HHS Public Access

Author manuscript

Chest. Author manuscript; available in PMC 2025 November 01.

Published in final edited form as:

Chest. 2024 November ; 166(5): 1093–1107. doi:10.1016/j.chest.2024.04.031.

Chest computed tomography provides more information than chest X-ray alone in determining extent of physiologic impairment in pulmonary sarcoidosis

Bryan S. Benn, MD, PhD[1,a], **William L Lippitt, MS, PhD**[1,b], **Isabel Cortopassi, MD**[c], **G.K Balasubramani, PhD**[d], **Eduardo Mortani Barbosa Jr., MD, MBA**[e], **Wonder P. Drake, MD**[f], **Erica Herzog, MD**[g], **Kevin Gibson, MD**[h], **Edward S. Chen, MD**[i], **Laura L. Koth, MD, MAS**[a], **Carl Fuhrman, MD**[*], **David A Lynch, MBBCh**[j], **Naftali Kaminski, MD**[g], **Stephen R Wisniewski, PhD**[h], **Nichole E Carlson, MS, PhD**[1,b], **Lisa A Maier, MD, MSPH**[1,k]

[a]Department of Medicine, University of California San Francisco, San Francisco, California

[b]Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado, Aurora, Colorado

[c]Department of Radiology, Mayo Clinic College of Medicine and Science, Jacksonville, Florida

[d]Department of Epidemiology and Clinical and Translations Sciences, School of Public Health, University of Pittsburgh, Pittsburgh, PA

[e]Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

[f]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD

[g]Section of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT

[h]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Pittsburgh School of Medicine

[i]Department of Medicine, Johns Hopkins University, Baltimore, MD

[j]Department of Radiology, National Jewish Health, Denver, Colorado

[k]Department of Medicine, National Jewish Health, Denver, Colorado; Department of Medicine, School of Medicine, Department of Environmental/Occupational Health, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Corresponding Author: Lisa A. Maier, MD MSPH, maierl@njhealth.org, 1400 Jackson St, G212, Denver, CO, 80207, Fax 303-398-1452.

[*] posthumous

[1.] These authors contributed equally to this manuscript

Authors Contributions: LAM, WL, NEC, LLK, WPD, and EH contributed to the conception and design of the study. BSB, IC, EMB, WPD, EH, KG, EC, LLK, CF, DAL, NK, SW and LAM contributed to the acquisition of the data. WL, GKB, and NEC ensured accuracy and completeness of the statistical analysis. BSB, WL, NEC, and LAM drafted and revised the manuscript. All authors reviewed, revised, and approved the manuscript before submission.

Abstract

Background: Sarcoidosis staging has primarily relied on the Scadding chest radiographic system, although chest CT is finding increased clinical use.

Research Question: Whether standardized CT assessment provides additional understanding of lung function beyond Scadding stage and demographics is unknown and the focus of this study.

Study Design and Methods: We used the NHLBI study Genomics Research in Alpha-1 Anti-Trypsin Deficiency and Sarcoidosis (GRADS) sarcoidosis cases(N=351) with Scadding stage and Chest CT scans obtained in a standardized manner. One chest radiologist scored all CT scans with a visual scoring system, with a subset read by another chest radiologist. We compared demographic features, Scadding stage and CT findings, and correlation between these measures. Associations between spirometry and DLCO and CT and Scadding stage were determined using regression analysis (N=318). Agreement between readers was evaluated using Cohen's Kappa.

Results: CT features were inconsistent with Scadding stage in about ~40% of cases. Most CT features assessed on visual scoring were negatively associated with lung function. Associations persisted for FEV1 and DLCO when adjusting for Scadding stage, although some CT feature associations with FVC became insignificant. Scadding stage was primarily associated with FEV1 and inclusion of CT features reduced significance in association between Scadding and lung function. Multivariable regression modeling to identify radiologic measures explaining lung function included Scadding stage for FEV1 and FEV1/FVC (P<0.05) and marginally for DLCO (P<0.15). Combinations of CT measures accounted for Scadding stage for FVC. Correlations among Scadding and CT features were noted. Agreement between readers was poor to moderate for presence/absence of CT features and poor for degree/location of abnormality.

Interpretation: CT features explained additional variability in lung function beyond Scadding stage, with some CT features obviating the associations between lung function and Scadding. Whether CT features/phenotypes/endotypes could be useful for managing patients with sarcoidosis needs more study.

Keywords

Sarcoidosis; Chest Computed Tomography; Scadding Stage; Lung Function; Genomic Research in Alpha-1Antitrypsin Deficiency and Sarcoidosis (GRADS); Phenotypes; Chest radiography

Introduction:

Sarcoidosis is a multi-systemic disease characterized by granulomatous inflammation.[1] Up to 90% of cases have lung involvement, demonstrated by abnormalities on chest x-ray (CXR) and/or pulmonary function testing(PFT).[1–3] Scadding stage[4] has long been used to assess CXR abnormalities with relative ease of imaging, low cost, and low risk.[5,6] Regardless, Scadding staging has several limitations[5–7]

Unlike traditional clinical staging systems in which patients progress from one stage to the next (e.g. in cancer), sarcoidosis patients do not demonstrate temporal or linear progression from one stage to the next, or through all stages.[5] While Stage IV disease portends a worse prognosis with more severe disease unlikely to resolve and Stage 0/I disease are

more likely to experience disease resolution,[4] overall, prognostic capabilities of Scadding are limited.[8] Individuals may present with varying extent or types of CXR abnormalities and be classified in the same Scadding stage.[4–6] Individuals with stage IV disease with fibrosis due to architectural/airway distortion versus honeycombing with traction bronchiectasis are not differentiated even though they may have distinct PFT abnormalities.[9] Furthermore, Scadding stage does not reliably correlate with lung function abnormalities or physiologic impairment[10–13] and changes in Scadding stage may not correspond with PFT changes.[14] These myriad challenges make assessment of disease status difficult. Other imaging modalities may allow more accurate assessment of pulmonary sarcoidosis and provide a relationship with physiologic impairment.

High resolution chest computed tomography(HRCT) is being used more frequently in sarcoidosis, with potential increased sensitivity to detect parenchymal abnormalities(PA) and better estimation of disease status and lung impairment.[14] HRCT detects and better quantifies micronodules, ground-glass, and reticular abnormalities that may not be apparent on CXR.[7,9,15] Furthermore, CT may provide prognostic findings with demonstration of nodules and ground-glass opacities associated with disease resolution while reticular abnormalities less likely to be associated with resolution.[16–18] Standardized objective assessment of CT findings has also correlated with lung function, further supporting a role for HRCT in sarcoidosis assessment.[18–20]

While different scoring systems have been proposed to quantify CT findings, including Oberstein[21] and Remy Jardin,[19] they are limited by small studies and lack of standardized imaging algorithms. As part of the extensive clinical phenotyping obtained through the multi-center study Genomic Research in Alpha One Anti-trypsin Deficiency and Sarcoidosis(GRADS), PFTs, CXR, and standardized HRCT imaging were obtained.[22,23] We sought to evaluate if HRCT findings would provide information beyond conventional CXR Scadding stage alone in regards to lung function impairment in patients with pulmonary sarcoidosis.

Methods

Study Enrollment, Design and Data

Subjects were enrolled as described previously,[22,23] at multiple centers throughout the United States based on the GRADS protocol(N=368). Subjects gave written informed consent according to site's institutional review board(IRB) of the overall protocol. Subject's diagnosis was confirmed according to accepted criteria,[2] including consistent clinical features, exclusion of alternative diagnoses, and biopsy showing non-necrotizing granulomas. They underwent self-administered questionnaires, including self-reported race, research CXR and HRCT examinations,[24] and PFTs.[25, 26] See Supplement for additional details.

CT scoring methods

A single visual assessment score (VAS) was derived for each HRCT including Oberstein score[21](e-Table 1). The scoring system was developed in conjunction with a chest

radiologist (CF) to evaluate the most common abnormalities noted in sarcoidosis and A1ATD as per the original design of the GRADS study[22]. A single chest radiologist (CF) blinded to disease diagnosis reviewed all HRCT scans using this system; a second chest radiologist (IC) interpreted the first 168 CT scans using an abbreviated VAS, limited to sarcoidosis variables without quantification of severity and Oberstein scoring (See Supplement).

Statistical Analysis

Baseline demographic features, clinical measures, and HRCT VAS measures were compared by Scadding stage (N=351). For baseline demographic features and clinical measures, Chi-square tests and one-way ANOVA tests were used for discrete and continuous variables respectively. For CT measures, Fisher's exact tests were used. Summary tables for the complete datasets(N=318) are in e-Tables 2 and 3.

We developed definitions of inconsistency between CXR and CT based on Scadding stage and the VAS (e-Table 4,N=351). The observed distribution of inconsistencies stratified by Scadding stage were computed, along with percentage of inconsistent findings.

Associations between PFT and CT were evaluated using linear regression for those with complete PFT data, age, height, BMI, sex, race/ethnicity, Scadding stage, and GRADS CT(N=318). When more than 5 individuals had a sarcoidosis CT feature of interest, it was included in the analysis. All models were adjusted for age, sex, height, race/ethnicity, and BMI. We used P-value=0.01 for statistical significance. We performed regression modeling, with separate models fitted for PFT outcomes: pre-/post-bronchodilator (BD) FVC, FEV1, and FEV1/FVC ratio, and post-BD DLCO. For each PFT measure, two base models were fitted: one included only age, height, BMI, sex, and race/ethnicity and a second included these variables and Scadding stage. One CT measure was added to each base model to assess whether the CT measure was independently associated with PFT. Multivariable regression modeling was performed including all CT measures and Scadding stage, applying backward selection, using P-values from a partial F test for significance of single measure inclusion with cutoff P=0.15 as stopping criterion for the backward selection. Age, sex, height, race/ethnicity, and BMI were forced in all models. Two CT measures, presence of micronodules and overall Oberstein score were not included in multivariable modelling as we used micronodule distribution and the 6 Oberstein component scores for selection. In total, five demographic measures, 23 CT measures, and Scadding stage were considered in multivariable modelling, totaling 29 features, or 48 accounting for representation of nominal variables.

To descriptively quantify associations among measures, a heat map of pairwise associations between CT VAS measures and/or Scadding stage was created, using Cramér's V with a bias correction. In accordance with Cohen,[27] we conservatively consider cutoffs of 0.1, 0.3, and 0.5 for small, moderate, and large associations.

Cohen's Kappa was used to compute agreement between VAS from two readers using both dichotomized (presence/absence) and assessment of location and extent of abnormality,

when available. A CT variable was not included if <5 individuals had the condition by one reviewer.

Results

351 sarcoidosis subjects enrolled in GRADS had complete CT VAS and Scadding stage data(Table 1), with Scadding stage reflecting the recruitment strategy of GRADS.[22] The distributions of sex, education status, and income status were comparable across stages. At enrollment, modest differences in Scadding stage were noted by race/ethnicity(P=0.09), with most White subjects having Stage I or II disease and most Black subjects having Stage II or IV disease. Subjects with Stage II and IV disease had significantly lower BMI than subjects in other stages. Subjects with Stage IV disease were slightly older, had obstructive lung disease, and decreased DLCO compared to all other stages.

Classification of CT by CXR

The distribution of CT VAS measures tended to differ significantly by Scadding stage(Table 2). CT features that did not differ by Scadding stage were rare with ≤10 subjects having the CT feature (e.g. emphysema, Oberstein score pleural thickening). A number of individuals with Scadding stage 0/I had indications on CT of PA, including micronodules, ground-glass and mosaic attenuation(Table 3). 39% of subjects had CT findings inconsistent with CXR-Scadding stage. For Scadding stages 0-III, at most 62% were consistent. Stages 0 and I were inconsistent most of the time. Specifically, 20.2% and 26.0% of Scadding stages II and III patients had PA on CXR but not on CT, while 31.9% and 48.0% of Scadding stages 0 and I patients had PA on CT but not CXR. Overall inconsistencies between CT and CXR were accounted for by PA and lymphadenopathy, with similar rates for each separately and smaller percentage for both together.

CT Findings Inform Lung Function

Because results for pre- and post-BD PFT were similar when comparing CT with Scadding stage, only post-BD analyses are reported for brevity. Nearly all individual CT measures were negatively associated with PFT measures(Figure 1, green circles), indicating that presence of CT abnormality was associated with worse lung function. Adjustment for Scadding stage attenuated associations such that some CT measures were no longer associated with lung function. For DLCO(Figure 1 left column), Oberstein parenchymal consolidation (PC) and presence of mosaic attenuation, honeycombing, ground-glass, and emphysema each remained associated with decrease in DLCO after adjustment for Scadding(green triangles). For FEV1(Figure 1 left middle column), traction bronchiectasis, bronchovascular bundle(BVB) distortion, consolidation, mosaic attenuation, and Oberstein subscales BVB and PC remained associated with CT findings after adjustment for Scadding. Unlike DLCO, honeycombing and ground-glass were no longer associated with FEV1 when including Scadding. After adjustment for Scadding(right middle column), many associations between CT measures and FVC became insignificant. Interestingly, the association between FEV1/FVC ratio and traction bronchiectasis, emphysema, consolidation, BVB distortion, and axial distribution of distortion remained significant after adjustment for Scadding(Figure 1 right column). Adjustment for Scadding stage reduced the effect of Obserstein PC by

8%−25% for DLCO and FVC and attenuated FEV1 by 35%. Scadding stage had a smaller confounding effect on emphysema and DLCO and FEV1, reducing the effect by 10–13% (e-Tables 5–8).

Next, we evaluated Scadding stage and PFTs and then included specific CT features(Figure 2). Scadding stage was significantly associated with FEV1 to a greater degree than with DLCO, FVC and FEV1/FVC ratio. While no one CT measure equated to Scadding, reductions in significance between Scadding and each lung function measure were noted for many CT features. Scadding was no longer associated with FVC when including traction bronchiectasis and Oberstein PC and with FEV1/FVC when including traction bronchiectasis and Oberstein BVB. When adjusting for many CT PA, such as reticular abnormalities, mosaic attenuation, ground-glass, consolidation, and Oberstein PC, association between Scadding and lung function was attenuated. Notable exceptions included nodules, LA, interseptal thickening and some Oberstein components.

Associations among CT Measures

Next, we assessed associations among various CT measures and Scadding stage(Figure 3). The strongest associations among CT VAS and Scadding were found between Oberstein components and VAS measures that directly assess the same feature. PC, BVB distortion, traction bronchiectasis, and Scadding stage formed a block of largely associated CT measures(Figure 3 upper right corner). More moderate associations were found among these measures, micronodules, and PA. Smaller associations were observed between measures of lymphadenopathy and micronodules and other associated measures. Ground-glass demonstrated a strong association with Oberstein PC and mosaic association, but only a small association with direct assessment of consolidation. Pulmonary artery enlargement and emphysema were moderately associated with each other and, with pleural thickening and conglomerate masses, were mostly unassociated with other measures.

Using multivariable regression modeling including all CT VAS measures with backward selection to identify CT measures explaining PFT, Scadding stage remained in final models for FEV1 and FEV1/FVC ratio($P<0.05$) and marginally for DLCO($P<0.15$,Figure 4 bottom panel and e-Table 9); this finding was only notable for Stage 3 or 4 compared to 0. A collection of CT measures (differing for each PFT outcome) mostly accounted for Scadding stage for DLCO and FVC. Only mosaic attenuation and Oberstein PC were associated with all PFT measures, while honeycombing, cystic changes, distribution axial, and emphysema were selected for three of four PFT measures. Six measures were not included in any model: mediastinal and hilar lymphadenopathy, ground-glass, and Oberstein BVB, nodule(ND), and lymphadenopathy(LN). Interestingly, five CT measures were unassociated with any PFT measure in the individual analysis and yet were associated in final multivariable models: micronodule distribution and conglomerate nodules, cystic changes, Oberstein pleural thickening(PLT), and pulmonary artery enlargement.

CT Reader Concordance

The above analyses were conducted using one reader. When comparing reader to reader concordance, mixed results were noted(Table 4 and S10), with kappas ranging

from 0.15(poor agreement) to 0.64(moderate agreement). Better agreement was noted for presence/absence of feature versus agreement in location or Oberstein severity(e.g. lymphadenopathy, micronodule distribution, and Oberstein components). Honeycombing, cystic changes, emphysema and subtypes, and evidence of thoracic surgery were found to be rare by both readers, although they disagreed on the presence of a condition in an individual(e-Table 10).

Discussion:

Leveraging the results of the multicenter GRADS study, we were able to compare CXR Scadding stage to HRCT features visually scored by thoracic radiologists to lung function. We found CT scoring was inconsistent with Scadding designation in almost 40% of subjects. We found Scadding CXR associated with spirometry and DLCO PFT data, although HRCT was able to explain additional variability in PFT data even when Scadding was included, suggesting that additional information is derived from some CT features(e.g. presence of mosaic attenuation or degree of Oberstein PC). Some HRCT features were associated with PFT measures even in the presence of Scadding stage (e.g. DLCO with ground-glass and honeycombing and FEV1 with BVB distortion and consolidation). HRCT features were associated with each other and with specific Scadding stage, suggesting potential “CT phenotypes.” This is further supported by finding of associations between CT features and Oberstein scores. Inter-reader variability in CT scans likely limit its use, as at best moderate agreement between presence or absence of CT features and at worst poor agreement in reference to location and/or severity was noted. Regardless, we present new information regarding utility of chest CT, revealing associations between PFT abnormalities and CT features in pulmonary sarcoidosis. Overall these results suggest that CT may provide additional characterization of lung abnormalities with implications for PFT to a greater degree than Scadding.

Scadding stage has been commonly used to categorize pulmonary sarcoidosis patients. In contrast to other interstitial lung diseases which rely on HRCT, CXR has been used to assess sarcoidosis disease status.[7] Over decades, experience with Scadding led to its use in prognosis, although with many caveats. However, it is widely accepted that HRCT provides additional detail lacking on review of CXR, as supported by prior smaller studies in which CT chest better detected lymphadenopathy and PA.[28,29] These studies did not seek to directly compare finding between Scadding stage and HRCT, as we did.

Evaluating specific CT features, we found significant variability across all stages(Table 2), including the presence of nodules, PA, BVB distortion and traction bronchiectasis, with many of these present in Scadding Stage 0/I disease. Using HRCT to define Scadding-like score in our study, we identified many subjects who were inconsistently categorized relative to Scadding stage(Table 3). These inconsistencies were seen widely across stages 0-III, with inconsistencies based on lymphadenopathy and/or PA with PA the most discrepant. Inconsistencies related to PA seen on CXR but not seen on CT were surprisingly frequent. A smaller recent study compared HRCT features with Scadding and demonstrated similar results to ours with discordance between CT and Scadding in 50% subjects, primarily due to differences in PA.[7,30] Our study was unable to address inconsistencies related to fibrosis

and may have overrepresented consistencies when comparing CXR to CT; the recent study reported high concordance with Stage IV disease and HRCT.

Previous studies have suggested that Scadding is a poor predictor of lung function,[10–13] while HRCT PA have correlated with PFT.[20] Similarly, we found CT features widely associated with worse lung function(Figure 1), with adjustment for Scadding attenuating some associations (Figure 1 blue triangles). However, Scadding was associated with spirometry and DLCO values (Figure 2 purple line), and significance decreased when various CT measures were included (Figure 2 red circle). Multivariable regression modeling did not include Scadding in the final model for FVC and included Scadding only marginally in DLCO final model, with a collection of CT measures providing approximately the same information as Scadding for DLCO and FVC(Figure 4). To our knowledge, no other study has evaluated association between CXR and CT independently and in combination as we have, supporting that Scadding demonstrates some association with lung function although more pronounced relationship is noted with CT findings. A limitation of our study is that it is cross sectional. A prior study demonstrated that serial CT changes moderately agreed with spirometry changes and only fair agreement was noted with CXR changes.[30] In contrast to our study, CXR-based findings did not strengthen the association between PFT and CT-based findings, although sample size was relatively small (N=73) and prognosis was the primary focus. These data support that additional information regarding lung function in sarcoidosis patients is gained from CT over Scadding stage, suggesting a potential role for HRCT imaging to guide clinical management. It will be interesting to determine if similar disease activity and response to treatment information can be gained from initial and serial HRCT as in the case of positron emission tomography studies, which are used to evaluate the intensity and extent of inflammatory activity of sarcoidosis throughout the body and have correlated well with both HRCT and PFT findings.[31–37] Future studies will be needed to further clarify these relationships, especially longitudinally.

Efforts to group radiographic parenchymal findings into categories that impart physiologic information have been attempted and scoring systems exist that analyze numerous HRCT components, including Oberstein score used in our study.[19,21] These approaches rely on quantitative categories and qualitative assessments of degree of an abnormality, thus making agreement between scorers challenging.[20] While initial studies were limited by size (N=21[21] and N=95[19]), correlation between CT findings and degree of disease inflammation was seen,[21] with limited prognostic assessment.[19] We found associations with Oberstein score components and PFT supporting this approach. We also noted similar PFT associations across numerous CT features(Figure 1 and 2), and groups of CT features highly associated with each other (Figure 3). The Oberstein BVB score in our study was associated with CT BVB distortion, consolidation and traction bronchiectasis, and Scadding stage, supporting that it may indicate a sarcoidosis phenotype(Figure 3). In addition, BVB distortion and consolidation were associated with ground-glass and reticulation CT features, suggesting fibrotic features.

It is possible that CT phenotypes may be defined by a limited number of key CT features[32] with correlation between features. To date, limited CT phenotypes have been defined as functionally relevant, besides, fibrotic phenotype/subphenotypes. In fibrotic sarcoidosis,

three CT patterns have been proposed with associated lung function abnormalities: predominant BVB distortion associated with obstruction, honeycombing with restriction and low DLCO, and linear PA with relatively minor impairment.[14,33] Similarly, we found BVB distortion associated with low FEV1 and obstruction, and interlobular septal thickening unassociated with PFTs. Extent of lung fibrosis on CT scan associated with mortality[34] and prognosis.[32] GRADS aimed to define gene expression phenotypes/endotypes, and found genes associated with progressive Scadding stage and CT features, with overlap with PFTs.[23] Reticular abnormalities associated with >750 genes and with genes associated with traction bronchiectasis, ground-glass, progressive Scadding stage, DLCO and spirometry to varying degree. CT features were associated with three of four gene modules and Scadding in only one where CT adenopathy was also associated with the module. These data support that overlap between CT features, Scadding and PFTs occur, and raise a question whether sarcoidosis phenotypes/endotypes using multiple data sources, both clinical and Omics, might provide clinically relevant information for evaluation and/or management of patients with sarcoidosis.

Our study is limited by interobserver variability as is any similar study using VAS. GRADS was set up with a scoring system to address two different diseases using one radiologist evaluating all CTs[22,23] as have other studies.[32] A subset of CTs were reviewed with a limited VAS. Based on this data we found mixed concordance across different CT measures although agreement was optimum for presence/absence of feature, versus location or severity, similar to other studies.[20] Even with CXR only fair agreement is noted among chest radiologists (e.g. fibrosis and lymphadenopathy presence)[38] and when evaluating change in Scadding stage over time.[39] This issue confounds all radiographic studies using VAS and thus efforts to improve reader agreement or other ways to assess radiographic abnormalities are needed.[40] Our study was secondary to the primary outcomes for the GRADS study[22], aiming to investigate lung microbiome and genome in sarcoidosis and A1ATD. Strengths include the size of the population, larger than most if not all compiled to date, standardized data and CTs and VAS from almost all participants, as well as the multi-center nature of our study.

Interpretation:

We evaluated a large population of sarcoidosis subjects and demonstrated that CT and Scadding stage provide different and overlapping information related to lung function. While Scadding is limited in its assessment, it associates with PFTs. CT provides additional information, and in FVC and to a lesser degree DLCO, CT alone obviates information provided by Scadding. Correlation between CT features raises a question about CT phenotypes/endotypes. Investigation into pulmonary phenotypes or endotypes that include clinical and Omics data in larger populations and investigating changes over time and prognosis are next steps to be considered to advance the care of patients with sarcoidosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

This work is supported by NIH grants: U01 HL112707, U01 HL112694, U01 HL112695, U01 HL112696, U01 HL112702, U01 HL112708, U01 HL112711, U01 HL112712, UL1 RR029882, UL1 RR025780, R01HL110883, R01 HL114587, R01 HL127349, U01 HL137159, CTSI U54 grant 9 UL1 TR000005, CDC NMVB 5U24 OH009077, CTSA UL1 TR002535, R01HL142049, and 5T32HL007085

Summary of COI:

LM has received grants from the National Institute of Health (R01HL140357, R01HL142049, and R01HL136681), Ann Theodore Foundation, the FSR, Mallinckrodt Pharmaceuticals, and the University of Cincinnati (Mallinckrodt Pharmaceuticals Foundation Grant) and serves on the Scientific Advisory Board for FSR, and Boeringer Ingelheim,

BSB has received a grant from Mallinckrodt Pharmaceuticals

ESC has received grants from the National Institutes of Health, the Foundation for Sarcoidosis Research (FSR), American Thoracic Society, serves on the Scientific Advisory Board for the FSR, and has participated in clinical trials sponsored by aTyr Pharma, LabCorp Drug

LK has received grants from the National Institute of Health (R01HL157533), Ann Theodore Foundation, and Mallinckrodt Pharmaceuticals

DAL was coinvestigator on a grant from the National Institutes of Health R01 HL142049 and served on a Scientific Advisory Board for Boehringer Ingelheim, Inc

NK is a scientific founder at Thyron, served as a consultant to Boehringer Ingelheim, Pliant, Astra Zeneca, RohBar, Veracyte, Augmanity, CSL Behring, Splisense, Galapagos, Fibrogen, GSK, Merck and Thyron over the last 3 years, reports Equity in Pliant and Thyron, and grants from Veracyte, Boehringer Ingelheim, BMS and non-financial support from Astra Zeneca.

NEC has received grants from the National Institutes of Health (R01HL142049)

WL, IC, GKB, EB, WPD, EH, KG, SW & CF have no COI to disclose

Abbreviations:

A1ATD	Alpha One Anti-trypsin Deficiency
AO	airway obstruction
BD	bronchodilator
BMI	body mass index
BVB	bronchovascular bundle
HRCT	High resolution chest computed tomography
CXR	chest X-ray
DLCO	diffusing capacity for carbon monoxide
FEV1	forced expiratory volume in one second
FEV1/FVC	ratio of FEV1 to FVC
FVC	forced vital capacity
GIC	Genetics and Informatics Core

GRADS	Genomic Research in Alpha-1 Anti-trypsin Deficiency and Sarcoidosis
IRB	institutional review board
LN	lymphadenopathy
ND	nodule
PA	parenchymal abnormalities
PC	parenchymal consolidation
PFT	Pulmonary Function Test
TLC	total lung capacity
VAS	visual assessment score

References:

1. Drent M, Crouser ED, Grunewald J. Challenges of Sarcoidosis and Its Management. N Engl J Med 2021;385(11):1018–1032. [PubMed: 34496176]
2. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020;201(8):e26–e51. [PubMed: 32293205]
3. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001;164(10 Pt 1):1885–1889. [PubMed: 11734441]
4. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. Br Med J 1961;2(5261):1165–1172. [PubMed: 14497750]
5. Levy A, Hamzeh N, Maier LA. Is it time to scrap Scadding and adopt computed tomography for initial evaluation of sarcoidosis? F1000Research. 2018;7. [PubMed: 29527296]
6. Culver DA, Baughman RP. It's time to evolve from Scadding: phenotyping sarcoidosis. Eur Respir J 2018;51(1).
7. Zhang Y, Du SS, Zhao MM, et al. Chest high-resolution computed tomography can make higher accurate stages for thoracic sarcoidosis than X-ray. BMC Pulm Med 2022;22(1):146. [PubMed: 35429968]
8. Lin NW, Arbet J, Mroz MM, et al. Clinical phenotyping in sarcoidosis using cluster analysis. Respir Res 2022;23(1):88. [PubMed: 35397561]
9. Bonella F, Culver DA, Israël-Biet D. Sarcoidosis. Vol 96: European Respiratory Society; 2022.
10. Harrison BD, Shaylor JM, Stokes TC, Wilkes AR. Airflow limitation in sarcoidosis--a study of pulmonary function in 107 patients with newly diagnosed disease. Respir Med 1991;85(1):59–64. [PubMed: 2014359]
11. Karetzky M, McDonough M. Exercise and resting pulmonary function in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 1996;13(1):43–49. [PubMed: 8865409]
12. Barros WG, Neder JA, Pereira CA, Nery LE. Clinical, radiographic and functional predictors of pulmonary gas exchange impairment at moderate exercise in patients with sarcoidosis. Respiration. 2004;71(4):367–373. [PubMed: 15316210]
13. Yeager H, Rossman MD, Baughman RP, et al. Pulmonary and psychosocial findings at enrollment in the ACCESS study. Sarcoidosis Vasc Diffuse Lung Dis 2005;22(2):147–153. [PubMed: 16053031]

14. Nunes H, Uzunhan Y, Gille T, Lamberto C, Valeyre D, Brillet PY. Imaging of sarcoidosis of the airways and lung parenchyma and correlation with lung function. Eur Respir J 2012;40(3):750–765. [PubMed: 22790910]
15. Daniloff EM, Lynch DA, Bartelson BB, Newell JD Jr, Bernstein SM, Newman LS. Observer variation and relationship of computed tomography to severity of beryllium disease. Am J Respir Crit Care Med 1997;155(6):2047–2056. [PubMed: 9196114]
16. Murdoch J, Müller NL. Pulmonary sarcoidosis: changes on follow-up CT examination. AJR Am J Roentgenol 1992;159(3):473–477. [PubMed: 1503008]
17. Brauner MW, Lenoir S, Grenier P, Cluzel P, Battesti JP, Valeyre D. Pulmonary sarcoidosis: CT assessment of lesion reversibility. Radiology. 1992;182(2):349–354. [PubMed: 1732948]
18. Akira M, Kozuka T, Inoue Y, Sakatani M. Long-term follow-up CT scan evaluation in patients with pulmonary sarcoidosis. Chest. 2005;127(1):185–191. [PubMed: 15653982]
19. Remy-Jardin M, Giraud F, Remy J, Wattinne L, Wallaert B, Duhamel A. Pulmonary sarcoidosis: role of CT in the evaluation of disease activity and functional impairment and in prognosis assessment. Radiology. 1994;191(3):675–680. [PubMed: 8184045]
20. Drent M, De Vries J, Lenters M, et al. Sarcoidosis: assessment of disease severity using HRCT. Eur Radiol 2003;13(11):2462–2471. [PubMed: 12811502]
21. Oberstein A, von Zitzewitz H, Schweden F, Müller-Quernheim J. Non invasive evaluation of the inflammatory activity in sarcoidosis with high-resolution computed tomography. Sarcoidosis Vasc Diffuse Lung Dis 1997;14(1):65–72. [PubMed: 9186991]
22. Moller DR, Koth LL, Maier LA, et al. Rationale and Design of the Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) Study. Sarcoidosis Protocol. Ann Am Thorac Soc 2015;12(10):1561–1571. [PubMed: 26193069]
23. Vukmirovic M, Yan X, Gibson KF, et al. Transcriptomics of bronchoalveolar lavage cells identifies new molecular endotypes of sarcoidosis. Eur Respir J 2021;58(6).
24. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. Copd 2010;7(1):32–43. [PubMed: 20214461]
25. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J 2005;26(1):153–161. [PubMed: 15994402]
26. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017;49(1).
27. Cohen J Set correlation and multivariate methods. Statistical Power Analysis for the Behavioral Sciences. 2nd *ed.* Hillsdale, NJ: Lawrence Erlbaum Associates, Inc. 1988:467–530.
28. Aleksonienė R, Zeleckienė I, Matačiūnas M, et al. Relationship between radiologic patterns, pulmonary function values and bronchoalveolar lavage fluid cells in newly diagnosed sarcoidosis. J Thorac Dis 2017;9(1):88–95. [PubMed: 28203410]
29. Ors F, Gumus S, Aydogan M, Sari S, Verim S, Deniz O. HRCT findings of pulmonary sarcoidosis; relation to pulmonary function tests. Multidiscip Respir Med 2013;8(1):8. [PubMed: 23384173]
30. Zappala CJ, Desai SR, Copley SJ, et al. Accuracy of individual variables in the monitoring of long-term change in pulmonary sarcoidosis as judged by serial high-resolution CT scan data. Chest. 2014;145(1):101–107. [PubMed: 24051950]
31. Lewis PJ, Salama A. Uptake of fluorine-18-fluorodeoxyglucose in sarcoidosis. J Nucl Med 1994;35(10):1647–1649. [PubMed: 7931664]
32. Walsh SL, Wells AU, Sverzellati N, et al. An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study. Lancet Respir Med 2014;2(2):123–130. [PubMed: 24503267]
33. Abehsera M, Valeyre D, Grenier P, Jaillet H, Battesti JP, Brauner MW. Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. AJR Am J Roentgenol 2000;174(6):1751–1757. [PubMed: 10845518]
34. Jeny F, Uzunhan Y, Lacroix M, et al. Predictors of mortality in fibrosing pulmonary sarcoidosis. Respir Med 2020;169:105997. [PubMed: 32442108]
35. Mostard RL, Verschakelen JA, van Kroonenburgh MJ, et al. Severity of pulmonary involvement and (18)F-FDG PET activity in sarcoidosis. Respir Med 2013;107(3):439–447. [PubMed: 23261309]

36. Cremers JP, Van Kroonenburgh MJ, Mostard RL, et al. Extent of disease activity assessed by 18F-FDG PET/CT in a Dutch sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis 2014;31(1):37–45. [PubMed: 24751452]

37. Vender RJ, Aldahham H, Gupta R. The role of PET in the management of sarcoidosis. Curr Opin Pulm Med 2022;28(5):485–491. [PubMed: 35869739]

38. Baughman RP, Shipley R, Desai S, et al. Changes in chest roentgenogram of sarcoidosis patients during a clinical trial of infliximab therapy: comparison of different methods of evaluation. Chest. 2009;136(2):526–535. [PubMed: 19395578]

39. Zappala CJ, Desai SR, Copley SJ, et al. Optimal scoring of serial change on chest radiography in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2011;28(2):130–138. [PubMed: 22117504]

40. Ryan SM, Fingerlin TE, Mroz M, et al. Radiomic measures from chest high-resolution computed tomography associated with lung function in sarcoidosis. Eur Respir J 2019;54(2).

Take-Home Point

Study Question:

Does standardized CT assessment provide additional understanding of lung function beyond Scadding stage and demographics?

Results:

Associations between lung function and CT feature persisted for FEV1 and DLCO when adjusting for Scadding stage and demographics, with some CT features obviating the associations between lung function and Scadding.

Interpretation:

These data support that additional information regarding lung function in sarcoidosis patients is gained from CT over Scadding stage and demographics alone, suggesting a potential role for CT imaging to guide sarcoidosis clinical management.

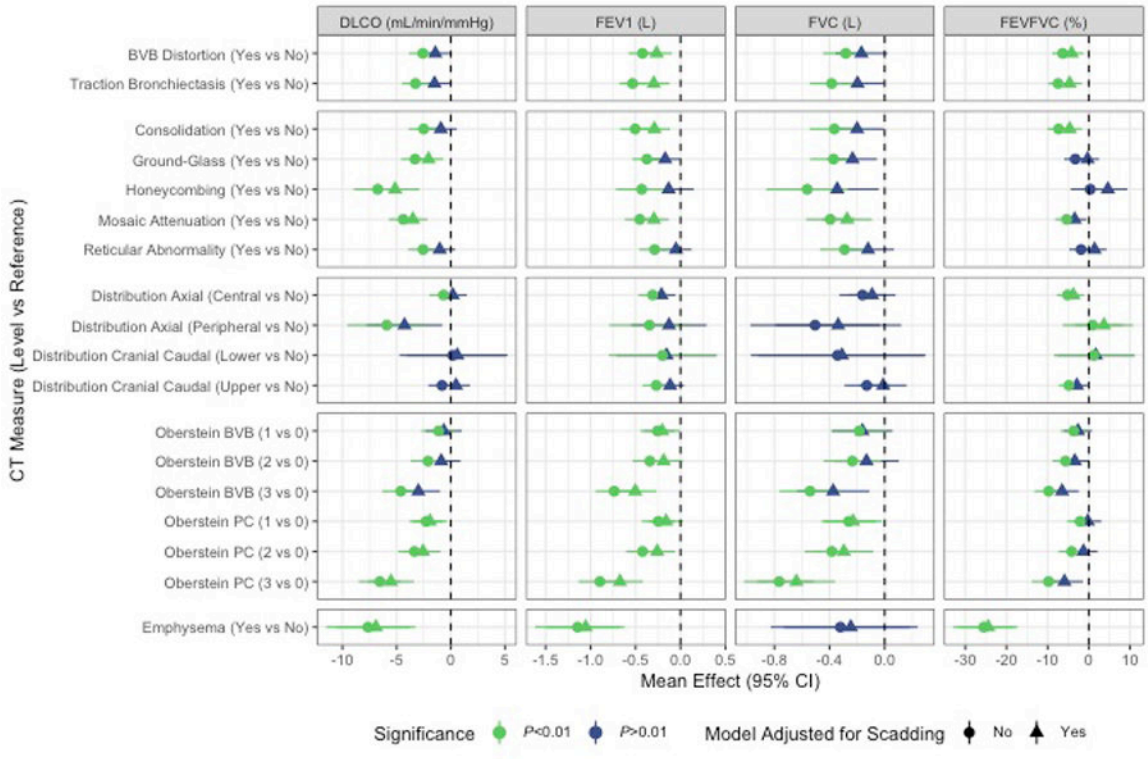

Figure 1:

Estimated associations between a single CT measure and each pulmonary function test variable. Coefficients and 95% confidence intervals are presented. The dashed black line demarks a coefficient estimate of 0. Circles are estimates from models with the base factors plus the CT measure. Triangles are models that also include Scadding stage. Green is a p-value <0.01 and blue a p-value>=0.01. Only models with a significant effect in at least one model across different pulmonary function tests are presented. Overall Oberstein is excluded as it was the only CT measure not treated as categorical.

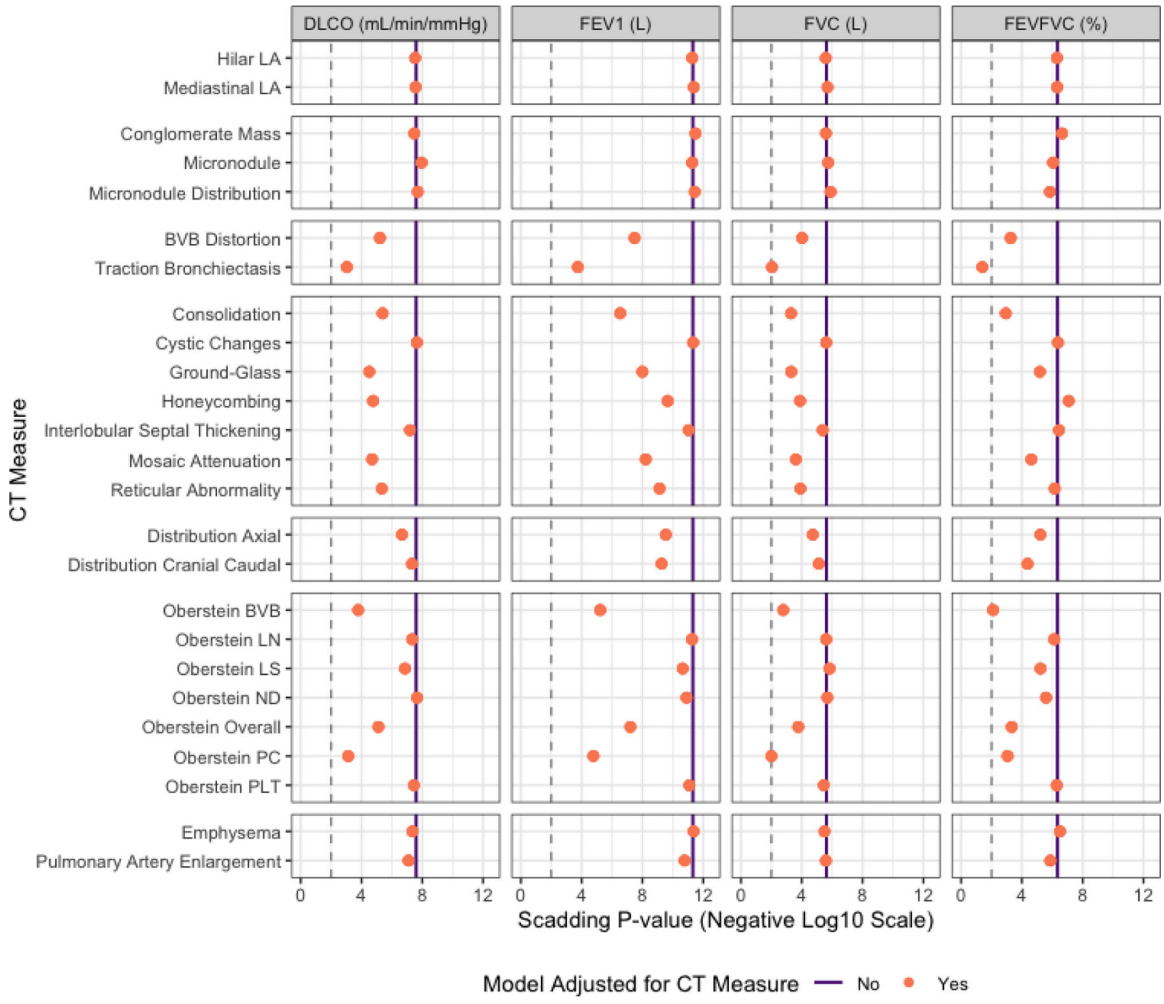

Figure 2:

Partial F-test p-values assessing significance of Scadding stage before (purple line) and after inclusion of an individual CT measure (red circles) in a linear model predicting a single PFT. All models included age, race/ethnicity, sex, height, and body mass index (BMI). P-values are plotted on a negative log base 10 scale. The dashed line indicates the threshold for significance P=0.01, with points to the right considered significant with respect to that threshold.

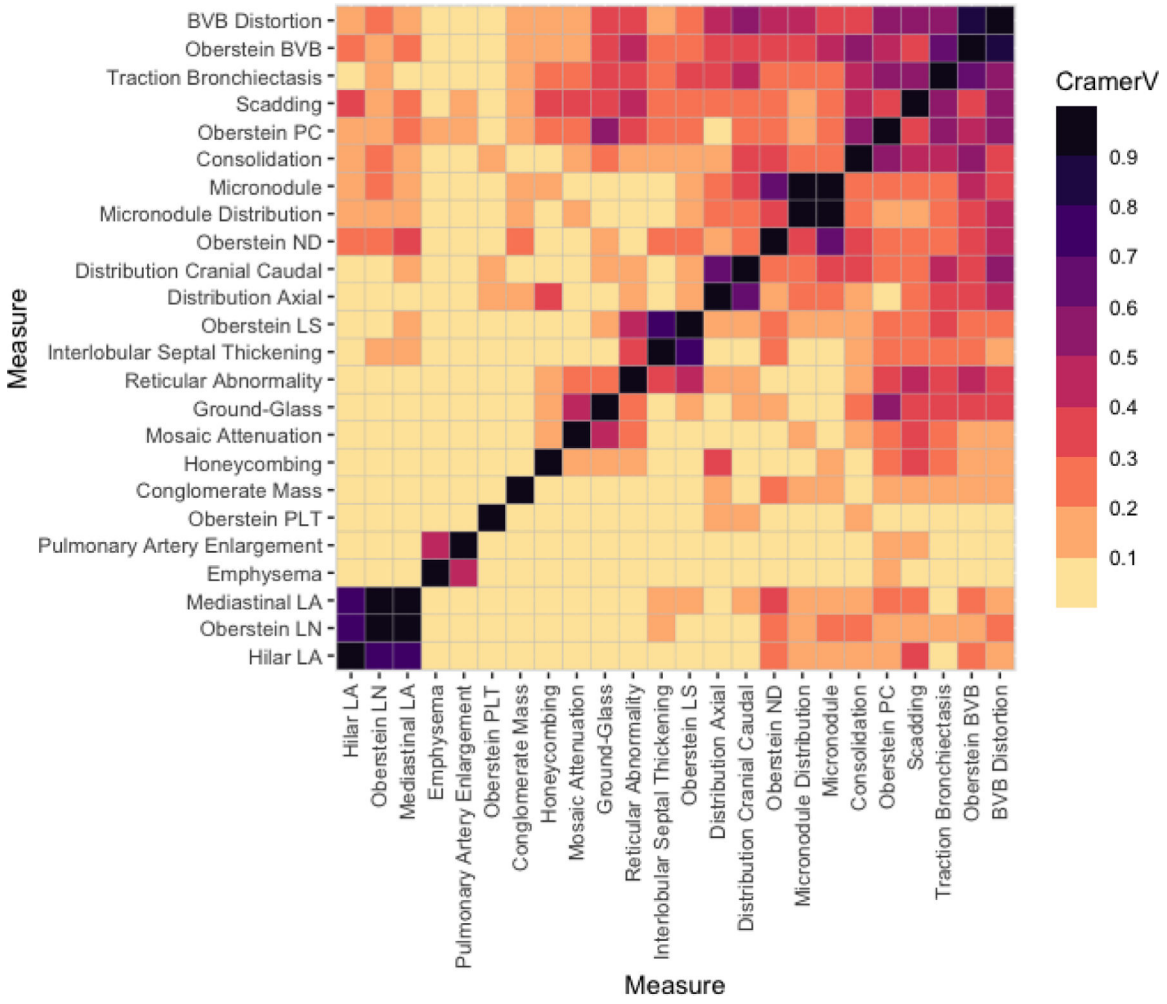

Figure 3:

A heatmap of strength of associations among CT measures and Scadding stage as measured by Cramer's V with bias correction.

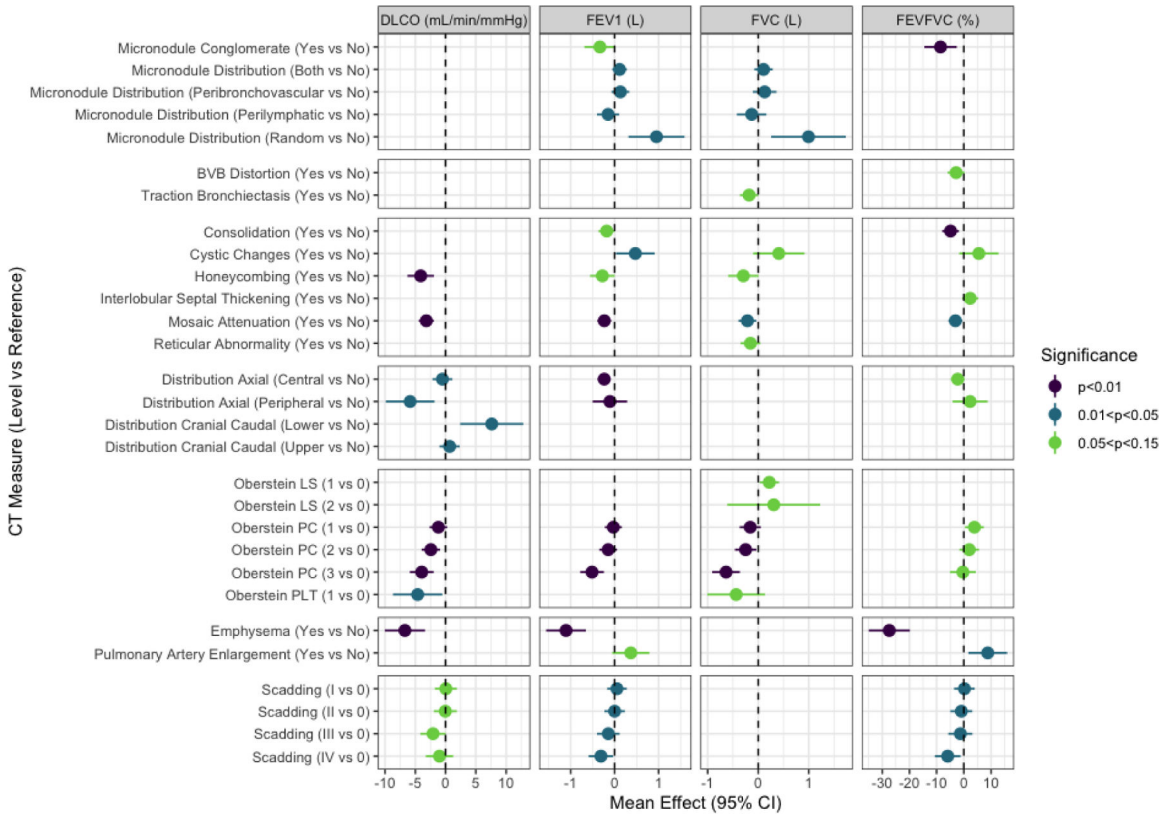

Figure 4:

Estimated associations in backwards selected models between each PFT and included CT measures. Coefficients and 95% confidence intervals are presented. The dashed black line demarks a coefficient estimate of 0. Dark purple indicates significance at the level $P<0.01$, medium blue indicates significance at the level $P<0.05$, and light green indicates significance at the level $P<0.15$.

Table 1:

Demographics and pulmonary function by Scadding stage

		Scadding Stage						
	N Missing	**0 (N=44, 12.5%)**	**I (N=75, 21.4%)**	**II (N=104, 29.6%)**	**III (N=46, 13.1%)**	**IV (N=82, 23.4%)**	**Total (N=351)**	**p value**
Demographics								
Sex (N (%))	4							0.15
Female		28 (63.6%)	44 (60.3%)	46 (44.7%)	23 (50.0%)	45 (55.6%)	186 (53.6%)	
Male		16 (36.4%)	29 (39.7%)	57 (55.3%)	23 (50.0%)	36 (44.4%)	161 (46.4%)	
Race/Ethnicity (N (%))	5							0.09
Asian, American Indian, Alaska Native, or not identifying a single primary race		1 (2.3%)	0 (0.0%)	6 (5.8%)	1 (2.2%)	2 (2.5%)	10 (2.9%)	
Black		6 (13.6%)	12 (16.4%)	25 (24.3%)	12 (26.7%)	29 (35.8%)	84 (24.3%)	
Hispanic		3 (6.8%)	4 (5.5%)	4 (3.9%)	1 (2.2%)	5 (6.2%)	17 (4.9%)	
White		34 (77.3%)	57 (78.1%)	68 (66.0%)	31 (68.9%)	45 (55.6%)	235 (67.9%)	
Education Status (N (%))	7							0.15
High School		8 (18.6%)	14 (19.2%)	24 (23.3%)	4 (8.7%)	17 (21.5%)	67 (19.5%)	
Some College		10 (23.3%)	33 (45.2%)	29 (28.2%)	20 (43.5%)	27 (34.2%)	119 (34.6%)	
College Diploma		14 (32.6%)	11 (15.1%)	32 (31.1%)	11 (23.9%)	22 (27.8%)	90 (26.2%)	
Graduate or Professional Degree		11 (25.6%)	15 (20.5%)	18 (17.5%)	11 (23.9%)	13 (16.5%)	68 (19.8%)	
Income Status (N (%))	12							0.74
<$50,000		14 (33.3%)	22 (31.0%)	27 (26.5%)	12 (26.1%)	31 (39.7%)	106 (31.3%)	
$50,000 - $99,999		12 (28.6%)	17 (23.9%)	30 (29.4%)	16 (34.8%)	23 (29.5%)	98 (28.9%)	
$100,000 - $149,999		7 (16.7%)	14 (19.7%)	20 (19.6%)	10 (21.7%)	14 (17.9%)	65 (19.2%)	
≥$150,000		9 (21.4%)	18 (25.4%)	25 (24.5%)	8 (17.4%)	10 (12.8%)	70 (20.6%)	
Age [Years (mean (SD))]	4	52.95 (9.42)	50.61 (11.53)	52.90 (9.40)	50.81 (10.84)	55.49 (9.01)	52.75 (10.10)	0.03
Height[Inches, (mean (SD))]	1	66.61 (4.05)	67.01 (3.41)	67.60 (4.26)	66.74 (4.51)	66.45 (4.07)	66.97 (4.06)	0.37
BMI [kg/m^2(mean (SD))]	1	33.36 (6.39)	32.58 (7.68)	29.46 (5.30)	32.43 (7.28)	28.14 (5.54)	30.69 (6.61)	< 0.01
Pulmonary Function (mean (SD))								
Pre-BD FVC (Liters)	12	3.74 (1.02)	3.78 (1.07)	3.79 (1.12)	3.56 (1.14)	2.98 (1.15)	3.57 (1.15)	< 0.01
Post-BD FVC (Liters)	18	3.69 (1.04)	3.77 (1.07)	3.84 (1.10)	3.58 (1.14)	3.08 (1.15)	3.60 (1.14)	< 0.01
Pre-BD FEV1 (Liters)	12	2.90 (0.76)	2.89 (0.88)	2.78 (0.87)	2.63 (0.97)	1.95 (0.87)	2.61 (0.94)	< 0.01
Post-BD FEV1 (Liters)	18	2.92 (0.82)	2.97 (0.91)	2.91 (0.88)	2.72 (0.99)	2.08 (0.90)	2.70 (0.96)	< 0.01
Pre-BD FEV1/FVC %	12	78.00 (5.35)	76.23 (8.35)	73.49 (8.01)	74.10 (11.93)	66.03 (13.59)	73.03 (10.68)	< 0.01

	Scadding Stage							
	N Missing	**0 (N=44, 12.5%)**	**I (N=75, 21.4%)**	**II (N=104, 29.6%)**	**III (N=46, 13.1%)**	**IV (N=82, 23.4%)**	**Total (N=351)**	**p value**
Post-BD FEV1/FVC %	18	79.77 (9.32)	78.42 (8.71)	75.83 (8.16)	76.14 (12.69)	68.14 (13.93)	75.08 (11.35)	< 0.01
Post-BD DLCO (mL/min/mmHg)	23	24.38 (7.44)	24.18 (7.60)	23.57 (7.21)	21.54 (8.06)	17.46 (7.12)	22.11 (7.85)	< 0.01

BD = bronchodilator, BMI = body mass index, DLCO = diffusing capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, SD = standard deviation

Table 2:

Distribution of each CT Visual Assessment Score measure by Scadding stage

	Scadding Stage						
N (%)	**0 (N=44, 12.5%)**	**I (N=75, 21.4%)**	**II (N=104, 29.6%)**	**III (N=46, 13.1%)**	**IV (N=82, 23.4%)**	**Total (N=351)**	**p value**
Lymphadenopathy							
Mediastinal LN	15 (34.1%)	45 (60.0%)	74 (71.2%)	13 (28.3%)	49 (59.8%)	196 (55.8%)	< 0.01
Hilar LN	10 (22.7%)	37 (49.3%)	63 (60.6%)	8 (17.4%)	39 (47.6%)	157 (44.7%)	< 0.01
Nodules							
Micronodules	9 (20.5%)	24 (32.0%)	66 (63.5%)	23 (50.0%)	42 (51.2%)	164 (46.7%)	< 0.01
Micronodule Distribution *							< 0.01
None	36 (81.8%)	51 (68.0%)	40 (38.5%)	23 (50.0%)	40 (48.8%)	190 (54.1%)	
Perilymphatic	4 (9.1%)	6 (8.0%)	4 (3.8%)	2 (4.3%)	6 (7.3%)	22 (6.3%)	
Peribronchovascular	3 (6.8%)	10 (13.3%)	17 (16.3%)	3 (6.5%)	11 (13.4%)	44 (12.5%)	
Both	1 (2.3%)	8 (10.7%)	42 (40.4%)	17 (37.0%)	24 (29.3%)	92 (26.2%)	
Random	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (2.2%)	1 (1.2%)	3 (0.9%)	
Conglomerate Mass	0 (0.0%)	0 (0.0%)	8 (7.7%)	2 (4.3%)	1 (1.2%)	11 (3.1%)	0.02
Parenchymal Opacity and Airway and Vascular Distortion *							
Ground-Glass	4 (9.1%)	14 (18.7%)	36 (34.6%)	15 (32.6%)	55 (67.1%)	124 (35.3%)	< 0.01
Honeycombing	1 (2.3%)	3 (4.0%)	2 (1.9%)	2 (4.3%)	19 (23.2%)	27 (7.7%)	< 0.01
Reticular Abnormality	5 (11.4%)	4 (5.3%)	25 (24.0%)	14 (30.4%)	48 (58.5%)	96 (27.4%)	< 0.01
Consolidation	0 (0.0%)	7 (9.3%)	25 (24.0%)	7 (15.2%)	46 (56.1%)	85 (24.2%)	< 0.01
Mosaic Attenuation	8 (18.2%)	17 (22.7%)	19 (18.3%)	9 (19.6%)	44 (53.7%)	97 (27.6%)	< 0.01
Interlobular Septal Thickening	3 (6.8%)	5 (6.7%)	19 (18.3%)	6 (13.0%)	27 (32.9%)	60 (17.1%)	< 0.01
Traction Bronchiectasis	1 (2.3%)	10 (13.3%)	37 (35.6%)	19 (41.3%)	74 (90.2%)	141 (40.2%)	< 0.01
Cystic Changes	3 (6.8%)	1 (1.3%)	2 (1.9%)	0 (0.0%)	2 (2.4%)	8 (2.3%)	0.31
BVB Distortion	5 (11.4%)	29 (38.7%)	79 (76.0%)	33 (71.7%)	78 (95.1%)	224 (63.8%)	< 0.01
Distribution and Pattern of Distortion							
Distribution Cranial Caudal *							< 0.01
None	42 (95.5%)	63 (84.0%)	54 (51.9%)	22 (47.8%)	32 (39.0%)	213 (60.7%)	
Upper	1 (2.3%)	12 (16.0%)	48 (46.2%)	23 (50.0%)	49 (59.8%)	133 (37.9%)	
Lower	1 (2.3%)	0 (0.0%)	2 (1.9%)	1 (2.2%)	1 (1.2%)	5 (1.4%)	
Distribution Axial *							< 0.01
None	42 (95.5%)	63 (84.0%)	65 (62.5%)	24 (52.2%)	45 (54.9%)	239 (68.1%)	
Central	1 (2.3%)	12 (16.0%)	37 (35.6%)	20 (43.5%)	33 (40.2%)	103 (29.3%)	
Peripheral	1 (2.3%)	0 (0.0%)	2 (1.9%)	2 (4.3%)	4 (4.9%)	9 (2.6%)	

	Scadding Stage						
N (%)	**0 (N=44, 12.5%)**	**I (N=75, 21.4%)**	**II (N=104, 29.6%)**	**III (N=46, 13.1%)**	**IV (N=82, 23.4%)**	**Total (N=351)**	**p value**
Oberstein Components							
Oberstein Bronchovascular Bundle Component							< 0.01
0	39 (88.6%)	41 (54.7%)	19 (18.3%)	11 (23.9%)	2 (2.4%)	112 (31.9%)	
1	3 (6.8%)	25 (33.3%)	32 (30.8%)	16 (34.8%)	13 (15.9%)	89 (25.4%)	
2	0 (0.0%)	9 (12.0%)	27 (26.0%)	16 (34.8%)	27 (32.9%)	79 (22.5%)	
3	2 (4.5%)	0 (0.0%)	26 (25.0%)	3 (6.5%)	40 (48.8%)	71 (20.2%)	
Oberstein Parenchymal Consolidation Component							< 0.01
0	37 (84.1%)	58 (77.3%)	40 (38.5%)	29 (63.0%)	8 (9.8%)	172 (49.0%)	
1	3 (6.8%)	12 (16.0%)	28 (26.9%)	9 (19.6%)	20 (24.4%)	72 (20.5%)	
2	3 (6.8%)	4 (5.3%)	23 (22.1%)	8 (17.4%)	31 (37.8%)	69 (19.7%)	
3	1 (2.3%)	1 (1.3%)	13 (12.5%)	0 (0.0%)	23 (28.0%)	38 (10.8%)	
Oberstein Intra-Parenchymal Nodules Component							< 0.01
0	35 (79.5%)	46 (61.3%)	31 (29.8%)	22 (47.8%)	27 (32.9%)	161 (45.9%)	
1	8 (18.2%)	29 (38.7%)	38 (36.5%)	14 (30.4%)	37 (45.1%)	126 (35.9%)	
2	0 (0.0%)	0 (0.0%)	21 (20.2%)	5 (10.9%)	13 (15.9%)	39 (11.1%)	
3	1 (2.3%)	0 (0.0%)	14 (13.5%)	5 (10.9%)	5 (6.1%)	25 (7.1%)	
Oberstein Septal and Nonseptal Lines Component							< 0.01
0	40 (90.9%)	68 (90.7%)	74 (71.2%)	34 (73.9%)	41 (50.0%)	257 (73.2%)	
1	3 (6.8%)	6 (8.0%)	30 (28.8%)	12 (26.1%)	40 (48.8%)	91 (25.9%)	
2	1 (2.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	3 (0.9%)	
Oberstein Pleural Thickening Component							0.69
0	44 (100.0%)	74 (98.7%)	102 (98.1%)	46 (100.0%)	78 (95.1%)	344 (98.0%)	
1	0 (0.0%)	1 (1.3%)	2 (1.9%)	0 (0.0%)	2 (2.4%)	5 (1.4%)	
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)	2 (0.6%)	
Oberstein Lymph Node Enlargement Component							< 0.01
0	29 (65.9%)	25 (33.3%)	27 (26.0%)	32 (69.6%)	31 (37.8%)	144 (41.0%)	
1	12 (27.3%)	26 (34.7%)	28 (26.9%)	9 (19.6%)	23 (28.0%)	98 (27.9%)	
2	3 (6.8%)	23 (30.7%)	47 (45.2%)	5 (10.9%)	27 (32.9%)	105 (29.9%)	
3	0 (0.0%)	1 (1.3%)	2 (1.9%)	0 (0.0%)	1 (1.2%)	4 (1.1%)	
Other Findings							
Emphysema	0 (0.0%)	1 (1.3%)	2 (1.9%)	2 (4.3%)	4 (4.9%)	9 (2.6%)	0.44
Pulmonary Artery Enlargement	0 (0.0%)	0 (0.0%)	2 (1.9%)	2 (4.3%)	6 (7.3%)	10 (2.8%)	0.04
Prior Thoracic Surgery	1 (2.3%)	2 (2.7%)	1 (1.0%)	1 (2.2%)	0 (0.0%)	5 (1.4%)	0.44

*For assessments of distribution, a marking of none is consistent both with a presence of abnormalities that lacked one of the specific distributional patterns listed and with an absence of abnormalities.

**no subjects were reported as having tree-in-bud or cavitary lesions

BVB = bronchovascular bundle, LN = lymphadenopathy

Table 3:

Distribution of Chest x-ray and CT inconsistencies by Scadding stage. Details of CT-based determination of inconsistencies is provided in e-Table 4.

	Scadding Stage					
	0 (N=44)	**I (N=75)**	**II (N=104)**	**III (N=46)**	**IV (N=82)**	**Total (N=351)**
Consistent	45.5%	30.7%	61.5%	54.3%	100.0%	61.0%
Inconsistent LN and PA	11.4%	13.3%	8.7%	4.3%	0.0%	7.4%
Inconsistent LN Only	22.7%	21.3%	18.3%	19.6%	0.0%	15.4%
Inconsistent PA Only	20.5%	34.7%	11.5%	21.7%	0.0%	16.2%

LN = lymphadenopathy, PA = parenchymal abnormalities

Table 4:

Concordance estimates and 95% confidence intervals of duplicate VAS reads for 168 individuals. Estimates are for concordance of presence/absence assessments unless otherwise indicated

Variable	Cohen's Kappa
Mediastinal LN	
Location	0.58 (0.47,0.7)
Presence	0.62 (0.5,0.74)
Hilar LN	
Location	0.54 (0.41,0.66)
Presence	0.55 (0.42,0.68)
Micronodule Distribution	
Location	0.15 (0.04,0.26)
Presence	0.25 (0.1,0.39)
BVB Distortion	0.46 (0.32,0.59)
Traction Bronchiectasis	0.4 (0.25,0.54)
Ground-Glass	0.48 (0.34,0.62)
Reticular Abnormality	0.28 (0.13,0.43)
Consolidation	0.33 (0.13,0.53)
Mosaic Attenuation	0.27 (0.11,0.43)
Oberstein BVB	
Severity	0.2 (0.1,0.3)
Presence	0.56 (0.42,0.69)
Oberstein PC	
Severity	0.26 (0.14,0.39)
Presence	0.42 (0.28,0.56)
Oberstein ND	
Severity	0.3 (0.19,0.42)
Presence	0.33 (0.18,0.47)
Oberstein LS	
Severity	0.19 (0.05,0.34)
Presence	0.24 (0.09,0.38)
Oberstein LN	
Severity	0.5 (0.39,0.61)
Presence	0.64 (0.52,0.76)

LN = lymphadenopathy, BVB= Bronchovascualar bundle distortion, PC= parenchymal consolidation, ND=nodule, LS=septal and non-septal lines