
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Measurement: Sensors 16 (2021) 100052

Contents lists available at ScienceDirect

Measurement: Sensors

journal homepage: www.sciencedirect.com/journal/measurement-sensors

# Current challenges in identification of clinical characteristics and detection of COVID-19: A comprehensive review

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ARTICLE INFO

*Keywords:*
Coronavirus
Characteristics of COVID-19
Diagnostic methods of COVID-19
RT-PCR
Point of care device

ABSTRACT

World Health Organization (WHO) declares the COVID-19 outbreak as a pandemic. The newly emerging infection has caused around one million deaths worldwide and still counting. There is no specific treatment for the disease, and it can only contain by breaking the spread. So that early and rapid diagnosis of the infection is the only way to control the outbreak. The COVID-19 virus affects the human respiratory system and subsequently infects other vital organs. In consideration of the diagnosis, the present review focuses on the critical diagnostic approaches for COVID-19, including RT-PCR, Chest-CT scan, some biosensor-based systems, etc. Moreover, this review is a specific bird's eye view on recent developments on the point of care devices and related technologies. Additionally, it presented a small glimpse of the pathophysiology and structural aspects of COVID-19. Therefore, the current review can motivate and help the reader to develop cutting-edge diagnostic technologies for the early and rapid detection of the COVID-19.

## 1. Introduction

The first laboratory corona infection was reported on December 1, 2019, in Wuhan, China. The corona outbreak initially involved in the local market of Huanan seafood market, with 41 cases were reported [1]. An epidemiological alert was issued on December 31, 2019 by the local health authority of China to shut down the market. On February 6, 2020, there were 28,276 confirmed corona cases, 565 deaths, outspread at least 25 countries. Followed by Hubei province, many other cities, provinces, and municipalities were affected by this virus, and it got transmitted to 215 countries globally. WHO issued a public health emergency of international concern (PHEIC) apprehension on January 30, 2020 [2].

According to the WHO report, till October 5, 2020, the confirmed cases with COVID-19 were around 34.8 million, reported deaths over 1 million, and 215 countries affected. WHO publishes novel coronavirus cases country-wise and are as follows, cumulative cases reported in USA is 7,256,234 confirmed and 207, 366 deaths, in Brazil 4,880,523 confirmed, and 145,388 deaths, in UK 480,021 confirmed, and 42, 317 deaths, in Russia 1,215,001 confirmed, and 21,358 deaths, whereas in India 6,549,373 confirmed and 101,782 deaths occurred till October 5, 2020 [3].

The outbreak of this mysterious pneumonia was characterized by dry cough, fever, sore throat, breathlessness, acute respiratory distress syndrome, acute respiratory failure, and other complications. According to the viral nomenclature guidelines, the formal name of the virus was given by the International Committee of Taxonomy of Viruses (ICTV). The new "COVID-19" which is the abbreviation of "coronavirus disease 2019" was announced by the WHO. The novel coronavirus is also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most of the questions related to COVID-19 remain unsolved, including its origin, extent, ability to infect other animals, duration of transmission in humans, and spectrum, the pathogenesis of infection. The outbreak of COVID 19 causes a severe threat to global health. So, effective vaccines and therapies must be developed as earliest as possible [4–6].

Coronavirus has "crown-like" spikes on the surface, and its enveloped with the positively charged single-stranded RNA. It has a size ranging from 60 nm to 140 nm in diameter with spike-like projections on its surface [7]. There are four types of coronaviruses, namely HKU1, NL63, 229E, and OC43, which cause mild respiratory symptoms in humans. About the genomic similarity, the virus differs from its ancestors, such as severe acute respiratory syndrome (SARS) by 79% and Middle East

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https://doi.org/10.1016/j.measen.2021.100052
Received 12 October 2020; Received in revised form 7 May 2021; Accepted 19 May 2021
Available online 5 June 2021

Respiratory Syndrome (MERS) by 50%. The genetic data available on the COVID-19 belongs to the beta-coronavirus genus member, and it can bind to the angiotensin-converting enzyme-2 (ACE-II) receptor in humans epithelial cells [8]. There have been two events in the past two decades wherein crossover of animal beta-corona viruses to humans has caused severe disease. The first such instance was in 2002–2003, when a new coronavirus of the β genera and origin in bats crossed over to humans via the transitional host of palm civet cats in China's Guangdong province. This virus, nominated as SARS coronavirus, affected 8422 people in China and Hong Kong and caused 916 deaths (mortality rate 11%) before being contained [9]. A decade later, in 2012, the MERS coronavirus, also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%) [10].

There are three main transmission routes for the COVID-19 viz. droplet transmission, contact transmission, and aerosol transmission. The epidemiology, biology, and physiology of COVID-19 are unique from SARS and MERS. COVID-19 affects different people in different ways, with various symptoms. The most common symptoms are fever, dry cough, tiredness. In contrast, less common symptoms are body pain, sore throat, diarrhoea, conjunctivitis, headache, loss of taste or smell, a rash on the skin, and discoloration of fingers or toes. The serious symptoms include difficulty breathing or shortness of breath, chest pain or pressure, and loss of speech or movement. The preventive measures must be followed in order to ensure safeguard in person and to the community spread of the virus. The preventive measures include washing hands, wear a face mask, avoid contact with sick people, and always cover while coughing and sneezing [11].

The early diagnosis of the infection is crucial to control the spreading and effective management of disease progression. Currently, well-developed molecular diagnostic tools such as RT-PCR and Chest-CT are extensively in use; however, researchers are extensively working on the development of various novel and sensitive diagnostic approaches. This review emphasizes diagnostic tools like RT-PCR, CT, LAMP, and other point-of-care devices. It also focused on the currently developing and developed cutting edge technologies and on a positive note we have also discussed the other potential alternatives for the development of rapid and specific sensors/kits for COVID-19.

## 2. Pathophysiology

Coronavirus genome is a single-stranded positive-sense RNA. It belongs to a subfamily of coronaviridae, also comprises four genera i.e., Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. The genomes and subgenomes of coronavirus contain six "open reading frames (ORF)." The genome near the 3′ terminus of ORFs encodes four structural proteins spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. In addition to the structural proteins, different coronavirus encodes particular structural and accessory proteins such as 3a/b protein, 4a/b protein, HE protein, etc. All the accessory proteins and structural proteins are translated from the subgenomic RNAs to coronaviruses [12]. The genome size of the coronavirus is ~30 kb largest among all RNA viruses with 5′-cap structure and 3′-poly-A tail. The giant genome size of the coronavirus might be related to the distinct feature of the coronavirus replicase transcriptase complex (RTC). The typical structural genome sequence of the coronavirus belongs to the cluster of beta coronaviruses that includes Bat-SARS-like (SL)-ZC45, SARS-CoV, Bat-SL ZXC21, and MERS-CoV. The genome orientation of coronavirus shows 58% identity to non-structural protein-coding region and 43% identity of the structural protein-coding region among different types of coronaviruses, with 54% at the whole genome level, suggesting the non-structural proteins are more conserved and the structural proteins have more variety to the suitable fluctuating environment [5,13]. Fig. 1 depicts the structure of SARS-COV-2.

The coronaviruses with α and β are prone to infect mammals, while γ and δ genera can infect birds [1,14]. The virus enters into a human being

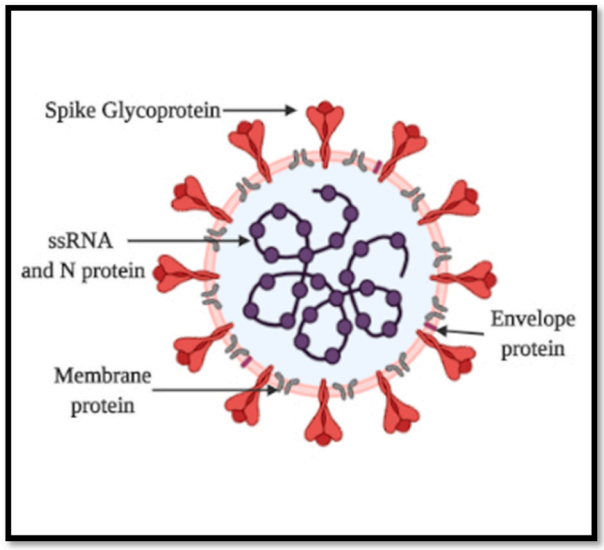


**Fig. 1.** The illustration for the structure of Novel coronavirus.

by the respiratory tract and reaches the alveoli. The alveoli contain two types of pneumocyte cells viz, type I and type II. Type I pneumocytes are involved in gas exchange, and Type II produces a respiratory surfactant [15]. The surfactant brings down surface tension within alveoli, and it results in comfortable and effortless breathing. Once the virus enters into alveoli, it will attack its primary target i.e. type II pneumocyte cells [16]. The spike part of the virus binds to ACEII present on the surface of type II pneumocytes [4,17]. After successful receptor binding, protease enzymes like TMPRRS2 and cathepsin present on cell membranes break the S protein and thereby, help the virus to access the cytosol of the host cell. The S- protein contains two subunits as S1 and S2. The S2 subunit results in two site cleavages in which one is important for separating the receptor-binding domain. The other is responsible for exposing fusion peptide that inserts into the membrane of the host cell [18]. This process leads to the formation of antiparallel bundles of six-helix, followed by fusion by mixing viral and cellular membranes. In this way, the viral genome releases into the host cell cytoplasm. The coronavirus RNA (+) contains polyproteins pp1a and pp1ab. These polyproteins get proteolyzed to form Replicase/Transcriptase protein, which plays an essential role in replication and translation respectively. In the next step, these proteins binds to the coronavirus RNA that results into formation of replicase/transcriptase complex (RTC) [19]. The RTC complex then replicates to form coronavirus genomic RNA (−), complementary to coronavirus RNA. The complementary coronavirus genomic RNA undergoes discontinuous transcription to form subgenomic RNA of different lengths that undergo translation to form various viral proteins. These viral proteins lead to form new coronavirus progeny. This progeny release forms the cell by means of exocytosis [20]. Fig. 2 demonstrates the illustration of the coronavirus cell entry and release mechanism.

## 3. Clinical symptoms

The signs and symptoms of the coronavirus are observed after its incubation period of 14 days. There are several common symptoms involved in this infection i.e. fever, cough and shortening of breath, loss of smell, diarrhoea, severe vomiting, etc. The people suffering from chronic diseases like diabetes, lung, kidney diseases, etc. are more prone to infection [11,21]. Moreover, In severe cases, it is observed that, patient have difficulty in walking, confusion, bluish face or lips, coughing up blood, kidney failure and decrease in WBC count. Another majority of the papulation is asymptomatic however some common compliance reported in such population is anosmia, ageusia and weakness [22]. The Fig. 3 illustration corroborates the COVID-19 effect on each organ and

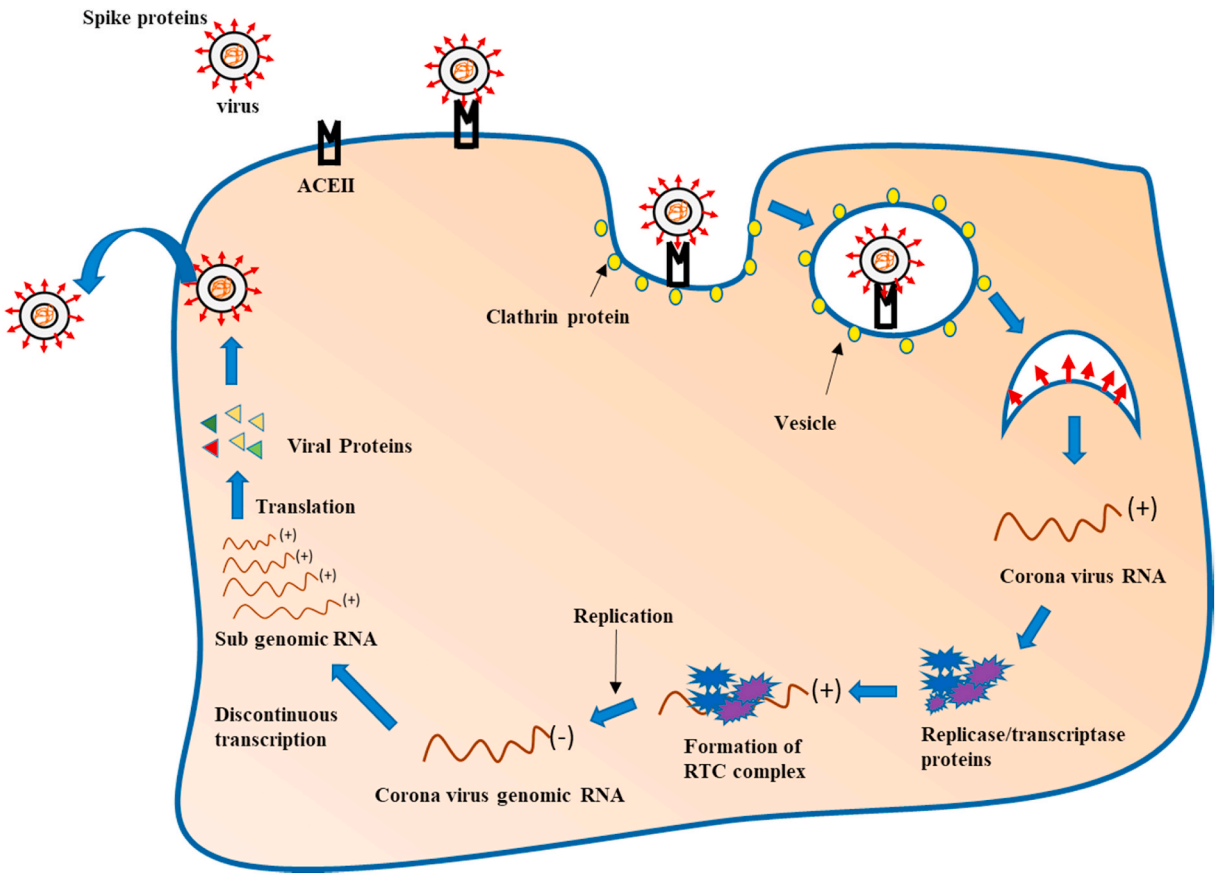


**Fig. 2.** The illustration for the coronavirus cell entry and release mechanism.

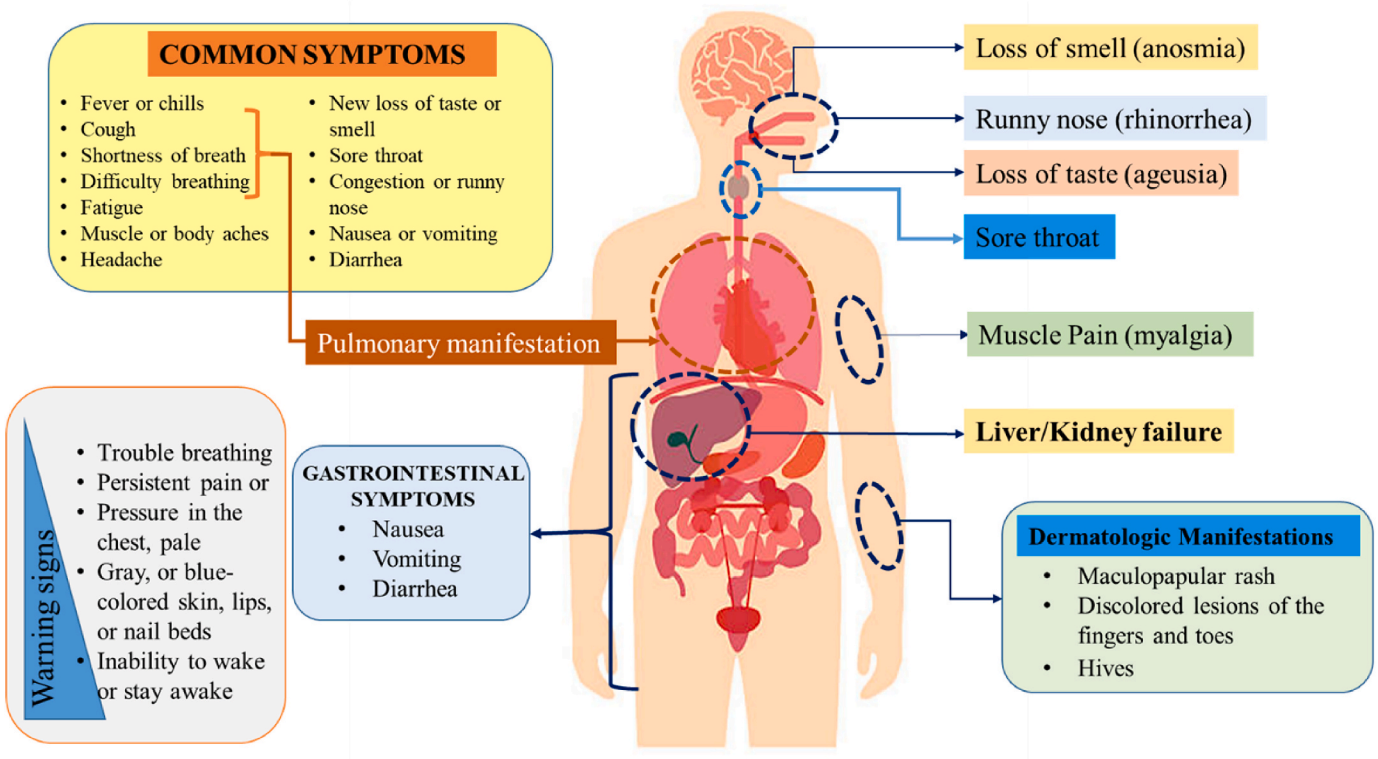


**Fig. 3.** The illustration for the clinical symptoms of the COVID-19.

organ system.

### 3.1. Treatments approaches

Presently there is no specific treatment available in the market for COVID 19. The available treatment is symptomatic [23]. Convalescent plasm therapy is used to decrease the death rate of COVID 19. The plasma obtained from COVID19 recovered patient is called convalescent plasma. This convalescent plasma contains antibodies against the virus [24]. Several randomized double blind clinical studies and case reports are already published in the evaluation of therapeutic efficacy and safety issue with this therapy. The recommended viral neutralization titer cut-off for convalescent plasma is at least $\geq$1: 160 for COVID-19. But still now, there is no standardize evidence based report is there which suggest that the convalescent therapy is completely safe. The only advantages with the convalescent therapy is that is can overcome the shortage of medications or the drugs and can be given to the patient during life threatening situation [25]. Another positive points with the convalescent therapy is that the clinical efficacy of this practise results very fast as compared to other drug based treatment. The use of convalescent plasma is limited due to proper exploration of molecular mechanism and unknown specific therapeutic components of the convalescent plasma. The possible adverse effects of the convalescent plasma therapy can be broadly categorizing into the three major aspects-immunological reactions, physiochemical reactions and infectious risks [26]. Under the immunological reactions various cross-reactivity has been observed such as anaphylactic/anaphylactoid reactions, mild allergic reactions, haemolysis, and transfusion-related acute lung injury. The physiochemical reactions due to convalescent plasma results fluid overload, citrate toxicity, and chemical toxicity.

Oxygen therapy is majorly used in the treatment intervention of patients with high risk. Several drugs are currently using to reduce the fatality rate, such as systemic corticosteroid, hydroxychloroquine, some antiviral drugs (lopinavir, and remdesivir, etc.) [14]. The systemic corticosteroid is used to treat viral pneumonia. At this time, remdesivir, chloroquine, and hydroxychloroquine are trending and the first choice of drugs for COVID19. It acts by manipulating the endosome's pH and preventing the virus [27]. Early diagnosis plays a crucial role for better treatment and mitigation so that various diagnostic approaches developed and underdevelopment have been spectaculated in the upcoming section.

## 4. Diagnostic tests

Early detection of the infection is critical aids to control and cure of the disease. The diagnostic approaches for the COVID-19 involve classical molecular biology tools, clinical symptom examination and most recent point of care devices. Most of the diagnostic tools are under development. Some of the vital diagnostic approaches have been emphasized as follows.

### 4.1. Molecular diagnostic tool: RT-PCR

Polymerase chain reaction (PCR) is a molecular biology technique to detect and amplify DNA and RNA sequences. PCR is highly sensitive and requires only a few hours for completion of the test. It requires minimal use of the template for the detection and amplification of the sequences. RT-PCR is the advanced form of PCR which uses RNA as a template. It is basically used for the detection and amplification of the RNA. The RNA sequence is transcribed into cDNA by the reverse enzyme transcriptase (RT), which is further amplified. The first step in this process is the formation of the DNA/RNA hybrid. The RNase H function of the RT results in the degradation of the RNA from the hybrid. The DNA dependent polymerase activity of the RT then completes the cDNA formation. Further, it undergoes denaturation, annealing, and amplification, just like basic PCR, to perform the sequence analysis.

Real-time RT-PCR is efficiently used to detect the genetic material from the pathogens like COVID-19 [28]. Fig. 4 illustrates the process of diagnosis by RT-PCR. After collecting the samples where COVID-19 resides viz. throat and nose, the samples are treated with a chemical to eliminate the fats and proteins. The extract now contains only the patient genetic material, and if infected by the virus, it also contains the RNA of coronavirus too. The RNA is then reverse transcribed into DNA by RT. The testing will be carried out by the addition of the complementary DNA of the virus. Table 1. gives the primer sequence for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain whose sequence has been obtained by Sah et al. from the patients returning to Nepal from Wuhan [29]. The binding of this complementary fragment to the viral DNA results in the detection of the virus. Various marker labels are used for the detection of viruses. The mixture is then placed in the PCR machine and undergone cycles of temperature (heat and cool) to allow the release of certain chemicals that result in the formation of copies of viral DNA. Each cycle results in the viral DNA viz amplification. one copy becomes two, and then two copies become four after each cycle. During the formation of new copies, a marker attached to the DNA strand releases a fluorescent dye. The fluorescence measured by the PCR machine, and the value is displayed in real-time on the computer screen. Once a certain level of fluorescence has been obtained, then the virus's presence is confirmed as a positive result. The number of cycles reveals the severity of the virus. The less the cycles to get sufficient fluorescence more severe is the infection. Still, the RT-PCR is the best know method for the diagnosis of COVID19, which is discussed later on in this section.

### 4.2. Computed tomography (CT) scan

The CT scan is a medical imaging technique that uses X-rays from different angles aimed towards the patient to produce the cross-sectional (slice) images of the targeted body parts. These sliced images are called the tomographic images, stacked digitally by using a computer program to produce the 3-D impression of the body's targeted area [31]. The COVID-19 infected patient has many lung oddities, and they mapped using CT. Fig. 5 represents the CT images of various age group people infected with COVID-19. The following are the researchers' findings in detecting the COVID-19 infection by both CT and RT-PCR.

CT plays a crucial role in detecting COVID-19, but it has been reported that the patient with positive COVID-19 by RT-PCR has shown normal CT in some cases [32]. COVID-19 pneumonia includes most discriminating features like peripheral distribution, vascular thickening, reverse halo sign, and ground-glass opacities [33,34]. Radiologists observed high specificity and moderate sensitivity in differentiating the COVID-19 with viral pneumonia by chest CT. It has been reported that three radiologists from china had observed 94, 88, 24% specificity and 72, 72, 94% sensitivity in differentiating 205 viral pneumonia cases from that of 219 COVID-19 cases. The USA radiologists had observed a 100, 93, 93, 100% specificity and 93, 83, 73, 73% sensitivity in the same [35]. Researchers had observed that 20/36 patients (56%) images within two days of the onset of the symptoms had shown normal CT findings [34]. Ai et al. reported that 21/601 COVID-19 positive patients detected by RT-PCR had shown normal CT findings [36]. In some cases, the CT reports are normal in symptomatic patients in initial stages and later showed abnormalities as the situation becomes severe [37]. Reports have also shown normal CT findings even after ten days of diagnosis by RT-PCR [34]. Therefore, the CT can be a good technique to detect the lung infection in COVID-19, but RT-PCR is the gold standard even in the virus's low load (very early stage of the infection).

### 4.3. Laboratory serological testing

Beside the molecular diagnostic and CT, there are some other testing protocols are also available for the diagnosis of COVID-19. These tests are broadly termed as serological tests or antibody tests. Commonly,

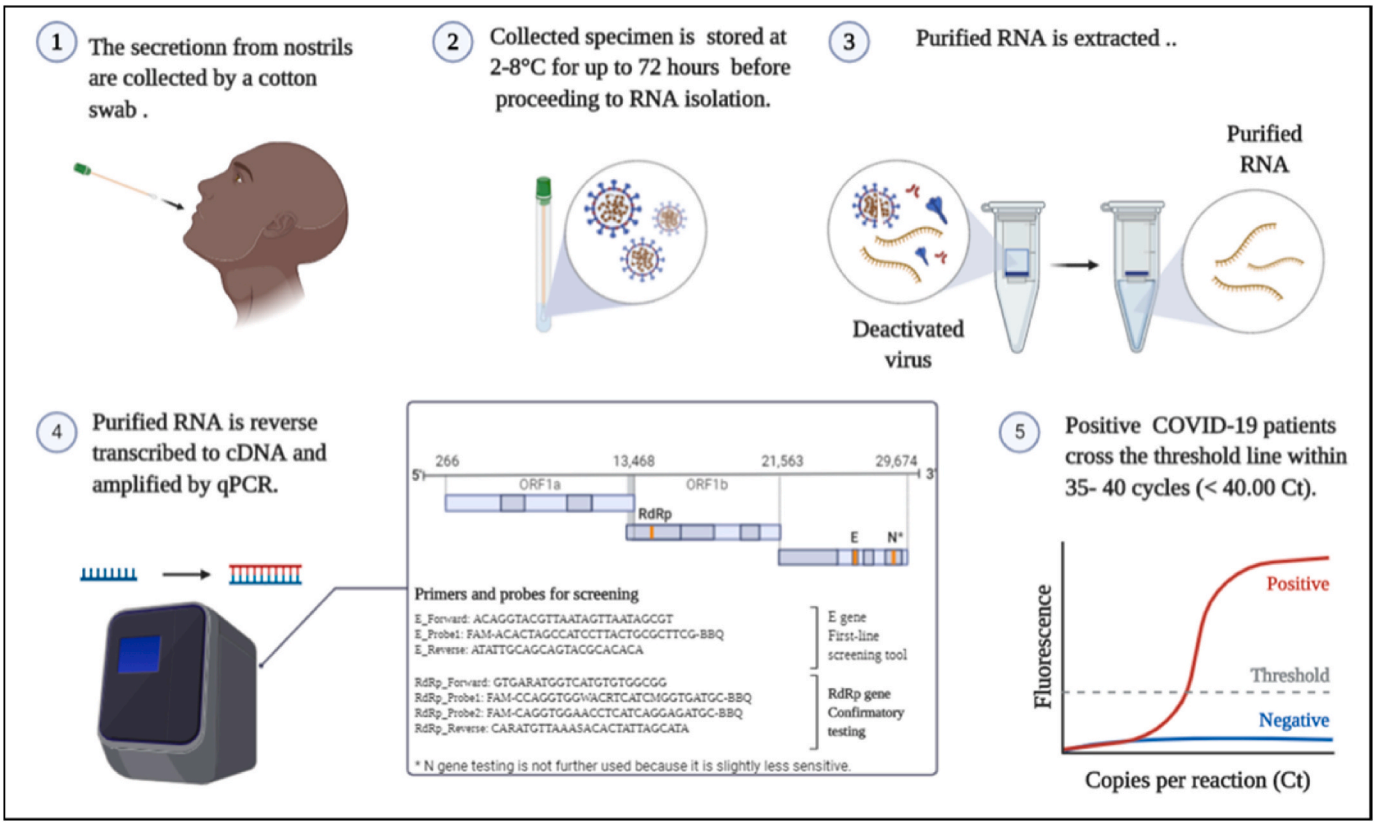


**Fig. 4.** The illustration for COVID-19 diagnostic test through RT-PCR.

**Table 1**
Primer sequence used for the specific genome of COVID-19 [30].

| Gene | Primers[a] |
|---|---|
| QRF1b | |
| a. Forward | 5′-TGGGGYTTTACRGGTAACCT-3′ |
| b. Reverse | 5′-AACRCGCTTAACAAAGCACTC-3′ |
| c. Probe | 5′-TAGTTGTGATGCWATCATGACTAG-3′ |
| N | |
| a. Forward | 5′-TAATCAGACAAGGAACTGATTA-3′ |
| b. Reverse | 5′-CGAAGGTGTGACTTCCATG-3′ |
| c. Probe | 5′-GCAAATTGTGCAATTTGCGG-3′ |

[a] Y is C or T; R is A or G; W is A or T.

Immuno-fluorescent Assay (IFA), enzyme-linked immunosorbent assays (ELISA), immune-chromatographic tests (ICT), neutralization assay and chemi-luminescent based assays are being developed and practiced for the detection of several viruses [38]. However, the US-FDA recommended the serological testing (e.g., IgM, IgG) is only for the identification of prevalence to identify the containment zones. Hence, these tests do not apply to the final confirmation of COVID19 [39]. According to a 23rd May 2020 CDC also implemented this serological testing to gather the statistical information regarding the spreading of SARS-CoV-2 [40]. Some of the standard serological tests have been given in Table 2. However, due to the higher frequency of false-negative results, the antibody tests are not widely used, but they are recommended for preliminary screening [41].

### 4.4. Point of care devices and technologies under development

Various medical bodies worldwide, including WHO, encouraging novel technologies in the knowledge of rapid detection, portable, cost-effective, and highly reliable diagnostic tools for COVID19. Some technologies are already reported, including paper-based colorimetric sensors for rapid detection, where the antibody-antigen (COVID-19) interaction provides a color change as a positive result for COVID19 infection. A similar kind of approach is the detection of the present host antibodies in the blood. Generally, the antibodies produced in response to the antigen is a normal immunological phenomenon. However, the antibodies' production depends upon several factors such as age, sex, nutrition status, and many more. This approach is more useful in the recovery phase of the COVID-19 infection, but early-stage detection will be a false negative. Hence, WHO not recommended this approach for regular diagnosis; however, it can be useful in vaccine development [48]. Therefore, the accurate, early stage, rapid detection technologies are highly needed to contain the disease. Various research groups around the globe are extensively working on the development of such technologies. For instance, a start-up from India, My Lab developed *CovE-Sens* technologies. They introduced, two platforms; modified PCR based methodology and portable chip-based assay. The firm claimed that technology could examine 50 samples per hour, which is relatively fast compared to the existing kits [49]. Similarly, Siemans Healthineer developed the Fast Track Diagnostic (FTD) SARS-CoV-2 Assay kit. The diagnosis kit is a modified PCR assay; the kit's performance was optimized with Biomerieux EasyMag Extraction System and the Applied Biosystems 7500 Real-time PCR Thermocycler [50]. The system's reported advantages are high specificity due to dual targeting in a single well, covers highly conserved genomic region within the N gene and ORF1ab, and doesn't require additional training assay setup since the protocol is the same as exiting PCR assay [51]. Bosch Healthcare Solutions recently developed rapid and point-of-care molecular diagnostic technology. It comprises the Bosch Vivalytic analyzer and Vivalytic test cartridges. The reported benefits of the technology are its a point of care device, no need for sample preparation & trained human resource, high specificity, and it can detect eight other pathogens along with COVID-19 [52]. The USA based firm Lab Corp. developed a home kit for the COVID

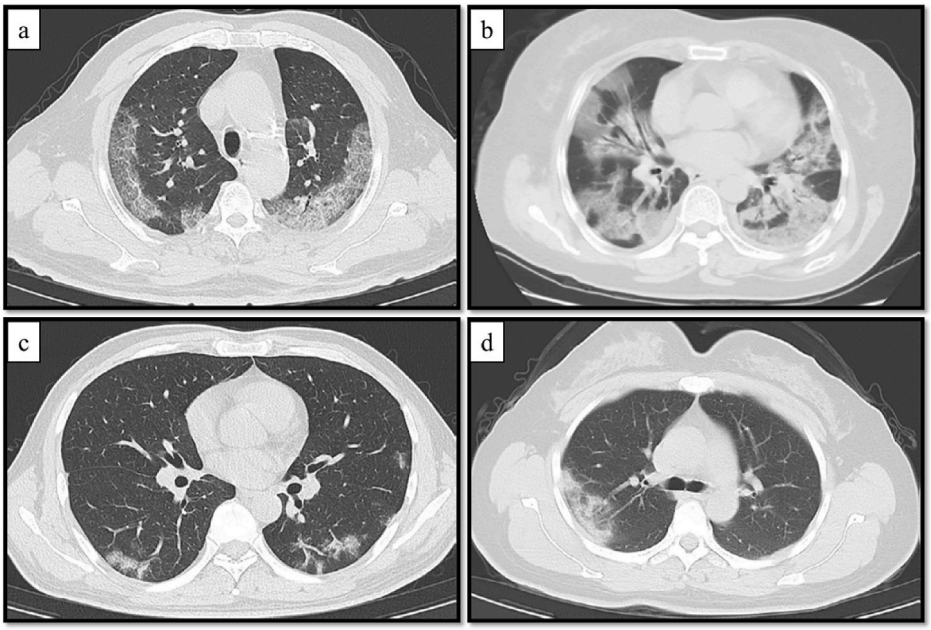


**Fig. 5.** Axial CT images of positive COVID-19 patients (a) 74-year-old male patient suffering with cough for 5 days and evident for subpleural ground-glass opacities, (b) 55-year-old female patient has cough for 7 days, showing bilateral ground-glass opacities and consolidations (c) CT of 43-year-old male patient experience symptoms like cough and fever for one week showing peripheral ground-glass opacities and minimal consolidation and (d) 43-year-old female patient with cough for 5 days showing peripheral consolidation at the right lung region.

**Table 2**
Common serological/antibody tests used in worldwide.

| Test name | Description | Manufacturer | Release date | Approval | Ref |
|---|---|---|---|---|---|
| qSARS-CoV-2 IgG/IgM Rapid Test | Lateral flow-based assay similar as pregnancy kit, detects IgM & IgG specific to the nucleocapsid protein of SARS-CoV-2. Sensitivity: 93.8% Specificity: 95.6% | Cellex (USA) | April 1, 2020 | CE approved, FDA issued for Emergency Use Authorization (EUA) | [42] |
| DPP® COVID-19 IgM/IgG System | An immune-chromatography-based IgM/IgG detector system. | ChemBio (USA) | April 14, 2020 | FDA issued Emergency Use Authorization (EUA) | [43] |
| VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack | Chemiluminescent based immunoassay test used for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum | Ortho-Clinical Diagnostics, Inc. | April 24, 2020 | FDA issued Emergency Use Authorization (EUA) | [44] |
| LIAISON® SARS-CoV-2 S1/S2 IgG | Fully automated antibody detection system against IgG Specificity: 98%. Sensitivity: 90% (samples obtained 5–15 days) | DiaSorin Inc. | April 24, 2020 | Approved for EUA by the FDA | [45] |
| Electro-chemiluminescence immunoassay (ECLIA) | A chemiluminescence based immunoassay technology with an electric pulse that enables rapid identification of captured viral N protein-antibody complexes from patient serum samples Sensitivity: 88.1% Specificity: 99.81% | Roche Diagnostics (USA/Switzerland) | May 2, 2020 | Received EUA | [46] |
| ELISA | An ELISA based assay uses viral S1 spike protein to identify IgG antibodies in serum samples. | Euroimmun AG | May 4, 2020 | FDA issued Emergency Use Authorization (EUA) | [47] |

diagnosis named as Pixel. The workflow of the Pixel is that after ordering an online kit, the subject has to give a nasal swab according to the instruction provided with it. Followed by the online slot booking and samples were collected by the Laboratory. Results of the subject will be provided online at the same time these results send to government authority [53]. Similarly, various diagnostic approaches have been tabulated as in Table 3.

Some of the miscellaneous diagnostic tools are under development; for instance, Srivastava et al. hypothesized graphene-based affinity biosensor. One can develop the biosensor platform by immobilizing the antibody, enzyme, or nucleic acid on the graphene-based material. The detection of the virus can be the interaction counterpart with immobilized bioelements [67]. Similarly, Seo et al. developed Field-Effect Transistor (FET)-Based biosensor for rapid and highly sensitive detection of the virus. The author fabricated FET-based devices by coating the graphene followed by immobilization of the specific antibodies for the spike proteins of COVID-19. The study revealed that the lower limit of detection for the culture sample is around 60 pfu/mL and $2.42 \times 10^2$ copies/mL for the clinical sample. This technique's advantages are high sensitivity, selectivity, label-free, and no need for special sample preparation [68].

Qiu et al. developed dual-functional plasmonic biosensors which comprise plasmonic photothermal and local surface plasmon resonance. The detection mechanism involves the generation of the thermoplastic heat on the gold nanoisland chip upon the illuminated at a plasmonic resonance frequency. This localized plasmonic photothermal heat has the ability to elevate the in-situ hybridization temperature, which further facilitates gene discrimination. Moreover, the reported lower limit of the biosensor detection is 0.22 pM and has specificity in multigene mixture samples [69]. In recent times, a unique and highly robust Loop-Mediated Isothermal Amplification technique (LAMP) has been widely explored by the several researchers for the one-pot, economical detection of target sequence of COVID. In this technique, a targeted specific sequence of DNA is amplified in a constant temperature with respect to the previously designed primer templates. The sensitivity of LAMP reaction is very high due to the application of 4 primers which recognize or binds to the 6 distinct region of the DNA [70]. The process is named as 'Loop mediated', due to the design of the primer, because in

**Table 3**
Different diagnostic technologies for COVID-19.

| Sr. No | Technology Table No.3.Different diagnostic technologies for COVID-19 | Organization | Mechanism | Advantage | Limitation | Reference |
|---|---|---|---|---|---|---|
| 1 | *CovE-Sens* | MyLab, Pune, India | Modified PCR (Molecular Diagnostic) | Fast detection 50 samples/hr, point of care devices, High sensitive & selective | * | [15] |
| 2 | Fast Track Diagnostic (FTD) SARS-CoV-2 assay kit. | Siemens Healthineer | Modified PCR (Molecular Diagnostic) | High specificity due to dual-target detection | Time-consuming and needs trained personal | [16] |
| 3 | Bosch rapid COVID-19 technology | Bosch Healthcare Solutions | Modified PCR (Molecular diagnosis) | Selective diagnosis, no need for special sample preparation and training, simultaneous determination of multiple pathogens | Time-consuming ~2.5 h/sample | [18] |
| 4 | STANDARD Q COVID-19 IgM/IgG Duo Test Kit | SD Biosensor | Colorimetric and Immunological (IgG and IgM antibodies) | Rapid detection in 10 min per test and qualitative | Non-specific, clinical symptoms need to correlate, proper sample collection, lack of quantitative analysis, a false-negative result may be possible if lack of sufficient quantity of antibodies. | [54] |
| 5 | Paper strip-based test | CSIR- Institute of Genomics and Integrative Biology (IGIB), Delhi | CRISPR-Cas9 technology | Rapid detection, low cost | * | [55] |
| 6 | ABBOTT REALTIME SARS-COV-2 ASSAY | Abbott | PCR based (Molecular Diagnosis) | Specific detection (RdRp and N-genes), qualitative estimation of nucleic acid, maxRation data analysis, up to 470 samples/day | Required trained personal, need GLP lab | [56] |
| 7 | ID NOW™ COVID-19 | Abbot | Molecular Diagnostic | Rapid detection, positive result within 5 min while the negative result will be in 13 min, no need for special storage condition. | Limited only for detection of SARS-CoV-2 nucleic acid | [57] |
| 8 | NeoPlex COVID 19 Detection kit | Genematrix Inc. | Molecular diagnostics | A quick diagnostic kit fulfills both WHO and CDC testing criteria. | * | [58] |
| 9 | GS COVID-19 RT-PCR kit | Genosensor Corp. | RT PCR (molecular diagnostics) | 100% target specificity | * | [29] |
| 10 | NxTAG and ARIES tests | Luminex Corp | Molecular diagnostics | Cost-effective, and it takes 4 h to process 96 samples. Specifically, ARIES gives results in 2hr., and can run 144 tests in one day. | * | [32] |
| 11 | Accula SARS-COV-2 test | Mesa Biotech Inc. | PCR (Molecular diagnostics) | Result within 30 min. | * | [59] |
| 12 | Allplex 2019-nCOV Assay test kit | Seegene Inc. | RT-PCR (Molecular diagnostics) | Result within 1 h. | | [34] |
| 13 | Quantivirus SARS-CoV-2 test kit | Diacarta Inc. | RT-PCR (Molecular diagnostics) | Requires less than 2 h and it detects different strains of SARS-COV-2. | * | [37] |
| 14 | DMGtest | Disaster Management Group LLC; Biomedomics Inc. | Lateral Flow Immunoassay | Requires a 10–15 min and visual detection | * | [39] |
| 15 | HEMEMICS technology | Hememics Biotechnologies Inc. | Immunosensor | Very quick (60 s) and cost-effective with high selectivity and sensitivity. | * | [60] |
| 16 | Smart Detect SARS-CoV-2 rRT-PCR Kit | Inbios International Inc. | RT-PCR (Molecular diagnostic) | Results in 4 h. | * | [61] |
| 17 | EDI Novel Coronavirus COVID-19 ELISA Kits | Epitope Diagnostics | ELISA | High sensitivity and specificity | Require clinical laboratory and skilled personnel. False positives by interacting with other COVID strains e.g. OC43 | [62] |
| 18 | qSARS-CoV-2 IgG/IgM Rapid Test | Cellex Inc. | Detection of immunoglobulins IgG, IgM | Robust and easy to handle and takes 10 min. | * | [63] |
| 19 | Xpert Xpress SARS-CoV-2 test | Cepheid Inc. | Molecular diagnostics | Able to detect within 45 min | * | [35] |
| 20 | Onsite and Aridia tests | CTK Biotech | Molecular diagnostics and PCR-fluorescent probe combination | Easy to use and can handle by non-skilled personnel. Low detection time (10 min) | * | [37] |
| 21 | SAFER Sample | Lucence Diagnostics Ptd. Ltd. | RT-PCR (Molecular diagnostics) | Saliva-based kit and no special storage conditions required | * | [42] |
| 22 | Microchip RT-PCR COVID-19 detection system | Lumex Instruments | RT-PCR (Molecular diagnostics) | Rapid (7 samples in 50 min) and, cost-effective | * | [64] |
| 23 | | Mobidiag Ltd. | RT-PCR | | Required skilled personnel | [65] |

(*continued on next page*)

**Table 3** (*continued*)

| Sr. No | Technology Table No.3.Different diagnostic technologies for COVID-19 | Organization | Mechanism | Advantage | Limitation | Reference |
|---|---|---|---|---|---|---|
| | Amplidiag COVID-19 assay | | | The result takes for 3 h and gives information about acute and post-infection. | | |
| 24 | Novodiag COVID-19 assay | Mobidiag Ltd. | RT-PCR | Results in 1 h and fully automated | Require specific skilled personnel. | [65] |
| 25 | XCR COVID-19 assay | XCR Diagnostics Inc. | XCR technology | Result within 30 min | * | [66] |

* Data is not available.

LAMP the selected primer is not perfectly complement to the target DNA rather it forms a loop like structure, which further helps to increase the amplification rate of the reaction [71]. Itou et al. also reported that the detection limit of LAMP is higher than that of PCR. As the LAMP can be performed at a constant isothermal environment (usually 60–65 °C), it overcomes the cost burden of highly expensive thermal cycler, which is necessary for the PCR or other common amplification processes [72]. For this aspect, LAMP has become more acceptable in middle and low income countries [73]. Another advantage of LAMP is that the final amplified product detection can be done by simple photometric method or even by the naked eyes. Yang et al. proposed RNA based loop-mediated isothermal amplification (LAMP) mediated point of care device methodology. The nasal swab from the patient or suspect will be collected and subjected to the LAMP analysis. The LAMP-based paper shows the colorimetric analysis, which can readily have captured by smartphone. Furthermore, the captured photograph of the colorimetric analysis is shared with clinicians and government agencies for further examination. Hence the whole diagnosis can be examined in home, so that unnecessary movement of the infected or suspect may be avoided. The Fig. 6 summarize the work flow of the proposed strategies [65].

Another interesting colorimetric biosensor was developed based on the change of the surface plasmon response of the gold nanoparticle. The gold nanoparticles were capped with antisense oligonucleotides specific for the nucleocapsid phosphoporotein. The positive result easily observable by the naked eye within 10 min with the limit of detection ~0.18 ng/μL of RNA having SARS-CoV-2 viral load [74]. However, these colorimetric assay gave qualitative information and high chances of false-positive and negative results. Whereas the conventional serological test such as ELISA and PCR is expensive and requires a sophisticated laboratory. The microfluidic-based devices resolve these constraints, Tan et al. fabricated microfluidic ELISA in which SARS-CoV-2 specific IgG antibodies were used. The study reveals that the result is depicted with 15–20 min with less quantity of the sample [74].

Artificial intelligence (AI) has recently gained significant importance in diagnostic biology, but COVID-19 is also not an exceptional case. AI-based models can be used for early diagnosis based on the chest CT of the suspect. Although extensive research is going in the diagnostic tools for COVID19 for high-sensitive and ultrafast results, indeed, these kind of technologies are highly needed [66].

## 5. Conclusion

We are all well aware that COVID 19 is devastating the entire world and all of us living in difficult times. The fatality rate of the infection was low but the rate of spreading is tremendously high so the health care systems are unable to handle the overhlmingly high numbers of patients at one time. To contain the infection, the best possible solution is to combat the spreading and it is only possible when isolating the infected subjects. So, there is rapid and accurate diagnosis system is required to achieve the object. There are various strategies were employed for the COVID 19 diagnosis but all of them have shown a limited success rate in

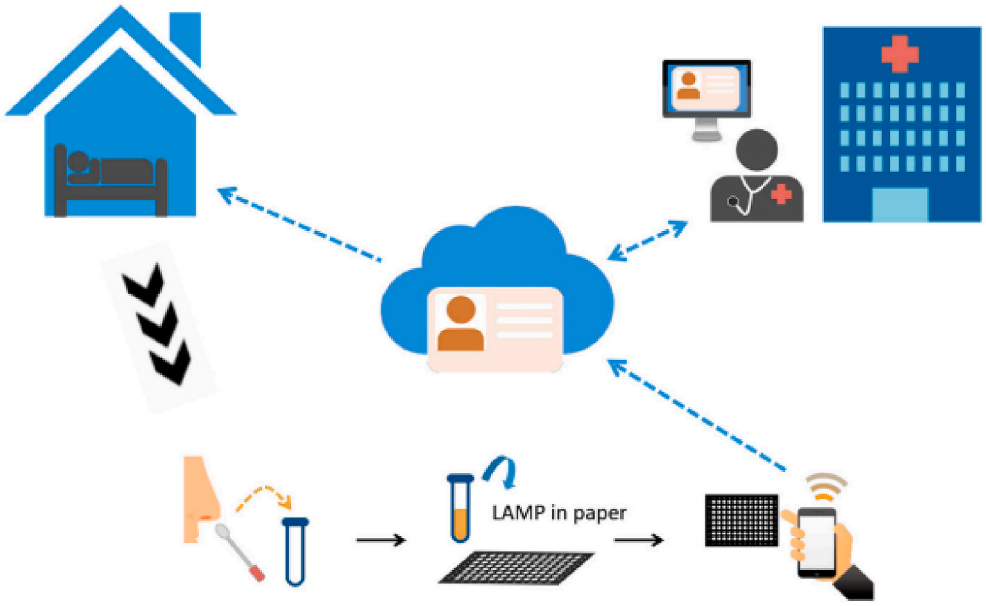


**Fig. 6.** The workflow of the point of care devices is proposed based on LAMP with a smartphone-based technology [65].

terms of accuracy. However, the gold standard RT-PCR is the only one reliable method and it was well accepted throughout the globe. Chest CT is also widely practicing to understand the severity of the infection. The major limitations of these methods are time-consuming and costlier, need sophisticated infrastructure, and required well-trained human resources. Hence, the challenge is the development of new technologies to overcome the limitations to make the diagnosis easier and economical to contain the infection of COVID19. Various research groups are working on that direction particularly technologies like FET-based and dual-functional plasmonic biosensors for the rapid detection of the COVID-19. In the current review, we summarised the avalbale literature on diagnosis methods and variable characteristics of COVID 19. Exclusively we disused the major limitations of the current diagnostic methods. Also, we suggested some of the best possible strategies for the development of rapid and accurate detection of COVID 19 technologies. Hence the review is highly beneficial to understand the highly complex characteristics of COVID 19 and it helps in finding a better diagnosis method.

## 6. Future perspective

RT-PCR and CT scan are extensively employed technique for the diagnosis of COVID-19 globally. However, they exhibit significant glitches like time-consuming, sophisticated facilities, complexity in bulk production, high cost, and false-positive results. Besides, the other technologies are primarily still in their evaluation stage. The antibody-based detection kits are providing results within minutes, but they largely show false results. In recent times many countries are using them as screening tests to identify the trend and the clusters of COVID-19.

Therefore, there is an urgent need to develop a highly specific and rapid diagnostic tool for COVID-19 detection. Possibly, transduction of specific antibody-antigen (virus) or identifying highly specific ACE-II binding with spike protein of COVID-19 are the best alternatives to developing rapid detection kits. A handful of literature available on rapid and selective detection of other viral diseases like Influenza can be adopted for the strategies mentioned above. Specialized nanoparticles or nano-seeds can be developed and interact with the virus to produce an optical signal, which may be the one more alternative for rapid detection. The electrochemical biosensor, immunological biosensor, lateral flow assay kits and many more techniques can be explored for the development of COVID-19 rapid diagnosis. Exceptionally, conductometry can be a useful method to easily employ by analyzing the variation of conductivity in the analyte (virus). Very few technologies have been reported for early detection and which are either non-specific or under development. So that present review encourages the researcher to explore the alternative diagnostic approaches for the rapid and specific detection of COVID-19.

As the speed of identification or diagnosis and clinical data evaluation is one of the major barriers for the current systems. So there is massive scope for developing digital platforms in which high speed and the communication barrier between the information sharing will be very efficient and fruitful. In the era of AI and IOT, an ample scope to develop a server consists of various *in-silico* tools for matching the patients' data with the reference databases and then evaluating the final confirmation or early diagnosis of the disease.

## 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.

## Acknowledgment

The authors would like to thank National Institute of Pharmaceutical Education and Research, Ahmedabad, Gandhinagar-382355 for supporting the students in the form of fellowships.

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