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TOPICAL REVIEW

Electrochemical Biosensing and Deep Learning-Based Approaches in the Diagnosis of COVID-19: A Review

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ABSTRACT COVID-19 caused by the transmission of SARS-CoV-2 virus taking a huge toll on global health and caused life-threatening medical complications and elevated mortality rates, especially among older adults and people with existing morbidity. Current evidence suggests that the virus spreads primarily through respiratory droplets emitted by infected persons when breathing, coughing, sneezing, or speaking. These droplets can reach another person through their mouth, nose, or eyes, resulting in infection. The ''gold standard'' for clinical diagnosis of SARS-CoV-2 is the laboratory-based nucleic acid amplification test, which includes the reverse transcription-polymerase chain reaction (RT-PCR) test on nasopharyngeal swab samples. The main concerns with this type of test are the relatively high cost, long processing time, and considerable false-positive or false-negative results. Alternative approaches have been suggested to detect the SARS-CoV-2 virus so that those infected and the people they have been in contact with can be quickly isolated to break the transmission chains and hopefully, control the pandemic. These alternative approaches include electrochemical biosensing and deep learning. In this review, we discuss the current state-of-the-art technology used in both fields for public health surveillance of SARS-CoV-2 and present a comparison of both methods in terms of cost, sampling, timing, accuracy, instrument complexity, global accessibility, feasibility, and adaptability to mutations. Finally, we discuss the issues and potential future research approaches for detecting the SARS-CoV-2 virus utilizing electrochemical biosensing and deep learning.

INDEX TERMS SARS-CoV-2, COVID-19, PCR, deep learning, electrochemical biosensor.

I. INTRODUCTION

The Director-General of the World Health Organization (WHO) declared the SARS-CoV-2 a pandemic on 12 March 2020 [1]. SARS-CoV-2 is extremely contagious and spreads similarly as SARS-CoV-1, by direct physical contact through respiratory droplets or touching of contaminated surfaces, as well as indirect contact by aerosolized SARS-CoV-2 [2]. Current evidence shows a significant proportion of those who are capable of transmitting the virus have no or barely visible

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symptoms while carrying the very high viral load [3]. This is noteworthy because asymptomatic COVID-19 patients are infectious and may act as silent drivers for the transmission of the virus.

Pathogenic coronaviruses (CoVs) are a type of positive-sense single-stranded RNA (+ssRNA) viruses [4]. Among the CoVs (previously identified MERS-CoV, SARS-CoV, and the novel one) SARS-CoV-2 is the most pathogenic. Figure 1 shows the structure of SARS-CoV-2 and its mode of host entry [5]. The spike protein on CoVs have two domains: SP1 binding to host cell receptors and SP2, the fusion peptide, facilitating viral cell entry. The angiotensin-converting enzyme 2 (ACE2) receptor on the cell membrane is the major receptor for SP1. Among the three CoVs (HCoV-NL63, SARS-CoV, and SARS-CoV-2) which use ACE2 to enter the host cell, the binding affinity of S1 to ACE2 is the highest in SARS-CoV-2 and lowest in HCoV-NL63 [6]. In other words, ACE2 is used by SARS-Cov-2 to enter the cell, which is the first stage of the virus multiplication cycle. When SARS-CoV-2 binds to ACE2, it further prevents ACE2 from regulating angiotensin II signaling, thus increasing the level of angiotensin II to damage blood vessel linings and injure tissues.

For the purposes of public health surveillance of SARS-CoV-2 in humans, nucleic acid amplification tests, most commonly the reverse transcription polymerase chain reaction (RT-PCR) assay, using nasal-swab samples is the WHO-recommended validation assay [7]. On average, the RT-PCR test results can take two to five days due to the time taken in the collection and transportation of samples to the labs. Although RT-PCR test is the gold standard, it has several limitations, including the cost of operation since the RT-PCR machines are expensive and long processing time. Moreover, there have also been reports of false-negative and false-positive results from the RT-PCR tests [8], [9].

A global call was issued for the effective diagnosis, treatment of SARS-CoV-2, and measures to control the spread of infection. For a better prognosis of COVID-19, early detection of disease is crucial. RT-PCR tests were the first to be developed and widely used when the COVID-19 pandemic broke out. Many approaches have been proposed as an alternate replacement for the RT-PCR test. Aside from viral genome detection, serologic tests such as ELISA (enzyme-linked immunosorbent assay) [10], LFA (lateral flow immunoassay) [11], and chemiluminescent (CLIA) [12], and chest CT scans combined with clinical symptoms have been used to diagnose the SARS-CoV-2. Besides these tests, researchers have also used novel approaches to reduce the cost of testing and offer more reliable test results. Among them, electrochemical biosensing- and deep-learning-based approaches stand out as illustrated in Figure 2 [13], [14], [15], [16]. In this review, we evaluate these two different approaches as potential alternatives for more accurate and affordable SARS-Cov-2 diagnostic tests.

Electrochemical biosensors are analytical tools that measure the concentration of an analyte of interest in a complex sample matrix, they can be used to detect viruses [17], cancers cells [18], bacteria [19], and small biomolecules such as glucose, dopamine, uric acid, and ascorbic [20], [21]. Electrochemical biosensors have been extensively studied for their unique advantages, such as portability, low cost, fast response, and high sensitivity, over other analytical devices [22]. The electrochemical biosensors produce a signal by interacting with receptors/bioreceptors and the particular analyte to produce or consume ions or electrons. This causes a change in the electrical properties of the electrolyte solution. The change in the electrical current or potential of the electrolyte solution is measured using functionalized electrodes, which generate an electrical signal that is correlated to the amount of target analyte in the test sample [23], [24]. Many recent studies have shown that electrochemical biosensors can be utilized for SARS-CoV-2 diagnosis [25]. In general, deep-throat saliva and nasopharyngeal samples [26] can be tested with or without the extraction of genetic material from SARS-CoV-2, improving the time taken for rapid diagnosis. For example, Raziq *et al.* vortexed the clinical samples from nasopharyngeal in lysis buffer to release proteins and reduce the inferencing species [14]. On the other hand, Beduk *et al.* developed an electrochemical immunoassay for the detection of SARS-CoV-2 using serum samples without any pre-treatment [27].

There is a high demand for deep learning-based approaches in various research fields such as medical [28] and agriculture [29]. Recently, deep-learning-based models (DLMs) were extensively studied for the diagnosis of the SARS-CoV-2 [30], [31], [32], [33]. The developed DLMs consist of data collection, data preparation, feature extraction, and lastly model evaluation [34]. Data collection is the first and crucial step. The quantity and quality of the computed tomography (CT) and X-ray lung images collected are used to validate the success of the developed model. The data preparation stage mostly includes data augmentation, noise removal, and resizing the input image [35]. The processed data are then divided into training, test, and validation sets. The model is developed using the training dataset, and its optimization is checked generally using a cross-validation technique [36]. The optimized model is then run on the test set to validate its performance on the unseen data. Feature extraction is the process of reducing the dimensionality in which the initial raw data are processed to more manageable groups by maintaining accuracy and still describing the original dataset. Finally, the developed model is evaluated using various metrics, such as accuracy, confusing matrix, sensitivity, specificity, precision, F1-score, etc. [37].

X-ray and CT are the most widely used imaging modalities in the field of artificial intelligence (AI) for the accurate diagnosis of SARS-CoV-2 [38]. The manual interpretation of medical images by radiologists is a time-consuming process and it is prone to human errors and bias. Recently, AI technology is evolving in the medical diagnosis of various diseases. Deep learning [15], machine learning [39], data science [16], the internet of things [40], and big data [41] are the main

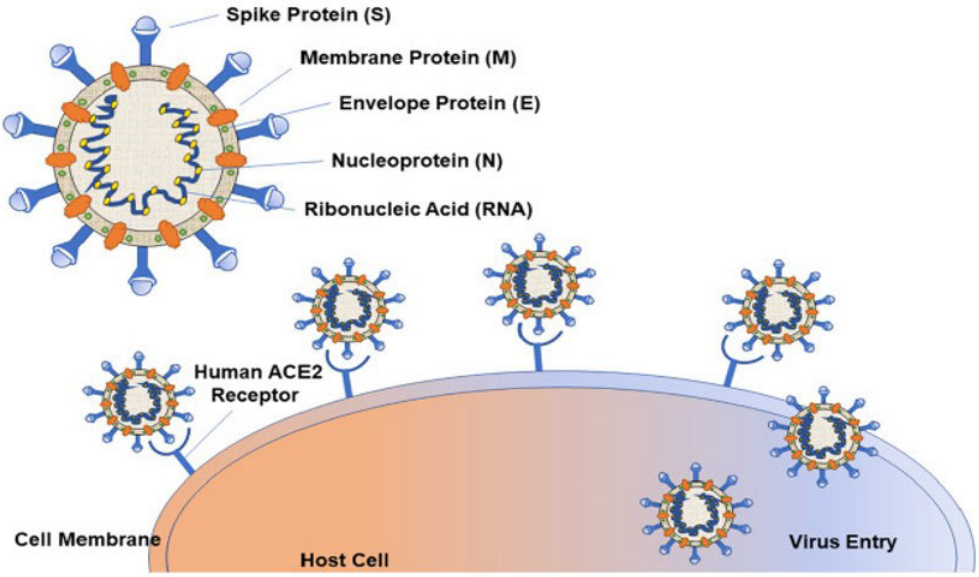

FIGURE 1. Schematic illustration of SARS-CoV-2 structure and its mode of host entry. Adapted with permission from Elsevier, Copyright (2022), 5234941355836 [5].

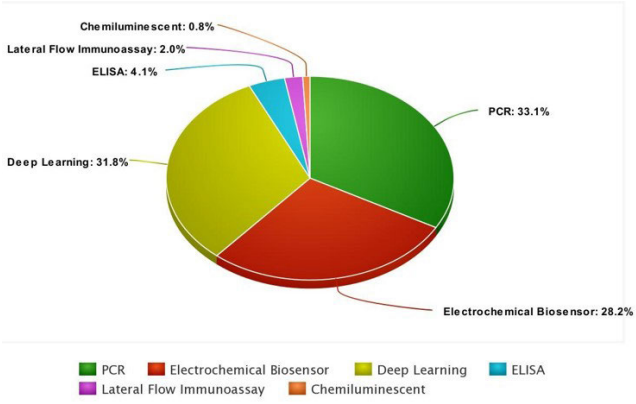

FIGURE 2. The percent of research articles on detection/diagnosis of SARS-CoV-2 related research since the start of the pandemic. (Source: ISI Web of KnowledgeSM, 01/20/22).

subsets of AI that are used to reduce the severity of the COVID-19 pandemic. The main advantage of AI techniques is to speed up the diagnoses while significantly decreasing the medical costs. Among the AI technologies, deep learning techniques have gained more popularity, especially in the medical field. Notably, convolutional neural network (CNN), a deep learning based model, is widely used in image processing applications. CNNs extract the high-level image features and convert the data into a high-dimensional and non-linear space, which can help solve various challenging problems in biomedical applications by achieving human-level accuracies [42] or even beyond in some cases [43].

This review aims to demonstrate the use of electrochemical biosensors and deep learning to detect SARS-CoV-2.Here,the survey article comprehensively reviews and compares electrochemical biosensing and deep learning methods as potential diagnostic tools for SARS-CoV-2. The strengths and limitations of these two techniques are discussed along with ways to minimize the limitations and increase the use of electrochemical sensors to combat with SARS-CoV-2. Finally, the future research directions in both fields as potential tools to reduce the dependency of RT-PCR tests and help minimize the severity of the pandemic are discussed.

II. BASIC PRINCIPLES

A. STATE-OF-THE-ART RT-PCR FOR SARS-COV-2 DIAGNOSIS

Influenza (flu) and Coronaviruses are typically identified by examining their genomes, particularly their ribonucleic acid (RNA) sequences [44]. The PCR process multiplies DNA sequences in a quick period, considerably improves the capability of infectious diseases diagnosis. Variants of PCR techniques, such as end-point PCR, quantitative PCR (qPCR), digital PCR have been developed and employed in diagnostics since its development [45]. A real-time reverse transcription step precedes the PCR (RT-PCR) for coronaviruses, as it does for other RNA viruses, and transcribes the RNA into cDNA. Due to its sensitivity and specificity, the PCR test has become the method of choice to detect SARS-CoV-2. It is theoretically capable of identifying a single copy of virus, resulting in a shorter diagnostic window than immunoassays.

Reliable laboratory diagnosis is vital to slow down of the respiratory diseases. When the COVID-19 pandemic broke out, RT-PCR diagnostics were the first to be developed and widely used. RT-PCR is commonly used to discover causal viruses from respiratory secretions in cases of acute respiratory illness [46]. The US Centers for Disease Control and Prevention, WHO, Chinese Center for Disease Control and Prevention, and commercial enterprises have each developed RT–PCR kits [47]. The test is minimally invasive and usually

performed using nasal swabs, throat swabs, and tests of saliva or other bodily fluids [48].

It has been a global and concerted effort to establish the RT-PCR tests for the diagnosis of SARS-CoV-2 in a short period. However, significant drawbacks were reported for its global usage, including high operating costs due to the high cost of RT-PCR instruments and extended processing times. Some people, particularly young toddlers, find deep nasal swabs painful as well. Furthermore, false-negative, and false-positive results from RT-PCR assays have been reported [49]. There have also been reports of positive RT-PCR cases in patients recovered from COVID-19 [50].

B. STATE-OF-ART ELECTROCHEMICAL BIOSENSING FOR COVID-19 DIAGNOSIS

Electrochemical biosensors typically consist of three-electrode systems: working (WE), reference (RE), and counter (CE) electrodes. The CE completes the circuit and allows the charge to flow, while the RE provides a steady potential to regulate the WE's potential. The WE is a hybrid of a biomolecular recognition device and a physiochemical transducer that serves as a transduction element [51]. It can be modified with nano-engineered materials (e.g., graphene, 2D nanomaterials, MXenes, metal oxides, or polymers) and biomolecules (e.g., enzymes, antibodies, proteins, or aptamers) for the detection of specific analytes with high sensitivity [52], [53], [54], [55].

Based on existing nano-engineered materials identifiable by their unique morphological, mechanical, and physicochemical properties through versatile chemical functionalization, nanomaterial-derived technology offers a promising approach to cope with the pandemic issue. Therefore, the modified WE can offer enhanced stability, selectivity, and sensitivity towards SARS-CoV-2. In a typical electrochemical SARS-CoV-2 biosensor, SARS-CoV-2 interacts with WE in an electrolyte solution, causing a difference in potential, current, electrochemical impedance, or capacitance. An electrochemical workstation senses the difference in the signal, which is then used to detect SARS-CoV-2 presence. Potentiometry, amperometry, electrochemical impedance, and capacitance are the four types of electrochemical sensors based on these signals. Electrochemical sensors attract great interest because they can be easily miniaturized. The electrochemical workstation can be built as portable device for on-site monitoring, where a computer or a handheld device (smartphones, laptops, etc.) equipped with the required software platforms can be used to analyze the tests data [56].

A robust, responsive, accurate, and on-site detection tool is essential in stopping the worldwide COVID-19 pandemic. Electrochemical methods are known for their low cost and fast analysis. While electrochemical biosensors may offer high selectivity, sensitivity, and reliability towards target analyte in complex media, it is also important to think of affordability, time of analysis, and sampling methods to promote widespread testing even in resource-limited settings.

To address the need for better sampling methods, noninvasive ways of screening may be an ideal approach for the identification of biomarkers in body fluids, including urine, saliva, tears, sweat, and breath for the screening of SARS-CoV-2. For example, Alefeef *et al.* recently reported a paper-based electrochemical sensor to detect SARS-CoV-2 [57]. In their design (Figure 3A), gold nanoparticles (AuNPs) were capped with highly specific antisense oligonucleotides (ssDNA) to target viral nucleocapsid phosphoprotein (N-gene). The issue with this prototype is that it requires RNA isolation from SARS-CoV-2, which makes it unsuitable for on-site detection. Yakoh *et al.* introduced a paper-based electrochemical biosensor using spike protein receptor-binding domain (SP RBD) of SARS-CoV-2 as a recognition group (Figure 3B) [58]. After immobilization of the SP RBD on the electrode surface, the square-wave voltammetry (SWV) technique was utilized for the detection of SARS-CoV-2. Unfortunately, the detection limit of this electrochemical sensor prevented the detection of SARS-CoV-2 in the actual nasal swab specimens.

One of the most promising studies on electrochemical detection of SARS-CoV-2 was carried out in [17]. In their study, the silicon dioxide layer was first placed on a silicon wafer, followed by 25-nm-thick thermally deposited titanium layers, and finally, a 350-nm-thick gold layer deposited via electron-beam assisted gold evaporation and patterned with photolithography to fabricate a platform (a chip). A redox probe (ferrocene) modified DNA was then attached to the chip, followed by the antiSARS-CoV-2 spike S1 antibody linked to the amine-terminated DNA. The as-fabricated chip was tested using chronoamperometry and the results were obtained in minutes. This is the first study that used undiluted saliva samples for the detection of SARS-CoV-2.

Besides its short analysis time and easy sampling method, the biosensors have about nine months of shelf-life [59]. In another study, Seo *et al.* reported a field-effect transistor (FET)-based electrochemical biosensor to detect SARS-CoV-2 in clinical samples without requiring sample pretreatment or labeling [60]. As shown in Figure 3C, the FET was coated with a graphene layer and modified with a specific antibody against SARS-CoV-2 spike protein. The biosensor was very sensitive to SARS-CoV-2 antigen protein and could distinguish the virus from the MERS-CoV antigen protein.

Raziq et al [14] used a gold-based thin-film electrode as a disposable sensor chip modified by SARS-CoV-2 nucleoprotein (ncovNP) molecularly imprinted polymer (MIP) to form an artificial receptor for the detection of ncovNP (Figure 3D). The sensor was designed to detect ncovNP which shows a linear response of up to 111 fM with detection and quantification limits of 15 fM. A portable potentiostat was utilized to test the as-fabricated sensor with nasopharyngeal swab samples of COVID-19 positive patients. Although the swab samples had to be vortexed for 30 min in a lysis buffer to release the viral protein before each test, the MIP technology is still very attractive due to its rapid, low-cost and sensitive detection capabilities, and

TABLE 1. Summary table of the reviewed biosensors for COVID-19 detection.

Sensory Array	Electrochemical Method	Biomarker	Recognition Element	LOD	Linear range	Time	Reference
Paper-based electrochemical sensor chip	Voltammetry	N-gene	Viral ssDNA	231 copiesμL	585.4-5.854×107 copiesμL	>5 min	[57]
Lateral flow-based assays	Square-wave voltammetry	IgG and IgM	SP RBD	0.11 ng/mL	1–1000 ng/mL	30 min	[58]
Electrochemical chip	Chronoamperometry	Whole virus	antiSARS-CoV-2 spike S1 antibody	4×103 viral particles per mL	4×103-4×107 viral particles per mL	5 min	[17]
FET	FET-current response	Whole virus	antiSARS-CoV-2 spike S1 antibody	1.6×101 pfu/mL	1.6×101-1.6×104 pfu/mL	N/R	[60]
MIP-based disposable sensor chip	Differential pulse voltammetry	ncovNP	Synthetic receptor	15 fM	0–111 fM	30 min	[14]
Laser-scribed graphene based disposable sensor	Differential pulse voltammetry	SARS-CoV-2 spike protein	anti-SARS-CoV-2 S1 antibody	2.9 ng/mL	5.0–500 ng/mL	1–5 min	[27]
Aerosol-Jet Nanoprinted 3D Electrodes	Electrochemical impedance spectroscopy	S1 and RBD	S1 and RBD antibodies	2.8×1015 (S1) 16.9×1015 (RBD)	1 fM - 1 nM (S1), 1 fM - 1 nM (RBD)	10s	[62]

highly selective receptors [61]. It may even be used to detect SARS-CoV-2 mutations. With the above-mentioned advantages, electrochemical biosensors are potential candidates for rapid detection of COVID-19.

Table 1 summaries the key parameters of the electrochemical biosensors for the detection of SARS-CoV-2 discussed in this review.

C. STATE-OF-THE-ART IN DEEP LEARNING FOR SARS-COV-2 DIAGNOSIS

Chest X-ray and chest CT imaging modalities play a key role in the diagnosis of COVID-19 and controlling the pandemic. Radiologists use images from CT and X-ray scans to diagnose COVID-19 as shown in Figure 4 [63]. X-ray is an inexpensive imaging technique and it poses a low-risk radiation hazard to human health [64]. However, it may be difficult to diagnose the stage of infection just by looking at the X-ray scans. This is due to the similarity of white spots, which may consist of water and pus that are associated with other lung diseases, such as tuberculosis. On the other hand, CT scans offer more precise detection but are more expensive than X-ray imaging [65], [66]. However, the detection accuracy from CT scans is still not satisfactory and defective in the diagnosis of COVID-19. Other techniques, in addition to the CT scan, can help improve the accuracy of the COVID-19 diagnosis [67]. Between these two imaging modalities, X-ray imaging is usually preferred since X-ray imaging poses less radiation, is cheaper and more accessible than CT imaging in hospitals.

In this section, only the state-of-the-art DLMs using CT and X-ray imaging modality for COVID-19 diagnosis are reviewed. The use of deep learning to assist the diagnosis stage of COVID-19 is divided into three main tasks, namely, classification, detection, and segmentation.

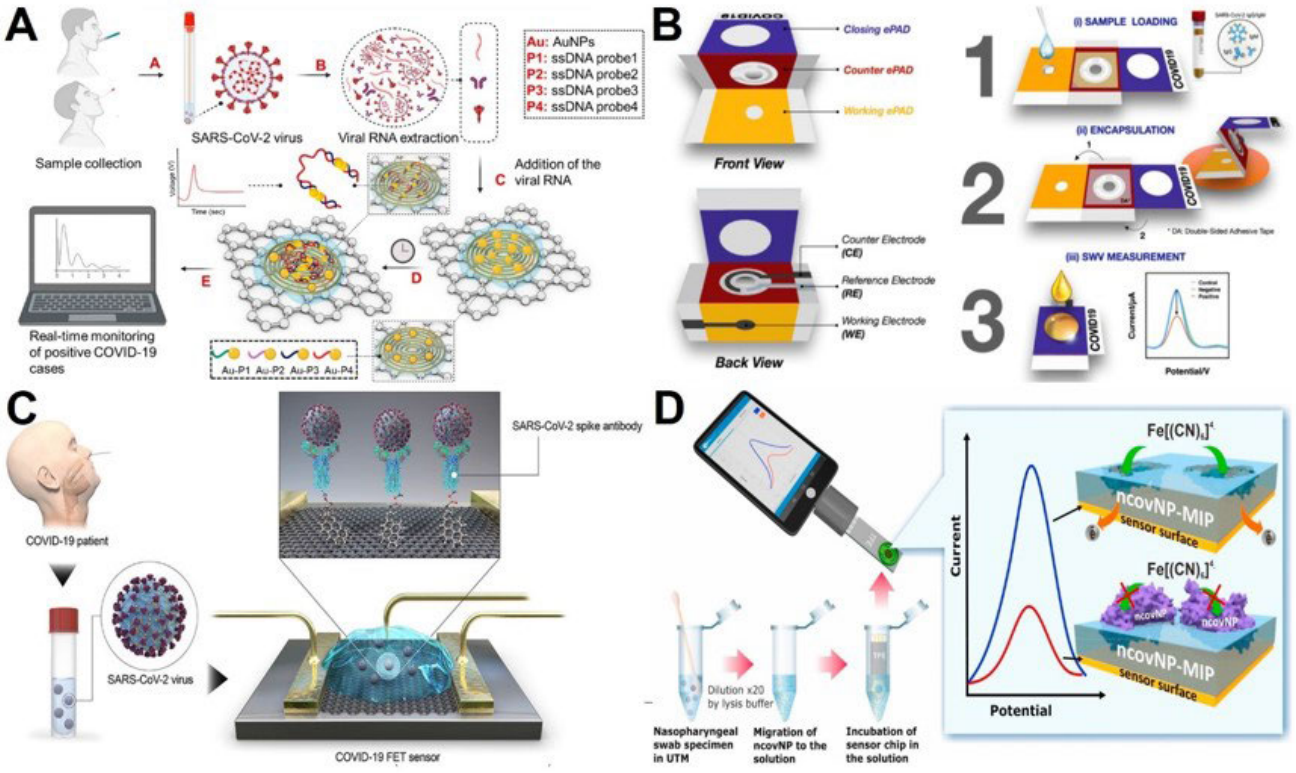

FIGURE 3. Various electrochemical SARS-CoV-2 biosensor platforms: A) paper-based electrochemical sensor chip detecting viral RNA extraction. Reprinted (adapted) fromal [57], part of the ACS COVID-19 subset. Copyright © 2022, American Chemical Society. B) paper-based electrochemical biosensor detecting whole virus, Reprinted (adapted) with permission from Elsevier, Copyright (2022), 5234950785940 [58], C) a field-effect transistor-based electrochemical biosensor device to detect SARS-CoV-2, Reprinted (adapted) from [60], part of the ACS COVID-19 subset. Copyright © 2022, American Chemical Society, D) a MIP-based electrochemical sensor for detection of SARS-CoV-2 nucleoprotein, Reprinted (adapted) with permission from Elsevier, Copyright (2022), 5234970620799 [14].

Classification task involves predicting the absence or presence of diseases, for example, classification of a brain tumor [68] or skin lesion [69]. The object detection is an automated method for locating the focal lesions in the medical image, for example, cerebral micro bleeding in magnetic resonance (MR) images [70]. Lastly, segmentation comprises sets of targeted pixels or voxels that include a structure of interest, for example, retinal vessel segmentation formulated by Fu *et al.* [71] through fully CNNs and fully connected conditional random fields (CRFs). Supervised and unsupervised learnings are the most common machine-learning concepts used for classification, detection, and segmentation tasks. In supervised learning, learning is conducted by mapping from inputs to outputs using pre-labeled data, while unsupervised learning does not involve labeled data such as clustering [72].

Apostolopoulos and Mpesiana achieved 96.8 % accuracy with the dataset of X-ray images in the classification of Covid-19 using VGG19 architecture [73]. Their image classes include only COVID-19 vs. pneumonia vs. normal. Transfer learning, a method where pre-trained models are used to transfer already learned features, was also adopted in their model, which helped in achieving remarkable results in detecting COVID-19. However, they did not consider data leakage that may come from multiple images belonging to the same patient, which would directly affect the accuracy of their suggested model. Ozturk *et al.* developed the DarkCovidNet model and achieved an accuracy of 98.1% for binary classification (COVID-19 vs. no-finding), and an accuracy of 87.0% for multi-class classification (COVID-19 vs. pneumonia vs. no-findings) [74]. In their model, a heat map of X-ray images was produced and interpreted by radiologists, and it was concluded that their model could assist radiologists and reduce the clinical workload in hospitals. They had used a limited number of datasets at the time of publication when developing the model, hence the model would require a larger dataset for future use. The researchers effort to limit the severity of the pandemic are affected by the lack of datasets when developing deep learning-based models [75]. The generative adversarial network (GAN) has helped to generate synthetic

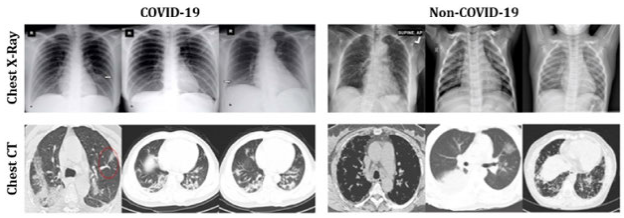

FIGURE 4. An illustration of X-ray and CT scans of patients. Adapted from reference [63] (CC BY).

X-ray images and minimized the effect of limited datasets that challenged the accuracy of the deep-learning models in the diagnosis of COVID-19 [76]. Sethy and Behera developed a model using a deep feature and support vector machine (SVM) with X-ray images, showing an average of 95.3% accuracy out of 20 independent executions [77]. In their model, deep features were extracted from the Resnet50 layer and then fed into SVM for the classification of COVID-19 vs pneumonia vs healthy people. SVM was shown to be an effective technique for the diagnosis of COVID-19 [78]. Resnet50 is also an effective backbone that is being used for the development of neural networks in various biomedical applications [79]. However, the best performing pre-trained neural network models require a comprehensive evaluation as reported in [80] and [81] to diagnose COVID-19 using X-ray images. Yoo *et al.* utilized a decision tree classifier for the detection of COVID-19 [32]. Since there is a shortage of datasets at the time of the outbreak, data augmentation techniques, such as rotation angle, horizontal flip were successfully implemented in their model to enlarge the dataset and simulate various attributes of visual perception. Three classifiers were used, which achieved an accuracy of 98% and 80 % for the first and second decision trees, whereas 95 % accuracy was obtained in the third tree using X-ray images. In their study, the first tree classifies the X-ray images as normal and abnormal, while the second and third trees classify the abnormal cases which show the signs of tuberculosis. Panwar *et al.* proposed nCovNet, a neural network-based technique, and achieved an average accuracy of 88% for the detection of COVID-19 positive patients using X-ray images of lungs [31].

CT imaging has also been used for the diagnosis of COVID-19. Wang *et al.* developed a weakly supervised deep-learning-based framework using 3D CT volumes which included 499 CT volumes for training and 133 CT volumes for testing, with an accuracy of 90% [82]. Singh *et al.* proposed a CNN-based model where its initial parameters were tuned using multi-objective differential evolution to classify positive and negative COVID-19 cases using CT imaging modality with an average accuracy of 90% [83]. Ahuja *et al.* proposed a model that consisted of three different phases which were data augmentation using wavelets, COVID-19 detection, and abnormality localization. In their research, Resnet18 had shown superior performance in the detection of the COVID-19 with an accuracy of 99.4% by the means of transfer learning [84].

Ardakani *et al.* also analyzed 10 different pre-trained models, and reported that Resnet-101 and Xception illustrated superior performance in distinguishing the COVID-19 from non-COVID-19 cases [33] with an accuracy of 99% using CT images, while the accuracy of radiologist diagnoses was 86%. In addition, the developed CovidCTNet also demonstrated 90% accuracy in comparison to the radiologist's accuracy rate which was 70% on CT images [85]. Various models have been commonly constructed on pre-trained models, such as Resnet-50 as in[86] and [87] to diagnose COVID-19 using CT images. Another iteration of Resnet-50 was developed along with a feature pyramid network design developed by Rahimzadeh *et al.* using very large CT images (48260 images from 282 healthy people, and 15589 images from 95 patients with COVID-19) [88]. In their model, around 99% accuracy was achieved over 7996 test images which was the largest dataset used for COVID-19 diagnosis. As the use of transfer learning reduces the chance of the model to overfit, He developed a self-trans-based approach in which the contrastive self-supervised learning with transfer learning was integrated synergistically to learn unbiased features which achieved 86% accuracy with DenseNet-169 using CT images [89].

The most popular Deep learning architectures for COVID-19 detection are shown in Table 2. COVID-19, Healthy, and Pneumonia are referred to as Multiclass, whilst COVID-19 and Healthy are referred to as Binary. VGG19, Resnet, Yolo, and Inceptions are deep learning models that have been pre-trained and have been used as backbone to build deep learning approaches.

III. COMPARISON OF ELECTROCHEMICAL BIOSENSING AND DEEP LEARNING FOR PUBLIC HEALTH SURVEILLANCE OF SARS-COV-2

The early and fast diagnosis of COVID-19 is crucial to combat the rapid spread of COVID-19 globally. In this section, the state-of-the-art in deep learning and electrochemical biosensors will be discussed in terms of cost, sampling, timing, accuracy, instrument complexity, global accessibility, feasibility, and adaptability to mutations.

A. COST

A PCR test kit consists of a combination of chemicals, nucleic acid extraction kits, and other elements. A PCR test usually costs about $60 for patients [90]. This cost can vary greatly from country to country depending on their economy, resources, and capabilities. Furthermore, due to the COVID-19 pandemic, many countries face a supply shortage of these kits and are unable to acquire them from the manufacturing countries [91].

As for using deep learning models, the cost of developing these models for COVID-19 diagnosis comes from the purchase of a GPU-powered PC and the data collection process. The initial development cost varies based on the training size, model size, and training volume. Once the model is developed and ready-to-deploy, there are no extra costs to the hospitals or clinics to maintain the system. The variable cost to the patient is the CT and X-ray scans. The costs of CT and X-ray scans vary based on the geographical location of the hospital. For example, in the USA alone, a chest CT scan can range from $1,072 upto 3,509$ while an X-ray scan can range from 82 *to* 417, depending on the hospital location [92]. It has to be noted that a CT machine is not often available in small or rural hospitals, as compared to a medical X-ray machine.

Despite numerous advancements in biosensor technology, glucose biosensor is considered the first biosensor and continues to dominate and accounts for roughly 85% of a $5

TABLE 2. Prominent deep learning architectures developed for COVID-19 detection.; TL: Transfer learning; CNN: Convolutional neural network.

Deep Learning Technique	Dataset	Accuracy	Classification	Reference
TL using VGG	X-ray images	96.8%	Multiclass	[73]
DarkCOVIDnet using Yolo	X-ray images	98.1%	Binary	[74]
TL using Resnet	X-ray images	95.3%	Multiclass	[77]
CNN	CT-Scan	90%	Binary	[83]
Inception based Resnet	CT-Scan	99%	Bonary	[33]

billion market [93]. Due to an existing market in the area of electrochemical biosensors, sensor platforms for the diagnosis of SARS-CoV-2 can be manufactured in great volume at a low cost. The initial upfront costs for the electrochemical SARS-CoV-2 biosensors are from (i) potentiostat and (ii) a single-use disposable electrode. The price for a large commercial potentiostat varies from $1,000 to $13,000, however, they are heavy, expensive, and time-consuming for trained person, and are not applicable to the point-of-care analysis [94]. On the other hand, a miniaturized potentiostat allows for point-of-care analysis, which facilities faster test results. A miniaturized potentiostat can be obtained at a much lower cost (between $30-$200) for initial investment by the government or companies [94], [95].

When a large commercial potentiostat is used to run the test samples, the single-use disposable sensor array costs around 3−10. However, when a miniaturized potentiostat is used, the cost of a single-use disposable electrode is much lower at around $0.50 due to the smaller size of the electrode. It must be noted that there are additional costs tied to the electrochemical biosensors for the diagnosis of SARS-CoV-2. These costs include but are not limited to the following: chemicals, antibodies, enzymes, proteins, etc. The additional costs are dependent on the designed sensor array for specific and sensitive detection in a complex medium. In some arrays, the sample must be pre-treated to extract nucleic acid before testing which would increase the cost of running the tests. A biosensor-based COVID-19 detection test may range from about 3-10 US$ to a patient, which can be further used by using electrodes and the production of sensors at a massive scale. In sum, in terms of cost, electrochemical sensors have more advantages than PCR and deep learning–based imaging systems.

B. SAMPLING

During a CT scan, several X-ray beams and electronic X-ray detectors move around the patient. These devices monitor the amount of radiation absorbed by the individual's body. During the scan, the exam table will shift, causing the X-ray beam to generate a series of images from various angles. This vast amount of data is processed by a special computer program to produce two-dimensional cross-sectional images of the body. This process is repeated several times to produce several slices until a detailed image of the region of interest is created. Chest CT scan is commonly used for the diagnosis of COVID-19. A CT scan provides more information than a standard X-ray.

During an X-ray scan, small amounts of radiation are used to produce images of the body's organs, tissues, and bones. It can detect abnormalities in the airways, blood vessels, and lungs when focused on the chest. Getting a chest X-ray does not require much planning on the part of the patient. The X-ray is performed in a special room equipped with a movable X-ray camera mounted on a long metal arm, where the patient is positioned next to a ''plate.'' This plate would contain an X-ray film or a special sensor that captures the images and saves them to a computer to be analyzed by the radiologist.

On the other hand, nasopharyngeal, and oropharyngeal swabs are routinely taken and studied to detect the SARS-CoV-2 virus. Urine, feces, sputum, plasma serum, and whole blood are also studied, but not as widely due to the difficulty of sampling for both patients and health care workers [96]. In most studies, the sampling principle relies on the extraction of viral RNA from the samples. This is considered a more reliable approach compared to CT and X-ray imaging because viral RNA can be detected 2–3 days before symptoms appear and can last for up to 25–50 days depending on the severity of the disease [97].

Alternatively, the surface antigens or whole virus particles from patients' swab samples can be detected without any prior treatment using an electrochemical biosensor, which is a possible time and cost-saving approach [60], [98]. In addition to nasopharyngeal, and oropharyngeal swab samples for the electrochemical detection of SARS-CoV-2, Miripour *et al.*, have used sputum samples for real-time tracing of SARS-CoV-2 [99]. Reactive oxygen species (ROS) by mitochondria are overproduced as a result of SARS-CoV-2-induced lung cell dysfunction and by tracing ROS in sputum samples, SARS-CoV-2 can be detected with more than 97% accuracy. PCR tests samples are usually taken from Nasopharyngeal, and oropharyngeal swabs, which may cause discomfort to the patient, as well as suffer from false positives and false negatives. In DLMs, the patients are exposed to radiations during CT-scans or X-rays. However, electrochemical sensors can be designed for nasopharyngeal, and oropharyngeal swabs urine, feces, and whole blood. These sensors are much more flexible and harmless, compared to PCR and DLMs.

C. TIME REQUIRED FOR DIAGNOSIS

The time taken for the deep-learning-based diagnosis of COVID-19 depends on the imaging modality used. A CT scan takes less than 30 s, and the whole procedure, including exam planning, takes about 30 min. For X-ray, the chest is photographed from two perspectives: from the back and the side. The patient is positioned with hands-on-hips and

chest pressed against the image plate by the technologist. The patient's side is against the image plate in the second view, with arms elevated. The entire chest x-ray examination takes about 15 min.

Early isolation of infection is key for the prevention of transmission. Unlike the RT-PCR tests and deep-learning approaches, many of the electrochemical biosensors designed for the detection of SARS-CoV-2 are rapid on-site tests. This means patients or their samples are not required to be in a laboratory for testing which saves time, and the results can be obtained as quickly as 10s [62]. For biosensors designed to detect viral RNA, extra time is required to extract RNA before testing and in this case, results can be obtained at least 30 min due to the sample collection [100], [101]. As a result, biosensors are more helpful than PCR and deep learning-based imaging systems in terms of diagnosis time.

D. ACCURACY

The accuracy of the DLMs for COVID-19 diagnosis was discussed in detail in section 2.2. Most DLMs demonstrate great accuracy for the diagnosis of COVID-19. For instance, Apostolopoulos and Mpesiana [73], Ozturk *et al.* [74], and Sethy and Behera [77] achieved an accuracy of 96.8%, 87.0%, and 95.3%, respectively for multi-class classification (COVID vs. Normal vs. Pneumonia) with X-ray images. During the outbreak, CT imaging is also used to diagnose COVID-19. Wang *et al.* achieved an accuracy of 90% [82] for COVID-19 classification and lesion localization, Singh *et al.* achieved an average accuracy of 90% to classify COVID-19 positive and negative cases [83], Ahuja *et al.* achieved an accuracy of 99.4% in the detection of the COVID-19 [84] using CT imaging modality. Ardakani *et al.* looked at ten different pre-trained models and found that Resnet-101 and Xception performed better than the others in identifying the COVID-19 and non-COVID-19 cases with a 99% accuracy using CT images [33]. In their study, the accuracy of detection by radiologists was 86%, which is 13% lower than the established neural network model. There are other studies that show even higher (22%) accuracy with deep learning models compared to radiologists evaluation of CT scans [85].

Most electrochemical biosensors show great accuracy, selectivity, and reproducibility towards target analytes due to the specific biological recognition reaction at the WE surface. The sensors designed for the detection of SARS-CoV-2 rely on the interaction between receptor-antibody (e.g., ACE2-SP1) or oligonucleotide against the target DNA or RNA [26]. Although these interactions are very specific, there may be certain issues that affect the accuracy and the sensitivity of the fabricated SARS-CoV-2 such as genetic mutations, and the complex nature of the samples.

For example, Zhao *et al.* designed an electrochemical biosensor based on a smartphone for targeting RNA of SARS-CoV-2 [96]. When they tested their biosensor with a total of 88 RNA extracts from sputum, throat swabs, urine samples, plasma samples, feces samples, oral swabs, serum samples, whole blood samples, and saliva samples which were obtained from 25 confirmed SARS-CoV-2 patients and eight recovered patients, their accuracy changed dramatically based on the sample type. For example, sputum, feces, whole blood, and saliva samples resulted in 100% true positive, while serum samples had only 40% true positive. There are also other works published with more than 92% accuracy using untreated saliva samples, which is a great sample property to use on a large scale [17], [60], [101].

E. INSTRUMENT COMPLEXITY

DLMs are run through a host computer that receives images from either CT or X-ray machines. Hence, the models developed by deep learning techniques do not add any complexity to the existing systems. However, the imaging modality used within the system is a significant parameter that has a direct impact on the complexity of the whole diagnosis procedure. An X-ray machine mainly consists of an X-ray generator and an image detector. The main parts of the X-ray generator are tube, high voltage generator, control console, and the cooling system. A CT scanner mainly consists of four main components. gantry (frame) houses the X-ray source, detectors, patient port (a large opening in the middle), subject table, and a computer system that gathers all data from the detectors. Finally images are produced based on the captured data [102]. A CT scanner must move around the patient being scanned; hence, an X-ray equipment is much smaller and less complicated than a CT machine.

Instruments used for electrochemical biosensors are less complex with very low cost compared to CT and X-ray instruments which costs between $15,000-90,000$. For accurate electrochemical biosensing of SARS-CoV-2, the potentiostat is required to ensure signal processing and cell conditioning. Potentiostat devices can be either bench-top or portable. Portable devices (miniaturized potentiostat) are usually equipped with a portable mobile device for read-out which is a great feature to monitor public health surveillance of SARS-CoV-2 on-site [95], [96]. On the other hand, bench-top models are not that user-friendly and require skilled personnel to operate.

F. GLOBAL ACCESSIBILITY AND FEASIBILITY

To date, there is no U.S. Food and Drug Administration (FDA)-approved system using deep-learning techniques with CT or X-ray imaging modality to diagnose COVID-19. Apart from FDA, the employment of DLM for COVID-19 diagnosis also depends on the acceptance of radiologists and clinicians. However, there are already FDA-approved software using DLM, such as the OsteoDetect to analyze X-ray images for wrist fracture [103], which demonstrates the potential reliability and feasibility of DLM for other types of medical devices, such as COVID-19 diagnosis.

Global accessibility and feasibility of the DLMs will depend on access to good imaging facilities in the hospitals. Therefore, access to CT and X-ray machines is one of the important concerns when it comes to the feasibility of using the deep learning models in hospitals. As COVID-19 is

an infectious disease, where infection safety concerns are associated with patient transport to CT suites, inefficiencies implemented in CT room decontamination, and a lack of CT availability in some areas of the world, portable chest X-ray would likely be the most widely used modality for detecting and monitoring lung anomalies [104]. Routine CT scan for COVID-19 diagnosis is also not recommended by radiologists unless in-depth investigations on the lung's conditions are required [105]. Chest X-ray equipment is the most widely used medical equipment in intensive care units (ICU) based on a global study of 52 medical institutions [106]. Since X-ray imaging is by far more accessible than CT scan, the former has the advantage of being globally utilized, and thus more likely to be used to develop deep-learning models.

Electrochemical biosensors have been commercially used as diagnostic instruments for the point-of-care analysis of glucose, uric acid, and cholesterol levels [107]. Therefore, there is an established platform worldwide for electrochemical biosensors which can be adapted to the electrochemical SARS-CoV-2 testing by modifying the sensor array and calibrating portable potentiostats. As a result, electrochemical SARS-CoV-2 biosensors could be commercialized and globally accessible to control the pandemic. There is already a commercially available electrochemical SARS-CoV-2 biosensor based on electrochemiluminescence measurement which was granted by the U.S. Food and Drug Administration-Emergency Use Authorization (FDA-EUA) [108]. The North American company (Roche Diagnostics, Indianapolis, IN) offers a rapid test (18 min.) compared to RT-PCR or ELISA tests with a 100 % true positive rate and 99.8% true negative rate using human serum and plasma samples.

Despite the demonstrated feasibility of electrochemical SARS-CoV-2 biosensors, the shelf-life and short storage time of the chemicals may limit its worldwide implementation. The use of toxic chemicals in the production, lengthy fabrication procedures, toxic material wastes, costly cleanroom processing requirements, and the inability to incorporate enzyme/electrode co-production are other possible limitations of the system. Furthermore, to use a benchtop potentiostat, a skilled worker is needed to operate and interpret the data. As a result, further research is needed to develop new processes with higher levels of customizability and sensitivities, at a lower cost, and portability for a wider usage of electrochemical SARS-CoV-2 biosensors. Thus, depending on a country's resources and economic size, deep-learning-based and electrochemical biosensor-based approaches may be adopted to reduce the cost of testing and false negative and false-positive results, if the above-mentioned limitations can be overcome.

G. ADAPTABILITY TO MUTATIONS

The SARS-CoV-2 genome structure was sequenced for the first time in Wuhan, China in January 2020. Understanding SARS-CoV-2 genome sequencing is important to interpret the virus's nature and mutation rate, as well as successful prevention strategies such as vaccines and drugs. Several investigations have noted the new coronavirus's genetic diversity and rapid evolution. Some mutations may have little or no impact, whereas others may affect the virus's properties, such as increased transmissibility. The significant mutations of Sars-CoV-2 presented in Figure 5 indicate the origin, date of the first detection, and the main concerns of the variants of SARS-CoV-2.

The procedure for collection, preservation, storage and processing of the samples affects the accuracy of RT-PCR. The lack of proofreading ability in the viral RNA polymerases results in a high rate of mutation. As a consequence, if the virus mutates in the targeting genomic region, which happens often, the precision of these diagnostic methods is adversely affected [62]. To the best of our knowledge, there are only few reports on electrochemical detection of SARS-CoV-2 mutations and the study by Beduk *et al.*, stands out from other work [110]. First, they earlier reported laser-scribed graphene (LSG) sensors for SARS-CoV-2 [29], then improved their study by adapting their systems for alpha (B.1.1.7), beta (B.1.351), delta (B.1.617.2) variants [110]. A machine learning approach was also integrated for quick interpretation of data with an accuracy of 99.37%. Moreover, it is possible to design a multichannel biosensor for simultaneous detection of SARS-CoV-2 and all mutations using the associated biorecognition element [111].

On the other hand, the DLMs developed must be adaptable to detect mutations since the replication of SARS-CoV-2 genomic information will cause the virus to mutate [112]. The virus's adaptability to mutations, B.1.1.7, B.1.351, P.1, B.1.617.2, and B.1.1.519, has recently been proven by researchers [113]. However, more attention is required in the area of diagnosis considering the high mutation rate of the SARS-CoV-2. Apart from developing DLMs to identify the different variants, estimating the mutation rate using DLMs has also drawn great attention from researchers worldwide [114]. This is because by knowing the mutation rate, scientists will be able to illustrate the risk of emergent SARS-CoV-2 infection [115]. DLMs can be developed to detect the mutations and are adaptable to new variants of SARS-CoV-2 as long as the datasets are accessible [116]. Since the development of the DLMs relies on the dataset used during the training procedure for the diagnosis of SARS-CoV-2, the developed models can easily be adapted to new variants of SARS-CoV-2. This procedure requires an update on the datasets used during the training process of the deep learning models.

A comparison of PCR, electrochemical biosensors, and deep-learning-based COVID-19 diagnostic tests are provided in Table 3 in terms of cost, sampling, the time required for diagnosis, accuracy, instrument complexity, global accessibility and feasibility, and adaptability to mutations. It is noted that the cost is given in USD throughout this study.

TABLE 3. A summary of SARS-CoV-2 diagnostic techniques.

Parameters	PCR	Electrochemical Biosensors	Deep Learning
Cost	60 US$	• $3-$10 for the single-use disposable electrodes, plus the cost for the functionalization of the electrode • Cost can be reduced to $0.5 with the size of the electrode [94]	• Requires only initial cost during deep-learning-based model development • CT scan ranging from $1072 up to $3509 and X-RAY scan ranging from $82 to $417 depending on the hospital location in the USA [92]
Sampling	Nasopharyngeal, and oropharyngeal swabs	• Depends on the designed sensor array: Nasopharyngeal, and oropharyngeal swabs urine, feces, sputum plasma serum, and whole blood [96]	• CT or X-ray scan
Timing	2-3 Hours	• For most samples, a laboratory visit is not required • Results from portable biosensors can be obtained as quickly as 10-s [62] • Biosensors designed for viral RNA detection can take at least 30 min [101]	• The CT scan, including exam planning, takes about 30 min • The entire chest X-ray examination takes about 15 min
Accuracy	From 71 to 98% [109]	• Depends on the sampling method and it ranges from 92 to 100%	• Ranging from 87% to 97% using X-ray images depending on the diagnosis technique [73], [74], [77] • Ranging from 90% to 99% Depending on the diagnosis technique using CT scan [82]–[84]
Instrument Complexity	• Requires a skilled professional • Costly	• Bench-rop or portable devices with user-friendly interfaces [95], [96] • Can be obtained at a very low cost	• The complexity comes only from the imaging modality used • X-ray is less complex than CT-scan
Global Accessibility and Feasibility	• Commercially available	• An electrochemical SARS-CoV-2 biosensor is already commercially available [108] • Due to the cost of each test, it has low accessibility in low-income countries	• X-ray is more accessible than CT imaging Portable X-ray has the potential to be employed widely [104]
Adaptability to Mutations	• Adaptable to the new variants of SARS-CoV-2	Adaptable to the new variants of SARS-CoV-2	• Adaptable to the new variants of SARS-CoV-2. • Depends on the data availability.

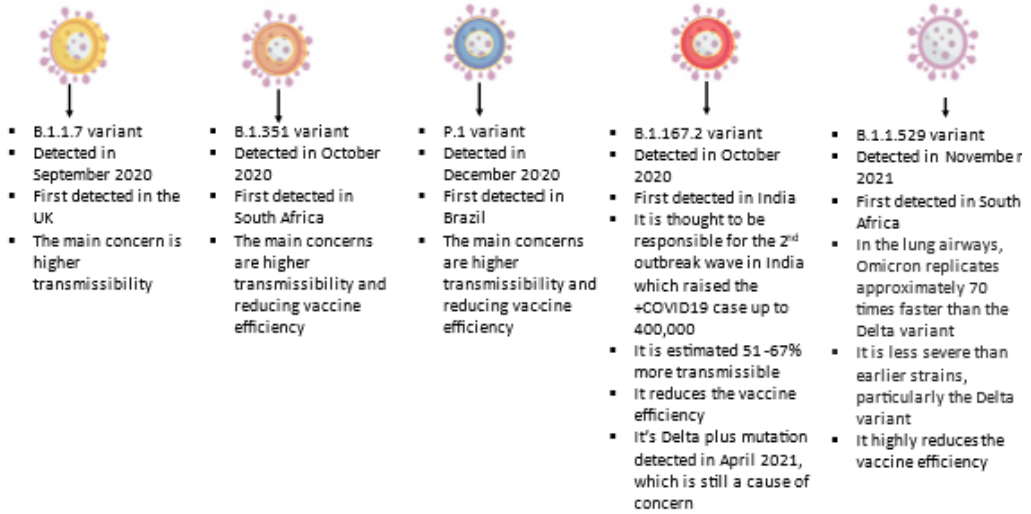

FIGURE 5. Current significant mutations of SARS-CoV-2.

IV. CONCLUDING REMARKS

The current gold standard for monitoring SARS-CoV-2 spread is based on RT-PCR test using nasophyrangeal swab samples, which is expensive, time-consuming, and produces a large number of false-positive or false-negative results. Earlier and faster diagnosis of the SARS-CoV-2 virus can decrease and slow down the spread of the COVID-19 disease. In this review, deep-learning models and electrochemical biosensors were compared to PCR in terms of cost, sampling, the time required for diagnosis, accuracy, instrument complexity, global accessibility and feasibility, and adaptability to mutations. Based on the studies reviewed, deep-learning-based models and biosensors can help minimize the severe effect of the pandemic. However, the deployment of these techniques will be dependent on a country's resources and economic size as mentioned in this study.

To date, electrochemical SARS-CoV-2 biosensors have been tested on various kinds of body fluids. According to a recent study, COVID-19 patients' exhaled breath contains a significant amount of SARS-CoV-2 virus [117]. Therefore, a diagnostic test using exhaled breath as a quick, non-invasive method in monitoring SARS-CoV-2 infections would be a tremendous step forward [118], [119], [120]. Since breath analysis has the added advantage of real-time and point-of-care analysis [121], there has been strong interest in the research community to develop noninvasive exhaled breath detection techniques using electrochemical enzymatic biosensors for COVID-19 diagnosis [122]. Electrochemical enzyme-based biosensors are among the largest commercially available group of biosensors and are of particular interest in this endeavor following the advancement of nanomaterials used in the biosensors which have resulted in high analytical sensitivity, stability at reduced costs of testing. To date, there have not been any reported electrochemical biosensors for the detection of COVID-19 virus using the breath as a sample. The demand for biosensors in the field of diagnostics is enormous, and they will be particularly successful in early viral detection.

A recent study reported that mutations in the S protein, which binds to the ACE2 receptor, may cause mutations in the SARS-CoV-2 virus during transmission among humans [123]. Tracking the virus variants is important in the global effort to prevent its spread. A multi-channel electrochemical detection system could be designed to detect mutations using associated biorecognition elements [110], [124]. This will help simultaneous detection of SARS-CoV-2 variants which may not be possible with current testing methods. In a recent study, the capacity to detect new variants such as Omicron is demonstrated using a novel plastic optical fiber (POF) U-shaped probe sensing approach for reliable detection of SARS-CoV-2 within 15 minutes [125].

Although a DLM can be adapted to the variants of SARS-CoV-2, the developed state-of-the-art in deep learning for diagnosis of SARS-CoV-2 should be evaluated on the variants of SARS-CoV-2. Since the correlations within the datasets have already been learned by the model, the developed models could be still showing promising diagnosis results with a cost of a slightly reduced accuracy. For this, researchers around the world should collaborate and create a benchmark dataset for SARS-CoV-2 variants to evaluate their models. This would speed up the development of DLMs. A powerful alternative for ending the pandemic can be the development of a DLM to forecast new strains so that new vaccinations may be developed to tackle the mutated virus.

With more publicly available databases, better-performing DLMs can be developed to accurately diagnose COVID-19. An accurate ground truth label by the experts is another area that needs attention when developing deep-learning models.

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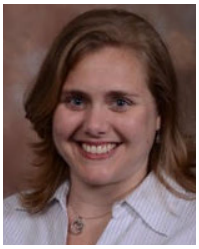

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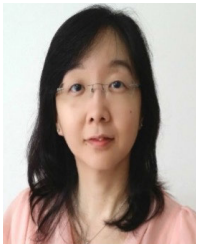

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