How Might AI and Chest Imaging Help Unravel COVID-19's Mysteries?

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Summary Statement

Artificial intelligence (AI) has the potential to expand the role of chest imaging in COVID-19 beyond diagnosis to enable risk stratification, treatment monitoring, and discovery of novel therapeutic targets. AI's power to generate models from large volumes of information – fusing molecular, clinical, epidemiological, and imaging data – may accelerate solutions to detect, contain, and treat COVID-19.

Two healthcare workers fell ill in Wuhan, China, where the first Coronavirus Disease 2019 (COVID-19) case was reported. Both were 29 years old and were hospitalized after contracting the virus. One survived, the other died. In a global pandemic that has suddenly pushed doctors, scientists, and healthcare workers to the frontlines, why some patients are falling critically ill while others have minimal or no symptoms is one of the most mysterious aspects of the disease caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). COVID-19 mortality correlates with age, male gender, and some chronic medical conditions. Yet, young and previously healthy patients have succumbed to the virus, so there may be more complex prognostic factors beyond age. Mortality among COVID-19 patients rises with increased burden on healthcare resources available in the community [1], which can raise the stakes on an already strained healthcare system.

The standard test for diagnosis, reverse transcriptase polymerase chain reaction (RT-PCR) is designed to detect SARS-CoV-2 RNA in the acute phase of infection, but the false negative rate is high (39-61%) [2,40]. Limited testing, false negatives, atypical symptoms, and strain on healthcare systems have spurred debate on chest imaging as a screening tool. In the early COVID-19 outbreak in Chinese hospitals, chest imaging was used as an adjunctive tool to detect COVID-19 pneumonia [3]; it was considered readily available, highly cost-effective, and reliable.

Computed tomography to the rescue?

There is compelling evidence of lung pathology in COVID-19 pneumonia, but there are many more unanswered questions. Hallmarks of the disease include bilateral and peripheral ground glass opacities with lower lobe predominance, typically with a focal or rounded appearance [4]

[5]. Four to 14 days after symptom onset, linear opacities, greater lung involvement and consolidation, "reverse halo sign" and "crazy paving" are seen [4][5]. Interestingly, "crazy paving" is not a typical feature of viral pneumonia [6]. Moreover, it is curious that other findings typically seen in lung infections - such as tree-in-bud opacities from bronchial spread and lymphadenopathy – are not common in COVID-19 pneumonia [5]. Given its predilection for the lungs, two studies [7.8] have compared RT-PCR with CT imaging for COVID-19 screening. One reported higher sensitivity of non-contrast chest CT compared to RT-PCR (98% vs. 71%, $p<0.001$) [7]. Across 1014 cases, chest CT was reported to have a 97% sensitivity [8] in patients who underwent both in Wuhan, China. These results should be interpreted cautiously given potential selection bias, differential timing, and pre-test probabilities. Nonetheless, these results prompted more in-depth investigation of the role of CT imaging as a detection tool for COVID-19.

In China, a surge in chest imaging requests for suspected cases put human efficiency and accuracy to test. On one hand, there was increased need for high-throughput screening, yet the state of knowledge on imaging signatures in COVID-19 pneumonia was – and still is – evolving. Artificial intelligence (AI) could provide a stopgap while practicing radiologists understood and incorporated new findings into the diagnostic workflow. Not surprisingly, medical imaging researchers in China and around the world started deploying AI to address these challenges.

This article describes how AI has the potential to expand the role of chest imaging beyond the debatable realm of diagnosis to risk stratification, treatment monitoring, and potential discovery of novel therapeutic targets. Supported by large-scale data, AI can integrate information from molecular, medical, and epidemiological scales [9] to seek solutions for detecting, containing, and treating COVID-19.

The promise. The perils.

Many studies reporting high sensitivity [7,8] likely overestimate the ability of chest imaging to detect COVID-19, especially if appropriate blinding is not used. These studies were performed on a hospital population, introducing selection bias towards the sickest patients. In addition to study design limitations, not all COVID-19 cases are associated with chest pathology. In fact, more than half of patients imaged 0-2 days after symptom onset had a normal chest CT [4]. Many patients had normal CT scans on admission, with only a subset converting to positive imaging findings [10]. It seems that a normal chest CT does not preclude COVID-19, and at the same time, chest CT findings in COVID-19 can also be attributable to other etiologies. Finally, there are also practical considerations regarding allocation of imaging resources and contamination risk from scanners.

In a review of recent expert consensus statements, most advise against chest imaging for initial COVID-19 screening and diagnosis. These guidelines describe a role of CT imaging in COVID-19 patients with complications, cases of diagnostic uncertainty, and critical illness [6,11-13]. The latest guidelines from China's National Health Commission do not include chest imaging as part of the diagnostic criteria but mention its role in ascertaining lung pathology [14]. At the time of writing, most clinical guidelines recommend chest CT when alternate diagnosis is suspected or when COVID-19 testing is unavailable or highly restricted. Further evidence is needed to understand the role of diagnostic point-of-care ultrasound [15]. Despite these factors, there may be opportunities to identify biomarkers that predict disease earlier and more reliably. It is an active area of investigation whether these biomarkers exist and can aid the clinical process.

AI for COVID-19 diagnosis

Chest radiography

Two studies provide proof-of-concept for deep learning-based triage of COVID-19 cases. COVID-Net, an open-source deep convolutional neural network achieved 83.5% accuracy in classifying normal, bacterial pneumonia, non-COVID viral pneumonia, and COVID-19 viral pneumonia on 5941 PA chest radiographs (including 68 COVID images) [16]. Bayesian Convolutional Neural Networks (BCNN) can estimate the uncertainty in deep learning models for identifying positive COVID-19 cases from chest radiography [17].

Chest CT

Most AI studies on chest CT have sought to differentiate COVID-19 pneumonia from other causes of pneumonia in hospital populations. Study designs have included both three-class classification problems (COVID-19 pneumonia vs. other pneumonia vs. healthy) and two-class classification (COVID-19 pneumonia vs. healthy).

Regarding three-class problems, a 3D convolutional neural network achieved 86.7% accuracy in differentiating COVID-19 pneumonia vs. Influenza A vs. other [18]. The authors assessed diagnostic certainty of the system by generating confidence scores of these predictions - a strength of this work. Another study trained a deep learning system (DeepPneumonia) that could localize lesions and classify a patient within 30 seconds with a reported AUC of 0.99 for COVID-19 findings (the system is available online for academic use) on 88 COVID-19 patients from 2 hospitals, 101 bacterial pneumonia patients, and 86 healthy patients [19]. However, a common weakness of both studies was the relatively low number of imaging studies compared to the complexity of the models. The latter increases the risk of overfitting. However, there was one

study that utilized 4356 chest CT exams to develop COVNet, a 3D deep learning model. Per exam sensitivity and specificity for detecting COVID-19 was 90% and 96% and AUC was 0.96. The median period of symptom onset to first chest CT exam was 7 days [20].

Several studies examined two-class classification using both 2D and 3D deep learning models. Gozes et al. (2020) assigned both a heat map and "corona score" – volumetric measurement of opacity burden – which they posited could assess disease progression over time [21]. Another report achieved a classification accuracy of 79.3% in external validation on a study differentiating images from 180 viral pneumonia cases from 79 COVID-19 cases using a transfer learning neural network based on Inception network [22].

The studies described above were retrospective, but prospective studies can further validate AI systems in real-time and provide new quality metrics within a hospital setting. A prospective system in China using 1136 training cases from 5 hospitals (sensitivity 0.974 and specificity 0.922 on test set) was deployed in 16 hospitals and is performing over 1300 screenings/day. The model improved with more cases while performing real-time screenings, a strength of the approach [23]. Another study trained a deep learning model on 46,096 anonymous images and UNet++ for medical image segmentation [24]. This paper reported decreasing average reading time by 65% in prospective testing.

We identify several limitations of these studies, which can be overcome. First, the existing studies can be bolstered by including more patient data to increase power relative to the complexity of the prediction models. There is an unmet need to assign appropriate control groups given the concern of a protracted course of this pandemic into the upcoming flu season. Furthermore, the ability to identify COVID-19 pneumonia on imaging may depend on the timing of CT acquisition in the patient's disease course. In these cases, quantifying change in disease

may be more valuable than AI use for diagnosis. Next, as more data become available, these models can be evaluated for robustness. We strongly advocate open-source datasets and code to enable the broader community to train, test, and evaluate the sensitivity and specificity of machine learning classifiers. Second, true generalizability will need to be assessed in real-time in a prospective study design. Third, given the trade-off between sensitivity and specificity, metrics such as training accuracy, test accuracy, sensitivity, specificity, and predictive values may provide a more complete picture of classifier performance.

We recognize time is of the essence in pandemic management. AI systems need to be designed, validated, and deployed within a span of weeks to months. At the same time, patient privacy and security are top priorities. These factors may favor the use of existing AI platforms – either commercial or research – rather than the development of novel algorithms. Industry has an important role as well. For example, the Gozes et al. (2020) study included a collaboration with industry [21]. Developers may consider adapting AI platforms used in other domains for pandemic management.

The global race to contain, trace, detect, and treat COVID-19

How might AI expand the role of chest imaging from diagnosis to risk stratification, treatment monitoring, discovery of novel therapeutic targets, and possibly a cure?

Can trajectory of early imaging changes predict hospital course?

Hospital resource allocation is a real-time challenge. As most cases of COVID-19 are mild [3], identifying severe and critical cases early is crucial. Currently, an open question is whether specific chest imaging features can predict hospital course. Multiple studies reported that CT

findings may correlate with severity of symptoms, duration of illness, and even recovery [5] [8,25]. Furthermore, CT abnormalities may predate a positive RT-PCR test in both symptomatic and asymptomatic patients [8].

Already, studies have identified some chest CT features and clinical characteristics that portend worse prognosis in hospitalized patients. Hospital stays <10 days and those ≥10 days were discriminated by a machine-learning CT radiomics model using both logistic regression and random forest on 31 patients and 6 second-order features [26]. Patients were categorized into groups with and without malignant progression in a retrospective study of 133 mild COVID-19 patients hospitalized at Wuhan Pulmonary Hospital [27]. Multivariate logistic regression found 6 risk factors for detrimental progression: age>55 years, HTN, decreased albumin, lymphopenia, progressive consolidation, elevated hypersensitive C-reactive protein. Fibrosis was a protective factor. The model identified mild patients at risk of deterioration with 79.2% accuracy, with deep learning outperforming the logistic regression model [27]. Among 164 patients with confirmed COVID-19, where patients were divided into mild and severe groups based on clinical criteria, an AI pneumonia detection system found that severe cases were more likely to be associated with older age, round lesions, fan-shaped lesions, crazy paving, fibrosis, "white lung", pleural thickening, and enlarged mediastinal lymph nodes [28].

Deep learning techniques can perform automated segmentation and quantification of infection from chest CT regions [29]. Quantitative scores, such as a "corona score" [21] may provide new radiomic biomarkers with potential clinical utility to assess progression over time in hospitalized patients. Soon, AI could help uncover disease progression across different populations, such as in patients with chronic lung conditions and long-term smokers [5]. More studies are needed in this area to determine whether certain features of lung pathology as

assessed on computed tomography portend increased morbidity or mortality. Machine learning may indicate trends that predict ventilator requirement over the course of an ICU admission [30] and imaging findings may play in important future role in risk stratification.

Immune modulation in COVID-19 lung disease and potential imaging correlates

Cytokines mediate a delicate balance between protecting the lung from infection and damaging the lung in inflammation [31]. Immune-mediated inflammation appears to play a role in COVID-19 mortality, as severe cases can be associated with cytokine release syndrome (CRS) [32] and lymphopenia [33]. In fact, plasma and/or broncho-alveolar IL-6 levels are predictive of respiratory failure from acute respiratory distress syndrome (ARDS) [34], with respiratory failure the leading cause of mortality among COVID-19 pneumonia patients in Wuhan [35]. Navigating the intricate link between lung pathology and immune inflammation in COVID-19 is a potential strategy to mitigate lung damage. For instance, a proposed approach is to block IL-6 [32] along with other cytokines like IL-1 and TNF.

Further research is needed to understand the relationship between COVID-19 lung pathology and immune inflammation. Interestingly, there is evidence that lung pathology may wax and wane with aspects of disease trajectory. Radiological abnormalities peaked around day 10 followed by regression starting around 2 weeks after symptoms in a cohort of 21 patients [25]. Radiological improvement before RT-PCR became negative was observed in 42% of the patients recovering from COVID-19 pneumonia [8]. AI provides a prime opportunity for "data fusion" of lung pathologic information with immunological information, especially on mapping the respective trajectories during hospitalization. In the future, AI may help identify the

immunological markers most associated with poor clinical course, which may yield new targets for immune modulation in therapeutic trials.

Personalizing drug choice through predictive imaging biomarkers of treatment response

Several hundred clinical trials are currently underway across the world [36]. China has randomized controlled trials on tocilizumab (IL-6 receptor blocker) for patients with COVID-19 pneumonia and elevated IL-6 [37]. In the United States, the National Institutes of Health (NIH) is currently running a double-blind trial of remdesivir vs. placebo in COVID-19 patients with pneumonia and hypoxia [36]. Both hydroxychloroquine and chloroquine have in vitro activity against the COVID-19 virus [36]. As the evidence continues to evolve, we may find that different drugs are suited for different sub-populations of patients or spectrum of clinical disease.

The promise of AI lies in its ability to construct complex models from broad sources of data to identify customized therapeutic targets. AI has successfully harnessed radiomics to characterize biological underpinnings of various disease processes, such as cancer, to predict response to treatment [38]. Similarly, in COVID-19, if one or a few of these models can be validated prospectively, they could inform treatment algorithms and guidelines customized for patients along the spectrum of COVID-19 ranging from mild symptoms to death. Chest imaging is only a piece of that puzzle. Traditional clinical data sources include history, vital signs, lab tests, and imaging, but soon we may consider novel modalities such as geospatial information and textual processing of the scientific literature.

Although chest imaging is not presently recommended for initial diagnosis of COVID-19 pneumonia, the scale of the COVID-19 pandemic calls for dedicated research on diagnostic and therapeutic approaches that are robust, reliable, and rapid. Data-driven AI applications could

address this unmet need to allocate resources in a timely manner. Already, numerous AI-based systems were conducted, tested, and published in a matter of weeks from the onset of this pandemic. The medical community should promote a rapid development cycle for COVID-19-related AI while critically assessing risks in underlying methodology through existing biomedical imaging principles and practices. Promoting dataset and source code sharing in a standardized fashion would fulfill our community's ethical responsibility per the FAIR guiding principles, and also could save lives [39]. The common goal of international coalitions to build data repositories to fuel COVID-19 AI research should be coupled with adequate standardization, curation, and compliance with ethical responsibilities to honor patients' privacy. Adequate reporting of scanner and acquisition parameters, feature extraction algorithm, and use of external validation are key elements per the TRIPOD [41] statement and CLAIM guidelines [42]. Coupled with a large and growing body of tools, AI has the potential to expand the role of chest imaging beyond diagnosis to facilitate risk stratification, treatment monitoring, and discovery of novel therapeutic targets in this global race to contain and treat COVID-19.

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