

Original Research

Visual Assessment of CT Findings in Smokers With Nonobstructed Spirometric Abnormalities in The COPDGene® Study

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Abstract

Within the COPD Genetic Epidemiology (COPDGene®) study population of cigarette smokers, 9% were found to be unclassifiable by the Global Initiative for chronic Obstructive Lung Disease (GOLD) criteria. This study was to identify the differences in computed tomography (CT) findings between this nonobstructed (GOLDU) group and a control group of smokers with normal lung function. This research was approved by the institutional review board of each institution. CT images of 400 participants in the COPDGene® study (200 GOLDU, 200 smokers with normal lung function) were retrospectively evaluated in a blinded fashion. Visual CT assessment included lobar analysis of emphysema (type, extent), presence of paraseptal emphysema, airway wall thickening, expiratory air trapping, centrilobular nodules, atelectasis, non-fibrotic and fibrotic interstitial lung disease (ILD), pleural thickening, diaphragmatic eventration, vertebral body changes and internal thoracic diameters (in mm). Univariate comparisons of groups for each CT parameter and multiple logistic regression were performed to determine the imaging features associated with GOLDU. When compared with the control group, GOLDU participants had a significantly higher prevalence of unilateral diaphragm eventration (30% vs. 16%), airway wall thickening, centrilobular nodules, reticular abnormality, paraseptal emphysema (33% vs. 17%), linear atelectasis (60% vs. 35.6%), kyphosis (12% vs. 4%), and a smaller internal transverse thoracic diameter (255 ± 22.5 [standard deviation] vs. 264.8 ± 22.4 , mm) (all $p < 0.05$). With multiple logistic regression, all of these CT parameters, except non-fibrotic ILD and kyphosis, remained significantly associated with GOLDU status ($p < 0.05$). In cigarette smokers, chest wall abnormalities and parenchymal lung disease, which contribute to restrictive physiologic impairment, are associated with GOLD- nonobstructed status.

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Abbreviations: Global Initiative for chronic Obstructive Pulmonary Disease, **GOLD**; computed tomography, **CT**; interstitial lung disease, **ILD**; forced expiratory volume in 1 second, **FEV₁**; forced vital capacity, **FEV**; GOLD-nonobstructed, **GOLDU**; body mass index, **BMI**; total lung capacity, **TLC**; diabetes mellitus, **DM**; ground glass opacity, **GGO**; qualitative CT, **QCT**; Hounsfield units, **HU**; emphysema index, **EI**%; wall area percentage, **WA**%; luminal area, **LA**; standard deviation, **SD**; pulmonary function test, **PFT**

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating lung disease and an important cause of morbidity and mortality, characterized by airflow limitation that is not fully reversible after administration of bronchodilators, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and other guidelines.^{1,3} The spirometric definition of COPD typically requires a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV₁/FVC) of less than 0.7. However, it has been determined that within cohorts of cigarette smokers, about 8-14% of individuals present with a normal FEV₁/FVC ratio, but a reduced FEV₁.⁴⁻⁶ A recent study comparing this group, called GOLD-nonobstructed (GOLDU), with spirometrically normal smokers demonstrated that GOLDU status was associated with increased body mass index (BMI), reduced total lung capacity (TLC), higher rates of non-white individuals and diabetes mellitus (DM), as well as increased bronchial wall thickness; however, substantial heterogeneity within this group was observed.⁷ GOLDU individuals are usually regarded as having restrictive lung disease, but many individuals have total lung capacity values within the normal range. Individuals with nonobstructed spirometric abnormalities have not been fully characterized by imaging, and it remains unclear how these individuals are radiologically different from smokers with normal FEV₁ values.^{4,6,8,9} Therefore, the purpose of our study was to identify the differences in CT findings between this GOLDU group of individuals and a control group of smokers with normal lung function.

Methods**Clinical Participants**

Individuals for this study were selected from participants in the COPDGene[®] Study, which recruited 10,300 current and former cigarette smokers, with and without COPD, from 21 institutions.¹⁰ Non-Hispanic whites or African-Americans between the ages of 45 and 80 years

with a minimum of 10 pack-years smoking history were included in the study. Exclusion criteria included pregnancy, history of significant fibrotic lung disease or diffuse bronchiectasis, previous surgical excision of at least one lung lobe (or lung volume reduction procedure), active cancer under treatment, known lung cancer, metal in the chest, and recent exacerbation of COPD. Two hundred smoking control participants and 200 GOLDU participants were randomly selected for this study, stratified so that the numbers of male and female participants were representative of the main cohort for each group. The institutional review boards from each clinical center approved the analyses of the clinical and imaging data. Individual, informed written consent was obtained from all patients.

CT Examination, Acquisition and Data Analysis

Volumetric CT scans were obtained for all participants using a standardized technique on multidetector CT scanners.^{10,11} The scans were obtained during deep inspiratory breath-hold at a standard CT dose, and at the end of a normal expiration (functional residual capacity) at reduced CT dose in a craniocaudal direction of the supine position. Standardized breathing instructions were provided. The typical CT parameters were as follows: submillimeter collimation (0.6-0.75 mm) and submillimeter reconstruction (thickness: 0.625-0.9 mm, interval: 0.45-0.625 mm) with both standard and high-frequency protocols, 120 kVp and 200 mAs for the inspiration scan and 50 mAs for the expiration scan.^{10,11} No patient received intravenous contrast medium. Anonymized DICOM CT data were transferred to the imaging core for archiving, quality assurance and quantitative analysis.

Lobe-Based Quantitative Visual Assessment of CT Images

Lobe-based visual assessment of CT images was performed by using standard reference images.¹² Two radiologists performed visual assessment: reader 1 and reader 2 were chest radiologists with 8 years and 10 years of experience, respectively. The readers were blind to any clinical and functional information. Image data sets

reconstructed with high spatial frequency algorithms were presented to each reader using AquariusNET (TeraRecon, Inc.). Images were presented in random order to the readers in a blinded fashion regarding disease stage. Expiratory volumetric CT images were evaluated after the inspiratory volumetric CT data and there was no time limitation for visual assessment. The CT images were visually inspected using a window width of 1500 Hounsfield units (HU) and a level of -700 HU. For the lobe-based visual emphysema assessment, readers were asked to determine the type of emphysema as normal, centrilobular, panlobular, or mixed. The extent of emphysema in each lobe was also assessed using a 6-point scale system: 0%, 1-5%, 6-25%, 26-50%, 51-75%, and above 75%. The lingula was regarded as a different lobe, resulting in 6 lobes for each case. The presence of airway changes, including bronchial wall thickening and bronchiectasis, was also determined in each lobe. The presence of centrilobular nodules, paraseptal emphysema, bullae, and mosaic attenuation pattern at inspiration CT was assessed and the presence of expiratory air trapping was also assessed by comparison of inspiration and expiration CT images. Bronchial wall thickening was visually defined by a ratio of the inner to outer lumen of less than 0.8.¹² Bronchiectasis was considered present when the diameter of the inner bronchial lumen was greater than the diameter of the accompanying pulmonary artery, or when a bronchus was visible within 1 cm of the pleural surface. Centrilobular nodules were defined if more than 50% of a segment was affected. Mosaic attenuation pattern was defined when more than 25% of the lobe showed patchwork of regions of differing attenuation on inspiratory CT, excluding areas of emphysema.¹³ Expiratory air trapping was defined on a side by side comparison of inspiratory and expiratory CT as the presence of parenchymal area with less than normal increase in attenuation and lack of volume reduction, which involves more than 25% of the lobe, excluding areas of emphysema.¹³ To evaluate pulmonary parenchymal and chest wall features which might contribute to restrictive lung abnormality, the following features were evaluated: presence of atelectasis (linear, segmental, lobar), fibrotic or nonfibrotic interstitial lung disease (ILD), including ground glass opacity (GGO), reticular opacity, honeycomb cyst, presence of pleural thickening (diffuse, focal), diaphragm change (eventration, hernia), and vertebral body change (kyphosis, scoliosis). Diaphragmatic eventration was defined as a focal abnormal contour of the diaphragmatic dome. Maximal transverse and anteroposterior internal thoracic diameters (mm) were measured. The number of wedged vertebral bodies was

counted. Presternal subcutaneous fat thickness (mm) was measured at the level of pulmonary trunk; if fat extended outside the field of view, the measurements were made to the edge of field of view. Diffuse pleural thickening was defined as involving more than 180 degrees of chest wall and more than 5 cm in craniocaudal direction. Focal pleural thickening was defined as involving less than 180 degrees of chest wall and less than 5 cm in craniocaudal direction.

Quantitative CT Measurements

Whole lung volumetric CT images for quantitative analysis were reconstructed using a standard algorithm. Using commercial software (Pulmonary Workstation, VIDA Diagnostics, Inc.), quantitative CT (QCT) measurements for the emphysema index (EI, %), wall area percentage (WA%), total lung capacity (TLC_{CT}, L), and gas trapping (%) were obtained.^{10,14-18} The software automatically calculated the EI (%), which is defined as the percentage of lung voxels at or below -950 HU on inspiratory CT. Quantitative assessment of airway dimensions was performed in the segmental, subsegmental, and subsubsegmental generations of the following bronchial pathways: RB1 (apical segment of RUL), RB4 (lateral segment of RML), RB10 (posterobasal segment of RLL), LB1 (apicoposterior segment of LUL), LB4 (superior segment of lingula), and LB10 (posterobasal segment of LLL). In each segmental pathway, airway dimensions, including WA, luminal area (LA), and WA% were measured. The wall area percentage was defined as $WA\% = WA / (WA + LA) \times 100$.¹⁹ The mean value of the measured dimensions of the segmental, subsegmental and subsubsegmental generations of bronchi was used for statistical analysis. TLC_{CT} was calculated as the volume of voxels of the lung and the gas trapping (%), which is defined as the percentage of lung voxels at or below -856 HU on expiratory CT, was also calculated automatically.¹⁰

Pulmonary Function Testing

Spirometry was conducted as recommended by the American Thoracic Society (ATS) by highly trained pulmonary function technicians and all spirometry data was collected using the ndd EasyOne Spirometer (Zurich, Switzerland).^{10, 20} Each instrument was calibrated daily, and usual assurance program for equipment checks and maintenance was strictly followed. FEV₁, FVC, and ratio of FEV₁/FVC were evaluated, and were expressed as a percentage of predicted value. Pulmonary function tests (PFTs) were performed on average within 2 days (mean, 1.71 ± 5.9) of obtaining volumetric CT scans (median 0 day).

Statistical Analysis

Results were expressed as mean \pm SD for continuous variables and as frequencies and percentages for categorical variables. With univariate analysis, differences in continuous data between the 2 groups were analyzed with t-test and categorical data were analyzed with the χ^2 test and Fisher's exact test. For the binary variables, if there were disagreements between 2 independent readers, final assignments were determined through a subsequent case review and adjudication. For the continuous variables, the mean of 2 readings was used. For extent of emphysema, the median of 2 readings was obtained. Multiple logistic regression analysis was used to determine the visual and quantitative radiologic variables associated with the GOLDU status, after adjustment for age, race, gender, pack years and BMI. The total visual extent of emphysema was calculated by adding the 6-point scale scores for all 6 lobes. The inter-reader agreement of the visual CT parameters was measured with Cohen's kappa statistics. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using JMP 9.0 (JMP; Cary, NC).

Results

The baseline characteristics of the 400 participants are shown in Table 1. Participants were classified as GOLDU (n=200) and a control group of smokers with normal lung function (n=200). The mean age of the GOLDU participants was 58.9 years \pm 8.2 standard deviation (SD), including 71 male (mean age, 58.8 years \pm 7.8) and 129 female (mean age, 58.9 years \pm 8.5) participants. The mean age of the control group participants was 60.1 years \pm 9.9, including 101 male (mean age, 59.5 years \pm 10.3) and 99 female (mean age, 60.7 years \pm 9.6) participants. Compared to the control group participants, GOLDU participants had significantly lower mean values of FEV1 percent predicted, FVC percent predicted, FEV1/FVC ratio and had significantly greater pack years of smoking and a higher mean BMI (all $P < 0.0001$).

Comparison Between GOLDU and Control Group Regarding Parenchymal Abnormalities

The results of comparison between the GOLDU group and the control group for CT parameters related to lung parenchymal abnormalities are shown in Table 2. Compared to the control group, GOLDU individuals had significantly greater prevalence of paraseptal emphysema (Figure 1), linear atelectasis, and non-fibrotic ILD and had a greater number of lobes involved by bronchial wall

Table 1. Participant Characteristics and Physiologic Measurements

Characteristics	All	GOLDU	Smoking Control	P value
No. of patients	400	200	200	
Male: n, (%)	172 (43)	71 (36)	101 (51)	0.0033
Age (y): mean \pm SD (range)	59.5 \pm 9.1 (45 - 80)	58.9 \pm 8.2	60.1 \pm 9.9	0.2055
BMI (kg/mm ²)	30.1 \pm 6.5	32.0 \pm 6.8	28.2 \pm 5.5	<.0001
FEV1 % pred	85.5 \pm 16.2 (36.2 - 149.9)	72.4 \pm 7.1	98.6 \pm 11.4	<.0001
FEV1, pre, L	2.5 \pm 0.7 (0.8 - 5.3)	2.0 \pm 0.5	2.8 \pm 0.7	<.0001
FEV1, post, L	2.5 \pm 0.7 (1.4 - 4.2)	2.1 \pm 0.5	2.9 \pm 0.7	<.0001
FEV1, reversibility, ^a n, (%)	35 (8.8)	21 (10.6)	14 (7.1)	0.22
FVC % pred	86.3 \pm 14.9 (39.3 - 139.5)	74.9 \pm 7.6	97.8 \pm 11.3	<.0001
FVC, pre, L	3.2 \pm 0.9 (1.2 - 6.6)	2.8 \pm 0.7	3.7 \pm 1.0	<.0001
FVC, post, L	3.2 \pm 0.9 (1.8 - 5.3)	2.8 \pm 0.6	3.7 \pm 0.9	<.0001
FVC, reversibility, ^a n, (%)	21 (5.3)	13 (7.0)	8 (4.0)	0.26
FEV1/FVC	0.76 \pm 0.05 (0.7 - 0.93)	0.75 \pm 0.04	0.78 \pm 0.05	<.0001
TLC, L	5.3 \pm 1.1 (3.2 - 9.0)	5.1 \pm 1.0	5.6 \pm 1.1	<.0001
Pack years: mean \pm SD (range)	41.5 \pm 24.5 (10 - 174.9)	46.4 \pm 27.2	36.5 \pm 20.2	<.0001
African American race : n, (%)	104 (26)	48 (24)	56 (28)	0.4250
Currently Smoking : n, (%)	210 (53)	109 (55)	101 (51)	0.4244

Data are presented as mean \pm standard deviation (SD) or percentage

^aReversibility of 200 ml in either FVC or FEV1

thickening, bronchiectasis, centrilobular nodules (Figure 2), mosaic attenuation, atelectasis, GGO, and reticular opacities (all $P < 0.05$). However, the prevalence of centrilobular emphysema, bullae, fibrotic ILD, honeycombing cysts and extent of emphysema and expiratory air trapping was not significantly different.

Comparison Between GOLDU and Control Group Regarding Chest Wall Abnormalities

Regarding the measurement of the subcutaneous fat thickness, in one case within the control group and 3 cases in GOLDU, measurements were restricted by the edge of field of view. The results of comparison between GOLDU and the control group regarding chest wall abnormalities are shown in Table 3. Compared to the

Table 2. Prevalence of Lung Parenchymal Abnormalities in GOLDU and Smoking Control

CT parameters (visual)	GOLDU (N=200)	Smoking Control (N=200)	P value
Presence of Emphysema ^a (%)	28	22.5	0.25
Type of Emphysema (centrilobular, %)	27	22.5	0.26
Extent of Emphysema ^a (scale, median)	0 (0, 2)	0 (0, 2)	0.37
Paraseptal Emphysema (%)	33	17	0.0003
Bullae (%)	16.5	13	0.40
Bronchial Wall Thickening (mean number of involved lobes)	2.87 ± 2.59	1.51 ± 2.41	<.0001
Bronchiectasis (mean number of involved lobes)	0.57 ± 1.14	0.46 ± 1.25	0.012
Centrilobular Nodules (mean number of involved lobes)	1.86 ± 2.38	1.63 ± 2.54	<.0001
Expiratory Air Trapping (mean number of involved lobes)	1.00 ± 1.63	0.60 ± 1.35	0.067
Mosaic Attenuation (mean number of involved lobes)	0.35 ± 1.1	0.21 ± 0.88	<.0001
Atelectasis (linear, %)	60	35.6	<.0001
Atelectasis (mean number of involved lobes)	1.04 ± 1.15	0.55 ± 0.83	<.0001
Fibrotic ILD (%)	3.5	1	0.17
Non-fibrotic ILD (%)	11.5	3	0.002
GGO (mean number of involved lobes)	0.39 ± 1.15	0.10 ± 0.58	0.027
Reticular (mean number of involved lobes)	0.40 ± 1.09	0.17 ± 0.79	0.002
Honeycomb (%)	0	0.5	1

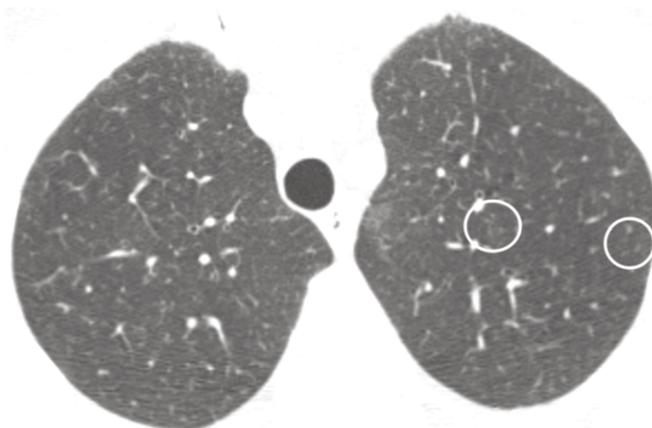
Data are presented as mean ± standard deviation (SD) or median (min,max) or percentage

^aEmphysema is expressed as centrilobular, panlobular or mixed type emphysema

Figure 1. Paraseptal Emphysema (Arrows) on Coronal CT Reconstruction in a GOLDU Participant**Table 3. Prevalence of Chest Wall Abnormalities and Quantitative CT Measurement in GOLDU and Smoking Control**

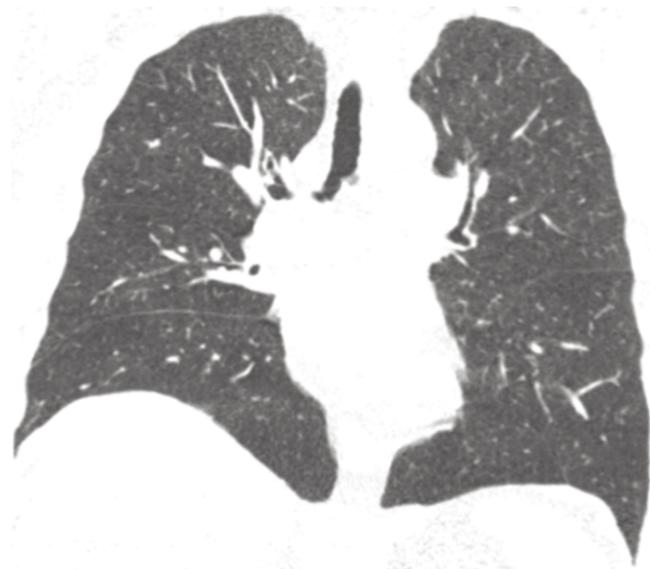
CT parameters	GOLDU (N=200)	Smoking Control (N=200)	P value
Pleural Thickening (%)			
Diffuse	2	0	0.25
Focal	10.5	6	0.35
Diaphragm Changes			
Unilateral Eventration (%)	30	16	0.004
Bilateral Eventration (%)	12.5	3.5	0.001
Hernia-Rt. (%)	1.5	0.5	0.62
Hernia-Lt. (%)	3	1.5	0.5
Internal Thoracic Diameter (mm)			
Transverse	255.0 ± 22.5	264.8 ± 22.4	<.0001
Anterior-Posterior	188.3 ± 20.1	188.8 ± 18.8	0.81
Subcutaneous Fat Thickness (mm)	23.4 ± 8.96	16.7 ± 7.78	<.0001
Kyphosis (%)	12	4	0.003
Scoliosis (%)	14	12	0.549
Vertebral Body Wedging (%)	2.5	2.0	1
CT Measurements (quantitative)	GOLDU (N=200)	Smoking Control (N=200)	P value
Emphysema Index (%)	2.02 ± 3.08	2.37 ± 2.26	0.189
Gas Trapping (%)	11.16 ± 8.04	12.42 ± 9.28	0.125
TLC (CT, liters)	5.06 ± 1.03	5.62 ± 1.14	<.0001
TLC (CT, % predicted)	91.15 ± 8.09	97.68 ± 10.54	<.0001
WA (%)	61.91 ± 2.89	59.48 ± 2.50	<.0001

Data are presented as mean ± standard deviation (SD) or percentage

Figure 2. Prominent Centrilobular Nodules (White Circles) on Axial CT in A GOLDU Participant

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Figure 3. Right Diaphragmatic Elevation in a GOLDU Participant.



control group, GOLDU participants had a significantly higher prevalence of diaphragmatic eventration (Figure 3) and kyphosis (Figure 4) (all $P < 0.01$). GOLDU participants had narrower transverse internal thoracic diameter and thicker subcutaneous fat than those of control group participants (both $P < 0.0001$). There were no prevalence differences in scoliosis, vertebral body wedging, and total involved number of vertebral body wedging.

Comparison Between GOLDU and Control Group Regarding QCT Measurements

The results of comparisons between GOLDU and the control group for QCT parameters are shown in Table 3. Compared to the control group, GOLDU participants had significantly lower TLC_{CT} (L) and higher WA% (all $P < 0.0001$), but none of the individuals in either group showed TLC_{CT} less than 80% predicted. There were no differences in EI (%) and gas trapping (%) between the GOLDU and control groups.

Significant Imaging Features Associated With GOLDU

After adjusting for age, race, gender, pack years, and BMI, multiple logistic regression analysis showed that significant features associated with GOLDU were the presence of paraseptal emphysema, linear atelectasis, diaphragmatic eventration, greater number of lobes involved in bronchial wall thickening, bronchiectasis, centrilobular nodules, mosaic attenuation, atelectasis, narrower transverse internal thoracic diameter, and thicker subcutaneous fat (all $P < 0.05$, Table 4). Presence

Figure 4. Moderate Kyphosis in a GOLDU Participant.



of non-fibrotic ILD, kyphosis, extent of GGO and reticular opacities, were not independently associated with the GOLDU group. Multivariate analysis suggested that the number of lobes involved in bronchial wall thickening, centrilobular nodules, linear atelectasis, and diaphragmatic eventration all were associated with reduction of TLC_{CT} (all $P < 0.05$). However, paraseptal emphysema, bronchiectasis, and mosaic attenuation did not show significant associations. One hundred and fifty-eight participants (79%) among the GOLDU group had one radiologic finding that could contribute to pulmonary restriction such as fibrotic or non-fibrotic ILD, GGOs, reticular abnormalities, atelectasis, diffuse or focal pleural thickening, or eventration of diaphragm compared with 103 participants (52%) in the control group.

Inter-rater agreements for visual assessment in GOLDU and smokers with normal lung function are shown in Table 5.

Discussion

In this study, we demonstrated that in the GOLDU group, radiologic features including parenchymal lung

Table 4. Results of Multiple Regression Analysis for Imaging Features on GOLDU^a

CT parameters	P value
Paraseptal Emphysema (%)	0.002
Bronchial Wall Thickening (mean number of involved lobes)	<.0001
Bronchiectasis (mean number of involved lobes)	0.0186
Centrilobular Nodules (mean number of involved lobes)	<.0001
Mosaic Attenuation (mean number of involved lobes)	<.0001
Atelectasis (linear, %)	0.0202
Atelectasis (mean number of involved lobes)	0.0059
Diaphragmatic Eventration-Lt. (%)	0.0275
Transverse Internal Thoracic Diameter (mm)	0.0183
Subcutaneous Fat Thickness (mm)	<.0001
Non-fibrotic ILD (%)	0.1253
GGO (mean number of involved lobes)	0.1348
Reticular (mean number of involved lobes)	0.1063
Kyphosis (%)	0.1469
Diaphragmatic Eventration-Rt. (%)	0.0767

^aAdjusted R² for multiple regression analysis on GOLDU = 0.5798

disease, as well as chest wall abnormalities, were present and could be discriminated from those of the control group of smokers with normal lung function. These findings could be helpful in explaining the unique physiologic features in GOLDU.

Reduced FEV₁ or FVC in the setting of a preserved FEV₁/FVC ratio is usually regarded as a restrictive pattern on spirometry. In keeping with this, GOLDU participants in our study showed significantly lower TLC_{CT} when compared with the control group participants. Despite having lower TLC values than control participants, none of the GOLDU participants had TLC values below 80% predicted. In general, reduced TLC_{CT} may be due either to intrinsic lung disease causing increased lung stiffness, or abnormalities of the chest wall, pleura, diaphragm, abdomen, or thoracic bony cage which affect ventilation. This study demonstrated that the GOLDU participants show not only higher prevalence of parenchymal abnormalities (paraseptal emphysema, atelectasis, non-fibrotic ILD, bronchial wall thickening, bronchiectasis, centrilobular nodules, mosaic attenuation, GGO, and reticular opacities), but also a higher prevalence of non-pulmonary findings, including diaphragmatic eventration, kyphosis, narrower transverse internal thoracic diameter and thicker subcutaneous fat. Furthermore, all of these findings, except GGO, reticular opacities of non-fibrotic ILD, and kyphosis, remained as significant and independent predictors after adjusting for age, race, gender, pack years, and BMI. These covariates

Table 5. Mean Inter-Rater Agreements for Visual Assessment in GOLDU and Smoking Control

CT parameters	GOLDU	Smoking control
Presence of Emphysema	0.75	0.76
Type of Emphysema	0.77	0.75
Extent of Emphysema	0.64	0.66
Paraseptal Emphysema	0.54	0.57
Bullae	0.58	0.48
Bronchial Wall Thickening ^a	0.37	0.33
Bronchiectasis ^a	0.23	0.19
Centrilobular Nodules ^a	0.25	0.27
Expiratory Air Trapping ^a	0.15	0.11
Mosaic Attenuation ^a	0.24	0.26
Atelectasis (linear)	0.69	0.51
Atelectasis ^a	0.53	0.49
Fibrotic ILD	0.72	0.50
Non-fibrotic ILD	0.39	0.24
GGO [*]	0.17	0.12
Reticular ^a	0.54	0.52
Pleural Thickening ^b	0.45	0.42
Diaphragm Changes ^c	0.49	0.43
Bony Thoracic Changes ^d	0.37	0.36

^aMean k coefficient for inter-rater agreement in 6 lobes

^bMean k coefficient for diffuse and focal pleural thickening

^cMean k coefficient for unilateral and bilateral diaphragmatic eventration

^dMean k coefficient for kyphosis and scoliosis

were chosen because they are known to affect pulmonary function.⁷

In previous studies, decreased FEV₁ and FVC with resultant preservation of the FEV₁/FVC ratio has been related to obesity with increased BMI.²¹⁻²⁴ In our study, the significantly increased subcutaneous fat thickness in the GOLDU group relative to that of the control group may suggest the importance of obesity as a cause of pulmonary restriction. However, high BMI alone does not account for the reduction of FEV₁ and FVC in the GOLDU group.^{22, 23}

Several studies have shown that WA% is related to BMI and WA% varies significantly by race and sex.^{25, 26} In our study, even after adjustment for age, sex, and BMI, the GOLDU group had a higher number of lobes involved in bronchial wall thickening on visual assessment and increased WA% on QCT than the control group. This may reflect a higher prevalence of bronchial inflammation or remodeling in the GOLDU group. The finding of paraseptal emphysema as a significant independent, associated factor with GOLDU status is interesting. We speculate that paraseptal emphysema may act as a space-occupying lesion in the lung parenchyma, maybe with resultant

decrease in TLC in contrast to the airway obstruction found in centrilobular and panlobular emphysema. The presence of centrilobular nodules and mosaic attenuation, both markers of small airways disease, in GOLDU participants suggests that small airways disease may sometimes be associated with restrictive physiology. Although smoking and COPD would more likely be associated with flattening of diaphragm, in our study, unilateral and bilateral diaphragmatic eventrations were significantly associated with GOLDU status on univariate analysis, and they persisted as an independently associated factor on multivariate analysis. This finding suggests that eventration may contribute importantly to pulmonary restriction and should be reported when found. The novel finding that the internal transverse thoracic diameter, but not the anteroposterior diameter, was associated with GOLDU status suggests that transverse narrowing of the chest wall may also contribute to pulmonary restriction.

Physiologically, decreased FEV₁ with preservation of FEV₁/FVC in GOLDU may be caused by volume derecruitment in alveoli during forced expiration. However, there were no significant differences in gas trapping index (%) between both groups, although we did not compare the gas trapping index (%) lobe-by-lobe in 6 regions of the lung.

Our study has some limitations. First, inter-rater agreements for visual assessment in GOLDU and smokers without COPD were variable and relatively low (kappa coefficient range: 0.23-0.69), especially in factors found to be different between the 2 groups, identified in adjusted analysis. However, when we consider the nature of lesions such as bronchiectasis, bronchial wall thickening, centrilobular nodules, and mosaic attenuation, these lesions were relatively subtle lesions compared to those in far advanced COPD and were liable to be subjective in radiologists' readings. Despite the relatively low inter-rater

agreements, the values were very similar in both groups, suggesting that the suggested significant imaging features associated with GOLDU might reflect the true differences by disease state rather than bias of radiologist's adjudication. Second, although standardized breathing instructions were employed, it is possible that participants were unable or unwilling to perform an adequate inspiration, which may have contributed to decreased TLC in the GOLDU participants. Third, inability to measure subcutaneous fat thickness in all cases (because of field of view restriction) is a further limitation.

In our study, we demonstrate that there were variables influencing disease processes identifiable on CT, which may also affect the results in FEV₁ and FVC. Under the current COPD criteria staging system, based on the results of spirometry, the heterogeneity of GOLDU may not be appreciated well in the diagnosis and treatment of COPD patients. Even though our results showed various meaningful CT parameters in the GOLDU participants, a new GOLD staging system will be needed for allowing the identification of GOLDU individuals having more than one concurrent disease process.²⁷

Conclusion

In cigarette smokers, chest wall abnormalities and parenchymal lung disease, which contribute to restrictive physiologic impairment, are associated with GOLD-nonobstructed status.

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Declaration of Interest

No conflicts of interest

References:

1. Global Initiative for Chronic Obstructive Lung Disease strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: an Asia-Pacific perspective. *Respirology*. 2005; 10(1):9-17.
2. Iqbal A, Schloss S, George D, Isonaka S. Worldwide guidelines for chronic obstructive pulmonary disease: a comparison of diagnosis and treatment recommendations. *Respirology*. 2002; 7(3):233-239.
3. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004; 23(6):932-946.
4. Kohler D, Fischer J, Raschke F, Schonhofer B. Usefulness of GOLD classification of COPD severity. *Thorax*. 2003; 58(9):825.
5. Arne M, Lisspers K, Stallberg B, et al. How often is diagnosis of COPD confirmed with spirometry? *Respir Med*. 2010; 104(4): 550-556.
6. Zielinski J, Bednarek M, Gorecka D, et al. Increasing COPD awareness. *Eur Respir J*. 2006; 27(4):833-852.
7. Wan ES, Hokanson JE, Murphy JR, et al; COPDGene Investigators. Clinical and radiographic predictors of GOLD-unclassified smokers in the COPDGene study. *Am J Respir Crit Care Med*. 2011; 184(1):57-63.
8. Arne M, Lisspers K, Stallberg B, et al. How often is diagnosis of COPD confirmed with spirometry? *Respir Med*. 2010;104(4): 550-556.
9. Rabe KF, Hurd S, Anzueto A, et al; Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007; 176(6):532-555.
10. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. *COPD*. 2010;7(1):32-43.
11. Han MK, Kazerooni EA, Lynch DA, et al; COPDGene Investigators. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. *Radiology*. 2011; 26(1):274-282.
12. Kim SS, Seo JB, Lee HY, et al. Chronic obstructive pulmonary disease: Lobe-based visual assessment of volumetric CT by using standard images--comparison with quantitative CT and pulmonary function test in the COPDGene Study. *Radiology*, 2013; 266(2): 626-635.
13. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology*. 2008;246(3):697-722.
14. Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med*. 1995; 152(2):653-657.
15. Tschirren J, Hoffman EA, McLennan G, Sonka M. Segmentation and quantitative analysis of intrathoracic airway trees from computed tomography images. *Proc Am Thorac Soc*. 2005; 2(6):484-87, 503-504.
16. Palagyi K, Tschirren J, Hoffman EA, Sonka M. Quantitative analysis of pulmonary airway tree structures. *Comput Biol Med*. 2006; 36(9):974-996.
17. Zhang L, Hoffman EA, Reinhardt JM. Atlas-driven lung lobe segmentation in volumetric X-ray CT images. *IEEE Trans Med Imaging*. 2006;25(1):1-16.
18. Hoffman EA, Simon BA, McLennan G. State of the Art. A structural and functional assessment of the lung via multidetector-row computed tomography: phenotyping chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2006; 3(6):519-532.
19. Okazawa M, Muller N, McNamara AE, Child S, Verburgt L, Pare PD. Human airway narrowing measured using high resolution computed tomography. *Am J Respir Crit Care Med*. 1996; 154(5):1557-1562.
20. Standardization of spirometry, 1994 update. American Thoracic Society. *Am J Respir Crit Care Med*. 1995; 152(3):1107-1136.
21. Mannino DM, Holguin F, Pavlin BI, Ferdinands JM. Risk factors for prevalence of and mortality related to restriction on spirometry: findings from the First National Health and Nutrition Examination Survey and follow-up. *Int J Tuberc Lung Dis*. 2005;9(6):613-621.
22. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. *Arch Intern Med*. 2002;162(13): 1477-1481.
23. Schachter LM, Salome CM, Peat JK, Woolcock AJ. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. *Thorax*. 2001;56(1):4-8.
24. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest*. 2006; 130(3):827-833.
25. Ogawa E, Nakano Y, Ohara T, et al. Body mass index in male patients with COPD: correlation with low attenuation areas on CT. *Thorax*. 2009;64(1):20-25.
26. Mair G, Maclay J, Miller JJ, et al. Airway dimensions in COPD: relationships with clinical variables. *Respir Med*. 2010; 104(11): 1683-1690.
27. Bon JM, Weissfeld JL, Sciruba FC. A unique spirometric phenotype in COPD. *Am J Respir Crit Care Med*. 2008;178(4):431-432.