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Review

Rapid diagnostics of coronavirus disease 2019 in early stages using nanobiosensors: Challenges and opportunities

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ABSTRACT

The rapid outbreak of coronavirus disease 2019 (COVID-19) around the world is a tragic and shocking event that demonstrates the unpreparedness of humans to develop quick diagnostic platforms for novel infectious diseases. In fact, statistical reports of diagnostic tools show that their accuracy, specificity and sensitivity in the detection of COVID hampered by some challenges that can be eliminated by using nanoparticles (NPs). In this study, we aimed to present an overview on the most important ways to diagnose different kinds of viruses followed by the introduction of nanobiosensors. Afterward, some methods of COVID-19 detection such as imaging, laboratory and kit-based diagnostic tests are surveyed. Furthermore, nucleic acids/protein- and immunoglobulin (Ig)-based nanobiosensors for the COVID-19 detection infection are reviewed. Finally, current challenges and future perspective for the development of diagnostic or monitoring technologies in the control of COVID-19 are discussed to persuade the scientists in advancing their technologies beyond imagination. In conclusion, it can be deduced that as rapid COVID-19 detection infection can play a vital role in disease control and treatment, this review may be of great help for controlling the COVID-19 outbreak by providing some necessary information for the development of portable, accurate, selectable and simple nanobiosensors.

1. Introduction

Viruses are important pathogens that dramatically increase the rate of mortality and adverse environmental conditions in the world. The inherent nature of viruses in rapid transmission and lack of efficient primary controls make their rapid detection one of the most important strategies in controlling and treating viral diseases. Currently, respiratory infections from viruses are a major cause of death among humans, which impose huge psychological, financial and social costs on countries. For example, in 9 months from December 2019 up to date, Coronavirus Disease 2019 (COVID-19) has developed in more than 203 countries with more than 32.3 million cases and more than 965,000 deaths with approximately 2.98% of fatality rate. Despite the low lethality of COVID-19 (below 3% with a range of 2–12% in different countries) compared to Middle East Respiratory Syndrome-coronavirus (MERS-CoV) (~40%) and Acute Severe Respiratory Syndrome-CoV (SARS-CoV) (~15%) [1], the rate of diagnosis and follow-up in the community should be increased due to the widespread prevalence and targeting many people with underlying diseases, to prevent further death and the possible unknown side effects. For example, late diagnoses in the USA, Italy, Spain, UK, India, Turkey, South America countries, Iran, Germany, and China have increased the mortality rates among people. Therefore, in addition to quarantine for preventing the transmission of the disease, one of the most important cases in COVID-19

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control and management is the rapid diagnosis of the COVID-19. Despite laboratory different methods in detecting CoV such as immunofluorescence and enzyme enzyme-linked immunosorbent assays (ELISA) [2], protein assay [3], viral plaque assay [4], hem-agglutination assay [5], and viral flow cytometry [6] due to lack of expertise, high cost, lack of sufficient time and laboratory limitations around the world, the use of new diagnostic methods based on portable kits such as nanobiosensors and ELIZA kits can reduce diagnostic limitations for control and treatment. For instance, Zuo, et al. [7] based on the binding of polyclonal antibodies to the level of piezoelectric crystals through protein A, were able to detect SARS-associated CoV in the range of 0.6–4 μg/mL less than 2 min. Also, Huang, et al. [8] were able to diagnose SARS-CoV based on the detection of nucleocapsid protein N by the development a localized surface plasmon coupled fluorescence fiber-optic biosensor with limit of detection (LOD) ~1 pg/mL in a linear range of 0.1 pg/mL to 1 ng/mL. In addition, based on silicon oxide optical biochips, Koo, et al. [9] enhanced the MERS-CoV detection level by 10 times the PCR method by amplifying and detecting the viral RNA without a labelling. In this regard, Layqah and Eissa [10], by producing electrochemical immunosensor based on gold (Au) NPs on a carbon electrode, were able to provide the LOD of MERS-CoV by less than 1.0 pg/mL with a best linear response between 0.001 and 100 ng/mL, in addition to reducing the detection time by 20 min.

Since a mutant CoV with a higher pathogenic power is expected to be identified in the world, it is necessary to provide the necessary preparation for the production of diagnostic nanobiosensors, which, in addition to rapid detection of CoVs, make it easy to transfer them to all parts of the world. In this paper, in addition to an overview on the clinical diagnosis of CoV, an attempt is made to provide an appropriate survey on the development of COVID-19 nanobiosensors. Therefore, it is hoped that this paper will provide sufficient incentive to develop diagnostic COVID-19.

1.1. History

The oldest and most important way to diagnose viruses since 1950 is to cultivate them [11]. Although this method is very accurate and sensitive, the result of this method lasts for several days. On the other hand, cultivating some viruses is very difficult and sometimes dangerous. Since 1980, with the introduction of immunoassay and PCR, the detection of viruses based on cultivation has entered a new phase of diagnosis [12]. Other techniques for detecting viruses include of protein-based capsid properties, antigens, receptors at the virus, and nucleic acids such as enzyme-linked immunosorbent assay, immunoprecipitation assay, hem-agglutination assay, immunofluorescence assay, chemiluminescent immunoassay, radioimmunoassay, immunostaining, single radial hemolysis, immunoblotting assay, and so on, which have some disadvantages including expensive apparatus, non-portable laboratory equipment, and time-consuming processes. Furthermore, the accuracy and reliability of the above-mentioned serological methods are challenged by the cross-reactivity of antibodies due to their highly positive false results and the diagnosis in the late stages of infection. Hence the development of nanomaterial-based biosensors for virus detection is considered. Therefore, the use of nanomaterials in virus detection began in 1990 and was used to detect human papillomavirus in cervical cells [13]. At present, there are various reports of the use of nanomaterials in the diagnosis of viruses, especially CoV, which in addition to increasing the accuracy of diagnosis, they have accelerated the process of virus diagnosis (Table 1). However, in order to improve the detection of viruses, it is recommended that nanomaterials be incorporated with specific biological compounds provided from the target virus.

1.2. Nanobiosensors

Briefly, a biosensor can be defined as a bio-receptor for measurement, and a signal transducer for the production of physical signals such as optical, electrical, thermal, and mechanical from biological changes [32,33]. In this regard, the biosensor needs to be independent of physical parameters such as temperature and pH [34]. The most common method of biosensors function in medical activities is based on antigen-antibody interaction, nucleic acid interaction (two complementary strands), enzymatic interaction (enzyme-substrate), cellular interaction (microorganisms, proteins), and the interaction of biomimetic materials [35,36]. However, all of the methods have very important challenges including reducing LOD, increasing signal-to-noise ratio and very low concentrations of the compounds under evaluation. Therefore, not only downsizing the device is very important for having a portable system, but also the improvement of the device performance by increasing the contact surface with the reaction agent via nanomaterials has been highly considered. Therefore, the use of nanomaterials to reduce these challenges in the construction of CoV diagnostic biosensors is recommended. In this regard, the arrangement or composition of nanomaterials used in nanobiosensors as well as the measurement method will be of great importance [37]. In recent years, various nanobiosensors especially electrochemical and optical nanobiosensors have been designed for developing a multi-platform approach for the detection of microorganisms [38]. In addition to these two methods, the use of thermal and mechanical nanobiosensors has also been effective in detecting immunogenic agents [39]. In general, the advantages of nanobiosensors-based diagnostic methods over conventional methods are: low cost; reproducibility; rapid measurements, reusable; suitable for enzyme loading; no need for calibration, appropriate for mass production, possibility of miniaturization, reducing power consumption due to voltage reduction, enabled label-free recognition, and upper signal-to-noise ratio [32,33,35].

Table 1
Summary of used nanobiosensors in virus detection.

Viruses	Nanoplatform	LOD	Range of detection	Ref (s).
Hepatitis				
HAV	ssDNA/AuNPs	0.65 pM	10 fg/μL-10 pg/μL	[14]
HBV	Silver nanocluster- MoS_2 nanosheet	10.7 nM	5–30 nM	[15]
HBV	Indium Tin oxide nanowires	1 fM	1 fM-10 μM	[16]
HCV	Carbon nanotube-Cobalt NPs	8.82 × 10^{-10} M	1.0 nM-12 μM	[17]
Human immunodeficiency				
	Antibody-graphene	100 fg/mL	1 fg/mL-1 μg/mL	[18]
	AuNPs	0.1 pg/mL	1000–0.1 pg/mL	[19]
	Copper sulfide nanoplate	25 pM	0.05–1 nM	[20]
Ebola				
	ssDNA- AuNPs	4.7 nM	–	[21]
	Graphene oxide- AuNPs	1 ng/mL	1–400 ng/mL	[22]
Influenza				
H1N1	Peptide-functionalized polydiacetylene	10^5 PFU	–	[23]
H5N1	AuNPs	40–0.1 ng	100–0.1 ng	[24]
H5N1	Magnetic	1.0 nM	–	[25]
Herpes				
HSV-1	Carboxymethyl-dextran polymer sensor chips	5.2 × 10^{-11} M	5.2 × 10^{-11}–1.3 × 10^{-7} M	[26]
KSHV	AuNPs	~1 nM	1 Mm-10 pM	[27]
HHV-5	Zinc–silver nanoblooms	97 copies/mL	113-10^3 copies/mL	[28]
Human papilloma				
	Carbon nano-onions	0.5 nM	0.5–20 nM	[29]
	Au nanosheets	0.15 pM	1 pM-1 μM	[30]
	Au nanotubes	1 fM	0.01 pM-1 μM	[31]

2. CoV detection

Despite the diverse techniques used to diagnose viruses, the most common diagnostic methods are still expensive, need well-developed

equipment, and require high-skill monitoring. In summary, COVID-19 diagnosis methods, regardless of symptoms, include imaging of the respiratory tract, laboratory methods, and diagnostic kits.

2.1. Clinical presentation of COVID-19

The World Health Organization (WHO) published that all ages, from infancy to old age, are susceptible to COVID-19. After the transmission of COVID-19 through contact with contaminated objects or coughing and sneezing, the The incubation period of COVID-19 is between 3 to 14 days without clinical symptoms [40]. Although 80–85% of people do not have a clinical features, or have a subclinical presentation, identifying COVID-19 within the golden time through laboratory tests, in addition to preventing its transmission to other people, can increase the recovery rate of patients. According to scientific reports, the clinical of people with COVID-19 based on the condition of the disease includes fever, cough, sore throat, headache, fatigue or myalgia, shortness of breath, conjunctivitis, pneumonia, dysfunction of several organs especially the liver, respiratory failure, and eventually death (Table 2) [41]. However, the clinical presentations of COVID-19 from fever to shortness of breath are a common symptom among patients with colds, influenza, and respiratory problems. Therefore, in the early stages of the disease without clinical symptoms and in the second stage of the disease with the clinical presentations, it is not possible to diagnose COVID-19 without laboratory tests.

2.2. Imaging testing

In addition to the symptoms of the disease in patients, it is possible to diagnose the COVID-19 based on imaging of the respiratory tract and comparing it with the normal condition and even other respiratory diseases. In this method, a chest radiograph or CT imaging of patients shows a bilateral pulmonary opacity and infiltrates based on the stage of the disease (Fig. 1A and B), while at the beginning of the disease the lung condition can be observed normally. For instance, the results of Ai et al. [49] showed that the sensitivity and accuracy of COVID-19 diagnosis through radiology technique are 97% and 68% compared to PCR as a reference method. Therefore, the use of imaging methods in the early diagnosis of COVID-19 seems desirable due to lower cost, rapid processing, lack of aggressive activities, and lack of sampling error. However, this strategy is associated with difficulties in examining the COVID-9 infection, which has reduced its apparent efficiency in diagnostic platforms such as a high coefficient of disease transmission, the existence of comparable samples, and high dependence on the quality of imaging equipment. For example, Guan, et al. [50] reported that the sensitivity of CT samples in the COVID-19 detection compared to the PCR reference method was 76%, which could be related to the quality of imaging tools. Overall, imaging techniques can be a viable alternative to diagnostic platforms in emergency conditions and allow for continuous monitoring of the patients to control and prevent COIVD-19 infection.

Table 2
Clinical characteristic of COVID-19 in patients.

Ref.	Percentage of symptoms in patients of COVID-19					
	Fever	Cough	Myalgia or fatigue	Headache	Dyspnoea	Diarrhea
Bhatraju et al. [41]	50.1	23.8	–	25.1	–	23.5
Huang et al. [42]	97.6	75.6	43.9	7.3	53.7	2.4
Chen et al. [43]	82.8	81.8	11.1	8.1	31.3	2.0
Wang et al. [44]	98.6	59.4	100	6.5	31.2	10.1
Yang et al. [45]	98.1	76.9	76.9	11.5	63.5	–
Team [46]	93.3	73.3	–	–	–	–
Feng et al. [47]	33.3	6.7	–	–	–	–
Liang et al. [48]	–	–	–	–	–	–

2.3. Laboratory testing

In addition to imaging techniques, the study of changes in blood parameters is used as an auxiliary method in the diagnosis of COVID-19. In this regard, hospital reports and published studies show that the levels of procalcitonin, C-reactive protein, lactate dehydrogenase, D-dimer, cTnI, and serum amyloid A are significantly increased in most patients with COVID-19 infection [51–54]. Also, with the presence of the COVID-19 infection, the number of white blood cells and neutrophils along with liver enzymes increases, whereas the amount of lymphocytes decreases significantly [52,53,55]. In addition, despite rising erythrocyte sedimentation rates, reports indicate a decrease in red blood cells and hemoglobin levels [51,54,55]. Despite the reported changes in blood parameters, due to the influence of health statues or different diseases on these parameters, it is not possible to prove that some specific changes in biochemical parameters induced by COVID-19 infection. However, laboratory tests are considered as relatively convenient and simple platforms in the early diagnosis of patients with clinical symptoms.

2.4. Kit-based diagnosis

The use of diagnostic kits based on nucleic acid is among the most highly sensitive methods for detecting viruses and bacteria. Although each of the immunoassay and polymerase chain reaction (PCR) strategies have advantages and disadvantages in virus detection, the nucleic acid assay is a gold standard in the detection of a wide range of infections.

2.4.1. COVID-19 nucleic acid testing

Briefly, CoV RNA by reverse transcription is transferred into cDNA. Then, the PCR is carried out and pursued by the PCR product detection (Fig. 1C). The use of gel visualization and sequencing after PCR are the current methods for the SARS-CoV-2 detection [56]. Although the detection of CoVs by PCR is more reliable due to its high sensitivity to other techniques, the use of this method in controlling and investigating the prevalence of the disease and clinical activities show some disadvantages such as high costs, time-consuming diagnostic process and the need for developed equipments. However, common methods in this strategy include conventional PCR, real-time reverse transcriptase-PCR (RT-PCR), and loop-mediated isothermal amplification (LAMP) methods [57] which have improved LOD of virus. In accordance with the principles of PCR, in the single RT-PCR process (a single tube is applied for the RT-PCR process), heat and reverse transcription release are performed during DNA reverse transcription, which can provide higher amplification speed, less contamination of samples, and sensitivity [58]. Therefore, using real time RT-PCR technique compared to real time PCR, in addition to simplicity of work, lead to a rapid and early diagnosis of COVID-19. In this field, Yip, et al. [59] by applying RT-PCR technique with two TaqMan probes instead of one probe, improved the accuracy and precision of SARS-CoV detection up to several times (1 copy RNA per reaction). While, Yu, et al. [60], in addition to simplifying the RT-PCR technique, showed that using real-time RT-PCR technique is able to identify SARS-CoV with a diagnosis of 10 copies/mL. Likewise, the findings of Corman et al. [61] using E gene and RdRp gene assays based on RT-PCR technique showed that the best diagnosis for COVID-19 included 3.9 copies per reaction for the E gene assay and 3.6 copies per reaction for the RdRp assay without cross-reaction with other

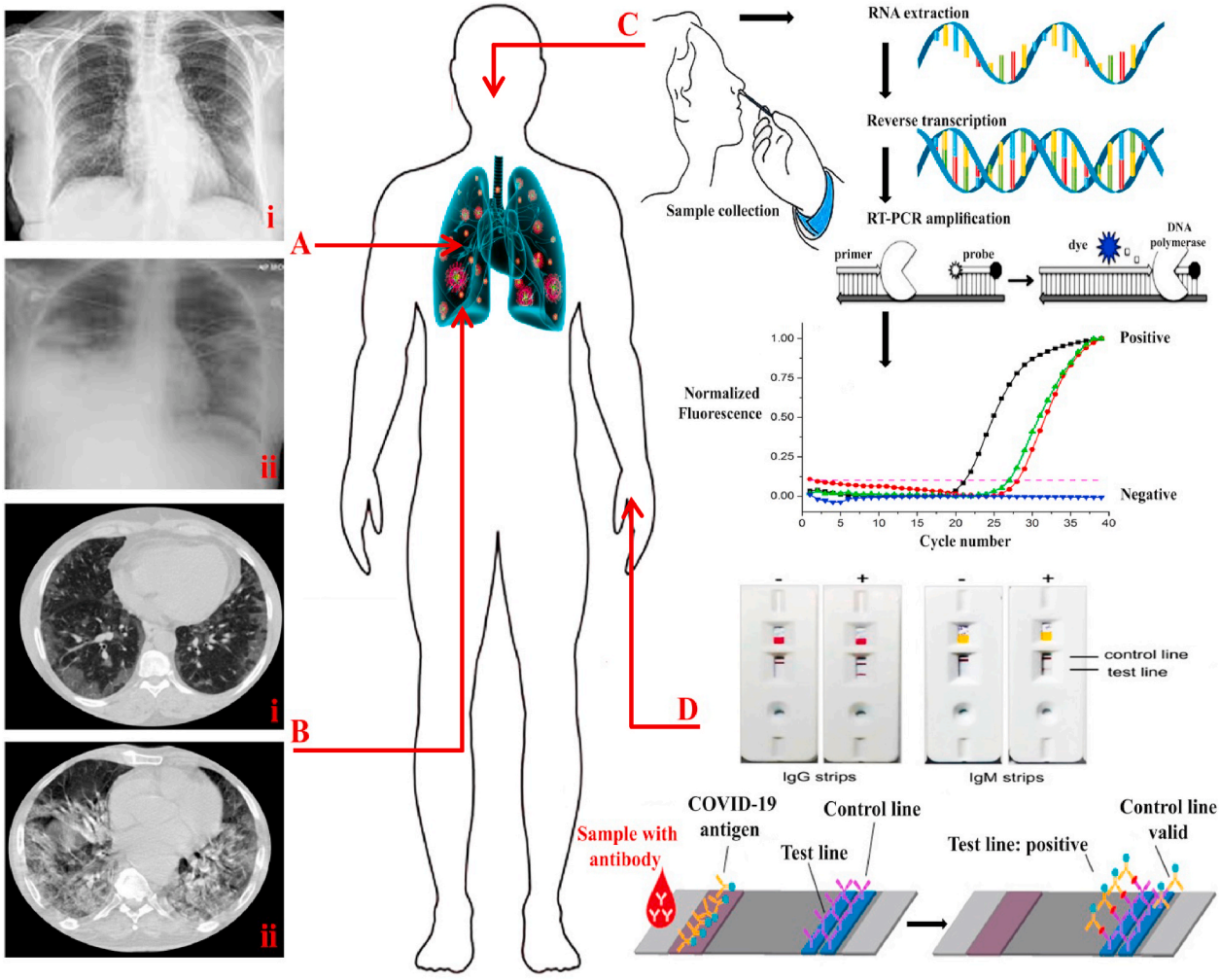

Fig. 1. (A) Chest radiograph on the sixth (i) and sixteenth (ii) days after the onset of COVID-19. (B) i: Chest CT showing the initial progression of COVID-19 (sixth days) in the left lower lobe. ii: Repeated chest CT in sixteenth days after the onset of COVID-19. (C): RT-PCR testing steps: A sample is taken from a person's nose or throat and RNA is extracted and transcribed into complementary DNA (cDNA). In the next step, the primers bind to the DNA and provide the starting point for DNA polymerase. Then, the DNA polymerase breaks down the probe and leads to an increase in the fluorescence signal. If the fluorescence level exceeds the threshold, the test result is positive. (D): A schematic of a COVID-19 lateral flow test by cassette made of filter paper and nitrocellulose that is based on the antigen-antibody binding; it determines the level of IgM and IgG.

CoVs. Also, studies by Wang et al. [44], Li, et al. [62], Chen, et al. [43] and Liang et al. [48] with a quality score of 19 (138 patients), 19 (425 patients), 19 (99 patients) and 17 (1590 patients) out of 20, respectively, confirmed that the use of RT-PCR technique is a golden way in diagnosing COVID-19. Although the use of the nucleic acids in the diagnosis of COVID-19 along with other studies mentioned in Table 3 has been successful, rapid and unpredictable mutations in COVID-19, the use of these techniques, especially based on previous methods, is doubtful. For example, despite confirmation of COVID-19 disease through imaging, clinical and laboratory symptoms, 25 to 40% of PCR tests results are negative, which can be related to sampling time and target [49,63]. For example, Chan, et al. [63] in clinical trials on COVID-19 definite patients showed that changing the source of samples from saliva (59/72 (81.9%)) to sputum (13/14 (92.9%)) increases the accuracy of diagnosis. In addition, non-pulmonary sources such as plasma (10/87 (11.5%)) and urine (0/33 (0.0%)) showed the lowest accuracy of the test compared to pulmonary sources [63].

The LAMP method is a much simpler, faster (2.5–3.0 folds), more sensitive (10–100 times) and even more efficient method in detecting viruses than PCR methods, which can be performed without complex and expensive experimental equipments [68–70]. The results obtained in this technique can be easily repeated and due to the use of a single-stage test tube in less than 50 min, it has a high speed and

Table 3
Commercial rapid diagnostic RT-PCR kits for COVID-19.

Company	Tests	Sensitivity	Specificity	Country
GENESIG [64]	RT-PCR Kit MasterMix and q16 reaction tubes. PCR MasterMix Kit.	Sensitive to <100 copies of target	High but lack of statistic	U·K.
Co-Diagnostics [65].	Commercial Kit. RT-PCR Kit.	High but lack of statistic	Claims with lower false positive	U·S.A.
BGI [66].	Fluorescent RT-PCR kit. In vitro RT-PCR combining fluorescent probing.	–	–	China
Altona-Diagnostics [67].	Commercial Kit. RT-PCR Kit.	–	–	Germany

efficiency in diagnosis [68]. However, the high sensitivity of LAMP method can show many false positive outcomes resulting from Trans and Cis priming between the oligonucleotide primer and non-specific detection of the amplicon. Therefore, to reduce this error, a special primer can be used to detect the COVID-19, which increases the test time (Table 4). Using the real-time LAMP strategy can reduce non-specific connections to increase detection accuracy. For example, Shirato, et al. [71] based on the RT-LAMP method, identified at least 3.4 copies of MERS-CoV RNA without cross-reacting with other respiratory viruses that occur in the PCR-based method. Likewise, Thai, et al. [72] using the RT-LAMP method, were able to detect MERS-CoV RNA very quickly (<40 min) with a detection limit of 0.02–0.2 plaque-forming units (5–50 PFU/mL) and 50–100 times more sensitive than RT-PCR method. Recently, Park, et al. [73] by applying the RT-LAMP technique, in addition to detecting COVID-19 with a detection limit of lower than 100 copies, prevented cross-reactivity with other respiratory viruses such as influenza and other common CoVs. Similarly, in order to accelerate the diagnosis of CoV, Lamb, et al. [74] and Zhu et al. [75] based on the RT-LAMP method, identified COVID-19 in less than 30 min with a high detection limit, which was highly effective compared to conventional PCR methods. In this line, Jiang, et al. [76] by comprising the two methods of RT-PCR and RT-LAMP in clinical samples showed that the RT-LAMP strategy with detection capacity of up to 500 viral copies in 30 min increased the speed and accuracy of the COVID-19 detection by 2 and 2.5 times, respectively.

Taken together, despite the high sensitivity of nucleic acid-based methods in detecting viruses, especially COVID-19, the analysis depends on expensive various equipment along with skilled experts and the required high temperatures in RT-PCR and RT-LAMP techniques, their use is still limited, regardless the lack of access in many areas. Although the golden standard for COVID-19 detection is still based on nucleic acid testing, some reports suggest that misdiagnosis in this strategy can cause problems for controlling and preventing COVID-19 if used alone due to the widespread prevalence of the disease. On the other hand, due to the uncertainty of the nucleic acids-based tests, physicians perform auxiliary methods such as blood tests and imaging, which has increased the cost of controlling and detecting COVID-19.

2.4.2. COVID-19 immunoassay testing

Because serological reactions are a common occurrence when viruses are present (Fig. 1D), the use of serological tests such as ELISA, neutralization tests, etc. can be used to check for COVID-19 infections and determine the level of invasion. On the other hand, due to the high fluctuation of the viral population during infection and its effect on measurement [63], the use of kit serological tests based on higher stability of protein responses caused by COVID-19 can be a relatively useful solution for indirect virus detection (Table 5). In this regard, serological tests have played a key role in the diagnosis of SARS-CoV and other CoV s [81,82]. In summary, the CoV family with large single-stranded, positive-sense RNA genome of around 27–32 kb, contains four types of structural proteins called spike (S), membrane (M), envelope (E), and (N) nucleocapsid, which are important sites for serological measurements [83,84]. Among the above structures, CoV S protein is of great importance due to its binding and fusion to the host [83,85]. The human serine protease TMPRSS2 is accountable for priming S protein, and the angiotensin-converting enzyme 2 is employed as a receptor for the entry of COVID-19 [84]. Also, N protein has received a lot of attention due to its important role in viral pathogenesis, RNA replication and packaging [86]. Among antibodies, rapid measurement of IgM and IgG undoubtedly play an important role in COVID-19 identification [87,88]. In this regard, the results of Hu et al. [89] illustrated that the levels of IgM and IgG have decreased by ~53.56% and ~49.54%, respectively, in the presence of COVID-19. However, there are two major challenges in serological testing, the first of which is the cross reactivity of COVID-19 antibodies with antibodies to other CoVs. For instance, Ou, et al. [90] showed that plasma samples from COVID-19 patients against S protein were not highly desirable due to cross-reactions with SARS-CoV. The next challenge is the optimal timing of serological tests, which are usually performed 14–28 days after the onset of COVID-19 [88,91]. Therefore, delaying the diagnosis of COVID-19 makes it difficult to prevent and control the disease. However, serological testing can indicate a person's level of safety in the community or hospital staff for health services.

3. Application of nanobiosensors in COVID-19 detection

With the advent of nanotechnology in the 1960s, this technology has received a great deal of attention in various fields of biomedicine, with the improvement of biological and chemical analysis based on unique optical, electrochemical, magnetical, and mechanical properties [33,92]. However, as mentioned earlier, the first use of nanomaterials in the viruses detection in the late 1990s was used to detect human papillomavirus [93]. Today, various types of organic and inorganic nanomaterials, especially AuNPs, magnetic NPs, and carbon-based NPs with biomolecular compounds loaded on their surfaces (for instance, nucleic acid, antibodies, antigens, or capsid peptides) for diagnosis viruses have been used [94,95]. One of the most important advantages of using nanomaterials compared to the methods mentioned above is the possibility of using several probes simultaneously with biological and non-biological labels in detecting viruses [96]. The results of

Table 4
Samples of special primers and probes for COVID-2019.

Gene target	Sequence 5 to 3	Final concentration
N1 gene [77]	F: GACCCCAAAATCAGCGAAAT	500 nM
	R:TCTGGTTACTGCCAGTTGAATCTG	500 nM
	Probe: FAM-ACCCCGCATTACGTTTGGTGGACC-BHQ1	125 nM
E gene [78]	F: ACAGGTACGTTAATAGTTAATAGCGT	400 nM
	R: ATATTGCAGCAGTACGCACACA	400 nM
	Probe: FAM-ACACTAGCCATCCTTACTGCGCTTCG-BBQ	200 nM
ORF1b-nsp14 gene [79]	F: TGGGYTTTACRGGTAACCT	–
	R:AACRCGCTTAACAAAGCACTC	–
	Probe: FAM-TAGTTGTGATGCWATCATGACTAC -TAMRA	–
RdRp gene [78]	F: GTGARATGGTCATGTGTGGCGG	600 nM
	R: CARATGTTAAASACACTATTAGCATA	800 nM
	Probe: FAM-CAGGTGGAACCTCATCAGGAGATGC-BBQ	100 nM
NIID gene [80]	F: AAATTTTGGGGACCAGGAAC	500 nM
	R: TGGCAGCTGTGTAGGTCAAC	700 nM
	Probe: FAM-ATGTCGCGCATTGGCATGGA-	200 nM

Table 5
Samples of serological kit for COVID-19 detection.

Kit name	Antibody detect	Performance	Manufacture
COVID-19 IgG/IgM	Combo IgM/IgG	Positive coincidence rate for IgM and IgG tests: 97.06%	PureChek
VivaDiag™ COVID-19 IgM/IgG	Combo IgM/IgG	Positive coincidence rate for IgM and IgG tests: 81.25% and 37.5%	VivaChek Laboratories
COVID-19 IgG/IgM	Combo IgM/IgG	Sensitivity for IgM test: 87.9% Sensitivity for IgG test: 97.2%	Healgen Scientific
Eugene® SARS-CoV2 IgG/IgM	Combo IgM/IgG	Sensitivity: 96.4% Specificity: 98.7%	Shanghai Eugene Biotech
COVID-19 IgG/IgM	Combo IgM/IgG	Sensitivity: 70%–98.6%	Pharmact
COVID-19 IgG	IgG	100% sensitivity 14 Days confirmation	Roche

nanotechnology studies based on Table 1 in the detection of viruses' types clearly show that the use of nanobiosensors due to the possibility of loading several simultaneous probes with high stability, simple operation, cheapness, portability, non-invasive activities, and ultimately quick response with accuracy based on high selectivity and specificity is superior to other methods [35,36]. On the other hand, the use of biological nanosensors in the viruses detection, especially COVID-19 with shape spherical: 120–160 nm, makes it possible to use them in point-of-care activities based on micro- or nano-chips, fluidic, etc. to control patients momentarily in the face of the virus. Whereas, in the mentioned methods, it is impossible to examine the patient scheduling to determine the antibody levels or virus density in the biological units with software/hardware problems and sometimes the inappropriate condition of the patients. Although the use of nanobiosensors in the diagnosis of COVID-19 has been very limited, few reports have shown an increase in the speed and accuracy of detection compared to conventional methods [97,98]. These studies showed that in addition to reducing the detection error of COVID-19 compared to PCR-based tests, the use of other expensive auxiliary methods such as imaging has been prevented for a more accurate diagnosis. In this regard, this review, by separating the process of detecting COVID-19 in two parts based on nucleic acid and antibodies, evaluates the possibility of using nanobiosensors in early diagnosis and diagnosis of COVID-19 in the treatment process based on antibody levels.

3.1. Nucleic acids- and protein-based nanobiosensors

Because nanobiosensors in biosensing activity are very fast, highly specific, selective, and sensitive to virus detection, their use is very useful in detecting nucleic acids or specific proteins of COVID-19. However, there are few reports of this method in the diagnosis of CoVs, the results of which indicate a rapid, simple diagnosis, and an increase in the extent of the diagnosis compared to conventional methods (Table 6). On the other hand, to isolate patients, the use of nucleic acids or special proteins will be much more effective than antibodies that increase generally after 14–28 days of illness.

In this line, in order to achieve the early diagnosis of COVID-19, Seo et al. [105] by producing a nanobiosensor based on the field-effect transistor (FET) method containing antibodies against S-protein loaded on graphene sheet not only increased the detection time of the COVID-19 down to 4 min, but also the detection limit of COVID-19 was improved to 2.42×10^2 copies/ml in clinical practice and 1.6×10^1 pfu/mL (linear range from 1.6×10^1 to 1.6×10^4 pfu/mL) in culture medium (Fig. 2A). One of the advantages of this sensor is that the samples are stable and does not need to be pretreated or labeled when obtain from the nasopharyngeal which simplify the sample process and analysis. Despite the lack of data on the selectivity/specificity of the nanobiosensor in the COVID-19 detection, as well as the information of the linear range in clinical conditions, this sensor has increased hopes for early detection of COVID-19. Similarly, in another report by Zhang et al. [106] it was determined that graphene-based FET nanobiosensor containing S-protein were able to detect COVID-19 with a LOD of <2 pM in real time without a label (below 2 min) with high affinity/selectivity (binding constant up to 2×10^{11} M^{-1} against the RBD) down to 0.1 pM concentrations. In the following, to increase the speed and accuracy of COVID-19 detection from salivary samples to isolate carriers without invasive or expensive measures based on proteins identification, Mahari, et al. [107] using AuNPs containing S-protein loaded on carbon electrodes, designed an in-house built biosensor device based on the electrochemical method that, in addition to increasing the rapid detection below 1 min and improving the LOD of the COVID-19 up to 90 fM (linear range from 1 fM to 1 μM), enabled low voltage operation (1.3–3 V). Therefore, by decreasing the voltage in nanobiosensor, reducing the laboratory costs, and increasing the detection limit, they increased the possibility sensor applying in point-of-care activities.

Similar to the above studies, for rapid COVID-19 detection with naked-eye, Moitra, et al. [108] designed a surface plasmon resonance-based colorimetric nanobiosensor containing N-protein loaded on AuNP that identified COVID-19 in samples after 10 min with the detection limit of 0.18 ng/L and linear range of 0.2–3 ng/L. However, the study did not provide information on the sensor's selectivity and specificity. The lack of data on selectivity and specificity of the sensors makes it impossible to assess the susceptibility of the sensors to the COVID-19 in the presence of other viruses such as MERS-CoV or SARS-CoV that have the same structure. To differentiate between CoVs, one study exhibited that using AuNPs and RdRp gene probe in a dual-functional plasmonic biosensor combining the plasmonic photothermal and localized surface plasmon resonance effects not only increased the sensitivity of COVID-19 detection up to 0.22 pM with the linear range from 0.1 pM to 1 μM, but also accurately detected COVID-19 in a mixture of several genes, especially SARS-CoV [97]. Nevertheless, the use of several techniques simultaneously in the diagnosis of COVID-19 increases the diagnosis time, cost and specialized laboratory equipment. Therefore, to increase the high specificity and affinity of sensors in COVID-19 detection, Zhao, et al. [109] by applying magnetic NPs coated with carboxyl groups and simultaneous loading of two probes, N-protein and opening reading frame 1a/b (ORF1a/b) RNA, were able to identify COVID-19 samples in less than 20 min with a resolution of 10 copies and a linear range of 10 to 10^5 copies. This method, in addition to the simplicity and excellent performance due to the high affinity, can significantly reduce the time and operational requirements in COVID-19 diagnosis. Likewise, in order to increase the

Table 6
Summary of nanobiosensors designed to detect CoV.

Name	Target	Method	LOD	Linear Range	Specificity	Ref.
SARS-CoV	PP1ab gene	Chip-based colorimetric method by AuNPs	60 fmol	–	–	[99]
SARS-CoV	N-protein	Fluorescence fiber-optic biosensor	~1 pg/mL	0.1 pg/mL to 1 ng/mL	–	[8]
SARS-CoV	N-protein	Field-effect transistor (FET)-based In2O3 nanowires	2–10 nM	–	High specific but lack of statics	[100]
SARS-CoV	Thiolate-gene probe	Electrochemical method based on spherical AuNPs	3 pM	5–300 pM	0.463 μA/pM	[101]
SARS-CoV	N-protein	AlGaN/GaN high electron mobility transistors	0.003 nM	0.4 pg	High specific (33-fold larger than RT-PCR)	[102]
MERS-CoV	PNA probes	Paper-based colorimetric DNA sensor based on AgNPs	1.53 nM	20–1000 nM	High specific but lack of statics	[103]
MERS-CoV	S-protein	Electrochemical method based on AuNPs	1.0 pg/mL	0.01–10,000 ng/mL	High selective	[10]
MERS-CoV	E-protein and open reading frames (ORF) gene	Colorimetric assays based on LSPR change	6×10^{11} copies/μL (1 pmol/μL)	1.5×10^3 to 6.7×10^3 copies/μL	High specific but lack of statics	[104]
Human CoV	S-protein	Electrochemical method based on AuNPs	0.4 pg/mL	0.001–100 ng/mL	High selective	[10]

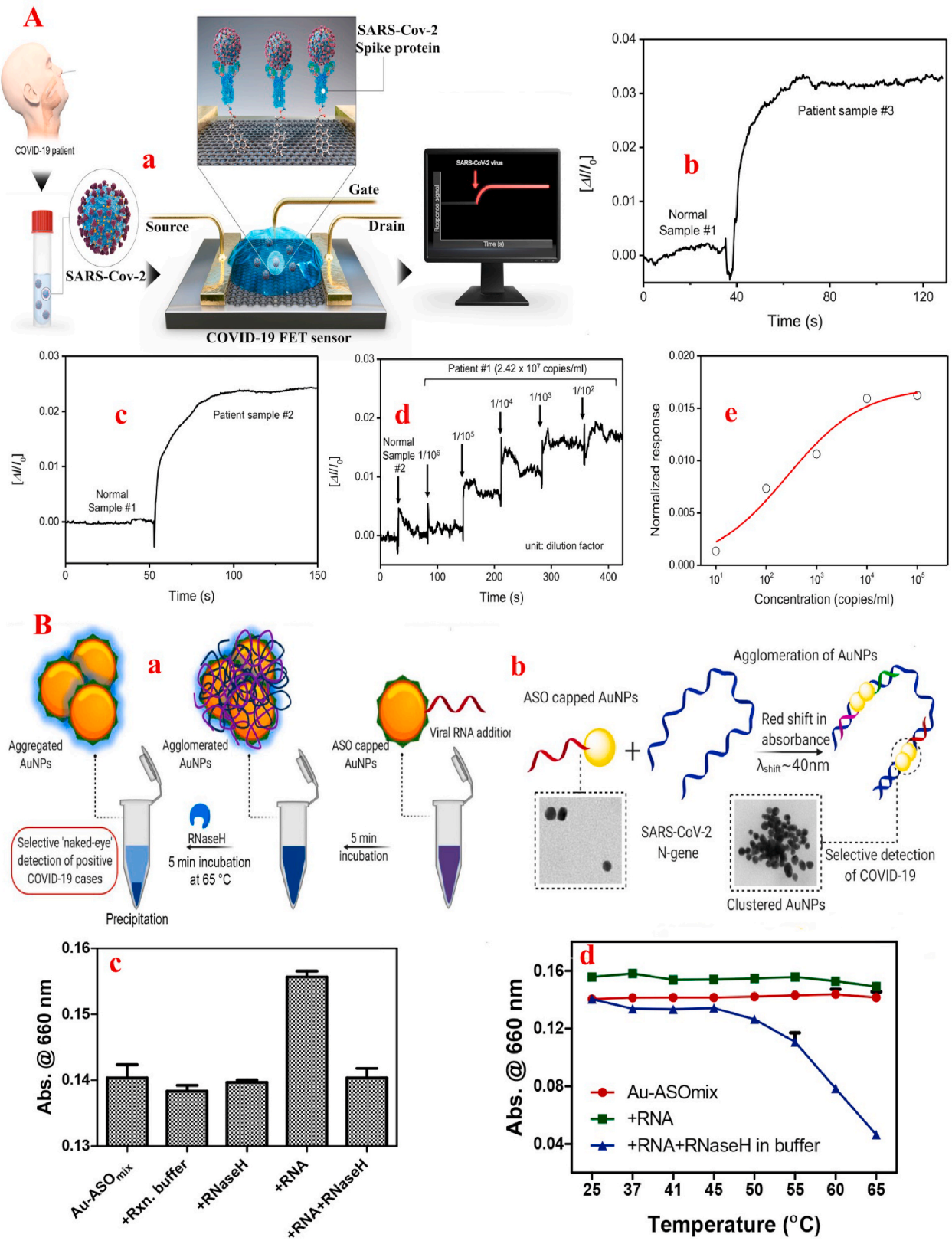

Fig. 2. (A) Rapid COVID-19 detection by field-effect transistor (FET)-based nanobiosensor. a: Schematic diagram of COVID-19 FET sensor operation procedure. Graphene as a sensing material is selected and COVID-19 S antibody is a probe linker. b and c are comparisons of response signals between normal samples and patient ones. d: Real time response of COVID-19 FET toward SARS-CoV-2 clinical sample and, e: related dose dependent response curve [105]. (B) Selective naked-eye COVID-19 detection by N Gene and plasmonic NPs. a: Schematic representation for the selective 'naked-eye' COVID-19 detection by the ASO capped AuNPs. b: The proposed concept behind the agglomeration of AuNPs, when capped with the ASOs. c: Comparison of response of the Au-ASO_{mix} NPs towards the RNA (1 ng/μL) isolated from non-infected Vero cells, MERS-CoV and COVID-19. Relative change in absorbance at 660 nm for the Au-ASO_{mix} NP treated with COVID-19 RNA (1 ng/μL) followed by the addition of RNase H has been plotted in (d) when the mixture was incubated at different temperatures for 5 min [108].

selectivity and specificity in the diagnostic platforms of COVID-19, Zhu et al. [75] with the help of NPs and simultaneous probes of N-protein and ORF 1a/b gene, were able to improve the specificity and sensitivity of RT-LAMP method in the COVID-19 samples obtained from the oropharynx (Fig. 3A).

Taken together, the reports show that the simultaneous use of probes, in addition to increasing the diagnostic sensitivity of nanobiosensors, increases the accuracy of the results without the need to additional tools or labels for detecting COVID-19. Therefore, instead of using expensive tools in diagnostic platforms, it is recommended to use uncomplicated approaches with several probes in the biosensing activities of COVID-19.

3.2. Immunoglobulin (Ig)-based nanobiosensors

Because the body's immune system is able to produce Ig in response to COVID-19 infection, using serological assays-based nanobiosensors to determine specific antibodies can be helpful. In this case, the response of IgG is revealed after almost two weeks of the disease, while the response of IgM can be observed four to ten days after the virus infection [110, 111]. In this regard, Zhang, et al. [112] illustrated that one day after the onset of COVID-19, the IgM and IgG increased by 81 and 50%, respectively. While five days after the disease, the rate of increase is 100 and 81%, respectively. Therefore, to identify achieve a fast, simple, and inexpensive approach for COVID-19 diagnosis, Chen et al. [113] designed a nanobiosensor by using lanthanide-doped polystyrene NPs

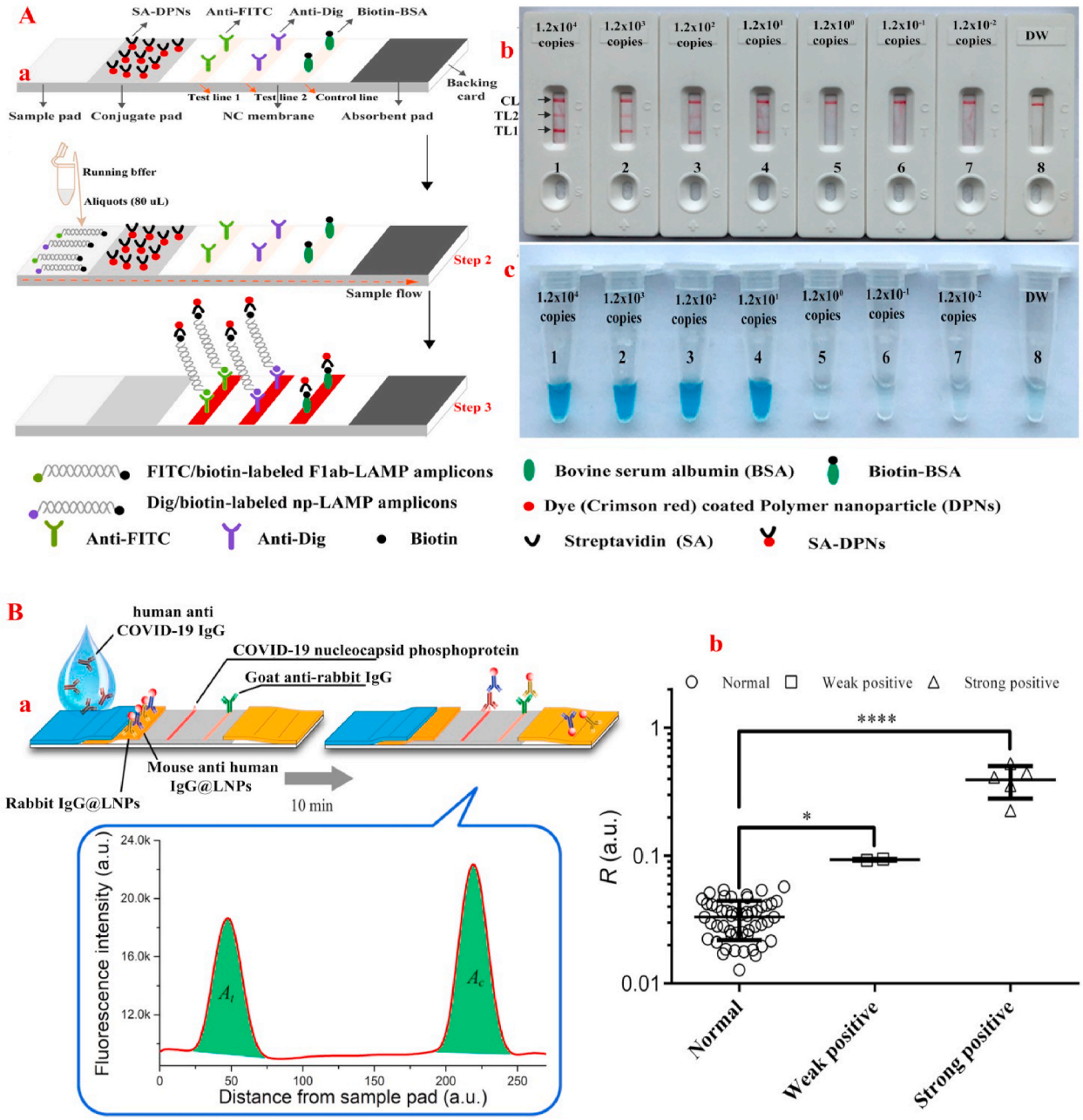

Fig. 3. (A)RT-LAMP combined with NPs-based biosensor for diagnosis of COVID-19. a: The principle of NBS for visualization of COVID-19 RT-LAMP products. b: NBS applied for reporting the results. c: VDR applied for reporting the results. NBS (b) Signals (c) 1–8 represented the plasmid levels of 1.2×10^4, 1.2×10^3, 1.2×10^2, 1.2×10^1, 1.2×10^0, 1.2×10^{-1}, 1.2×10^{-2} copies per reaction and blank control. The plasmid levels of 1.2×10^4 to 1.2×10^1 copies per reaction produced the positive reactions [75]. (B) Rapid and sensitive detection of anti-COVID-19 IgG using lanthanide-doped NPs-based lateral flow immunoassay. a: Schematic illustration of the developed assay. b: Test results for 58 serum samples, including 51 normal and 7 positive samples. *P < 0.05, ****P < 0.0001 [113].

containing anti-COVID-19 IgG based on lateral flow immunoassay, which, in addition to improving detection speeds below 10 min, enhanced the nanobiosensor detection sensitivity with the improvement of the cutoff value of R up to 0.066 similar to RT-PCR method with R value of 0.066 (Fig. 3B). Similarly, Li, et al. [114] using simultaneous IgG and IgM on AuNPs based on the PCR method, were able to increase the sensitivity and specificity of nanobiosensors up to 88.66% and 90.63%, respectively. Therefore, the simultaneous use of multiple Ig can improve the sensitivity and specificity of COVID-19 nanobiosensors.

4. Challenges and future perspective

Because COVID-19 is an undeniable fact with a widespread prevalence in the coming days, it is necessary to describe the preventive activity of the COVID-19 based on rapid, cheap and accessible tools for COVID-19 detection to reduce the rate of prevalence and mortality. For this purpose, the following challenges include:

1. One of the major challenges in detecting COVID-19 is the lack of high specificity and selectivity of nanobiosensors and diagnostic equipment such as RT-PCR, which increases the diagnostic error in clinical samples due to the presence of mutations in major CoV mRNA and proteins. According to the reports, it seems that the simultaneous use of several diagnostic factors such as ORF 1a/b, RdRp genes, etc. with N- and S-proteins can significantly increase the selectivity of the sensor.
2. The source of the analyzed samples has also created serious ambiguities in the sensitivity and specificity of the nanobiosensors to detect COVID-19. Definitely access to the source of contamination in the larynx, olfactory ducts and mouth can increase the COVID-19 diagnostic accuracy. However, blood samples are used to detect Ig for diagnosis of COVID-19. Therefore, the use of blood samples in the COVID-19 detection seems to be more appropriate due to the access to all the exclusive factors of COVID-19.
3. Due to the widespread prevalence of COVID-19 in the world, the design and manufacture of simple nanobiosensors with high performance and accuracy, similar to blood sugar sensors, is essential. However, nanobiosensors produced in the COVID-19 detection are complex and require sample preparation. Therefore, the production and distribution of a simple nanobiosensor with high specificity and sensitivity for public access is a major challenge.
4. Lack of a proper platform for detecting viruses or bacteria is one of the main challenges in development of nanobiosensors in this field. Remarkable advances in smart phones technology can provide a platform for identifying viruses in a cost-effective manner, in addition to controlling contaminated areas, however, progress in this field has been slow.

The bitter experience of the past few months shows that an early warning system is needed to control the outbreak of viruses, especially COVID-19, in the future. However, after several years of research into the production of virus or bacterial nanobiosensors, some specific nanobiosensors have not been synthesized for the early COVID-19 detection infection. With the spread of the COVID-19 virus, similar to influenza, nanobiosensors are expected to be developed for specific viruses detection or bacteria based on smartphones to control the spread of COVID-19 and advancement of point-of-care systems.

5. Conclusion

Due to the rapid outbreak of the COVID-19 around the world and its hidden movement among carriers (for ten to fourteen days), the use of quick, easy, inexpensive diagnostic methods and available to all is very important. Despite the use of common methods in the diagnosis of COVID-19, such as imaging, blood tests, PCR, etc. due to high costs, low sensitivity in some cases, low specificity and selectivity, and lack of sufficient expertise due to limited personnel and advanced equipment generally show some limitations. To this end, this review attempts to explain the advantages and disadvantages of current methods and the possibility of their improvement by using new technologies, especially nanotechnology. Expression of nanotechnology features in the improvement of COVID-19 diagnostic methods based on pre-designed patterns can increase the hopes of diagnosing and controlling COVID-19 infection. On the other hand, the use of nanotechnology in diagnosis can enable point-by-point and low-cost control of patients during treatment with high sensitivity and selectivity. As well, the results of this study show that the simultaneous use of several diagnostic factors in COVID-19 can increase the sensitivity and selectivity of diagnostic tools that can be easily implemented in nanobiosensors. Finally, due to the lack of vaccine, the control and prevention of the COVID-19 is a priority for healthcare institutions. Therefore, the use of nanobiosensors can hold a great promise in providing a cost-effective strategy for the rapid and sensitive COVID-19 detection infection.

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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