Identification of Early Interstitial Lung Disease in Smokers from the COPDGene Study

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Rationale and Objectives: The aim of this study is to compare two subjective methods for the identification of changes suggestive of early interstitial lung disease (ILD) on chest computed tomographic (CT) scans.

Materials and Methods: The CT scans of the first 100 subjects enrolled in the COPDGene Study from a single institution were examined using a sequential reader and a group consensus interpretation scheme. CT scans were evaluated for the presence of parenchymal changes consistent with ILD using the following scoring system: 0 = normal, 1 = equivocal for the presence of ILD, 2 = highly suspicious for ILD, and 3 = classic ILD changes. A statistical comparison of patients with early ILD to normal subjects was performed.

Results: There was a high degree of agreement between methods ($\kappa = 0.84$; 95% confidence interval, 0.73–0.94; $P < .0001$ for the sequential and consensus methods). The sequential reading method had both high positive (1.0) and negative (0.97) predictive values for a consensus read despite a 58% reduction in the number of chest CT evaluations. Regardless of interpretation method, the prevalence of chest CT changes consistent with early ILD in this subset of smokers from COPDGene varied between 5% and 10%. Subjects with early ILD tended to have greater tobacco smoke exposure than subjects without early ILD ($P = .053$).

Conclusions: A sequential CT interpretation scheme is an efficient method for the visual interpretation of CT data. Further investigation is required to independently confirm our findings and further characterize early ILD in smokers.

Key Words: Early interstitial lung disease; CT scan; smoker.

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial lung disease (ILD), with an estimated 3-year survival rate of 50% (1–3). IPF is typically diagnosed 3 to 4 years after the development of symptoms, by which time most patients have advanced pulmonary fibrosis that does not respond to therapeutic intervention. Some authors have speculated that the poor response to medical therapy is due to advanced organ remodeling, although it is unclear, if initation of therapy at the earliest stages of disease would alter its clinical course (4,5).

Our group has previously demonstrated both chest computed tomographic (CT) and pathologic evidence of early ILD in asymptomatic members in 18 kindreds affected with familial IPF (6). These findings suggest that screening high risk populations may, in some cases, detect early subclinical stages of ILD. Although early disease detection may lead to a better understanding of the natural history of IPF, strategies for detection and screening in high-risk populations have not been formally investigated. To address this issue, we compared an efficient sequential reading method (7) to a consensus reading method for the identification of early ILD in a population of smokers (both with and without chronic obstructive pulmonary disease [COPD]) enrolled in the COPDGene Study. We report a high degree of correlation between methods and present the comparison of the clinical characteristics of subjects identified as having early ILD in the COPDGene Study.

MATERIALS AND METHODS

COPDGene

The COPDGene Study is a multicenter investigation focused on examining the genetic and epidemiologic basis of COPD

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and other smoking-related lung diseases. Study participants complete a protocol that includes questionnaires, medical record review, physical examination, and spirometric measures of lung function before and after the administration of a short-acting inhaled bronchodilator. Common metrics of lung function reported from this maneuver include forced expiratory volume in 1 second (FEV_1), which is the volume of gas that a subject can forcibly exhale during the first second of effort, and the forced vital capacity (FVC), which is the total volume of gas that can be forcibly exhaled from the lungs. Both measures are expressed as percentages of their predicted values on the basis of those found in a normal population. Additional testing included 6-minute walk tests, collection of blood samples for genetic testing, and high-resolution CT scanning of the chest at full inspiration and expiration. The first 100 COPDGene subjects enrolled at a single institution were included in this analysis. All subjects provided written informed consent for participation in COPDGene. The study was approved by the institutional review boards of all participating COPDGene centers.

CT Scans

All subjects were scanned with 16-detector or 64-detector CT scanners (Definition 16 or Sensation 64; Siemens Medical Solutions, Forchheim, Germany). Imaging was performed during breath hold at full inflation (total lung capacity) and expiration (functional residual capacity) with the patient in the supine position. Every patient was carefully instructed in how to breathe before the scan. Only the inspiratory images were used in this investigation.

Multislice CT scanning parameters were as follows: collimation, 0.5 mm; tube voltage, 120 kV; tube current, 200 mA; gantry rotation time, 0.5 s; and pitch, 1.1. The images reviewed for this analysis were reconstructed using a high-resolution reconstruction algorithm with a slice thickness of 1 mm and a reconstruction interval of 10 mm. All images were reviewed on picture archiving and communication system (PACS) workstations (Centricity; GE Healthcare, Milwaukee, WI) using axial images, with a window level of −700 Hounsfield units and a window width of 1500 Hounsfield units.

CT Scoring

CT findings were scored by four readers (including one pulmonologist and three radiologists) as follows: 0 = no evidence of ILD, 1 = equivocal for ILD, 2 = suspicious for ILD, and 3 = ILD. "Equivocal for ILD" (a score of 1) was defined as focal or unilateral ground-glass attenuation, focal or unilateral reticulation, and patchy ground-glass abnormality (<5% of the lung). "Suspicious for ILD" (a score of 2) was defined as nondependent ground-glass abnormality affecting >5% of any lung zone, nondependent reticular abnormality, diffuse centrilobular nodularity with ground-glass abnormality, honeycombing, traction bronchiectasis, nonemphysematous cysts, and architectural distortion. "ILD" (a score of 3) was defined as bilateral fibrosis in multiple lobes associated to honeycombing and traction bronchiectasis in a subpleural distribution.

Sequential Reading Method

The sequential reading process is similar to a method similar to that proposed by Lynch et al (7). In the sequential reading process (Fig 1), the 100 CT scans were divided among four PACS workstations. Reader 1 would review the scans at his or her station and provide a score of 0, 1, 2, or 3. CT scans including those scans given scores of 1 or 2 and a random selection of approximately 20% of the normal scans (scored 0) would be provided to reader 2, who was blinded to the initial interpretation. Finally, reader 3, who was blinded to the interpretations of readers 1 and 2, provided majority opinion on those scans discordantly scored between readers 1 and 2.

Consensus Reading Method

Once scored by the sequential method, consensus opinion for each CT scan was provided by the group after collectively reviewing the all of the CT scans.

Statistical Analysis

Kappa statistics were calculated to evaluate the agreement between the 2 CT interpretation schemes. Positive and negative predictive values (identifying scores of 2 vs scores of 1 and 0) were determined to compare the effectiveness of the sequential reading method in comparison to the consensus method.

A comparison of patients with early ILD to normal subjects was performed using Fisher's exact test (used to examine the significance of the association between two small sample sizes of binary variables) (8) and Wilcoxon's rank-sum tests for continuous variables (nonparametric method for comparison of the medians of two populations) (9). Data analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). P values $< .05$ were considered statistically significant.

RESULTS

Cohort Demographics

The demographic and functional data of the study cohort are provided in Table 1. The median age of the cohort was 61 years, and 44% were men. Forty-seven of the subjects were current smokers, and the median tobacco history (average number of packs per day multiplied by the number of years smoked) was 37.6 pack-years. The median FEV_1 expressed as a percentage of the predicted value was 87% (interquartile range, 73%–100%), and the median FVC expressed as a percentage of the predicted value was 94.5 (interquartile

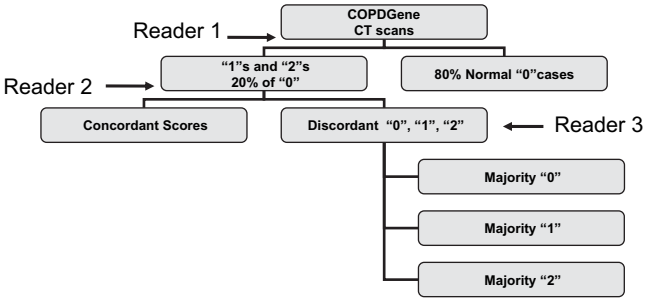

Figure 1. Sequential computed tomographic (CT) interpretation.

TABLE 1. Demographic and Functional Data of the Study Cohort (*n* = 100)

Characteristic	Value
Men	44
Age (y)	61.5 (56.6–67.1)
Age started smoking (y)	16 (14.5–18.5)
Current smoker	47
Tobacco history (pack-years)	37.6 (24.2–53.9)
FEV_1 (% predicted)	87 (73–100)
FVC (% predicted)	94.5 (83–103.5)
FEV_1/FVC	0.73 (0.63–0.81)
Normal spirometric results	61
GOLD stage	
1	11
2	20
3	8
4	0
6-min walking distance (ft)	1695 (1400–1860)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease.

Data are expressed as numbers or as median (interquartile range).

TABLE 2. Comparison of the CT Scan Evaluation Methods

	Score			
Analysis	0	1	2	Number of Readings
Sequential	69	23	8	166
Consensus	64	26	10	400

CT, computed tomographic.

In sequential analysis, each scan was reviewed in series, and in consensus analysis, each score was agreed on by three simultaneous readers. The number of readings was calculated as the total number of CT interpretations. For the correlation between these two methods, κ = 0.84 (95% confidence interval, 0.73–0.94; $P < .0001$).

TABLE 3. Computed Tomographic Findings of the 10 Patients Assigned Scores of 2 by Consensus Review

Patient	Description
1*	Mild basal asymmetric reticular abnormality with septal thickening
2	Patchy upper lobe ground-glass opacities
3*	Upper lobe irregular cysts
4	Basal linear scarring or dependent ground glass
5	Mild basal peripheral ground glass
6	Basal bronchiectasis and centrilobular nodules, right basal ground glass
7	Upper lobe centrilobular nodules with mild ground glass
8	Mild basal asymmetric reticular and ground glass
9	Patchy bilateral basal ground-glass and reticular abnormality and traction bronchiectasis
10	Mild asymmetric bibasilar ground glass with traction bronchiectasis

*Scored 1 on sequential read and 2 on consensus evaluation.

range, 83%–103.5%). The median ratio of FEV_1 to FVC was 0.73 (interquartile range, 0.63–0.81). Sixty-one of the 100 subjects had normal spirometric results, 11 had Global Initiative for Obstructive Lung Disease (GOLD) stage 1 disease, 20 had GOLD stage 2 disease, and 8 had GOLD stage 3 disease. None of the 100 subjects included in this analysis had very severe GOLD stage 4 disease.

Sequential Reading Method

Of 100 patients, 69 were classified as normal (score 0), 23 as having equivocal ILD (score 1), and 8 as having suspected ILD (score 2). No subjects were assigned a score of 3. Forty-four of the initial 100 patients (29 with scores of 1 or 2 and 15 with scores of 0) were then evaluated by reader 2. In 50% of cases (n = 22), the first and second readers agreed on the scoring, and there was disagreement in the remaining 22 cases, requiring a third review. Reader 3 provided majority opinion for the discordant readings. Of 15 patients with scores of 0 by the first reader, 10 had final scores of 0, and the remaining five had final scores of 1. Importantly, throughout the sequential analysis of the CT scans by readers 1, 2, and 3, no subject initially given a score of 0 was upgraded to a score of 2. The total number of interpretations performed by the first, and second, and third readers was 166 (100 + 44 + 22) (Table 2).

Consensus Reading Method

Following the sequential and modified sequential visual scoring of the CT scans, the four readers simultaneously viewed and scored the CT scans on a single PACS workstation. Using this method, 64 subjects were classified as normal (score 0), 26 as having equivocal IDL (score 1), and 10 as having suspected ILD (score 2). A total of 400 interpretations (100 CT scans and four readers for each scan) were performed using this method (Table 2). A description of the CT findings for each of the 10 cases is provided in Table 3. These interpretations were provided by an independent reader (D.A.L.), who was not part of the sequential or consensus reading methods. Of the 10 CT scans described in Table 3, cases 1, 3, 7, 9, and 10 were felt to be most consistent with early ILD. The findings

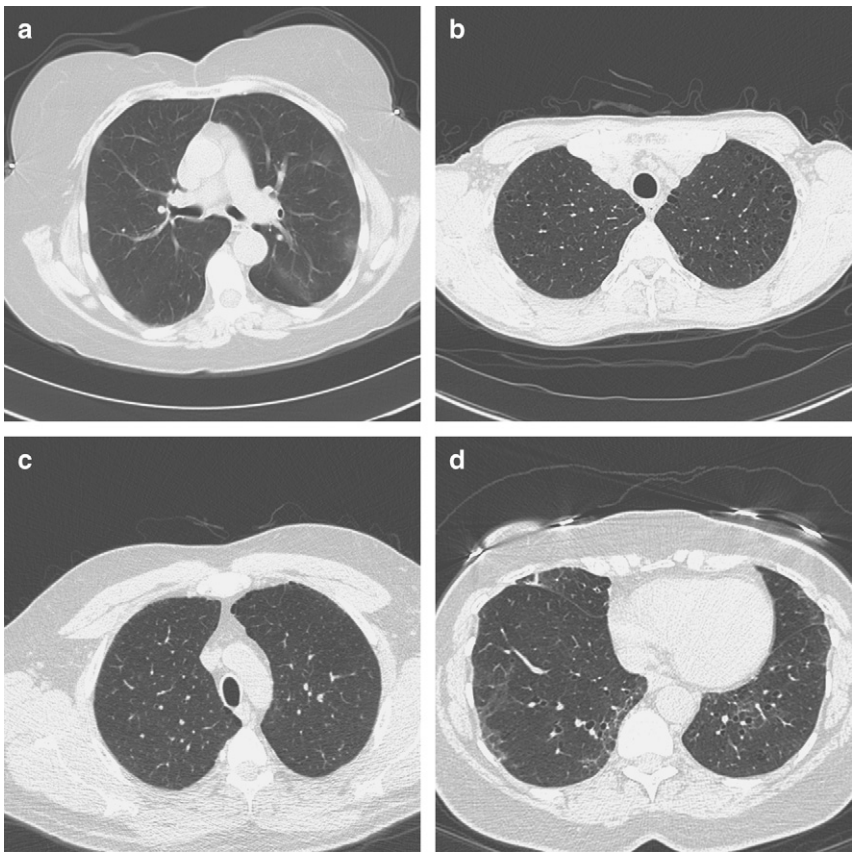

Figure 2. **(a)** Example of patchy upper lung ground-glass opacities (case 2 in Table 3). **(b)** Example of upper lobe irregular cysts (case 3 in Table 3). **(c)** Example of upper lobe centrilobular nodules with mild ground glass (case 7 in Table 3). **(d)** Example of patchy bilateral basal ground-glass and reticular abnormality and traction bronchiectasis (case 9 in Table 3).

in the remaining cases were felt to be either too nonspecific (cases 2, 5, 6, and 8) or not representative of ILD (case 4). Selected examples of these findings are shown in Figures 2a to 2d.

Comparison of Reading Methods

There was a high degree of agreement between methods (κ = 0.84; 95% confidence interval, 0.73–0.94; $P < .0001$ for the sequential and consensus methods). A score of 2 by the sequential method had a positive predictive value of 1 for being scored as a 2 by the consensus method. A combined score of 0 or 1 had a negative predictive value for 0.98 for being scored as either a 0 or 1 by the consensus method. A score of 0 had a negative predictive value of 0.97 for being scored as a 0 by the consensus method. The sequential reading method resulted in 59% fewer chest CT evaluations per reader. Regardless of interpretation method, the prevalence of chest CT changes assigned scores of 2 in this subset of smokers from COPDGene varied between 8% and 10%.

Clinical Characteristics of Early ILD by Consensus Reading

A comparison of the differences between subjects with early ILD and normal subjects (identified by the consensus method) is presented in Table 4 (10,11). There was a trend toward a statistically significant difference in the number of pack-years of tobacco smoke exposure between subjects with early ILD and normal smokers ($P = .05$). A large percentage of subjects with early ILD were current smokers (70%) in contrast to those subjects without early ILD (42%), although this difference was not statistically significant ($P = .20$).

DISCUSSION

In this report, we present the first comparison of chest CT reading methods for the identification of subjects with early ILD. To establish an efficient sequential CT evaluation method that objectively qualifies early ILD changes, we have undertaken a review of a subset of 100 chest CT scans from the COPDGene Study.

Our data demonstrate a high degree of correlation between a sequential reading method and a consensus reading method. The sequential reading method is an effective and efficient methodology approach for screening large numbers of CT scans for subjects at risk of developing early ILD, as it involves a 58% reduction in the number of chest CT evaluations compared to a consensus reading.

The chest CT abnormalities observed in this study, including increased septal lines, peribronchovascular thickening, reticulation, and ground-glass opacities were suggestive of diverse histologic subtypes of ILD previously described in smokers (nonspecific interstitial pneumonia, respiratory bronchiolitis–associated ILD, Langerhans cell histiocytosis, and

TABLE 4. Clinical Characteristics of COPDGene Subjects Stratified by Early ILD Status

Characteristic	Score 0 (*n* = 65)	Score 2 (*n* = 10)	*P**
Age (y)	61 (56–65)	64 (60–69)	.40
Age started smoking (y)	17 (15–18)	17 (14–18)	.80
Women	36 (55%)	5 (50%)	1.00
White	57 (88%)	9 (90%)	1.00
COPD diagnosis†	16 (25%)	3 (30%)	.70
Current smokers	27 (42%)	7 (70%)	.20
Tobacco history (pack-years)	33 (23–48)	43 (33–90)	.053
FEV_1 (% predicted)‡	93 (77–108)	82 (79–99)	.20
FVC (% predicted)‡	101 (90–109)	89 (86–102)	.20
FEV_1/FVC	0.73 (0.61–0.82)	0.69 (0.66–0.76)	.70
6-min walking distance (ft)	1700 (1400–1861)	1739 (1560–1780)	.70

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; ILD, interstitial lung disease.

A comparison of the differences in the clinical characteristics of subjects with computed tomographic findings suggestive of early ILD subjects and normal subjects from the COPDGene study identified by the consensus chest computed tomographic reading method is presented. Data are expressed as median (interquartile range) or as numbers (percentage).

**P* values presented resulted from the comparison of early ILD status and normal subjects by Fisher's exact tests (for binary variables) and Wilcoxon's rank-sum tests (for continuous variables).

†COPD was defined using modified GOLD stage 2 criteria (10) (FEV_1/FVC < 0.7 and FEV_1 < 80% of the predicted value).

‡Predicted values for FEV_1 and FVC were derived from Hankinson et al (11).

cryptogenic organizing pneumonia) (12). Our study suggests that increasing amounts (pack-year history) of tobacco smoke exposure may predispose subjects to the development of early ILD. Previous findings from our research group have also identified tobacco smoke exposure as a risk factor the development of early ILD among both subjects with rheumatoid arthritis and asymptomatic family members of kindreds with familial pulmonary fibrosis (6,13). These findings are intriguing, as numerous epidemiologic studies have identified smoke exposure as a risk factor for IPF (14–18).

Of note, 20% to 30% of patients affected with ILD do not have histories of smoking, and most patients who smoke do not develop ILD, suggesting that gene-by-environment interactions may be important in the development of this disease. This concept is further supported by family studies demonstrating clustering of ILD cases (19–24) and recent evidence that heterozygous mutations in telomerase reverse transcriptase and telomere shortening are present in up to 8% of kindreds affected with pulmonary fibrosis and may be more frequent in smokers (24,25).

Our study had several limitations. First, the cases presented here as being suspicious for early ILD were not confirmed by open-lung biopsies. Indeed, we describe a broad spectrum of radiographic abnormalities in this subset of subjects with scores of 2, not all of which are typical of ILD. Additional disease entities may be present in this cohort, such as aspiration, pneumonia, drug reaction, or even pulmonary hemorrhage. Although five of the 10 subjects displayed findings more suggestive of the presence of early ILD, such as centrilobular nodularity with ground-glass or patchy reticular abnormalities associated with traction bronchiectasis, the CT findings in the remaining subjects were too nonspecific to make such a judgment. Further longitudinal investigation is required to determine if such radiographic changes persist and evolve into a more recognizable disease state. Second, the small sample size limited some of the conclusions that can be drawn from our study. Finally, our analysis was performed in a cohort of both former and current smokers with a relatively high prevalence of COPD. Caution should be exercised in extrapolating the prevalence of early ILD noted in our study to heterogeneous populations.

In summary, we compared two chest CT evaluation methods for the identification of early ILD in a population of smokers enrolled in the COPDGene Study. Our findings suggest that a sequential chest CT reading method may be an effective and efficient method for identifying subjects with early ILD in larger cohorts. We believe that further characterization of early ILD could positively affect future clinical care by allowing us to detect and treat early stages of pulmonary fibrosis in subjects at risk for developing IPF.

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