Perspective

Integrating Artificial Intelligence in the Diagnosis of COPD Globally: A Way Forward

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Running Head: Integrating AI in the Diagnosis of COPD

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Abbreviations:
COPD- chronic obstructive pulmonary disorder
AI- artificial intelligence
PFT- pulmonary function test
CT- computer tomography
ML - machine learning
AUC – area under curve
GOLD- Global Initiative for Chronic Obstructive Lung Disease
ECLIPSE - Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
CanCOLD- Canadian Cohort Obstructive Lung Disease
mMRC- modified Medical Research Council dyspnea scale
IEAs- Image-Expression Axes
IEAemphysema - emphysema axis IEA
IEAAirway - airway axis IEA
SGRQ- St George Respiratory Questionnaire
HICs- high-income counties
WHO – World Health Organization
LMICs- low- and middle-income countries
TB- tuberculosis

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Abstract

The advancement of artificial intelligence (AI) capabilities has paved the way for a new frontier in medicine, which has the capability to reduce the burden of COPD globally. AI may reduce healthcare-associated expenses while potentially increasing diagnostic specificity, improving access to early COPD diagnosis, monitoring of COPD progression, and subsequent management. We evaluated how AI can be integrated into COPD diagnosis globally and leveraged in resource-constrained settings. AI has been explored in diagnosing and phenotyping COPD through auscultation, pulmonary function testing (PFT), and imaging. Clinician collaboration with AI increased performance of COPD diagnosis and highlights the important role of clinical decision-making in AI integration. Likewise, AI analysis of computer tomography (CT) imaging in large population-based cohorts has increased diagnostic ability, severity categorization, and prediction of outcomes related to COPD. Moreover, a multi-modality approach with CT imaging, demographic data, and spirometry has shown improvement in machine learning prediction of progression to COPD compared to each modality alone. Prior research has primarily been conducted in high-income country settings, which may lack transferability to a global population. AI is a World Health Organization priority with the potential to reduce healthcare barriers in low- and middle-income countries. We recommend a clinical collaboration between clinicians and an AI-supported multimodal approach to COPD diagnosis is a step towards achieving this. We believe the interplay of CT imaging, spirometry, biomarker, and sputum analysis may provide unique insights across settings that could provide a basis for clinical decision-making that includes early-intervention for those diagnosed with COPD.
Introduction

An estimated 328 million people have chronic obstructive pulmonary disease (COPD) worldwide, and COPD is expected to become the leading cause of death by 2030 [1]. The advancement of artificial intelligence capabilities has paved the way for a new frontier of medicine that has the potential to reduce morbidity and mortality rates associated with non-communicable diseases globally, including COPD. Artificial intelligence (AI) is defined as computers performing high order tasks that previously required human intellect and types of AI include machine learning (ML), deep learning, and artificial neural networks. There has been increasing uptake of AI due to its advantage of reliability, processing speeds, cost-effectiveness, ability to decipher complex issues, and skill to analyze large amounts of data issues [2]. AI has the potential to improve the efficiency and access to high quality healthcare services [3,4]. For this reason, the role of AI in medicine has generated significant interest, especially in the early detection of COPD progression in at-risk populations and diagnosis of COPD [5-9]. The question remains how can AI be integrated into COPD diagnosis globally and leveraged in resource-constrained settings?

Artificial Intelligence in COPD Diagnosis

AI is currently being explored in diagnosing and phenotyping COPD through auscultation, pulmonary function testing (PFT) and imaging. Deep learning analyzed 12-channel lung sounds on auscultation among 41 participants with varying levels of COPD severity in Turkey [10]. Altan and colleagues found high accuracy and classification performance above 94% with area under the curve (AUC) value of 0.9659 [10]. AI’s role in improving COPD identification and classification with a simple tool like auscultation that may be easily in resource-constrained settings. Moreover, a multicenter European intervention recently assessed preferential and
differential diagnostic accuracy of pulmonary function tests (PFTs) with collaboration between pulmonologists and explainable AI [11]. The authors found an overall increase in mean preferential and differential diagnosis percentage with the supplementation of AI compared to pulmonologists alone (p<0.0001). However, the supplementation of AI with pulmonologist expertise appeared deleterious to their diagnostic accuracy for some pulmonologists [11]. This highlights the importance of clinical expertise in clinical decision-making and in providing extensive training with AI framework before integrating in clinical settings. Additionally, further studies are ultimately warranted to see if clinical AI decision support technology improves longitudinally with AI integration in clinical settings.

Research integrating imaging modalities, such as computer tomography (CT), has been coupled with AI to monitor and stage COPD [7,8,11-13]. Hasenstab and colleagues have utilized CT quantification to measure the percentage of lung emphysema and air trapping as an emerging COPD diagnostic tool [7]. The CT machine learning model had similar performance in COPD staging as spirometry in Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging. Furthermore, CT imaging coupled with AI can provide utility in predicting COPD-related outcomes. An analysis including 8,983 participants from the COPDGene and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort studies used a deep learning approach to evaluate CT images among smokers with COPD [9]. Almost 50% of COPDGene participants were accurately GOLD staged and 75% were labeled within one GOLD stage [9]. This study characterized well-performing and calibrated AI models that could predict patients with COPD who were most likely to have COPD exacerbation events and those with highest mortality [9]. AI also classified these participants into emphysema categories to extrapolate and effectively predict performance on the 6-minute walk distance and
St. George’s Respiratory Questionnaire (SGRQ) measuring health-related quality of life [8]. AI can be a beneficial tool for characterizing unique aspects of imaging that are consistent with high-risk groups and patients with COPD. Therefore, AI analysis of CT imaging in patients with COPD can further be employed for overall risk stratification in clinical settings, which can have important implications on COPD management and treatment. Furthermore, AI analysis can inform progression and prognosis of COPD.

While these studies have shown promise in diagnosing, stratifying, and predicting outcomes of COPD, there are limitations to this approach. Unfortunately, AI algorithm utility can be constrained by data quality and quantity. The quality of AI models depends on the training data and these studies often lack patient diversity and can have small sample sizes. There is a need for larger prospective cohort studies recruiting diverse patient populations to increase quality and transferability to the general population. Many of these studies are secondary analyses of large prospective cohorts of patients with COPD risk factors (i.e., COPDGene, ECLIPSE, CanCOLD). Recognizing the limitations of AI can preclude its overuse and misuse, especially to prevent erroneous associations without appropriate clinical context. Clinicians should critically evaluate AI performance and results for clinical context. Clinician expertise can complement AI as a solution to this. A potential concern for some is the black box problem where only the input and output are understood. Learning by example is one of the most powerful and not fully comprehend forces that drive intelligence. For example, our brain recognizes patterns to understand experiences, but we don’t fully understand the neural networks taken to reach the designated outcome [14]. AI can be thought of in a similar manner. Nonetheless, it’s critical that clinicians provide substantial oversight to ensure proper use. Another concern of AI in overall COPD management is overdiagnosis. These imaging
studies often include analysis of CT imaging of COPD, which is not currently the standard of care and cost-prohibitive in some medical settings. However, the AUC value of CT imaging in identifying COPD was 0.89 and the positive predictive value was 0.847 in a sample of 2153 participants with CT imaging in the ECLIPSE cohort [15]. These results clearly depict the capacity to advance precision medicine with AI.

The Multi-Modal Diagnostic Approach

Although these studies highlight the potential of AI in imaging alone, using a multi-modality approach may further enhance COPD diagnostic capabilities and provide a solution to these cited limitations. A recent population-based study of the Canadian Cohort Obstructive Lung Disease (CanCOLD) cohort found that the combination of quantified CT imaging (texture-based radiomic features), demographic data, and spirometric measurements improved machine learning prediction of progression to COPD compared to each modality alone [12].

Similarly, biomarkers associated with lung abnormalities consistent with emphysema and airway-predominant COPD features may present as an avenue for AI to diagnose COPD and monitor COPD progression. A recent study by Chen and colleagues analyzed CT imaging and blood RNA-seq gene expression utilized deep learning to determine similarities in inflammatory patterns and lung structural changes called Image-Expression Axes (IEAs) in 1,223 participants from the COPDGene study [13]. The emphysema axis IEA (IEA\textsubscript{emphysema}) was associated with lower lung function, higher proportion of neutrophils, and radiological central emphysema. The airway axis IEA (IEA\textsubscript{airway}) was associated with thicker airways and higher white blood cell count. Participants classified as high IEA\textsubscript{emphysema}/IEA\textsubscript{airway} had worse outcomes including highest St. George Respiratory Questionnaire (SGRQ), highest modified Medical Research Council dyspnea scale (mMRC), and shortest 6-minute walk distance [13]. This study
distinguished multiple IEAs related to specific inflammatory pathways associated with emphysema and airway-predominant COPD. Emerging research combining CT imaging, blood transcriptomics and phenotypic data can be applied to AI to increase understanding of the influence of lung structure and systemic inflammatory mechanisms implicated in COPD. Therefore, the addition of sputum [16] and biomarker analysis [17] may be utilized in conjugation to the aforementioned features to further enhance the capabilities of AI to diagnose COPD and predict COPD exacerbations and outcomes. This information could be used as a prognostic indicator in COPD and implicated in the emerging “treatable trait” strategy in COPD treatment [18].

The Need and Utility of Artificial Intelligence in Low- and Middle-Income Countries

Globally, there is great interest in defining early-onset COPD among at-risk individuals (e.g., SPIROMICS Study of Early COPD Progression) and early detection of COPD in order to initiate timely treatment. The Lancet Commission’s *Towards the Elimination of COPD* similarly advocates for early identification of COPD among populations high-risk for developing COPD based on symptoms and risk factors using technology in LMIC healthcare systems [19]. The Lancet Commission calls for prevention and detection of early stage COPD using diagnostic methods such as blood and radiological biomarkers before irreversible changes have developed. Similarly, they suggest computer-assisted CT and biomarker interpretation with AI to increase the feasibility of implementation in resource-constrained settings [19]. However, most studies assessing AI capacities in COPD diagnosis have predominantly taken place in high-income counties (HICs). A recent scoping review of the use of AI for delivery of essential health services across World Health Organization (WHO) regions identified 81.3% (n=74) of studies occurring in HIC settings. Similarly, a systematic review of AI in COPD management found
63% (n=42) of studies occurred in HICs [20]. However, the burden of COPD is disproportionately concentrated in low- and middle-income countries (LMICs) [1]. There is a unique interplay of COPD risk factors in LMICs including biomass smoke exposure, ambient air pollution, malnutrition, prior tuberculosis infection, which may influence COPD phenotype. Therefore, studies in HICs may have reduced generalizability to global populations, specifically in LMICs due to significant variation in the COPD endotype and pathophysiology. Increasing inclusion of ethnic and COPD endotype diversity into AI-related research would allow greater transferability to the global population. For this reason, we advocate for population-based data collection in LMIC settings to generate an AI algorithm.

Many LMICs face barriers to high-quality healthcare delivery that include limited radiological equipment and shortage of long-term medical professionals, such as radiologists and pulmonologists [21]. Altogether this leads to high rates of under-diagnosis and misdiagnosis of COPD observed in national and international surveys in LMICs [22]. Moreover, prior research by the European Respiratory Society has shown that chest CT is as available or more available than spirometry in many global settings [18]. Therefore with radiological imaging AI can help reduce barriers of care by identifying negative radiological exams and labeling appropriate exams that require further review by the appropriate medical professionals. Additionally, this approach could be broadly integrated into other biological and clinical tests and exams. Using AI may help overcome the shortage of healthcare providers and may help improve patient care alike in LMICs. AI can assist in diagnosis and assessment of COPD to improve patient care and enhance diagnostic capabilities [5]. For example, AI technology has high sensitivity and specificity in the detection of tuberculosis (TB) through AI-supported detection of acid-fast stained TB bacillus, reducing the workload of healthcare workers and enhancing disease
surveillance in China and Pakistan [17,23]. AI has primarily been used primarily infectious
disease monitoring and management in LMICs with increasing use in non-communicable disease
interventions such as diabetes and cancer [23-26].

There are few studies to date in LMICs integrating AI in the diagnosis of COPD [4]. These limited studies include small sample sizes under 400 participants located in Turkey,
Brazil, India, China, and Bosnia and Herzegovina focusing on COPD diagnosis and
classification of COPD severity [27-31]. Most AI interventions focused on developing
algorithms to evaluate COPD decision support systems using demographic data, spirometry, and
biomarkers to collaborate with clinicians [27-31]. This further highlights the potential
acceptability and role of AI to support clinicians especially in resourced constrained settings.
These AI algorithms were highly accurate (over 80%) in diagnosing COPD and predicting
related outcomes such as acute exacerbation risk, disease severity indices, and hospitalization
[30,31]. Thus, we recognize the need for larger population-based studies in LMICs to build AI
infrastructure where the burden of COPD is higher and can have the greatest impact on the
global COPD burden.

**Applying and Integrating Artificial Intelligence in Clinical Practice**

COPD is the optimal condition for AI application due to its chronic progressive nature with
complex genetic and environmental interactions; fluctuating presentations over time; and vast
array of multimodal testing available. Clinician expertise and knowledge to provide patient-
specific COPD diagnosis is essential, AI will likely not be a replacement for clinical judgment
for the foreseeable future. Nonetheless, it is fundamental to develop an AI approach that can be
implemented in LMICs to help address barriers to high-quality healthcare. Prior research has
shown that ML can be effectively implemented in LMIC settings with robust routine health
information readily available but often underused [32,33]. AI infrastructure development in LMICs is currently supported by WHO and international organizations through capacity-building and training programs [34]. In fact, the World Health Organization (WHO) has recently made AI top priority calling for development and implementation of AI to address challenges in global settings [35]. WHO asserts that AI can improve clinical decision-making made by healthcare providers and assist in disease screening and evaluation in resource-constrained settings such as in LMICs [31]. To mitigate the growing burden of COPD in LMICs, a multivariate approach that utilizes available resources may be more effective. For example, utilizing sputum and biomarker analysis may provide unique insights to the lungs microbiome to facilitate COPD endotype diagnosis and risk assessment of COPD exacerbations that imaging may not detect alone. Not only may this approach improve clinical decision-making, but this approach is also typically low-cost.

We summarize our proposed approach to apply and integrate AI in clinical practice in Figure 1. We recommend an emphasis on improving access to quality healthcare services to diagnose COPD in resource-constrained settings such as in LMIC is of the utmost importance globally. We suggest clinical collaboration between clinicians with AI-supported multimodal approach to COPD diagnosis as a step towards achieving this. We believe the interplay of CT imaging, spirometry, biomarker analysis, and sputum analysis may provide unique insights across settings that could provide a basis for clinical decision-making that includes early-intervention for those diagnosed with COPD. Clinician expertise is irreplaceable and supplementing with AI technology can improve COPD endotypes classification and predict disease trajectory, which may improve COPD outcomes.
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Declaration of Interests

We have no competing interests to declare.
References


Figure 1. An approach to apply and integrate artificial intelligence in clinical practice.