Automated Quantification of High-Resolution CT Scan Findings in Individuals at Risk for Pulmonary Fibrosis

Ivan O. Rosas, MD; Jianhua Yao, PhD; Nilo A. Avila, MD; Catherine K. Chow, MD; William A. Gahl, MD, PhD; and Bernadette R. Gochuico, MD

Background: Automated methods to quantify interstitial lung disease (ILD) on high-resolution CT (HRCT) scans in people at risk for pulmonary fibrosis have not been developed and validated.

Methods: Cohorts with familial pulmonary fibrosis ($n = 126$) or rheumatoid arthritis with and without ILD ($n = 86$) were used to develop and validate a computer program capable of quantifying ILD on HRCT scans, which imaged the lungs semicontinuously from the apices to the lung bases during end-inspiration in the prone position. This method uses segmentation, texture analysis, training, classification, and grading to score ILD.

Results: Quantification of HRCT scan findings of ILD using an automated computer program correlated with radiologist readings and detected disease of varying severity in a derivation cohort with familial pulmonary fibrosis or their first-degree relatives. This algorithm was validated in an independent cohort of subjects with rheumatoid arthritis with and without ILD. Automated classification of HRCT scans as normal or ILD was significant in the derivation and validation cohorts ($P < .001$ and $P < .001$, respectively). Areas under receiver operating characteristic curves performed independently for each group were 0.888 for the derivation cohort and 0.885 for the validation cohort. Pulmonary function test results, including FVC and diffusion capacity, correlated with computer-generated HRCT scan scores for ILD ($r = -0.483$ and $r = -0.532$, respectively).

Conclusions: Automated computer scoring of HRCT scans can objectively identify ILD and potentially quantify radiographic severity of lung disease in populations at risk for pulmonary fibrosis.

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Abbreviations: CAD = computer-aided diagnosis; HRCT = high-resolution CT; ILD = interstitial lung disease; ROC = receiver operating characteristic

High-resolution computed tomography (HRCT) scans of the chest are routinely performed to evaluate interstitial lung diseases (ILDs). This imaging modality serves as an important diagnostic test for individuals with suspected ILDs, including idiopathic pulmonary fibrosis, sarcoidosis, and lymphangioleiomyomatosis.^{1–3} For these diseases, classic HRCT scan findings with compatible clinical histories may obviate the need for lung biopsy and/or bronchoscopy. HRCT scans can also identify early lung disease in populations at risk for pulmonary fibrosis, such as individuals with rheumatoid arthritis, systemic sclerosis, Hermansky-Pudlak syndrome, familial pulmonary fibrosis, and smokers, as well as in smokers within a large population-based cohort of older adults.^{4–9}

Given the role of HRCT scans in evaluating people with lung disease, programs providing automated readings to facilitate the diagnosis and quantification of parenchymal lung diseases have been developed.^{10–15} However, studies focusing on ILDs have been limited by small numbers of subjects, analysis of scans performed in a supine position, and lack of independent validation of computer program findings. Most studies have included cohorts with symptomatic disease; a paucity of information is available regarding use of automated computer readings of HRCT scans to identify early radiographic abnormalities in populations at risk for pulmonary fibrosis.

To complement subjective readings of HRCT scan findings, there is a need to develop and validate methods

that objectively measure HRCT scan features of ILD within populations at risk. These automated methods would facilitate screening of people predisposed to ILD or pulmonary fibrosis, improve serial assessments for disease progression, and enhance clinical research focusing on fibrotic lung disease. Digitized image texture analysis is a robust approach that, combined with automated decision-making algorithms, has been successfully used to predict a condition or perform disease classification.^{16,17} In this study, we report development and validation of an automated computer program to identify and quantify the severity of ILD in two independent cohorts who are at risk for pulmonary fibrosis.

MATERIALS AND METHODS

Subjects

The derivation or training cohort consisted of 126 individuals at least 18 years of age with familial pulmonary fibrosis or their first-degree relatives.⁷ Subjects with familial pulmonary fibrosis were eligible if they and one of their first-degree relatives had a lung biopsy and/or HRCT scan findings consistent with idiopathic pulmonary fibrosis as outlined by American Thoracic Society/European Respiratory Society guidelines.¹ First-degree relatives of individuals with familial pulmonary fibrosis were also eligible for enrollment. The derivation cohort, which is a subset of a group of 164 subjects from kindreds with familial pulmonary fibrosis, consisted of subjects whose HRCT scans were performed using identical methods. The validation cohort consisted of 86 individuals at least 21 years of age with rheumatoid arthritis with or without isolated parenchymal ILD or pulmonary fibrosis.⁴ Rheumatoid arthritis was diagnosed according to American College of Rheumatology criteria, and pulmonary fibrosis was diagnosed by lung biopsy.¹⁸ Subjects were excluded if they had other collagen vascular disorders, chronic pulmonary disorders other than ILD, or history of known inhalational exposure to fibrogenic substances. Relatives of individuals with familial pulmonary fibrosis and subjects with familial pulmonary fibrosis, rheumatoid arthritis, or rheumatoid

arthritis with pulmonary fibrosis were recruited using advertisements online or in local newspapers. Subjects were enrolled in protocols approved by the institutional review board of the National Human Genome Research Institute (99-HG-0056 or 04-HG-0211). Written informed consent was obtained, and subjects underwent evaluations at the National Institutes of Health.

CT Scan

HRCT scans of the chest in prone position were performed without IV contrast during end-inspiration using 1-mm collimation at 30-mm intervals and a high spatial frequency reconstruction algorithm as previously described (General Electric Medical Systems; Milwaukee, Wisconsin).^{4,6,19,20} Dose was determined by body size; 120 kVp was used in 45% of scans, and 140 kVp was used in 55% of studies. The reconstruction matrix was 512 × 512; in-plane pixel spacing ranged from 0.46 to 0.86 mm (mean 0.70 ± 0.06 mm). Each cohort was divided into subjects with no ILD or with minimal, mild, moderate, or severe ILD based on consensus readings of HRCT scans by two independent radiologists. For discrepant radiologist readings, HRCT scans were re-reviewed by the two radiologists to determine consensus scores. The methods used by the radiologists to score HRCT scan findings have been previously summarized.^{4,6,19,20} The radiologists reviewed HRCT scans from each cohort separately and were blinded to other clinical information and computer scores. Eleven HRCT scans in the derivation cohort were excluded from analysis due to motion artifact.

Computed Scoring

A computer-aided diagnosis (CAD) system was developed to automatically analyze HRCT scans and to quantify the severity of ILD. The quantitative score was derived in two steps. First, the pixels in the segmented lung were classified as either normal or fibrotic based on a mathematical model trained using texture patterns identified by an expert radiologist. Second, the percentage of fibrotic lung was calculated using the CAD system explained here. The model was trained using the derivation cohort, and the same model was used to generate computer scores for subjects in the validation cohort. No ILD was designated as a score of 0; completely diseased lung was indicated by a score of 100. The CAD system consists of five stages: segmentation, texture analysis, training, classification, and grading.

Lung segmentation relied on the grayscale contrast between lung parenchyma and surrounding tissues. After a segmented position of the trachea was established, two seed points were located in the right and left lungs. Using a two- and three-dimensional region-growing algorithm, the points were expanded to segment both lungs. A histogram-based threshold technique was used to remove blood vessels, and a rolling ball algorithm was applied to the lung boundary. The lung was then subdivided into 8 × 8 texture blocks. A multidimensional feature vector composed of 25 different texture features was computed and used to differentiate and group each texture block. These features included histogram statistics (ie, mean, skewness, deviation, variance, kurtosis), co-occurrence matrices (ie, energy, inertia difference, correlation, average difference, entropy difference, inertia, entropy, average sum, entropy sum), and run-length matrices (ie, long run emphasis, run length nonuniformity, low gray-level run emphasis, short run low gray-level emphasis, long run low gray-level emphasis, short run high gray-level emphasis, long run high gray-level emphasis, short run emphasis, run gray-level nonuniformity, run percentage, high gray-level run emphasis). In the training stage, the computer program learned the texture patterns of normal lung and regions affected by ILD through regions manually identified by an expert radiologist. A support vector machine was generated to distinguish normal and fibrotic lung.²¹ In the classification stage, the computer program automatically grouped the segmented lung

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Affiliations: From the Pulmonary-Critical Care Medicine Branch, National Heart, Lung, and Blood Institute (Dr Rosas); Radiology and Imaging Sciences, Clinical Center (Drs Yao, Avila, and Chow); Medical Genetics Branch, National Human Genome Research Institute (Drs Gahl and Gochuico), National Institutes of Health, Bethesda, MD; the Division of Pulmonary and Critical Care (Dr Rosas), Brigham and Women's Hospital, Boston, MA; and the Veterans Affairs Medical Center (Dr Avila), Washington, DC.

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Correspondence to: Bernadette R. Gochuico, MD, 10 Center Dr, MSC 1851, Bethesda, MD 20892-1851; e-mail: gochuicb@mail.nih.gov

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as normal or fibrotic lung using the support vector machine. Grading measured disease severity based on percentage of affected regions, calculated as volume of diseased region divided by volume of segmented lung.

Pulmonary Function Testing

FVC and diffusion capacity were measured. Testing was performed in accordance with American Thoracic Society and European Respiratory Society guidelines.^{4,7,22,23}

Statistical Analysis

Data are presented as mean $\pm$ SE (95% CI). Data for each cohort were grouped by radiologist score; box-and-whisker plots were generated for each group (GraphPad Prism, version 5.0; GraphPad Software; San Diego, California). Tests for linear trend, receiver operating characteristic (ROC) analyses, and Fisher exact tests were independently performed for each cohort; two-tailed *P* values and areas under ROC curves were calculated. Statistical regression analyses were performed between computer scores and percentages of predicted FVC or diffusion capacity, and Spearman correlation coefficients were calculated.

RESULTS

Subject Characteristics

The derivation cohort included subjects with familial pulmonary fibrosis and their first-degree relatives (Table 1).⁷ Twenty-three of 126 subjects (18%) had pulmonary fibrosis. Mean age of subjects in the derivation cohort was 48.7 ± 1.43 years, and 67 subjects (53%) were women. A history of active or former smoking was found in 46 subjects (37%) in the derivation cohort.

The validation cohort included subjects with rheumatoid arthritis with or without ILD or pulmonary fibrosis.⁴ Their mean age was 52.5 ± 0.96 years, and 66 of 86 subjects (77%) were women. Forty subjects (47%) were former smokers; none were active smokers. Methotrexate was used for treatment in 38 subjects (44%). Pulmonary fibrosis was diagnosed in 10 subjects (12%).

Table 1—Subject Characteristics

Characteristic	Derivation Cohort (n = 126)	Validation Cohort (n = 86)
Age, y	48.7 ± 1.43	52.5 ± 0.96
Gender, M (F)	59 (67)	20 (66)
History of smoking	46	40
Methotrexate	0	38
Pulmonary fibrosis	23	10
HRCT scan reading		
No ILD	41	46
Minimal ILD	17	18
Mild ILD	23	9
Moderate ILD	14	7
Severe ILD	20	6
Motion artifact	11	0

Data are presented as No. unless otherwise noted. F = female; HRCT = high-resolution CT; ILD = interstitial lung disease; M = male.

HRCT Scan Detects Variable Severity of Interstitial Lung Disease

To determine whether subjects at risk for pulmonary fibrosis had radiographic findings of ILD, HRCT scans of the chest were performed and scored independently by two radiologists. Discrepant readings were re-reviewed, and consensus scores were assigned. As previously reported, there was statistically significant agreement among independent HRCT scan readings of the validation cohort by these two radiologists ($\kappa = 0.972$, $P < .001$).⁴ Eleven HRCT scans in the derivation cohort had motion artifact due to breathing and were excluded from analysis.

In the derivation cohort, we found that 41 of 115 HRCT scans (35.7%) did not have ILD. Based on radiologist scores, 17 scans were classified as minimal ILD, 23 as mild disease, 14 as moderate disease, and 20 as severe disease. Representative HRCT scan images are shown in Figures 1A-1D. In the validation cohort, 46 of 86 HRCT scans (53.5%) did not have ILD. Radiologist HRCT scan readings classified 18 scans as minimal ILD, nine as mild disease, seven as moderate disease, and six as severe disease.

Automated Quantification of HRCT Scan Findings of ILD Correlates With Radiologist Readings and Detects Mild Disease

To objectively quantify findings of ILD, HRCT scans were also analyzed by a computer program that generated a numerical score from 0 to 100. Computer analysis of HRCT scans that were scored by radiologists as having ILD generated scores ≥ 1 , indicating that at least 1% of the imaged lung volume was affected by ILD. For this study, 1-mm-thick images were obtained semicontinuously (ie, every 30 mm) from the apices to the bases of the lung. In a derivation cohort of familial pulmonary fibrosis kindreds, we found that higher computer scores were associated with greater degrees of ILD on HRCT scans by radiologist readings, and trends across groups (ie, no ILD, minimal ILD, mild ILD, moderate ILD, severe ILD) were significant ($P < .001$, $P < .001$, $P < .001$, and $P < .001$, respectively) (Fig 2A). A second, independent cohort with rheumatoid arthritis with and without ILD or pulmonary fibrosis was used to validate this method, and these data confirmed that higher automated scores quantifying ILD were associated with expert readings of more advanced ILD on HRCT scans (Fig 2B). The trends across groups in the rheumatoid arthritis cohort were also significant ($P < .001$, $P < .001$, $P = .012$, and $P = .002$, respectively). In addition, tests for linear trend were performed between groups in the familial pulmonary fibrosis and rheumatoid arthritis cohorts. These analyses revealed that for the derivation and validation cohorts the linear

FIGURE 1. Representative high-resolution CT (HRCT) scan images from four different subjects in the derivation cohort of individuals with familial pulmonary fibrosis or their relatives with or without familial interstitial lung disease (ILD). A, Minimal ILD. B, Mild ILD. C, Moderate ILD. D, Severe ILD. Arrows indicate representative areas of interstitial reticulation.

trend is highly significant ($P < .001$ and < 0.001 , respectively). Notably, radiographic findings of mild, as well as moderate and severe, disease were detected by this computer program.

Computer Scoring Accurately Classifies HRCT Scans

To evaluate the performance of this computer program, data for each cohort were independently analyzed using Fisher exact test and ROC curves. Sensitivity, specificity, and accuracy are provided for an HRCT scan score of 4 using the radiologist readings as a gold standard (Table 2); radiologist scores of 0 were classified as normal cases. Data are shown for the derivation cohort and the validation cohort. The derivation cohort was used to develop an automated rule to identify ILD. An HRCT scan score of 4 was associated with a sensitivity of 86% (77%-92%), a specificity of 86% (71%-94%), and an accuracy of 86%. Using a score of 4 as a threshold, we found that automated computer classification of HRCT scans as normal or disease cases was significant in the derivation cohort ($P < .001$) with high agreement among radiologist readings and automated HRCT scan score classification ($\kappa = 0.691$ [0.551-0.830]) (Table 2). The same rule to identify ILD was used in the validation cohort. A threshold HRCT scan score of 4 was associ-

ated with a sensitivity of 88% (74%-95%), a specificity of 70% (55%-81%), and an accuracy of 78%. Our data demonstrated that automated computer classification in the validation cohort was also significant ($P < .001$), and there was agreement among radiologist readings and automated HRCT scan score classification ($\kappa = 0.562$ [0.392-0.733]). The areas under the ROC curves were 0.888 (0.831-0.945) for the familial pulmonary fibrosis cohort, 0.885 (0.813-0.958) for the rheumatoid arthritis cohort with and without ILD, and 0.886 (0.837-0.933) for all subjects in both cohorts (Figs 3A-3C).

Pulmonary Function Tests Correlate With Computer-Generated HRCT Scan Scores for ILD

To determine whether HRCT scan quantification by computer scoring correlates with physiologic measurements, pulmonary function tests were compared with computer-generated HRCT scan scores for either the derivation or validation cohort. We found that percentages of predicted FVC and diffusion capacity correlated with automated HRCT scan scores in these two cohorts ($r = -0.483$ and $r = -0.532$, respectively) (Figs 4A, 4B). For forced vital capacity, a subgroup analysis showed that the r value for 186 subjects with mild disease (ie, HRCT scan score ≤ 25) was -0.349 , and the r value for 15 subjects with

FIGURE 2. A, Box-whisker plot of findings of ILD on HRCT scan of the chest in the derivation cohort reviewed by two independent radiologists compared with computer-generated scores. B, Box-whisker plot of computer scores and radiologist readings of ILD findings on HRCT scan of the chest in a validation cohort of subjects with rheumatoid arthritis with and without preclinical ILD or pulmonary fibrosis. The trends across groups (ie, no ILD, minimal, mild, moderate, severe) in both cohorts were significant. See Figure 1 legend for expansion of abbreviations.

moderate to severe disease (ie, HRCT scan score ≥ 26) was -0.544 . For diffusion capacity, the r values for subjects with mild and moderate to severe disease were -0.411 and -0.489 , respectively. These data indicate that correlation between HRCT scan abnormalities and pulmonary function was more accurate in those with moderate to severe disease. Among subjects with normal lung physiology, 60% of HRCT scans in

the familial pulmonary fibrosis cohort and 41% of HRCT scans in the rheumatoid arthritis cohort were read as abnormal.

DISCUSSION

Although computer scoring of HRCT scans has been reported, quantification of ILD on HRCT scans has not been performed using objective, automated methods that were developed using one cohort and validated in a separate, independent cohort. Analysis of HRCT scans from a derivation cohort composed of subjects with familial pulmonary fibrosis or their first-degree relatives demonstrated correlation between computer-generated scores and radiologist readings of ILD. Computer scoring to quantify HRCT scan findings was validated in an independent cohort consisting of subjects with rheumatoid arthritis with and without ILD. For this study, it was unlikely that HRCT scan changes were due to atelectasis or breathing artifact, because the HRCT scans were obtained in prone subjects and images with breathing artifact were excluded from analysis. Our data for each cohort demonstrated that computer scores accurately classified HRCT scans as normal or ILD. We also demonstrated that this computer program was able to detect varying severity of ILD, including early or mild disease, and we found correlation between computer scores and pulmonary function tests that was most evident in subjects with moderate to severe ILD.

Studying two independent cohorts with widely variable severities of ILD to develop and validate the computer scoring program is an important contribution to this field. Other groups have evaluated computer program scoring of ILD in populations with known lung disease.²⁴⁻²⁶ Our findings demonstrate that this automated computer scoring method may be applied to other populations with early ILD or pulmonary fibrosis, including people with Hermansky-Pudlak syndrome, dyskeratosis congenita, scleroderma, or systemic lupus erythematosus.^{4,5,7,27-31}

It is unknown whether this method can be used to diagnose or screen for idiopathic pulmonary fibrosis within the general population who have a low risk of fibrotic lung disease and who may have other comorbid pulmonary abnormalities (eg, emphysema, airway disease, lung nodules, pleural effusion). HRCT scans have a central role in diagnosing idiopathic pulmonary fibrosis. However, given the relatively limited number of subjects with idiopathic pulmonary fibrosis and enrichment of subjects at risk for pulmonary fibrosis in this study, it is uncertain whether this automated method can provide accurate scores that distinguish idiopathic pulmonary fibrosis from other types of ILDs. In addition, the sensitivity and specificity

Table 2—Statistical Calculations for Automated HRCT Scan Score of 4

Score	Derivation Cohort	Validation Cohort
Sensitivity, % (95% CI)	86 (77-92)	88 (74-95)
Specificity, % (95% CI)	86 (71-94)	70 (55-81)
Accuracy, %	86	78
κ Coefficient (95% CI)	0.691 (0.551-0.830)	0.562 (0.392-0.733)

See Table 1 legend for expansion of abbreviations.

FIGURE 3. Receiver operating characteristic (ROC) curves plotting 1 minus specificity on the x-axis and sensitivity on the y-axis. A, Familial pulmonary fibrosis cohort. B, Rheumatoid arthritis cohort with and without ILD. C, Subjects in both cohorts. The area under the ROC curve was 0.888 for the familial pulmonary fibrosis cohort, 0.885 for the rheumatoid arthritis cohort with and without ILD, and 0.886 for both cohorts combined. The dashed identity line represents a CT score that performed no better than flipping a fair coin to classify CT scans as with or without ILD. See Figure 1 legend for expansion of abbreviation.

of automated HRCT scan scores in our cohorts of subjects at risk for pulmonary fibrosis were dependent on the threshold score. For example, an automated score of 3 had a sensitivity of 95% to 98% and a specificity of 59% to 67%, and a score of 6 had a sensitivity

of 59% to 80% and a specificity of 89% to 100%. The need to develop sensitive high-throughput methods to screen large populations at risk for future development of pulmonary fibrosis is highlighted by recent reports of early ILD in large cohorts of smokers and in smokers within a population-based sample of older adults who were screened using CT scans.^{8,9,32} Further studies are required to determine the accuracy of computer scoring for diagnosing idiopathic pulmonary fibrosis and to quantify ILD or pulmonary fibrosis in these and similar at-risk populations.

The ability to perform quantitative analysis of HRCT scan findings may enhance objective analysis of aggregate and individual subject data from clinical trials. Many clinical trials focusing on treatment of pulmonary fibrosis have used lung physiology parameters or survival as end points. Our study indicates that objective computer scoring of HRCT scans may also serve as an end point. For some people with very mild ILD, HRCT scans, and not pulmonary function

FIGURE 4. A, Correlation of FVC % predicted with computer-generated scores in cohorts of subjects with familial pulmonary fibrosis and ILD associated with rheumatoid arthritis (r value = -0.483). B, Correlation of DLCO % predicted with computer-generated scores in cohorts of subjects with familial pulmonary fibrosis and ILD associated with rheumatoid arthritis (r value = -0.532). DLCO % = percentage of predicted diffusing capacity of the lung for carbon monoxide. See Figure 1 legend for expansion of other abbreviation.

tests, detect early lung disease.^{4,7} Although extended longitudinal data are not available to determine the natural history of lung disease in this cohort, we have recently reported that two asymptomatic siblings with normal lung function, normal chest radiographs, and a functional mutation in *TERT* progressed to familial pulmonary fibrosis over 2 to 3 decades.³³ Thus, it is possible that some subjects with normal pulmonary physiology and abnormal HRCT scans may develop progressive lung disease. Overall, these results suggest that quantification of HRCT scans may be an end point that complements other study parameters for clinical trials focusing on ILD or pulmonary fibrosis and may be potentially useful in measuring individual response to therapy.

In conclusion, these results show that computer-generated scoring of ILD on HRCT scan correlates with radiologist readings in two independent cohorts composed of different populations at risk for pulmonary fibrosis. This strategy may be used in screening appropriate people for ILD or as an end point for certain clinical trials focusing on pulmonary fibrosis.

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Dr Rosas: contributed to designing the experiments, analyzing the data, and writing the manuscript.

Dr Yao: contributed to designing the experiments, analyzing the data, and writing the manuscript.

Dr Avila: contributed to designing the experiments, analyzing the data, and writing the manuscript.

Dr Chow: contributed to analyzing the data and writing the manuscript.

Dr Gahl: contributed to writing the manuscript.

Dr Gochuico: contributed to designing the experiments, analyzing the data, and writing the manuscript.

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