REVIEW

Host-dependent molecular factors mediating SARS-CoV-2 infection to gain clinical insights for developing effective targeted therapy

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Abstract
Coronavirus disease 2019 (COVID-19), a recent viral pandemic that first began in December 2019, in Hunan wildlife market, Wuhan, China. The infection is caused by a coronavirus, SARS-CoV-2 and clinically characterized by common symptoms including fever, dry cough, loss of taste/smell, myalgia and pneumonia in severe cases. With overwhelming spikes in infection and death, its pathogenesis yet remains elusive. Since the infection spread rapidly, its healthcare demands are overwhelming with uncontrollable emergencies. Although laboratory testing and analysis are developing at an enormous pace, the high momentum of severe cases demand more rapid strategies for initial screening and patient stratification. Several molecular biomarkers like C-reactive protein, interleukin-6 (IL6), eosinophils and cytokines, and artificial intelligence (AI) based screening approaches have been developed by various studies to assist this vast medical demand. This review is an attempt to collate the outcomes of such studies, thus highlighting the utility of AI in rapid screening of molecular markers along with chest X-rays and other COVID-19 symptoms to enable faster diagnosis and patient stratification. Several molecular biomarkers such as C-reactive protein, IL-6 eosinophils, etc. showed significant differences between severe and non-severe cases of COVID-19 patients. CT findings in the lungs also showed different patterns like lung consolidation significantly higher in patients with poor recovery and lung lesions and fibrosis being higher in patients with good recovery. Thus, from these evidences we perceive that an initial rapid screening using integrated AI approach could be a way forward in efficient patient stratification.

Keywords COVID-19 · SARS-CoV-2 · Molecular biomarkers · Multiomics · Artificial intelligence

Introduction
Coronavirus Disease 2019 (COVID-19), a 2019 pandemic, is caused by the SARS-CoV-2, a novel strain of coronavirus. Other respiratory illnesses such as SARS and MERS are also caused by coronavirus family of viruses (Poutanen 2018). These viruses cause mild to severe respiratory infections, affecting mammals and birds. Between December 2019 and April 2020, COVID-19 infection rose as a rapidly spreading pandemic, affecting 1,119,109 people in 181 different countries in the world (statistics till manuscript submission). While the total death toll increased beyond 58,955 people across different countries, recovery rates stood higher constituting more than 226,873 people (Johns Hopkins University 2020a, b; World Health Organization 2020).

Although highly contagious, only ~20% of the infected needed severe hospitalization. However, the extremely severe cases demand high medical attention and utilize major hospital resources from patient beds, intensive care units (ICU), respiratory support to ventilators. With limited availability of these healthcare resources, the condition turned unmanageable (Grasselli et al. 2020; Rosenbaum 2020).
While age and symptoms matter in COVID-19 patient care, they are not necessarily accurate predictors of disease severity and deaths. Molecular biomarkers like C-reactive protein, interleukin-6 (IL-6), eosinophils and chest X-ray/computed tomography (CT) findings like lung consolidation, lung lesions and fibrosis have shown significant associations with COVID-19 disease severity as evidenced by several studies (Huang et al. 2020; Yun et al. 2021; Broman et al. 2020; Hashemian et al. 2020).

Since only few of these markers are tested clinically in COVID-19 patients, a robust and high-throughput technique like AI-enabled multiomics can integrate and assist in rapid screening of patients for efficient stratification. This way, valuable information like disease severity can be acquired at a high pace (Kumar et al. 2020).

We at iNDX.AI, as AI innovators in precision oncology, are also enduring to repurpose our platforms like iCore (image analytics) and iCE (Integrated Correlation Engine—AI-based multiomics investigation software) to COVID-19 investigation so as to achieve rapid utility of enormous patient data, powerful patient stratification and feature prediction. Due to the limited knowledge of the molecular aspects of COVID-19 infection so far, an AI-enabled comprehensive evaluation of host molecular pathways in SARS-CoV-2 replication could also facilitate a better understanding of the disease. This review article thus aims to address the combined benefits of molecular biomarkers and clinical findings in efficient COVID-19 patient screening and stratification.

**Current status of COVID-19**

**Disease origin/progression mechanisms**

The infection was first detected in Wuhan, Hubei province, China, and is believed to have spread from wildlife wet market. The disease is caused by a strain SARS-CoV-2, that is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses, raising a possibility of bats to be its primary hosts. The virus after its ingress into human system, incubates and replicates before infecting multiple cells causing serious symptoms like upper respiratory tract infection, fever, sore throat, myalgias, etc. However, some infected cohort are asymptomatic with internally aggravating and advancing disease. A list of all immediate and persistent symptoms are presented in Table 1.

With its rapid spread, COVID-19 has invaded more than a 100 countries across the world with various degrees of illnesses and fatalities. Regarded as pandemic by the World Health Organization (WHO), infections started overwhelming hospitals, healthcare professionals and medical resources (World Health Organization 2020). There are no clinically approved drugs/therapies for COVID-19; however, broad spectrum antibodies are under investigation in clinical trials.

### Table 1 Table presents immediate and persistent symptoms of COVID-19 infection

| Immediate symptoms | Persistent symptoms (even after recovery) |
|--------------------|------------------------------------------|
| **Common symptoms** | **Severe symptoms** | **References** | **Symptoms** | **References** |
| Fever or chills | Breathing trouble/shortness of breath (pneumonia) | Centers for Disease Control and Prevention (2020) | Cough | Ladds et al. (2020) |
| Cough | Continuous pressure in the chest | Breathlessness |
| Fatigue | Inability to wake or stay awake | Fever |
| Muscle or body aches | Bluish lips or face | Sore throat |
| Headache | Neurological symptoms |
| Loss of taste or smell | Chest pain |
| Sore throat | Palpitations |
| Congestion or runny nose | Myalgia |
| Nausea or vomiting | Neurological symptoms |
| Diarrhea | Skin rash |
| Tingling or numbness in hands and feet | Diarrhea |
| Harvard Health Publishing (2021a, b) | Low oxygen saturations |
| Delirium and confusions | | | |
| Seizures and stroke | | | |
Vaccine investigations are also ongoing with several efforts approved by the US Food and Drug Administration (FDA) (Shereen et al. 2020; The New York Times 2021).

**Factors of predisposition and patient severity**

While any healthy individual in a population is vulnerable to SARS-CoV-2 infection, several health factors and comorbidities elevate the risk of some individuals for both infections and deaths. Smoking and alcohol can be major lifestyle risk factors of COVID-19 infections. However, there is no large statistical evidence to prove this phenomenon.

In a retrospective multicenter cohort study conducted in affected patients in Wuhan, China, several compulsive comorbidities have been explored. Majority (~30%) of the affected individuals have been identified with hypertension, making it the major susceptible factor. Diabetes was the second most susceptibility factor followed by coronary heart disease which were 19% and 8%, respectively. Old age was also identified to be a significant factor for infection severity and death (Zhou et al. 2020).

**Global diagnostic tools**

As the virus rapidly progresses to the respiratory tract through 5–7 days of infection, a nasopharyngeal (NP) swab and/or an oropharyngeal (OP) swab is recommended for screening and early diagnosis (Tang et al. 2020). For more severe symptoms, lower respiratory specimens such as sputum and/or endotracheal aspirate or bronchoalveolar lavage is investigated. Blood and stool samples are also considered for additional examinations. Since coronaviruses are enveloped single stranded ribonucleic acid (RNA) viruses, laboratory diagnosis is performed using real-time reverse transcription polymerase chain reaction (rRT-PCR) reactions (Center for Infectious Disease Research and Policy 2020).

In addition, chest X-rays and CT scans are also regularly captured to diagnose severe respiratory conditions like pneumonia in critically ill patients. Viral genome sequencing is also a developing scenario to monitor any evolving mutations in the virus which, however, has not been widely adapted for clinical investigation (World Health Organization 2020; ScienceDaily 2020).

**Treatment/control methods**

As per Centers for Disease Control and Prevention (CDC), there are no current preventive or treatment drugs approved by FDA. However, several drugs and strategies are being utilized for palliative care. As a measure for supportive care, oxygen supplementation and mechanical ventilation are being utilized in intensive care facilities for COVID-19 infection (Centers for Disease Control and Prevention 2020).

Several broad-spectrum antiviral drugs such as remdesivir are being extensively investigated for treating COVID-19 infected patients. Certain antimalarial and anti-inflammatory drugs such as hydroxychloroquine and chloroquine are also under clinical trials for use as prophylactic and therapeutic for COVID-19 infections (Centers for Disease Control and Prevention 2020).

Precautions, strict quarantining and patient isolation are also effective strategies followed for containing the viral spread and transmission (Centers for Disease Control and Prevention 2020).

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**Table 2** Table presents a list of COVID-19 primary management medications, drug class and treatment indications

| Medication | Drug class | Indications | References |
|------------|------------|-------------|------------|
| Corticosteroids (Dexamethasone, Prednisone, Methylprednisolone) | Anti-inflammatory | Recommended during hyper-immune reactions/cytokine storm upon viral infection that damages lungs and other organs | Harvard Health Publishing (2021a, b) |
| Remdesivir | Anti-viral | Recommended against viral replication | Harvard Health Publishing (2021a, b) |
| Anticoagulation drugs (“blood thinners”) | Anti-coagulant | Recommended to prevent/treat blood clots | Harvard Health Publishing (2021a, b) |
| Bamlanivimab, Casirivimab and Imdevimab | Monoclonal antibodies | Recommended against viral attachment to host cells (action against coronavirus’s spike protein) | Harvard Health Publishing (2021a, b) |
| Convalescent plasma | Antibody therapy | Antibodies from recovered patients recommended to act against replication and spread of virus | Harvard Health Publishing (2021a, b) |
Challenges in clinical settings during viral pandemics

Viral pandemics have a history of invading and destroying millions of people across the world since the very known “Spanish flu pandemic” in 1918. Death rates recorded back then were extremely high across the globe with various contributing factors like availability and access to healthcare facilities, public health infrastructure, population density, nutritional factors, etc.

Apart from frontline medical resources, intense research on viral characteristics, drug/vaccine discovery in limited time span and large scale production of the discovered vaccines are all equally challenging. However, economic and technological developments are powerful resources against evolving global emergencies (Oshitani et al. 2008).

The recent COVID-19 pandemic has been a clinically challenging threat to more than 100 countries, with Europe, North America and China hit the hardest. Novel viruses such as COVID-19 display continuously evolving genomic patterns and sequences, which could also vary among different races or ethnicities. In such cases, treatment/management decisions cannot depend only upon clinical manifestations. This contributes to the challenge as their sequences and/or protein structures may not be available for deeper investigations (Li et al. 2020). Several retrospective analyses of integrated patient data including deoxyribonucleic acid (DNA), RNA, host immune profile, cytokine profile, blood and biochemical reports yield direct correlations with patient recovery, disease severity and even death (Thevarajan et al. 2020). Several other technological developments such as virtual reality, AI, AI-assisted robots, AI-assisted chatbots, remote and virtual diagnosis and consultation, etc., also aim to assist healthcare professionals with more rapid and accurate solutions (BROOKINGS 2020; The British Broadcasting Corporation 2020).

This article is one such endeavor to emphasize existing clinical challenges and the routes through which the high throughput AI-enabled multiomics is beginning to assist healthcare from disease prediction, patient stratification to drug/vaccine discovery in COVID-19 pandemic crisis.

Role of AI-enabled multiomics in COVID-19 investigation

The aggressive nature of COVID-19 has led to its intractable spread across various countries rapidly increasing the death rates. Due to its unpredictable complexity and novelty, clinical diagnosis and treatment are burdensome for healthcare professionals.

With the rapidly progressing nature of the virus, a high-throughput approach to detect physical and molecular characteristics more rapidly is essential to keep up diagnostic accuracy and enable drug/vaccine development. Thus several AI-enabled platforms are spiking into COVID-19 investigation from diagnosis to discovery (UC San Diego Health 2020). With better algorithms and quicker analysis, faster patient care can be clinically adopted. In this section, we discuss some of the AI-enabled tools and their usefulness in COVID-19 interventions.

AI-enabled multiomics and patient stratification

The SARS-CoV-2 has been identified to cause infections irrespective of an individual’s current or previous medical conditions. However, multiple host-dependent molecular factors contribute to recovery/serious illness in addition to clinical manifestations. Clinically, most of the infected patients have been documented to present varying degrees of fever, cough, fatigue, myalgias, shortness of breath, to name a few. However, some are physically asymptomatic with or without internal advancement as mentioned earlier (Qiu et al. 2020; Pan et al. 2020; World Health Organization 2020). This suggests that clinical presentations alone cannot be predictive of virus penetration and progression internally.

For instance, a case study published in 2020 by Thevarajan et al., utilized multiomics approach to investigate host immune responses of a 47-year-old female COVID-19 patient. Upon retrospective investigations at different time points throughout her infection, several factors like antibody secreting cells (ASCs), Follicular helper T cells (T_{fh} cells), activated CD4+ T cells, CD8+ T cells, immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies were found to be elevated. Upon cytokine and chemokine profiling during symptomatic phase of the disease, decreased pro-inflammatory cytokines and chemokines were observed. A risk genotype in Interferon Induced Transmembrane Protein 3 gene (IFITM3 gene) (rs12252) for influenza was also observed on genetic testing. Interestingly, 26% of the Chinese population carried the risk genotype as per 1000 Genomes Project which was surmised to reflect COVID-19 spectrum in china (Thevarajan et al. 2020). This case study illustrates the diverse spectrum of essential host-dependent molecular parameters that could contribute to patient recovery in COVID-19 disease. However, healthcare professionals are needed to be focused on treating healthcare needs of patients. Thus AI-enabled multiomic models could efficiently stratify patients based on strictly trained algorithms promoting appropriate care, faster recovery and proper allocation of hospital resources.

Polymorphisms in genes like Angiotensin I Converting Enzyme 2 (ACE2) are also contributing to increased vulnerability of COVID-19 infection (Alimadadi et al. 2020).
AI-based algorithms can be trained with large genomic datasets and can be utilized as powerful tools to screen huge population for polymorphisms at high-throughput. Neural network based algorithms can also be utilized for large-scale screening and prediction of COVID-19 infections using complex data like patient respiratory patterns (Alimadadi et al. 2020).

Other significant molecular stratifiers of COVID-19 patients include immune markers, metabolome (e.g., liver enzyme alanine aminotransferase), cell surface receptors, genes responsible for other comorbidities such as cardiac diseases, diabetes and so on (Jiang et al. 2020). IL-6 is one such molecular marker, which has been identified to significantly increase with the disease severity among COVID-19 infected cohort and are also strongly associated with the need for mechanical ventilation. Increasing levels of this marker also predicted respiratory failure with high accuracy as shown in studies (Herold et al. 2020). Figure 1 depicts the levels of IL-6 in severely affected patients as compared with non-severe cases among COVID-19 infected patients investigated from 9 studies.

In addition to the clinical and molecular biomarkers, AI has been intelligently utilized by researchers in Massachusetts Institute of Technology (MIT) to predict cough patterns of asymptomatic COVID-19 patients. The study utilizes thousands of cough patterns to develop an AI model that can discriminate cough of an asymptomatic individual from uninfected individuals. If approved by FDA, this AI-based model can be an efficient tool for asymptomatic patient stratification from healthy individuals thereby assisting in reduction of viral spread and infections (MIT News 2020).

**Patient surveillance and tracking, virtual healthcare assistance and high-speed data capture and retrieval**

Migration and community gathering are the major causes of rapid multiplication of pandemic infections. Since, SARS-CoV-2 is capable of incubating asymptomatic for ~7–14 days inside the human system, early isolation before clinical presentation has been challenging. In such cases, AI acts beneficial to monitor migration in populations at risk or affected so as to enable efficient tracking. AI-enabled algorithms can also accurately predict individual risk of infection with sufficient information on family history, lifestyle, social and travel history, etc., AI models are also trained as information bots to deliver reliable general information about infection, speed of transmission, recovery rates, etc., catering general awareness (Panch et al. 2019; Kuziemsky et al. 2019).

Multiple AI-based data dashboards are also functional and beneficial in tracking infected cases, recoveries and

![High interleukin-6 levels consistent in severe COVID-19 infections as shown in literature](image)

**Fig. 1** Relationship between IL-6 and COVID-19 disease severity. IL-6 levels are reported to be higher in severe COVID-19 infections than non-severe patients in studies mentioned below. Figure 1 is a compiled reanalysis of IL-6 data from 7 studies which consistently showed increased levels of IL-6 in severe cases than non-severe ones (Chen et al. 2020; Gao et al. 2020; Liu et al. 2020a, b; Yang et al. 2020; Qin et al. 2020; Fu et al. 2020; Thevarajan et al. 2020; Wu et al. 2020; Wang et al. 2020)
IL-6 regarded as “cytokine storm syndrome”, being inter-
patients presented excessively high levels of ferritin and
study in China, it has been identified that some infected
extremely elevated cytokine profiles. From a retrospective
predictor of disease severity.
patients who recovered from infections showed an increas-
(TLM) (Tan et al. 2020). The study also identified that the
and fatal disease using time-lymphocyte percentage model
accurately predict the need for immunosuppressive drugs
all be responsible for elevating patient fatality. Application
protein (MIP)-1alpha and tumour necrosis factor alpha could
interferon-γ-inducible protein-10, macrophage inflammatory
information resulting in increased levels of interleukin-2 (IL-2),
interleukin-7 (IL-7), granulocyte colony stimulating factor,
preted as a cause of mortality. Virus induced hyperinflam-
article investigations.

**AI-enabled multiomics in disease severity, clinical trial recruitment and drug development studies**

Age has been considered a major risk factor of COVID-
infection based on worldwide statistics. A model-based
investigation of age group vs case fatality ratio also rendered
a linear relationship of 0.32% vs 6.4% in individuals older
than 60 years of age (Verity et al. 2020). However, infect-
ion and disease severity ratios may not necessarily follow
age relationships, as the infections have been recorded in
younger population as well (Verity et al. 2020).

Recently, an AI-based prediction of COVID-19 severity,
investigated by NYU Grossman School of Medicine and the
Courant Institute of Mathematical Sciences at New York
University, in partnership with Wenzhou Central Hospital
and Cangnan People’s Hospital, both in Wenzhou, China,
was able to predict the need for patient respiratory support
based on molecular factors. Three major features were utili-
ized in the study which includes liver enzyme alanine ami-
notransferase (ALT) levels, myalgia and hemoglobin levels
reaching an accuracy of up to 80% (ScienceDaily 2020).

Similarly, another study by Tan et al., identified signifi-
cantly lower lymphocyte percentages in patients with severe
and fatal disease using time-lymphocyte percentage model
(TLM) (Tan et al. 2020). The study also identified that the
patients who recovered from infections showed an increas-
ing trend of lymphocyte percentage making them a useful
predictor of disease severity.

Mortality also hits some patient cohorts who present
extremely elevated cytokine profiles. From a retrospective
study in China, it has been identified that some infected
patients presented excessively high levels of ferritin and
IL-6 regarded as “cytokine storm syndrome”, being inter-
preted as a cause of mortality. Virus induced hyperinflamm-
ating results in increased levels of interleukin-2 (IL-2),
interleukin-7 (IL-7), granulocyte colony stimulating factor,
interferon-γ-inducible protein-10, macrophage inflammatory
protein (MIP)-1alpha and tumour necrosis factor alpha could
all be responsible for elevating patient fatality. Application
of AI-enabled multiomics analysis in these areas could
accurately predict the need for immunosuppressive drugs
which could otherwise be life-threatening in viral infections
(Mehta et al. 2020). A compiled representation of multiple
molecular markers from over 450 individuals accumulated
and reanalyzed from different studies and case reports on
COVID-19 is depicted in Fig. 2 (Huang et al. 2020; Bro-
man et al. 2020; Hashemian et al. 2020). This shows the
contribution of molecular representatives in determining
potential candidates for clinical trial and/or drug develop-
ment investigations.

In addition to patient stratification and clinical trial
recruitment, AI-based drug prediction models are highly
evolving. With the advancing availability of enormous
patient data and viral structural/sequential information, it is
achievable to train AI algorithms to predict efficacy against
certain class-specific drugs. For instance, an AI-based model
developed by researchers in Korea and United States has
been identified to predict targeted drugs to inhibit the rep-
lication of 2019-nCoV. The model utilizes 1 dimensional
(1D) string of input sequences as against the unavailabil-
ity of 3 dimensional (3D) protein structures, predicting the
inhibitory potencies of antitrioviral drugs like atazanavir,
efavirenz, retronavir and dolutegravir using $K_s$, $K_d$ and IC50
values. Molecular docking studies have also been utilized
for deeper investigation of prediction accuracies (Beck et al.
2020). Due to the flexibility of AI-enabled models, they
show great potential in several drug developmental studies.

**AI-enabled high throughput prediction of clinical images for early signs of pneumonia**

Pneumonia is a major cause of severity and death in COVID-
infections. However, even expert radiologists are over-
whelmed with huge radiomic data with increasing numbers
of CT scans and chest X-rays of affected individuals. Thus,
regular monitoring of images for early diagnosis is a chal-
lenge due to continuously increasing burden of infections.

UC San Diego Health has developed an AI-assisted model enabled by Amazon Web Services (AWS) to accu-
rately predict, monitor and diagnose pneumonia with patient
CT scans and chest X-ray images. This model has provided
experts with new insights in about 2000 clinical images.
Interestingly it has also predicted a patient’s risk of develop-
ing pneumonia with early signs in chest X-ray, which would
have been missed otherwise (ScienceDaily 2020).

Several other AI algorithms are being investigated for
image analytics in COVID-19 patients. These algorithms
are usually trained with equal/sufficient data under 3 major
categories including chest X-rays from healthy individuals,
pneumonia and COVID-19 affected patients. Training is
usually focused to maintain consistent prediction accuracy
even with low quality data with appropriate preprocessing.
Radiomic features are then extracted, balanced and trained
under various data classifiers such as Random Forest (RF),
Decision Trees (DT), etc. Such models have established a
maximum accuracy of 0.973 using RF (Kumar et al. 2020).
AI-enabled multiomics studies, apart from the early prediction of pneumonia, can also be utilized to extract various other useful information for treatment surveillance and monitoring, which includes pulmonary consolidation, disease resolution and fibrosis from chest X-rays and CT scans. This information at a higher accuracy and faster pace can assist timely stratification and resource allocation (Castiglioni et al. 2020).

A compiled representation of chest CT findings from severe and non-severe COVID-19 patients is depicted in Fig. 3. The figure shows significantly high prevalence of ground glass opacities and lung consolidation, fibrosis and air bronchogram in severe COVID-19 patients as compared with non-severe counterparts. Figure 2 also represents an increased prevalence of these measurement parameters during disease progression which dropped during the phase of recovery (Yun et al. 2021).

Though developers claim further investigation for AI-assisted prediction models, efforts like this are much required for high-speed clinical interventions before witnessing serious health effects.

**AI-enabled COVID-19 vaccine investigation**

The enormous predictive strength of AI has also been reflected as a potential aid in vaccine development for COVID-19. Many tools are being developed to thus enhance the laboratory efforts of vaccine development. The “AlphaFold”, a 3D structure prediction tool for genetic sequences, developed by Google DeepMind has predicted the structure and spike of SARS-CoV-2 enabling scientists to better understand their receptor binding and cellular entry. A researcher from the University of Texas at Austin, has also created a 3D atomic scale map to predict the spike protein. Many other efforts are also underway in this field so as to assist in the development of anti-viral components and vaccines (Bullock et al. 2020).

Another notable contribution by Inovio pharmaceuticals, in the generation of DNA-based vaccine called INO-4800. The technique has utilized viral genetic sequences to train the machine learning algorithm (Thanh et al. 2020). Similar approaches by Moderna therapeutics generated a modified messenger RNA (mRNA)-based vaccine called mRNA-1273 (Thanh et al. 2020), which has been currently approved in Switzerland and for emergency use in U.S., U.K., E.U., others (The New York Times 2021). Several other vaccine efforts like Comirnaty (Pfizer-BioNTech), AZD1222 (an Oxford-AstraZeneca effort) which are currently in clinical phase trial 2 and 3 have been approved by FDA for use in several countries (Information dated February, 2021) listed in Table 3 (The New York Times 2021). These approved vaccines were developed based on many strategies such as
Fig. 3 A retrospective investigation of chest CT findings to assist in COVID-19 patient stratification of severe and non-severe disease pattern. The chest CT findings presented in the figure shows 2 vital findings. The first major finding is that the prevalence of COVID-19 patients exhibiting conditions like ground glass opacities, lung consolidation, fibrosis and air bronchogram were higher during disease progression which dropped upon recovery phase of the disease. The 2nd major finding is that all the parameters (ground glass opacities, lung consolidation, fibrosis and air bronchogram) were higher in patients with severe disease pattern than non-severe disease pattern. From these evidences, an initial screening of COVID-19 patients using chest CT could be a beneficial strategy towards patient stratification.

Table 3 Table presents a list of COVID-19 vaccines, method of development and clinical approval status

| Vaccine            | Method of development | Status of clinical trial | Status of approval                  | Efficacy  | Country of origin | References                          |
|--------------------|-----------------------|--------------------------|------------------------------------|-----------|-------------------|-------------------------------------|
| Pfizer-BioNTech    | mRNA                  | 2, 3                     | Approved and emergency use         | 95%       | United States and Germany | The New York Times (2021)            |
| Moderna            | mRNA                  | 3                        | Approved and emergency use         | 94.5%     | United States     |                                     |
| Gamaleya           | Ad26, Ad5             | 3                        | Early and emergency use            | 91.6%     | Russia             |                                     |
| Oxford-AstraZeneca | ChAdOx1               | 2, 3                     | Emergency use                      | 82.4%     | United Kingdom and Sweden |                                     |
| CanSino            | Ad5                   | 3                        | Limited use                        | 91.6%     | China              | Logunov et al. (2021)               |
| Johnson & Johnson  | Ad26                  | 3                        | Not approved yet                   | 72%       | United States     | The New York Times (2021)           |
| Vector Institute   | Protein               | 3                        | Early use                          | 100%      | Russia             | Thomson Reuters (2021)              |
| Novavax            | Protein               | 3                        | Not yet approved                   | 89.3%     | United States     | The New York Times (2021)           |
| Sinopharm          | Inactivated           | 3                        | Approved and emergency use         | 79.34%    | China              |                                     |
| Sinovac            | Inactivated           | 3                        | Conditional approval and emergency use | 50.38% | China              |                                     |
| Bharat Biotech     | Inactivated           | 3                        | Emergency use                      |           | Unknown            | India                              |
mRNA, protein, inactivated viruses, etc. (The New York Times 2021). Many of these vaccines have utilized AI-enabled systems for initial screening for vaccine development to pace up the whole process of laboratory investigations and clinical trials thus developing solutions faster than expected.

Viral epidemics or pandemics usually experience multiple evolutionary stages with its nuclear material thus developing newer strains. Sometimes these new strains may be more infectious even than the original counterparts (Johns Hopkins University 2020a, b). These strains are a common pattern in any viral or bacterial outbreak before the invading organisms reach the state of non-infectiousness (Johns Hopkins University 2020a, b). Similarly, the 2019 pandemic also gave rise to newer strains of SARS-CoV-2 coronavirus detected in many parts of the world (Johns Hopkins University 2020a, b). A particular strain called B.1.1.7 was detected in southeastern England in September 2020 which soon became common in the United Kingdom, accounting for more than 60% of the new COVID-19 cases in December. Several other variants were also detected in areas including South Africa, Brazil, California and others. Unfortunately, several of these strains also alter the composition of the spike protein making them “stickier” (Johns Hopkins University 2020a, b).

More evidences are still required to understand the severity of the disease due to these new strains and most importantly, the efficacy of the current vaccines (Johns Hopkins University 2020a, b). However, many vaccine developers claim that some of these developed vaccines (e.g., mRNA vaccines) could still offer protection against the changing viral pattern and the spike protein but more evidences are still warranted (Johns Hopkins University 2020a, b).

Conclusions and future implications:
AI-enabled multilayer data analysis to assist COVID-19 and other global pandemics in the future

Some significant molecular markers and AI-enabled patient tracking, screening and disease detection approaches were discussed in the study. Each of these markers individually and together contribute to efficient patient stratification, prediction of disease severity and therapeutic interventions of COVID-19 as discussed in various sections of the article. With the use of integrated AI-enabled multilayer models, it could be possible to generate high-throughput outcomes from various data sources like clinical, pathological, DNA, RNA, proteome, metabolome, etc. With large data being accumulated over time in different COVID-19 patients and conditions, effective set of training instructions can be delivered to render more accurate predictions of unknown future events (Grapov et al. 2018). Since AI-assisted models function with minimal manual interventions, handling large cohorts under stressful circumstances becomes highly feasible (Davenport and Kalakota 2019; Rong et al. 2020; Azuaje 2019). Additionally, AI-enabled multilayer models can relieve biologists of complex data interpretations with the use of simpler visualizations for effective medical decisions (Chakraborty et al. 2017; Chin-Yee and Upshur 2019).

We at iNDX.Ai, are keenly enduring to investigate AI-enabled screening and prediction methods of COVID-19 infections for patient stratification, image analytics and drug discovery using our AI platforms namely iCE and iCore.

We signify that several such multomics efforts are collectively required to overcome the challenges of COVID-19 in treatment, long-term prevention, prognosis ad response prediction, risk analysis, surveillance, etc. which are also presented in Fig. 4. Thus, this article plays its substantial role in emphasizing the competencies of molecular biomarkers and AI-enabled multilayer model in COVID-19 pandemic interventions.

Author contributions GS: contributed to generation of figures, manuscript design and revision; SD: contributed to manuscript design and revision; KS: contributed to manuscript design and figure generation; AR: contributed to manuscript writing and revision; RC: contributed to manuscript revision and data compilation; MU: contributed to manuscript design and revision.
Availability of data and material Will be disclosed upon acceptance.

Code availability Will be disclosed upon acceptance.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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