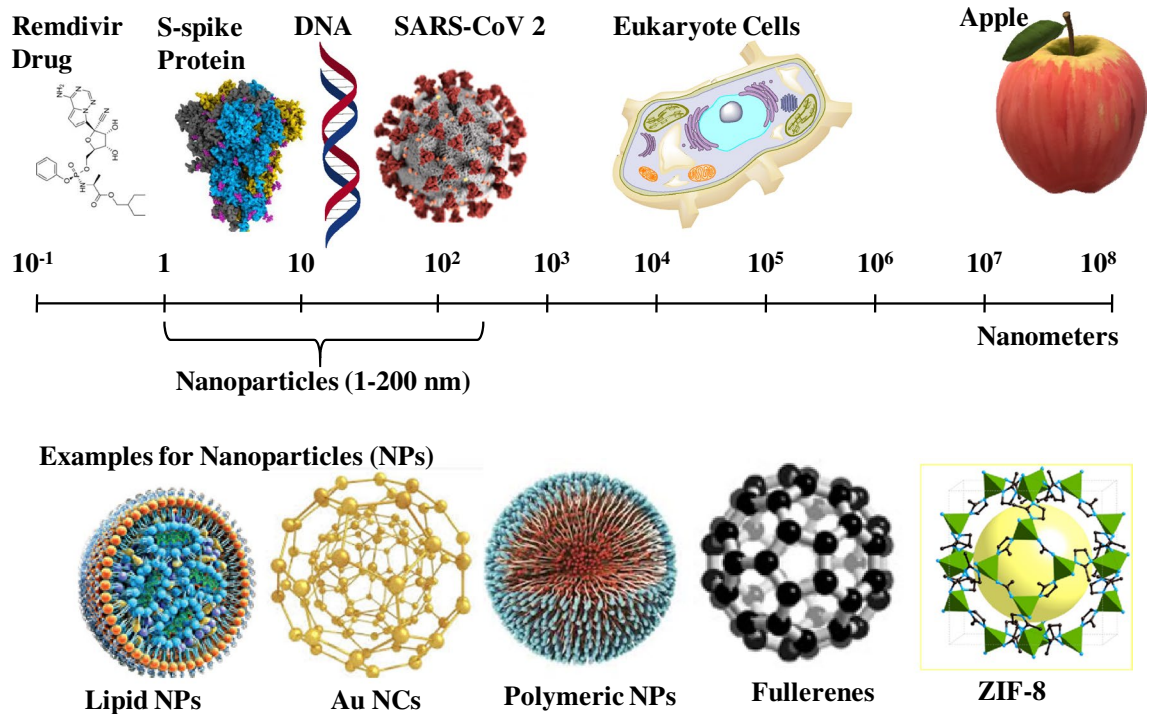


Fig. 1 Scale of nanoparticles with some examples

of infection. Therefore, this review article summarized the current findings and future prospective of nanotechnology for the diagnosis of COVID-19.

Corona virus: structure and infection

Coronavirus (CoVs) refers to virus strain with club-shaped protein spikes on their surface, i.e., crown-like appearance. There are four classes of CoVs, such as alpha, beta, gamma, and delta. All these classes consist of a single-stranded positive-sense ribonucleic acid (RNA) genome. There are two types of alpha-coronaviruses (229E and NL63) and two types of beta-corona viruses (OC43 and HKU1), which can circulate in humans, causing common cold [88]. The human infection by beta coronavirus class (β -CoVs) was previously reported for the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [89]. The new coronavirus, i.e., SARS-CoV 2, belongs to the beta class [90]. The infection with SARS-CoV 2 showed human-to-human transmission leading to the spread of infection in more than 122 countries worldwide [91–94]. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) warned the people from the spread of the infection via cough and touch [91–93].

SARS-CoV 2 virus is an enveloped and non-segmented viruses of a single-stranded RNA genome (4 kilobases) with a nucleocapsid (Fig. 2). It contains two main compartments; protein and non-protein structures [95]. The nucleotide

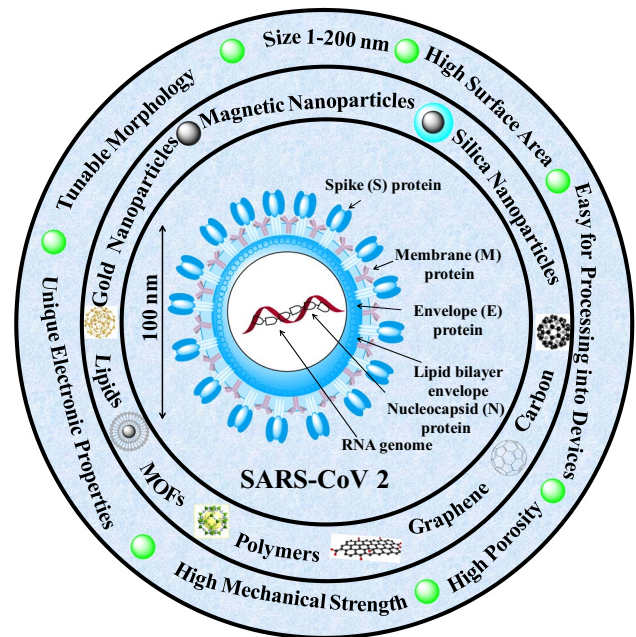


Fig. 2 Examples of nanoparticles and their properties. The core of the image represents the structure and size of SARS-CoV 2

genome of COVID-19 is 80% and 96% identical to the SARS-CoV and the BatCoV RaTG13, respectively [96, 97]. SARS-CoV 2 contains four proteins: (i) S-protein (Spike glycoprotein, PDB: 5XL3), (ii) M-protein (Membrane or

Matrix), (iii) E-protein (Envelope), and N- protein (Nucleocapsid phosphoprotein) [98–103]. These proteins play a vital role for the infection.

S-protein enables the attachment of the virus to host cells. M-protein promotes the entry of the SARS-CoV 2 virus into the host cells and maintains SARS-CoV 2 viral particles' membrane integrity. The E-protein is the smallest protein and plays a structural role in the assembly of the virus. The N-protein binds to the RNA and supports nucleocapsid formation [98–103]. Thus, they can be classified into core protein, e.g., N-protein, and (ii) envelope protein, e.g., S, M, and E proteins. The assembly of these constituents produces a particle size of 100 nm (Fig. 2).

SARS-CoV 2 infects the respiratory system and then spreads systemically to the heart, liver, and kidney [104]. A significant number of patients with SARS-CoV 2 suffers from mild to moderate symptoms. However, 15% of patients with SARS-CoV 2 exhibit severe pneumonia and approximately 5% progress acute respiratory distress syndrome (ARDS), leading to septic shock and multiple organ failure [105, 106]. A study showed that patients with severe SARS-CoV 2 exhibited substantially elevated serum levels of pro-inflammatory cytokines including Interleukin 6 (IL-6) and IL-1 β , as well as IL-2, IL-8, IL-17, Granulocyte colony-stimulating factor (G-CSF), Granulocyte–macrophage colony-stimulating factor (GM-CSF), Interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP1 α), and tumor necrosis factors (TNF), characterized as cytokine storm [107]. The infected person's analysis showed high expression of angiotensin-converting enzyme 2 (ACE2) in the respiratory tract and other organs [108, 109].

Data analysis (245 surface samples) and air places from hospital rooms of COVID-19 patients for SARS-CoV 2 RNA were reported [110]. The study revealed that 56.7% of the investigated rooms had at least one environmental surface contaminated with the virus (Fig. 3). Air sampling (from airborne infection isolation rooms (AIIRs) in the intensive care unit (ICU) and the general ward) is performed in three of the 27 AIIRs in the general ward. It detects SARS-CoV 2 PCR-positive aerosol particles of sizes > 4 μ m and 1–4 μ m in two rooms [110]. The analysis of wastewater is critical to monitor the emergence and spread of infectious COVID-19 disease at a population level [111]. There are several protocols for the extraction of the virus or its antigens from wastewater. The detection of SARS-CoV 2 in wastewater is paramount for monitoring public health [112].

Nanotechnology

Nanotechnology is the technology of nanoparticles with a size of 1–200 nm (Fig. 2). Nanoparticles can be classified to:

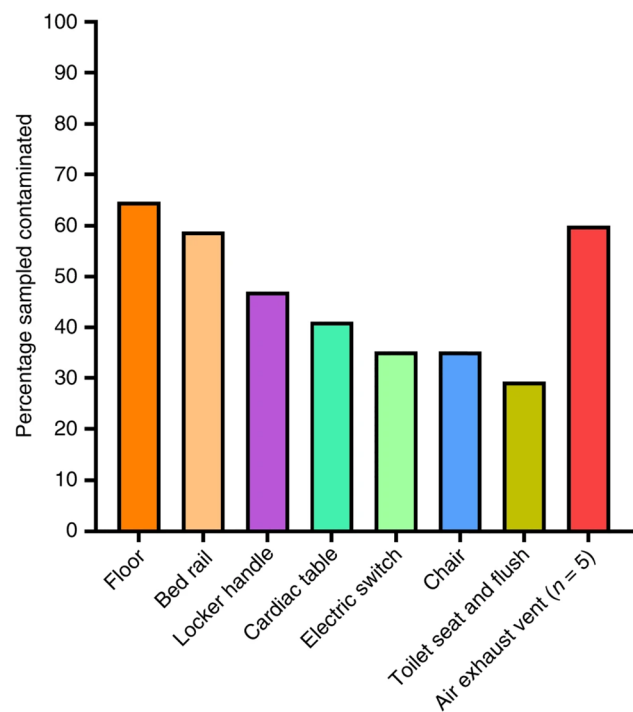


Fig. 3 Percentage of contaminated swabs from surface samples in hospital rooms. The figure was reprinted from Ref. [110]. This is an Open Access article distributed under the terms of the Creative Commons CC BY license

1. Metallic nanoparticles, e.g., gold nanoparticles (Au NPs), silver nanoparticles (Ag NPs);
2. Metal oxide nanoparticles, e.g., iron oxide magnetic nanoparticle (Fe₃O₄ NPs);
3. Carbon nanomaterials including 0-dimensional (0D, e.g., fullerenes (C₆₀), carbon dots (C-dots)), 1D (carbon nanotubes (CNTs)), 2D (e.g., graphene (G), graphene oxide (GO)), and 3D (e.g., graphite);
4. Quantum dots (QDs): CdS QDs, CdTe QDs, carbon QDs.
5. Porous materials: metal–organic frameworks (MOFs), covalent organic frameworks (COFs)[113], silica;
6. Polymers: natural polymers (e.g., chitosan, cellulose), and synthetic (e.g., polythiophene, polypyrrole);
7. Lipid nanoparticles (LNPs): triglycerides, fatty acids, steroids, and waxes.

Nanoparticles exhibit several unique properties such as large surface area and simple modification with inorganic [114, 115], organic [116], and biomolecules such as enzymes and protein [117]. They exhibit properties such as catalytic activity [118–123], nanozyme [124–126], and antimicrobial [127, 128]. The large surface areas of nanoparticles ensure simple modification of their surface via chemical engineering. The particle size of nanomaterials

(1–200 nm) is close to the viral particle size of SARS-CoV 2 (Fig. 2). Thus, they interact strongly, leading to significant changes in the electronic properties of nanoparticles. These interactions offer high selectivity and better sensitivity. They can be used for diagnosis, protection, and prevention [129–132].

Nanoparticles offer distinct properties compared to bulk materials. Metallic nanoparticles such as Au NPs, Ag NPs provide unique optical and electronic properties such as surface plasmonic resonance (SPR) [133–135], and localized surface plasmon resonance (LSPR) [136]. Thus, they can be used as a probe for conventional SPR, nanoplasmonic sensors, surface-enhanced Raman spectroscopy (SERS), plasmonic-enhanced fluorescence, and colorimetric method. Some metal oxides or chalcogenides such as molybdenum oxide (MoO_{3-x}) [71] and molybdenum disulfide (MoS_2) [137] also exhibited plasmonic properties. Carbon nanomaterials such as graphene show unique electronic, optical, and electrochemical properties [138]. They are promising for point-of-care tests (POCT).

Laboratory diagnosis of COVID-19

The early detection of SARS-COV-2 is necessary to control the widespread infection [139–160]. Several methods can be used for the diagnosis of COVID-19 [161–183]. The diagnosis of COVID-19 depends on the analysis of the patient’s response due to the infection or the analysis of virus contents, e.g., RNA or their protein (Fig. 4). The patient’s temperature (elevated temperature), feeling fatigued, and difficulty in breathing indicate infection (Fig. 4). However, these symptoms are lack specificity and may be observed due to the infection with other pathogens. The patient’s pathological changes in organs such as the chest can be monitored via computerized tomography (CT) scan (Fig. 4). Like other pneumonia types, a CT scan may be a reliable test for screening SARS-COV 2 cases [184, 185]. However, the analysis required specialized equipment and failed to meet a large scale of requirement, and it may not provide benefit for point-of-care (POC) diagnosis of COVID-19. COVID-19 can be diagnosed via laboratory measurements [106] such as (1) hematologic (the increase in lymphocyte and white cell counts); (2) biochemical

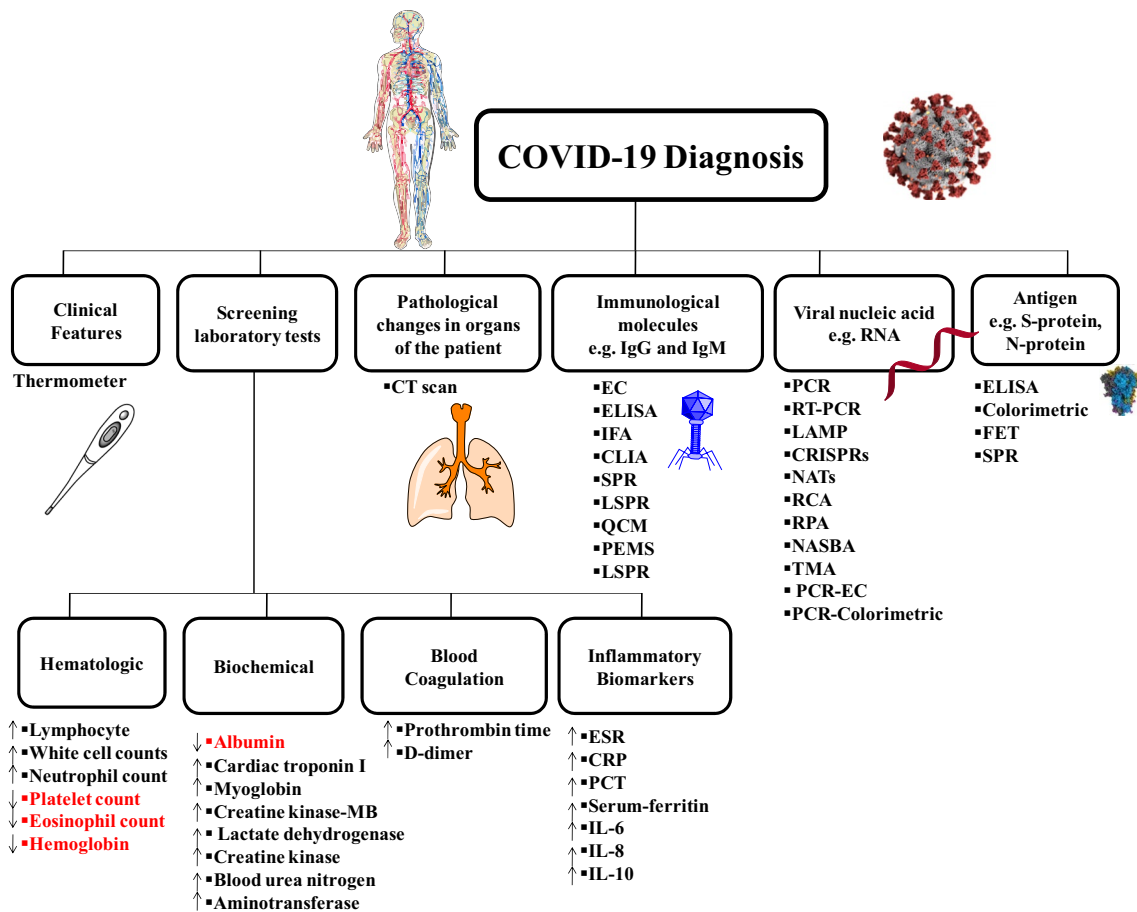


Fig. 4 Diagnosis methods for COVID-19

change due to the rise of liver function damage biomarker (Lactate dehydrogenase (LDH), α -hydroxybutyric dehydrogenase (α -HBDH), creatine phosphokinase (CPK), AST/ALT ratio (the concentration ratio between enzymes aspartate transaminase (AST) and aka alanine transaminase (ALT)); (3) kidney dysfunction (Creatinine levels in the blood); (4) increase in the inflammation biomarkers (Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Procalcitonin (PCT)); (5) changes in the blood properties such as the increase in the time blood takes to clot (Prothrombin time, PT), fibrin degradation fragment (D-dimer) and plasma viscosity (PV). The analysis of markers such as pro-inflammatory cytokines [107] and ACE2 [90, 186] can also be used. These methods are usually used for the analysis of patients. They cannot be used for the analysis of contaminated samples such as surface and air. They are universal and can only be used as an indicator for any infection, i.e., lack of specificity. The laboratory screening is a qualitative analysis method and an indication of an illness related to COVID-19 or other diseases.

Several analytical methods can be used for the diagnosis of COVID-19. There are three main tests called molecular tests (e.g., genetic-based tests or nucleic acid tests (NATs)), antigen tests, and antibodies tests (e.g., serological tests). These methods can be classified to:-

- I. **Genetic tests** (viral nucleic acid tests): analysis of viral genome using techniques such as real-time-quantitative reverse transcription-polymerase chain reaction (RT-qPCR), isothermal amplification (e.g., Loop-mediated isothermal amplification (LAMP), nucleic acid sequence-based amplification (NASBA), transcription-mediated amplification (TMA), rolling circle amplification (RCA), Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)), and nanopore targeted sequencing (NTS) [187].
- II. **Antigen tests**: analysis of the viral proteins (membrane-bound spike proteins or the nucleocapsid proteins) using techniques such as colorimetric, field-effect transistor (FET), enzyme-linked immunosorbent assay (ELISA), and mass spectrometry (MS).
- III. **Serological tests**: analysis of the antibodies (Immunoglobulin M (IgM) and Immunoglobulin G (IgG)) against the virus [188–190]. The study of patient's antibodies can be achieved using methods such as electrical (EC) biosensors, localized surface plasmon resonance (LSPR), surface-enhanced Raman scattering (SERS), quartz crystal microbalance (QCM), fluorescence-based biosensor, colorimetric biosensor, gold immunochromatography, ELISA, chemiluminescence immunoassay, and piezoelectric microcantilever sensors (PEMS).

SARS-CoV 2 can be detected in various samples such as feces (1×10^7 copies/mL) [191], urine (1×10^2 copies/mL) [192, 193], saliva (5×10^4 copies/mL) [194], and respiratory tract (10^3 – 10^7 copies/mL) [195–197]. The commonplace for sample collection is respiratory tract (upper part (pharyngeal swabs, nasal swabs, and nasal discharges), and lower part samples (sputum, airway secretions, and bronchoalveolar lavage fluid)). Nasopharyngeal samples are widely used due to the ease of collection, high viral load (10^3 – 10^7 copies/mL), and high stability during transportation or storage [198]. Sample can be self-collected at home via anterior nares swabs. However, the sample collection is painful because it requires the deep insertion of cotton-tipped plastic swabs. Other invasive places such as saliva, feces, and urine can also be used [199–201]. However, they contain low viral load and contain interfering species make the use of this specimen challenging for the diagnosis of COVID-19. The concentration of antibodies (IgG and IgM) generated in response to infection is found in blood with a concentration of 0.43–187.82 and 0.26–24.02 (chemiluminescence values divided by the cutoff), respectively.

Nanoparticles offer several advantages for bioanalytical methods that can be applied for the diagnosis of COVID-19. The large surface area of nanoparticles offers high sensitivity. Nanoparticles can be used for the preconcentration and enrichment of the low SARS-COV2 load. The surface can be modified to ensure high specificity.

Thermal scanning

Measuring a patient's body temperature using a thermometer or thermal scanner has been vastly used as one of the detection techniques for monitoring the infection of COVID-19 in public places such as airports, schools, and universities. This method can only detect elevated skin temperatures, which is different from the core body's temperature. Therefore, it lacks high precision to determine whether the individual possesses a fever or not. The body temperature can also be elevated due to other reasons such as exercise, walking, etc. Furthermore, fever is not one of the common symptoms in almost 75% of COVID-19's patients. Nanoparticles are useful for wearable electronic temperature sensors temperature-sensitive artificial skin [202].

Genetic-based analysis: PCR, RT-qPCR, LAMP, and CRISPR

The virus analysis, including SARS-CoV 2 using their genetic materials, is based on their nucleic acid analysis via amplification tests (NAATs). However, the content of the gene is usually low. Thus, there are several amplification methods, including PCR, strand displacement assay (SDA), or transcription-mediated assay (TMA). All these methods

are based on Watson–Crick base pairing based on a primer molecule (single-stranded probe) capture DNA/ RNA target molecules.

Polymerase chain reaction (PCR) is a standard method for gene analysis. It aims to amplify DNA samples to several million to billions of copies using a tiny DNA sample. The technique uses three reagents: (1) primers (a short single-strand DNA fragments (oligonucleotides) that are a complementary sequence to the target DNA region), (2) a DNA polymerase (heat-stable DNA polymerase, such as Taq polymerase), and (3) deoxynucleoside triphosphates (dNTPs, the building blocks from which the DNA polymerase synthesizes a new DNA strand). The first step of the process includes: (1) denaturation (physical separation of DNA), (2) annealing (the primers attach to each of the single-stranded DNA templates), (3) extension/elongation in which DNA polymerase synthesizes a new DNA strand via adding free dNTPs in the 5'-to-3' direction. The process is repeated n cycles to produce 2^n copies. The whole process uses 10–200 μ L in small reaction tubes (0.2–0.5 mL volumes) in a thermal cycler based on the Peltier effect. It requires a series of 20–40 repeated temperature changes, with each cycle commonly consisting of 2–3 discrete temperature steps.

Real-time quantitative reverse transcription-polymerase chain reaction (RT-qPCR) is a genetic-based method for detecting and quantifying the virus. The procedure is based on converting viral RNA to complementary DNA (cDNA) using the reverse transcription method. In real-time RT-PCR, DNA amplification is monitored in real time as the PCR progresses using a fluorescent dye, a specific DNA probe labeled with a fluorescent molecule, and a quencher molecule (such as TaqMan assays). The process is a repeated amplification process for about 40 cycles until the viral cDNA can be detected, usually by a fluorescent or electrical signal.

The diagnosis of SARS-CoV 2 using RT-qPCR involved several steps: (1) Nasopharyngeal swab (15 min): cotton swab is inserted into the nostril to absorb secretions; (2) Collecting specimen is stored at 2–8 °C for up to 72 h or proceed to; (3) RNA extraction (requires 45 min); (5) The purified RNA is reverse transcribed to cDNA and amplified by qPCR. Positive SARS-CoV 2 patients cross the threshold line within 40 cycles. The specimen for diagnosis of early infection is usually collected via a nasopharyngeal (NP) swab or an oropharyngeal (OP) swab [203, 204]. Collecting combined NP and OP specimens seems to be the most effective approach [204]. A cotton swab must be inserted deeply into the nasal cavity for 10 s. This procedure is painful. RT-qPCR was also used for the detection of SARS-COV 2 in wastewater [205].

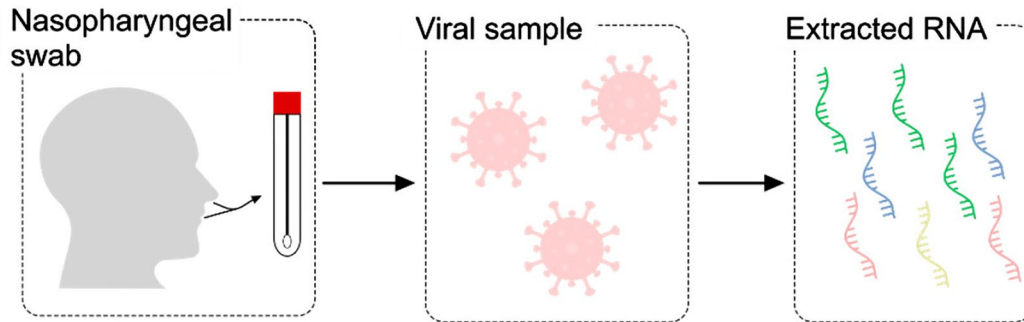
Isothermal amplification methods (e.g., recombinase polymerase amplification (RPA) and loop-mediated isothermal amplification (LAMP) were used for a nucleic acid

amplification technique. The procedure takes place at one temperature, i.e., isothermal (no need of a thermocycler), and the amplification is continuous. The sample preparation is simple and requires no complicated steps. The method offers high specificity, efficiency, and rapidity under isothermal conditions. Several point-of-care RNA detection technologies that do not require special instruments exist, including reverse transcription–RPA (RT–RPA) and reverse transcription-LAMP (RT-LAMP). The stringency of detection by these isothermal amplification methods can be improved by incorporating an additional sequence-specific detection module, such as hybridization-based fluorescent oligonucleotide probes [206].

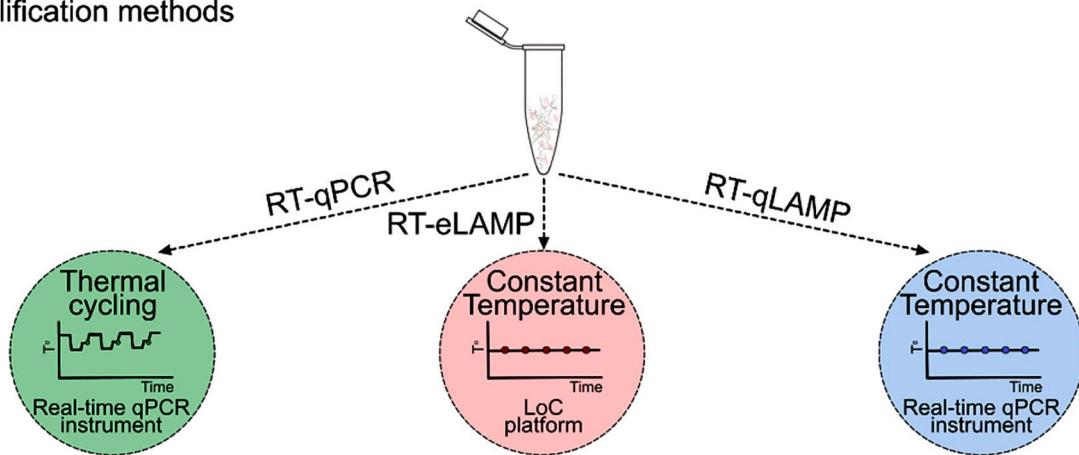
A rapid POC diagnostic test (< 20 min) based on RT-LAMP was reported using semiconductor technology (Fig. 5) [207]. The method depends on the detection of SARS-CoV 2 from an extracted RNA samples. The developed LAMP assay was tested on a real-time benchtop instrument (RT-qLAMP), showing a lower limit of detection of 10 RNA copies per reaction [207]. The results showed sensitivity and specificity of 91% and 100%, respectively, compared to RT-qPCR and average positive detection times of 15.45 ± 4.43 min (Fig. 5) [207]. Another POC diagnostic test based on microfluidic platforms was reported to detect viruses using the rolling circle amplification (RCA) method [208]. Viral samples can be detected via DNA hydrogel formation utilizing a platform of isothermal amplification of complementary targets (DhITACT) in microfluidic channels [208]. Self-assembled DNA hydrogel was briefly formed on the surface of microfluidic channels using single-stranded RCA via the isothermal amplification process [208]. These methods are promising for POC diagnosis. They can be used for public services in places such as airports, universities, and shops.

Clustered regularly interspaced short palindromic repeats (CRISPR)-based diagnostic systems were also proposed for COVID-19 diagnosis. CRISPR is a family of DNA sequences found in the genomes of prokaryotic organisms such as bacteria [209–211]. They are used to detect and destroy DNA similarly to bacteriophages during infections. Hence, these sequences play a vital role in the antiviral (i.e., anti-phage) defense system of prokaryotes. The CRISPR-Cas system is a prokaryotic immune system that confers resistance to foreign genetic elements. The CRISPR-Cas9 (CRISPR-associated) genome editing technique awards Nobel Prize in Chemistry 2020. It uses collateral cleavage activity of bystander nucleic acid probes of RNA-guided CRISPR-associated 12/13 (Cas12/13) nucleases [212]. A report incorporated RT-LAMP with CRISPR-Cas12a to detect SARS-CoV 2 in respiratory swab RNA extracts in a colorimetric lateral flow assay [213]. This method is promising and can be conjugated with well-established methods such as the colorimetric method.

A Sample collection and preparation



B Amplification methods



C Point-of-Care detection by RT-eLAMP

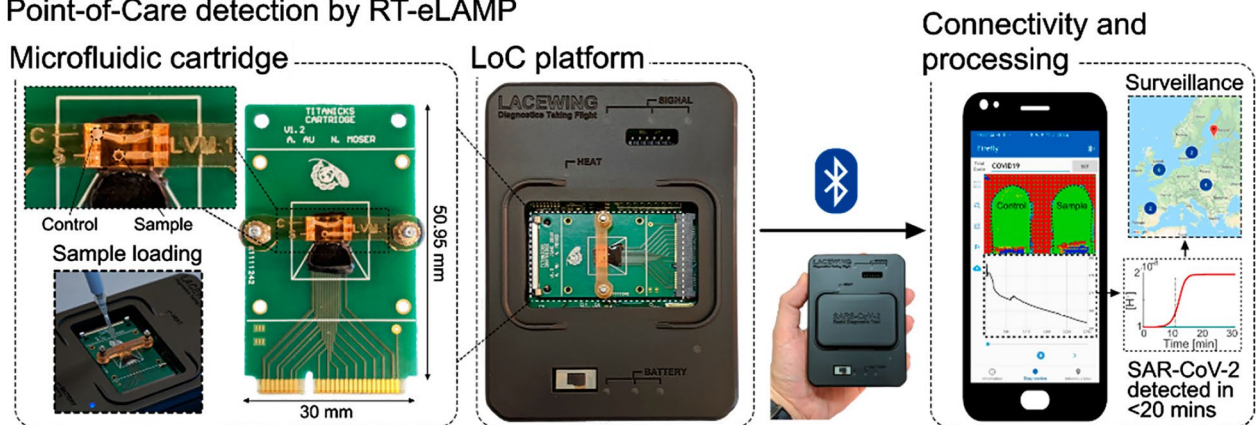


Fig. 5 Diagnosis workflow of COVID-19. Figure reprinted with permission Ref. [207]. Copyright belongs to the American Chemical Society (ACS)

Genetic-based methods exhibit several advantages. It offers high specificity. The technique is the standard protocol for the diagnosis of COVID-19. A single-tube assay RT-LAMP, CRISPRs, and the CRISPR-associated (Cas) enzyme Cas12a was recently proposed [214]. The method is simple and can be developed for POC. The technique offered high specificity, although sensitivity depends on the timing of disease presentation, sampling location, and severity of illness [203]. It usually takes about 4–24 h.

The genetic-based method is the standard method for virus analysis. However, it was reported that 20–50% of patients with SARS could not be confirmed by RT-PCR diagnostic [215]. The technique shows only sensitivities of 61–68%, 65–72%, 50–54%, and 58–63% for nasopharyngeal aspirate specimens, throat swab specimens, urine specimens, and stool specimens, respectively [215]. qPCR assay did not produce a detectable target signal in samples containing less than five copies of its amplified DNA target. Real-time

RT-PCR may lead to false-negative results due to variations in several possible factors, such as the quality of the collected specimen, the viral load, the source of the reagents, and RNA preparation steps, and fluctuations in the viral load during different phases of the process. RT-qPCR requires sample concentration and preparation. It requires thermal cycling and multiple heating and cooling. It requires various protocols with labor work. The testing procedure requires special laboratory equipment that is often located at a central laboratory. However, portable approaches based on nanopore sequencers are promising for POC detection. The analysis requires at least up to 3 days. Thus, it is a time-consuming method. The sampling is painful. However, other sample places such as tears [216] and saliva [217] were reported. The genetic-based process requires a well-known target sequence to generate the primers that will allow its selective amplification. The small amount of contaminating DNA can also be amplified, resulting in misleading or ambiguous results. The PCR amplification can also be inhibited due to environmental samples such as humic acids. RT-RPA and RT-LAMP methods suffer from nonspecific amplification under isothermal conditions, leading to false-positive results. The false-positive results are exacerbated in the presence of non-sequence-specific probes, such as pH-sensitive dyes [218].

Lateral flow assay based on CRISPR-based diagnostic systems was reported [209]. The method is rapid (<40 min), easy to implement, and showed high accuracy for the detection of SARS-CoV 2 from respiratory swab RNA extracts [213]. The process extracted the patient's sample RNA via DNA endonuclease-targeted CRISPR trans reporter (DETECTR) [219]. It depends on simultaneous extraction of RNA and detection of predefined coronavirus sequences. This method relies on a custom CRISPR Cas12a/gRNA complex that can be detected via a fluorescent probe (CRISPR-based fluorescent detection system, CRISPR-FDS) [220]. This assay showed a limit of detection (LOD) of 2 copies per sample [220]. Another method using specific high-sensitivity enzymatic reporter unlocking (SHERLOCK) assay was reported [221]. The process showed a LOD of 42 RNA copies per reaction with high specificity and sensitivity of 100% with a fluorescence readout, and 100% specific and 97% sensitive with a lateral flow readout [221].

Analysis based on nucleic acid sequencing such as nanopore sequencing was implemented for the detection of COVID-19. These techniques provide base-pair level information essential to mutation tracing and COVID-19 strain recognition [222, 223]. The method relies on electrophoretic force to translocate DNA, RNA, or protein molecules through an orifice. Nanopore sequencing is commercially available through the Oxford MiniION sequencer [224]. The two-dimensional gold nanoislands (Au NIs) functionalized with complementary DNA receptors can perform a sensitive

detection of the selected sequences from SARS-CoV 2 through nucleic acid hybridization. The thermoplasmonic heat is generated on the same Au NIs chip for better sensing performance when illuminated at their plasmonic resonance frequency. The localized PPT heat is capable of elevating the in situ hybridization temperature and facilitating the accurate discrimination of two similar gene sequences. Our dual-functional LSPR biosensor exhibits a high sensitivity toward the selected SARS-CoV 2 sequences with a lower detection limit down to the concentration of 0.22 pM. It allows precise detection of the specific target in a multi-gene mixture [225].

Analysis of nucleic acid using other bioanalytical methods was also reported. Nucleic acid-based electrochemical biosensors were developed to detect the SARS-CoV 2 via the N protein gene's detection using gold nanoparticle-modified electrodes [226]. This method showed good sensitivity. However, it requires sample preparation, such as the RNA extraction step. The plasmonic photothermal (PPT) effect and LSPR were integrated into a dual-functional plasmonic biosensor to detect nucleic acid from SARS-CoV 2 [225]. The device is a chip-based application. The method is based on the use of two-dimensional gold nanoislands (Au NIs) that can form Au-S bonds with the thiol-cDNA receptor of RdRp, ORF1ab, or the E gene sequence. The plasmonic Au NIs generated local PPT heat that promoted fast and sensitive detection of nucleic acids. Au NIs improved the hybridization kinetics of fully matching strands. The dual-functional LSPR sensing system offered selective hybridization detection toward SARS-CoV 2 and SARS-CoV 1. The method provided sensitive detection of SARS-CoV 2 sequences with a LOD of 0.22 pM [225].

An electrochemical-based method using gold nanoparticles (Au NPs) was reported for the analysis of viral nucleocapsid phosphoprotein (N-gene, Fig. 6) [226]. The surface of Au NPs was capped with highly specific antisense oligonucleotides (ssDNA) targeting to ensure high selectivity toward N-gene. The sensing probes, e.g., ssDNA@Au NPs, were immobilized on a graphene paper-based electrochemical platform. The output signals can be recorded with a simple handheld reader [226]. This method offered rapid analysis (<5 min), showed low cost, and can be easy to implement. It provided quantitative analysis with a broad linear detection range of $585.4\text{--}5.854 \times 10^7$ copies/ μL and sensitivity of 231 copies/ μL . It exhibited a LOD of 6.9 copies/ μL without the need for nucleic acid amplification [226].

An electrochemical biosensor based on RNA amplification using isothermal RCA and differential pulse voltammetry (DPV) was reported (Fig. 7) [227]. It involves 4 simple steps: (1) sample collection, (2) extraction of RNA/DNA, (3) hybridization using RCA reaction, and (4) detection (Fig. 7) [227]. The extracted RNA/DNA was purified and separated using magnetic beads coated with streptavidin. Silica nanoparticles (SiNPs) were coated with two dyes redox system

Fig. 6 Operation steps for the COVID-19 electrochemical sensing platform: (A) sample collection via the nasal swab or saliva, (B) RNA extraction, (C) immobilization of RNA extract on the top of the graphene-ssDNA-AuNP platform, (D) incubation of 5 min, and (E) record the digital electrochemical output. Figure reprinted with permission from Ref. [226]

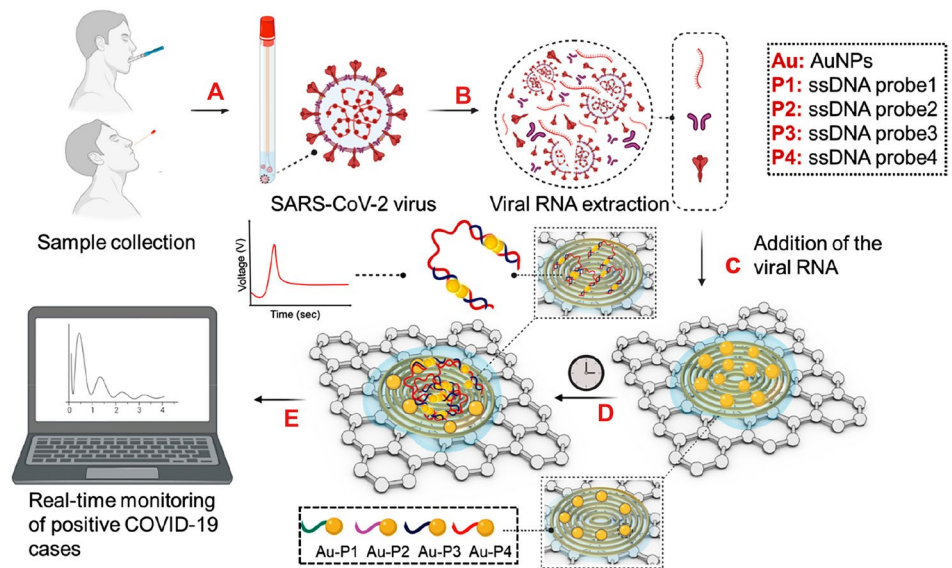
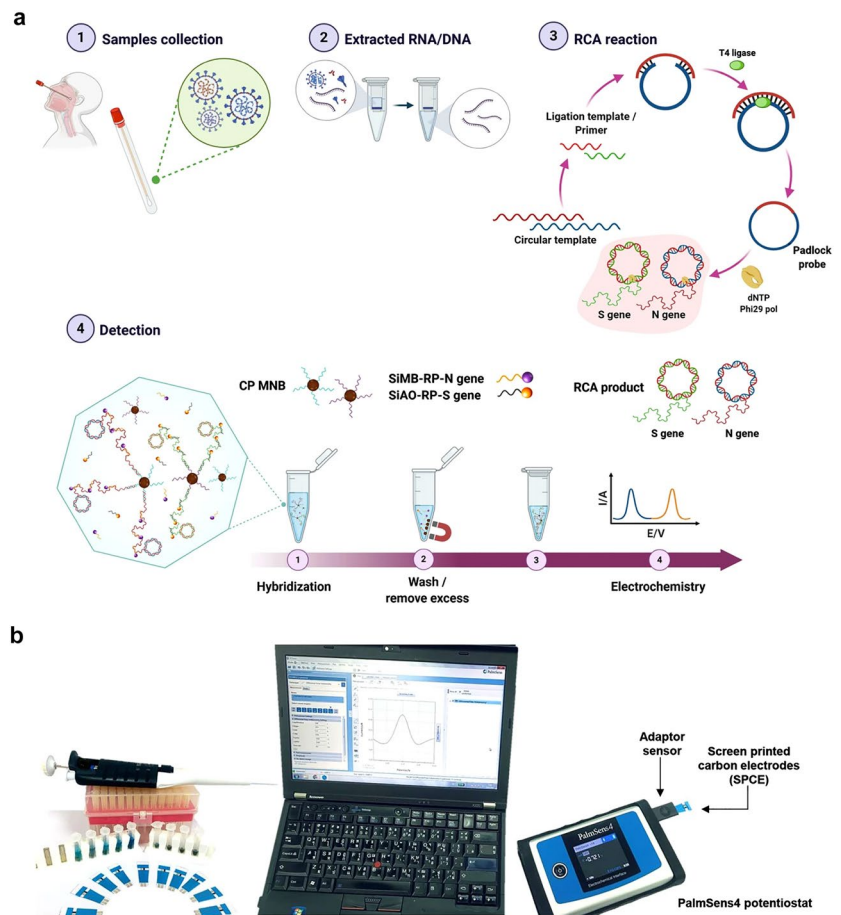


Fig. 7 a Schematic representation showing the detection workflow of SARS-CoV2 and **b** the detection setup using a portable PalmSens4 potentiostat device connected to a laptop. Figure reprinted with permission from Ref. [227]. This article is licensed under a Creative Commons Attribution 4.0 International License



of methylene blue (MB) and acridine orange (AO), producing silica-methylene blue (SiMB) and silica-acridine orange (SiAO). SiMB and SiAO were used for the electrochemical measurements using a portable potentiostat called PalmSens4 connected to a laptop. This assay offers a LOD of 1

copy/ μL of N and S genes (Fig. 7) [227]. This method is a one-step sandwich hybridization assay, rapid (2 h), sensitive, and accurate (100% concordance result with qRT-PCR). Furthermore, the potentiostat (PalmSen4) is portable, offering on-site, real-time diagnostic tests for COVID-19 [227].

Nucleic acid analysis using the colorimetric method was also reported. The plasmonic properties of nanoparticles such as Au NPs offer a simple colorimetric analysis of E gene of SARS-CoV 2 [228]. The method depends on the change of the plasmonic peak of Au NPs coated with nucleic acids for visual detection of PCR products of SARS-CoV 2 template [228]. The changes can also be observed via naked eyes [228]. This method is simple, sensitive, and can be implemented into strip-based technologies.

Antigen-bases methods

The SARS-CoV 2 antigen analysis, such as S-protein, N-protein, has been reported using different bioanalytical methods such as electrochemical bases sensors, field-effect transistors (FET). These types of procedures are well stabilized in the literature. They offered high sensitivity and selectivity. They can be easily implemented into portable devices. They did not require high experience for operation.

Electrochemical immunosensor (EC) can be used for viral analysis [229]. An electrochemical immunosensor based on an array of carbon electrodes (DEP)/Au NPs was reported to detect the recombinant on the surface of microfluidic channels [230]. Au NPs were electrodeposited into the glass carbon electrode. The layer of Au NPs immobilized S1 protein for a fixed concentration of antibody (10 $\mu\text{g}/\text{mL}$) that recognized the MERS-CoV antigen. The detection method of MERS-CoV was based on measuring the current changes for the reduction peak of the Ferro/ferricyanide redox. The reduction in the peak current was due to the electron transfer efficiency reduction due to antibody–antigen binding. The immunosensor required 20 min for the analysis and offered a LOD of 1.0 pg/mL for MERS-CoV protein with a high selectivity degree. The LOD resulted lower than the LOD of ELISA (1 ng/mL). It was successfully applied to spiked nasal samples. Electrochemical sensors offered high sensitivity compared to commercial biosensors such as SPR-based chip (BIAcore systems) for viral analysis such as Influenza virus H1N1 and Dengue virus with LOD of 1 $\mu\text{g}/\text{mL}$, and 2.125 pM, respectively [231, 232]. An electrochemical-based method using electrode-tethered sensors bearing an analyte-binding antibody was reported (Fig. 8) [233]. The surface of the electrode was modified with a negatively charged DNA linker containing a redox system (ferrocene) and antibody (anti-spike) (Fig. 8). The antibody moiety binds to the virus's S-protein, causing changes in the kinetic of transport for a DNA–antibody complex (Fig. 8). This method is reagent-free viral sensing within 5 min (Fig. 8) [233].

A cotton-tipped electrochemical immunosensor was reported for the detection of SARS-CoV 2 virus antigen (Fig. 9) [234]. The carbon nanofiber (CNF) screen-printed electrode was fabricated via diazonium electrografting

(Fig. 9). The electrode was further modified with virus nucleocapsid (N) protein using cross-linking chemistry. The changes in square wave voltammetric (SWV) technique before and after interaction can be correlated with the SARS-CoV 2 load. This method offered a LOD of 0.8 pg/mL for SARS-CoV 2 (Fig. 9) [234]. It is a sensitive, selective, and fast analysis procedure. It can also be further modified to ensure high producibility and throughput analysis. The portable PalmSen4 potentiostat was used for S-protein or N-protein detection using magnetic beads to support immunological chain and secondary antibody with alkaline phosphatase [235]. A screen-printed electrode modified with carbon black nanomaterial was used for monitoring the enzymatic byproduct 1-naphthol. This method offered LODs of 19 ng/mL and 8 ng/mL for S and N-protein, respectively [235]. This method is sensitive and required a short analysis time (30 min).

Antigen analysis can be achieved using graphene [236], and gold (Au) nanoparticles [237] via FET, and Terahertz plasmonic metasensors, respectively. A novel antibody-based biosensor using FET was reported to detect the S-protein from SARS-CoV 2 (Fig. 10) [236]. The method is based on graphene sheets coated with a specific SARS-CoV 2 antibody (Fig. 10). The technique offered a LOD of 1 fg/mL , 100 fg/mL , and 16 pfu/mL (pfu refers to plaque-forming unit) in phosphate buffer saline, universal transport medium, and culture medium, respectively. The SARS-CoV 2 FET sensor discriminated between infected and non-infected individuals with a LOD of 242 copies/mL [236]. Terahertz plasmonic metasensors using Au NPs were used for the quantitative and qualitative detection of S-protein from SARS-CoV 2 [237]. It offered a LOD of 4.2 fM [237].

Serological-based tests (SB-T)

Serological-based tests (SB-T) measure the body's immune response to the infection. They aim to the analysis of antibodies and proteins in the blood caused due to the infection by pathogens such as SARS-CoV 2. The SB-T measurements aren't related to the virus itself [238]. It is reliable to study the immune response and can be used to identify the recovery or post-infected people. It is also an invaluable test to determine the level of immunity reached in the population. The Food and Drug Administration (FDA) has approved several hundred tests, and most of them are based on molecular technology of immunoglobulin M (IgM) and IgG (Table 1) [239].

The detection of IgG and IgM in serum or whole blood has been demonstrated to be a reliable method for diagnosing COVID-19 with high specificity and sensitivity [240]. A point-of-care lateral flow immunoassay (LFIA) test using Au nanoparticles was used for the detection of IgM and IgG antibodies simultaneously against SARS-CoV 2 virus in

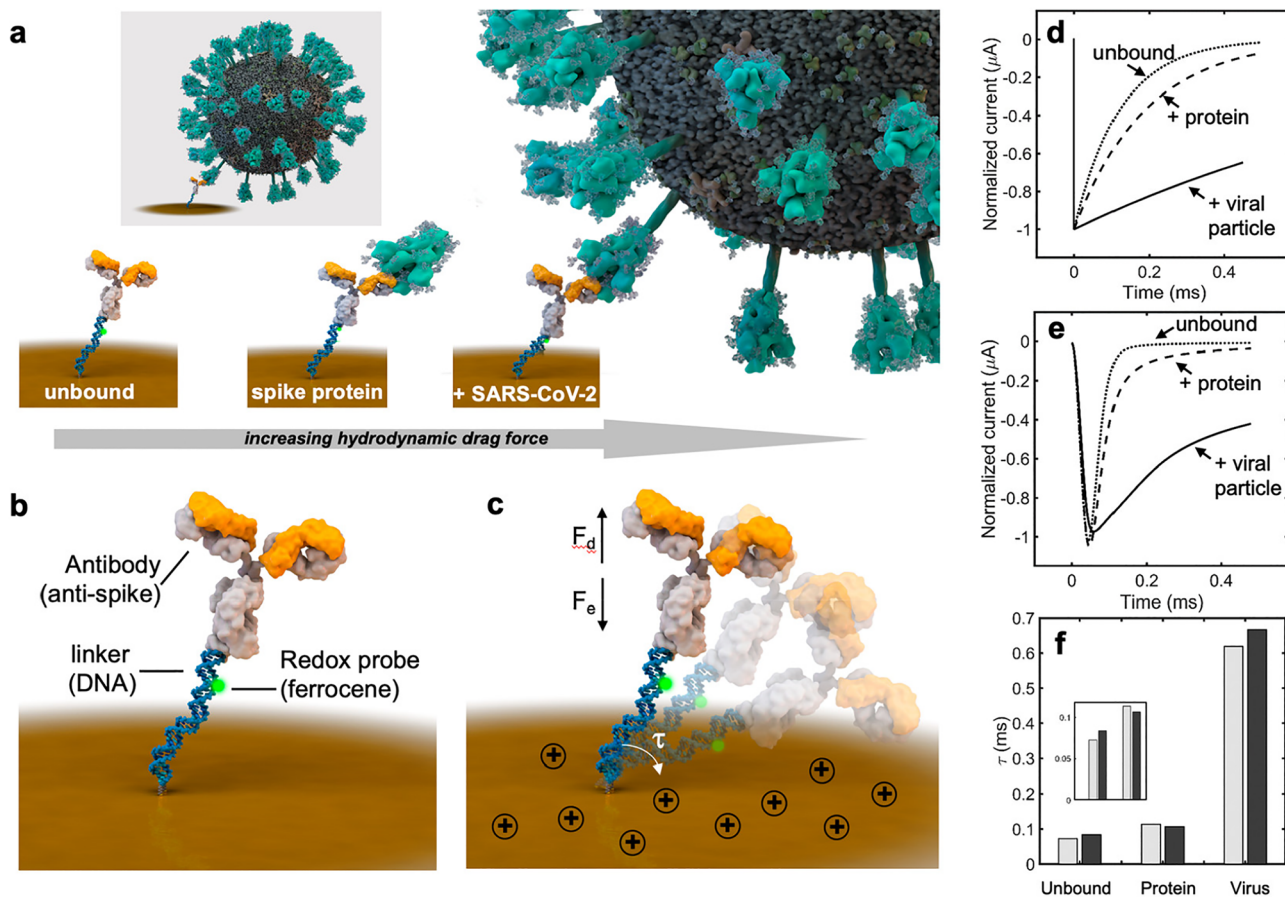
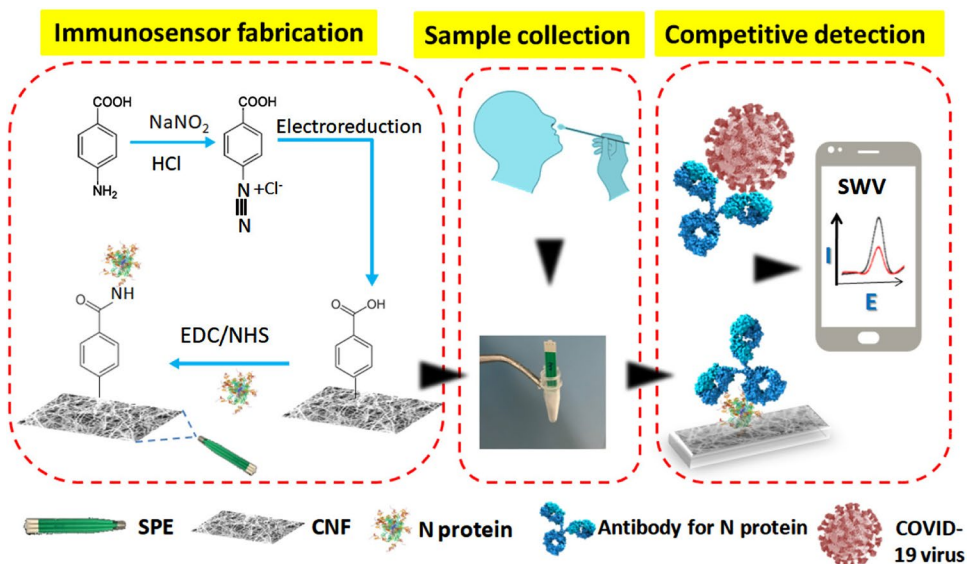


Fig. 8 An electrochemical approach for monitoring the kinetics of transport for a DNA–antibody complex. The figure was reprinted with permission from Ref. [233]. Copyrights belong to ACS, 2020

Fig. 9 Schematic of the Cotton-Tipped Electrochemical Immunosensor for COVID-19 virus. Figure reprinted with permission from Ref. [234]. Copyright belongs to ACS, 2020



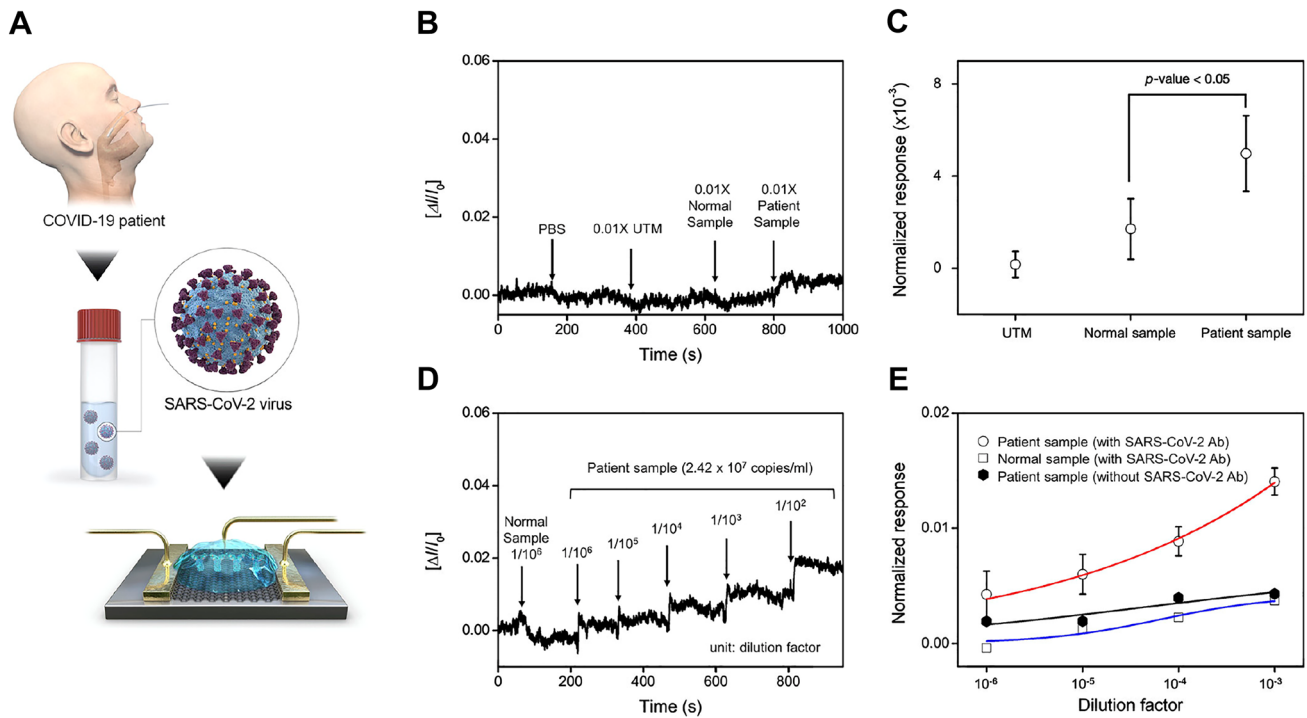


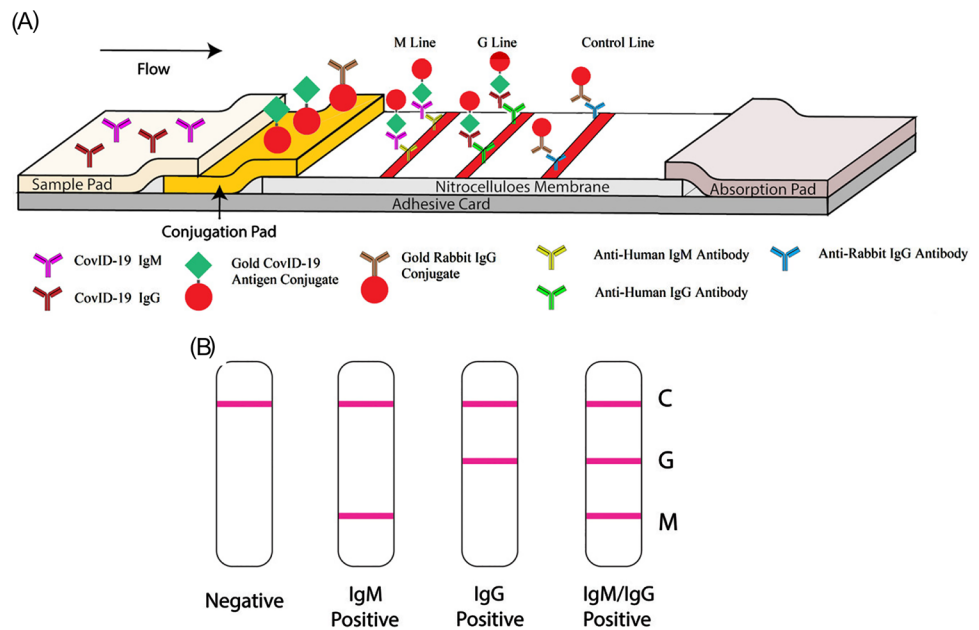
Fig. 10 (a) Detection of SARS-CoV 2 virus from clinical samples using FET sensor for detection of SAR-CoV-2 virus from COVID-19 patients, (b) Real-time response of COVID-19 FET toward COVID-19 clinical sample and (c) scatter plot and error bar graph of normal-

ized response, (d) Real-time response of FET toward the clinical sample and (e) related dose-dependent response curve. Figure reprinted with permission from Ref. [236]. Copyrights belong to ACS, 2020

Table 1 Examples of approving methods based on serological and immunological tests for SARS-CoV 2 virus

Test name	Company	Type	Sample source	Analyte	Time (min)
m2000 SARS-CoV-2 assay	Abbott Core Laboratory	Chemiluminescent micro-particle immunoassay	Serum Plasma	IgG	
COVID-19 IgG/IgM LF	Advagen Biotech	Lateral flow immunoassay	Whole blood	IgG	10
COVID-19 IgM/IgG rapid test	BioMedomics			IgM	15
COVID-19 IgG/IgM Point of Care Rapid test	Aytu Biosciences/Orient Gene Biotech				2–10
One-Step COVID-2019 test	Celer Biotechnologia				15
qSARS-CoV-2 IgG/IgM rapid test	Cellex Inc				15–20
DPP COVID-19 IgM/IgG system	Chembio Diagnostics				15
VivaDiag COVID-19 IgM/IgG rapid test	Everest Links Pte Ltd				15
COVID-19 IgG/IgM rapid test cassette	Hangzhou Biotest Biotech Co. Ltd				15–20
SARS-CoV-2 rapid test	PharmACT				20
Standard Q COVID-19 IgM/IgG Duo	SD Biosensor				10
COVID-19 Ag Respi-Strip	Coris Bioconcept		Nasal mucus swabs	Viral antigen	15
iFLASH-SARS-CoV-2-IgG/IgM	Shenzhen Yhlo Biotech Company	Immunoassay	Serum/plasma/ whole blood	IgG/IgM	
MAGLUMI IgG/IgM de 2019-nCoV (CLIA)	Snibe Diagnostic (China)	Chemiluminescence immunoassay	Serum/ plasma		30

Fig. 11 **a** Schematic illustration of a point-of-care lateral flow immunoassay (LFIA) for SARS-CoV 2 IgM-IgG combined antibody test, and **b** an illustration of different testing results; C refers to control line; G refers to IgG line; M refers to IgM line. Figure reprinted with permission from Ref. [241]. Reference [241] is an Open Access article distributed under the terms of the Creative Commons CC BY license



human blood (Fig. 11) [241]. The test strip's main body consists of five parts, including plastic backing, sample pad, conjugate pad, absorbent pad, and NC membrane (Fig. 11). The analysis using this method can be achieved within 15 min at 88.66% with a specificity of 90.63% [241]. A colorimetric method using Au NPs was also reported [242]. The analysis takes place in a solution. Au NPs were functionalized with antibodies for targeting three surface proteins of SARS-CoV 2, e.g., spike, envelope, and membrane. The detection of these proteins depends on the red-shifted SPR peak of Au NPs. The analysis requires few minutes [242]. These methods offer high sensitivity, selectivity and needed short analysis time (Table 1).

Magnetic chemiluminescence enzyme immunoassay (MCLIA) was reported for the detection of SARS-COV 2 via the analysis of IgG and IgM [240]. MCLIA showed high specificity and sensitivity in detecting serum IgG and IgM [240]. The positive rate of IgG and IgM was 71.4% and 57.2%, respectively [240]. The method exhibited high specificity compared to other respiratory pathogens, including influenza A virus, influenza B virus, parainfluenza virus, with high stability (coefficient of variation (CV) was below 6%) [240]. The serological testing using MCLIA may be helpful for the diagnosis of suspected patients with negative RT-PCR results and for the identification of asymptomatic infections [243].

A portable microfluidic immunoassay system was proposed to detect SARS-CoV 2 (Fig. 12) [244]. This method was easy to use, sensitive, rapid (< 15 min) and offered on-site detection of IgG/IgM/Antigen of SARS-CoV 2 simultaneously [244]. This method's cost is only about 5 yuan (0.71 dollars) and required only 10 min for analysis. The

analysis required a spot of 10 μ L of the specimen (blood, serum, plasma, pharyngeal swabs, alveolar lavage fluid, or fecal suspension) into the loading chamber of the microchip (Fig. 12). This was followed by the addition of sample dilution buffer (70 μ L). The biomarkers of SARS-CoV 2 (IgG/IgM/antigen) are specifically bound to the fluorescent microspheres (FMS) labeled capture antibody [244]. The method showed the detection of the virus on different days for patients. It was also approved by the Center for Medical Device Evaluation (CMDE) in China and obtained European CE certification (Fig. 12) [244]. Groltex and Sanford Burnham Prebys Medical Discovery Institute developed a graphene-based biosensor platform consisting of deposited gold nanoislands, handheld reader units, and disposable plastic testing chips [245]. The "graphene sensor chip on plastic" platform required a small biological sample and can perform up to 4 to 12 viral tests [245]. Gold nanospikes were fabricated using electrodeposition and applied for pto-microfluidic sensing platform (localized surface plasmon resonance (LSPR) and microfluidic device)[246]. The antibody concentration was correlated with the LSPR wavelength peak shift of Au nanospikes caused due to the local refractive index change because of the antigen-antibody binding [246]. This method is a label-free microfluidic platform with a LOD of 0.08 ng/mL (0.5 pM) [246].

Other methods

A functionalized magnetic nanoparticle (MNPs) using S-protein was proposed for the detection of SARS-CoV 2 using a mimic SARS-CoV 2 consisting of spike proteins and polystyrene beads (Fig. 13) [247]. The method depends

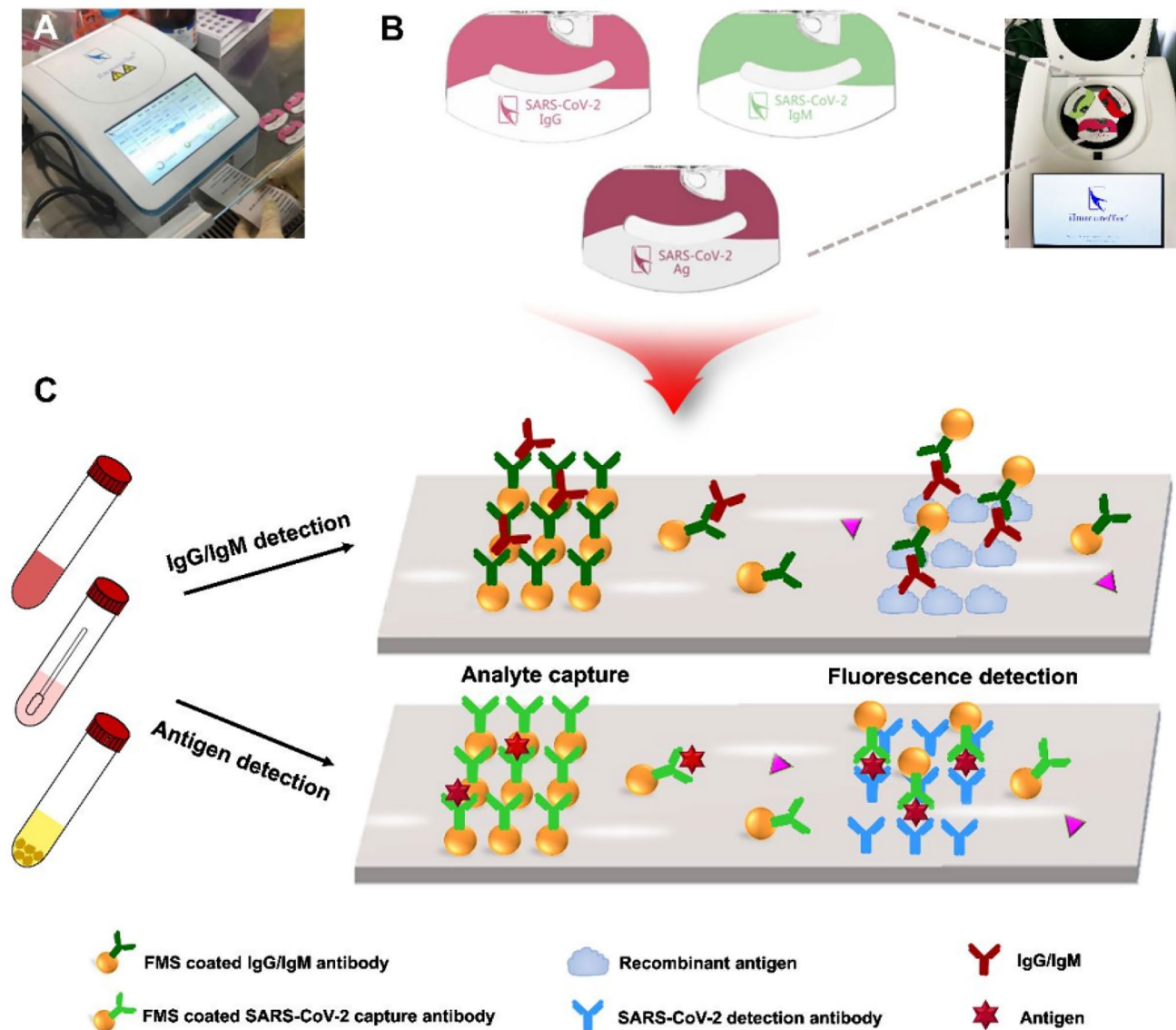


Fig. 12 (A) Photograph of the portable home-made fluorescence detection equipment; (B) photograph of the immunoassay microchip ready to use; (C) schematic illustration of the microfluidic fluores-

cence immunoassay for IgG/IgM/antigen detection of SARS CoV 2. Figure reprinted with permission from Ref. [244]. Copyright belongs to ACS, 2020

on measuring the magnetic response of MNPs in an ac magnetic field with and without the virus (Fig. 13). This method offered rapid and sensitive detection of SARS-CoV 2 with a LOD of 0.084 nM (5.9 fmoles) [247].

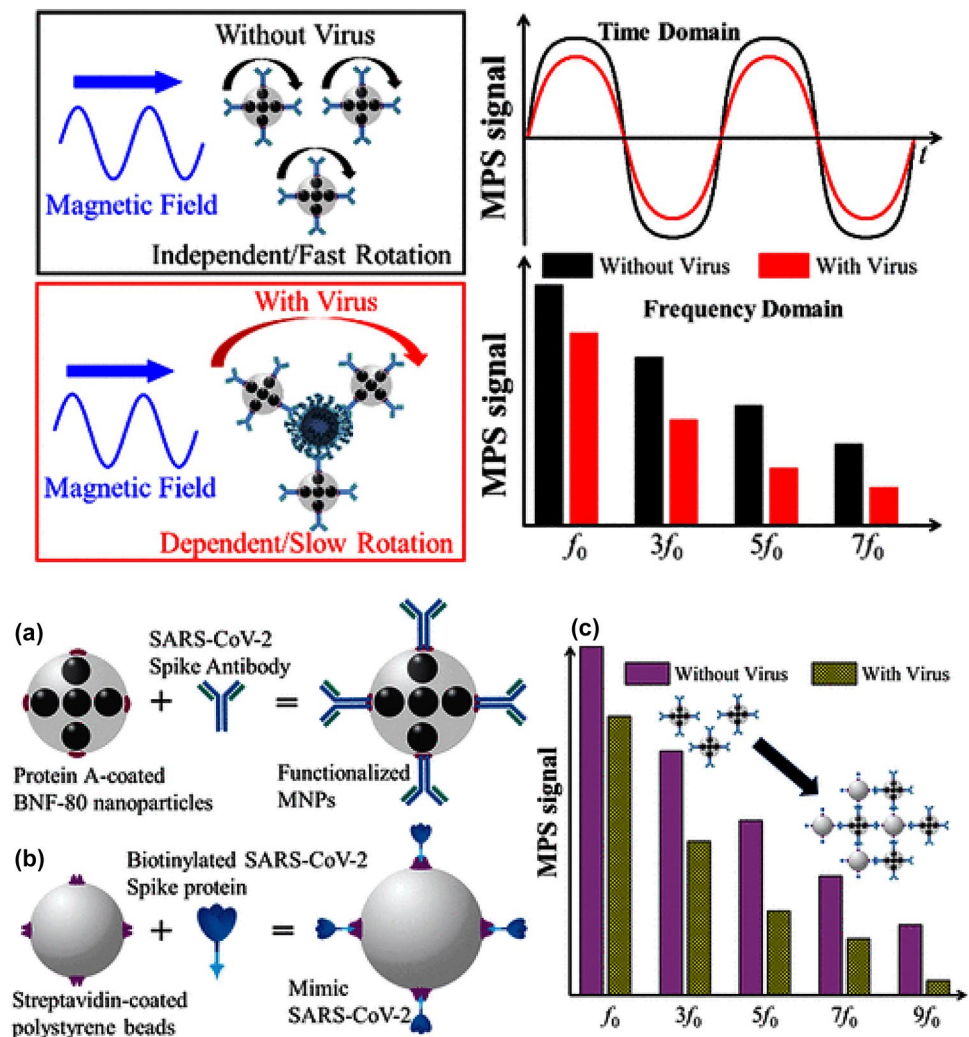
Mass spectrometry (MS) has advanced the analysis of virus [248]. MS depends on the ionization of the viral contents, e.g., protein or RNA. Soft ionization techniques such as matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) are promising for direct detection of the intact virus [25, 41, 76, 249–256]. Nanoparticles are essential as the surface for MALDI-MS, i.e., surface-assisted laser desorption/ionization mass spectrometry (SALDI-MS). The method is label-free, offering high sensitivity.

The presence of proteins such as S, E, N, and M enables simple analysis for SARS-CoV 2 using mass spectrometry [257]. Blood analysis using advanced MS-based proteomics approaches will help identify the essential protein patterns of COVID-19's patients [258].

Concluding remarks

The past investments to discover viruses, detection, and antiviral treatment have rarely been made in the past, except for very few viruses. Thus, coronavirus has several accessory proteins that seem to be essential for the

Fig. 13 Principle of magnetic field changes using (a) functionalized MNPs with and without (b) mimic SARS-CoV 2, and (c) the MPS signals response with and without mimic virus. Figure reprinted with permission from Ref. [247]. Copyright belongs to ACS, 2020



virus [100]; however, their functions aren't entirely characterized. Our knowledge about this novel virus remains very limited [94]. There are not enough nanotechnology approaches being explored to tackle the current outbreak using a sensitive diagnostic method. This task requires network coordination among pharmaceutical companies, scientists, governments, and WHO. The virus's analysis inside the body via analytical techniques such as imaging and tracking their places is highly required and essential for future threats.

The surface contamination by SARS-CoV 2 has been found to be more significant in the spread of COVID-19. The contamination of latex/nitrile gloves, N95 respirators, hospital scrubs, overshoes, and floors in a nosocomial environment has been considered a severe issue [259, 260]. It causes uncontrolled spreading of the disease and passes the infection to other patients and their families [261]. The detection of SARS-CoV 2 contamination using a simple bioanalytical method for these necessary tools is essential for protecting people in contact with infected persons. It is

supposed to control the virus's spread and alert people by the infected places and surfaces.

Serological-based tests may help diagnose suspected patients with negative RT-PCR results and identify asymptomatic infections [243]. The test is susceptible, specific, and required a short time. However, the results of these methods may be varied significantly with interferences [262]. These methods lack high accuracy for the analysis within the first days after the onset of disease [263]. Computed tomography imaging, whole-genome sequencing, and electron microscopy are more precise [264]. A study indicated that an initial chest CT has a higher detection rate (98%) compared to reverse transcriptase-polymerase chain reaction (RT-PCR) (70%) in infected patients. Analysis using genetic-based methods such as PCR demonstrated that about 3% of patients have no primary positive RT-PCR but have a positive chest CT; therefore, both tests are recommended for COVID-19 patients [265]. Electrochemical-based methods conjugated nanotechnology is promising for several reasons [266].

Table 2 Examples for FDA-approved handheld tests for COVID-19

Device	Company	Sample Collection	Biomarker	LOD	References
PerkinElmer New Coronavirus Nucleic Acid Detection Kit	PerkinElmer, Inc	OPS, NPS	Nucleic acid	3 cp/rxn (50 cp/mL)	[273]
Quest SARSCoV-2 rRT-PCR	Quest Diagnostics Infectious Disease, Inc	NPS, NS, NW, BAL		3.4 cp/rxn (136 cp/mL)	[274]
1copy™ COVID-19 qPCR Multi Kit	1drop Inc	NPS, OPS		4 cp/rxn (200 cp/mL)	[275]
COVID-19 Genesig RealTime PCR Assay	Primerdesign Ltd	NPS, OPS, BAL		6.6 cp/rxn (330 cp/ mL)	[276]
Xpert® Xpress SARS-CoV-2	Cepheid	NPS NW		75 cp/rxn (250 cp/mL)	[277]
BioFire® COVID-19 Test FilmArray	Biofire defense, LLC	NPS NW		1155–1815 cp/rxn (330 cp/mL)	[278]
AvellinoCoV2 Test	Avellino Lab USA, Inc	NPS, OPS		275 cp/rxn (55,000 cp/mL)	[279]
Simplexa COVID-19 Direct Assay	DiaSorin Molecular LLC	NPS, NS, NW, BAL		25 cp/rxn (500 cp/mL (NPS)), 12.1 cp/rxn (242 cp/mL (NS)), 25 cp/rxn (500 cp/mL (NW)), 60.4 cp/rxn (1208 cp/mL (BAL))	[280]
Abbott Real Time SARS-CoV-2 Assay	Abbott Diagnostics Inc	OPS, NPS		100 cp/mL	[281]
NeoPlex COVID-19 Detection Kit	GeneMatrix	NS, NPS, OPS		50 cp/rxn (2500 cp/ mL)	[282]
COVID-19- RT-qPCR Detection Kit	Gnomegen LLC	NPS, OPS		10 cp/rxn (666 cp/mL)	[283]
Quick SARSCoV-2rRT-PCR Kit	Zymo Research Co	NS, NPS, OPS		15 cp/rxn(250 cp/mL)	[284]
OPTI SARSCoV-2 RT PCR Test	OPTI Medical Systems, Inc	NPS, Sp		17.5 cp/rxn (700 cp/mL (sputum) 22.5 cp/rxn (900 cp/mL (NP)	[285]
FTD SARSCoV-2 ePlex SARSCoV-2 Test	Siemens Healthineers GenMark Dx	NS, NPS, OPS NS, NPS, OPS		0.0023 TCID50/mL 200 cp/rxn (1000 cp/mL)	[286] [287]
Panther Fusion SARS-CoV-2 Assay	Hologic, Inc	NS, OS, NW		1×10^{-2} TCID50/mL	[288]
Aptima SARS-CoV-2 Assay	Hologic, Inc	NP, OP		324 cp/rxn (83 cp/mL)	[289]
ID NOW COVID-19	Abbott Diagnostics Inc	NS, NPS, TS		25 cp/rxn (125 cp/mL)	[290]
Accula™ SARS-Cov-2 Test	Mesa Biotech Inc	NS, TS		200 cp/rxn (3300 cp/mL),	[291]
Sherlock CRISPR SARS-CoV-2	Sherlock Biosciences	BAL NS, NPS, OPS, NW	ORF1ab and N genes	17.5 cp/rxn (700 cp/mL (sputum) 22.5 cp/rxn (900 cp/mL (NP)	[291]
Sofia SARS Antigen FIA	Quidel Corp	NS, NPS	Nucleocapsid protein antigen	113 TCID50 / mL	[292]
Elecsys IL-6 Immunoassay	Roche Diagnostics	Plasma or serum	IL-6	1.5 pg/mL	[293]

cp: copies; rxn: reaction; NPS: nasopharyngeal swabs; TS: throat swabs; OPS: oropharyngeal swab; NS: nasal swabs; NW: nasal wash/aspirate; BAL: bronchoalveolar lavage; Sp: sputum

They can be used for gene detection of (1) gene such as nucleocapsid phosphoprotein (N-gene) [226], RdRp gene [267]; (2) antigen [234]; and (3) antibodies. The method

can be easily implemented into portable devices offering simple operation and on-site detection [227].

Nanotechnology may help to improve diagnosis [268, 269] using techniques such as advanced POCT (point of care tests) approaches [139]. The future development of portable microfluidic-based cartridges and lyophilized reagents to run the assay could enable POCT outside of the clinical diagnostic laboratory, such as airports, local emergency departments, and other clinic locations [270]. US Food and Drug Administration (FDA) approved several handheld methods for detecting COVID-19 (Table 2). The approved devices depend on the analysis of nucleic acid [271], biomarker IL-6 and CRP [272]. However, they are still costly and lack to quantify the total viral load in the infected person. There is no standard value to represent the viral load.

The sample collection and data analysis require careful investigation. There is no test with complete accuracy (100%) all of the time. Several things may affect the test's accuracy. A person may have the virus infection, but the swab might not collect the virus from the nose or throat due to short contact time or low viral load. The virus may be present due to accidental contamination during sample collection, storage, or analysis. The storage conditions may also destroy the virus due to incorrect temperature or contamination with a disinfectant such as alcohol. The process and chemicals used during the analysis or sample preparation, such as RNA extraction, may affect the test result. These points should be considered during sample collection, storage, and analysis.

Nanotechnology can advance the diagnosis of COVID-19 and offer an advanced diagnostic approach based on a POC sensing technology [294]. It can be interfaced with the Internet of things artificial intelligence (AI) techniques, [295], and internet of medical things (IoMT)-integrated biosensors [296] for investigating practical informatics via data storage, sharing, and analytics. They can circumvent conventional techniques such as low sensitivity, low selectivity, high cost, and long diagnostic time [297]. They can be used for no pain sample analysis, such as the analysis of patient's saliva using graphene oxide (GO)/Au/Fiber Bragg grating (FBG) probe [298]. Nanotechnology can be used to advance technologies such as paper lateral flow assays [299], label-free biosensors [300–302], optical technologies [160, 303], and digital technologies [304].

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Declarations

Conflicts of interest The authors declare no competing financial interests.

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