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Published in final edited form as:
Acad Radiol. 2011 July ; 18(7): 885–891. doi:10.1016/j.acra.2011.02.015.

Smoking Inhibits the Frequency of Bronchovascular Bundle Thickening in Sarcoidosis

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Abstract

Rationale/Objectives—Smoking has been associated with decreased incidence and prevalence of sarcoidosis, but few studies have evaluated effects of smoking on clinical parameters of the disease. The objectives were to determine the association of smoking with radiographic patterns and to evaluate the associations of these smoking-related radiographic patterns on airflow obstruction in sarcoidosis.

Methods—Clinical data and CT scans of 124 patients with sarcoidosis were reviewed. CT scans were assessed for lymph nodes, nodules, bronchiectasis, bronchovascular bundle thickening, displaced hilum, fibrosis, ground glass, emphysema, pleural changes, and alveolar opacities. CT patterns were compared between patients with and without a history of smoking. The effect of smoking on the associations between radiographic patterns and airflow obstruction was assessed with multivariable analysis.

Results—Smokers had less frequency of bronchovascular bundle thickening than nonsmokers (11/38 subjects(29%) vs. 50/86 subjects(58%),p=0.003) and more emphysema (7/38 subjects(18%) vs. 1/86 subjects(1%),p=0.001). Patients who had bronchovascular bundle thickening were less likely to have ever smoked (11/61 subjects(18%) vs. 27/63 subjects(43%), p=0.003) or be current smokers (4/61 subjects(7%) vs. 15/63 subjects(24%),p=0.008). Age (p=0.003) and bronchovascular bundle thickening (p=0.02) were independent predictors of airflow obstruction. There were no differences in smoking history between patients with airflow obstruction versus those without (10/37 subjects(27)% vs. 28/87 subjects(32%),p=0.63).

Conclusions—In patients with sarcoidosis, smoking is associated with decreased frequency of bronchovascular bundle thickening, a very important clinical manifestation of the lung disease.

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IRB: 200702715. The University of Iowa Institutional Review Board

Further, bronchovascular bundle thickening and age are the only independent predictors of airflow obstruction, and smoking does not confound these associations.

Keywords

Smoking; CT scan; X-ray; Sarcoidosis; Airway Obstruction; Granuloma

INTRODUCTION

Sarcoidosis is an inflammatory disease of unknown etiology predominately affecting the lungs. Noncaseating granulomas are the hallmark of the disease, and can cause decreased pulmonary function, impairment of gas exchange, and fibrosis of lung parenchyma. The natural history of the disease is not completely understood, adding complexity to clinical management and treatment.[1] Thus, further study of clinical parameters is warranted.

Multiple epidemiologic studies have found smoking to be associated with decreased incidence and prevalence of the disease.[2-5] A case control etiologic study of sarcoidosis (ACCESS) showed that smoking subjects were less likely to have sarcoidosis (OR 0.62, CI 0.5-0.77), and Visser *et al.* found that patients presenting with sarcoid arthritis were much less likely to be smoking (OR 0.09, CI 0.02-0.37).[6,7] However, there are few studies that have evaluated the effect of smoking on patients who have sarcoidosis. For instance, two descriptive studies of sarcoidosis populations have not indicated that smoking affects progression or severity of disease, or that smoking prevents respiratory failure in this group.[3,8,9] The mechanisms behind this paradoxical phenomenon (decreased incidence, but no effect on disease severity) are unclear, and the question of how smoking has an overall effect on sarcoidosis remains unanswered.

In this study, the objective was to evaluate the effects of smoking on clinical parameters of the disease. First, we analyzed high resolution CT scans of sarcoidosis patients to determine differences in radiographic patterns between smokers and nonsmokers. Second, we evaluated the effect of these smoking-associated radiographic patterns on obstructive sarcoidosis lung disease.

METHODS

A chart review was performed on 275 adult patients (ages 18-75) diagnosed with pulmonary sarcoidosis between 2001 and 2007. Patients were included if they had been evaluated by a pulmonary physician and had a diagnosis of sarcoidosis with a consistent clinical presentation and a biopsy showing noncaseating granulomas. Each patient was required to have spirometry and CT scan imaging of the chest within 30 days of each other and available for review. Patients were excluded if there was a diagnosis of an alternative cause of granulomatous disease such as histoplasmosis, silicosis, berylliosis, malignancy, or talc-induced granulomas. One hundred and twenty-four patients fulfilled these criteria. The primary reason for exclusion was lack of CT data within thirty days of lung function testing. Due to retrospective review, the indications for CT scans were not available. Other data collected included race, age, gender, smoking history, organ involvement (other than lung), reported asthma and obstructive sleep apnea history, and treatment history.

CT Scans

CT scans (Siemens, USA) were performed using a volume scan and high resolution reconstruction algorithm at 1 mm and 3 mm slice thickness. These were independently reviewed by two pulmonologists with expertise in sarcoidosis and a chest radiologist for the presence or absence of lymph nodes, nodules, ground glass changes, thickened

bronchovascular bundles, bronchiectasis, displaced hilum, fibrosis, emphysema, alveolar consolidation, or pleural changes. Differences in readings were adjudicated after discussion between the examiners. Kappa scores calculated for the primary finding of bronchovascular bundle thickening prior to adjudication indicated good to very good agreement (kappa range 0.65 to 0.83) between the three examiners. The examiners were blinded to the clinical data of smoking status, pulmonary function tests, and prior CT readings.

Pulmonary Function Tests

Pulmonary function tests were performed using the American Thoracic Society guidelines.[10] FVC, FEV1, and FEV1/FVC prior to bronchodilators were recorded for each patient. Obstructive lung disease was defined as an FEV1/FVC ratio less than 70%. Total lung capacity (TLC) and diffusing capacity (DLco) were also recorded. Pulmonary function results are reported as percentages of predicted values.

Analysis

Tests of normality (Shapiro-Wilk tests) were performed prior to comparisons of continuous data. Age, FVC, FEV1, and TLC were presented as means with standard deviations (SD), while FEV1/FVC and DLco were presented as medians with interquartile range (IQR). Student's T-tests were performed for comparisons of normally distributed data, while Wilcoxon rank sum tests were performed for data that were not normally distributed. Comparisons of categorical data were evaluated using Pearson chi-square tests or Fisher's exact tests depending on frequency of occurrence. To evaluate the effect of smoking on the relationship between radiographic patterns and obstructive lung disease, stepwise logistic regression analysis was used initially to establish independent predictors of obstruction. Radiographic patterns that were significant at $p=0.1$ level in the univariate analysis were entered as covariates and kept in the model if significant at $p<0.05$. Based on this analysis, a final logistic regression model was established, which included age, smoking status, race, and bronchovascular bundle thickening as covariates. Linearity of age was examined by fitting a logistic regression model where the variable age was categorized based on quartiles using the lowest quartile as reference. The estimates corresponding to each age category were plotted against the midpoint of each interval. From this, we concluded that age was a linear effect and kept it as a continuous variable. P-values of <0.05 were considered statistically significant. Kappa analysis was performed to assess interobserver variability. All analyses were performed using SAS 9.2 statistical package (SAS, Cary, North Carolina). This study was approved by the Institutional Review Board (Approval #200702715).

RESULTS

Patient Characteristics

The study included 124 patients with pulmonary sarcoidosis. Demographic characteristics, smoking status, systemic and inhaled treatment histories, pulmonary function, and CT findings are described in Table 1. Ninety-four (76%) of patients underwent systemic treatment. The indication for treatment was pulmonary disease in 49 patients (52% of those treated) and organ-threatening extrapulmonary disease in 45 patients (48% of those treated). Of patients treated with systemic medications, the CT scans were obtained prior to treatment in 35%, during treatment in 36%, and after completion of treatment in 15% of patients. The most common CT findings were bronchovascular bundle thickening (Figure 1), lymphadenopathy, and nodules.

Comparison of Smokers versus Non-smokers

Findings between smokers and nonsmokers are summarized in Table 2. The only significant differences between smokers and nonsmokers on lung CT were the frequencies of bronchovascular bundle thickening and emphysema. Patients who smoked were more likely to be younger (42 years vs. 48 years, p=0.01) and African-American (26% vs. 10%, p=0.03). The median pack-year smoking history was 10 pack-years for subjects who had ever smoked (IQR 5-30), and was also 10 pack-years for both ex-smokers (IQR 5-30), and current smokers (IQR 7-30). The median time from smoking cessation to CT scan was 9.0 years (IQR 1-15). In the subgroup of ten people with a smoking history who were obstructed, three had thickened bronchovascular bundles and three had emphysema. Smoking was not associated with the prevalence of obstructive lung disease in this population.

Similarly, patients who had bronchovascular bundle thickening were less likely than patients without bronchovascular bundle thickening to have ever smoked or be current active smokers and were more likely to have associated CT patterns of nodules (89% vs. 46%, p<0.0001), fibrosis (39% vs. 13%, p=0.0007), and displaced hilum (21% vs. 2%, p=0.0005) (Table 3).

CT Findings in Patients with Airflow Obstruction

The demographics, pulmonary function, smoking history, treatment histories, and frequencies of CT findings in obstructed versus non-obstructed patients are summarized in Table 4. Multivariate logistic regression modeling, including race and smoking status as covariates, revealed age (OR: 1.06 per year of age, 95% CI: 1.02-1.11, p=0.003) and bronchovascular bundle thickening (OR 3.28, 95%CI 1.31-8.22, p=0.02) to be independently associated with obstructive lung disease in sarcoidosis patients. These effects of bronchovascular bundle thickening was similar to that found in a model without smoking history (OR: 2.74, 95% CI: 1.17-6.38). Thus, a history of smoking did not confound these effects.

DISCUSSION

In this study, analysis revealed that patients with sarcoidosis with a history of smoking had a significant decrease in frequency of bronchovascular bundle thickening compared with nonsmokers with sarcoidosis. Further, a history of smoking was not predictive for obstructive lung disease in this population. Rather, age and bronchovascular bundle thickening were the primary determinants of airflow obstruction in a population of patients diagnosed with sarcoidosis.

The bronchovascular bundles are made up of the bronchi and accompanying pulmonary arteries which extend out radially from the hila of the lungs. Bronchovascular bundle thickening on CT scans refers to the appearance of branching lines with a beaded appearance along a peri-bronchovascular distribution.[11] Previous data have shown that radiographic findings correlate to pathologic findings in patients with sarcoidosis.[12] Our data suggest that granulomas along the airways and lymphatic vessels, as seen on CT as thickened bundles, are less frequent in those patients with a smoking history. The effect is apparent in patients who were ex-smokers and in those who currently smoke.

This is the first study to show an effect of smoking on bronchovascular bundle thickening. However, the idea that smoking may affect expression of the disease has been previously surmised due to a number of prior epidemiologic studies indicating decreased incidence and prevalence in smokers. The largest case control study to date (ACCESS) found that the odds of sarcoidosis risk in patients who ever smoked was significantly lower (OR 0.65, CI 0.51-0.82, p<0.001).[6] Our data provide a biologic correlate to this epidemiologic data, and

show that smoking also suppresses important indicators of disease in patient who already have sarcoidosis. Smoking has also been shown to have an effect on development of hypersensitivity pneumonitis, another granulomatous disease, although this effect cannot be generalized to all granulomatous diseases.[13,14]

Patho-physiologically, it has been suggested that smoking may decrease inflammatory cytokines that contribute to formation of granulomas.[15] Tobacco smoke decreases the release of TNF-alpha by alveolar macrophages in normal subjects and in those with sarcoidosis.[16] Similarly, nicotine has been shown to inhibit the formation of granulomas in hypersensitivity pneumonitis in a murine model.[17] Further, smokers with sarcoidosis have decreased alveolitis and decreased CD4:CD8 ratio as compared to nonsmoking sarcoidosis patients.[4,18] Our findings support cellular and animal model evidence of the effect of cigarette smoke on disease expression, providing further translational evidence of an effect in human subjects. It is currently unclear whether these effects are due to nicotine alone, or rather, one of the many components of tobacco smoke.

Previous authors have suggested that smoking has no effect on the extent, severity, or course of disease.[9,19] However, these studies did not utilize CT imaging in the methods, and this study is the first to methodologically assess these parameters. Although this study was not designed to assess prognosis, the marked effect of smoking on the presence of bronchovascular bundles on CT scans warrants further inspection of this phenomenon. If bronchovascular bundle thickening is a surrogate marker for airway obstruction or burden of granulomas in the airway, it could have implications for this disease. The effect of smoking may be more pronounced in early stages, particularly if the effects are due to changes in macrophage and lymphocyte function during development of the disease or in clearing a potential antigen exposure. Perhaps, as other studies have noted, there is no difference in prognosis between smokers and nonsmokers with sarcoidosis because smoking introduces as second insult on the lung that also contributes to the overall burden of lung disease and its prognosis, as clearly, emphysema is more prevalent in these patients.

It is also important to note that smoking was not independently associated with obstruction, which is likely related to the relatively young age of the population with a low prevalence of chronic obstructive pulmonary disease and emphysema. In addition, similar observations have also been noted in patients with both emphysema and pulmonary fibrosis.[20,21] It is likely that the presence of a parenchymal lung disease that causes lung restriction decreases the obstruction associated with emphysema because of its effect on elastic recoil of the lung. Radiographically, only eight subjects (6%) had evidence of emphysema in our study.

One previous study has shown that airflow obstruction in sarcoidosis is most strongly associated with smoking history and emphysema, and a correlation between the CT pattern of air trapping and obstruction occurred only in smokers.[22] A study in Japanese patients indicated that age, bronchovascular bundle thickening, chest radiographic stage IV (suggestive of pulmonary fibrosis), and smoking are associated with a lower FEV1/FVC, although multivariate analysis was limited by low frequencies of airway obstruction and bronchovascular bundle thickening in the population.[23] Only five patients with airflow obstruction had bronchovascular bundle thickening. Thus, it was not clear from this study which of these parameters was the primary determinant of obstruction. Our population includes a markedly higher frequency of obstructive lung disease and abnormal lung CT findings, and shows that bronchovascular bundle thickening and age are the main predictors of obstruction. Hansell *et al*. also described CT patterns in 45 patients with sarcoidosis and found that reticular patterns reflective of fibrosis were associated with airflow obstruction when compared with mosaic pattern, ground-glass opacities, nodules, or intense opacification with or without air bronchograms.[24] Bronchovascular bundle thickening was

not evaluated in that study. If bronchovascular bundle thickening had not been included in our study, the results would have resembled those of Hansell *et al*.

The strength of our study is that it includes a large number of patients in order to determine the influence of smoking on the interpretation of lung function and imaging results in sarcoidosis. For practical clinical purposes, these data emphasize that obstructive lung physiology should not automatically be attributed to smoking in patients with sarcoidosis, as subjects in this subgroup had an equally likely chance of having either bronchovascular bundle thickening or emphysema. Although smoking was not found to be a predictor, age was associated with obstruction. This factor appeared to be independent and did not interact with any particular CT pattern. This implies that bronchovascular bundle thickening may be driving the obstruction in sarcoidosis, but age is also contributing independently to the risk of obstruction. This may reflect an expected physiologic reaction to age.

Limitations exist due to the observational nature of this study. The percentage of airflow obstruction is high compared to the ACCESS study (30% versus 14%, respectively) and all subjects were required to have had a CT scan. In terms of patient characteristics, data was not available regarding alternative comorbidities that may also contribute to parenchymal findings and obstructive lung disease, and symptom severity was not available to incorporate into the analysis. The indications for the CT scans were not known which could have introduced selection bias in the study population. It is possible that only the most severe manifestations of the disease were selected in nonsmokers, whereas there was more liberal use of CT scanning in smokers to differentiate symptoms related to smoking related lung disease versus sarcoidosis that led to selection of less severe cases. The low incidence of emphysema in the population would suggest that this bias, if present, is rather small. Further, we were not able to study the interacting effects of race and smoking, given the demographics and low percentage of African-Americans in the referral population of this region. Another potential limitation is that the CT scans were performed over a seven year period which could have introduced variation in technique. However, all were high resolution scans performed on the same brand of CT scanner, and each was read with similar thickness of slice cuts.

In conclusion, the effects of smoking on sarcoidosis have now been shown in two ways: 1) the ACCESS study showed that smoking was associated with lower overall expression of sarcoidosis, and 2) this study shows that, in patients with sarcoidosis, smoking decreases a very important clinical manifestation of the lung disease, i.e. bronchovascular bundle thickening. In our study, this lung CT finding was strongly associated with airway obstruction. These associations cannot be deemed causal at this point, as the exact mechanisms behind this phenomenon are not delineated. It does, however, raise the question of whether smoking inhibits the immune response that leads to the formation of granulomas in sarcoidosis. Further study regarding this process may give further insight into mechanisms and development of this disease.

Acknowledgments

Funding: This work was supported in part by the National Institutes of Health, Grant 1KL2RR024980: Institute of Clinical and Translational Science, University of Iowa.

Abbreviation List

ACCESS	A Case Control Etiologic Study of Sarcoidosis
CT	Computed Tomography

FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
TLC	Total Lung Capacity
DLco	Diffusing Capacity
SD	Standard deviation
IQR	Interquartile range

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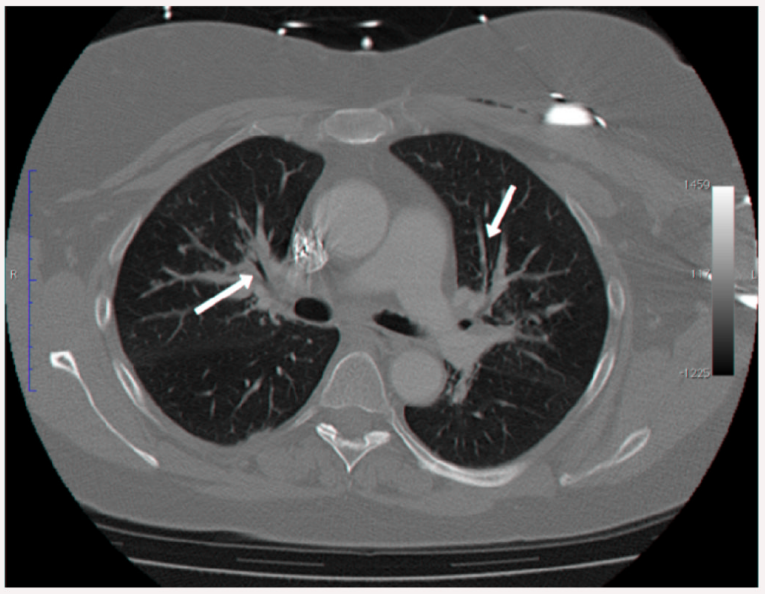

Figure 1.
Bronchovascular bundle thickening in sarcoidosis. An example of a subject with severe bronchovascular bundle thickening in the right lung and more subtle thickening in the left (arrows).

Table 1

Patient characteristics and CT findings

Variable	Population (n=124)
Age (years) *	45 (11) (range 16-75)
Gender	
Female	82 (66%)
Race	
African-American	19 (15%)
Caucasian	105 (85%)
Smoking Status	
Never Smoked	86 (69%)
Ever Smoked (Past or Active)	38 (31%)
Active Smoker	20 (16%)
Obstructive Lung Disease	37 (30%)
Pulmonary Function (%) *	
FVC	85 (19)
FEV1	83 (22)
FEV1/FVC	75 (67-80)
TLC	89 (18)
DLco	75 (64-85)
Asthma History	16 (13%)
Obstructive Sleep Apnea	16 (13%)
Systemic Treatment History	94 (76%)
Prednisone therapy	87 (70%)
Methotrexate	59 (48%)
Reason for Treatment	
Pulmonary Disease	49 (40%)
Extrapulmonary Disease	45 (36%)
Inhaled Therapies	51 (41%)
Corticosteroid Inhaler Only	13 (10%)
Bronchodilator Inhaler Only	12 (10%)
Steroid and Bronchodilator	26 (21%)
CT Findings	
Lymph Nodes	111 (90%)
Nodules	83 (67%)
BVB Thickening	61 (49%)
Fibrosis	32 (26%)
Bronchiectasis	29 (23%)
Ground Glass	23 (19%)
Alveolar Opacities	15 (12%)
Displaced Hilum	14 (11%)
Emphysema	8 (6%)

Variable	Population (n=124)
Pleural Changes	7 (6%)

* Age , FVC, FEV1, and TLC are presented as means with standard deviations (SD) . FEV1/FVC and Dlco are presented as medians with interquartile ranges (IQR).

Table 2

Patient characteristics and frequencies of CT findings according to smoking history

	Ever Smoked (n=38)	Never Smoked (n=86)	P-value
Age (years) *	42 (13)	48 (8)	0.01
Gender			
Female	28 (74%)	54 (63%)	0.2
Race			
Caucasian	28 (74%)	77 (90%)	0.03
African American	10 (26%)	9 (10%)	0.03
Obstructive Disease	10 (26%)	27 (31%)	0.6
Pulmonary Function (%) † *			
FVC	85 (21)	86 (18)	0.8
FEV1	83 (22)	83 (24)	0.98
FEV1/FVC	77 (70-82)	74 (66-78)	0.08
TLC	88 (19)	89 (17)	0.7
DLco	71 (55-83)	76 (66-88)	0.1
Treatment			
Total Treated	28 (74%)	66 (76%)	0.7
CT scan prior to treatment	15 (40%)	28 (32%)	0.5
Ongoing treatment during CT	11 (29%)	25 (29%)	1.0
Completed treatment	2 (5%)	13 (15%)	0.1
Reason for Treatment			
Pulmonary Disease	9 (24%)	40 (61%)	0.02
Extrapulmonary Disease	19 (50%)	26 (39%)	0.03
Type of Treatment			
Prednisone	24 (63%)	63 (73%)	0.3
Methotrexate	17 (45%)	42 (49%)	0.7
Inhaled Therapy	12 (32%)	39 (45%)	0.2
Corticosteroid Only	2 (5%)	11 (13%)	0.3
Bronchodilator Only	6 (16%)	6 (7%)	0.2
Steroid and Bronchodilator	4 (11%)	22 (26%)	0.09
CT Findings			
Lymph Nodes	36 (95%)	75 (87%)	0.2
Bronchiectasis	9 (24%)	20 (23%)	0.9
Nodules	23 (61%)	60 (70%)	0.3
Thickened BV Bundles	11 (29%)	50 (58%)	0.003
Ground Glass	10 (26%)	13 (15%)	0.1
Displaced Hilum	3 (8%)	10 (12%)	0.8
Emphysema	7 (18%)	1 (1%)	0.001
Alveolar Opacities	3 (8%)	12 (14%)	0.6
Pleural Changes	0 (0%)	7 (8%)	0.1

	Ever Smoked (n=38)	Never Smoked (n=86)	P-value
Fibrosis	9 (24%)	23 (27%)	0.8

*Age , FVC, FEV1, and TLC are presented as means with standard deviations (SD) . Student's t-tests were used for comparisons of these variables.

†FEV1/FVC and Dlco are presented as median with interquartile range (IQR). Wilcoxon rank sum tests were used for comparisons of these variables.

Table 3

Characteristics of patients with the CT finding of bronchovascular bundle thickening

	Thick BV Bundles (n=61)	No Thick BV Bundles (n=63)	P-value
Age (years) *	47 (13)	45 (9)	0.4
Smoking Status			
Current Active Smokers	4 (7%)	15 (24%)	0.008
Ever Smoked†	11 (18%)	27 (43%)	0.003
Never Smoked	50 (82%)	36 (57%)	0.003
Obstructed	25 (41%)	12 (19%)	0.008
Ever Treated	51 (84%)	43 (68%)	0.04
Prednisone	48 (79%)	39 (62%)	0.05
Methotrexate	30 (49%)	29 (46%)	0.9
Inhaled Therapies	29 (48%)	22 (35%)	0.2

*Age values are expressed as means with standard deviations (mean (SD)). Student's t-tests were used for comparisons of this variable.

†Includes those who are current active smokers and those who have smoked in the past.

Table 4

Characteristics of obstructed and non-obstructed patients

Variable	Non-Obstructed (n=87)	Obstructed (n=37)	P-value
Age (years) †	43 (11)	51 (10)	0.0008
Gender			
Female	57 (65%)	25 (68%)	0.8
Race			
African-American	17 (20%)	2 (5%)	0.06
Caucasian	70 (80%)	35 (95%)	0.06
Smoking Status			
Never Smoked	59 (68%)	27 (73%)	0.6
Ever Smoked	28 (32%)	10 (27%)	0.6
Obstructive Disease			
Pulmonary Function (%) * †			
FVC	88 (20)	80 (16)	0.05
FEV1	90 (20)	67 (18)	<0.0001
FEV1/FVC	78 (75-82)	64 (57-67)	<0.0001
TLC	87 (17)	92 (19)	0.3
DLco	76 (60-84)	74 (65-88)	0.6
Asthma History	9 (10%)	7 (19%)	0.2
Obstructive Sleep Apnea	9 (10%)	7 (19%)	0.2
Treatment History			
Prednisone therapy	57 (65%)	30 (81%)	0.09
Methotrexate	39 (45%)	20 (54%)	0.3
Inhaled therapies	27 (27%)	24 (65%)	0.0005
Steroid/Bronchodilator	14 (16%)	12 (32%)	0.04
Corticosteroid	6 (7%)	7 (19%)	0.06
Bronchodilator Only	7 (8%)	5 (14%)	0.3
CT Findings			
Lymph Nodes	79 (91%)	32 (86%)	0.5
Nodules	53 (61%)	30 (81%)	0.03
BVB Thickening	36 (41%)	25 (68%)	0.008
Fibrosis	18 (21%)	14 (38%)	0.04
Bronchiectasis	17 (20%)	12 (32%)	0.1
Ground Glass	13 (15%)	10 (27%)	0.1
Alveolar Opacities	8 (9%)	7 (19%)	0.1
Displaced Hilum	5 (6%)	8 (22%)	0.02
Emphysema	4 (5%)	4 (11%)	0.2
Pleural Changes	5 (6%)	2 (5%)	0.9

* Age , FVC, FEV1, and TLC are presented as means with standard deviations (SD) . Student's t-tests were used for comparisons of these variables.

[†]FEV1/FVC and Dlco are presented as median with interquartile range (IQR). Wilcoxon rank sum tests were used for comparisons of these variables.