Respiration

Thematic Review Series

Respiration 2021;100:277–290
DOI: 10.1159/000513642

Received: April 23, 2020
Accepted: December 2, 2020
Published online: February 23, 2021

The Emerging Role of Quantification of Imaging for Assessing the Severity and Disease Activity of Emphysema, Airway Disease, and Interstitial Lung Disease

Jonathan Gerald Goldin

Department of Radiological Sciences, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA, USA

Keywords
Emphysema · Interstitial lung disease · Quantitative CT

Abstract
There has been an explosion of use for quantitative image analysis in the setting of lung disease due to advances in acquisition protocols and postprocessing technology, including machine and deep learning. Despite the plethora of published papers, it is important to understand which approach has clinical validation and can be used in clinical practice. This paper provides an introduction to quantitative image analysis techniques being used in the investigation of lung disease and focusses on the techniques that have a reasonable clinical validation for being used in clinical trials and patient care.

Introduction

Quantitative CT scanning was introduced in the 1980s, but in the last decade, there has been an explosion in the rate of development of both image acquisition and postprocessing technology, including machine and deep learning, resulting in novel investigation of both obstructive lung disease and interstitial lung disease (ILD) [1–3]. Volumetric thin-section CT imaging permits the assessment of lung volume, regional gas volume, lung parenchyma, fissures, bronchovascular structures, and functional parameters such as regional perfusion and ventilation. These predominantly CT-derived parameters have been used to detect, quantitate, and follow the structural abnormalities in emphysema airway disease and ILD. This in turn has resulted in a growing interest for rigorous validation of quantitative imaging measures in the setting of drug/device discovery as well as for clinical care of patients. Conventional magnetic resonance imaging (MRI) even with new ultrashort echo time imaging of the lung parenchyma remains challenging [4]. Using more advanced techniques with hyperpolarized gases, MRI provides unique strategies for evaluating pulmonary structure and function at the alveolar level. Recent changes in the commercial landscape of the hyperpolarized gas field may allow this innovative technology to potentially move into the clinical environment, but for now, it remains

From the Thematic Review Series: "Emerging Techniques in the World of Respiratory Imaging." Series Editors: Lowie E.G.W. Vanfleteren and Dirk-Jan Slebos.

Jonathan Gerald Goldin
Department of Radiological Sciences, Santa Monica-UCLA Medical Center
David Geffen School of Medicine at UCLA
1250 16th Street, Suite #2340, Santa Monica, CA 90404 (USA)
jgoldin@mednet.ucla.edu

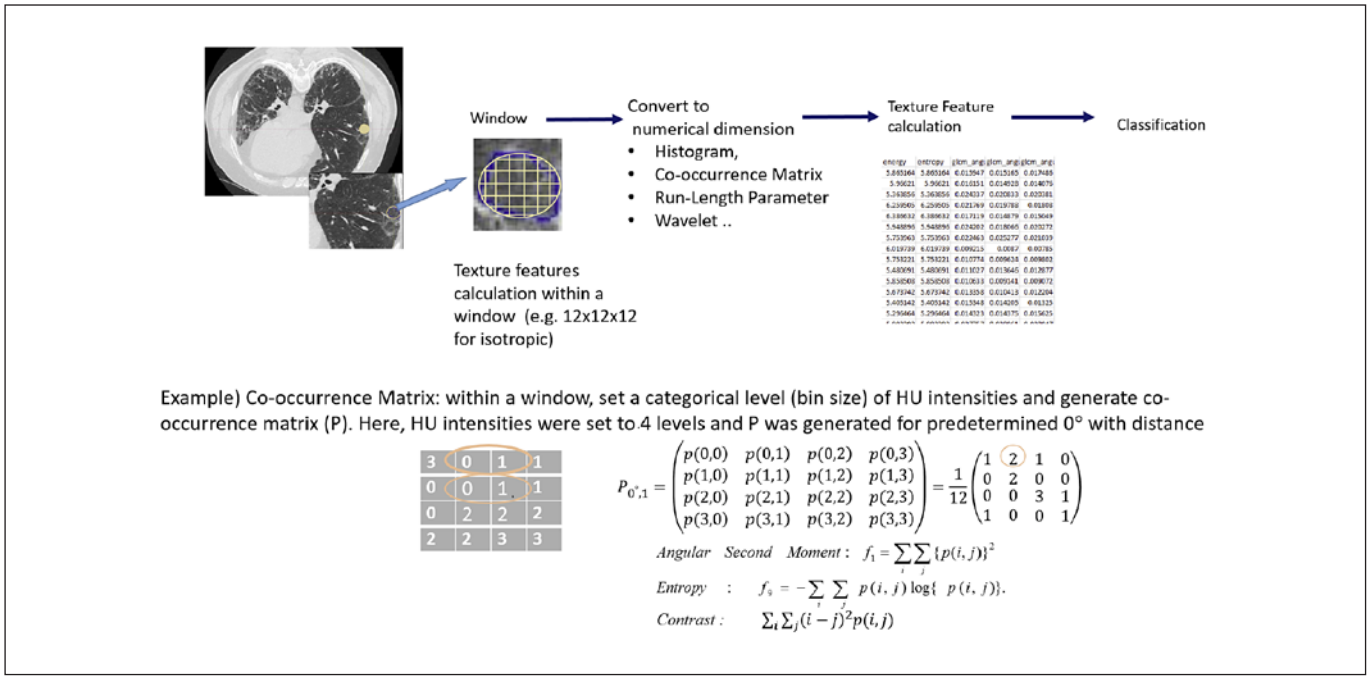


Fig. 1. The classification of a parenchymal abnormality can be extended beyond density measures by using texture analysis which takes into account the pattern, the spatial relationships between voxels, and the magnitude of attenuation. Texture features are derived from a region of interest converted to a numerical dimension, and the following calculation classification can be attributed to similar clusters of features. In a machine-learnt model, the classification is driven by visual classification of parenchymal pattern within the region of interest by an expert eye. Image courtesy of Grace Kim UCLA.

mostly a research tool [5]. This review summarizes the emerging role of quantitative image analysis (QIA) of chest CT for assessing the severity and disease activity of emphysema, airway disease, and ILD in routine clinical practice.

QIA Overview

Parenchyma

CT densitometry is the most established method of quantifying lung parenchyma on volumetric thin-section CT, acquired usually at total lung capacity (TLC). In the lung parenchyma, CT density measured in Hounsfield units (HU) is determined by the relative amounts of air, soft tissue, and blood in each volume element (voxel). Most scanner manufacturers now provide automated densitometry software, making density quantification more available. For the evaluation of ILD, the global histogram of lung density measures (skewness, kurtosis, and mean lung density) has been used. The deposition of interstitial and alveolar matrix results in an increase in lung density manifest by a rightward shift of the CT frequency histogram and reduction of its peak (i.e., increasing mean, skewness, and kurtosis) [6, 7]. For emphysema, these algorithms calculate the percentage of low-attenuation voxels at or below a given attenuation threshold, referred to as the percent emphysema or percent low-attenuation area. The optimal cutoff for thin-section CT is between −950 and −970 HU on the basis of comparisons with macroscopic and microscopic morphometry of pathologic specimens [8, 9]. Another approach to quantify emphysema is the "15th percentile" method or "Perc 15," which reports the HU at the lowest fifteenth percentile of a cumulative frequency distribution for all HU values [10, 11].

Low-attenuation voxels can be due to both parenchymal destruction and air trapping. As both can occur in COPD, it is important to evaluate each component. The densitometric parameters for quantification of air trapping include the ratio of expiratory to inspiratory mean lung density [12, 13], the expiratory to inspiratory relative volume change of voxels with attenuation between −860 and −950 HU [14, 15], and the percentage of voxels below −856 HU in expiration [16]. Volumetric nonrigid registration of inspiratory and expiratory allows biphasic

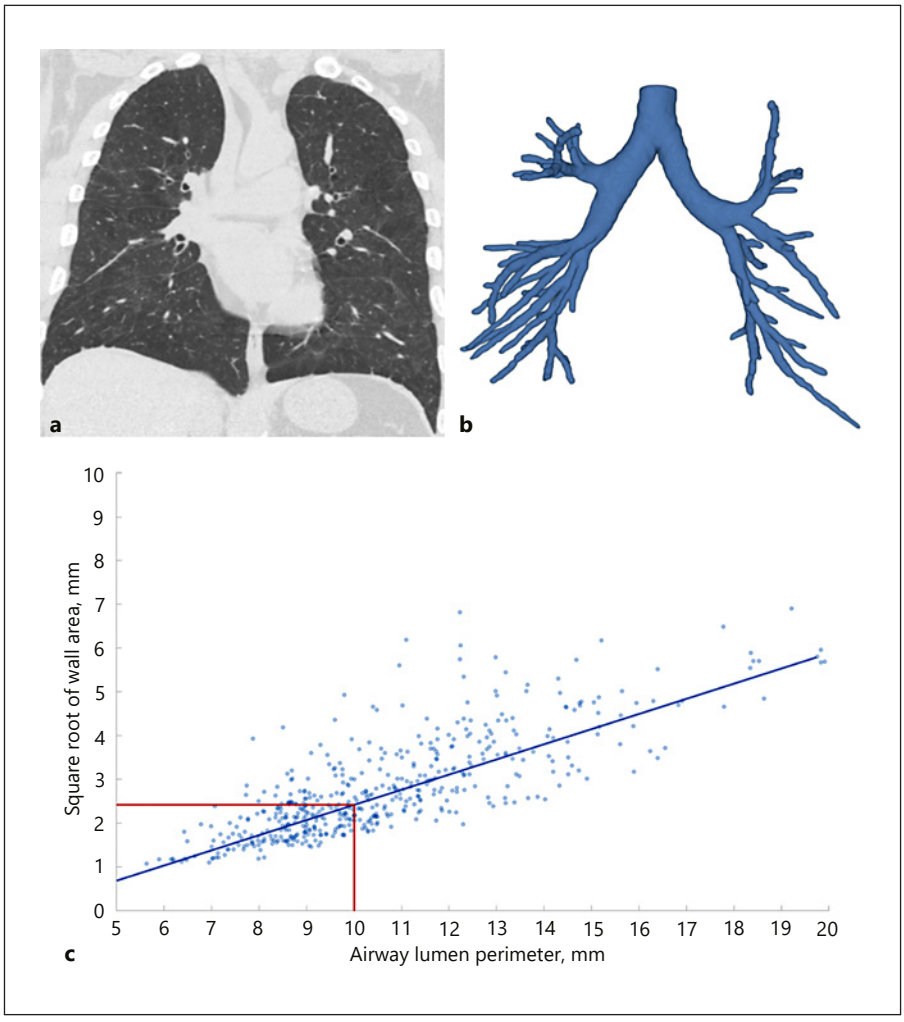


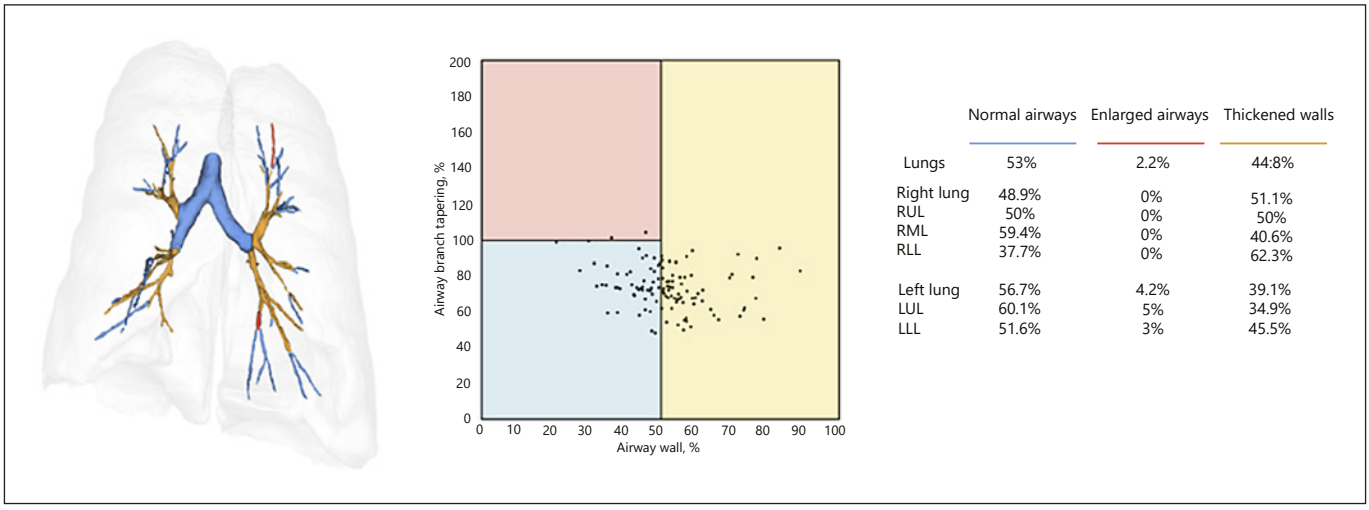
Fig. 2. The airways can be segmented to the level of the first 6 to 10 bronchial generations (**a**, **b**), from which measurements can be made using multiplanar reformatted images. The radiologic assessment of airway disease severity is more challenging due to the substantial variability in airway size within and between subjects, even among healthy individuals. To facilitate comparisons between individuals, a useful measure known as Pi10 which represents the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm has become popular. The Pi10 is based on the linear relationship between the square root of the airway wall area and the internal perimeter of the airway (**c**) (courtesy of Eva Van Rikxoort Thirona).

characterization of each voxel for quantification of air trapping. To address the overlap with air trapping and emphysema parametric, response mapping has been proposed. In this technique, volumetric nonrigid registration of inspiratory and expiratory enables biphase characterization of each voxel for classification and quantification of normal lung emphysema and air trapping [17–20].

Beyond density measures, texture analysis takes into account the pattern, the spatial relationships between voxels, and the magnitude of attenuation values to enable further characterization and quantitation of parenchymal pathology (Fig. 1) [21–23]. Methods such as run-length matrices, fractal measures, and gray-level co-occurrence matrices can be used to determine uniformity, shape, and other morphologically distinct features. In addition, different types of image filtration can be performed to remove noise, enhance edges, and emphasize or extract certain features. This can be used to suggest specific subtypes of emphysema or to differentiate among visually and pathologically distinct causes of diffuse low-attenuation areas, such as air trapping and other cystic lung processes. In the setting of diffuse lung disease, texture features can differentiate the characteristics of ground glass, reticulation with and without architectural destruction, and honeycomb cysts.

Airways

The airways can be segmented to the level of first 6 to 10 bronchial generations, from which measurements can be made using multiplanar reformatted images (Fig. 2) [24–34]. The common parameters obtained from airway measurements include the total bronchial area or outer airway wall area, the wall area, the internal or lumen area, and the wall thickness. The radiologic assessment of airway disease severity is more challenging due to the substantial variability in airway size within



	Normal airways	Enlarged airways	Thickened walls
Lungs	53%	2.2%	44:8%
Right lung	48.9%	0%	51.1%
RUL	50%	0%	50%
RML	59.4%	0%	40.6%
RLL	37.7%	0%	62.3%
Left lung	56.7%	4.2%	39.1%
LUL	60.1%	5%	34.9%
LLL	51.6%	3%	45.5%

Fig. 3. COPD is widely recognized as a complex heterogeneous syndrome including emphysema and airway disease. There has been increasing interest in including visual and QIA assessments of emphysema (CT density scores) and airways (direct airway and indirect air trapping) to better phenotype patients with COPD. Patients with airway-dominant phenotype are associated with increased chronic cough and exacerbations. In patients with COPD, there is an increased number of airways with thickened walls but not dilated lumens as shown visually in this tribox plot, and the number of thickened airways can be expressed as the percentage of airways within the lung or lobe to show the distribution and heterogeneity of the airway involvement (courtesy of Eva Van Rikxoort Thirona). QIA, quantitative image analysis.

and between subjects, even among healthy individuals. To facilitate comparisons between individuals, a useful measure known as Pi10 which represents the square root of the wall area for a hypothetical airway with an internal perimeter of 10 mm has become popular. The Pi10 is based on the linear relationship between the square root of the airway wall area and the internal perimeter of the airway (Fig. 3) [33, 35]. Functional respiratory imaging is a postprocessing technology that utilizes computational fluid dynamics to assess airway volume and resistance [36]. Despite a lot of work, the reproducibility, clinical validity, and ease of use of airway measurements remain challenging, and they have not been widely used in the clinical setting.

Blood Vessels

New QCT methods are being developed to assess vessel structure and perfusion to better understand the relationship between these changes, emphysema and ILD. Several approaches exist for automated vessel segmentation allowing for some measurements including total cross-sectional area, volume of the small vessels (3D), and the ratio of blood vessel volume in vessels <5 mm^2 in cross section (BV5) to total blood vessel volume (as a measure of pruning). Cross-sectional area of subsegmental small pulmonary vessels has been shown to correlate with the extent of CT density measures of emphysema and reflects difference between COPD phenotypes [37, 38]. The volume of segmented pulmonary vessels, including arteries and veins but excluding vessels at the hilum, expressed as a percentage of lung volume has been proposed as an independent measure of IPF severity [39–41]. Beyond structure perfusion can be assessed using dual-energy CT. This has led to the identification of regional perfusion heterogeneity within subjects with the same pattern and can be used to monitor and document reversible vasoconstriction[42, 43]. The clinical significance of these findings still needs to be clarified.

Fissures

The fissures subdivide the human lungs into different lobes, and air may flow through between lobes resulting in interlobar collateral ventilation (Fig. 4) [44]. Identifying the fissures is achieved using an anatomic knowledge-based model (usually airways and vessel trees), gray-level, and shape information [45–49]. The assessment of the completeness or integrity of fissures, as a biomarker for collateral flow, was first applied in a subgroup analysis of subjects undergoing endobronchial valve (EBV) placement for treatment of emphysema [45]. In this prespecified analysis, patients with a fissure integrity score >90% of the fissure abutting the treatment lobe were shown to

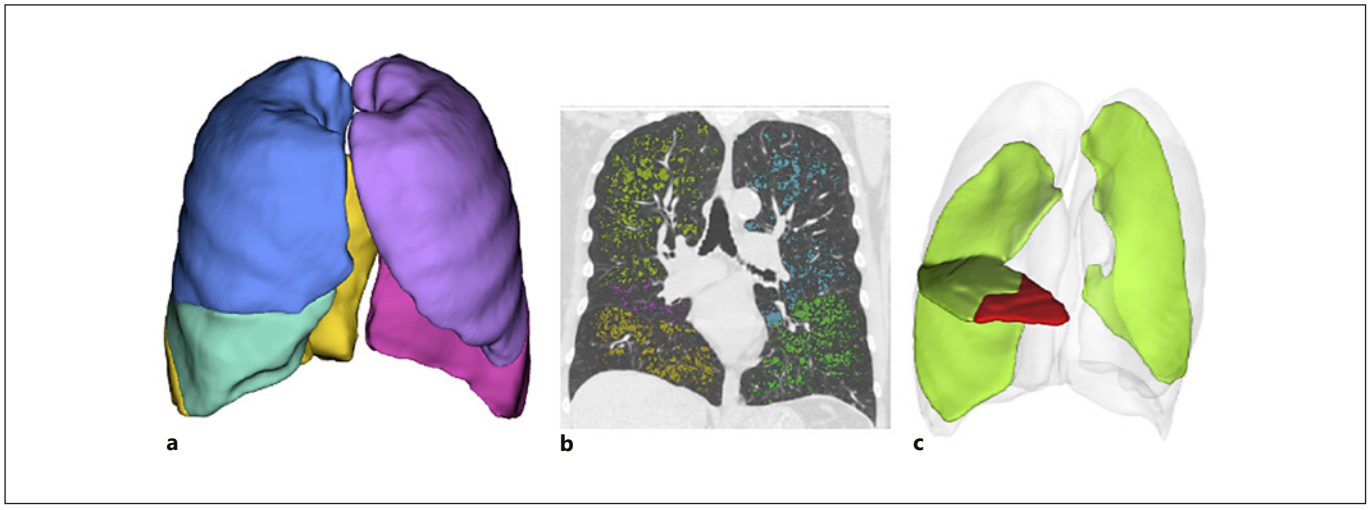


Fig. 4. For the selection of subjects for EBV, QCT is an essential component of both patient selection and lobe selection for treatment. Using automated algorithms, the lungs are segmented to the lobar level (**a**), the fissure integrity or completeness is measured using a second algorithm (**b**) (incomplete coverage shown in red for minor fissure), and the percentage of pixels below −920 and/or −950 HU (depending on valve manufacture guidelines) in each lobe (shown by the pixel overlay) is calculated to assess disease severity in each lobe and the homogeneity in disease destruction between upper and lower lobes (**c**) (courtesy of Eva Van Rixoort Thirona). EBV, endobronchial valve.

have significant improvement in their forced expiratory volume in 1 s (FEV1) compared to those whose FIS was <90% [41]. The majority of automated fissure detection methods use feature descriptors targeted toward normal fissure anatomy [46–56]. Validation of fissure integrity, as a marker for collateral flow between lobes, has been confirmed both indirectly by improved treatment outcome as well as directly from local flow measurements within the lobes [57–60]. There is no relationship between fissure integrity and type or extent of emphysema and association between fissure integrity and pulmonary function measures, such as FEV1 and FEV1/FVC [61–64].

Ventilation/Perfusion

MRI using hyperpolarized gases allows direct visualization of the airspaces of the lung and provides for evaluation of pulmonary structure and function. Recent studies in humans using hyperpolarized ^{3}He and increasingly the more available hyperpolarized ^{3}XE to measure ventilation, diffusion, and partial pressure of oxygen have been useful [65–75]. Inhaled ^{3}Xe is also readily dissolvable in lung tissue allowing for the evaluation of gas exchange, uptake, and transport [76]. While still very much limited to centers of expertise, recent advances in gas polarization technology make it increasingly feasible to deploy these techniques into the clinical setting [77].

QIA Assessing the Severity and Disease Activity of Emphysema

COPD Phenotypes

COPD is widely recognized as a complex heterogeneous syndrome including emphysema and airway disease. There has been increasing interest in including visual and QIA assessments of emphysema (CT density scores) and airways (direct airway and indirect air trapping) to better phenotype patients with COPD [78, 79]. These approaches have classified patients into emphysema or airway-dominant and mixed phenotypes with variable proportions of patients falling into these categories in different COPD populations [80, 81]. The emphysema-dominant CT phenotypes have been shown to correlate with different pulmonary function parameters [82], body mass index [83], dyspnea severity [84], exacerbations [85], rapid decline of FEV1 [86], and pulmonary-related mortality [87]. Patients with airway-dominant phenotype are associated with increased chronic cough and exacerbations [88]. The mixed phenotype has shown associations with more severe dyspnea and more frequent hospitalizations than the other CT-based phenotypes [89]. The relationships of these phenotypes with clinical parameters and outcome measures have however varied between different studies suggesting a need to reach a consensus on the most appropriate method for quantifying emphysema and airways in COPD studies.

Quality of Life and Symptom Measures

CT density measures of emphysema extent have correlated with several QOL tools including the ST Georges Respiratory Questionnaire (SGRQ), multidimensional *Body Mass Index, Airflow Obstruction, Dyspnea, Exercise* (BODE) score, and Medical Research Council (MRC) tool. Increased CT density scores reflecting increased parenchymal destruction have been shown to be predictive of clinically significant changes in these scores [90–95]. Interestingly, airway-predominant disease phenotype cohorts are associated more strongly with changes in the SGRQ, while emphysema-predominant phenotype shows more changes with BODE. Increased dyspnea has been independently associated with both emphysema and airway disease identified on chest CT scans of subjects with COPD [96, 97]. Even among individuals without COPD, emphysema on chest CT has been associated with dyspnea. Airway wall thickening (Pi10) has been associated with higher COPD Assessment Test scores, and the patient reported presence of cough, wheeze, and sputum [96–100].

Lung Function

CT density measures of emphysema are for the most part inversely correlated with both absolute and percent-predicted FEV1 [101–103], although there is heterogeneity in the published data. Much of the heterogeneity is due to differences in acquisition parameters, as well as differences in segmentation and quantitation algorithms [103]. The importance of standardized noncontrast thin-section CT performed at suspended full inspiration is very important. CT density and gas transfer measures are also significantly correlated with the variation again being reduced by standardizing for CT acquisition parameters. Functional respiratory imaging is an alternative approach for observing changes in airway volume and resistance and has been shown to be more sensitive than FEV1 [104, 105]. CT-based measures of TLC demonstrate good correlation with TLC measured by plethysmography, the former may be underestimated, particularly in the presence of air trapping [106, 107]. Thus, a normal TLC on chest CT suggests the absence of restrictive lung physiology, and a high TLC likely indicates the presence of hyperinflation.

Longitudinal studies designed to evaluate lung function decline have found CT density measures are independently associated with the rate of annual FEV1 decrease. Functional small airway disease on parametric response mapping has also been correlated with lung function decline in patients with emphysema. CT measures of small airway abnormality have been demonstrated in current and former smokers even without spirometric evidence of obstruction. These results suggest that subjects with mild to moderate COPD and smokers with preserved pulmonary function who have evidence of emphysema or air trapping on chest CT may be at increased risk for disease progression.

Collateral Ventilation

Quantitative CT analysis of fissure integrity or completeness has been shown to be a useful surrogate measure of collateral ventilation in selecting patients for endobronchial treatment of emphysema (Fig. 1) [50, 108–110]. QCT Fissure Integrity Score (FIS) has been validated in this setting using the Chartis device, which directly measures collateral flow and treatment outcome defined as target lobe value reduction (TLVR) ≥350 mL [111]. Patients with an incomplete fissure (and thus significant CV) have a significantly lower benefit from valve treatment, as the occluded lobe can be backfilled with air through the collateral channels [111, 112]. The accuracy for correctly classifying and predicting therapeutic TLVR with EBV was similar for physiologic measurement using the Chartis system and structure assessment of fissures on HRCT. Patients with TLVR ≥350 mL had statistically significant improvement in respiratory function, exercise performance, and quality of life measures [60, 111–114]. More recent data support the use of quantitative CT measurements to screen in patients for further analysis and/or treatment with fissure completeness [56, 104, 113]. The QCT evaluation is noninvasive and thus is increasingly used as the screening test of choice.

Exacerbations

QCT measures of emphysema extent, change in emphysema extent score, airway lumen, and wall thickness have been shown to be associated with an increase in annual COPD exacerbation rate and duration irrespective of degree of spirometry measure airflow limitation in the COPD gene study [88, 115–118]. Another QCT measure of the ratio of the pulmonary artery diameter to the aorta diameter >1 has also been demonstrated to be a strong and independent predictor of severe exacerbations, even when adjusted for lung function and prior history of exacerbations [119].

Mortality

A higher CT density score for emphysema reflecting increased amount of emphysema is a significant independent predictor of all-cause, respiratory, or cardiovascular

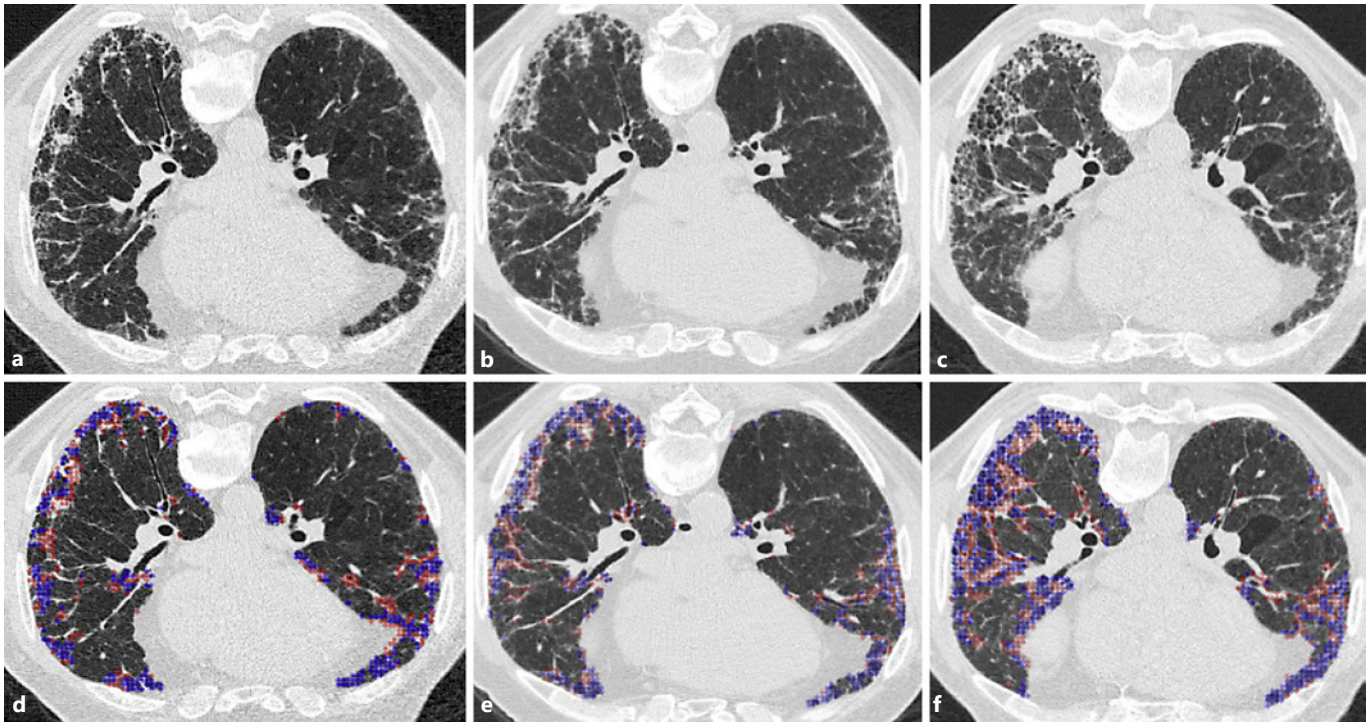


Fig. 5. QLF can be used to measure the extent of fibrosis at baseline and also the change in fibrosis over time. A case of an 81-year-old male with IPF with baseline and follow-up with clear progression HRCT longitudinal TLC scans (top): baseline (**a**), 1 year (**b**), and 2 years (**c**); overlays of color QLF (blue + red) score at baseline QLF 9% (415 mL) (**d**), 1-year QLF 14% (581 mL) (**e**), and 2-year QLF 31% (1102 mL) (**f**); image courtesy of Grace Kim UCLA. TLC, total lung capacity.

mortality in smokers with and, notably, without COPD [87, 120–122]. This is true for both visual and quantitative assessments of emphysema. There is a well-documented relationship between QCT emphysema scores and the Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise (BODE) index, a well-validated predictor of mortality in subjects with COPD [87, 99, 123–127]. This relationship is strongest with FEV1, but there are independent significant relationships between emphysema and the other BODE components including body mass index, modified Medical Research Council dyspnea scale (mMRC), and exercise tolerance as measured by the 6-min walk distance (6MWD). The relationship between quantitative measures and patient outcomes in COPD is less well defined. In one study, a relationship between segmental wall area percentage and BODE score was demonstrated, albeit it is much weaker than the relation with quantitative emphysema measures [128]. However, in other studies, airway wall thickness as measured by Pi10 was not associated with increased mortality. The extent of bronchiectasis has been shown to be associated with decreased survival in patients with COPD [87, 124].

Drug and Device Discovery

QCT has the potential to offer new biomarkers to accelerate drug discovery through either enriching cohorts based on CT phenotypes or offering more specific regional measures not possible with conventional techniques. The most validated of these biomarkers is the use of CT density measures for assessing therapy in the setting of alpha-1 antitrypsin deficiency patients. In 2 trials, changes in CT density were the primary outcome measure [129, 130]. The Perc CT density measure was a log-transformed and volume-adjusted study. The duration of this study was 2–3 years, and the rate of density decline was measured in g/L^{-1} per year. In these studies, only a low-to-moderate correlation between CT density and FEV1, KCO, and exercise tolerance was shown, further emphasizing role of CT density as an independent biomarker. QCT has also been used to enrich cohorts for trials evaluating EBV therapies by assessing extent of emphysema fissure integrity scores to ensure target lobes were good candidates for therapy. Also, TLVR has been used as a measure of successful lobar volume reduction with an MICD of 350 mLs proposed as meaningful treatment response.

Interstitial Lung Disease

ILD Phenotype

HRCT is an essential component of an initial ILD evaluation and also has become part of the armamentarium of tools used for routine management of these patients. The visual pattern and distribution of fibrosis on HRCT diagnosis is a standard method for diagnosing the nature of the clinical diagnosis and outcome [131–135]. However, radiologic evaluation of ILD and further characterization of pulmonary fibrosis can be difficult even for the subspecialist radiologist. Studies have found only fair to moderate interobserver agreement for overall CT classification of pulmonary fibrosis [136, 137]. Machine-learnt texture feature algorithms have been shown to be powerful in distinguishing between normal parenchyma and abnormal parenchymal patterns due to fibrosis and ground glass (Fig. 5) [138, 139]. More recently, deep learning techniques have been shown to classify fibrotic lung disease with essentially equivalent performance to subspecialist radiologists [140]. These approaches may strengthen our ability to make predictions regarding outcomes in patients with ILD, such as response to specific therapies and mortality, which could substantially improve patient management [7, 140, 141].

Physiology

The relationship between pulmonary function tests and QCT measures of diffuse lung disease has been shown both at a single point intime and changes overtime. Several machine-learnt algorithms have shown an inverse relationship between the quantitated extent of fibrosis and forced viFVC measures on spirometry. In the setting of scleroderma lung, a similar relationship has been shown between the extent of lung involvement and DLCO [142]. Change in texture-based and QCT scores has been shown to correlate with changes in forced vital capacity (FVC). Interestingly, change in QCT texture measures after 4–6 months has been shown to predict >10 FVC decline at 12–18 months [143]. In this context, it is feasible that parenchymal changes occur prior to deterioration of pulmonary function tests. This has led to the increased use of CT to follow-up patients with diffuse lung disease, with the additional advantage of being able to better assess disease progression in patients with coexistent emphysema, since PFTs may be confounded by this overlap.

The GAP (gender, age, and physiology) model has been developed to improve the prognostication for patients with IPF. The addition of QCT measures of fibrosis extent has been shown to further improve the prognostication over the conventional model [7]. This suggests that QCT measures of structural abnormalities representing fibrosis are measuring additional attributes of the disease process that add to the evaluation of these patients. QCT fibrosis score has also been shown to be an alternative to DLCO diffusion capacity of carbon in a modified GAP assessment maybe offering a simpler method for determining risk of death in patients with IPF.

Mortality

IPF has a poor prognosis, with an overall median survival time of approximately 3 years [144, 145]. Predicting which course a patient's disease will take remains a difficult challenge for clinicians and researchers [146–148]. A greater extent of fibrotic changes on HRCT is known to be predictive of mortality across the spectrum of ILD including IPF, RA-ILD, SSc-ILD, chronic HP, pulmonary sarcoidosis [149], and unclassifiable ILD [150]. The extent of fibrosis by several QCT measures has been consistently associated with survival in patients with IPF [151, 152]. The extent of emphysema at CT (i.e., the emphysema score) also has been associated with survival in patients with IPF; however, the findings are less consistent among studies. Using QCT in addition to PFTs provides more tangible evidence to help monitor patients with IPF, guide treatment decisions, and plan for transplant or palliative care.

Drug Discovery

QCT methods for quantifying disease on HRCT could provide rapid, objective measurement of disease extent and change over time. In recent years, some of these tools have been used to analyze CT imaging data in clinical trials both retrospectively and prospectively [153–157]. For QCT measures to be used as biomarkers for drug or device efficacy, the algorithms must be stable. There must be cutpoints defined for the detection of disease and established predictive or surrogate outcome measures of disease. For treatment efficacy to be assessed, the derived measure of disease extent must have algorithms that are stable and have established cutoff points for meaningful change. This requires extensive clinical validation beyond the initial development and analytic validation. Almost all the algorithms have initial analytic validation within the setting of a drug trial and few have had extensive clinical validation, but clearly this is an area of active research [149].

Clinical Application of QCT

The implementation of QCT into clinical practice requires that the workflow be optimized from scan request

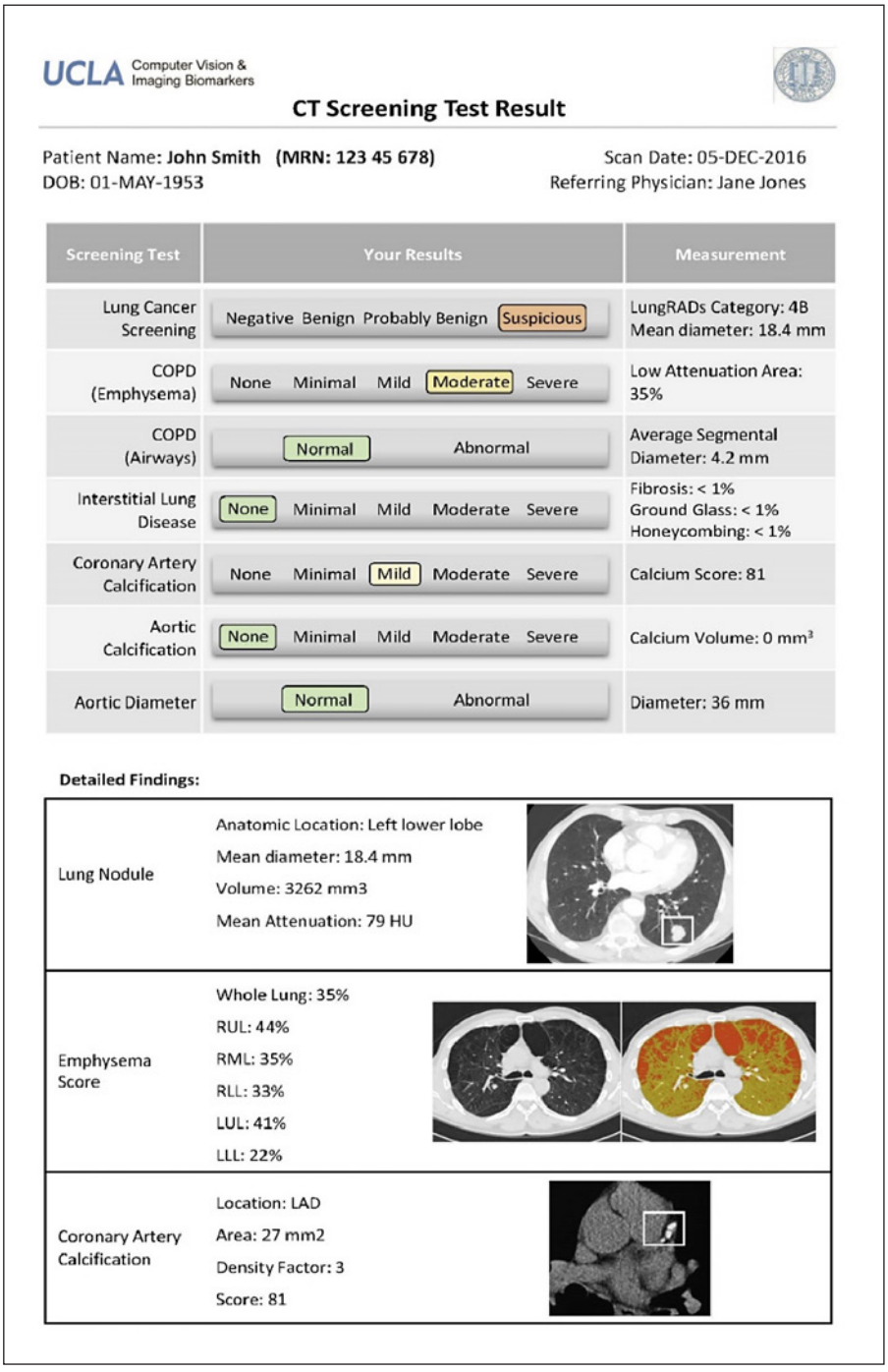


Fig. 6. QCT is being used increasingly in patient care outside of the clinical trial setting. CT chest reports are evolving from the traditional descriptive report with sometimes subjective qualitative estimate for disease burden by the radiologist to an automated report multiple algorithms running simultaneously to measure and populate a report with the information needed for clinical care. An example of this is shown in the QCT report for chest CT studies in which the different findings are presented in a table with easy-to-identify normal and abnormal results, measures, and index image.

through image acquisition, analysis, and workflow. It is important that referring clinicians identify the clinical question to be addressed by the imaging and not simply order an imaging study. The acquisition protocol to perform quantitative analysis needs to be performed using the correct set of parameters including usually noncontrast, thin section <1 mm, and nonenhancing reconstruction Kernel [158, 159]. It is important to acquire the images at the correct suspended lung volume usually TLC for parenchyma measures of disease, functional residual capacity for airway measurements, or at residual volume for assessment of air trapping [160]. Follow-up studies to assess

change should be performed on the same CT machine if possible and with the same acquisition parameters and breathold. Artifacts such as patient motion, beam hardening, variation in inspiratory effort, differences in image acquisition and reconstruction techniques, or inaccurate preprocessing steps such as segmentation of anatomic structures affect accuracy and reproducibility of measures. The imaging chain should be automated to allow image processing, including segmentation and quantitative analysis, to be performed before the images are reviewed and reported on [161]. Ideally, the report should be structured to easily capture and depict the quantitative data (Fig. 3).

Conclusion

Increasingly, quantitative chest CT is finding application in routine clinical care of patients (Fig. 6). Clinicians need to understand the different measures available from a plethora of software applications. They also must understand which algorithms have robust clinical validation, so that they can be used safely in clinical practice. It is important that standardized good-quality CT studies are acquired, requiring clear communication between clinicians and radiologists. This communication will ensure that the correct CT study is performed and the correct quantitative measures are made to answer the clinical question.

Conflict of Interest Statement

There are no conflicts of interest.

Funding Sources

The author did not receive any funding.

References

1 Hayhurst MD, MacNee W, Flenley DC, Wright D, McLean A, Lamb D, et al. Diagnosis of pulmonary emphysema by computerised tomography. Lancet. 1984;2(8398):320–2.
2 Hoffman EA, Sinak LJ, Robb RA, Ritman EL. Noninvasive quantitative imaging of shape and volume of lungs. J Appl Physiol Respir Environ Exerc Physiol. 1983;54(5):1414–21.
3 Riemuller RK, Behr J, Kalender WA, Schatzl M, Altman M, Merin M, et al. Standardized quantitative high resolution CT in lung disease. J Comput Assist Tomogr. 1991;15:742–9.
4 Ohno Y, Koyama H, Yoshikawa T, Matsumoto K, Takahashi M, Van Cauteren M, et al. T2* measurements of 3-T MRI with ultrashort TEs: capabilities of pulmonary function assessment and clinical stage classification in smokers. AJR Am J Roentgenol. 2011;197(2):W279–85.
5 Kern AL, Vogel-Claussen J. Hyperpolarized gas MRI in pulmonology. Br J Radiol. 2018 Apr;91(1084):20170647.
6 Best AC, Lynch AM, Bozic CM, Miller D, Grunwald GK, Lynch DA. Quantitative CT indexes in idiopathic pulmonary fibrosis: relationship with physiologic impartment. Radiology. 2003;228:407–14.
7 Kim HJ, Brown MS, Chong D, Gjertson DW, Lu P, Kim HJ, et al. Comparison of the quantitative CT imaging biomarkers of idiopathic pulmonary fibrosis at baseline and early change with an interval of 7 months. Acad Radiol. 2015;22(1):70–80.
8 Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med. 1995;152(2):653–7.
9 Madani A, Zanen J, de Maertelaer V, Gevenois PA. Pulmonary emphysema: objective quantification at multi-detector row CT-comparison with macroscopic and microscopic morphometry. Radiology. 2006;238:1036–43.
10 Shaker SB, Dirksen A, Laursen LC, Maltbaek N, Christensen L, Sander U, et al. Short-term reproducibility of computed tomography-based lung density measurements in alpha-1 antitrypsin deficiency and smokers with emphysema. Acta Radiol. 2004;45(4):424–30.
11 Newell JD Jr, Hogg JC, Snider GL. Report of a workshop: quantitative computed tomography scanning in longitudinal studies of emphysema. Eur Respir J. 2004;23(5):769–75.
12 Eda S, Kubo K, Fujimoto K, Matsuzawa Y, Sekiguchi M, Sakai F. The relations between expiratory chest CT using helical CT and pulmonary function tests in emphysema. Am J Respir Crit Care Med. 1997;155(4):1290–4.
13 O'Donnell RA, Peebles C, Ward JA, Daraker A, Angco G, Brobert P, et al. Relationship between peripheral airway dysfunction, airway obstruction, and neutrophilic inflammation in COPD. Thorax. 2004;59:837–42.
14 Matsuoka S, Kurihara Y, Yagihashi K, Hoshino M, Watanabe N, Nakajima Y. Quantitative assessment of air trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. AJR Am J Roentgenol. 2008;190(3):762–9.
15 Hersh CP, Washko GR, Estepar RS, Lutz S, Friedman PJ, Han MK, et al. COPDGene Investigators: paired inspiratory-expiratory chest CT scans to assess for small airways disease in COPD. Respir Res. 2013 Apr 8;14:42.
16 Yuan R, Nagao T, Paré PD, Hogg JC, Sin DD, Elliott MW, et al. Quantification of lung surface area using computed tomography. Respir Res. 2010;11:153.
17 Gaban CJ, Han MK, Boes JL, Chughtal KA, Meyer CR, Johnson TD, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and diseases progression. Nat Med. 2012 Nov;18(11):1711–5.
18 Hoff BA, Pompe E, Galbán S, Postma DS, Lammers JJ, ten Hacken NHT, et al. CT-based local distribution metric improves characterization of COPD. Sci Rep. 2017;7(1):2999.
19 Labaki W, Gu T, Murray S, Hatt C, Galban C, Ross B, et al. Voxel wise longitudinal parametric response mapping analysis of chest computed tomography in smokers. 2019 Feb 18.
20 Murphy K, van Ginneken B, Reinhardt JM, Kabus S, Ding K, Deng X, et al. Evaluation of registration methods on thoracic CT: the EMPIRE 10-challenge. IEEE Trans Med Imaging. 2011;30:1901–20.
21 Nuzhnaya T, Ling VMH, Kohn M, Steiner. R: classification of texture patterns in CT lung imaging. Proceedings Volume 7963, Medical Imaging 2011, Computer Aided Diagnosis; 796336 (2011).
22 Uppaluri R, Hoffman EA, Sonka M, Hartley PG, Hunninghake GW, McLennan G. Computer recognition of regional lung disease patterns. Am J Respir Crit Care Med. 1999;160(2):648–54.

23 Xu Y, Sonka M, McLennan G, Guo J, Hoffman EA. MDCT-based 3-D texture classification of emphysema and early smoking related lung pathologies. IEEE Trans Med Imaging. 2006;25(4):464–75.
24 Palagyi K, Tschirren J, Sonka M. Quantitative analysis of intrathoracic airway frees: methods and validation. Inf Process Med Imaging. 2003;18:222–33.
25 Tschirren J, McLennan G, Palágyi K, Hoffman EA, Sonka M. Matching and anatomical labeling of human airway tree. IEEE Trans Med Imaging. 2005;24(12):1540–7.
26 Saba OI, Hoffman EA, Reinhardt JM. Maximizing quantitative accuracy of lung airway lumen and well measures obtained from X-ray CT imaging. J Appl Physiol. 2003;95:1063–75.
27 King GG, Muller NL, Whittall KP, Xiang QS, Pare PD. An analysis algorithm for measuring airway lumen and wall areas from high-resolution computed tomographic data. Am J Respir Crit Care Med. 2000;161:574–80.
28 Nakano Y, Whittal KP, Kalloger SE, Coxson HO, Pare PD. Development and validation of human airway analysis algorithm using multidetector row CT. Proc SPIE. 2002;4683:460–9.
29 Reinhardt JM, D'Souza ND, Hoffman EA. Accurate measurement of intrathoracic airways. IEEE Trans Med Imaging. 1997;16(6):820–7.
30 Tschirren J, Hoffman EA, McLennan G, Sonka M. Intrathoracic airway trees: segmentation and airway morphology analysis from low-dose CT scans. IEEE Trans Med Imaging. 2005;24(12):1529–39.
31 Niimi A, Matsumoto H, Amitani R, Nakano Y, Mishima M, Minakuchi M, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. Am J Respir Crit Care Med. 2000;162(4 Pt 1):1518–23.
32 Nishimura M. Application of three-dimensional airway algorithms in a clinical study. Proc Am Thorac Soc. 2008;5(9):910–4.
33 Nakano Y, Wong JC, de Jong PA, Buzatu L, Nagao T, Coxson HO, et al. The prediction of small airway dimensions using computed tomography. Am J Respir Crit Care Med. 2005;171(2):142–6.
34 Hasegawa M, Nasuhara Y, Onodera Y, Makita H, Nagai K, Fuke S, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;173(12):1309–15.
35 Mets OM, Schmidt M, Buckens CF, Gondrie MJ, Isgum I, Oudkerk M, et al. Diagnosis of chronic obstructive pulmonary disease in lung cancer screening computed tomography scans: independent contribution of emphysema, air trapping and bronchial wall thickening. Respir Res. 2013;14:59.
36 De Backer JW, Vos WG, Vinchurkar SC, Claes R, Drollmann A, Wulfrank D, et al. Validation of computational fluid dynamics in CT-based airway models with SPECT/CT. Radiology. 2010;257(3):854–62.
37 Matsuoka S, Washko GR, Dransfield MT, Yamashiro T, San Jose Estepar R, Diaz A, et al. Quantitative CT measurement of cross-sectional area of small pulmonary vessel in COPD: correlations with emphysema and airflow limitation. Acad Radiol. 2010;17(1):93.
38 Yu N, Wei X, Li Y, Deng L, Jin CW, Guo Y. Computed tomography quantification of pulmonary vessels in chronic obstructive pulmonary disease as identified by 3D automated approach. Medicine. 2016;95(40):e5095.
39 Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J. 2017;49(1):1601011.
40 Puxeddu E, Cavalli F, Pezzuto G, Teodori E, Rogliani P. Impact of pulmonary vascular volume on mortality in IPF: It is time to reconsider the role of vasculature in disease pathogenesis and progression? Eur Res J. 2017;49:1602345.
41 Jacob J, Nicholson AG, Wells AU, Hansell DM. Impact of pulmonary vascular volume on mortality in IPF: is it time to reconsider the role of vasculature in disease pathogenesis and progression? Eur Respir J. 2017;49(2):1602524.
42 Iyer KS, Newell JD Jr, Jin D, Fuld MK, Saha PK, Hansdottir S, et al. Quantitative dual-energy computed tomography supports a vascular etiology of smoking-induced inflammatory lung disease. Am J Respir Crit Care Med. 2016 Mar 15;193(6):652–61.
43 Alford SK, van Beek EJ, McLennan G, Hoffman EA. Heterogeneity of pulmonary perfusion as a mechanistic image-based phenotype in emphysema susceptible smokers. Proc Natl Acad Sci U S A. 2010 Apr 20;107(16):7485–90.
44 Hogg JC, Macklem PT, Thurlbeck WM. The resistance of collateral channels in excised human lungs. J Clin Invest. 1969;48(3):421–31.
45 Ukil S, Reinhardt JM. Anatomy-guided lung lobe segmentation in x-ray CT images. IEEE Trans Med Imaging. 2008;28(2):202–14.
46 Doel T, Matin TN, Gleeson FV, Gavaghan DJ, Grau V. Pulmonary lobe segmentation from CT images using fissureness airways, vessels and multilevel b-splines, in Biomedical Imaging (ISBI). In: 2012 9th IEEE International Symposium on, 2012. p. 1491–4.
47 Lassen B, van Rikxoort EM, Schmidt M, Kerkstra S, van Ginneken B, Kuhnigk JM. Automatic segmentation of the pulmonary lobes from chest CT scans based on fissures, vessels, and bronchi. IEEE Trans Med Imaging. 2013;32(2):210–22.
48 Van Rikxoort EM, van Ginneken B, Klik M, Prokop M. Supervised enhancement filters: application to fissure detection on chest CT scans. IEEE Trans Med Imaging. 2008;27(1):1–10.
49 Ross JC, Kindlmann GL, Okajima Y, Hatabu H, Díaz AA, Silverman EK, et al. Pulmonary lobe segmentation based on ridge surface sampling and shape model fitting. Med Phys. 2013;40(12):121903.
50 Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med. 2010;363(13):1233–44.
51 Pu J, Leader JK, Zheng B, Knollmann F, Fuhrman C, Sciurba FC, et al. A computational geometry approach to automated pulmonary fissure segmentation in CT examinations. IEEE Trans Med Imaging. 2009;28(5):710–9.
52 Pu J, Fuhrman C, Durick J, Leader JK, Klym A, Sciurba FC, et al. Computerized assessment of pulmonary fissure integrity using high resolution CT. Med Phys. 2010;37(9):4661–72.
53 Pu J, Zheng B, Leader JK, Fuhrman C, Knollmann F, Klym A, et al. Pulmonary lobe segmentation in CT examinations using implicit surface fitting. IEEE Trans Med Imaging. 2009;28(12):1986–96.
54 Mahmut M, Nishitani H. Evaluation of pulmonary lobe variations using multidetector row computed tomography. J Comput Assist Tomogr. 2007;31(6):956–60.
55 Gu S, Wilson D, Wang Z, Bigbee WL, Siegfried J, Gur D, et al. Identification of pulmonary fissures using a piecewise plane fitting algorithm. Comput Med Imaging Graph. 2012 Oct;36(7):560–71.
56 Lassen-Schmidt BC, Kuhnigk JM, Konrad O, van Ginneken B, van Rikxoort EM. Fast interactive segmentation of the pulmonary lobes from thoracic computed tomography data. Phys Med Biol. 2017 Jul;62(16):6649–65.
57 Van Rikxoort EM, Goldin JG, Galperin-Aizenberg M, Abtin F, Kim HJ, Lu P, et al. A method for the automatic quantification of the completeness of pulmonary fissures: evaluation in a database of subjects with severe emphysema. Eur Radiol. 2011 Oct 7;22(2):302–9.
58 Koster TD, Slebos DJ. The fissure: interlobar collateral ventilation and implications for endoscopic therapy in emphysema. Int J Chron Obstruct Pulmon Dis. 2016;11:765–73.
59 Gomplemann D, Eberhart R, Slebos DJ, Brown MS, Abtin F, Kim HJ, et al. Diagnostic performance comparison of the Chartis System and high-resolution computerized tomography fissure analysis for planning endoscopic lung volume reduction. Respirology. 2014 May;19(4):524–30.
60 Koster TD, van Rikxoort EM, Huebner RH, Doellinger F, Klooster K, Charbonnier JP, et al. Predicting lung volume reduction after endobronchial valve therapy is maximized using a combination of diagnostic tools. Respiration. 2016;92(3):150–7.
61 Higuchi T, Reed A, Oto T, Holsworth L, Ellis S, Bailey MJ, et al. Relation of interlobar collaterals to radiological heterogeneity in severe emphysema. Thorax. 2006;61(5):409–13.

62 Magnussen H, Kramer MR, Kirsten AM, Marquette C, Valipour A, Stanzel F, et al. Effect of fissure integrity on lung volume reduction using a polymer sealant in advanced emphysema. Thorax. 2012;67(4):302–8.
63 Gompelmann D, Eberhardt R, Herth FJ. Collateral ventilation. Respiration. 2013;85(6):515–20.
64 Muller J, Lim HJ, Eichinger M, Jobst BJ, Eberhardt R, Gompelman D, et al. Influence of fissure integrity on quantitative CT and emphysema distribution in emphysema-type COPD using a dedicated COPD software. Eur J Radiol. 2017 Oct;95:293–9.
65 Patz S, Hersman FW, Muradian I, Hrovat MI, Ruset IC, Ketel S, et al. Hyperpolarized 129Xe MRI: a viable functional lung imaging modality? Eur J Radiol. 2007;64:335–44.
66 Patz S, Muradian I, Hrovat MI, Ruset IC, Topulos G, Covrig SD, et al. Human pulmonary imaging and spectroscopy with hyperpolarized 129Xe at 0.2T. Acad Radiol. 2008;15:713–27.
67 Kaushik SS, Cleveland ZI, Cofer GP, Metz G, Beaver D, Nouls J, et al. Diffusion-weighted hyperpolarized 129Xe MRI in healthy volunteers and subjects with chronic obstructive pulmonary disease. Magn Reson Med. 2001;65(4):1154–65.
68 Altes TA, Mugler JP, Dregely IM, Ketel S, Ruset IC, de Lange EE, et al. Hyperpolarized xenon-129 ventilation MRI: preliminary results in normal subjects and patients with lung disease (abstract). In: Proc 18th Annual Meeting ISMRM. Stockholm; 2010. p. 2529.
69 Driehuys B, Cleveland ZI, Nouls J, Kaushik SS, Cofer GP, Jimenez-Martinez S, et al. Quantitative scoring of hyperpolarized 129Xe ventilation imaging: correlation with pulmonary function testing and age (abstract). In: Proc 19th Annual Meeting ISMRM. Montreal; 2011. p. 550.
70 Wang C, Mugler JP, de Lange EE, Rupport K, Herman W, Dregely IM, et al. Measurement of the diffusion of hyperpolarized 129Xe in human lungs over short and long time scales during one breath hold (abstract). In: Proc 18th Annual Meeting ISMRM. Stockholm; 2010. p. 2543.
71 Miller GW, Mugler JP, Altes TA, Russet IC, Mata JF, Qing K, et al. Motion-corrected pO2 mapping in human lungs using hyperpolarized Xe-129 MRI (abstract). In: Proc 18th Annual Meeting ISMRM. Stockholm; 2010. p. 2558.
72 MacFall JR, Charles HC, Black RD, Middleton H, Swartz JC, Saam B, et al. Human lung air spaces: potential for MR imaging with hyperpolarized He-3. Radiology. 1996;200(2):553–8.
73 Yablonsky DA, Sukstantanskii AL, Leawoods JC, Gierada DS, Bretthorst GL, Lefrak SS, et al. Quantitative in vivo assessment of lung microstructure at the alveolar level with hyperpolarized 3He diffusion MRI. Proc Natl Acad Sci U S A. 2002;99:3111–6.
74 Swift AJ, Wild JM, Fichele S, Woodhouse N, Fleming S, Waterhouse J, et al. Emphysematous changes and normal variation in smokers and COPD patients using diffusion 3He MRI. Eur J Radiol. 2005;54(3):352–8.
75 Kirby M, Mathew L, Wheatley A, Santyr GE, McCormack DG, Parraga G. Chronic obstructive pulmonary disease: longitudinal hyperpolarized 3He MR imaging. Radiology. 2010;256:280–9.
76 Ruppert K, Mata JF, Brookeman JR, Hagspiel KD, Mugler JP 3rd. Exploring lung function with hyperpolarized (129)Xe nuclear magnetic resonance. Magn Reson Med. 2004;51(4):676–87.
77 Mugler JP, Altes TA. Hyperpolarized 129Xe MRI of the human lung. J Magn Reson Imaging. 2013;37(2):313–31.
78 Han M, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010;182(5):598–604.
79 Subramanian DR, Gupta S, Burggraf D, Vom Silberberg SJ, Heimbeck I, Heiss-Neumann MS, et al. Emphysema- and airway-dominant COPD phenotypes defined by standardised quantitative computed tomography. Eur Respir J. 2016;48(1):92–103.
80 Mohamed Hoesein FA, Schmidt M, Mets OM, Gietema HA, Lammers JW, Zanen P, et al. Discriminating dominant computed tomography phenotypes in smokers without or with mild COPD. Respir Med. 2014;108:136–43.
81 Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grenier PA, et al. Clinical and radiologic disease in smokers with normal spirometry. JAMA Intern Med. 2015;175(9):1539–49.
82 Sun XW, Gu SY, Li QY, Ren L, Shen JM, Wan HY, et al. Pulmonary function parameters in high-resolution computed tomography phenotypes of chronic obstructive pulmonary disease. Am J Med Sci. 2015;349(3):228–33.
83 Ogawa E, Nakano Y, Ohara T, Muro S, Hirai T, Sato S, et al. Body mass index in male patients with COPD: correlation with low attenuation areas on CT. Thorax. 2009;64(1):20–5.
84 Boschetto P, Quintavalle S, Zeni E, Leprotti S, Potena A, Ballerin L, et al. Association between markers of emphysema and more severe chronic obstructive pulmonary disease. Thorax. 2006;61(12):1037–42.
85 Cheng T, Wan HY, Cheng QJ, Guo Y, Qian YR, Fan L, et al. Obvious emphysema on computed tomography during an acute exacerbation of chronic obstructive pulmonary disease predicts a poor prognosis. Intern Med J. 2015;45(5):517–26.
86 Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011l;365(13):1184–92.
87 Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, et al. CT scan findings of emphysema predict mortality in COPD. Chest. 2010;138(3):635–40.
88 Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. Radiology. 2011;261:274–82.
89 Van Tho N, Ogawa E, Trang le TH, Ryujin Y, Kanda R, Nakagawa H, et al. Mixed phenotype of airway wall thickening and emphysema is associated with dyspnea and hospitalization for chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2015;12:988–96.
90 Stolk J, Ng WH, Bakker ME, Reiber JH, Rabe KF, Putter H, et al. Correlation between annual change in health status and computer tomography derived lung density in subjects with alpha1-antitrypsin deficiency. Thorax. 2003;58(12):1027–30.
91 Dowson LJ, Guest PJ, Hill SL, Holder RL, Stockley RA. High-resolution computed tomography scanning in alpha1-antitrypsin deficiency: relationship to lung function and health status. EUR Respir J. 2001;17(6):1097–104.
92 Barjaktarevic I, Springmeyer S, Gonzalez X, Sirokman W, Coxson HO, Cooper CB. Diffusing capacity for carbon monoxide correlates best with tissue volume from quantitative CT scanning analysis. Chest. 2015;147(6):1485–93.
93 Motohashi N, Kimura K, Ishii T, Wakabayashi R, Kurosaki H, Motegi T, et al. Emphysema on imaging is associated with quality of life in elderly patients with chronic obstructive pulmonary disease. Geriatr Gerontol Int. 2010;10(1):17–24.
94 De Torres JP, Bastarrika G, Zagaceta J, Sáiz-Mendiguren R, Alcaide AB, Seijo LM, et al. Emphysema presence, severity, and distribution has little impact on the clinical presentation of a cohort of patients with mild to moderate COPD. Chest. 2011;139(1):36–42.
95 Martinez CH, Chen YH, Westgate PM, Liu LX, Murray S, Curtis JL, et al. Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease. Thorax. 2012;67:399–406.
96 Kim V, Han MK, Vance GB, Make BJ, Newell JD, Hokanson JE, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. Chest. 2011;140(3):626–33.
97 Gjrydeland TB, Dirksen A, Coxson HO, Eagan TM, Thorsen E, Pillai SG, et al. Quantitative computed tomography measures of emphysema and airway wall thickness are related to respiratory symptoms. Am J Respir Crit Care Med. 2010;181:353–9.
98 Jones PW. St. George's respiratory questionnaire: MCID. COPD. 2005 Mar;2(1):75–9.
99 Han MK, Bartholmai B, Liu LX, Murray S, Curtis JL, Sciurba FC, et al. Clinical significance of radiologic characterizations in COPD. COPD. 2009;6(6):459–67.

100 Mair G, Maclay J, Miller JJ, McAllistera D, Connell B, Murchison JT, et al. Airway dimensions in COPD: relationship with clinical variables. Respir Med. 2010;104:1683–90.
101 Nakano Y, Muro Sakai H, Hirai T, Chin K, Tsukino M, Nishimura K, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers: correlation with lung function. Am J Respir Crit Care Med. 2000;162:1102–8.
102 Schroder JD, McKenzie AS, Zach JA, Wilson CG, Curran-Everett D, Stinson DS, et al. Relationship between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. AJR Am J Roentgenol. 2013;201:W460–470.
103 Hasegawa M, Nasuhara Y, Onodera Y, Makita H, Nagai K, Fuke S, et al. Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;173(12):1309–15.
104 De Backer LA, Vos W, De Backer J, Van Holsbeke C, Vinchurkar S, De Backer W. The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study. Eur Respir J. 2012;40(2):298–305.
105 De Backer LA, Vos WG, Salgado R, De Backer JW, Devolder A, Verhulst SL, et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. Int J Chron Obstruct Pulmon Dis. 2011;6:637–46.
106 Brown MS, Kim HJ, Abtin F, Da Costa I, Pais R, Ahmad S, et al. Reproducibility of lung and lobar volume measurements using computed tomography. Acad Radiol. 2010 Mar; 17(3):316–22.
107 Garfield JL, Marchetti N, Gaughan JP, Steiner RM, Criner GJ. Total lung capacity by plethysmography and high-resolution computed tomography in COPD. Int J Chron Obstruct Pulmon Dis. 2012;7:119–26.
108 Magnussen H, Kramer MR, Kirsten AM, Marquette C, Valipour A, Stanzel F, et al. Effect of fissure integrity on lung volume reduction using a polymer sealant in advanced emphysema. Thorax. 2012;67(4):302–8.
109 Criner GJ, Delage A, Voelker K. Improving lung function in severe heterogenous emphysema with the spiration valve system (EMPROVE) a multicenter, open-label randomized controlled clinical trial. Am J Respir Crit Care Med. 2019 Dec 1;200(11): 1354–62.
110 Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T, et al. A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med. 2018 Nov 1;198(9):1154–64.
111 Slebos DJ, Shah PL, Herth FJ, Valipour A. Endobronchial valves for endoscopic lung volume reduction: best practice recommendations from expert panel on endoscopic lung volume reduction. Respiration. 2017; 93(2):138–50.
112 Schulmann M, Raffy P, Yin Y, Gompelmann D, Oguz I, Eberhardt R, et al. Computed tomography predictors of response to endobronchial valve lung reduction treatment. Comparison with Chartis. Am J Respir Crit Care Med. 2015 Apr 1;191(7):767–74.
113 Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med. 2015;373(24):2325–35.
114 Majid A, Kheir F, Sierra-Ruiz M, Ghattas C, Parikh M, Channick C, et al. Assessment of fissure integrity in patients with intrabronchial valves for treatment of prolonged air leak. Ann Thorac Surg. 2019 Feb 1;107(2): 407–11.
115 McAllister DA, Ahmed FS, Austin JH, Henschke CI, Keller BM, Lemeshow A, et al. Emphysema predicts hospitalization and incident airflow obstruction among older smokers: a prospective cohort study. PLoS One. 20114;9:e93221.
116 Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, Wilks M, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170(4):400–7.
117 Bhatt SP, Terry NL, Nath H, Zach JA, Tschirren J, Bolding MS, et al. Association between expiratory central airway collapse and respiratory outcomes among smokers. JAMA. 2016;315:498–505.
118 Martinez-Garcia MA, Soler-Cataluna JJ, Donat Sanz Y, Catalan Serra P, Agramunt Lerma M, Ballestin Vicente J, et al. Factors associated with bronchiectasis in patients with COPD. Chest. 2011;140:1130–7.
119 Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamary AJ, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med. 2012;367:913–21.
120 Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, et al. Mortality by level of emphysema and airway wall thickness. Am J Respir Crit Care Med. 2013;187(6):602–8.
121 Zulueta JJ, Wisnivesky JP, Henschke CI, Yip R, Farooqi AO, McCauley DI, et al. Emphysema scores predict death from COPD and lung cancer. Chest. 2012;141(5):1216–23.
122 Oelsner EC, Hoffman EA, Folsom AR, carr JJ, Enright PL, Kawut SM, et al. Association between emphysema-like lung on cardiac computed tomography and mortality in persons without airflow obstruction: a cohort study. Ann Intern Med. 2014;161(12):863–73.
123 Martinez-Garcia MA, de la Rosa Carrillo D, Soler-Cataluna JJ, Donat-Sanz Y, Serra PC, Lerma MA, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187:823–31.
124 Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, et al. Mortality by level of emphysema and airway wall thickness. Am J Respir Crit Care Med. 2013;187(6):602–8.
125 ZuluetaWisnivesky JJJP, Henschke CI, Yip R, Farooqi AO, McCauley DI, Chen M, et al. Emphysema scores predict death from COPD and lung cancer. Chest. 2012;141: 1216.
126 OelsnerHoffman ECEA, Folsom AR, Carr JJ, Enright PL, Kawut SM, Kronmal R, et al. Association between emphysema-like on cardiac computed tomography and mortality in persons without airflow obstruction: a cohort study. Ann Inter Med. 2014;161:863–73.
127 Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–12.
128 Martinez CH, Chen YH, Westgate PM, Liu LX, Murray S, Curtis JL, et al. Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease. Thorax. 2012;67:399–406.
129 Chapman KR, Burdon JG, Pitulainen E, Sandhaus RA, Seersholm N, Stocks JM, et al. Intravenous augmentation treatment and lung density in severe q 1 antitrypsin deficiency (RAPID): a randomized, double-blind, placebo-controlled trial. Lancet. 2015; 386(9991):360–8.
130 Dirksen A, Piitulainen E, Parr DG, Deng C, Wencker M, Shaker SB, et al. Exploring the role of CT densitometry: a randomized study of augmentation therapy in alpha 1-antitrypsin deficiency. Eur Respir J. 2009; 33(6):1345.
131 Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017; 389(10082):1941–52.
132 Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax. 2003;58(2):143–8.
133 Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6(2):138–53.
134 Shin KM, Lee KS, Chung MP, Han J, Bae YA, Kim TS, et al. Prognostic determinants among clinical, thin-section CT, and histopathologic findings for fibrotic idiopathic interstitial pneumonias: tertiary hospital study. Radiology. 2008;249(1):328–37.
135 Edey AJ, Devaraj AA, Barker RP, Nicholson AG, Wells AU, Hansell DM. Fibrotic idiopathic interstitial pneumonias: HRCT findings that predict mortality. Eur Radiol. 2011; 21(8):1586–93.

136 Ominaga J, Sakai F, Johkoh T, Noma S, Akira M, Fujimoto K, et al. Diagnostic certainty of idiopathic pulmonary fibrosis/usual interstitial pneumonia: the effect of the integrated clinic-radiological assessment. Eur J Radiol. 2015;84:2640–5.
137 Walsh SL, Calandriello L, Sverzellati N, Wells AU, Hansell DM. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. Thorax. 2016;71(1):45–51.
138 Maldonado F, Moua T, Rajagopalan S, Karwoski RA, Raghunath S, Decker PA, et al. Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. Eur Respir J. 2014;43(1):204–12.
139 De Goacomi F, Raghunath S, Karwoski R, Bartholmai BJ, Moua T. Short-term automated quantification of radiologic changes in the characterization of idiopathic pulmonary fibrosis versus nonspecific interstitial pneumonia and prediction of long-term survival. J Thorac Imaging. 2018;33:124–31.
140 Walsh SLF, Calandriello L, Silva M, Sverzellati N. Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study. Lancet Respir Med. 2018 Nov;6(11):837–45.
141 Christie A, Peters AA, Drakopoulos D, Heverhagen J, Geiser T, Stathopoulou T, et al. Computer-aided diagnosis of pulmonary fibrosis using deep learning and CT images. Invest Radiol. 2019 Oct;54(10):627–32.
142 Tashkin DP, Volkmann ER, Tseng CH, Kim HJ, Goldin J, Clements P, et al. Relationship between quantitative radiographic assessments of interstitial lung disease and physiological and clinical features of systemic sclerosis. Ann Rheum Dis. 2016 Feb;75(2):374–81.
143 Humphries SM, Yagihashi K, Huckleberry J, Rho BH, Schroeder JD, Strand M, et al. Idiopathic pulmonary fibrosis: data-driven textural analysis of extent of fibrosis at baseline and 15-month follow-up. Radiology. 2017;285(1):270–8.
144 Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med. 2005;142(12 Pt 1):963–7.
145 Fernandez PER, Daniels CE, Schroder DR, St Sauver J, Hartman TE, Bartholmai BJ, et al. Incidence, prevalence and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest. 2010;137(1):129–37.
146 King TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med. 2001;164(7):1171–81.
147 Wells AU, Desai SR, Ruben MB, Goh NS, Cramer D, Nicholson AG, et al. Idiopathic fibrosis: a composite physiologic index derived from disease extent observed by computer tomography. Am J Respir Crit Care Med. 2003;167(7):962–9.
148 Du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184(4):459–66.
149 Wu X, Kim GH, Salisbury ML, Barber D, Bartholmai BJ, Brown KK, et al. Computed tomographic biomarkers in idiopathic pulmonary fibrosis. The future of quantitative analysis. Am J Respir Crit Care Med. 2019 Jan 1;199(1):12–21.
150 Adegunsoye A, Oldham JM, Bellam SK, Montner S, Churpek MM, Noth I, et al. Computed tomography honeycombing identifies a progressive fibrotic phenotype with increased mortality across diverse interstitial lung diseases. Ann Am Thorac Soc. 2019 May;16(5):580–8.
151 Nakagawa H, Ogawa E, Fukunaga K, Kinose D, Yamaguchi M, Nagao T, et al. Quantitative CT analysis of honeycombing area predicts mortality in idiopathic pulmonary fibrosis with definite usual interstitial pneumonia pattern: a retrospective cohort study. PLoS One. 2019;14(3):e0214278.
152 Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J. 2017;49(1):1601011.
153 Maher TM, van del Aar EM, Van de Steen O, Allamassey L, Desrivot J, Dupont S, et al. Safety, tolerability pharmacokinetics and pharmacodynamics of GLPG1690, a novel autotoxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomized placebo-controlled trial. Lancet Resp Med. 2018;6:627–35.
154 MusscheVan Holsbeke CC, De Backer J, Vos W, Lanclus M, Mignot B, et al. Late breaking abstract responder phenotype using functional respiratory imaging (FRI) in IPF patients treated with anti-CGTG monoclonal antibody FG3019. Eur Respir J. 2017;50:PA2811.
155 Van den Blink B, Dillingh MR, Ginns LC, Morrison LD, Moerland M, Wijsenbeek M, et al. Recombinant human pentraxin-2 therapy in patients with idiopathic pulmonary fibrosis: safety, pharmacokinetics and exploratory efficacy. Eur Respir J. 2016;47(3):889–97.
156 Ragu G, Scholand MB, de Andrade J, Lancaster L, Mageto Y, Goldin J, et al. FG-3019 anti-connective tissue growth factor monoclonal antibody, results of an open-label clinical trial in idiopathic pulmonary fibrosis. Eur Respir J. 2016 May;47(5):1481–91.
157 Tashkin DT, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil, versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II); a randomized controlled, double blind parallel group trial. Lancet Respir Med. 2016 Sep;4(9):708–19.
158 Kim H, Goo JM, Ohno Y, Kauczor HU, Hoffman EA, Gee JC, et al. Effect of reconstruction parameters on the quantitative analysis of chest computed tomography. J Thorac Imaging. 2019;34(2):92–102.
159 Gierada DS, Bierhals AJ, Choong CK, Bartel ST, Ritter JH, Das NA, et al. Effects of CT section thickness and reconstruction kernel on emphysema quantification relationship to the magnitude of the CT emphysema index. Acad Radiol. 2010;17(2):146–56.
160 Madani A, Van Muylem A, Gevenois PA. Pulmonary emphysema: effect of lung volume on objective quantification at thin-section CT. Radiology. 2010;257(1):260–8.
161 Brown M, Browning P, Wahi-Anwar MW, Murphy M, Delgado J, Greenspan H, et al. Integration of chest CT CAD into the clinical workflow and impact on radiologist efficiency. Acad Radiol. May 2019;26(5):626–31.