Leveraging Computed Tomography Imaging to Detect Chronic Obstructive Pulmonary Disease and Concomitant Chronic Diseases

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Chronic obstructive pulmonary disease (COPD) is a global major public health problem (1). It affects nearly half a billion people worldwide and carries high morbidity and mortality rates (2). However, only 20–30% of adults living with COPD have been diagnosed with it (3). This underdiagnosis is associated with a substantial burden at the individual, societal, and healthcare-system levels. Compared with individuals without COPD, those with undiagnosed COPD experience more symptoms, worse quality of life, poorer work productivity, and higher mortality rates (4, 5).

The U.S. Preventive Services Task Force continues to recommend against population-based screening for COPD with spirometry in asymptomatic individuals (6). This recommendation should be interpreted with caution because the key word here is "asymptomatic," defined as "adults who do not recognize or report respiratory symptoms." However, patients with COPD often deny, minimize, or dismiss respiratory symptoms and may instead attribute them to aging, deconditioning, or excess weight. Further, they may limit their physical activity to avoid the discomfort associated with dyspnea. This has led to renewed calls to perform spirometry in asymptomatic individuals at risk of developing COPD such as those with a history of smoking or occupational and environmental exposures (7).

Although multiple COPD case-finding tools have been developed during the past 20 years, none have been broadly adopted in clinical practice (8). Chest computed tomography (CT) examinations are routinely ordered for many clinical indications, including lung cancer screening and pulmonary embolism evaluation. The U.S. Preventive Services Task Force and several medical societies recommend annual screening for lung cancer with low-dose chest CT in adults 50–80 years of age with at least a 20 pack-year smoking history who are still smoking or have quit smoking within the previous 15 years (some societies have no "years since quit" criterion) (9). This patient population is at higher risk for not only lung cancer, but also COPD. In fact, at least one third of individuals who meet the criteria for lung cancer screening have airflow obstruction on spirometry, most of whom have no prior diagnosis of COPD (10–12). Besides lung cancer, patients with COPD often experience other pulmonary, cardiovascular, and musculoskeletal conditions, some of which can be identified on chest CT (13, 14). The burden of comorbidities negatively impacts the survival and quality of life of patients with COPD as captured by instruments such as the COPD-specific Comorbidity Test and the Comorbidities in Chronic Obstructive Lung Disease Index (15, 16). Given the importance of non–lung cancer–related abnormalities on screening chest CT scans, the American College of Radiology developed a quick reference guide to describe common incidental findings and provide recommendations for their management (17). This guide notes that 18.8% of screening examinations had one or more "S" modifiers, indicating significant or potentially significant incidental findings.

Although case-finding tools for COPD and other chronic conditions may be time-consuming and challenging to implement in primary-care settings, radiology reports of chest CT scans are readily available and contain a wealth of information beyond the original clinical indication (e.g., lung cancer screening). However, physicians do not consistently act on this information, resulting

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in missed opportunities for the timely diagnosis and early treatment of COPD and comorbidities (18). In this perspective, we discuss: *1*) the potential of chest CT to identify and characterize undiagnosed COPD, *2*) the potential of chest CT to detect undiagnosed chronic conditions that often coexist with COPD (i.e., multimorbidity), and *3*) challenges and opportunities associated with leveraging chest CT data in clinical practice, including the role of artificial intelligence.

Leveraging Chest CT to Detect COPD

Emphysema

Emphysema is a hallmark lesion of COPD identified on chest CT as areas of low attenuation with accompanying vascular distortion and thinning (Figure 1A). In the Lung Screen Uptake Trial, the prevalence of emphysema of any severity was similar in participants with known COPD (73%) and those with undiagnosed COPD (68%) (10). In the Pittsburgh Lung Cancer Screening Study, 65% of participants with evidence of emphysema on low-dose CT had airflow obstruction on spirometry (19). Notably, only 12% of those with emphysema had neither airflow obstruction nor symptoms. Additionally, the presence of emphysema on CT in individuals without COPD is associated with progressive airflow obstruction and 10-year mortality (20, 21). A standardized visual scoring system for emphysema has been shown to help detect COPD and independently predict mortality, but such systems have not achieved wide use in clinical practice (22, 23). Quantifying emphysema using automated densitometry methods, which are currently available through many commercial companies, is an alternative (Figure 1B). In an analysis of the National Lung Screening Trial, quantitative emphysema $\geqslant$1% (using a threshold lower than −950 Hounsfield units [HU]) on low-dose CT showed good discriminative ability for airflow obstruction on spirometry (24). Because image noise on low-dose scans may simulate emphysema, processing techniques such as median filtering or kernel normalization may be necessary for more reproducible quantitative measurements (25, 26). These data strongly suggest that the detection of visual or quantitative emphysema on CT should prompt clinicians to order spirometry and assess for COPD risk factors and symptoms if this has not been done recently.

Airway Abnormalities

Chronic exposure to inhalational irritants results in several inflammatory and structural changes in the airways of patients with COPD, including smooth muscle enlargement, goblet cell hyperplasia, mucus gland hypertrophy, and airway wall fibrosis (27). These changes typically result in a disproportionately larger decrease in the airway lumen area relative to the decrease in the airway wall area (28). Therefore, the appearance of narrowed airways with thick walls on CT should raise suspicion for COPD (Figure 1C). However, visual assessment of airway morphology on CT is impacted by CT slice thickness and remains limited by significant interreader variability (29). Several quantitative measurement methods to evaluate segmental and

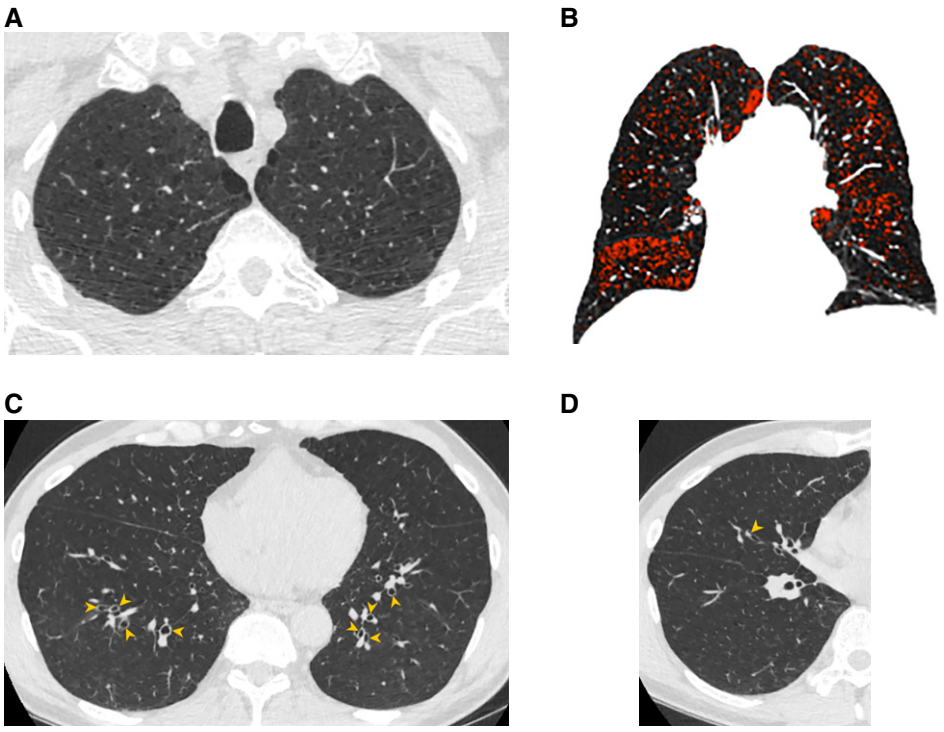

Figure 1. Examples of common chronic obstructive pulmonary disease–related findings on lung cancer screening computed tomography examinations: (*A*) mild upper-lobe centrilobular and paraseptal emphysema, (*B*) density map of same patient in *A* (coronal view) demonstrating that 9% of the total lung volume is affected by emphysema (shown in red) using an attenuation threshold of lower than −950 Hounsfield Units, (*C*) mild lower-lobe small-airway wall thickening with mild cylindrical bronchiectasis (arrowheads), and (*D*) subsegmental mucoid impaction (arrowhead) in the right middle lobe.

subsegmental airways have been developed and used in research. They are not widely adopted in clinical practice, partially because of the difficulty of their interpretation and the narrow range of their values across the spectrum of health and disease (30).

Mucus Plugging

CT evidence of airway mucus plugging is found in 40–70% of individuals with smoking-related COPD, and its severity is associated with lower lung function and higher 10-year mortality rates (Figure 1D) (31, 32). Interestingly, the presence of airway mucus plugs on CT is not consistently accompanied by clinical chronic bronchitis (33); in an analysis of the Subpopulations and Intermediate Outcome Measures in COPD Study, only 33% of participants with high CT mucus plug scores reported mucus-related symptoms (32). These findings indicate that, among patients with COPD, CT evidence of mucus plugging is highly prevalent, may be silent, is associated with more severe disease, and carries prognostic implications. Therefore, mucus plugs are not benign bystanders, and their mention on a radiology report should trigger a diagnostic evaluation for COPD and other airway diseases.

Air Trapping

Air trapping is common in COPD, asthma, and other respiratory diseases. It reflects disease at the level of the small airways and is best assessed on paired inspiratory and expiratory chest CT examinations to identify areas of lung that fail to empty or to become smaller on expiration. Air trapping may also be visible on inspiratory scans when a patient is unable to take a full breath in. Quantitatively, imaging tools are being applied to detect functional small-airway disease as a surrogate of nonemphysematous air trapping. These include Parametric Response Mapping, an analytic technique that measures point-by-point differences in lung density between coregistered inspiratory and expiratory scans (34). Individuals with COPD and mild airflow obstruction have a greater extent of functional small airway disease than those without COPD (35). Even younger individuals with a smoking history and no airflow obstruction have CT evidence of quantitative small-airway disease, the extent of which is associated with a subsequent decrease in FEV_1 (36). In a study of 1,140 male participants with low-dose inspiratory scans for lung cancer screening who also underwent expiratory scans, a model incorporating quantitative emphysema, quantitative air trapping (defined as the mean lung density expiratory-to-inspiratory ratio), smoking pack-years, smoking status, and body mass index had an area under the curve of 0.83 for COPD confirmed on spirometry (37). In a subsequent analysis of the same cohort, CT air trapping independently contributed to the diagnosis of COPD and had a modest incremental yield when combined with CT measurements of emphysema and bronchial wall thickness (38). Routine acquisition of expiratory scans as part of lung cancer screening is currently not recommended by any medical organization. The added value of this practice remains to be determined pending analysis of various visual and quantitative CT assessments of air trapping in diverse patient cohorts.

Leveraging Chest CT to Detect Concomitant Chronic Diseases in Patients with COPD

Interstitial Lung Disease and Interstitial Lung Abnormalities

Fibrotic interstitial lung disease (ILD) can occur with emphysema in a syndrome called combined pulmonary fibrosis and emphysema (CPFE) (Figure 2A) (39). The identification of concurrent interstitial fibrosis and emphysema on CT has important clinical implications for prognosis and management. Compared with patients with emphysema alone, those with CPFE have worse survival (40). In addition to the optimization of their COPD-related therapy, patients with CPFE should undergo evaluation and targeted management of their underlying ILD and be considered for antifibrotic therapy initiation, pulmonary hypertension assessment, and early lung transplantation referral as appropriate.

Even when extensive fibrosis is absent, interstitial lung abnormalities (ILAs) can be detected on CT. ILAs are nondependent ground-glass opacities, reticular abnormalities, traction bronchiectasis, honeycombing, or nonemphysematous cysts affecting $>5\%$ of any lung zone (41). ILAs are common in the general population and are associated with smoking history (42), with an estimated prevalence of 7% in lung cancer screening cohorts (43). Among patients with COPD, ILAs are associated with lower lung function, a higher incidence of COPD exacerbations, and higher mortality rates (44, 45). In a recent analysis of the COPDGene cohort, half of participants with ILAs had reduced FVC, reduced D_{LCO}, or definite lung fibrosis on CT, suggesting ILD (46). At a minimum, individuals with incidentally found ILAs should undergo a clinical evaluation for ILD, including measurement of spirometry and D_{LCO}. More research is needed to determine the best management and follow-up strategies for ILAs in the absence of ILD.

Bronchiectasis

Bronchiectasis, characterized by the pathologic dilation of airways and impaired mucus clearance, is common in patients with COPD (47). It may be a manifestation of the underlying COPD (as a continuum from mild airway wall thickening to severe bronchiectasis) or related to other coexisting pulmonary or systemic conditions (e.g., rheumatoid arthritis). It is identified on CT by the presence of dilated airways that do not taper toward the periphery of the chest and are often filled with mucus. Visual assessment of bronchiectasis on CT is subject to variability and has not been standardized. Recently developed quantitative metrics of bronchiectasis, such as an airway-to-artery ratio greater than 1, are attractive complementary tools that need to be further validated (48). Compared with patients with COPD without bronchiectasis, those with COPD and bronchiectasis have a higher risk of respiratory exacerbations and mortality (14, 47, 49). Clinical management includes evaluation of the etiology of the bronchiectasis, optimization of pharmacological and nonpharmacological mucus clearance therapies, and initiation of respiratory exacerbation prophylactic therapies as indicated.

Coronary Artery Disease

Coronary artery disease is common in individuals with COPD and is a leading cause of death in those with mild to moderate airflow obstruction (50). Additionally, fatal and nonfatal cardiovascular events often occur following COPD exacerbations (51). Coronary artery calcium (CAC) is one of the most common incidental findings on low-dose CT ordered for lung cancer screening (Figure 2B) (17). CAC severity can be assessed visually (none, mild, moderate, severe) or quantitatively through the Agatston score (52); both

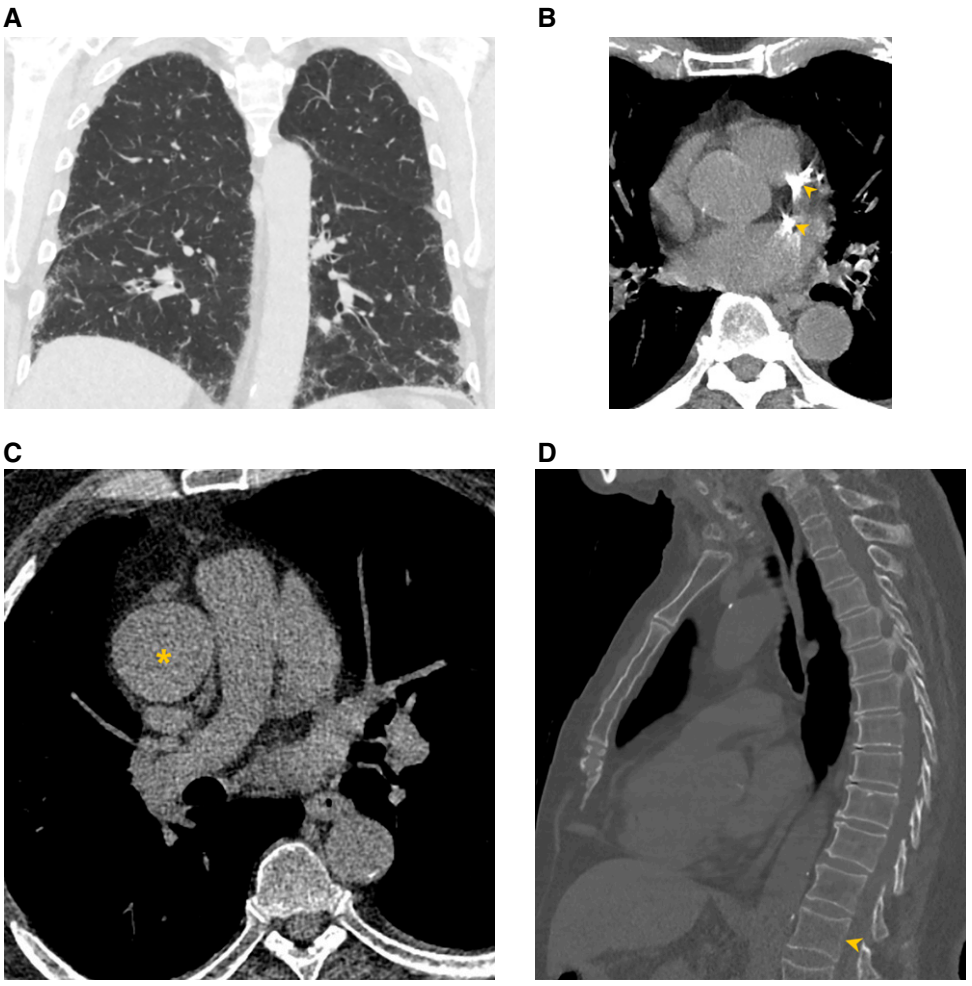

Figure 2. Examples of clinically significant non–chronic obstructive pulmonary disease–related findings on lung cancer screening computed tomography examinations: (*A*) mild lower lung–predominant fibrotic interstitial lung disease with emphysema, (*B*) severe coronary arterial calcification (arrowheads), (*C*) fusiform ascending aorta dilation (asterisk) measuring a maximum diameter of 44 mm, and (*D*) osteoporosis suggested based on severe diffuse bone demineralization with a density measurement of 57 Hounsfield Units in the L1 vertebral body (arrowhead).

methods have been found to be equivalent for the prediction of death due to coronary artery disease when applied to low-dose chest CT scans (53). The addition of CAC scoring to traditional risk factors significantly improved cardiovascular risk stratification and should be leveraged to guide patient care when available (54).

Pulmonary Hypertension

COPD can be complicated by pulmonary hypertension, which confers a worse prognosis. In patients with severe COPD, a ratio of the pulmonary artery diameter to the aorta diameter (PA:A) greater than 1 on CT was more accurate for the diagnosis of pulmonary hypertension confirmed on right heart catheterization than the pulmonary artery systolic pressure estimated on echocardiography (55). In analyses of the COPDGene cohort, a PA:A ratio greater than 1 was associated with higher risks of mortality and severe respiratory exacerbations in patients with COPD (56, 57). In the population-based Rotterdam study, the PA:A ratio on CT was also associated with mortality in individuals with COPD, but not in the older general population (58). Consideration should be given to the inclusion of the PA:A ratio in CT radiology reports of patients with COPD given its clinical implications with regard to risk stratification and pulmonary hypertension evaluation.

Thoracic Aortic Aneurysm

Individuals with COPD, especially those with emphysema, have larger thoracic aorta diameters than individuals without COPD (Figure 2C) (59). This association is maintained even after adjustment for demographic characteristics, anthropometric measurements, smoking history, and cardiovascular risk factors. Recommended ascending aorta diameter thresholds for surgical repair of asymptomatic aneurysms vary from 4.0 to 5.5 cm depending on the sporadic versus heritable nature of the aneurysm, rate of growth of the aneurysm, risk factors for aortic complications, and surgical center experience (60).

Osteoporosis

Patients with COPD are susceptible to osteoporosis as a result of cigarette smoking, decreased mobility, vitamin D deficiency, and inhaled and oral corticosteroid use. In a patient who is able to take a good inspiration or with hyperinflation, chest CT captures the vertebral column from at least the first thoracic to the first lumbar vertebral bodies

and can provide valuable information on bone mineral density and incidental compression fractures (61). In an analysis of the NELSON (Nederlands-Leuvens Longkanker Screenings On-derzoek) lung cancer screening trial, COPD was independently associated with lower vertebral bone mineral density on low-dose CT (62). In the American College of Radiology reference guide for incidental findings on lung cancer screening CT, an L1 vertebral body density $<$100 HU is consistent with osteoporosis, with a recommendation to consider dual-energy X-ray absorptiometry correlation (Figure 2D), whereas a density of 100–130 HU is used to define osteopenia (17). These recommendations are based on data correlating CT L1 vertebral body density measurements with bone densitometry (63). Although a chest CT scan ordered for lung cancer screening also conveniently helps to screen for osteoporosis, it remains to be determined whether a finding of low vertebral bone density on CT can obviate confirmatory dual-energy X-ray absorptiometry for the purposes of diagnosis and treatment.

Cachexia and Sarcopenia

At least one in five patients with COPD develop cachexia during their lifetime (64). Low body mass index alone does not fully capture the complexity of anthropometric parameters in relation to COPD severity (65). Muscle mass and density can be measured on CT and have significant prognostic implications in COPD. Other metabolic-related CT findings include epicardial fat and liver steatosis. Chest CT–derived pectoralis muscle area, erector spinae muscle area, and psoas muscle density are all independently inversely associated with mortality risk in patients with COPD (14, 66, 67). How to best incorporate such metrics into radiology reports and in the routine clinical care of patients with COPD should be further explored.

Challenges and Opportunities in Clinical Practice

Chest CT represents a unique opportunity as a "one-stop" test to detect various pulmonary and nonpulmonary conditions that may otherwise not be systematically assessed in patients with or at risk for COPD (e.g., coronary artery calcification, osteoporosis). Because additional findings revealed by CT are not consistently acted upon in clinical practice, there is an urgent need to develop and implement strategies to leverage visual and quantitative imaging data for improved detection of COPD and comorbidities. These strategies may include the standardization of radiology reports and the development of CT-based risk assessment tools that take end-user input into account. More specifically, these tools should be understandable by patients and provide pragmatic, actionable, and clinically meaningful information to physicians.

Personalized risk reports have the potential to alter physician and patient behavior. In a randomized controlled trial, patients with incidental CAC on chest CT were assigned to have a notification sent to them and their primary care provider or follow usual care (68). The notification included an image of the patient's CT scan highlighting areas of CAC and a reference to the American College of Cardiology/American Heart Association guidelines on the management of blood cholesterol. At 6 months, statin prescription rate (51.2% vs. 6.9%) and CAD testing (15.1% vs. 2.3%) were significantly higher in the notification arm compared with the usual care arm. In another pilot study of patients undergoing low-dose CT for lung cancer screening, personalized reports containing data on quantitative emphysema and information on the potential benefits of smoking cessation increased short-term readiness to quit smoking (69).

Ideally, CT findings related to COPD should not be examined individually. For the best diagnostic and prognostic performance, they should be leveraged simultaneously (e.g., emphysema, airway abnormalities, pulmonary vascular abnormalities) and combined automatically with other demographic and clinical characteristics (e.g., age, sex, smoking history, symptoms) that are readily available in electronic health records and Digital Imaging and Communications in Medicine files. The application of artificial intelligence to chest CT images may help fill this gap (70). Chest CT–based deep learning algorithms identified spirometrically defined COPD with good accuracy in proof-of-concept studies (71, 72). Their performance in staging the severity of COPD and predicting exacerbations and deaths was more modest but promising (71). Density, texture, and shape radiomics features of the lung parenchyma and airways detected COPD with areas under the curve of 0.90 and 0.87 on inspiratory standard-dose and low-dose scans, respectively (73). Chest CT–based deep learning algorithms are also being developed to estimate lung cancer risk and CAC score (74, 75).

The implementation of personalized CT reports and artificial intelligence CT applications comes with many challenges. These include cost, generalizability, impositions on radiologists' time, integration within standardized workflows, perceived value by patients and clinicians, and the differentiation of clinically meaningful findings from those that are not. Exploring these questions is important given the large, yet mostly untapped, potential of such applications.

Conclusions

Chest CT scans performed for lung cancer screening or other clinical indications contain a wealth of information that is largely ignored in clinical practice. These CT studies represent a unique opportunity to improve COPD diagnosis and care at a population level. Therefore, it is paramount to increase awareness among radiologists to consistently include incidental CT findings in reports. It is equally important to guide clinicians on how to determine the clinical relevance of these radiologic findings (e.g., ILAs, enlarged thoracic aorta) and how to best act on them. Health systems should make it a priority to standardize and streamline workflows to leverage the full potential of chest CT imaging in coordination with all stakeholders, including patients, primary care providers, pulmonologists, radiologists, and information technology specialists. ■

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