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Review Article

Current trends and new methods of detection of SARS-CoV-2 infection

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A B S T R A C T

SARS-CoV-2 is the causative agent of the global pandemic, also known as Covid-19. This virus belongs to a group of coronaviruses and has affected more than ten million people across the globe, causing nearly half a million deaths worldwide. The pandemic has spread worldwide, originating in the Wuhan Hubei province of China in 2019. The disease is a significant challenge as there is no antiviral treatment. This review will address current trends and emerging new methods for detecting SARS-CoV-2 in the laboratoryat present. Reverse transcriptase PCR or RT-PCR is the gold standard for detecting SARS-CoV-2 disease. The seroprevalence of Covid-19 is performed using antibody detection tests using ELISA and antigen detection as rapid tests. In clinical practice, preliminary disease identification is made based on Chest radiographs, computed tomography, and positron emission tomography (PET) scans. As the pandemic has progressed, newer methods of detection like CRISPR, nanotechnology-enabled solutions, and biosensors have emerged as new methods of detecting SARS-CoV-2.

1. Introduction

Belonging to the family of coronaviridae, including the four genera Alphacoronavirus, Betacoronavirus, Deltacoronavirus, and Gammacoronavirus, as well as several subgenera and species, coronaviruses are found in a large variety of animals and humans. In the genus Alphacoronaviruses, Human coronaviruses (HCoVs) include HCoV-229E and HCV-NL63. The first human coronavirus was isolated in 1960 by cell culture and later characterized into HCV-229E and HCV-OC43[1]. Beta coronaviruses of the lineage B originated in 2002, then spread to civets and humans, giving rise to the first epidemic of severe acute respiratory syndrome or SARS CoV in the province of Southern China[2].

Later in 2012, another lineage C emerged in beta coronaviruses and spread from camels to humans, an epidemic observed in Saudi Arabia commonly taking the name of middle east respiratory syndrome or MERS CoV [3, 4]. The year 2019 marked the emergence of a global pandemic and the spread of novel coronaviruses, which first set their foot in the Wuhan Hubei province of China and now are popularly known as the SARS-CoV-2 or Covid -19. Genetic studies of coronaviruses have shown that the novel coronavirus shows 88% of genetic relatedness to the beta coronaviruses of bats [5]. In terms of morphology, coronaviruses are single-stranded positive-sense RNA viruses. The virions of coronaviruses are enveloped with spiked glycoproteins. Other additional structural proteins include Envelop (E), Matrix (M), and the nucleocapsid (N). Transmission between one species to the other and genetic recombination is the main contributing factors to the emergence of novel coronaviruses.

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2. Epidemiology, Clinical, and Public health Significance

The coronavirus endemic species include HCV-229E, HCV-NL63, HCV-OC43, and HCV-HKU1, while the epidemic species include SARS-CoV-1, MERS-CoV, and SARS-CoV-2). Endemic HCoVs cause infections commonly in the winter season, while other species are a common cause of respiratory infections throughout the year[6]. The first epidemic of the SARS-CoV came to an end in the year 2003. However, other respiratory syndromes such as the MERS-CoV remain predominantly in Saudi Arabia. Both these species of coronaviruses, i.e., the SARS-CoV and MERS-CoV, are harbored largely in the zoonotic reservoirs. The global pandemic of the SARS-CoV-2 infection is believed to have originated as an epidemic in Wuhan, in a market in China selling exotic animals for human consumption. Therefore, based on genetic relatedness, the present novel coronavirus has a zoonotic reservoir[4].

It is, however, yet established the exact source of the infection to humans. As the pandemic progressed, SARS- CoV-2, later recognized as COVID-19, became a highly contagious infection. Its variability and distribution among various species are highly unknown; however, the susceptibility of animal reservoirs and their role in the epidemiology of diseases is similar to that of humans in terms of angiotensin-converting enzyme 2 or the ACE-2 receptors [7].

2. 1. Clinical significance and Symptoms

Coronaviruses cause cold-like flu-like infections with an incubation period of 2 to 5 days; however, severe HCV-induced lower respiratory tract infections are rare. In patients with SARS-CoV-2, the clinical symptoms include fever, headache, myalgias, and dry cough. The incubation period is 4-5 days, and respiratory symptoms include cough and dyspnea. These symptoms may remain for up to a week. In individuals with a weakened immune system, atypical pneumonia may develop in 30% of the cases. The incubation period is approximately 5.2 days. In most patients, the onset of the illness begins with fever and cough. Later the disease is characterized by dyspnea and, in severe cases, respiratory distress. Lower respiratory infection sets within 1 week after acquiring the infection[8].

Since December 2019, SARS- CoV-2 has been reported globally in more than 134 countries, evolving faster. As per the WHO data outside China, the greatest number of COVID-19 cases have been reported in Asia and Europe. Case fatality rates vary and depend on the risk factors such as age, diabetes, hypertension, and cardiovascular disorders and malignancies. Therefore, the severity of the Covid -19 disease has been classified into mild, moderate, and severe. It has been observed that patients with chronic underlying diseases pneumonia caused due to SARS-CoV-2 died in 28 days. The mortality is higher in older persons greater than 60-75 years[9]. Among the pediatric cases between the age of 1-17 years, SARS-CoV-2 often causes milder symptoms, and no so far deaths have been reported.

2. 2. Current molecular methods for detection of Covid- 19

2. 2.1. Specimen Collection

Proper standard operating procedures (S.O.P) should be accurately followed before collecting any specimen[10]. It must be noted that appropriate sample collection is of utmost importance in the laboratory diagnosis of SARS-CoV 2 infection[11]. Therefore, the staff should be trained accurately about the collection, packaging, storage, and transport of the samples. The staff should be aware of the guidelines and follow WHO interim protocol[11].

The collected specimen should be considered infectious at every stage, and all specimens should be handled with utmost precaution. Detection of SARS-CoV-2 requires the collection of Nasopharyngeal and oropharyngeal swabs collected appropriately from the nasopharynx and throat. It must be noted that inappropriate sample collection can result in false-negative reports. The swabs should always be transported and placed in the Viral transport medium (VTM)[11]. It is recommended to follow the proper use of personal protective equipment or the PPE during sample collection[12]. The upper respiratory specimen is considered in patients

with milder to moderate symptoms and is easy to collect. Another specimen however, e.g., the bronchoalveolar lavage fluid (BAL) is recommended through bronchoscopy, which is a highly sophisticated procedure requiring well-trained staff. It should be performed under extreme precaution due to the generation of aerosols [13]. Other specimens in severely sick patients include endotracheal aspirates and sputum. SARS-CoV-2 RNA can also be detected from stool, urine, and blood specimens, but they are less reliable for detection compared with respiratory samples [14].

COVID-19 RNA can be re-detected in the stool about two weeks after the onset of symptoms. The upper respiratory specimen should be collected within the first few days of the onset of symptoms as it may reflect the RNA shedding, severity of the illness, and other underlying risk factors. A peak in the RNA levels has been observed within 7-10 days after the onset of the symptoms and a decline after that; however, in patients with the lower respiratory tract infection, the RNA levels remain higher for 3 weeks and more [15]. Biosafety guidelines should be accurately followed, and all the protocols of sample processing should be undertaken during molecular testing, which requires BSL-2 or equivalent facilities. The culture of the virus requires minimum BSL-3 facilities. Molecular methods for detecting SARS-CoV-2 include nucleic acid-based methods such as reverse transcription PCR, a gold standard for diagnosing SARS-CoV-2 infection. These tests may directly detect the genetic material SARS-CoV-2 or indirectly determine the humoral response to Covid-19 infection[12, 16].

RT-PCR uses the reverse transcription of viral genetic material (RNA) into complementary DNA (cDNA) to amplify certain cDNA regions. Probes with the marked sequences are used to identify the genetic targets, and specific primers of the RNA are used to replicate the viral RNATo to identify these goals; repeated serial reinforcement cycles are necessary. In the SARS-CoV-2 genome, four regions include the RdRp gene (RNA-dependent RNA polymerase), the structural protein genes E (virus coat) and N (virus nucleocapsid), and the ORF1ab gene (open reading frame 1a and 1b) [[17, 18].

Commercial kits use various probes and primers for the RdRp, E, and N genes, indicating excellent sensitivity and being special [19]. The present commercial kits use the same protocol for sequential use of the primer/probe for other genetic purposes. Positive real-time RT-PCR test results depend on the cycle threshold (Ct) values. Indicates the number of amplification cycles required by the target gene to cross the threshold level. Thus, CT values are inversely related to viral load and can provide an indirect way to quantify the number of viral RNA copies in a sample. A Ct value of 15-35 is considered positive for Covid-19; however, it may vary in different kits. If no viral RNA is detected, the test is regarded as negative. CT values are, therefore; Therefore, it can be said that using Ct values as a viral load proxy is affected by self-measurement and the factors in the sample matrix can affect the amplification efficiency[20, 21].

Although a gold standard for detecting SARS-CoV-2 infection, the sensitivity and specificity of RT-PCR are estimated to be approximately 70% and 95%. Several factors can interfere with the outcome of the results. They can be attributed to the virus, methodology, sample collection, viral load, the onset of the symptoms, and disease severity. Mutations in viral genomes are also a contributing factor to the delivery of primers/probes in obsolete kits. Still, to date, SARS-CoV-2 has been mutated, but no significant results have been found in the diagnosis of RT-PCR. A mismatch between primer/probe can also cause false-negative results. Thus, ideally, more than one region of the virus genome should replicate simultaneously or sequentially [19, 22]. Nasopharyngeal swabs should be immediately transported to the laboratory if storage is required. The samples should be refrigerated. False-positive results are often related to errors in sample collection handling or contamination from external sources.

Simpler techniques do not require sophisticated devices but can produce faster results. Qualitative detection of the E and N

protein genes is achieved through the GeneXpert (Cepheid Company) platform, where the amplification process takes place within a cartridge and provides results in 45 min. Spot tests for SARS-CoV-2 proteins, which use lateral flow assays, are beneficial for detection in areas that do not have specialized laboratories. The genetic material in respiratory tract secretions has no direct relationship with virus viability or infectivity since inactive or dead virus particles can be identified [23]. Therefore, a patient with a positive RT-PCR test is not always able to infect other people. The viability of SARS-CoV-2 and consequent infectivity can be assessed directly, *in vitro*, by its ability to penetrate the cells and, indirectly, through the threshold cycles (the lower the Ct, the higher the viral load) or identification of sub-genomic RNA (which are transcribed only by viable viruses) [24].

Serological tests identify the presence of humoral response to SARS-CoV-2. Antibodies of IgA, IgM, and IgG isotypes specific to different virus proteins are detected by enzyme-linked immunosorbent assay (ELISA) or chemiluminescence immunoassays (CLIA), and the latter is more sensitive[25]. It is known that the priority immune response to the virus is related to the cytotoxic activity of NK cells and CD8 + T lymphocytes. There is evidence of robust cellular response to SARS-CoV-2, regardless of the results of serological tests [15]. However, tests to evaluate the specific cellular immune response for SARS-CoV-2 are not yet commercially available. Antibodies against S protein, where the receptor-binding domain (RBD) is located, are particular for SARS-CoV-2[26]; their levels correlated with the virus's neutralization capacity[27].

However, the role of antibodies directed to other proteins in the pathogenesis of COVID-19, even promoting a greater penetration of the virus into cells, still need to be elucidated. The sensitivity and specificity of serological tests vary according to the testing technique, specificity of the antibody studied, duration of symptoms at the time of collection, and immunocompetence of the individual[28]. However, these tests' actual sensitivity and specificity values are difficult to define, considering that a gold standard for diagnosis with high sensitivity is not yet available [29]. Most of the tests used in scientific journals have not been reviewed.

Evaluation of specific antibodies is more sensitive and less specific to N protein because it is higher in coronaviruses. Antibodies directed to S protein are more specific to SARS-CoV-2 because this protein is RDB [23]. In addition, other factors that interfere with the results are the duration of symptoms when the blood is collected and the severity of the clinical picture. IgM is identified from the fifth day of symptoms and, more significantly, from the eighth day onwards. The specific dose of IgA is probably more sensitive, and the values appear to increase earlier than the IgM level. Specific IgG levels will be detectable from the tenth day of symptoms and signs from the fourteenth day onwards. Therefore, these tests are not suitable for the early detection of COVID-19[30]. However, when RT-PCR is not available to us or is negative in the face of the proposed clinical picture when the patient has had symptoms for more than 14 days is relevant or to assist in the diagnosis of COVID-19-related multisystemic inflammatory syndrome [31].

Some studies report patients with mild (or even asymptomatic) COVID-19 present lower levels of SARS-CoV-2-specific antibodies or may even not develop detectable levels. In comparison, patients with more severe conditions have higher levels of these. This data raises questions about the protective capacity of antibodies and may suggest the participation of specific antibodies in the pathogenesis of COVID-19 [31, 32].

A study has shown that positive serological tests are not associated with reduced virus removal, which may indicate that these tests are positive. necessarily imply prompt resolution of the disease or absence of infectivity [33]. It has recently been shown that specific IgG levels significantly decline after two/three months. Although the immune response to the virus is primarily cellular, it is not yet clear what the consequences of this reduction in virus protection might be. Regardless of the tests used to diagnose,

whether identifying the genetic material of the virus or serological tests, interpret the results based on accuracy.

Test itself, and also on the estimated disease risk before the results. This means that tests developed in regions where the prevalence of SARS-CoV-2 infection is high tend to have lower sensitivity when used in regions where the prevalence is lower. In turn, a positive RT-PCR has greater strength to confirm the diagnosis than a negative test has to discard since it presents high specificity with only moderate sensitivity [34].

Point-of-care tests for antibodies against SARS-CoV-2 using lateral flow assays (usually immunochromatography) are numerous, and many have not been validated. They were tested in the laboratory using serum or plasma; however, they were used with whole blood, which can change its sensitivity to a greater extent. They are not recommended for the individual diagnosis of COVID-19 but may be useful in implementing public policies [35].

2. 3. Emerging methods for the detection of SARS-CoV-2

CRISPR (clustered regularly interspaced short palindromic repeats) based technologies is a new and emerging method for the detection of SARS-CoV-2 from nasopharyngeal swabs. It is a rapid and accurate method based (< 40 min) on the CRISPR–Cas12-based lateral flow assay for the detection of SARS-CoV-2 (Figure 1). This technology utilizes CRISPR-based DETECTOR (DNA Endonuclease-Targeted CRISPR Trans Reporter) and has a visual read for results. This assay performs both reverse transcription and the Loop-mediated isothermal amplification (LAMP) in one step and simultaneously[36].

Cas12 detection from the pre-defined sequences of SARS-CoV-2 follows, leading to the cleavage of the reporter molecule, which confirms the presence of the virus [37]. As reported in a study, the sensitivity and specificity were 95% and 100%. SHERLOCK (Specific High Sensitivity Enzyme Reporter UnLOCKing) is another CRISPR-based detection system targeting the S and ORF1ab gene fragments of SARS-CoV-2 as described by the manufacturer[38].

Sample collection for the Feluda test is similar to RT-PCR from the nasopharyngeal swabs. The first step is to extract the genetic material (RNA) from the sample viral RNA to DNA and its amplification to multiple copies. To increase the probability of detection of the SARS-CoV-2 is the amplification [39]. A Feluda mixture that contains the amplified viral DNA, the guide RNA, and the Cas9 protein is prepared. If the patient's sample has the SARS-CoV-2 RNA it will be detected by the binding of Cas9 protein leading to the formation of a complex [40]. Then a paper strip is immersed in the mixture where the complex moves in a lateral flow. A single line indicates a negative result, while the double line a positive result. Previously Cas9's cousins–Cas12 and Cas13, have been used for the detection of SARS-CoV-2 by some investigators in the US known as Detectr' and 'Sherlock' mentioned in this review above Feluda has been considered on the world's first kit test employing the Cas -9 technology. The kit was tested on over 2000, nasopharyngeal samples and achieved 96% sensitivity and 98% specificity – comparable to that of the RT-PCR [36, 40].

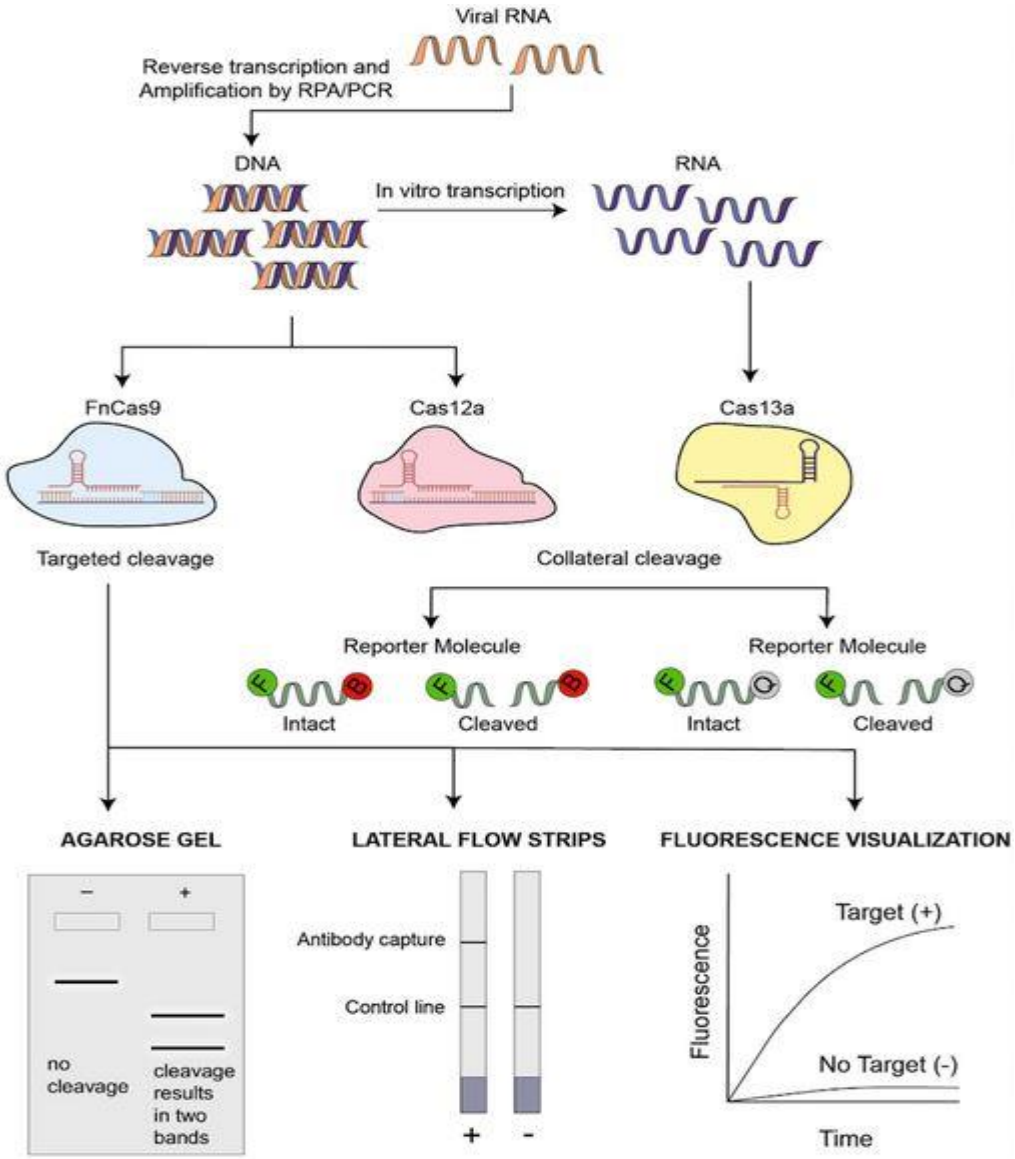

Fig. 1. An overview of the general schematic of CRISPR/Cas based COVID-19 testing methods [36].

2. 4. Dry Swab Test for detection of Covid-19

The nasopharyngeal swab, collected in viral transport media, is the most widely used method for testing SARS-CoV-2 from clinical samples. RNA is extracted from the commercially available kits and detected by reverse transcription PCR. However, it was evaluated [41] the importance of dry swabs and the extraction-free protocol to detect SARS-CoV-2 using simplified direct elution from the dry swab for RT-PCR protocols collected directly into simple Tris EDTA buffer (TE) without compromising the sensitivity of the RT-PCR test. This study also elucidated that further confirmation is required while testing a larger sample size and other parameters [41].

2. 5. Nanotechnology to Detect SARS-CoV-2

Researchers across the globe are now working on the detection of SARS-CoV-2 based on several techniques of analytical chemistry. Today, many research teams are working on diagnosing coronavirus, and various techniques based on the principles of analytical chemistry have been proposed. The great competition among scientists in treating and detecting this virus had terrific results. However, the routine techniques require special laboratory facilities. Detecting the virus outside the human body or any living thing can help prevent infection. In this

regard, nanotechnology can greatly help scientists detect viruses outside living organisms with greater accuracy and selectivity [42, 43].

This review article aims to have a literature survey to provide a logical and scientific solution for detecting the virus at different levels using optical techniques. In this context, using porous nanostructures capable of absorbing/absorbing the virus is essential. For example, scientists can use different nanoparticles of silver or gold to optimize them based on the size and functional groups of their surface (Figure 2). In the next step, the color of these NPs or modified nanostructures change as per the presence of a virus, or even the concentration of the virus in the Air can be measured using different color spectrums and fingerprint techniques. The proposed technique in this work is based on the optical doping properties of NPS in porous nanostructures coated on them, the surface of the mask, and clothes [42, 43].

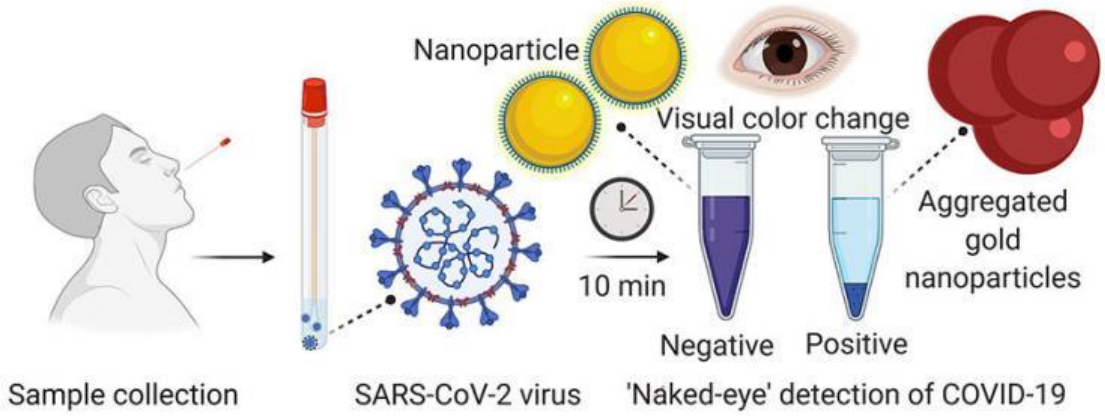

Fig. 2. A nasal swab containing a test sample is mixed with a simple lab test. It contains a liquid mixed with gold nanoparticles attached to a molecule that binds to the novel coronavirus. If the virus is present, the gold nanoparticles turn the solution a deep blue color (bottom of the tube), and precipitation is noticed. If it is not present, the solution retains its original purple color [42].

2. 6. Biosensors as a method for the detection of SARS-CoV-2

As the COVID-19 pandemic is becoming alarming and severe due to its massive spread, various health agencies are focusing on developing rapid kits for detecting SARS-CoV-2, thus developing innovative diagnostic tools based on the protein structure of the virus. The development of first biosensor for the detection of SARS-CoV-2 was developed by Nguyen *et al*. 2020 [44]. Biosensors work on the molecular detection of viral genomic RNA, membrane proteins, and spike glycoproteins.

To overcome the limitations of conventional detection methods, a particular method known as the RT-LAMP (Reverse Transcription Loop-Mediated Isothermal Amplification) was developed by Zhu *et al*. in 2020.[33]The investigators have evaluated the one-step RT-LAMP mediated with Nanoparticles-Based Biosensor (NBS), RT-LAMP-NBS assay for rapid and accurate diagnosis of SARS-CoV-2 where LAMP primer sets, F1ab (open- reading frame 1a/b), and np (nucleoprotein) genes of SARS-CoV-2 are simultaneously amplified and detected in a one-step and single-tube reaction. NBS could easily interpret these detection results. This method could detect 12 copies (each of the detection targets) in one reaction. This method was less error-prone, thus providing high specificity and very few false-positive results [45].

The method had 100% sensitivity in one hour of detection in clinical samples. Modified gene editing as a biological sensor using CRISPR-Chip coupled with a graphene-based Field Effect Transistor (FET) can detect up to 1.7 FM quantity of nucleic acid without amplification. This method can be completed within 15 minutes. CRISPR–Cas12-based lateral flow assay technique is also gaining a

lot of interest as an accurate method for detecting SARS-CoV-2 [37]. Utilization of coating of the graphene sheets of the FET with a monoclonal antibody against the SARS-CoV-2 spike protein is used in FET-based biosensing devices. The sensitivity of this method was determined using antigen protein, cultured virus, and nasopharyngeal swab specimens from COVID-19 patients. The present FET biosensor device could detect 1 pg/mL concentration (cont.) of SARS-CoV-2 spike protein in phosphate-buffered saline (PBS) and 100 fg/mL conc. in the clinical transport medium[46].

3. Imaging Methods

3. 1. Role of X-ray

X-ray chest has played an immense role in the management of COVID pneumonia. From the early manifestation to follow-up, it plays a significant role in assessing disease severity and identifying the extent of pulmonary involvement. Guidelines from the Fleischner Society for thoracic radiology recommend considering chest radiography and covid-19 testing when inpatients have marked respiratory symptoms, which they define as "hypoxemia, moderate-to-severe dyspnoea," after considering appropriate differential diagnoses [47].

3. 2. Role of CT

Though X-ray can identify the pulmonary involvement, the three-dimensional analysis and exact characterization of pulmonary involvement is not possible by plain X-ray. This limitation is overcome by a CT scan of the chest, preferably HRCT. Apart from the diagnosis of covid pneumonia, it also helps in scoring the severity, which directly helps in the management as well as prognostication of the patients. Though it has specific findings, HRCT cannot differentiate viral pneumonia from the same virus family, which manifests with similar findings. Also, it has been found at times that adenoviral infections can manifest with similar CT findings [48].

Before initiation of treatments, the sum score of pacification size in the HRCT positively correlates with the days from illness onset to initial CT. Also, with the follow-up CT examination, the extent of progression and characterization of the lesion can be done along with the correlation of other laboratory parameters [49].

It has also been observed that imaging manifestations of early-stage COVID-19 infection are relatively mild, and the imaging findings of some patients are not typical, which can easily lead to missed diagnoses. Thus, suspected cases need to be closely monitored, and epidemiological history and clinical laboratory examination should also be considered during diagnosis [50].

3. 3. Role of Positron Emission Tomography (PET/CT)

PET/CT (positron emission tomography) is a hybrid technique that allows both anatomical and metabolical evaluation using different radiopharmaceuticals. 18F-FDG (Fluoro deoxy glucose) is a common radiopharmaceutical with immense potential for clinical use in various malignancies, infections, and inflammatory conditions [51]. PET/CT is not a routinely recommended investigation for COVID infection. As many cancer patients also get infected with COVID-19 infection, during the routine investigation, either for staging or in follow-up, incidental observations have been reported in the literature. It has been able to diagnose many asymptomatic cancer patients [52].

FDG PET/CT, however, has the potential to identify extrapulmonary involvement of the COVID-19 infection, as evidenced by Minamimoto et al. They observed even GIT, kidney, heart, blood vessels, and bone marrow involvement can be identified in the same patient infected with COVD19 [53].

4. Conclusion

Molecular diagnostic methods, cruisers, dry swab tests, nanotechnology methods, biosensors, and CT scans can all be powerful diagnostic tools for detecting COVID-19. Ensuring the quality of the developed diagnostic kits is also very important in this scenario. Although much progress has been made recently in the serological diagnosis of COVID-19, there are still concerns about the sensitivity and specificity of the assays. This study demonstrates the importance of

different methods of detecting Covid-19, each of which is very important.

Abbreviations

CLIA: Chemiluminescence Immunoassays
CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
CT: Cycle Threshold
ELISA: Enzyme-Linked Immunosorbent Assay
FDG: Fluoro Deoxy Glucose
FET: Field Effect Transistor
FET: Field Effect Transistor
LAMP: Loop-Mediated Isothermal Amplification
NBS: Nanoparticles-Based Biosensor
PBS: Phosphate-Buffered Saline
PET: Positron Emission Tomography
RBD: Receptor-Binding Domain
RBD: Receptor-Binding Domain
VTM: Viral Transport Medium

Conflict of Interests

All authors declare no conflict of interest.

Informed Consent

The authors declare not to use any patients in this research.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publication

All authors read and approved the final manuscript for publication.

Availability of data and material

All the data are embedded in the manuscript

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Author contributions

All authors are equally involved in the preparation of this manuscript and endorse the manuscript.

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