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A REVIEW ON POTENTIAL OF ARTIFICIAL INTELLIGENCE IN DIAGNOSIS, DRUG DISCOVERY AND VACCINE DEVELOPMENT AGAINST COVID-19

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ABSTRACT

The past two decades were marked with the outbreaks of many viral diseases such as Chikungunya, Ebola, Zika, Nipah, H1N1, SARS, H7N9 Bird flu, and MERS. The world woke up to this decade with a new disease outbreak. An outbreak of a novel Corona virus emerged in Wuhan city in the Hubei province of China in December 2019. The main challenges in mitigating COVID-19 are effective vaccination, treatment, and agile containment strategies. In this review, we focus on the potential of Artificial Intelligence (AI) in COVID-19 diagnosis, outcome prediction, drug discovery and vaccine development. A significant amount of new scientific research and data sharing is underway due to the pandemic which is still rapidly spreading. There is now a growing amount of corona virus related datasets as well as published papers that must be leveraged along with artificial intelligence (AI) to fight this pandemic by driving news approaches to drug discovery, vaccine development, and public awareness. With the help of big data, AI tries to mimic the cognitive capabilities of a human brain, such as problem-solving and learning abilities. Machine Learning (ML), a subset of AI, holds special promise for solving problems based on experiences gained from the curated data. Advances in AI methods have created an unprecedented opportunity for building agile surveillance systems using the deluge of real-time data generated within a short span of time. During the COVID-19 pandemic, many reports have discussed the utility of AI approaches in prioritization, delivery, surveillance, and supply chain of drugs, vaccines, and non-pharmaceutical interventions. Drug discovery is not a trivial task and AI technologies like deep learning can help accelerate this process by helping predict which existing drugs, or brand-new drug-like molecules could treat COVID-19. AI techniques can also help disseminate vital information across the globe and reduce the spread of false information about COVID-19. The positive power and potential of AI must be harnessed in the fight to slow the spread of COVID-19 in order to save lives and limit the economic havoc due to this horrific disease.

Keywords: Artificial intelligence, COVID-19, Diagnosis, Drug Discovery, Vaccine development.

INTRODUCTION

Corona virus disease 2019 (COVID-19) was firstly reported in December 2019 [1,2]. It has caused a large number of deaths and negatively impacted people's lives worldwide, with more than 100 million confirmed cases of the new corona virus (SARS-Cov-2) and more than 200 million cumulative deaths worldwide as of late January 2021[3]. The etiological agent was named as SARS-CoV-2 by the International Committee on Virus Taxonomy on 11 February2020. SARS-CoV-2 is a beta corona virus of zoonotic origin belonging to the subgenus *Sarbecovirus*in the *Orthocoronavirinae* sub family of the family *Coronaviridae* transmitted to humans in a spill over event. Bats are thought to be the animal reservoir of SARS-CoV-2 but the other likely intermediate animal host is yet to be identified. The virus is a spherical particle of 70-90 nm [4], having spikes of glycoprotein projecting from its surface that bind to receptor angiotensin-converting enzyme 2 on the surface of the cell. These spikes give the virus a crown-like appearance. The glycoprotein of SARS-CoV-2 has a furin polybasic cleavage site (PRRARS|V) located between the residues 682 and 685 at the boundary of two subunits S1/S2 that is catalyzed during biogenesis [5]. The presence of this cleavage site in SARS-CoV-2 that is observed in avian influenza viruses but not related viruses like SARS-CoV and SARSr-CoVs makes it distinct and has an impact on entry, tropism, spread and pathogenicity of the virus [5,6]. Expression of furin proteases in the respiratory tract, brain, pancreas, liver, gastrointestinal tract and reproductive organs of the host enables the virus to infect different organs and also facilitates its release into the surrounding environment in many ways. At present, 249 protein structures and 255 whole-genome sequences belonging toSARS-CoV-2 is available in the public domain. A recent study suggested a single-source origin of SARS-CoV-2, as genomic sequences collected from different patients showed strikingly high identity and also indicated that SARS-CoV-2 is phylogenetically closer to bat-SLCoVZC45 and bat-SL-CoVZXC21 [7]. Its genome size is approximately 30 kb [8]. A vast portion of the genome is occupied by two open-reading frames (ORF1a and ORF1b) that translate into pp1a and pp1ab polyproteins, which are then cleaved to 16 non-structural proteins (NSP) like cysteine proteases, chymotrypsin-like, RNA-dependent RNA polymerase, helicase and so on. The rest of the genome encodes structural proteins like the spike(S), envelope (E), membrane (M) and nucleocapsid protein and 6-7 accessory proteins [9]. Genetic analysis revealed that SARSCoV- 2 has evolved in two lineages: ancestral S type and other more prevalent, aggressive and virulent L type derived from S type [10]. It is interesting to note that in the early stages of the epidemic, L type was more frequent, but its frequency decreased later and the frequency of S type increased, which can be attributed to differential selection

pressure and epidemiological features [10]. COVID-19 mainly spreads from human to human through direct contact by respiratory droplets during coughing or sneezing and through indirect contact route by fomites and regularly touched surfaces [11]. SARS-CoV-2 can remain viable on various surfaces for several hours to days [12]. Air-borne transmission is possible in a medical or hospital setting in processes that generate aerosols. Although fecal-oral transmission of COVID-19 has not been reported to date, it remains a potential route [13,14]. Most patients experience mild flu-like symptoms including fever, cough, malaise, fatigue, sputum production and respiratory problems. Less common symptoms such as headache, haemoptysis and gastrointestinal symptoms with diarrhoea and serious symptoms like pneumonia and bronchitis were also observed. Complications like Acute Respiratory Distress Syndrome, RNA aemia, acute cardiac injury, acute kidney injury and secondary infections [15] were reported in some patients. Other lab parameters associated with COVID-19 were low white blood cells and lymphocyte count, an increase in erythrocyte sedimentation rate, C-reactive protein, infiltrates and bilateral ground-glass opacity in lung CT scans. It is imperative to adopt control measures such as case isolation, contact tracing, quarantine to limit human-tohuman COVID-19 transmission. Personal hygiene measures such as frequent hand washing, respiratory hygiene, social distancing, use of face masks/shields and disinfection of surfaces can help in reducing the transmission. Discriminant clinical features like hyposmia (loss of smell) and hypogeusia (loss of taste) can be explored for preliminary diagnosis in telemedicine and mass screening [16]. Specimen samples collected from oropharyngeal and nasopharyngeal swabs or blood samples are used for diagnosis. Although routinely used for COVID-19 diagnosis in outbreak settings, sole reliance on CT scans can be misleading due to indistinguishable images with other viral pneumonia. Molecular test reverse transcriptase-PCR (RT-PCR) is recommended by WHO as the method of choice for detecting the SARS-CoV-2 nucleic acid for diagnosis of COVID-19. As the false-negative rate of RT-PCR is high, it is imperative to use CT scan of the chest as a supplementary diagnostic measure to confirm the diagnosis. Point-of-care immunodiagnostic assays that detect proteins from the COVID-19 virus or human antibodies generated against the virus in blood samples are also being used routinely to complement molecular tests due to low cost and fast results, but these methods suffer from poor sensitivity and are only qualitative. Utility of these serological methods in public health settings for contact tracing and evaluating the success of non-pharmaceutical interventions has been discussed elsewhere [17]. These serological methods have now received Emergency Use Authorization by the US FDA. CRISPR-Cas12-based assay that provides

rapid results can be used in point-of-care testing in the future [18]. According to recent data from WHO, 13 candidate vaccines are being evaluated. An experimental vaccine developed by the University of Oxford/AstraZeneca has entered Phase III of clinical trials while vaccine candidates from CanSino Biological Inc./Beijing Institute of Biotechnology and Moderna/NIAID have reached Phase II trials and ten vaccine candidates have reached Phase I/II and Phase I stages. 129 other candidate vaccines are in the preclinical stage (WHO) and many are in pipeline [19,20]. Some of the potential drugs against COVID-19 being considered and evaluated are remdesivir (GS-5734), baricitinib, a combination drug ritonavir/lopinavir, Ribavirin, umifenovir and IFN-β and other broad spectrum antiviral agents. Remdesivir was not found to be effective in treating COVID-19 patients in a placebo-controlled randomized trial of remdesivir[21]. In a recent development, the FDA has approved the use of remdesivir in confirmed and suspected cases of COVID-19. As of 25 June 2020, about 1235 clinical trials for various therapeutic agents against COVID-19 are being conducted across the globe [22].

Advancement of Computational Methods to Combat Covid-19 Pandemic

In the last two decades, evolvement in computational approaches and modelingled to a paradigm shift in research methodologies related to infectious diseases. Advancements in AI algorithms have helped to analyze a great volume of data and make meaningful predictions, conclusions, and automation [23]. AI is described as an effort to mimic the cognitive functions of a normal brain, such as problem solving and learning with the help of data [24]. The wide spectrum of AI in healthcare includes rule-based systems, classical ML and deep learning (DL). ML is a branch of AI that solves problems based on experiences gained from the curated data, usually referred to as training data, and makes predictions or decisions without any explicit instruction by the user [25]. Based on the input data, ML can be divided into two categories- supervised and unsupervised ML. The supervised ML model is constructed based on labeled data, known as training data and this model is used to make predictions on new data. Conversely, in unsupervised ML, the supplied data are unlabeled and categorized without any previous knowledge [25]. Apart from the classical ML algorithms such as support vector machines, random forest classifiers, k-means and hierarchical clustering etc., recently, artificial neural networks (ANN) have become quite popular. ANNs are ML algorithms that mimic biological neural networks based on the mathematical structure to solve complex data-oriented problems [26]. Deep learning comprises advanced ANN-based ML algorithms in which multiple layers of processing units are used to deduce higher-level features from the data [27]. Most of the supervised ML algorithms can work with small datasets that are

organized and labeled, whereas deep-learning programs can work with raw, unstructured data and require much larger volumes[28,29]. AI is being utilized in healthcare and biomedical research with a variety of tasks such as basic research, medicine, patient and disease management, image analysis and medical devices [30]. For example, IBM's Watson for Oncology tool has convincingly predicted drugs for the treatment of cancer patients. Similarly, Microsoft's Hanover Project proposes a personalized cancer treatment option based on AI [31]. Predicting drug toxicity using ML techniques has also gained popularity over the years [32]. After the onset of the COVID-19 pandemic, several efforts have been made to apply AI techniques on data such as CT scans, X-ray images, and cough sounds to follow infection [33-35]. Several studies have utilized omics data to find repurposed drug candidates for COVID-19 treatment [36, 37]. In addition to this, data from social media, mobile phones and news articles have been utilized to track potential hotspots and community infections [38]. Usage of these big datasets requires a careful balance between public health and protecting data privacy [39]. In this review, we will discuss how AI has been utilized during this pandemic to address key issues such as rapid diagnosis, drug discovery and vaccine development. Furthermore, we will discuss several examples of ML and other AI applications that have been used previously in fighting complex diseases such as cancer and tuberculosis and can be applied in the case of COVID-19.

Role of AI in Diagnosis

Machine learning-based diagnostic applications

The first priority of ML was suggested as technical support for early detection and diagnosis of infections. A recent study demonstrated that the more accurate diagnosis could be generated using a computational model trained on large clinical datasets [40]. An association between males and higher serum lymphocyte and neutrophil levels was identified by applying ML to reanalyze COVID-19 data from 151 published studies. The COVID-19 patients could be classified into three clinically relevant subtypes based on serum levels of immune cells, gender, and reported symptoms. A sensitivity of 92.5% and a specificity of 97.9% were achieved to discriminate COVID-19 patients from influenza patients using a computational classification model. Another study reported that early identification could be performed by a ML model based on the clinical symptoms without CT images at the time of fever clinicadmission[41]. Peng M et al reported that 18diagnostic indicators for COVID-19 were highly associated with a significant diagnosis of COVID-19using AI screening, which improved the accuracy of the clinical diagnosis [42]. Chen et al described a ML random forest model used to classify
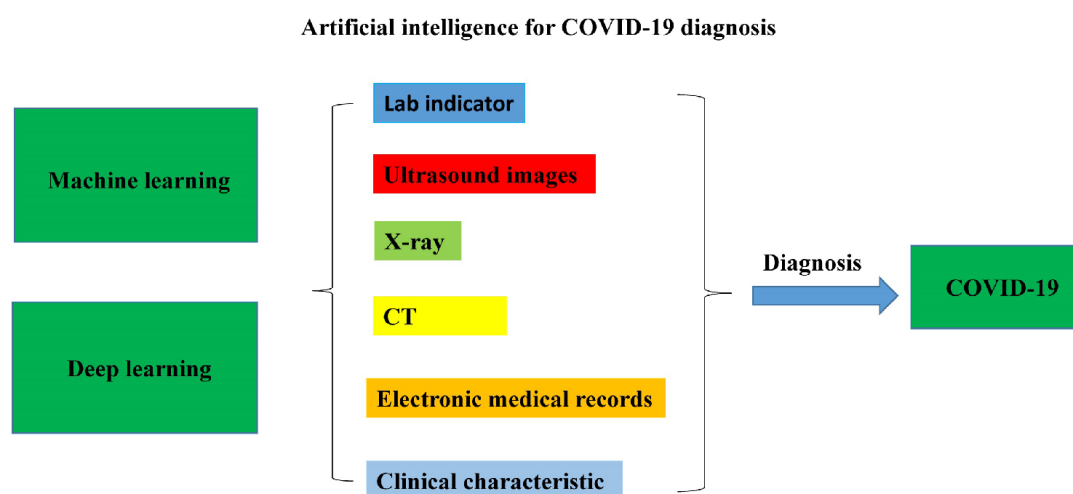
COVID-19clinical types, which achieved >90% predictiveaccuracy[43]. Zoabi et al generated a ML model that trained on data from 51831 tested individuals in Israel. This model resulted in high accuracy using only eight binary features [44]. A combination of seven ML algorithm based on data from UCLA Health System in United States was established to diagnose COVID-19 in the inpatient setting [45]. In the test set (n=392), the combined model achieve excellent diagnostic metrics compared to RT-PCR. An et al developed five ML algorithms for death prediction in a case dataset that was provided by the Korean National Health Insurance Service (KNHIS)[46]. In prediction of mortality, the sensitivity and specificity exceeded 90% while the areas under the curves (AUC) exceeded 96%.Chest CT has been used to evaluate the patients with suspected SARS-CoV-2 infection. AI system had equal sensitivity as compared to a senior thoracic radiologist. The radiologists with less expertise in chest imaging demand AI-assisted screening. In a test set of 279 patients, an AI algorithm combining chest CT presentation correctly identified 68%, while radiologists classified all of these patients asCOVID-19 negative [47]. Developed ML models are suitable for surveillance efforts to predict the SARS-CoV-2infection risk of patients with severe diseases. Monahan et al reported that two unique ML models were generated to predict the risk of the hemodialysis(HD) patients having the undetected SARS-CoV-2infections [48]. Through analyzing more than ten thousand patients, they identified top predictor of an HD patient having a SARS-CoV-2 infection in the prior week.

Deep learning-based diagnostic applications

DL, as a subset of ML, has been explored extensively in the diagnosis of COVID-19, especially in the field of lung detection images, including CT images, X-ray images and ultrasound images. Wu et al developed a DL-based screening framework for corona virus through a multi-view chest CT imaging [49]. The framework trained onmulti-view images of chest CT images from two different hospitals in China through a Convolution Neural Network (CNN) variant, ResNet 50, with a total dataset of 495 patient images, including 368confirmed cases and 127 images of suspected pneumonia cases. Based on DL method, the proposed diagnosis model showed 76% accuracy, 81.1%sensitivity, 61.5% specificity, and 81.9% AUC. Ardakani et al developed a variant system based on CT images in combination with the CNN architectures for COVID-19 diagnostic detection in which ten convolutional neural networks were used to discriminate positive COVID-19 infections from non-infection groups. Among all networks, ResNet-101 showed the best performance with 99.51%accuracy, 100% sensitivity, 99.4% AUC, and 99.02%specificity [50]. Cifci et al diagnosed infections from CT images used Alex Net and

Inception-V4,pre-trained models that are widely used in medical image analysis [51]. The dataset consists of a public database of 5800 CT images (4640 CT images, with4640 training samples and 1160 test sets). The dataset analysis has shown a sensitivity of 94.74% and specificity of 87.37%. Hybrid systems show the higher accuracy than a single model. Hasan et al generated a hybrid system that combined Q-deformed entropy and DL features(QDE-DF) with LSTM from extracting deep features of CT images [52]. The dataset contains 321 chest CT samples, including 118 of COVID-19 cases images, 96images of pneumonia cases, and 107 images of healthy individuals. As the result, 16 core attributes were extracted by the proposed composite model. The analysis achieved 99.68% accuracy in the training and test sets in the ratio of 7:3. Multitask DL based model can be used to detectCOVID-19 lesions on CT scans. A multitask DL model, including segmentation, classification and reconstruction, was used to detect COVID-19 patient and segment COVID-19 lesion from chest CT images[53]. The proposed model was used to analyze a data set of 1369 patients including 449 patients withCOVID-19, 425 healthy individuals, 98 with lung cancer and 397 cases of other diseases. The model hadan accuracy of 86%, a sensitivity of 94%, a specificity of 79%, and an AUC of 93%. Moreover, transfer learning has been applied for the early diagnosis of corona viruses based on X-ray imaging. Apostolopoulos and Bessiana proposed a system for the automatic diagnosis of COVID-19 cases in which five CNN variants (VGG19, MobileNetv2, Inception, Xception, and Inception-ResNetv2) were used to analyze a dataset of X-ray images from patients with common bacterial pneumonia, confirmed Covid-19 disease, and normal incidents[54]. The dataset analysis suggests that DL with X-ray imaging has a high accuracy, sensitivity, and specificity (96.78%, 98.66%, and 96.46%, respectively). A generative adversarial network (GAN) with deep transfer learning has been proposed for corona virus detection in chest X-ray images [55]. The total number of X-ray images in the collection was 307 and contained four categories: COVID-19, normal, pneumonia bacteria, and pneumonia virus. The models contain the Alexnet, Google net, and Restnet18. The accuracy of selecting Alexnet as the primary deep transfer model can reach 80.6% when four categories are included, while the accuracy of selecting Google net as the primary model can reach85.2% when three classes are included. AnotherCOVID-19 diagnosis-Net based on an X-ray image was proposed by Ucar and Korkmaz[56]. Image data from three public datasets obtained 98.26% accuracy, 98.25% specificity and 97.39% F1-score in the proposed system. In another study, a DarkNet model for automatic COVID-19 detection using chest X-ray images has been developed [57]. The Dark Netmodelis a classifier used as a "you only look-once"

(YOLO)real-time object detection system. The proposed model was evaluated for binary classification (COVIDvs. No-Findings, the classification accuracy of 98.08%)and multi-class classification (COVID vs. No-Findings. Pneumonia. It has shown a classification accuracy of 98.08%. In addition, the generated heat maps can assist the clinicians to locate the affected regions on chest X-rays. Lung Ultrasonography (LUS) has been used for the detection and management of acute respiratory disorders. A recent study shows that DL techniques may assist clinician for the analysis of LUS images from COVID-19 patients [58]. A model with three different tasks on LUS imaging: frame-based classification, video-level grading and pathological artefact segmentation, was proposed in the diagnosis of COVID-19. It demonstrated accurate prediction and localization of LUS imaging biomarkers inCOVID-19 patients.

Artificial intelligence for COVID-19 diagnosis

Machine learning	Lab indicator		
Deep learning	Ultrasound images		
	X-ray	Diagnosis →	COVID-19
	CT		
	Electronic medical records		
	Clinical characteristic		

AI in Predicting COVID-19 Outcome

While the accurate detection of SARS-CoV-2 in patients is the critical step towards treatment, a fast and early clinical assessment of the disease severity is also crucial to support decision making and logistical planning in healthcare systems [59-61]. Patients' characteristics such as age, varied clinical symptoms, and co morbidities can help in categorizing the infection severity, need for hospitalization and predict the disease outcome [61,62]. Such prognosis-based prediction models for a given disease support the physician's decision-making and assist in the screening of high-risk patients. The mortality of COVID-19 patients can be potentially reduced by an early intervention, which is only possible by an accurate and early prediction of disease progression. XG Boost classifier, a high-performance ML algorithm, is used to identify three potential biomarkers; lymphocytes, Lactate dehydrogenase (LDH),

and high-sensitivity C-reactive protein (HS-CRP). The XG Boost algorithm has great interpretability potential due to its recursive tree-based decision system and is shown to be ~90% accurate in predicting patient mortality approximately 2 weeks in advance [63]. Similarly, in another study, SARS-CoV-2 induced pneumonia was predicted based on seven laboratory parameters (prothrombin activity, urea, white blood cell, interleukin-2 receptor, indirect bilirubin, myoglobin, and fibrinogen degradation products) [64]. These parameters were identified by applying the least absolute shrinkage and selection operator (LASSO) logistic regression model based on features selected by the mRMR algorithm. This study showed that these multiple feature-based models can produce ~98% sensitivity and ~91% specificity in predicting SARS-CoV-2 pneumonia prognosis [64]. AI modalities can also help in predicting the personalized risk of adverse events or COVID-19 disease trajectory [65,66]. Further, different datasets such as patient health, travel history, geographical location, and demographic data were combined to build an Ada Boost Random Forest model. This model predicted the possible outcome of a COVID-19 patient with ~94% accuracy [67]. A study on a cohort of 13,690 patients has shown that the ML model can be applied effectively on a combined feature set. In this study, the patients' clinical, demographic, and co morbidities data were analysed to predict COVID-19 outcome, which helps the physician in decision-making [68]. Another example describes the better predictability of ventilation requirements for COVID-19 patients. This prediction uses ML models over physiological scoring based on modified early warning systems (MEWS). This model successfully predicted the need for a mechanical ventilator for a COVID-19 patient during hospitalization and helps in management of COVID-19 and improved patient care [69]. Another mortality prediction model for COVID-19 patients was built using the XG Boost algorithm based on clinical and demographic data. A combination of three main features, namely the type of patient encounter, minimum oxygen saturation, and age, showed high accuracy (AUC score of 0.91). This model can be easily implemented due to these three highly accessible clinical features pertaining to COVID-19 disease [70].

Drug Discovery and Vaccine Development

General background for the vaccine

In general, there are two main approaches to fighting the worldwide COVID-19pandemic: a vaccine-based pipeline for prevention and a chemical-based pipeline to cure infected patients. For the vaccine-based approach, at the time of writing this review article, the total number of candidate vaccines has reached 292, 108 of which are now undergoing clinical trials. Currently, 38 are in phase 1,

28 in phase 1/2, 10 in phase 2, 9 in phase 2/3, 19in phase 3, and 8 in phase 4 as summarized by the WHO [71]. The non-profit organization Our World in Data, established by the University of Oxford teams, stated that more than28.5% of the world population had received at least one COVID-19 vaccine as of 3 August2021 [72]. Under the current circumstances, the majority of the vaccinated public has been vaccinated by the two mRNA-based vaccines, BNT162b2 (Pfizer, New York, NY, USA) andmRNA-1273 (Moderna, Cambridge, MA, USA), which have been authorized for emergency use by the U.S. Food and Drug Administration (FDA). A study conducted between 4 May2020 and 22 June 2020, showed that the response of BNT162b2, which encodes a full-length membrane-anchored spike (S) protein of SARS-CoV-2, and the response of BNT162b1, which encodes a secreted trimerized SARS-CoV-2 receptor-binding domain, are similar with respect to factors such as S1-binding IgG concentration and 50% neutralization titer. However, BNT162b2 yields a lower incidence and severity than BNT162b1, particularly in older adults [73]. In addition, BNT162b2 can neutralize several SARS-CoV-2 variants [74]. COVID-19-convalescent individuals with or without mRNA vaccines were investigated for the follow-up cohort study, which indicated that the neutralization activity againstSARS-CoV-2 one year after infection was stable in the non-vaccinated group, but enhanced in vaccinated groups in terms of the components of the immune system, such as the plasma IgG antibody that can bind to the SARS-CoV-2 receptor-binding domain (RBD), N-protein, and plasma neutralizing activity [75]. It was noted that the data from the seven vaccines and convalescent cohorts show that the neutralizing activity can predict immune protection from SARS-CoV-2 infection. The model indicates that protection from severe disease can be retained, but protection from SARS-CoV-2 infection would decrease [76]. Regarding mRNA-1273, efficacy and safety have been investigated, and a 94.1% efficacy in preventing COVID-19 has demonstrated [77]. The use of mRNA-1273 and BTN162b2in pregnant and lactating women has also been examined, indicating that women can acquire immunogenicity under these conditions [78]. Similar to BNT162b2, the neutralizing activity persists for at least six months after mRNA-1273 vaccination [79], and miRNA-1273-elicited antibodies were more targeted towards SARS-CoV-2 RBD than naturally elicitedantibodies[80].

AI-driven drug discovery

Although encouraging evidence about the ability of the abovementioned mRNA based vaccines to prevent COVID-19 has accumulated, there is still a demand for new vaccines or drugs for the following

reasons: (1) Vaccines that can be stored at room temperature or even in a freezer are needed. BNT162b2 needs to be stored at -90 to-60^{0}C and mRNA-1273 needs to be stored at -25 to -20^{0}C. It is a difficult technological challenge, especially in low-income countries, to gather a sufficient amount of the necessary equipment such as deep freezers with power supplies. Hence, the development of such vaccines would accelerate an effective and strategic COVID-19 vaccination program for global mass immunization. (2) Vaccination for COVID-19 causes certain unavoidable sideeffects[81]. Therefore, vaccines that lead to fewer side effects are desirable. (3) There are four variants of concern (Alpha, Beta, Gamma, and Delta), which are recognized asSARS-CoV-2 virulent variants and four variants of interest (Eta, Iota, Kappa, and Lambda), which have been detected in multiple countries or cause clusters. These variants have been categorized by the WHO [82], and thus far, limited studies have investigated whether currently available vaccines are useful against them [83-85]. Furthermore, some patients have become infected after vaccination [86], and reduced vaccine efficacy has been report ed against some variants [87]. Exploratory studies for vaccines and drug discovery to tackle COVID-19 are actively ongoing. A DL approach can identify therapeutic candidate antibodies by predicting antigenspecificity[88]. Major histocompatibility complex analysis with recurrent integrated architecture (MARIA) was trained on HLA-DR ligands identified by mass spectrometry based profiling, public HLA-II peptide binding data (IEDB), and gene expression levels top redict potential epitopes [89]. Fast et al. further expanded this method to identify T-cell epitopes for SARS-CoV-2 RBD [90]. Antibody-epitope classification using deep neural networks (DNNs) was reported using input two-dimensional images generated from a three-dimensional image projection created by the Rosetta antibody software [91]. The ML platform REDIAL-2020 estimates small compound activities in a broad range of SARS-CoV-2-related assays [92]. ML can predict activity from chemical structures, and an ML-based drug discovery pipeline was developed to identify effective therapeutic drugs for COVID-19 from FDA-registered and approved drugs and purchasable chemicals [93]. Note that to target SARS-CoV-2 with AI, freely available datasets are deposited at the nCov-Group DataRepository[94]. In silico drug discovery with tensor decomposition-based unsupervised feature extraction was performed on lung cancer cell lines infected with SARS-CoV-2 and successfully screened for chemical compounds such as ivermectin, which is undergoing clinical trial for SARS-CoV-2 [95]. The fragment-based drug discovery approach facilitates the identification of lead compounds, and their crystallographic screening approach identified 71 hits[96].For drug repurposing or repositioning, protein–protein

interaction networks have been identified by expressing 26 out of 29 SARS-CoV-2 proteins in human cells [97] and two high-throughput repurposing screenings using HeLa cells expressing ACE2 and lung epithelial Calu-3 cell lines [98]. To screen anti-viral drugs for COVID-19, matrix completion techniques have been used to predict the drug–virus association for drug repositioning using a manually curated comprehensive dataset [99]. Another study showed that an A platform with two different training datasets identified existing drugs with potential [100]indicating that the AI approach for drug screening is now feasible. COVID-19 mortality prediction using ML and DL in USA, China, and Korean cohorts has surged recently. The COVID-19 Moon-shot project, which united academic institutions such as Oxford, Imperial College London, and Memorial Sloan Kettering with industry partners, was launched to specifically focus on developing the SARS-CoV-2 main viral protease (Mpro),which is known to be a good candidate for antivirals owing to its distinctiveness from host proteases[101]. The Moonshot project combines crowd sourcing medicinal chemistry insights with high-throughput crystallography, a computational chemistry environment, and ML for drug development to actively determine drug candidates [102, 103].

Integrative medicine

Thus far no aspects of integrative medicine have specifically been validated for the management of COVID-19 in randomized controlled trials.8 However, there certainly is interest in the use of integrative medicine for the management of COVID-19. Currently, it is known the virulence and pathogenicity is associated with viral activation of cytoplasmic NLRP3 inflammasome. This inflam-masome in upregulated NFkb macrophages and Th1 cells results in proinflammatory cytokines (IL-1B and IL-18). These cytokines help mediate the pathogenic inflammation involved with much of the virulence and symptoms of COVID-19. This knowledge has enabled many potential integrative medicine considerations for risk reduction of COVID-19. This includes adequate sleep, stress management, zinc, Vegetables/ fruits +/- isolated Flavonoids, cur-cumin, melatonin, and Sambucusnigra (Elderberry). As more is learned about pathogenicity of SARS-CoV-2, an AI based approach may provide great benefit in screening possible integrative medicine techniques for the risk reduction of COVID-19. AI based screening methods could be used to specifically screen for integrative options that can help mediate the inflammatory responses to SARS-CoV-2 infection. Such an AI based approach can lead to a far more rapid deployment of integrative medicine tech-niques in the fight against COVID-19 [104].

Challenges and Limitations Associated with AI

AI is poised to play an increasingly important role in all areas of healthcare. However, the real-world scaling of such solutions poses many challenges and limitations. Validation, generalization, explain ability, interpretability, risk mitigation, fairness, and inclusiveness are some of the key challenges in making AI-based decisions in medical and public health settings. Generalization refers to the ability of AI-based algorithms to perform efficiently in different settings. Several concerns need to be addressed as the use of ML and other AI tools are increasing day to day in critical decision making. In AI, generalizability usually attributes to the ability of an ML algorithm to be effective across a range of inputs and applications. The narrow context models always have risks that they can fail at the broad level when applied with different datasets. However, generalizability cannot be summarized by a universally agreed definition. Owing to the participation of AI in different applications, it is critical to create and govern these techniques in a credible and fair manner. In clinical and health care setups, the absence of transparency within the models, the privacy of the patient data, and the safety and liability-related issues are major challenges in terms of ethical and regulatory aspects of AI. AI governance deals with issues such as bias and lack of transparency by engaging different stakeholders. The prime focus of ethical governance should be on handling ethical issues involved in clinical operations such as fairness, transparency, and privacy. Explain ability and interpretability are two important factors that need governance to monitor and enhance AI algorithmic fairness, transparency, and accountability. In addition to this, ethical auditing can examine the inputs and outputs of AI algorithms and models for bias and potential risks. One of the drawbacks of AI-based models is that their real utility remains largely untested. For example, in the case of COVID- 19 research, AI-based models are theoretical. For instance, although minimum oxygen saturation was identified as an important mortality predictor, it needs to be modelled alongside the supplemental oxygen delivered, a piece of data that may be missing in many models. However, most of these challenges are being proactively addressed by the AI researcher community. In the clinical settings, COVID-19 has triggered the need to go digital, improve data literacy and explore assistive algorithms. Grassroot-level applications of AI in addressing public health and the supply chain are also helping in connected care. In the near future, some of the AI tools may be employed in the decision making in medical supplies, humanitarian aids, population risk assessment, and at a certain level, clinical care and treatment [105].

Discussion and Conclusions

The world is going through another wave of COVID-19 infections. Worldwide, daily rates of new infections have jumped significantly since March 2020, with deaths rising-this horrid emergency is again putting strain on the heavily-burdened healthcare system throughout the world. To control the pandemic and related stress on healthcare, scientists are testing the applicability of AI strategies. The computational approaches have proven very effective in basic research, diagnosis, and treatment to fight against infectious diseases. AI-based approaches have emerged as a useful tool/method in surveillance, diagnostic and discovery of new therapeutics. Combining a vast variety of data such as blood exams, clinical images, and recording of cough sound with advanced ML techniques provides a quick and reliable alternative for diagnosis and assessment of the disease severity. COVID-19 patients show symptoms such as fever, fatigue, muscle ache, cough and respiratory issues. Since clinicians cannot identify patients who succumb to the disease early on, the AI/ML tools are shown to be effective and helpful in making clinical decisions. From evaluating the safety and efficacy of therapeutics, to help with imaging data analysis or contact tracing, AI has provided novel solutions in the fight against COVID-19. For example, AI is helping overcome barriers between repurposed drugs, clinical testing of therapeutic strategies, and drug authorization. The application of AI strategies in COVID-19 also faces certain challenges. To fully utilize these strategies, it is important to address issues related to data privacy, concerns on data collection and handling practices, and governmental oversight. Even in the pre-pandemic 2019, many experts believed that AI has the potential to revolutionize healthcare, and while the risk of algorithmic bias and data privacy concerns are very real, there is little question that AI has proven its utility in the fight against COVID-19.

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