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COVID-19 diagnostics: Molecular biology to nanomaterials

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\textbf{ABSTRACT}

The SARS-CoV-2 pandemic has claimed around 6.4 million lives worldwide. The disease symptoms range from mild flu-like infection to life-threatening complications. The widespread infection demands rapid, simple, and accurate diagnosis. Currently used methods include molecular biology-based approaches that consist of conventional amplification by RT-PCR, isothermal amplification-based techniques such as RT-LAMP, and gene editing tools like CRISPR-Cas. Other methods include immunological detection including ELISA, lateral flow immunoassay, chemiluminescence, etc. Radiological-based approaches are also being used. Despite good analytical performance of these current methods, there is an unmet need for less costly and simpler tests that may be performed at point of care. Accordingly, nanoparticle-based testing has been extensively pursued. In this review, we discuss the currently used diagnostic techniques for SARS-CoV-2, their usefulness, and limitations. In addition, nanoparticle-based approaches have been highlighted as another potential means of detection. The review provides a deep insight into the current diagnostic methods and future trends to combat this deadly menace.

1. Introduction

The COVID-19 pandemic has affected 606 million individuals, killing around 6.4 million people worldwide as of September 2022 [1]. The most highly impacted regions include America, Europe, Eastern Mediterranean, South-East Asia, Western Pacific and Africa according to World Health Organization (WHO) [1]. The etiological agent of COVID-19 is severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a positive-sense single-stranded ribonucleic acid (+ssRNA) virus from the family Coronaviridae. Under the electron microscope, it appears as a crown shaped virus due to the surface proteins. The SARS-CoV-2 genome is approximately 30 kilobases, of which 66.6 % codes for open reading frame 1a and 1b and 33.3 % encodes proteins such as spike protein (S), membrane protein (M), an envelope protein (E), nucleocapsid protein (N), and RNA-dependent RNA polymerase (RdRP) [2,3]. The variants of SARS-CoV-2 have been identified to have mutations in these structural proteins. The Centers for Disease Control and Prevention (CDC) has classified these variants as “variants of concern” and “variants of interest” [4], Alpha, Beta, Gamma, and Delta are the variants of concern [3,4] whereas Epsilon, Zeta, Eta, Theta, Iota, and Kappa are the variants of interest [5]. Recently, the new variant Omicron with 32 mutations in spike protein alone is also designated as a variant of concern. These variants have specific mutations in structural proteins and exhibit either an increased infection rate or facilitate replication of the virus in the host cell [6].

Available data indicates that the virus primarily transmits via air droplets. The spike protein of SARS-CoV-2 recognizes the angiotensin-converting enzyme 2 (ACE2) present on the host cell surface causing its entry into the cell [7]. The viral RNA is then translated to produce viral replica polyproteins that are self-cleaved to produce non-structural proteins. Some of the non-structural proteins coalesce with each other to form a replicase/transcriptase complex. The complex facilitates the transcription to produce genomic and sub-genomic mRNA. The sub-genomic mRNA gives rise to S, E, M, and N structural proteins. The assembly of genomic RNA and structural proteins takes place in the ER-Golgi apparatus component and the newly formed SARS-CoV-2 are 
Some of the symptoms that an active patient displays are fever, fatigue, smell loss, dry cough, anorexia, and breathing trouble. Several others remain asymptomatic for a long time and can transmit the virus to immune suppressed population. Thus, testing on a large platform is necessary to win the battle against the virus [10,11].

After sequencing the whole genome of the virus, molecular testing approaches were put forward to carry out the testing and diagnosis. The approaches where specific SARS-CoV-2 sequences are targeted and detected were seen as the gold standard to segregate the infected ones from the unaffected population and provide them with the appropriate care and medications to eliminate the transmission chain. Examining the sera of the individual for SARS-CoV-2 antigen or antibodies against the virus complemented the molecular approaches by providing a rapid point-of-care diagnosis. To combat the global pandemic, the application of nanotechnology has also been scrutinized for rapid testing [12].

Herein, various diagnostic approaches for SARS-CoV-2 detection are discussed in detail. The methods are classified as molecular biology-based techniques, immunology-based techniques, radiology diagnostics, and nanomaterial-based diagnostics. The methods are compared based on their specificity, sensitivity, the limit of detection, and turnaround time.

2. Molecular biology-based diagnostics approaches

The application of molecular biology approaches has upgraded the diagnostic procedure and is currently one of the most relied diagnostic platforms for COVID-19. The early sequencing of the SARS-CoV-2 genome accelerated the use of molecular diagnostic approaches. Some of the widely used diagnostic tools are discussed in the following section.

2.1. RT-PCR

Reverse transcriptase-polymerase chain reaction (RT-PCR) is a widely used molecular technique that has been exploited for the diagnosis of COVID-19 ever since its outbreak [13]. The process involves the collection of samples usually from the upper respiratory system (nasal swab or oropharyngeal swab) of the individuals. RT-PCR reaction relies on reverse transcriptase for the conversion of extracted RNA to complementary DNA (cDNA) and amplification of targeted sequence using specific primers and DNA polymerase [8,14]. A real-time RT-PCR observes viral RNA in the sample collected from the suspected individuals by amplifying the targeted sequence as the reaction progresses (Fig. 2). Some of the targeted genomic sequences for detection of coronavirus are nucleocapsid (N), helicase (Hel), transmembrane (M), envelope (E), open reading frames ORF1a and ORF1b spike protein (S) and RNA-dependent RNA polymerase (RdRp) genes [15,16]. It is recommended to amplify two or more genes for the confirmatory assay (one conserved and one specific gene); thus, different RT-PCR test includes combinations of different genes [17]. Some of the RT-PCR kits used for COVID-19 diagnosis are discussed in Table 1, describing their sensitivity, specificity, the limit of detection, and turnaround time.

Fig. 1. Life cycle of SARS-CoV-2. The SARS-CoV-2 virus recognizes the ACE-2 receptor present on the host surface. Post-receptor interaction, the virus particles enter the cell via endocytosis. The envelope of the virus fuses with the cell membrane releasing the viral RNA into the cell. The viral genome is translated to produce polyproteins. Self-proteolysis of polyproteins forms non-structural proteins. These non-structural proteins amalgamate to form a replicase/transcriptase complex (RTC) which facilitates the replication of genomic RNA. Transcription of the viral genome generates sub-genomic RNA that is translated to produce the S, M, E, N, and ORF1a proteins by the ERGIC (Endoplasmic reticulum-Golgi intermediate compartment) complex. The newly assembled viral particles are released out of the cell through exocytosis.

![Life cycle of SARS-CoV-2](image-url)
requirement. The genes that are amplified in this kit are ORF1b and N genes and the results can be determined within 90 min. They observed 100% result agreement, both positive and negative, between the Idylla™ SARS-CoV-2 Test and SOC RT-PCR. Thus, the Idylla™ SARS-CoV-2 Test is a robust point-of-care procedure for COVID-19 diagnosis [18]. Another advanced RT-PCR is droplet digital RT-PCR (dd RT-PCR). Here, the complete reaction solution is partitioned into thousands of microdroplets comprising either one or no target sequence with primers, probes, and reagents. The amplification occurs in microdroplets possessing the target sequence. The number of positive droplets for amplification provides the total number of copies of the target in the sample. The dd RT-PCR has high sensitivity (10 copies/test) as the reaction partition decreases the competition between templates for the primers and the nanoliter volume of the microdroplets efficiently raises the concentration of target in the droplets favoring reaction kinetics and efficiency [19,20].

Detection of SARS-CoV-2 by RT-PCR of nasal or oral swabs remains a gold standard for COVID-19 detection [21,22]. But since the procedure is invasive and results in discomfort to the patients, biological fluids like saliva, and urine could be used as an alternative. Being non-invasive with ease in sample collection, this method is highly used when dealing with the pediatric population [23]. Meta-analysis and systematic reviews suggest that there is no substantial variation in COVID-19 detection by saliva and nasopharyngeal swab, making saliva test a better option for diagnosis [24]. Laura et al. conducted a study to evaluate the suitability of diagnostic tests using saliva in a pediatric population. For the study 156 pediatric participants displaying clinical symptoms related to SARS-CoV-2 were selected. This diagnostic test exhibited sensitivity and specificity of 82.3% and 95.6% respectively [23]. Another study conducted by To et al., confirms the high sensitivity and specificity of a saliva test for the detection of respiratory viruses. The time and cost related to sample collection are also reduced by using the saliva test [25]. Apart from qualitative diagnosis of the virus, saliva tests can also provide information regarding the clinical evolution of the disease [21]. It offers a better alternative to doctors and healthcare workers as it reduces the risk of infection via aerosol transfer. There are certain devices for the collection of saliva samples for commercial use. Further research on biomarkers associated with saliva for COVID-19 detection would be beneficial for designing cost-effective and easy detection tools [26]. RT-PCR has high specificity (>95%) and sensitivity (~93–95%) i.e., the chances of giving false positives and false negatives are very low. But sampling error or cross-contamination restricts the reliance of COVID-19 diagnosis only on RT-PCR. Additionally, the coronavirus is continuously evolving with variants prevailing in the population, hence it is difficult to detect a new variant with mutations at the targeted sequences with the old primers. Other drawbacks are the lengthy turnaround duration of 2 days, robust infrastructure, trained personnel, and sample storage and preservation [16,27,28].

2.2. Isothermal amplification techniques

Isothermal amplification techniques are based on the amplification of a target sequence at a single temperature thus excluding the need for a thermocycler to maintain the temperature variations required during standard RT-PCR. The potential to provide point-of-care application makes isothermal amplification significant for COVID-19 diagnosis. Some of the molecular techniques based on isothermal amplification are loop-mediated isothermal amplification, recombinase polymerase amplification, rolling circle amplification, exponential amplification reaction, and exponential strand displacement amplification [8,43].

The reverse transcriptase loop-mediated isothermal amplification (RT-LAMP) technique is used for the detection of SARS-CoV-2 with a modification i.e., along with the nucleotides and reverse transcriptase, Bst DNA polymerase and given set of primers (two outer primers, two inner primers, and two loop primers) as main constituents are also added to the above cocktail. It operates at 60–65 °C and amplifies the target sequence rapidly within 1 h with high specificity due to loop primers comparable to standard RT-PCR. Initially, SARS-CoV-2 RNA is converted to cDNA by reverse transcriptase. To the cDNA produced, the LAMP
primers bind to their complementary target sequence and produce dumbbell-shaped DNAs. Amplification of this dumbbell-shaped DNA by the Bst DNA polymerase that has intrinsic strand displacement activity produces various sizes of amplified product at the end of the reaction.

The results can be read out either by turbidity level or colorimetric readout [8]. The dNTPs are added to the growing chain by the Bst DNA polymerase that has intrinsic strand displacement activity. A change in color from yellow to pink can be observed [48].

Table 1

Description of some of the RT-PCR kits used for the diagnosis of SARS-CoV-2.

| S. No. | Name of the kit | Developer | Target gene | Limit of detection | Sensitivity | Specificity | Turnaround duration | Reference |
|-------|----------------|-----------|-------------|-------------------|-------------|-------------|---------------------|----------|
| 1     | CDC 2019 Novel  | CDC-US    | N gene (N1, N2, and N3; where N1 and N2 are SARS-CoV-2 specific, N3 universally detects viruses within the subgenus Sarbecovirus) | 5 RNA copies per reaction | –           | –           | 2–3 hrs             | [29]     |
| 2     | Coronavirus Real-Time RT-PCR Diagnostic Panel | BioFire | E, N, and RdRp | > 20,000 copies/ml, 4,000 copies/ml | 75.5% 100% | 69 min | [30] |
| 3     | AccuPower SARS-CoV-2 Multiplex RT-PCR Kit | Bioneer, South Korea | E, N, and RdRp | 96.5% 93.75% | 2 h | [30] |
| 4     | Allplex 2019-nCoV Assay | Seegene, South Korea | E, N, and RdRp | 96.5% 93.75% | 2 h | [30] |
| 5     | Multiplex real-time reverse transcription polymerase chain reaction (rRT-PCR) assay | Institute for Research and Medical Consultations (IRMC) | RdRP and E gene | 10^3 and 10^4 copy/µL | – | – | 2 h | [31] |
| 6     | GeneFinder COVID-19 Plus RealTime Kit | OSANG Healthcare Co., Anyang, Korea | ORF1ab, RdRp, E and N gene | 500 copies/ml | 93.88% 100% | – | [32] |
| 7     | Sansure Biotech RT-qPCR method | Sansure Biotech Inc., Changsha, China | ORF1ab and N gene | 200 copies/ml | 94.83% 91.67% | 2 h | [25] |
| 8     | TagPath COVID-19 CE-IVD RT-PCR kit | Thermo Fisher Scientific, Waltham, USA | ORF1ab, N and S gene | 10 genomic copies equivalents | 88% 100% | – | [26] |
| 9     | QuantuMDx Q-POC SARS-CoV-2 RT-PCR assay | QuantuMDx | ORF1ab, N and S gene | 1000 genome equivalent copies/ml | 96.88% 98.3% | –2 min | [35] |
| 10    | LabGun COVID-19 RT-PCR kit | Lab-Genomics | RdRp and E gene | 20 copies/µL | 95% 95% | 100 min | [34] |
| 11    | Coronavirus COVID-19 genesig® Real-Time PCR assay | Genesig | ORF1ab | 15.73 copies/reaction | 93.88% 97.78% | 80 min | [28] |
| 12    | Smart Detect™ SARS-CoV-2 rRT-PCR Kit | InBios | E, N, and ORF1b | 12.5 genomic equivalent copies/ml | 96.55% 100% | – | [33] |
| 13    | Lifesriver novel coronavirus nucleic acid detection kit | Shanghai Zhijiang Biotechnology co., Ltd. | ORF1ab, N, and E | 1000 copies/µL | 100% 100% | 80 min | [37] |
| 14    | Deng novel coronavirus nucleic acid detection kit | DaAn Gene Co., Ltd. | ORF1ab and N | 500 copies/µL | 100% 100% | 75 min | [38] |
| 15    | FOSUN COVID-19 RT-PCR Kit | Fosun | E, N, and ORF1ab | 300 copies/µL | 95.2% 100% | – | [39] |
| 16    | Xpert Xpress SARS-CoV-2 (Xpert) test | Cepheid, USA | N2 and the E gene | 0.01 PFU/µL | 95.8% 99.5% | 45 min | [40] |
| 17    | RADI COVID-19 Detection Kit | KH Medical, Korea | S & RdRp | 0.66 copies/µL | 100% 100% | 1 h | [41] |
| 18    | VitaPCR™ SARS-CoV-2 assay | Credo Diagnostics Biomedical, Singapore | E, ORF1a, N gene | – | 90% 99% | 20 min | [42] |
| 19    | DiaFlexQ Novel Coronavirus (2019-nCoV) Detection Kit | Solgent, Korea | N & ORF1a | 200 copies/µL | 98% 100% | 2 h | [41] |
(PS-T) centrifugal microfluidic device, controlled by a fidget spinner with automated colorimetric detection. Their findings displayed that the microfluidic device can detect approximately $10^{-3}$ copies of SARS-CoV-2 RNA in the sample [50].

Recombinase polymerase amplification (RPA) also operates at isothermal conditions amplifying DNA sequence at 37–42 $^\circ$C, providing the result within 10–15 min. In this diagnostic technique, the recombinase enzyme first interacts with primers and forms a recombinase-primer complex. The primer seeks its complementary sequence and occupies the target site and the recombinase disassembles the target strand. Extension of the disassembled strand is performed by DNA polymerase. The other strand is stabilized by single-stranded DNA binding protein and the recombinase is accessible for the next rounds of extension to occur [11]. RT-RPA is an upgraded version of RPA for the detection of coronavirus, having one additional step i.e., reverse transcription. Lau et al. developed an RT-RPA procedure where the endpoint can be determined either via SYBR green or lateral flow strip technique within 15 min. The result can be analyzed by lateral flow assay, where two bands represent the positive sample and one band corresponds to the negative sample. The chip displayed a sensitivity of 97 % and specificity of 100 % with no cross-reactivity to other viruses like influenza, respiratory syncytial, and coronavirus OC43. Thus, the chip-based RT-RPA assay has the potential to be developed as an alternative to RT-PCR [54].

2.3. CRISPR-based detection techniques

Clustered regularly interspaced short palindromic repeats (CRISPR) based techniques are used for the detection of nucleic acids either DNA or RNA in the sample. The CRISPR-Cas system is a prokaryotic-acquired immune defense against invading viruses [55]. The main components of the CRISPR system are the conserved CRISPR-associated genes (Cas genes) with endonuclease activity and guide RNA that directs Cas to target sequences for cleavage. The guide RNA is transcribed from the non-repeating spacer sequences that belong to different viruses. When a bacterium is encountered by a virus particle, the spacer sequences are transcribed to CRISPR-RNA (crRNA) that guides the Cas enzymes to the invading DNA or RNA. The 2–4 bp protospacer adjacent motifs (PAM) facilitate the unwinding of foreign DNA thus causing the binding of
crRNA with its complementary foreign sequences. The association activates the cleavage activity of the Cas enzyme that cuts foreign nucleic acid along with other ssDNA or ssRNA in the solution [55,56]. The collateral cleavage activity of the CRISPR-Cas system is exploited for the diagnosis of COVID-19. The short single-stranded nucleic acids are used as signaling reporters that are labeled with a fluorophore and a quencher. So, after the activation of the Cas enzyme, it cleaves the reporter molecule releasing fluorophore from the quencher, which can be visualized in real-time using either fluorescence signal or lateral flow assay. For diagnostic purposes, Cas 12 and Cas13 are much explored, where Cas 12 targets ssDNA while Cas 13 cleaves ssRNA (Fig. 4) [8,57].

Broughton et al. developed a CRISPR-Cas12-based detection system, called SARS-CoV-2 DNA Endonuclease-Targeted CRISPR Trans Reporter (DETECTR). The method begins with the extraction of RNA from the collected sample and the production of cDNA by reverse transcription. The cDNA is amplified using isothermal amplification techniques, designing primers to determine the amplification of the N gene and E gene of SARS-CoV-2. The result can be achieved within 30–40 min with the help of lateral flow assay using FAM (fluorescein amidite)-biotinylated reporter molecule. The CRISPR-Cas12-based assay can detect 10 copies per μl without the requirement of expensive instruments [58]. Some of the other methods based on Cas 12 nuclease activity are AIOD-CRISPR [59], CRISPR-ENHANCE [60], CRISPR/Cas12a-NER [61], and SENA [62]. The isothermal amplification and Cas-based detection occur in a two-tube format that can lead to post-amplification contamination. Thus, joung et al., employed thermostable Cas12b from Alicyclobacillus acidiphilus (AapCas12b) to combine the amplification and detection procedure in a single tube format, called STOP Covid (SHERLOCK Testing in One Pot). The limit of detection of the protocol is 2 viral RNA copies per μl [63]. Hou et al. evaluated the performance of a CRISPR-based diagnostic tool with that of metagenomic sequencing and RT-PCR. They developed a rapid detection assay based on Cas13a endonuclease activity termed CRISPR-COVID. RT-RPA was employed for the amplification of the ORF1a gene of SARS-CoV-2. They observed that the method can be performed within 40 min as compared to metagenomic sequencing and RT-PCR analysis which take approximately 20–24 h for result determination. The assay result can be determined by fluorescence readout displaying 100 % specificity for SARS-CoV-2 [64]. Other CRISPR-based methods employing Cas 13 endonuclease are SHERLOCK [65], CREST [66], and SHINE [67]. All these methods can be performed within 60 min with 100 % specificity. Azhar et al. explored the cleavage activity of Cas9 isolated from Francisella novicida (FnCas9) and developed a protocol called FELUDA (FnCas9 Editor Linked Uniform Detection Assay). This assay can be completed in 32 min with high specificity and easy readout [68].

Fig. 4. CRISPR-Cas methods for RNA Detection. The method proceeds with the conversion of SARS-CoV-2 RNA into dsDNA by reverse transcription. Cas13 recognizes SARS-CoV-2 ssRNA, the dsDNA is converted to ssRNA. The binding of the target sequence to the Cas enzyme activates its catalytic activity which further cleaves fluorescent ssRNA reporter for detection (Sherlock CRISPR SARS-CoV-2 Kit) (A). Cas12 identifies SARS-CoV-2 dsDNA, thus the binding of a target sequence to Cas12 activates the cleavage activity of the enzyme and cleaves fluorescent ssDNA reporter for visualization and detection (SARS-CoV-2 DETECTR Reagent Kit) (B).
where the selection of specific regions of the SARS-CoV-2 genome for designing gRNA is necessary to eliminate the chances of off-target occurrence. Further, engineering the CRISPR-Cas protein could be an obstacle in the development of CRISPR-based testing [69,70].

3. Immunological diagnostics approaches

Immunological assays are based on the recognition of viral antigens or the detection of antibodies like IgG and IgM against the virus in the sample. When a person is exposed to SARS-CoV-2, the virus interacts with the angiotensin-converting enzyme-2 surface receptor and enters the host cells generally epithelial cells of bronchiolo and alveoli [9,71]. Upon its entry, SARS-CoV-2 uses the cellular replication machinery, activates NOD-like receptors and inflammasome, and downregulates the NF-κβ pathway. These alteration triggers amplified production of pro-inflammatory cytokines like as IL-1, IL-6, IL-8, IL-2 receptor (IL-2R), IL-10, TNF-α (tumor necrosis factor-α), and chemokine, activating other immune cells and leading to hyper-inflammation [72,73]. The cytokines released lead neutrophils to the site of infection, which initiates phagocytosis and the formation of neutrophil extracellular traps (NET). NET further activates other immune cells causing an upsurge in the release of cytokine and chemokines. These circumstances lead to

| S. No. | Method                                      | Name of the Test                          | Developer                          | Target protein | Sensitivity | Specificity |
|--------|--------------------------------------------|-------------------------------------------|------------------------------------|----------------|-------------|-------------|
| 1.     | Lateral flow                               | CareStart COVID-19 IgM/IgG                | Access Bio, Inc.                   | S and N        | 98.4 %     | 98.9 %     |
|        |                                             | WANTAI SARS-CoV-2 Ab Rapid Test          | Beijing Wantai Biological Pharmacy Enterprise Co., Ltd. | S              | 100 %     | 98.8 %     |
|        |                                             | Rightsign COVID-19 IgG/IgM Rapid Test    | Hangzhou Biotest Biotech           | S              | 100 %     | 100 %     |
|        |                                             | Cassette                                 |                                    |                |            |            |
|        |                                             | Innovita 2019-nCoV Ab Test (Colloidal Gold) | Innovita (Tangshan) Biological Technology Co., Ltd. | S and N        | 100 %     | 97.5 %     |
|        |                                             | Rapid COVID-19 IgM/IgM Combo Test Kit    | Megna Health, Inc.                 | N              | 100 %     | 95.0 %     |
| 2.     | Enzyme-linked Immunoassay (ELISA)           | WANTAI SARS-CoV-2 Ab ELISA               | Beijing Wantai Biological Pharmacy Enterprise Co., Ltd. | S              | 96.7 %     | 97.5 %     |
|        |                                             | Platelia SARS-CoV-2 Total Ab              | Bio-Rad Laboratories, Inc          | N              | 98.0 %     | 99.3 %     |
|        |                                             | SARS-CoV-2 RBD IgG test                   | Emory Medical Laboratories         | S              | 100 %     | 96.4 %     |
|        |                                             | COVID-SeroKlit, Kantaro Semi-             |                                    |                |            |            |
|        |                                             | Quantitative SARS-CoV-2 IgG Antibody Kit | BioCheck, Inc.                    | S              | 99.1 %     | 97.2 %     |
| 3.     | Semi-quantitative 2-Step ELISA              | BioCheck SARS-CoV-2 IgG and IgM Combo    | BioCheck, Inc.                    | S              | 99.1 %     | 97.2 %     |
|        |                                             | Test                                      |                                    |                |            |            |
| 4.     | Chemiluminescence immunoassay (CLIA)        | Diazyme DZ-Lite SARS-CoV-2 IgM CLIA Kit  | Diazyme Laboratories, Inc.         | S and N        | 94.4 %     | 98.3 %     |
|        |                                             | IDS SARS-CoV-2 IgG                       | Immunodiagnostic Systems Ltd.      | S and N        | 97.6 %     | 99.6 %     |
| 5.     | High Throughput CLIA                        | Babson Diagnostics ac19G1                 | Babson Diagnostics, Inc.           | S              | 100 %     | 100 %     |
| 6.     | Semi-quantitative High Throughput CLIA      | Diazyme DZ-Lite SARS-CoV-2 IgG CLIA Kit  | Diazyme Laboratories, Inc.         | S and N        | 97.4 %     | 100 %     |
| 7.     | Semi-quantitative Bead-based Fluorescent    | Access SARS-CoV-2 IgG II                  | Beckman Coulter, Inc.             | S              | 98.9 %     | 100 %     |
| 8.     | Fluorescence Immunoassay                    | QUANTA Flash SARS-CoV-2 IgG              | Inova Diagnostics, Inc.            | S and N        | 99.9 %     | 100 %     |
|        |                                             | BioPlex 2200 SARS-CoV-2 IgG              | Bio-Rad Laboratories               | S              | 93.9 %     | 99.9 %     |
|        |                                             | LumiraDx SARS-CoV-2 Ab Test               | LumiraDx UK Ltd.                  | S              | 100 %     | 100 %     |
|        |                                             | FREND COVID-19 total Ab                   | NanoEntek America, Inc.           | N              | 96.7 %     | 98.8 %     |

* S represents spike protein and N corresponds to the nucleocapsid protein of SARS-CoV-2.

Table 2

Immunological kits adapted and approved by Food and Drug Administration under emergency use administration for detection of SARS-CoV-2[91].

Fig. 5. SARS-CoV-2 antibodies detection by lateral flow immunoassay. The blood sample is collected from the patient and loaded on the test strip (1). A buffer solution is then added to the test strip and incubated (2). The sample flows through the strip via capillary action and Antigen-Antibody interaction takes place (3). SARS-CoV-2 specific antigens are immobilized on nitrocellulose membrane along with gold rabbit conjugated antibodies. The test sample upon contact with the membrane forms a complex with SARS-CoV-2 specific antigens, that are further captured by immobilized anti-human antibodies that give a positive test line. The gold rabbit conjugate antibodies are captured further by anti-rabbit antibodies that give a control line (4). The results of lateral flow can be analyzed visually where the appearance of both the test line and control line indicates a positive test whereas the appearance of only the control line indicates a negative test (5).
cytokine storm that causes tissue damage and disease severity [73,74]. Adaptive immune response holds a vital role against SARS-CoV-2 infection. Dendritic cells phagocytose the viral particles and present them to the T-cells. CD4 + T cells are helper cells that have anti-viral activity, stimulate B cells and promote tissue repair, whereas CD8 + T cells are cytotoxic cells that kill the infected cells [75,76]. Antibody-mediated immune responses are vital for restricting viral infections and can be exploited for diagnostic purposes. The early immunoglobulins produced after exposure is IgM (during the 1st week), then specific antibodies IgG are released after 1st week of infection. IgA number elevates between 4 and 10 days after infection [15,28]. However, the order of immunoglobulin production may vary from individual to individual [73].

Immunological assays aid in the detection of ongoing and former infections whereas molecular techniques determine viral infection during its preliminary phase. Thus, both approaches compensate each other and reduce the chances of false negative cases [47]. Immunological assays have been advanced to provide a rapid diagnosis in the chaos of COVID-19. Further, the antigens and antibodies are highly stable and least prone to degradation as compared to RNA [11,17]. Some of the immunological-based approaches examined for diagnosis of COVID-19 are discussed in this section. Table 2 describes the efficacy of kits based on these approaches that were approved by the Food and Drug Administration under emergency use administration.

3.1. Lateral flow immunoassay

Lateral flow immunoassay is a technique that relies on the biochemical interaction between the antigen and serum antibodies [77]. It is a user-friendly, point-of-care diagnostic technique that detects antibodies or specific SARS-CoV-2 antigens in the collected sample. It provides qualitative results either positive or negative for the presence or absence of antigens and antibodies [28]. The sample source could be serum, plasma, whole blood, nasopharyngeal or oropharyngeal swabs. Based on the sample source, lateral flow immunoassay can be discussed as serological lateral flow immunoassay and rapid antigen assay. The sample source for the serological assay is blood, serum, plasma, sputum, and saliva where the antibodies presence is detected. For rapid antigen tests, a nasopharyngeal specimen is collected for determination of antigen availability [16].

In the serological assay, the sample obtained is applied on the sample pad that has immobilized the SARS-CoV-2 antigen. The samples move via capillary action. The antibodies in the sample interact with the immobilized antigen on the chip. The complex moves further until they via capillary action. The antibodies in the sample interact with the immobilized antigen on the chip. The complex moves further until they move further until they are captured by immobilized anti-human antibodies. The captured antigen–antibody association can be detected by the test band appearance (Fig. 5) [16]. Efficacy of some of the serological kits like ALLTEST 2019-nCoV IgG/IgM Rapid Test, Dynamiker 2019-nCoV IgG/IgM Rapid Test, ASK COVID-19 IgG/IgM Rapid Test, and Wondfo SARS-CoV-2 Antibody Test were evaluated by Wu et al., and the study concluded that all the four kits possess 100 % sensitivity and 100 % specificity after 3 weeks of symptom onset [78]. The LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescence assay is an automated serological assay designed by DiaSorin to detect IgG antibodies produced against SARS-CoV-2 native S1/S2 proteins. The assay can be completed in 35 min with 97.98 % specificity and 91.3–95.7 % sensitivity [79].

Rapid antigen test is based on a similar principle. Here, the IgG antibodies are immobilized on the test strip and the SARS-CoV-2 antigen in the sample is detected. The spike protein (S) and nucleocapsid protein (N) are two of the most important antigens for the development of immunological assays [17]. Albert et al. examined the sensitivity of the Panbio™ COVID-19 Ag Rapid Test for the diagnosis of 412 symptomatic patients. The result indicated that the rapid kit has high specificity and sensitivity of 100 % and 79.6 % respectively, taking RT-PCR as control [80]. An open-label clinical trial was performed to investigate the sensitivity and specificity of the Standard Q COVID-19 Ag-test developed by SD Biosensor INC. The nasopharyngeal swab of 4697 participants was taken to perform this trial. The trial got completed in early 2021 and the results are yet to be posted (ClinicalTrials.gov Identifier: NCT04689399).

Lateral flow immunoassay is a rapid, inexpensive diagnostic tool that can determine the result in 10–15 min with no trained staff required [40]. The major limitation of this technique is poor sensitivity, as an early stage of infection cannot be determined since antibodies are formed after the first week of infection, and this can lead to a false diagnosis of COVID-19, further quantification of antibodies cannot be determined [8,81,82].

3.2. Enzyme-linked immunosorbent assay (ELISA)

ELISA is considered the gold standard for immunoassays. It is based upon antibody-antigen reaction, where the antibodies developed in an individual after exposure to SARS-CoV-2 interact with immobilized antigens or proteins coated on the plates [83]. It allows qualitative as well as quantitative analysis of antigens and antibodies and additionally aids in the determination of the intensity of immune response [84,85]. The blood, serum, or plasma samples are introduced into the wells coated with antigens. Later, secondary antibodies tagged with reporter molecules are added, which gives out results in the form of color change or fluorescence [11]. Evaluation of SARS-CoV-2 specific ELISA test is obligatory, thus Sil et al., investigated ELISA for detection of anti-SARS CoV2 IgG in RT-PCR positive patients. Recombinant nucleocapsid protein was immobilized on the plate and the serum sample was incubated with the antigens at 37 °C for 15 min. Post incubation, optimized goat anti-human IgG coupled with horse radish peroxidase was added. 3,3′,5,5′-Tetramethylbenzidine is used as the substrate which can be read by color change. Finally, optical density was measured at 450 nm using the ELISA plate reader for quantitative analysis. The test displayed a sensitivity of 92 % and a specificity of about 97 % [86]. Mehdi et al. optimized the Receptor Binding Domain (RBD)-based IgG ELISA test and converted this assay into a kit format. The developed kit showed enhanced specificity of 99.79 % and higher sensitivity when compared with other commercial IgG ELISA kits [87]. ELISA immunoassay is the widely used technique with an average turnaround time of 4 h. A labor-intensive process with the need for costly antibodies is the major pitfall of ELISA [27,84].

3.3. Other immunological approaches

Multiplex bead-based immunoassay has been developed that can precisely detect antibodies in the sample against SARS-CoV-2, MERS-CoV, and other coronavirus strains. It also enables us to understand the dynamics of an immune response upon infection. Ravindran et al. developed and standardized quantitative multiplex bead immunoassay to detect IgG and IgM against spike and nucleocapsid proteins. Specific antigens were covalently coated on the microbeads and the plasma samples were incubated with them. The detection of antibodies can be done using biotinylated anti-human IgM and biotinylated anti-rabbit IgG. The sensitivity (94 %) and specificity (98 %) of this procedure were comparable to other immunoassays [88]. Lin et al., used a magnetic beads protocol incorporated with chemiluminescence immunoassays for serological testing. Chemiluminescence immunoassays detect specific antibodies in the samples via photon emission rather than a color change. Their protocol displayed 60.76 % sensitivity and 92.25 % specificity against IgM antibodies and 82.28 % sensitivity and 97.5 % specificity against IgG antibodies [89]. For the automated determination of antibodies in the sample microarray-based serological assay was evaluated. Martinaud et al. used the MosaiQ® COVID-19 Antibody Microarray procedure for the evaluation of spike protein antibodies of SARS-CoV-2. The assay provides high-throughput testing combining antigen–antibody interaction with automated image capture [90].
network models like VGG 19 can accurately test COVID-19 using chest
intra- and inter-lobular septal thickening, consolidations i.e., amplified
damage and the study of the disease dynamics [92,102] . Ates et al. performed a study where 32 patients underwent CT and MRI and were
diagnosed with COVID-19. The common findings of CT and MRI are
observed cannot positively confirm SARS-COV-2 infection depending on
the skilled radiologist, and sterilization of the CT machine after every
use [98,99].

Some of the other radiological methods used as an alternative to CT are X-ray imaging and MRI (Magnetic Resonance Imaging). X-ray imaging facilitates the non-destructive investigation of internal organs using electromagnetic waves. The major limitation of this technique is substandard sensitivity and specificity [92]. Computer-aided diagnosis using chest X-ray imaging has also been explored [100]. A study by Rahaman et al., depicted how the application of convolutional neural network models like VGG 19 can accurately test COVID-19 using chest X-ray imaging [101]. MRI is a powerful tool to analyze the anatomical and functional characteristics of various organs, without exposure to ionizing radiation. It permits the evaluation of the degree of tissue damage and the study of the disease dynamics [92,102]. Ates et al. performed a study where 32 patients underwent CT and MRI and were diagnosed with COVID-19. The common findings of CT and MRI are glass ground opacification and consolidations. MRI detected nodules in the infected individual with a high specificity of 100 % and sensitivity of 91.67 %. Thus, MRI can be used as an alternative to a CT scan to reduce the burden of testing [103]. Several shortcomings of MRI are poor quality images, decreased signal-to-noise ratio, inferior anatomic reso-
lution, unavailability of MRI machine and inflated charges for the MRI scanning restrict its application as compared to CT scan [99,102].

5. Nanomaterials for the rapid diagnosis of COVID-19

The above-described diagnostic tools have been extensively used for the COVID-19 diagnosis, yet the limitations associated with these assays like longer turnaround time of RT-PCR, optimization of LAMP reactions, poor sensitivity of immunological approaches, exposure to radiations in case of CT scan paves way for exploring other fields that can collaborate in the development of diagnostic methods. Nanotechnology is one such domain that has been exploited to tackle the perils posed by Covid-19 [105]. The antiviral activities of various nanoparticles are of great in-
terest. In this section, the applications of nanomaterials for the diagnosis of viral infections specifically SARS-CoV2 are discussed in detail.

5.1. Gold nanoparticles based diagnosis

Gold-based nanoparticles (AuNPs) are known to have excellent physiochemical properties like chemical stability, water solubility, broad shape, and size controllability. AuNPs are renowned for their high surface density of free electrons responsible for inherent electrical, optical and catalytic properties. Due to these properties, they continue to remain a popular choice for biomedical applications [106]. Gold-based nanoparticles have been used as signal transducers in terms of optical signal amplifiers, current amplifiers, and resonance light scattering [107]. Localized surface plasmon resonance (LSPR) is the physical process underlying the class of nanoparticle-based biosensors. LSPR refers to the coherent and non-propagating oscillations of free electrons in metal nanoparticles [108,109]. Another method of detection of viral antigens based on AuNPs is colorimetric detection, where the change in color that occurs in a colloidal suspension because of LSPR coupling among the nanoparticles is exploited [110]. In colorimetric detection, the aggregations of AuNPs are controlled by employing biological mechanisms like antigen–antibody interactions. Different strategies are used for the proper immobilization of the antigen–antibody complex on the surface of the nanoparticle [111,112]. In recent times, various functionalized versions of AuNPs are being used for the rapid detection of SARS-CoV-2. A few of the most notable studies conducted so far have been reviewed in the following paragraphs.
Making use of the LSPR effect of two-dimensional gold nano-islands (AuNIs), Qiu et al., [113] developed a dual-functional plasmonic system capable of sensitive, fast and reliable diagnosis of COVID-19. They designed a single cost-effective 2D-AuNI-based chip through the self-assembly of thermally de-wetted gold nanofilm on a BK7 glass surface. The AuNIs used in this system were functionalized with SARS-CoV-2 complementary DNA receptors which aid in the detection of selected virus sequences through the process of nucleic acid hybridization. By exciting the plasmonic resonance of LSPR at two different wavelengths, the hybridization kinetics was significantly improved, thereby enhancing the accuracy with which different gene sequences were detected. This way, the dual-functional plasmonic system developed was capable of real-time and label-free detection of viral sequences with a 0.22 pM detection limit.

Moitra et al., [114] reported a colorimetric biosensing approach for the detection of SARS-CoV-2 based on AuNPs capped with thiol-modified antisense oligonucleotides [AuNPs-ASOs]. Colorimetric biosensing facilitates naked-eye detection of viral infectious diseases without involving sophisticated techniques. Once the RNA sample is obtained from the subject, it is tested to identify the presence of nucleocapsid phosphor protein (N-gene) of SARS-CoV-2. If the sample contains an RNA sequence of SARS-CoV-2, then selective agglomeration of the nanostructures occurs, which further causes a red-shift in the UV-absorbance spectrum due to the surface plasmon resonance effect. This way, the colorimetric biosensing assay confirms the diagnosis of COVID-19 in less than 10 min. Moitra et al., [114] also found that the addition of RNaseH helps cleave the RNA-strand from the RNA-DNA hybrid, thus allowing visual detection of the precipitates from the solution caused due to the agglomeration of the AuNPs-ASOs. The detection limit of this colorimetric assay was reported to be 0.18 ng/μL, along with a dynamic range of 0.2–3 ng/mL. The schematic representation of this colorimetric assay has been presented in Fig. 7.

As far as naked-eye detection of SARS-CoV-2 is concerned, Kumar et al., [115] reported a cost-effective AuNP-based rapid colorimetric assay designed to target RdRp-specific gene targets. The surface plasmon resonance property of AuNPs is once again responsible for the success of this method of detection. According to Corman et al., [116], RdRp has higher analytical power than the envelope protein and nucleocapsid protein in addition to being vital for viral replication; and was hence used by Kumar et al., [115] in the development of this colorimetric assay. It is to be noted that this assay is primarily based on the fact that AuNPs preferentially absorbs ssRNA/ssDNA samples over dsRNA/dsDNA sample. When COVID-19-infected RNA samples were hybridized with the RdRp oligo probe, a visual change in the gold colloid color from pink to blue was observed, whereas the colloid color remained pink in the absence of hybridization. The colorimetric assay exhibits a sensitivity of 85.29 % and specificity of 94.12 % for the cost-effective detection of COVID-19 in approximately 30 min.

Pramanik et al., [117] presented a novel anti-spike antibody with attached gold nanoparticles for the rapid diagnosis and inhibition of SARS-CoV-2. Through a simple colorimetric change observation in less than 5 min, anti-spike antibody-attached AuNPs are highly efficient and effective in the detection of SARS-CoV-2 in human samples. The naked-eye assay developed by Pramanik et al. prides on the fact that their colorimetric assay is capable of detecting the COVID-19 antigen even at concentrations of about 1 ng ml\(^{-1}\). Additionally, the group was also successful in demonstrating the combined potential of anti-spike antibody attached AuNPs and 4-aminothiophenol attached AuNP-based surface-enhanced Raman spectroscopy in detecting SARS-CoV-2 at lower concentrations (4 pg ml\(^{-1}\)) in less than 5 min. Finally, Pramanik et al., [117] also reported the use of anti-spike attached AuNP to inhibit the binding of SARS-CoV-2 to cell receptors. Anti-spike antibody-attached AuNPs have been reported to have 100 % viral inhibition efficiency and hence serve as an effective method for the rapid diagnosis.

![Fig. 7. Naked eye detection of SARS-CoV2 using gold nanoparticle agglomeration-based approach. (Reproduced from Moitra et al. with permissions from the American Chemical Society [114]).](image-url)
and prevention of COVID-19.

Lew et al., [118] developed a colorimetric serological assay using short antigenic epitopes conjugated to AuNPs, without the use of recombinant viral proteins or anti-human antibodies. Amr et al. reported the discovery of four immunodominant B-cell linear epitopes namely S14P5, S20P2, S21P2, and N4P5, which were identified as antigenic targets of IgGs present in the plasma samples of COVID-19 patients. Based on the work done by Amr et al., [119], Streptavidin-mediated conjugation of the epitope to AuNPs was developed by Lew et al., to produce nanosensors for the recognition of SARS-CoV-2 IgG antibodies in human samples. This detection of antibodies was signaled in the form of changes in the absorption spectra of AuNPs. Out of all epitope functionalized AuNPs, S14P5-AuNPs, and S21P2-AuNPs were the most sensitive and N4P5-AuNPs were the least sensitive in recognizing SARS-CoV-2 IgG, although all epitope functionalized AuNPs showed nano-molar range limits of detection. The study also reported enhanced assay sensitivity in human plasma on the passivation of the nanosensor surface with polyethylene glycol (PEG). The PEGylation of S14P5/S21P2-functionalized AuNPs allowed the detection of SARS-CoV-2 IgGs in plasma samples of even recovering patients and was able to discriminate between COVID-positive and COVID-negative samples. This way, the platform as proposed by Lew et al., has a great potential to serve as a highly specific cost-effective serodiagnostic method for the detection of the COVID-19 antigen.

5.2. Carbon-nanomaterials-based diagnosis

Carbon nanomaterials such as carbon nanotubes (CNT), Graphene, and carbon–dots have shown promising diagnostic applications [120]. Shao et al. constructed a field effect transistor (FET) based on high purity semiconducting single-walled carbon nanotube (SCWNT) which was further functionalized with SARS-CoV-2 antibody to assay the presence of SARS-CoV-2 antigen in less than 5 min. In one instance, an anti-SARS-CoV-2 spike protein antibody (SAB) could detect the S antigen (Sag) and in another instance, an anti-nucleocapsid protein antibody, detected the N antigen (Nag) [121]. The density of CNTs in FETs has a tremendous impact. According to Ishikawa et al., it was established that lower-density nanotubes offered higher sensitivity in terms of both detection limit and magnitude of response. These biosensors were also tested against the SARS virus which was able to detect the nucleocapsid (N) protein of the same [122]. Nanobiosensors are explored to provide rapid point-of-care testing with improved specificity and sensitivity and enhanced limit of detection [123–125]. The electrochemical sensors based on screen-printed electrochemical cells (SPEs) have gained attention due to their reliability and sensitivity. Since SPEs can be easily modified with nanomaterials, Fabiani et al. have incorporated carbon black as a nanomaterial for improved electro-analytical performance along with better sensitivity. The magnetic bead-based immunoassay combined with a carbon black-modified screen printed electrode uses spike and nucleocapsid protein as analytes which one can detect the virus present in untreated saliva as a sample [126]. Keeping with this, graphene-based electrodes are also of great interest because of their low cost, ease of fabrication, and high production rate. Choi et al., have reported that the screen-printed graphene electrodes which are made by incorporating graphene with carbon paste or by substituting carbon with graphene especially have superior electrochemical properties owing to its higher electron transfer and a larger surface area [127].

Like CNTs, metal nanoparticles are incorporated in graphene sheets for virus detection and can be used in SARS-CoV-2 testing [128]. Ozmen et al. described a graphene-encrusted electrochemical sensor platform for multiplex sensing of SARS-CoV-2 markers. Recently, Zhao et al., have made use of graphene to make an ultrasensitive sandwich-type-electrochemical detection technology for SARS-CoV-2 [129]. Seo et al., [130] designed FET–based biosensor, where graphene was used as a sensing material. SARS-CoV-2 spike antibody is conjugated onto the graphene sheet via 1-pyrenobutyric acid N-hydroxysuccinimide ester (PBASE), which acted as a highly sensitive and stable virus detection platform. Upon application of cultured SARS-CoV-2 as low as 1.6 × 10^3 pfu/mL, the FET sensor could detect the virus.

Similarly, Zhang et al., connected antibody-antigen interaction with highly sensitive graphene-based FET to give rise to a coronavirus immunosensor that could rapidly capture SARS-CoV-2 spike protein S1 [131]. Krishna et al., functionalized reduced Graphene Oxide FET with SARS-CoV-2 monoclonal antibodies (mAbs). The breakthrough was the reduced limit of detection (0.002 M) hence, a sample with a low copy number of SARS-CoV-2 could be detected [132].

5.3. Quantum dots-based detection

Quantum dots (QDs) also have a significant role to play in diagnostic approaches. The reason behind this is their photo-physical properties and the characteristics of being an inorganic fluorophore. They have a high molar absorption coefficient, are resistant to chemical degradation, and exhibit unique optoelectronic properties [133,134]. Chen et al., made use of thiol-modified niobium carbide MXene quantum dots (Nb2C-SH QDs) to make a novel label-free surface plasmon resonance (SPR) apta-sensor by the detection of N-gene of SARS-CoV-2. The sensor showed high stability, selectivity, and a low limit of detection (LOD) of 4.9 pg mL^-1 [135].

Recently, barcoded-bead assays/systems are developed for use in PoC testing. Udagama et al., have used inorganic quantum dots for barcoding the complex signals which can be discerned in smartphones [136]. Along the same lines Zhang et al., have made use of quantum dot microbeads to capture target antibodies in serum. Later, the results of the quantum barcode serological assay are displayed on a smartphone through an app. This accuracy and effectiveness are advantageous for PoC testing and real-time surveillance of patients infected with SARS-CoV-2 [137].

Another rapid and one-time diagnosis of COVID-19 is developed where SARS-CoV-2 antibody conjugated magnetic graphene quantum dots (QD)–based magnetic relaxation switch (MRSw) recognizes SARS-CoV-2 effectively. Besides that, limit of detection is as low as 248 Particles mL^-1 and the detection time is 2 min, hence making it an efficient diagnostic approach [138].

5.4. Lanthanide nanoparticles-based diagnosis

Owing to unique electronic configurations, lanthanide-doped nanoparticles possess long-luminescence life-times and large and sharp emission bands, among other interesting optical properties. Especially, because of their long luminescence lifetimes, lanthanide-doped nanoparticles are being used for highly sensitive biosensing applications [139,140]. As opposed to the traditional colloidal gold-based lateral flow immunoassays (LFIA), the use of lanthanide-doped nanoparticles ensures better quantification capabilities and avoids the problems of poor stability, photo-bleaching, and unsatisfactory quantum yields which are commonly faced when using conventional fluorescent dyes [141].

Chen et al. [142] used lanthanide-doped polystyrene nanoparticles to detect anti-SARS-CoV-2 IgG in human serum. A nitrocellulose membrane containing a recombinant nucleocapsid phosphoprotein of SARS-CoV-2 was used to capture the specific IgG from the serum. Self-assembled lanthanide-doped polystyrene nanoparticles functionalized with a mouse anti-human IgG antibody were used as the fluorescent reporter. The turnaround time for this lateral flow immunoassay is around 10 min.

5.5. Magnetic nanoparticles-based diagnosis

Landro et al., have given a comprehensive analysis of the application of magnets in biosensor technologies for the medical sector [143]. According to Salazar et al., viral protein from the blood/serum can be
Table 3
Comparative analysis of diverse conventional diagnostic approaches exploited to detect SARS-CoV-2.

| Diagnostic approaches          | Diagnostic types                                      | Turnaround duration | Specificity | Sensitivity | Description | References |
|-------------------------------|-------------------------------------------------------|---------------------|-------------|-------------|-------------|------------|
| Molecular biology approaches  | Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) | 4 h                 | >95 %       | 93.95 % (0.14 copies per μl) | Advantages | [27,33,41] |
|                              | Reverse Transcriptase-Loop Mediated Isothermal Amplification (RT-LAMP) | 1 h                 | 97.6 %      | 100 % (1.0 × 10⁷ copies per μl) | Advantages | [46,48] |
|                              | Reverse Transcriptase-Recombinase Polymerase Amplification (RT-RPA) | 15-20 min           | 100 %       | 97 % (7.659 copies per μl) | Advantages | [51] |
|                              | CRISPR-Cas based technique                            | 30-40 min           | 100 %       | High sensitivity (10 copies per μl) | Advantages | [151] |
| Immunological approaches      | Lateral flow immunoassay                              | 10-15 min           | 97-98.5 %   | 91.3-95.7 % | Advantages | [78,79] |
|                              | Enzyme-Linked Immunosorbent Assay (ELISA)             | 4 h                 | 97 %        | 92 %        | Advantages | [86] |
| Radiological approaches       | Computed Tomography (CT)                              | –                   | 68 %        | 97 %        | Advantages | [96] |
|                              | Magnetic Resonance Imaging (MRI)                      | –                   | 100 %       | 91.67 %     | Advantages | [103] |
| Nanoparticle-based approaches | Dual functional plasmonic biosensor-based Au-NPs      | –                   | The limit of detection is around 0.22 pM | High sensitivity | Advantages | [113] |

(continued on next page)
detected by the magneto-plasmonic biosensing method which employed magnetic nanoparticles for further amplification of surface plasmon resonance signal [144]. Recently, MNPs were used in the amplification of nucleic acid for the detection of a synthetic complementary DNA of the SARS-CoV-2 RNA-dependent RNA polymerase coding sequence. Tian et al., have proposed a novel one-pot circle-to-circle amplification that does not need additional monomerization and ligation steps [145].

5.6. Other nanoparticles-based diagnoses

An arsenal of novel nanoparticle-based diagnostic methods has been developed. In a recent study, thermal detection to quantify SARS-CoV-2, using nano-molecularly imprinted polymers (nanoMIPs), electrografted over low-cost screen printed electrodes has been done. MIPs have high-affinity binding sites for the target and have been used for the recognition of various biomarkers and pathogens. These high affinities and porous nano-MIPs have better binding kinetics and biocompatibility, low cost of manufacturing, and short process of production. The thermal detection of the virus using this technique provided fast and precise detection, along with durability in extreme temperature and pH conditions, leading to improved storage and shelf life in contrast to other antigen detection methods [146]. In another study by Ashkarran et al., super-paramagnetic iron oxide nanoparticles (SPION) were designed with magnetic levitation (MagLev) device utilized as an efficient technology for the levitation of different biogenic cells, biological and non-biological species, incubated in a paramagnetic fluid. In this device, two magnets are placed along the gravity with like poles being opposite to each other. SPION can aid in levitating plasma proteins, providing point-of-care detection of disease. Combining this technique with other sensor platforms would provide a better insight into the fatal bio-molecular patterns denoting high association with SARS-CoV-2 cases [147,148].

### Table 3 (continued)

| Diagnostic approaches                                                                 | Diagnostic types                                                                 | Turnaround duration | Specificity                                      | Sensitivity | Description                                      | References |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------|------------------------------------------------|-------------|--------------------------------------------------|------------|
| Colorimetric biosensing approach based on AuNPs capped with thiol-modified antisense oligonucleotides | Less than 10 min                                                                 | Detection limit 0.18 ng/μL | High sensitivity                                |             | Implement. Improves diagnostic accuracy          | [114]      |
| AuNP-based rapid colorimetric assay                                                  | 30 min                                                                           | 94.12 %             | 85.29 %                                        |             | Advantages. Affordable and Naked-eye detection   | [115]      |
| Anti-spine antibody attached AuNPs based colorimetric assay                         | 5 min                                                                            | Detection limit 4 pg mL\(^{-1}\) | High sensitivity                                |             | Advantages. One-step rapid detection             | [117]      |
| Single-walled carbon nanotubes-based field effect transistor                        | Less than 5 min                                                                  | High specificity with detection limits ranging between 0.55 fg/mL for S-antigen and 0.016 fg/mL for N-antigen | High sensitivity |             | Advantages. Extremely rapid                     | [121]      |
| Carbon-black modified screen-printed electrochemical immunoassay                    | 30 min                                                                           | High specificity with detection limits ranging between 19 mg/mL for S-antigen and 18 mg/mL for N-antigen | –             | Advantages. Sampling not invasive                | [126]      |
| Surface plasmon resonance-based biosensor using niobium carbide MXene QDs functionalized with a thrid group | –                                                                                | A detection limit of 4.9 pg/mL | High sensitivity                                |             | Advantages. Superior sensing performance         | [135]      |
| SARS-CoV-2 antibody conjugated magnetic graphene quantum dot-based magnetic relaxation switch | 2 min                                                                            | The limit of detection is 248 particles per ml | High sensitivity                                |             | Advantages. One-step rapid detection            | [138]      |
| Lanthanide-doped nanoparticles-based lateral flow immunoassay                       | Less than 10 min                                                                 | –                   | –                                             |             | Advantages. Rapid and sensitive detection        | [142]      |
enabling the capacity of RT-qPCR for RNA detection. Plasmonic thermocycling along with multispectral fluorescence monitoring was used for the amplification and detection of the inactivated SARS-CoV-2 virus [149]. Certain other methods have also been reviewed including PLGA (poly lactic co glycolic) nanoparticles, where nanoparticles are conjugated with the S protein of the virus, followed by incubation with antibodies against them, in microplates. Color change of the solution is used for the detection of S protein, at a concentration of femtogram/ml. Other studies showed the detection of SARS-CoV-2 using Europium-chelate nanoparticles conjugated with 59.6 antibodies. The test exhibited 100 % sensitivity and 99 % specificity [150]. The comparative analysis of diagnostic approaches against COVID-19 has been discussed in Table 3.

6. Conclusion

The Coronaviridae family has been responsible for a lot of unexpected outbreaks over the last 2 decades such as Middle Eastern respiratory syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [152]. The outbreak of COVID-19 has again caused immense suffering and deaths. Further, the continuously evolving nature of the virus makes it difficult to contain the infection in the global population of 7.9 billion. Since no specific medicines are prescribed to cure COVID-19, testing and diagnosis at a higher rate deployed in mass quantities is the only way out to curb the global pandemic. The vital features of diagnostic methods are (1) they should be rapid, (2) provide point-of-care, (3) display high sensitivity and specificity, and (4) should be cost-effective.

Molecular-based diagnostic approaches and immunological approaches have been explored extensively to overcome the testing burden. The molecular-based approaches provide higher specificity and reduced turnaround duration but lack rapid testing, quicker optimization, risk of false positive results, and decreased efficacy due to mutations at primer binding sites [43,44,153]. On the other hand, the immunological approaches are rapid, and provide point-of-care but depict average specificity and sensitivity. Nano diagnosis is in its infancy and is continuously being investigated to encounter the drawbacks of these approaches. Diagnostic methods based on nanotechnology are simpler, cost-effective, sensitive, non-labor intensive, and rapid, meeting the heavy demand for diagnosis. Imaging technology with artificial intelligence is a way forward method collaborating in COVID-19 diagnosis. Artificial intelligence facilitates safer, more precise, and more effective imaging [154]. The combination of CT with an artificial intelligence-deep learning approach can overcome the limitation of result determination and be applied to screen the population for COVID-19 with higher precision, specificity and sensitivity. Several deep-learning models have already been proposed for COVID-19 diagnosis [155–158].

Resurgence of COVID-19 pandemic in several regions causes mining of newer efforts to support public health. Precision medicine offers a more targeted approach to prevent COVID-19 infection [159]. It aids in providing specific diagnosis and treatment to individuals based on an array of biomarkers such as genetic variation and phenotypic classification of infected individuals based in their lifestyle and surroundings. This approach will provide personalized medications to infected person resulting in more specific infection mitigation strategy [160,161].

Since, the health, social, economic and educational bodies were focused on controlling the pandemic; the number of new COVID-19 cases are declining. The lessons to learn from this outbreak is that there is an urgent need of an ideal diagnostic approach that can efficiently detect novel diseases witnessed by the human race.

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.

Data availability

No data was used for the research described in the article.

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