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REVIEW ARTICLE

# Smart healthcare: A prospective future medical approach for COVID-19

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**Abstract:** COVID-19 has greatly affected human life for over 3 years. In this review, we focus on smart healthcare solutions that address major requirements for coping with the COVID-19 pandemic, including (1) the continuous monitoring of severe acute respiratory syndrome coronavirus 2, (2) patient stratification with distinct short-term outcomes (eg, mild or severe diseases) and long-term outcomes (eg, long COVID), and (3) adherence to medication and treatments for patients with COVID-19. Smart healthcare often utilizes medical artificial intelligence (AI) and cloud computing and integrates cutting-edge biological and optoelectronic techniques. These are valuable technologies for addressing the unmet needs in the management of COVID. By leveraging deep learning/machine learning capabilities and big data, medical AI can perform precise prognosis predictions and provide reliable suggestions for physicians' decision-making. Through the assistance of the Internet of Medical Things, which encompasses wearable devices, smartphone apps, internet-based drug delivery systems, and telemedicine technologies, the status of mild cases can be continuously monitored and medications provided at home without the need for hospital care. In cases that develop into severe cases, emergency feedback can be provided through the hospital for rapid treatment. Smart healthcare can possibly prevent the development of severe COVID-19 cases and therefore lower the burden on intensive care units.

**Keywords:** Artificial intelligence; Big data; COVID-19; precision medicine; SARS-CoV-2; Smart healthcare

## 1. INTRODUCTION

### 1.1. COVID-19

The COVID-19[1] pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[2] has lasted for almost 3 years, and at present, this pandemic still continues. The virus that causes COVID-19, SARS-CoV-2, is a betacoronavirus with a single-strand RNA genome containing roughly 29903 base pairs (NC_045512.2). It is related to SARS-CoV (the virus that caused the 2003 pandemic) and the Middle East respiratory syndrome coronavirus.[3] They share a common spike protein (S) as a bridge to attach to the surface of human host cells through membrane receptor binding to angiotensin-converting enzyme 2.[4] Because the S variant protein mutates frequently,[5,6] the virus is able to escape the host immune system and thus cause new waves of transmission. Since the outbreak in 2019, the virus has mutated many times and produced many variants of concern (VOC). Recently, the Delta[7] and Omicron strains (from BA.2 to BA.5)[8,9] have dominated the viral species sequentially, with Omicron, in particular, having a relatively low death rate.[10] Fever and coughing are no longer sufficient to identify all COVID-19 cases.[11] The loss of taste and olfactory function (ageusia and anosmia)[12] and a sharp sore throat have been identified as two new symptoms of SARS-CoV-2 infection. High numbers of asymptomatic COVID-19 cases have been reported.[13] Confirmation of infection is increasingly difficult.

To deter the spread of COVID-19, pandemic monitoring (including rapid viral detection and surveillance of COVID-19 diagnoses),[14,15] effective treatment (antiviral drugs and adequate healthcare provision),[16] and large-scale vaccination (with continual boosters from next-generation vaccines)[17] are all essential (**Fig. 1**). VOC whole genome sequencing[18] is crucial for monitoring the evolution of SARS-CoV-2 variants; however, the economic burden of medical examination is high. Although quarantine measures and contact tracing are effective methods to reduce transmission, space is a limited resource. Moreover, the widespread adoption of public health measures for an extended time period has had a global economic impact. For

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*Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.*

*Journal of Chinese Medical Association. (2023) 86: 138-146.*

*Received August 5, 2022; accepted September 9, 2022.*

*doi: 10.1097/JCMA.0000000000000824.*





<zdoi: 10.1097/JCMA.0000000000000824>

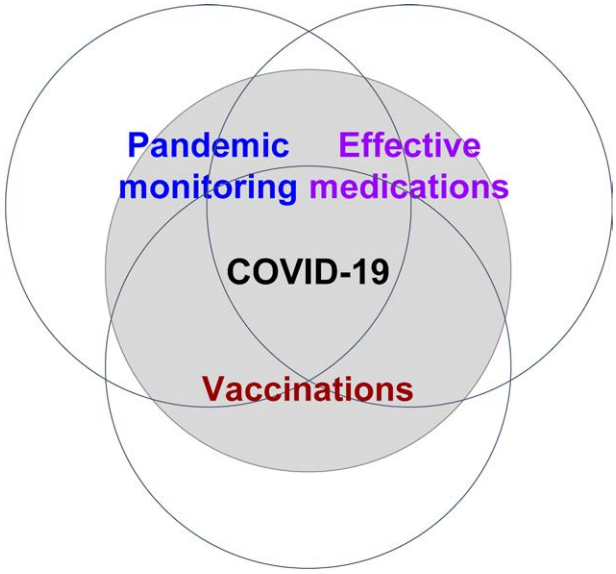


**Fig. 1** Areas of smart healthcare for the management of COVID-19.

citizens, the avoidance of unnecessary contact with the hands, nose, and eyes remains an effective method to prevent SARS-CoV-2 infection. As mask use decreases in numerous Western countries, new methods to contain the impacts of COVID-19 are being developed, such as consumer technology combined with cloud computing and big data.[19]

### 1.2. Medical artificial intelligence

Ever since the emergence of artificial intelligence (AI), researchers have continued to investigate the numerous applications of big data across various fields, such as biomedical science and medical care.[20–23] Big data in medicine utilizes four types of information: (1) coded data (diagnostic codes, drug codes, and disposition codes), (2) free text (descriptions by patients and pathological reports by physicians), (3) biophotonic data (including X-ray imaging, angiography, computed tomography, and magnetic resonance imaging), and (4) bioelectronic data (eg, heartbeat, blood pressure, breathing, and brain wave). For coded data, the International Statistical Classification of Diseases and Related Health Problems, 10th Revision recommends that bar code medication administration (BCMA) be replaced by a radiofrequency identification (RFID) or near-field communication (NFC). Free text can sometimes be collected through the recording of patient interactions with inquiry robots, such as Pepper, which was developed by Professor Ohe Kazuhiko of the University of Tokyo as part of a Japanese research group committed to the standardization of structured medical record exchange. These texts can be analyzed using natural language processing (eg, Cortana, Siri, Alexa, Google Home, and Apple HomePod). For biosignal (biophotonic and bioelectronic) data, wearable devices or the Internet of Medical Things (IoMT) can be used for data collection.

Medical AI can prevent ethical problems, which often arise in healthcare applications of big data and smart healthcare.[24] Medical AI is not susceptible to errors related to human nature (biased or incomplete dataset recordings or incorrectly obtained consent for certain clinical treatments) or to mishandling of private data (insecure or intentionally leaked data).[25] Medical AI uses machine learning (ML) or deep learning (DL) to conduct large-scale big data analysis of unstructured data and narrative texts from various individuals; however, medical AI often produces incorrect or inappropriate predictions.[26] This problem can be overcome through the integration of medicine, computer science, and other disciplines.[27] A well-designed medical AI can provide fast and valuable suggestions on disease prevention and effective therapeutic treatments by using data analysis methods including pattern recognition, analysis of various cloud computing platforms (eg, Amazon, Google, Microsoft), and the aforementioned biosignal data.[28] For cloud calculations using certain algorithms, patient records not only can be stored and recorded but also can be applied to the analysis of clinical data to provide valuable suggestions for physician decision-making.[29] Medical AI can play a promising role in healthcare provision and thus may threaten to displace human doctors.[30] To date, cardiology, internal medicine, and radiology are three medical fields that make extensive use of medical AI.[31,32]

Despite the promising applications of medical AI to the management of various diseases,[21–23] patient privacy is a serious concern.[33] Electronic healthcare data (including medical big data, coded data, text data, and biosignals) used in picture archiving and communications systems should be collected and handled with care whether such data originates from hospitals and national institutes (eg, Taiwan's National Health Insurance Research Database and Taiwanese biobanks) or from international data sources (eg, PubMed). The digital footprint of individual data contains personal information not only relating to health parameters but also to details, such as credit card information or even party affiliation. With regard to portable or wearable medical AI devices (eg, heart rate monitors or sleep trackers), such data may be recorded, tracked, and even stored through commercially available software for social media such as Facebook and other apps. The potential leak of personal information presents a substantial challenge to the retrieval of medical data.[33] A human-centered approach to medical AI should be adopted; for example, in federated learning (FL), all personal data should be stored in a system unique to each individual.[34] Taiwan AI Labs presents a model example of patient privacy management. The company, founded by Yi-Chin Tu in 2017, is the first Asian human-centered open AI laboratory. It aims to protect the privacy of individuals while gathering essential information through the precise filtering of individual information.[35] The goal of this innovative lab is to develop models to help humans to live a good life. This is an ideal goal for precision medicine. Following cross-trial and validation, the cross-hospital network and central platform can share valuable data and benefit from sharing large-scale clinical research.

## 2. PANDEMIC MONITORING OF COVID-19 AND MEDICAL AI

To identify the SARS-CoV-2 virus either at the genetic or protein level (detection of viral substances, **Section 2.1**; **2.2**) and to confirm COVID-19 cases through the evaluation of illness status (evaluated with clinical images and related symptoms, **Section 2.3**; **2.4**) are both key tasks to quantify confirmed cases for pandemic monitoring.[36] Through this combined approach, the majority of SARS-CoV-2 cases can be identified (**Fig. 2**).

### 2.1. Detection of SARS-CoV-2

The prevailing view is that detection of SARS-CoV-2 within the human body is the ultimate diagnostic definition of a confirmed case, regardless of patient symptomology. The most direct method of identifying SARS-CoV-2 infection is to detect virus-derived substances (either nucleic acids or proteins) through the analysis of nasopharyngeal swabs, saliva, or other sources.[37] The gold standard of viral detection is real-time reverse-transcription polymerase chain reaction (real-time RT-PCR). This is a nucleic acid amplification-based test (NAAT).[38] The virus can

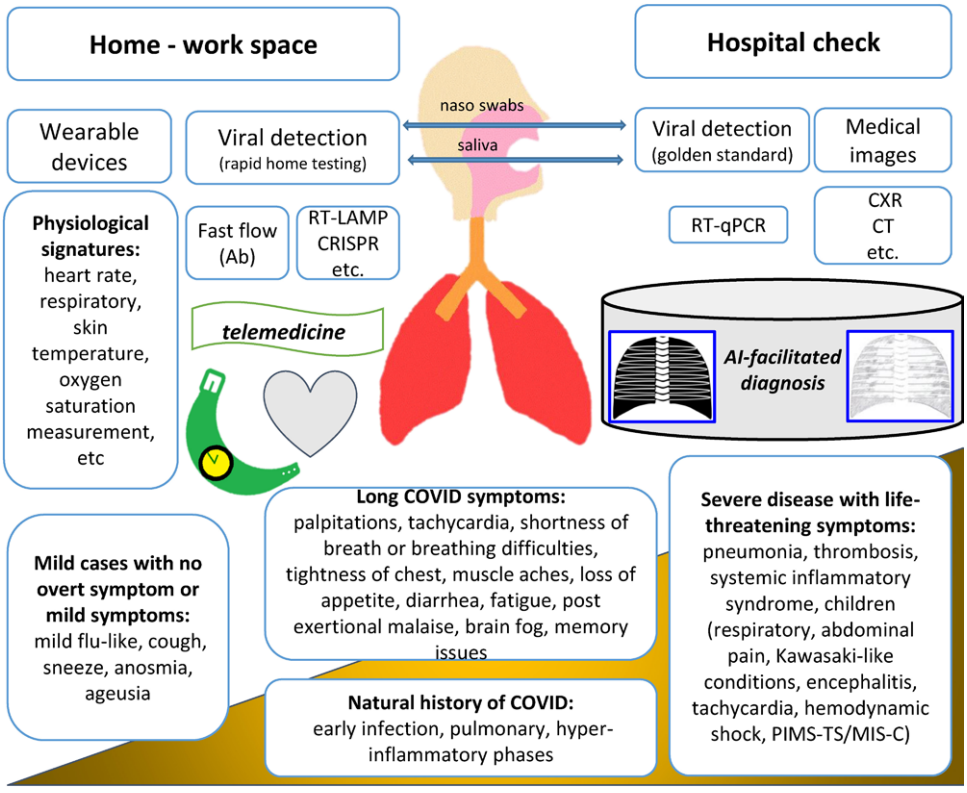


**Fig. 2** Smart healthcare for mild and severe COVID-19 diseases. For viral detection, RT-qPCR is the gold standard (hospital-only). For home testing, the FDA-approved fast flow kit (through antibody detection) allows for rapid detection of SARS-CoV-2. Although the accuracy of fast flow home testing is low, RT-LAMP and CRISPR have acceptable accuracy and are alternatives. For the symptom-derived signs of COVID-19 illness, wearable devices that can measure some physiological signatures including heartbeat rate, respiratory status, and even oxygen saturation can be connected with smartphone apps to supply prompt warning. These are more readily available than standard medical imaging confirmed by CXR or CT scan (hospital-only). Transferring such data to medical AI with cloud calculation ability can further facilitate prognosis prediction and provide medical suggestions. AI = artificial intelligence; CRISPR = clusters of regularly interspaced short palindromic repeats; CT = computed tomography; CXR = chest X-ray; FDA = food and drug administration; RT-LAMP = real-time loop-mediated isothermal amplification; RT-qPCR = reverse-transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

be detected through the design of specific primer sequences at the conserved viral genome regions of certain gene locations, namely (1) the RNA-dependent RNA polymerase (RdRp, within ORF1ab), (2) the envelope protein (E), and (3) the nucleocapsid protein (N) within SARS-CoV-2.[39] In addition, the cycle threshold (Ct) values generated through RT-qPCR testing can provide information on the viral infection status of patients and thus reveal chronological and geographic information (**Table 1**).

The RT-qPCR assay is time-consuming (from <8 hours to 1 or 2 days), and the performance of RT-qPCR depends on the hospital examination capacity. Therefore, reliance on this gold standard alone does not produce rapid results. Alternatively, loop-mediated isothermal amplification (LAMP) and related methods, such as real-time LAMP (RT-LAMP) and LAMP sequencing, and advanced biotechniques such as clusters of regularly interspaced short palindromic repeats (CRISPR)-Cas (Cas3, Cas9, Cas12, and Cas13)-based biosensors can also perform NAAT-like SARS-CoV-2 detection (the primer design can be the same or different to RT-qPCR) within 40 minutes or less.[40,41] Because NAATs require a special platform to read and process the data of clinical samples, the popularity of LAMP-related and CRISPR-related techniques is limited despite their testing speeds being as low as 15 minutes.[42]

The use of antibodies against viral proteins such as spike constitute protein-based tests for the rapid detection of SARS-CoV-2. This method requires even less time than NAATs.[43] This method may exceed the popularity of RT-qPCR. Such tests can be adapted from existing US Food and Drug Administration (FDA)-approved lateral-flu test kits for rapid home testing (eg, the SARS-CoV-2 Antigen Self-Test Nasal manufactured by F. Hoffmann-La Roche, Abbott, or other companies).[44] However, a drawback of these protein-based tests is insufficient accuracy when compared with RT-qPCR.[45,46] Asymptomatic false-negative cases may lead to the undetected transmission of VOCs. Mutated spike proteins can evade vaccination, the human immune system, and also protein-based rapid-testing antibodies. Despite these disadvantages, home testing as a rapid diagnostic tool remains a useful method of pandemic monitoring.

### 2.2. Smartphone-based viral detection

Medical AI used with smartphones and advanced biotechnology has great potential for viral infection monitoring. New optoelectronic devices integrated with a test chamber or with home testing papers can serve as fast and powerful viral detectors. These devices can be used in conjunction with cloud computing for both the retrieval and storage of detected signals. The information provided through this method is valuable for monitoring SARS-CoV-2 transmission.

LAMP-related rapid home testing has been approved for emergency use authorization by the FDA for COVID-19 (eg, Abbott ID NOW and Cue COVID-19 Diagnostic Test). RT-LAMP used in conjunction with the novel technique of particle diffusometry (PD) displayed excellent SARS-CoV-2 detection capability; a limit of detection (LOD) of 30 virus particles per μL or less ($35 \times 10^4$ viral particles per mL) within 35 minutes in saliva was reported. In addition, PD-LAMP is compatible with

**Table 1**

**Viral detections for severe acute respiratory syndrome coronavirus 2 and the combination with medical artificial intelligence**

| | Nucleic acid-amplification detection | | |
|---|---|---|---|
| **Methods** | **RT-qPCR** | | |
| **Place to exam** | Hospital | | |
| **Sampling** | Naso swabs (some saliva) | | |
| **LOD (sensitivity)** | 97% (reference 42) Ct < 40 | | |
| **Accuracy (specificity)** | gold standard | | |
| **Time to get the data** | 3.5-4 hours (reference 42) | | |
| **Commercial availability** | Roche, LabCorp, PerkinElmer (RUO), Mesa Biotech, Cepheid, Qiagen, Thermo Fisher, BioRAD (Research Use Only, RUO) | | |
| **Commercial with medical AI** | Cobas® SARS-CoV-2 6,800 (96 results in 3h; 384 in 8h) and 8,800 systems (1056 in 8h) (Roche Molecular Diagnostics, Pleasanton, CA, USA) | | |
| | Abbott Molecular (Des Plaines, IL, USA) the m2000 system 96 samples simultaneously, 470 test results in ~24 h; sensitivity (93%); specificity (100%) | | |
| | **Nucleic acid-isothermal amplification detection** | | |
| **Methods** | **RT-LAMP** | | |
| | **CRISPR-Cas 12 or Cas13** | | |
| **Place to exam** | Home (hospital for mega usage) | | |
| **Sampling** | Naso swabs (some saliva) | | |
| **LOD (sensitivity)** | 10 (iLACO, reference 40), 30 (PD-LAMP, reference 47) copies/μL 97% (reference 48); 1 copies/μL (Cas13a), 10 copies/μL (Cas12a/b) (reference 41) | | |
| **Accuracy (specificity)** | 89.9% (reference 40) iLACO 95% (reference 48) | | |
| **Time to get the data** | 10 min (NEAR, FDA-EUA), 20 min (iLACO), 30 min (PD-LAMP) 30-90 min | | |
| **Commercial availability** | Atila Biosystems, Abbott Mammoth Biosciences (DETECTR), SHERLOCK Biosciences (FDA-EUA) | | |
| | **Protein-based rapid home testing** | **Indoor air quality monitoring** | **Exhaled breath detection** |
| **Methods** | **Fast flow detection (antibody)** | **Space Monitoring Device** | **Wearable** |
| **Place to exam** | Home only on-site | Home, work, hospital, on-site | Home, work, hospital, on-site |
| **Sampling** | Naso swabs (some saliva) | Air | Air (collected from mask) |
| **Time to get the data** | 15 min | 30 mins | N.A. |
| **Commercial availability** | Fast flow kit (FDA-approved) | N.A. | N.A. (reference 53) |

AI = artificial intelligence; CRISPR = clusters of regularly interspaced short palindromic repeats; FDA = food and drug administration; LOD = limit of detection; PD = particle diffusometry; RT-LAMP = real-time loop-mediated isothermal amplification; RT-qPCR = reverse-transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
The cited references are: 40, 41, 42, 47, 48, 53

**Table 2**

**Diagnostic and monitoring methods for COVID-19 and the commercial (personal) availability**

| **Medical imaging** | **Chest X-ray (CXR)** | **CT scanning** | | |
|---|---|---|---|---|
| **Place to exam** | Hospital | Hospital | | |
| **Sampling** | In vivo on-site | In vivo on-site | | |
| **Time to get the data** | N.A. | N.A. | | |
| **Commercial (personal) availability** | N.A. | N.A. | | |
| **Wearable electronics device** | **Respiratory rate** | **Heart rate** | **Skin temperature** | **Oxygen saturation** |
| **Place to exam** | Home, work, hospital | Home, work, hospital | Home, work, hospital | Home, work, hospital |
| **Sampling** | In vivo on-site | In vivo on-site | In vivo on-site | In vivo on-site |
| **Time to get the data** | real-time | real-time | real-time | real-time |
| **Commercial (personal) availability** | WHOOP Strap; Oura Ring | Apple WatchE; 4 wristband; Fitbit;WHOOP Strap; Oura Ring | Fitbit; Oura Ring | Apple Watch; Fitbit; Oura Ring |

The cited references are: 74, 75, 76, 77, 78.

digital connectivity for point-of-care testing.[47] For advanced NAAT, CRISPR-Cas12a integrated with smartphone-based fluorescence devices (with low-cost three-dimensional-printed housing and optics) under a DL/ML-driven environment has been applied for the detection of SARS-CoV-2.[48] The LOD of this device is approximately 6.25 RNA copies/μL (based on laboratory samples). It exhibited a test accuracy of 95% and a sensitivity of 97% on 96 nasopharyngeal swab samples with transmissible viral loads (**Table 1**). Furthermore, without nucleic acid amplification and reverse transcription (not NAAT, but nucleic acids are still detected), a novel portable electrochemical smartphone biosensor was developed to achieve the ultrasensitive detection of SARS-CoV-2 RNA.[49] This method is based on the super-sandwich recognition strategy that utilizes calixarene-functionalized graphene oxide as the key biosensor. The LOD of this method to a clinical specimen is 200 copies/mL. This LOD is reported to be the lowest among the published RNA measurements to date.

For the detection of viral protein level, a smartphone-assisted immunoassay-based method integrated with magnetic beads and colorimetry was established for testing saliva and nasopharyngeal swab samples.[50] The LOD of this 96-well wax-printed paper plate assay is 0.1 μg/mL. A Spotxel free-charge app for use with this specific assay was also developed. The primary advantage of this cost-effective method is accurate detection within 30 minutes, even when used with samples with low viral load (Ct numbers as high as 30 have been reported from RT-PCR results). It is also crucial to evaluate the quantity and quality of SARS-CoV-2 neutralizing antibodies in blood samples of patients with COVID-19 and vaccinated individuals. A smartphone can serve as track-etched membrane microplate readers for high-throughput quantitative measurement of antibodies.[51]

With regard to the application of novel photoelectric technology, Kawasaki et al[52] described a label-free smartphone-based optical sensor for SARS-CoV-2 testing. The imprinted photonic crystal film inside this optical sensor is functionalized with an anti-SARS-CoV-2 spike protein antibody and thus can conduct the corresponding immunoassay. This novel device can detect SARS-CoV-2 at a low LOD of 429 fg/mL from saliva samples.

Knowledge of the viral genome or proteins from tested samples enables the physical identification of the virus within the human body. However, the results of viral detection (Sections 2.1, 2.2) can be influenced by many factors, such as sampling error and infection status (see the following Sections 2.3, 2.4). For example, the viral load of each infected person may vary depending on the day of infection and vary according to individual immune ability (regardless of vaccination status). In reality, many patients report negative home rapid-testing results (when no reason to undergo RT-qPCR at their own expense exists) while reporting novel COVID-19 symptoms such as ageusia, anosmia, and sharp sore throat without fever and cough (**Fig. 2**). Whether such cases (rapid test negative but symptom positive) should be viewed as confirmed cases is a matter of debate. False viral detection results statistically influence confirmed case data.

For sample collection, which generally uses nasopharyngeal swabs or saliva, a unique, disposable, and inexpensive wearable collection device was designed for the on-site airborne viral collection.[53] It can adhere to the inside of various masks (textile, surgical, KN95, or N95) to collect the virus exhaled in the breath. The efficacy of this collection method was confirmed with the following detection methods: RT-qPCR, RT-LAMP, and antibody-based dot blot assays. Such a device will be highly useful when smartphone-based detection methods (eg, smart RT-LAMP and smart CRISPR) or rapid paper home testing have been developed for widespread application.

### 2.3. Specific illness of COVID-19: medical imaging and medical AI

Although the majority of suspected cases that are asymptomatic or exhibit few symptoms seem to be mild cases (or may not be recognized as confirmed cases), such cases may not necessarily have good prognoses. The oversight of such possible infections might lead to the underground transmission of SARS-CoV-2. In the absence of notification, such cases can constitute unknown sources of transmission. Conversely, severe cases exhibiting serious symptoms cause major concern because the virus threatens the lives of patients with comorbid conditions, such as those with chronic diseases, metabolic syndrome (including diabetes), or cancers.[54] Aggressive treatment is required for such patients, either in the hospital or at home, to achieve the goal of zero severe cases and to reduce the death rate among severe cases.

Confirmation of a COVID-19 diagnosis generally takes place in hospitals but not exclusively so. The clinical diagnosis of COVID-19 can be confirmed using various physical examinations and medical imaging techniques—for example, chest X-ray (CXR) imaging and computed tomography (CT) scanning.[55] CXR imaging is a simple method for diagnosing pneumonia. CT scanning allows for rapid diagnosis.[56] Similar to RT-qPCR, medical imaging requires medical resources and personnel. The continuation of the pandemic places a burden on such resources.

AI-based classification of pneumonia during the COVID-19 pandemic can be performed using ML-based automated systems with CXR or CT scan images acquired from hospitals and analyzed using medical AI such as NHIA-TAIMedimg, DeepCheX, GoogleNet, Choquet Fuzzy with Xception, and others.[57,58] The preliminary results are then returned to the Centers for Disease Control for the final decision.

### 2.4. Specific illness of COVID-19: wearable devices and medical AI

The use of physical checks similar to CXR and CT imaging, for example—wearable devices that can detect COVID-19 outside the hospital, is another potential monitoring technique. Through the redefinition of the specific criteria of COVID-19, medical AI can use DL and ML to recalculate acceptable physical parameters for further applications. Medical AI used in conjunction with big data analysis allows for the large-scale continuous retrieval of data for simulation and prediction.[57] Because CXR and CT can only be performed in clinical settings and only specialist radiologists may perceive subtle anomalies, other tools such as wearable medical devices or sensors have the potential for the rapid and accurate confirmation of SARS-CoV-2 infection at home.[59,60] Through the recording of subtle physiological changes such as heart rate, respiratory rate, and skin temperature and through comparison with confirmed cases, early digital biomarkers of infection can be determined (as discernible symptoms of suspected COVID-19 cases). However, a review article analyzed numerous published papers (MEDLINE, Web of Science, etc.), protocols, and data (Embase, Cochrane Central Register of Controlled Trials, International Clinical Trials Registry Platform, ClinicalTrials.gov, etc.) investigating the use of wearable devices for this purpose. They unexpectedly reported that the majority of this research exhibited a moderate risk of bias, and the accuracy of their results is doubtful.[60] It is still not possible to conclude that the aforementioned three physiological parameters can be used as new gold standard parameters for the diagnosis of COVID-19. Medical AI prediction can test the efficacy of such parameters.

Conversely, fingertip pulse oximeters are rapid point-of-care and home care medical devices for the measurement of oxygen saturation values (proportions of oxygenated and deoxygenated hemoglobin) to evaluate the condition of the respiratory system. Oxygen saturation measurement is particularly crucial during the SARS-CoV-2 pandemic because many infected individuals are suspected to be in a silent hypoxic state without overt dyspnea. In the UK, pulse oximeters are provided as home care devices to high-risk patients with COVID. Fingertip pulse oximeters can be an integral component of IoMT against COVID. One such cloud-based monitoring system has been implemented by National Yang Ming Chiao Tung University in Taiwan. The fingertip pulse oximeters are connected wirelessly to smartphones using Bluetooth technology. The app then communicates with the cloud-based monitoring system to send out warning messages to patients when abnormal patterns of measurements are detected.

Further, several smartphone apps have been developed, such as the Zoe COVID study app, the CoroNotes app (University of Tübingen), and the COVID Control App (John Hopkins University). These are either designed for the detection of age-based and sex-based early symptom discrepancies, to enhance user well-being, or to record the daily body temperature of patients. Lovey et al[61] recently demonstrated the possibility of remotely monitoring SARS-CoV-2 confirmed cases by conducting a prospective cohort study using a smartphone app called Illness Tracking in Tested Persons. Through this tracking system, significant high odds ratios of difficulty breathing (3.35), a reduced sense of taste (ageusia, 5.45), and a reduced sense of smell (anosmia, 18.24) can be detected. These top three symptoms display COVID-19-specific signs (compared with the SARS-CoV-2 negative set). Fatigue was the only single symptom to considerably influence the daily activities of confirmed cases. This type of tracking system or another platform such as the Blue Dot AI system[23] may be applied in various settings

including schools, hospitals, companies, sport clubs, or music groups to detect signs of developing infection (once the alternative three can be confirmed as new gold standards of COVID-19 diagnosis). Such systems may be used to control transmission and predict epidemiological trends.

## 3. PATIENT CATEGORIZATION AND PROGNOSIS PREDICTION

To date, SARS-CoV-2 has infected more than 550 million people globally. The vast spread of the disease over 2–3 years has drastically increased the burden on medical service providers who lack the capacity to cope with a pandemic of this scale. In some areas, medical systems have been overburdened to the point of breakdown. COVID-19 presents diverse symptoms with varying severity among different people, ranging from no symptoms to mild flu-like symptoms such as coughing and sneezing and to severe diseases such as pneumonia, thrombosis, and systemic inflammatory syndrome (**Fig. 2**). For children, symptoms include respiratory symptoms, gastrointestinal conditions such as abdominal pain, Kawasaki-like conditions, encephalitis, cardiovascular conditions such as tachycardia and hemodynamic shock, and pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS; i.e., a multisystem inflammatory syndrome in children).[17] Facilities such as negative pressure rooms and intensive care units are in limited supply, and hence, medical resources must be used wisely, and patients should be triaged according to the severity of their symptoms.

The reliable prediction of a patient's clinical courses can enable personally optimized patient care and the efficient use of medical resources (**Fig. 3**). Information from the time of infection may be useful for predictions. First, the viral strain (Alpha, Beta, Delta, or Omicron) and viral load (determined by RT-PCR) can affect the clinical course. Second, the exacerbation of preexisting comorbidities also affects the clinical course. Third, age, sex, genetics, ethnicity, serum biochemistry profiles, immunological profiles, and environmental factors may also affect the clinical course. The utilization of data related to viral, host, and environmental factors may effectively predict whether an infected person will exhibit mild symptoms or severe symptoms requiring hospitalization or even intensive care (**Fig. 2**). The two types of outcomes are not proportional. Mild cases account for >90% of infections, and severe cases account for <10%.[62] Hence, the sensitivity and specificity of prediction are both crucial. Big data gathered from the information hub can be integrated and calculated through DL to provide valuable suggestions for the treatment of COVID-19 cases.

A laboratory study conducted in South Korea with 561 adult patients with COVID-19 demonstrated that age, sex, and serum concentrations of C reactive protein, lactate dehydrogenase, and hemoglobin are major independent factors associated with the progression to severe pneumonia, which is defined as resting oxygen saturation <93%, $PaO_2/FiO_2$ ≤300 mmHg, or the need for mechanical ventilation.[63] The patients were treated at Keimyung University Daegu Dongsan Hospital (KDDH), and the constructed KDDH score using five independent factors achieved an area under the receiver operating characteristic curve of 88.4% in the training dataset and 82.8% in the validation dataset. Apart from age and sex, the independent factors are derived from common laboratory examinations of peripheral blood. The COVID-19 care apps in intelligent devices, such as Zoe, CoroNotes, and COVID Control (as described in Section 2.4), or other similar apps should incorporate a severe disease

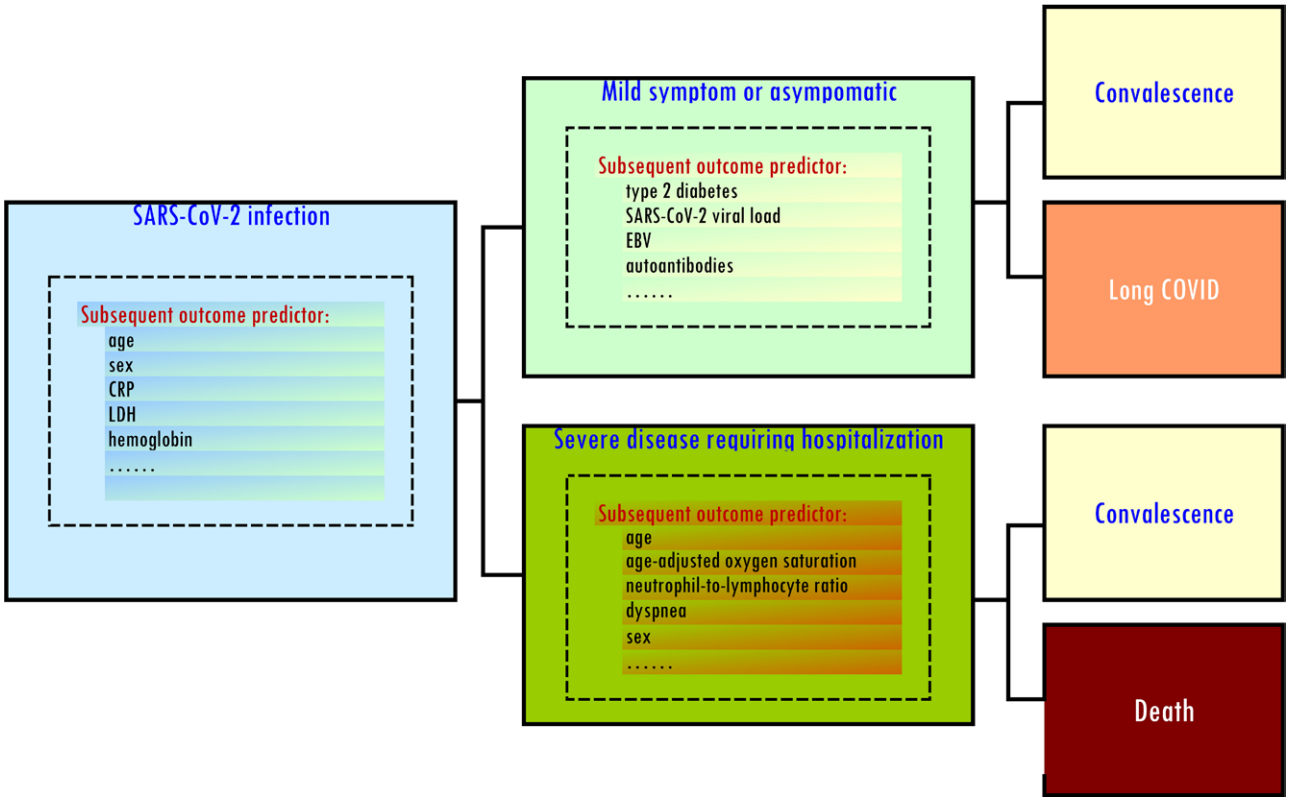


**Fig. 3** Successive predictors for clinical courses of patients with COVID-19. A roadmap of the COVID-19 clinical course with three predictors incorporated to facilitate optimized patient care and medical resource allocation. The predictors can be implemented as apps in mobile devices or integrated into the computer systems of hospitals.

risk predictor that allows users to input the values of the five factors and receive a prediction (**Fig. 3**).

### 3.1. Mild cases with prognosis prediction

Mild symptoms usually resolve within a few days. After the acute symptoms resolve, some symptoms may appear or reappear several weeks after the infection, including palpitations, tachycardia, shortness of breath or breathing difficulties, tightness of the chest, muscle aches, loss of appetite, diarrhea, fatigue, postexertional malaise, brain fog, and memory issues. These symptoms are collectively known as long COVID.[64] Approximately one in five patients with COVID develop long COVID.[65] In Britain, the Zoe (as described in Section 2.4) smartphone-based COVID Symptom Study app was developed to collect self-reported long COVID conditions.[66] Status at the time of infection may be used to predict the long-term prognosis with or without long COVID conditions.

A multiomics study was conducted to reveal factors associated with long COVID. It was found that type 2 diabetes, SARS-CoV-2 viral load, and the detection of Epstein–Barr virus and specific autoantibodies are correlated with long COVID.[67] An app for mobile devices should be developed for users to input this information and calculate their risk using an established algorithm (**Fig. 3**).

### 3.2. Severe cases with prognosis prediction

The clinical course of severe COVID-19 can be categorized into three phases: early infection phase, pulmonary stage, and hyperinflammatory phase.[68] Different treatments are required in different phases. For those with severe disease, whether the patient requires intensive care is a major concern.

A predictive model for 30-day mortality was recently constructed based on cohorts of 4035 and 2126 hospitalized and laboratory-confirmed patients, and these were used for the model construction and validation stages, respectively.[69] The patients were recruited from 127 Spanish hospitals. Factors employed in the model include age, age-adjusted oxygen saturation, neutrophil-to-lymphocyte ratio, estimated glomerular filtration rate according to the chronic kidney disease epidemiology collaboration equation, dyspnea, and sex. The constructed model achieved 82.2% and 84.5% area under the receiver operating characteristic curves in the model construction and validation cohorts, respectively. The predictive model could be implemented in a hospital software system or as an app for smartphone devices. Currently, oxygen saturation measurements are mostly measured by electronic point-of-care devices (also mentioned in Section 2.4). These devices can be readily designed to send measurements wirelessly to hospital systems or mobile devices where the apps are installed (**Fig. 3**).

## 4. EFFECTIVE MEDICATIONS AND FUTURE PERSPECTIVES

When transmission remains high and quarantine measures no longer slow viral transmission, it may be necessary to diagnose cases through either of the aforementioned techniques (Section 2; **Fig. 2**). The combined monitoring of the medical information and health activities of individuals meet the FL requirement of respecting patient privacy. AI-ML with advanced software as medical device (SaMD) can be developed to provide accurate predictions of COVID-19 status on a large-scale (also discussed in Section 3).[70] The Taiwan Social Distancing App is a practical example of SaMD for COVID-19.[71] Each datapoint collected through Bluetooth from individuals is decentralized before being reported as a confirmed case with geographic distance between the patients with COVID-19 and the users of concern. However, it seems that insufficient data are provided for the users of this app. This is primarily because of obedience to primary protection; for example, it accounts for the lack of data concerning when and where the user has been in short-distance "contact" with unknown numbers of confirmed cases. Further improvements of such apps would provide valuable information on the transmission of COVID-19 for the users while still maintaining individual privacy.

In the period following the COVID-19 pandemic, it is likely that SARS-CoV-2 will be a permanent presence in our lives, similar to the pandemic of influenza A. Thus, we should focus on prognosis prediction (Section 3, **Fig. 3**) and effective medications. Generally, the medication process contains four steps after the confirmation of illness: (1) prescription (smart healthcare systems can help to confirm the correct prescription), (2) dispensation of medication (a robot can assist in the provision of correct medication), (3) administration (confirm correct drug given, BCMA, RFID, NFC), (4) compliance (a smartphone app can remind patients to medicate, and the learning health system can prevent adverse drug reactions). Medical AI can assist in all of these steps to lower the risk of medical and follow-up errors. The future AI hospital service will integrate disease prevention (including precision health assistance and prehospital consultation plus prediction), AI clinics (assisted diagnosis and treatments), AI nursing (assisted care), and a smart workflow for the entire medical care and telemedicine system (when the burden of a hospital is considerable enough that some mild cases should not present at the hospital but rather receive remote healthcare).

Telemedicine combines mature medical AI with versatile IoMT (eg, AI-assisted medical documentation, voice recognition and decentralization, and wearable monitoring system)[71,72] and the analysis of big data through AI-DL/ML cloud computing to develop strategies and algorithms. This may combat the shortage in human resources of hospitals and clinics and has great potential to help patients with COVID-19 at home.[73] The IoMT being linked to the available data from hospitals or personal smartphones will increase the speed of case confirmation and of the following steps, such as quarantine or discharge, prognosis prediction, and suggestions for individualized treatments. With the help of telemedicine systems, physicians can first confirm the results of FDA-approved lateral flow home testing and the reported symptoms of suspected cases through smartphone apps online with clinics. Doctors will be responsible for each confirmed case. Adherence to medication can be assisted by medical AI and IoMT.

Big data containing the identification information of individuals will be stored and represented through an Internet interface and can be used for personal medications, treatments, and possible prognosis prediction and tracing (**Figs. 2 and 3**). Doctors responsible for case confirmations can make decisions regarding the prescription of essential medications and, with the help of IoMT, delivery of anti-SARS-CoV-2 drugs to individual patients. Such measures will allow for long-term control of COVID-19. In the future, medical AI can also contribute to new vaccine design to combat new variants beyond Delta and Omicron BA.2–BA.5 and also to the development of antiviral drugs.

## ACKNOWLEDGMENTS

This study was supported by Ministry of Science and Technology of Taiwan, MOST (105-2320-B-075-002, 108-2745-8-075-001, 110-2320-B-075-005) and Taipei Veterans General Hospital (V-110-018, V111C-088).

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