CHAPTER FIFTEEN

A step toward better sample management of COVID-19: On-spot detection by biometric technology and artificial intelligence

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1. Introduction of SARS-COV2

The Severe Acute Respiratory Syndrome (SARS) is a form of beta coronavirus that caused the first outbreak in 2002 in China. In 2012 another outbreak named the Middle East Respiratory syndrome virus (MERS) was reported in Saudi Arabia. Seven years later, toward the end of 2019, a new mutation in the same family of viruses resulted in SARS-CoV-2 which caused a pandemic with irreversible lung damage and pneumonia-like symptoms in human population.[1] Till date, this virus has caused the most disastrous global health calamity of the century. More than 195 million people are affected with above 4.2 million deaths worldwide (https://www.worldometers.info/coronavirus/?utm_campaign=homeAdUOA?Si visited at 08.03.2021). According to some initial research data, SARS-CoV-2 was first detected at a live sea food wet market in Wuhan in the Hubei province of China.[2] Soon after that, the number of positive and critical cases mounted noticeably in China and across the world. On 30th January 2020, the World Health Organization (WHO) announced coronavirus outbreak as a public health emergency of international concern followed by

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Table 1 Data given as per WHO report as on 24th June 2021.

Name	Confirmed cases—cumulative total	Confirmed death—cumulative total
Global	**179,241,734**	**3,889,723**
America	71,232,746	1,873,241
Europe	55,535,235	1,177,734
South-East Asia	34,351,183	478,700
Eastern Mediterranean	10,793,326	213,897
Africa	3,880,790	93,100
Western Pacific	3,447,690	53,038

declaration of a pandemic on 11th March 2020.[3] As of 24th June 2021, globally 179,241,734 confirmed cases have been reported along with 3,889,723 deaths (WHO report attached as Table 1, as on 24th June 2021) (Table 1).[4] In the past week (14th–20th June 2021), the number of cases and deaths continued to decrease worldwide with more than 2.5 million new cases weekly (COVID-19 Weekly Epidemiological Update: Edition 45, published 22 June 2021). Researchers are continuously working on epidemiological stories of this virus along with unknown activity and the origin of SARS-CoV-2 in detail. In the later sections of this chapter, the epidemiological features and structure of SARS-CoV-2 was discussed.

1.1 Epidemiological characteristic of SARS-CoV-2

SARS-CoV-2 is a member of the *Coronaviridae* family and is a genuine human pathogen like that of the other corona viruses such as HCoV-229E, HCoV-HKU1, SARS-CoV, MERS-CoV, HCoV-NL63, and HCoV-OC43.[5] In general, viral RNA was isolated from bronchoalveolar lavage (BL) as a fluid sample from infected individuals with severe pneumonia symptoms followed by using metagenomic RNA sequencing. Thus Chinese scientists identified that the beta-coronavirus is the causative agent of the recent outbreak that was not discovered earlier.[6,7] The whole genome sequencing (WGS) of this viral strain was performed for the first time to determine the genomic information. On 12th January 2020, the sequences closer to the whole genome were confirmed by various research institutes and those data were submitted to the GenBank (accession no. MN908947.2).[8,9] From those studies, a detailed epidemiologic structure was disclosed, indicating that different animals like bats, pangolins, and snakes may promote SARS-CoV-2 as an intermediate host for the transmission of human beta-coronavirus to the human.[8] So far, no conclusion has been drawn on when and where the virus first entered the human body.[10,11] On 2nd January 2020, the first human-to-human transmission occurred, where one of the family members was exposed to a close contact transmission with this virus and then the infection spread rapidly within the hospital in China.[12] Researchers have calculated the basic reproduction number (R0) based on transmission dynamics of COVID-19. Initially, China recorded the R0 to be 2.24–3.58.[13] The incubation period of SARS-CoV-2 is around 14 days with moderate time of 4–5 days. Various reports indicated that the upper respiratory tract has the highest viral shedding within the first three days of symptoms.[14] According to the researchers, SARS-CoV-2 is transmitted via aerosols in an enclosed space and urine, in addition to short distance and contact transmission. Recent investigations also indicated the transmission of this virus from a mother to her child.[15–17]

1.2 Structure of SARS-CoV-2

Researchers have studied the structure of SARS-CoV-2 via electron microscopy and found that this virus is made up of an icosahedral viral head with spherical structure. The diameter of the spherical head ranges from 100 to 200 nm containing a dense vitro-plasm and bounded by a lipid bilayer.[18] Further, studies mentioned that the virus is enveloped with four structural proteins such as the spike protein (S), the transmembrane glycoproteins (M and E), and the nucleocapsid protein (N). Each of them has a crucial function within the structure of the virus particle and also participate in the alternative aspects of the replication cycle[19] (Fig. 1B). The details of genomic organization of SARS-CoV-2 are stated as follows (Fig. 1A):

- The coronaviruses have a large envelope which carries a positive-sense single-stranded RNA (+ssRNA) sized around 30 kb which encodes 9860 amino acids as their genome. The content of G + C is 38%. It compromises 14 open reading frames (ORFs) with 9 subgenomic mRNAs units, which influence and conserve the spreadhead sequence, 9 transcription regulatory sequences, and 2 terminal untranslated regions.
- The 16 nonstructural proteins contain viral cysteine proteases such as NSP3 (papain-like protease) and NSP5 (main protease), NSP12 (RNA-dependent RNA polymerase, NSP13 (helicase), and other NSPs. These proteins help in transcription and replication of the virus.[20]
- Mutations have been detected in NSP2, NSP3, and the spike protein which show important role in SARS-CoV-2 infectivity.[21]

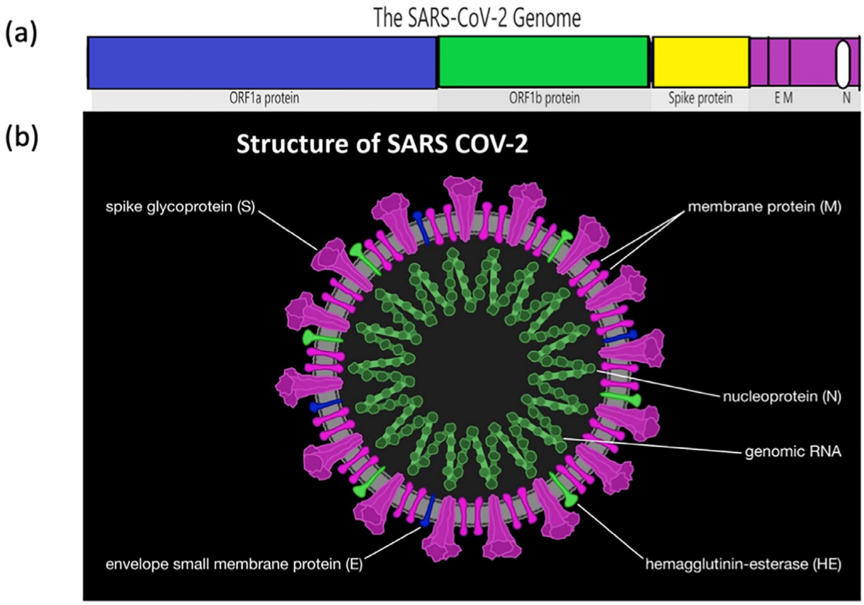

Fig. 1 Structural details of SARS-CoV-2. (A). Schematic illustration of SARS-CoV-2 genome. (B) The typical viral structure of SARS-CoV-2 with four kinds of protein component.

Molecular weight of the spike or S glycoprotein is around 150 kDa.[22] S glycoproteins create homotrimers on the viral surface and promotes the binding of enveloped virus onto the host cells through the angiotensin-converting enzyme 2 (ACE2).[23,24] In addition, S glycoprotein is cleaved by protease, which is a type of cell fusion into two subunits such as S1 and S2. S1 determines the host-virus range and cellular tropism with the receptor-binding domain. Almost 70% of coronavirus is shared by S1 subunit which contains a signal peptide, followed by an N-terminal domain and receptor-binding domain. On the other hand, the function of S2 is intermediate virus fusion into transmitting host cells and it shares 99% match with other coronaviruses like bats SARS-like CoVs and human SARS-CoV.[25] Besides, the nucleocapsid protein N is the structural component of CoV which influence this N protein to attach with nucleic acid, especially with RNA of the virus.[26,27] M protein is also a structural protein, and it is one of the key fragments of this virus that defines the envelope's structure.[28] The E protein is the smallest protein in the SARS-CoV-2 and it helps in the assembly and evolution of this virus.[29]

Further, the coronaviruses are classified under the subfamily of *Ortho-Coronaviridae*. Based on the genetic and antigenic principles, coronaviruses have been organized into 4 groups: alpha-coronavirus (α-CoV), beta-coronavirus (β-CoV), gamma-coronavirus (γ-CoV), and delta-coronavirus (γ-CoV).[30,31] There are 6 CoVs have been known as human-susceptible virus such as α-CoVs HCoV-229E, HCoV-NL63, β-CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, since it caused mild respiratory symptoms like a common cold. The other coronaviruses like β-CoVs, SARS-CoV, and MERS-CoV showed severe and potentially fatal respiratory tract infections in human beings.[32] About 79.5% of the SARS-CoV-2 genome sequence is identical with the other coronaviruses such as β-coronavirus, thus infecting human beings.

1.3 Current detection kits and technologies

Diagnosis plays an important role in a disease which outbreaks from any novel pathogen for which the population is not preimmunized. COVID-19 is among such infectious disease, which is highly contagious and lethal.[11,33,142] Later on, when the asymptomatic carriers of COVID-19 were reported, the scenario of symptom-based diagnosis changed. This eventually intensified the necessity for adequate diagnosis of majority of the population to combat the rapid transmission of the virus.[143] Collecting samples on proper time and accurate anatomical location is essential to determine the correct molecular diagnosis.[34–37] Prompt diagnosis and on-spot detection is of primary importance to combat the disease and reduce the transmission by quickly isolating the critical patients in intensive care.[38] Several detection methods (listed in Table 2) and kits (listed in Table 3) for SARS-CoV-2 are being used worldwide. These commercial kits received approval of an Emergency Use Authorization (EUA) from FDA. Thus these established processes can spot (i) specific viral gene regions by nucleic acid amplification techniques such as Real-Time Reverse Transcription Polymerase Chain Reaction [RT-PCR] and isothermal nucleic acid amplification mainly by loop-mediated isothermal amplification (LAMP)[39–43] along with other molecular diagnosis system, (ii) the antibodies produced by the immune system in response to the viral infection (serology/Immunoglobulin M (IgM)/Immunoglobulin G (IgG) tests), and (iii) the antigen testing by lateral flow assays.[44,45] Most of the COVID-19 diagnostic kits are based on genomic analysis, using RT-PCR assays, which is the usual gold standard for virus detection.[46] Nowadays on-spot detection techniques have become much easier and cost effective by using sensor-based diagnostic approaches. There are few readily available materials which made detection process much simpler than

Table 2 Detection methods of SARS-CoV-2.

Mode of detection	Detection methods
Radiology-based technology	• X-ray • Chest computed tomography
Culture-based detection	• Virus propagation in cell line
Molecular technology	• Real Time-RT PCR • Isothermal amplifications • CRISPR-Cas technology • Lab-on-chip
Immunoassay technology	• ELISA • Neutralization assay • Chemiluminescent assay • Lateral flow assay • Dip-stick
Alternative developing methods	• Aptameter • Molecular imprinting technology (MIT) • Microarray • Biosensor MALDI-TOP profiling
Sequencing technologies	• Sanger sequencing • Next generation sequencing • Nanopore sequencing

conventional methods, such as sensor chips and paper-based identification.[47–50] The antigen detection test is primarily based on the spotting of viral antigens by using specific antibodies. It is rapid, cost effective, usable at the POC and, therefore, is ideal for large-scale COVID-19 detection.[51,52] At-home COVID-19 detection kit such as RT-PCR Test-Home Collection Kit, developed by LabCorp, is used by the public to self-collect nasal samples at home.[53] The current market price of the collection kit is 119$ (USD). Hence, these kits are used for sample collection from infected individuals and sent back to diagnosis center and nearby hospitals for further analysis.[54]

Despite the challenges related to the cost and time, molecular test remains the most reliable technique due to its ability to find proper specificity and high sensitivity. Besides, the recent revolution in nanotechnology is also helping to reduce the cost and making the detection much simpler.[55–57] However, fast, portable, and accurate diagnostic tests are still vital and necessary because millions of people still need to be diagnosed. Therefore a cheap, reliable, and rapid test is needed. The recent revolution in nanoparticle-based

Table 3 Summarized list of commercially available SARS-CoV-2 detection kits approved by FDA and EUA for COVID-19 diagnosis.

Source of manufacturer/ company	Name of diagnostic kits	Technology/platform	Regulation/ validation	Collection process
Rutgers Clinical Genomics laboratory at RUCDR Infinite biologics—Rutgers University	Rutgers Clinical Genomics laboratory Taq Path SARS-CoV-2-Assay	rRT-PCR	EUA	Oropharyngeal (throat) swab, nasopharyngeal swab, anterior nasal swab, mid-turbinate nasal swab, and saliva specimens
Zymo Research Corporation	Quick SARS-CoV-2 rRT-PCR kit	rRT-PCR	EUA	Upper respiratory and lower respiratory systems
1 drop (Republic of Korea)	1 copy COVID-19 MDx Kit	rRT-PCR	CE Mark	Pharyngeal swab
Sherlock BioSciences, Inc.	Sherlock CRISPR SARS-CoV-2 Kit	CRISPR	FDA	Nasal swab, nasopharyngeal swab, oropharyngeal swab, or bronchoalveolar lavage (BAL) specimen
BioMerieux SA	SARS-CoV-2 RESPI-R-gene	rRT-PCR	EUA	Nasopharyngeal swab
Fast Track Diagnostics Luxembourg Sarl (A Siemens Healthineers Company)	FTD SARS-CoV-2	rRT-PCR	FDA and EUA	Nasopharyngeal swab and oropharyngeal swabs
Sansure BioTech Inc.	Novel Coronavirus (2019-nCoV)-Nucleic acid diagnostic kit (PCR-fluorescence probing)	rRT-PCR	FDA	Nasopharyngeal swabs, oropharyngeal (throat) swabs, anterior nasal swabs, mid-turbinate swabs, nasal washes, and nasal aspirates

Continued

Table 3 Summarized list of commercially available SARS-CoV-2 detection kits approved by FDA and EUA for COVID-19 diagnosis—cont'd

Source of manufacturer/ company	Name of diagnostic kits	Technology/platform	Regulation/ validation	Collection process
Bio-Rad Laboratories, Inc.	Bio-Rad SARS-CoV-2 ddPCR Test	Digital Droplet rRT-PCR	EUA and FDA	Nasopharyngeal swab and oropharyngeal swabs
Bio Fire diagnostics, LLC	Bio FireRespiratory Panel 2.1 (RP2.1)	rRT-PCR	FDA	Nasopharyngeal swab in transport media
Lab Genomics Co. Ltd.	Lab Gun COVID-19 RT-PCR kit	rRT-PCR	FDA	Nasopharyngeal swab and mid-turbinate swabs
Rheonix, Inc.	Rheonix COVID-19 MDx Assay	rRT-PCR	FDA	Nasopharyngeal swabs, oropharyngeal swabs, anterior nasal swabs, mid-turbinate nasal swabs, nasal washes, nasal aspirates, and bronchoalveolar lavage (BAL) fluid
Seasun Biomaterials	U-Top COVID-19 detection kit	rRT-PCR	FDA	Nasopharyngeal swabs, oropharyngeal swabs, anterior nasal swabs, mid-turbinate nasal swabs, nasal washes, nasal aspirates, as well as bronchoalveolar lavage (BAL) fluid and sputum specimen
Geno-Sensor LLC	GS COVID-19 RT PCR kit	rRT-PCR	FDA	Nasopharyngeal swabs, oropharyngeal swabs, anterior nasal swabs, mid-turbinate nasal swabs
Atila BioSystems Inc.	iAMP COVID-19 detection kit	Isothermal amplification (OMEGA), patented	FDA	Nasopharyngeal swab and oropharyngeal swabs

Becton, Dickinson and Company	BD SARS-CoV-2Reagents for BD MAX system	Antigen (chromatographic digital immunoassay)	FDA	Nasopharyngeal swab and oropharyngeal swabs
PerkinElmer. Inc.	PerkinElmer: New Coronavirus-nucleic acid detection kit	rRT-PCR	FDA	Nasopharyngeal swabs, oropharyngeal swabs, anterior nasal swabs
Mesa Biotech Inc.	Accula SARS-CoV-2 Test	PCR and lateral flow	FDA	Nasal swab
Thermo Fisher Scientific. Inc.	Taq Path COVID-19 combo kit	rRT-PCR	FDA	Nasopharyngeal swab, nasopharyngeal aspirates, and bronchoalveolar lavage
Centers for Disease Control and Prevention (CDC)	CDC-2019-nCoV-Real-Time RT-PCR diagnostic panel (CDC)	RT-PCR	FDA	Nasopharyngeal/Oropharyngeal swabs, lower respiratory tract aspirates, nasopharyngeal wash/aspirates or nasal aspirates, sputum, and bronchoalveolar lavage
Lucira Health, Inc. (Emeryville, CA, USA)	Lucira COVID-19—All in one single test kit	RT-LAMP	FDA	Self-collected nasal swab specimen
Detectachem Inc. (Sugar Land, TX, USA)	Mobile-Detect Bio BCC19 (MD-Bio BCC19) test kit	RT-LAMP	FDA	Nasopharyngeal swabs, oropharyngeal swabs, anterior nasal swabs, mid-turbinate nasal swabs
Seasun Biomaterials Inc. (Seoul, Korea)	AQ-TOP COVID-19 Rapid detection kit Plus	RT-LAMP	FDA	Oropharyngeal (throat) swab, nasopharyngeal swab, anterior nasal swab, mid-turbinate nasal, nasopharyngeal aspirate specimens, bronchoalveolar lavage, and sputum

Continued

Table 3 Summarized list of commercially available SARS-CoV-2 detection kits approved by FDA and EUA for COVID-19 diagnosis—cont'd

Source of manufacturer/ company	Name of diagnostic kits	Technology/platform	Regulation/ validation	Collection process
Abbott Diagnostics Scarborough, Inc. (Scarborough, ME, USA)	ID NOW-COVID-19	RT-LAMP	FDA	Nasal, nasopharyngeal, or throat swabs
Color Genomics, Inc. (Burlingame, CA	Color SARS CoV-2 diagnostic assay	RT-LAMP	FDA	Oropharyngeal (throat) swab, nasopharyngeal swab, anterior nasal swab, mid-turbinate nasal, nasopharyngeal aspirate specimens, bronchoalveolar lavage, and sputum
Euroimmun US Inc.	Anti-SARS-CoV-2 ELISA (IgG)	Serology (IgG)	FDA	Euroimmun US Inc.
Roche Diagnostics	Elecsys anti-SARS-CoV	Serology Antibody	EUA	Roche Diagnostics
Wadsworth Centre, New York State Department of Health	New York SARS-CoV Microsphere Immunoassay for Antibody detection	Serology Total antibody	FDA	Wadsworth Centre, New York State Department of Health
Wondfo (China)	Wondfo SARS-CoV-2 Antibody Test	Serology (IgG, IgM)	CFDA	Wondfo (China)
Rapid Test methods (Ireland)	COVID-19—IgG/IgM Lateral flow kit	Serology (IgG, IgM)	FDA	Rapid Test methods (Ireland)
CTK Biotech (USA)	On site COVID-19 IgG/ IgM rapid test	Serology (IgG, IgM)	FDA	CTK Biotech (USA)

Edinburg Genetics (UK)	COVID-19 colloidal Gold Immunoassay Testing kit	Serology (IgG, IgM)	FDA and EUA	Edinburg Genetics (UK)
Everest Links Pte (Singapore)	VivaDiag COVID-19 IgG/IgM rapid test	Everest Links Pte (Singapore)	FDA	Everest Links Pte (Singapore)
SD Biosensor (Korea)	Standard Q COVID-19 IgG/IgM duo	Serology (IgG, IgM)	FDA and EUA	Serum and plasma

EUA, FDA: U.S. Food and Drug Administration.

technologies is also very useful for any disease diagnosis as quickly as possible than any conventional process.[58–60] As this is a global challenge, science and research must pay close and continuous attention to the development and improvement of infectious disease detection at the POC.[46]

2. Biometric systems for COVID-19 management

In modern smartphones, we commonly see the authentication features like face detection and fingerprint sensors. These sensors are typically designed to detect certain features unique to a person and create a unique identity associated with the person. The authentication methods used by these systems are called biometric authentication. We can define biometric techniques as automated systems to verify and identify a living person using the person's physiological or behavioral features.[61,62] Biometric systems must not be confused with forensic methods which are also employed to detect a human or any other living organism. The key aspect which defines this field is the automated detection of only living humans.

Although these techniques essentially help in identifying people, they extensively help in other important aspects, viz. differentiating between a set of people, determining probabilistic similarity for a defined set of people.[63] The segregation of population can be done on the basis of any parameters, viz. gender, age, and nationality, and is done by externally making an entry for the biometric information. Due to this advantage, systems are often used by many states to control or monitor the spread of a disease. Especially during the current COVID-19 pandemic, these technologies have been extensively used in contact tracing, thereby helping in curbing the spread of the virus.[141] Essentially biometric data of citizens have been ethically linked with their geolocation to monitor whether they have been in contact with any potential COVID-19-infected person.[64–66] In this section we will specifically investigate the areas where biometric systems have been helpful in tackling the spread of the current pandemic. We describe their operation and discuss the concerns associated with data privacy.

2.1 Working mechanism of biometric devices

A biometric device can recognize either behavioral or physiological characteristics via handwriting, keystroke, retina, fingerprint, voice, face, etc.[67] Selection of a human characteristic from the above-mentioned list depends on the requirement and applications in places. However, few qualities such as robustness, accessibility, specificity, and availability must be considered before making a choice of the biometric system.[68] Robustness is measured by the number of times that matches a submitted input to a wrong identity. Accessibility can be attributed to the number of entries the device can process in a given amount of time. Even after identifying and quantifying the desired qualities, there still remains a void for the selection of best biometric system because all the biometric characteristics are explicitly dependent on the details of the purpose for which it is to be used.[69] Therefore it is very important to discuss the subsystems which fulfill the entire system. To build a biometric system for home security, designing the framework for contextual attributes is important to enhance the determination of a legitimate user. For that, servers need to be created separately with secure networking system and an end user smartphone, laptop, or any other electronic items need to be connected for continuous monitoring. For both the cases, backup storage is required to store daily incidents (Fig. 2).[70]

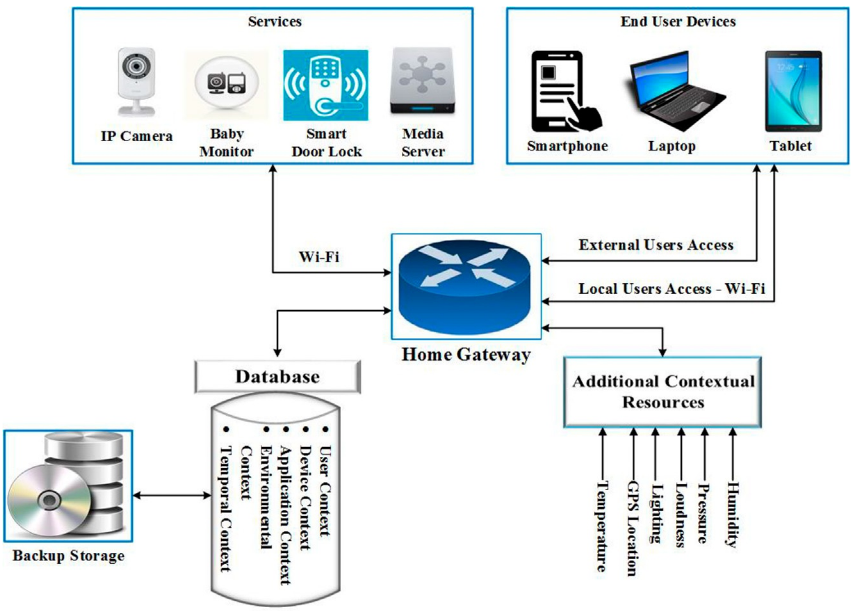

Fig. 2 A high level of proposed framework, where biometric devices show about the place of data collection, different circumstances, and potential determination to accomplish some information using biometric devices. *(This figure is adopted from Ashibani Y, Kauling D, Mahmoud QH. Design and implementation of a contextual-based continuous authentication framework for smart homes.* Appl Syst Innov *2019;***2** *(1) with permission.)*

Based on this concept, a biometric system can be divided into four components: data collection unit, signal processing, decision, and data processing. The data collection unit takes the defined user characteristic as an input which depends on factors like measurement, technical characteristic of the sensor, and the method for the measurement. Depending on the application of the system the data collected can be either kept enclosed or it might have to be first standardized (in case of open system where data collected from multiple systems must be matched) before sending it to signal processing unit. Optionally, a transmission system is often used post data collection to transmit the data to a centralized data processing unit. The user data tagged with the biometric characteristic received from the data collection unit is first segmented into different data sets based on the requirement. After segregation, the data is used in the pattern matching algorithms to distinctly distinguish individuals without error. Once data processing is done, the refined data is now stored into databases which can be localized or central[71,72] and is further used as a tool by the decision-making system. This system uses the fed data and matches it with the incoming user input to generate matched or no matched signal. Having discussed the basics of the structure and mechanism of a generic biometric system, it is important to discuss how it has been used in recent times to counter the spread of COVID-19.[73,74]

2.2 Application of biometric systems against COVID-19 vaccines

The most important implementation was to geo-tag a citizen to monitor whether they have come in close proximity of an infected individual or not. Meanwhile these apps are linked with an identity number of a citizen, when geotagged these applications can now spot a COVID-19 patient in proximity. Based on the range of proximity, viz. 500 m and 1 km., the citizen can now be classified under different threat levels.[75,76] Therefore if a person tests positive, all the citizens he/she might have come in contact with can be alerted. This directly impacts in reducing a further transmission of the virus, otherwise which could have been at an astronomical scale. Similarly, when the same user data is linked with the vaccination status, it gets much easier to track a vaccinated person.

2.3 Issues related to data privacy

Biometric systems have helped significantly in contact tracing and therefore, helping in curbing the spread of the virus. They have also helped in tracking a citizen's vaccination status which helps a lot in tracking the vaccination status of a country. However, with such huge pool of data generated from a country's citizens, some important concerns in the population are inevitable. For instance, to what extent states are using the user data, is the collected user data safe against cyberattacks, is it used for unethical surveillance on the citizen, etc.[77,78] Many countries that have deployed such systems during the current pandemic ensured that they are not collecting any personally identifiable information and only collecting geographical locations.[79,80]

3. Artificial intelligence and its applications for COVID-19 management

Adding to the earlier discussion on biometric systems, another great technological addition that can enhance the detection of viral transmission, identify the high-risk individuals, and assist with the real-time infection control is artificial intelligence (AI). AI is a technology that utilizes computer software to simulate human intelligence. It can correctly estimate the mortality risk based on historical data. AI is a proof-oriented clinical method which will help in the battle against SARS-CoV-2 by providing public monitoring, hospital care, notifications, and preventative guidance.[81–83] The common practice of AI and non-AI-related apps that aid general doctors in executing activities is depicted in Fig. 3.[84] Briefly, it depicts the flow of minimum non-AI therapies versus AI-based treatments. The flowchart also shows how AI is utilized in crucial stages of high-accuracy care, decreasing the complexity, and time it takes. Physicians may use AI technology not only to focus on the patient's treatment but also to improve illness prevention.

3.1 AI for early detection and diagnosis of COVID-19

AI can identify the usual and unusual symptoms of COVID-19, thereby alerting the patients and healthcare providers.[85,86] It supports a more cost-effective and quicker decision-making process. It aids in the identification and management of novel COVID-19 through the application of helpful algorithms. It can also aid in diagnosing infected persons using medical imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) scans of human body parts.

A false-negative result might prolong the diagnosis and treatment procedure, as well as raise the danger of viral transmission, therefore making early detection of COVID-19 patients very critical. Furthermore, not all hospitals

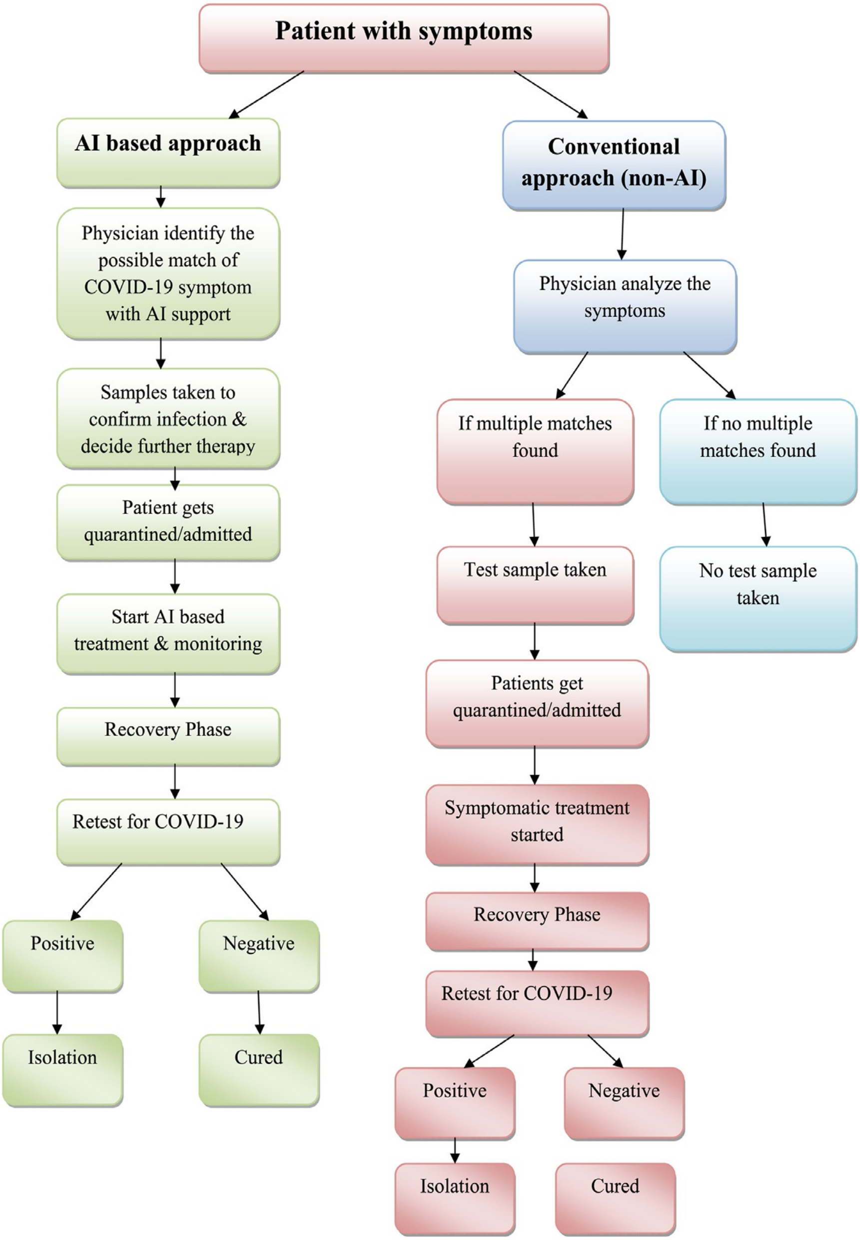

Fig. 3 AI- and non-AI-based applications that assist general practitioners in identifying COVID-19 symptoms. *(This figure is adopted with the permission from Vaishya R, et al. Artificial intelligence (AI) applications for COVID-19 pandemic. Diabet Metab Syndr Clin Res Rev 2020;**14**(4):337–9.)*

have radiologists with chest imaging competence, necessitating AI-assisted diagnosis.[86] This highlights the possible importance of a highly accurate AI system in quickly detecting patients. The suggested AI method by Mei et al.[87] includes CT imaging and medical information which has the same precision as a senior chest radiologist.

In the proposed technique, a deep convolutional neural network (CNN) was first designed to understand the radiological characteristics of patients with COVID-19 on the first CT scan.[87] They employed support vector machine (SVM), random forest, and multilayer perceptron (MLP) classifiers to categorize COVID-19 patients based on clinical data. MLP has the best tuning range performance. Therefore only MLP's output was recorded. Finally, utilizing radiological and medical records, they created a neural network[87] models to predict COVID-19 status. Three AI models are used to determine the likelihood of a patient having COVID-19: the first one is based on a chest CT scan, the next on clinical evidence, and the final is based on a combination of the chest CT scan. Moreover, the chance of possessing a parenchymal abnormality, as predicted by the CNN model (slice collection CNN), a comprehensive pulmonary tuberculosis (PTB) model that has a 99.4% accuracy in recognizing irregular lung slices from chest CT images. The 10 leading irregular CT images per patient were put into the next CNN (diagnosis CNN) to assess the chance of COVID-19 positive (P1). Demographic and medical data (the patient's age and sex, exposure history, symptoms, and laboratory tests) were input into a machine-learning model to differentiate COVID-19 positive cases (P2). To produce the joint model's final performance, an MLP network integrated the features provided by the diagnostic CNN model with the nonimaging clinical knowledge machine-learning model (P3). In a study, 279 patients achieved a zone under the 0.92 curve and had the good sensitivity as a senior thoracic radiologist in the thoracic system by AI models. The AI approach has improved the RT-PCR diagnosis of COVID-19 patients with routine CT scans by 68%.

3.2 AI for monitoring the treatment of COVID-19

AI can create an intelligent platform that can automatically track and forecast the progress of a virus. The visual characteristics of this condition can also be established by using a neural network which will help in tracking and managing the infected individuals.[88–90] It is capable of providing patients with regular reminders and remedies for the COVID-19 pandemic.

Current trends in machine learning (ML) and deep learning (DL) have increased the effect of imaging tools and are now being utilized for a variety of remote tasks that needs the presence of medical professionals. Rohmetra et al.[91] investigated the research possibilities for tracking COVID-19 contamination and quarantined individuals using DL and image/signal processing techniques. Most of these techniques could be implemented on a mobile device or a personal computer using simple cameras and sensors. Remote control on vital signs of health may be very useful for controlling the pandemic scenario. The vital signs of the patient can be routinely checked by physicians and taken care of when required. Their research shows how remote monitoring based on ML and imaging may be utilized to predict crucial indicators for early detection and to track remote patients on a regular basis.[91] In hospitals, contact-based monitoring equipment are utilized, although it is challenging to use them for active monitoring. Other challenges of AI technologies are for a specific domain in drug discovery and drug repurposing. With the implementation of this concept, the therapeutic processes will be robust, rapid, and cost effective. Combination of AI algorithms and network medicine for drug repurposing is a good prospect during the pandemic to combat SARC-CoV-2 (Fig. 4).[92]

The Massachusetts Institute of Technology's (MIT) Computer Science and AI Laboratory (CSAIL) has developed a system that can remotely follow individuals with the extremely infectious COVID-19 illness and thereby prevent the virus from spreading to healthcare workers.[93] The Emerald[94] is a new system that can not only measure critical patient parameters like breathing, but also monitor sleep patterns and send the information to the healthcare professionals through wireless signals. The Emerald was produced by a group headed by MIT scientist Dina Katabi.[95] It includes a WiFi-like box that detects wireless signals and tests them using AI. Emerald can reduce interaction and infection risk while simultaneously increasing healthcare capacity by allowing several patients to be watched at once.[96] This would also allow healthcare providers to evaluate and track fewer severe patients at home, instead of overburdening hospitals and health systems which could have been used exclusively for the most critical cases.[97] As a result, contact tracing by AI is a critical public health technique for controlling infectious disease. AI can aid in determining the depth of the virus's infection, finding clusters and "hot spots".[98–100] According to these studies, more than 36 countries (like Spain, Norway, Italy, Germany, Singapore, South Korea, and Israel) have successfully implemented automated contact tracing using centralized, decentralized, or a combination of both strategies to reduce effort and improve the efficacy of conventional healthcare diagnostic processes.

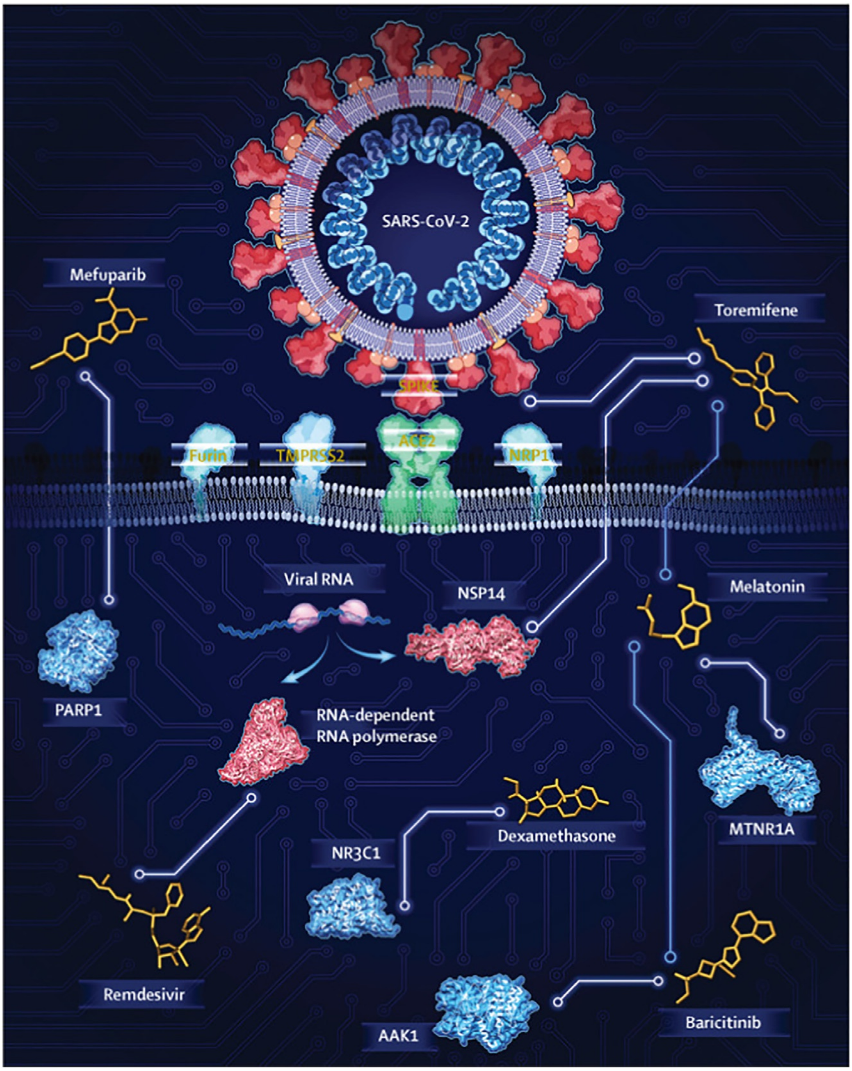

Fig. 4 An algorithm overview of AI-based concept that can be utilized for drug repurposing for COVID-19 that can make rapid and cost-effective way to invent the new therapy and many several options. *(This figure is adopted from Zhou Y, et al. Artificial intelligence in COVID-19 drug repurposing.* Lancet Digital Health *2020;**2**(12):e667–76 with permission.)*

3.3 AI for projecting the outbreak and mortality

Currently, only a few treatments are available for COVID-19. Ko et al.[101] have created a new model called EDRnet (ensemble learning model based on deep neural network and random forest models) to forecast in-hospital death using a regular blood test as an initial assessment in order to solve this problem. They chose 28 blood biomarkers and used patient's information such as age and gender as model inputs. They used an ensemble approach that combined both the models to enhance mortality prediction. EDRnet offered high sensitivity (100%), specificity (91%), and consistency in the testing data sets (92%). To enhance the amount of data points collected from patients, they created a web application (BeatCOVID19) that allows everyone to access the mortality prediction model and register their own blood laboratory results. This system could anticipate the presence of the virus, as well as the risk of disease transmission using accessible data, social networks, and news outlets. This system helps to identify the most susceptible areas, communities, and nations so that necessary measures can be implemented to prevent the spread.

3.4 AI for the development of drugs and vaccines

Scientists and medical practitioners have been asking for a feasible alternative to address the creation of a medicine and vaccine for the SARS-CoV-2. AI is used for drug research based on existing information on COVID-19. It may be used to create medication guidance systems and design them. AI-based technology helps to accelerate real-time drug testing in situations when traditional testing takes a lengthy period.[8,9] It could assist in the innovation of proper medicines for COVID-19 patients. Hence, it became an important method for producing screening tests and vaccinations.[102,103]

In biochemistry, AI aids scientists in better understanding the protein implicated in SARS-CoV-2 and identifying prospective threats.[104] ML leads to quick analysis of the complete viral proteins, enabling for more efficient and perhaps low-cost scientific investigation than prior vaccine development procedures.[104–106] Covax-19TM is a COVID-19 vaccine developed in Australia and developed using AI-based technology.[107,108] Vaxign-ML is a supervised ML algorithm that predicts the protegenicity score (the protegenicity score is the percentile rank score from the Vaxign-ML classification model) of all SARS-CoV-2 proteins.[109,110] Taiwanese scientists are doing research on a novel model on Deep Neural Network (DNN) to help in the development of COVID-19 medication such as homoharringtonine, salinomycin, boceprevir, tilorone, and chloroquine. Which were also shown to be effective on COVID-19 patients.[111]

Researchers from the United States and Korea proposed a novel molecular transformer-drug target interaction model[112] to address the need for an antiviral medication that could really treat COVID-19. The study compares AutoDock Vina, an open-source virtual screening and molecular docking tool, to a model based on a DL algorithm that uses COVID-19's 3C-like proteinase and FDA-approved 3410 existing medicines. Atazanavir (Kd of 94.94 nM), a common antiretroviral medicine used to treat HIV, was shown to be the best medicine for COVID-19 treatment, followed by Remdesivir (Kd of 113.13 nM). Moreover, after discovering a decade of medication research based on ML and AI technology, a merging of computational screening technique with docking application and machine learning for picking alternative medicine to research on SARS-CoV-2 was proposed.[113] Researchers point to the successful identification of Ebola[114] and the Zika virus[115] to conclude that the same technique might be used to identify drugs for COVID-19 and future viral pandemics.

4. Benefits and pitfalls of AI-based technologies

The COVID-19 pandemic has advanced the age of digital transformation. To combat the pandemic, AI and, in particular, ML and DL are being used in numerous fronts. However, in order to effectively manage the worldwide pandemic, several physicians and medical specialists have embraced the usage of AI. Following that, six areas have been identified where AI might help with successful pandemic management: early warnings and timely notifications, forecasting and monitoring illness prevalence, data dashboards, diagnosis and prognosis, treatment and cure, and social control. However, plenty of barriers stand in the way of widespread use of these cutting-edge technologies in larger scale clinical settings.

4.1 AI toward decreasing healthcare professionals' workload

Due to an unexpected and huge rise in the number of patients during the COVID-19 pandemic, medical personnel are overburdened. In this situation, AI is used to alleviate the strain on health professionals.[116–119] It assists in early diagnosis and intervention of this growing condition by employing digital methods and data analytics, as well as providing the best training to students and clinicians.[120,121] AI has the potential to improve future patient care and solve other potential issues, therefore decreasing the strain on clinicians. The introduction of robotics and AI can help considerably lower the risk of coronavirus transmission by decreasing human contact, safeguarding frontline healthcare professionals, administrative staff, and the general public. For instance, a trained DL system took

4.51 s on average to detect COVID-19 on CT chest, but a radiologist required 10 min and 9 s.[122,123] This indicates that if an AI software is trained to be as accurate as a radiologist, it will be able to provide findings 135 times quicker and operate around the clock without committing fatigue-related mistakes.[124]

Furthermore, AI can assist patients in getting into the proper position for computed tomography. Clinicians can place the patients appropriately in a control room with cameras, speakers, and AI-assisted positioning, eliminating personal contact with prospective victims and the risk of infection.[125] While AI is assisting in the optimization of healthcare operations by automating as many stages as feasible, it is not intended to replace human clinical reasoning and decision-making; rather, it is being utilized as a decision aid to improve efficiency, safety, and patient outcomes.

4.2 Challenges of large-scale screening

AI has the ability to analyze massive volume of data very efficiently. It is crucial in preventing the COVID-19 pandemic. As mentioned in the previous section, AI models are as effective as a skilled radiologist in diagnosing COVID-19.[87] Even if some COVID-19-infected people are asymptomatic, they do have the ability to spread the virus.[126,127] COVID-19 individuals with pneumonia-like symptoms could exhibit a pattern on their chest X-ray or CT imaging that only clinicians can understand.[128,129]

In the fields of biomedicine and cancer diagnostics, image processing techniques are interesting.[130] For the discovery of many illnesses, ML and DL approaches have proven to be useful.[131] Despite the fact that some people have been already diagnosed with SARS-CoV-2, their chest CT scans are normal. As a result, chest CT scans have a limited negative predictive value and do not clear out infection completely. The precision of a single AI diagnosis is currently being questioned. Thus, in order to meet clinical needs, AI algorithms must integrate chest imaging with clinical manifestations, exposure record, and clinical trials in the diagnosis of COVID-19.

However, before AI management, we need to think about appropriate clinical sample management such as proper packaging, less contamination, proper handling of the samples, proper media preparation to carry the samples from onsite to the hospitals or in any diagnostic center. In the following section, this chapter summarizes the clinical sample management and handling issues in detail.

5. Clinical sample management of infected patients

During the incubation phase of SARS-CoV-2, some infected individuals are symptomatic whereas some are asymptomatic. Hence, sample collection with proper expertise is important to diagnose the disease at an earlier stage. Collecting samples from COVID-19 patients is very challenging to handle and should be transferred as quickly as possible to the diagnostic centers.[2] The samples collected from nasopharyngeal swabs are highly recommended for confirmatory results, since the viral load is highest in the upper respiratory tract.[132] Sputum and blood samples are collected from the confirmed symptomatic patients with cough, high fever, and other general symptoms of COVID-19. In general, sputum samples are not recommended much due to aerosols production which can increase the chance of transmission.[132] For those patients who are in ventilators and/or in urgent care units, lower respiratory tract aspirate, BL fluids are recommended as samples for further assessment. In this section, we have discussed the sample collection process and on-spot collection challenges.

5.1 On-spot sample collection and laboratory confirmation

The main flow of sample gathering starts from swab collection from patients by a trained clinician who follows the proper guidelines by CDC, wearing personal protective equipment (PPE) and other safety measurements. Swabs are kept inside in a vial containing viral transport media and then transferred to nearby hospitals or diagnostic centers for various testing processes.[133] High amounts of viral RNA of SARS-CoV-2 are found in upper and lower respiratory tract of infected patients.[134] However, the viral load can be detected in stool and urine samples also. Samples from patients are collected by three main steps: (a) collection, (b) transport, and (c) storage. Quality of the samples depends on the operation and handling way of the collectors.[135] In general, first swabs are collected with cotton buds with plastic shafts and then kept into a sterile plastic container which contains viral transport media. It is highly recommended by WHO that any wooden shafts or calcium alginate swabs are not to be used as they may inactivate the virus and create false-negative results in RT-PCR test.[136] After the treatment and isolation, samples are repeatedly collected from the same infected patients to test until the result comes out to be negative. The frequency of sample collection should be every 2–4 days until two negative test results to confirm the patients are free from COVID-19.[137] Recently, there are many on-spot devices with advance protocol developed with biosensor technologies, molecular technologies, and antigen-based technologies for rapid confirmatory tests. Based on these technologies, many rapid kits (summarized in Table 3) are developed for quick and on-spot diagnosis for COVID-19. The most recommended test is RT-PCR test on respiratory samples. FDA has approved various rapid diagnostic tests which can provide on-spot and quick outcomes.[33]

5.2 Isolating high-risk groups

After sample management, the main critical step is to manage the infected patients. The patient management should be mainly done by isolation depending on the risk factors.[138] Soon after the confirmed test results, the patients need to be separated by 4 main categories such as extreme high-risk, high-risk, intermediate-risk, and low-risk case. Patients with extreme high-risk and high-risk need immediate medical support within 24 h.[139] Extreme high-risk patients may need invasive urgent care with ventilators, oxygen cylinders, and other life supports. Those patients need to be cared with high safety and precaution management since the viral loads of those patients could be extremely high and there could be a high chance of transmission from the patient to the caregiver. Isolating those patients completely in one cabin and providing them all separate facilities are highly recommended. Patients with intermediate-risk was evaluated by taking them in a separated and isolated area for further treatment with several RT-PCR tests. With the low-risk infected person, it is highly recommended that the action should be taken at home. They should be isolated at home with all immediate help from doctors over the phone. On the other hand, the hospital facilities such as number of beds, isolation rooms, ICU rooms, doctors, clinicians, nurses, and availability of oxygen cylinders need to be increased to handle the peak influx for COVID-19-infected patients.[140] Overall infrastructure and easy availability of laboratories and operators are needed to be very active due to the high demand of hospitalization of COVID-19 patients. Hence, the government, health sectors, and other frontline communities and individuals need to play a key role in terms of stopping this virus from spreading and to manage the crowd of patients properly. Healthcare workers should be more trained in the clinical and patient handling management. The healthcare professionals are actively participating during this pandemic and to control the infection, researchers are working continuously to mitigate the pandemic as early as possible. As a result, vaccination has been started and as per statistics shown in "Our world in data" 1.03 billion people worldwide which is around 13.2% of the world's population are vaccinated so far (https://ourworldindata.org/covid-vaccinations?country=OWID_WRL visited on 21.07.2021).

6. Conclusion and future prospective

Currently, there are numerous processes that have been developed to diagnose SARS-CoV-2 based on molecular and antigen-based technology. Nevertheless, concerning about time taking methodologies, the new approaches such as biosensor on-spot devices, biometric systems, and AI-based technologies are a quick mode of early detection during this pandemic situation. Several, AI- and biometric-based systems are forecasting about future probability of spreading this virus as well as providing the exact scenario of how many individuals are getting infected. The most important step is to geo-tag a citizen by a smartphone that has been considered very useful to monitor a COVID-19 patient for POC diagnosis as quick as possible. These contactless methodologies not only supply patient's field data but also provide risk-free direct contact between patients and clinicians. The AI- and ML-based technologies have also helped in identifying the existing and designing the new drugs which are effective against SARS-CoV-2. Perhaps, it is still important to have a precise, low-cost, reliable, rapid diagnostic method and testing kits to face this global pandemic. Scientists and researchers are still digging into these challenges and trying to solve them in order to fabricate a portable and user-friendly model for the accurate detection of COVID-19 which will help in enhanced management and prevention of any future pandemic.

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