CHEST Online Supplement

Subtyping COPD by Using Visual and Quantitative CT Imaging Features

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CHEST 2020; 157(1):47-60

 DOI: 10.1016/j.chest.2019.06.015

e-Appendix 1.

Supplementary Methods

Subjects

COPDGene (ClinicalTrials.gov ID NCT00608764)[16] is a longitudinal multi-center prospective cohort study focused on the genetic epidemiology of COPD. Between 2007 and 2011, 10,263 current and former smokers (with at least 10 pack-years of smoking history) with and without COPD were enrolled in COPDGene at 21 clinical centers. Institutional review board approval for the study was obtained at all clinical centers, and written informed consent was obtained from all participants. All subjects were self-identified as non-Hispanic African American or non-Hispanic white race. Subjects with respiratory conditions other than asthma and COPD were excluded from participation. Eighteen subjects underwent lung volume reduction surgery or lung transplantation during follow-up and were excluded from this analysis. For purposes of this manuscript, we analyzed quantitative and visual phenotypes from the baseline chest CT scans of 9,080 COPDGene participants with both inspiratory and expiratory chest CT scans. We used the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines to determine the severity level of airflow limitation based on post-bronchodilator spirometry. Smokers with normal spirometry were defined based on forced expiratory volume in 1 second [FEV_1] ≥ 80% predicted and ratio of FEV_1 to forced vital capacity [FEV_1/FVC] ≥0.70. Subjects without COPD but with Preserved Ratio Impaired Spirometry (PRISm) were identified based on reduced FEV_1 (< 80% of predicted) but a normal FEV_1/FVC ratio (≥ 0.70). Comorbidities were ascertained by self-report of physician diagnosis, except for obesity, which was defined as a BMI of 30 kg/m_2 or greater.[17]

Quantitative CT analysis

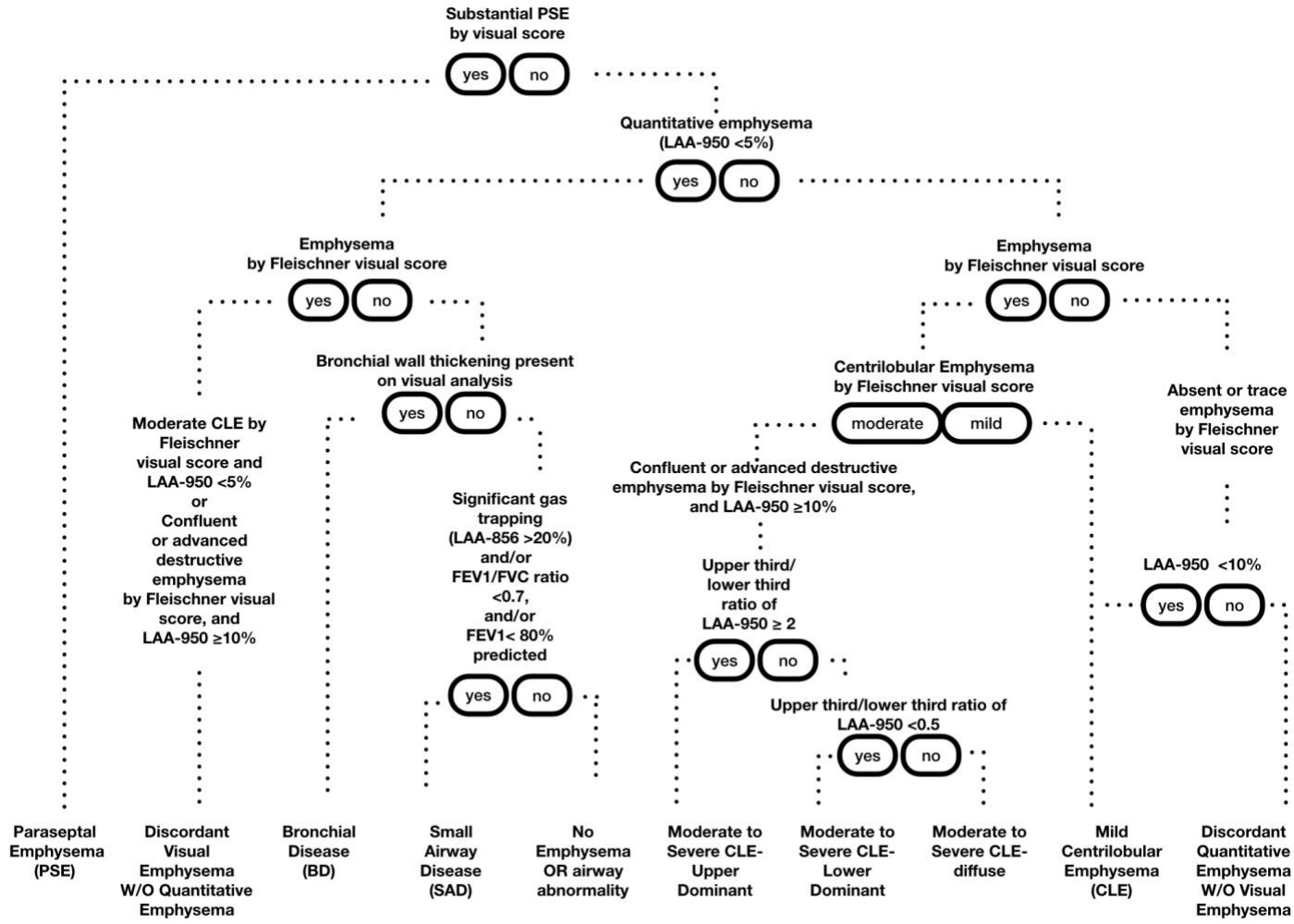
All subjects underwent volumetric inspiratory and expiratory CT using a standardized imaging protocol.[16,18] De-identified scans were transferred to a central imaging laboratory at National Jewish Health for quality control assessment and visual CT analysis. Quantitative analysis of emphysema severity was assessed on inspiratory CT both as the percent of low attenuation area (LAA) less than -950 Hounsfield units (HU) (3DSlicer; http://www.slicer.org) and as the HU value at the 15th percentile of the lung density histogram (Perc15). Small airway disease was evaluated using the Parametric Response Map functional small airway disease (PRM_{fSAD}) value defined by the relative percent of lung area < -856 HU on quantitative CT at normal expiration[19]. The square root of wall area of a hypothetical 10 mm internal perimeter airway (Pi10) was measured using Vida Pulmonary Workstation 2; Diagnostics (Vida Coralville, Iowa). We used the lung density at the 15th percentile of the HU distribution adjusted for predicted total lung capacity (measured using CT imaging) on baseline and follow-up scans as the main longitudinal CT emphysema measure (Thirona BV, Nijmegen, The Netherlands) [20]. For longitudinal analysis of PRM_{fSAD}, Thirona measurements at COPDGene Phases 1 and 2 were compared.

Statistical evaluation

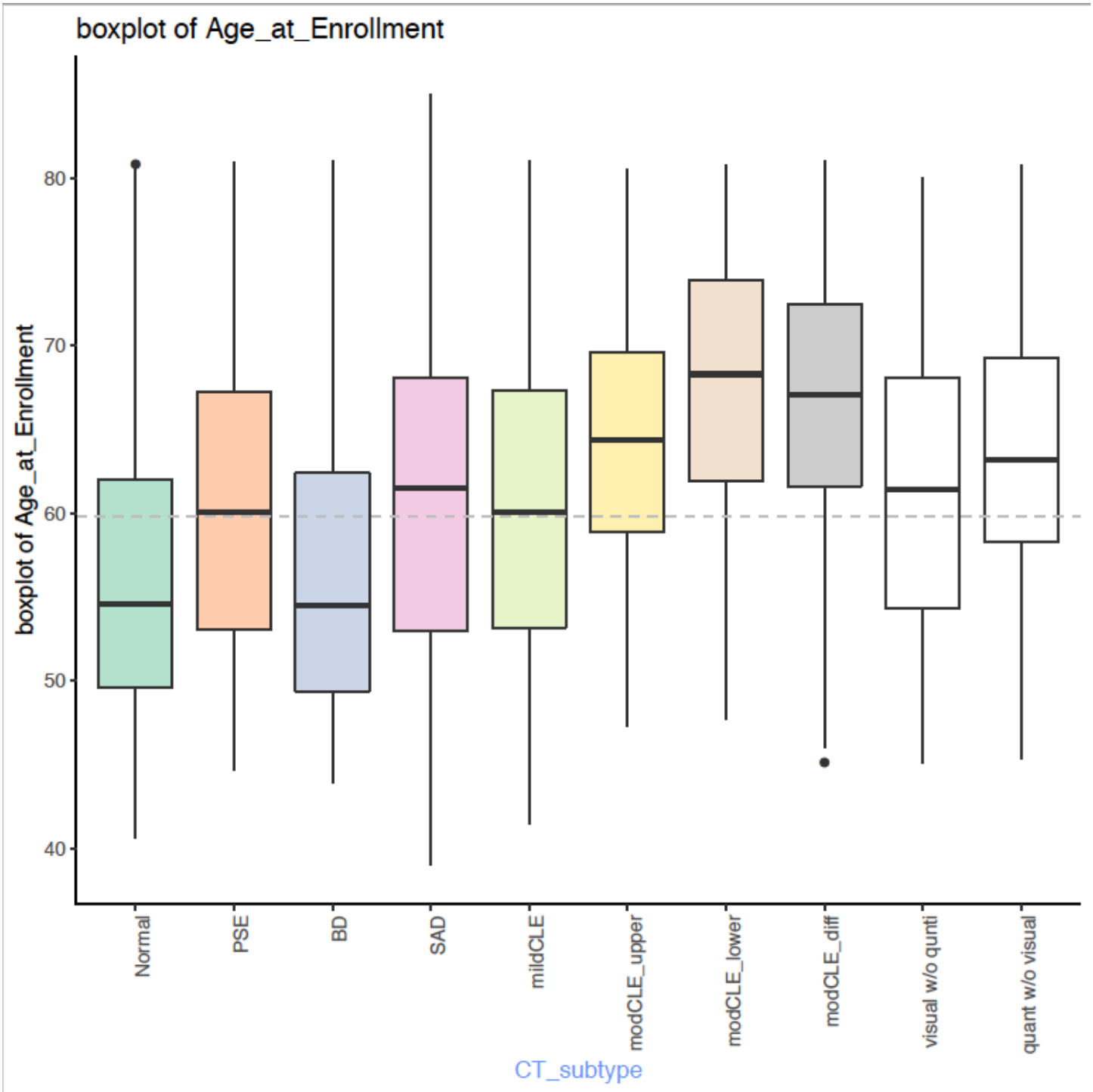
Both univariate and multivariate analyses were conducted for the ten specific CT subtypes. Means and standard deviations were used to describe the distributions of continuous variables. Categorical variables were presented as frequencies and percentages. To compare across multiple groups, one-way analysis of variance (ANOVA, suppl. Fig2) with Tukey test for post hoc analysis and chi-square tests for categorical variables were performed. For longitudinal analyses, we conducted linear mixed model (LMM) analysis for lung function, 6MWD, and PRM_{fSAD} on CT. Age, gender, race, body mass index (BMI), current smoking status, and pack-years of smoking were included as covariates in the multivariable models. Because the measured outcomes over time

within each patient are not independent from one another, the correlations between those outcomes were considered by application of LMM methods. For the evaluation of survival times, we used information from the Social Security Death Index and the COPDGene Longitudinal Follow-up Program to determine a survival or censoring time for each subject. The median length of follow-up in this mortality data set was 6.6 years (95% confidence interval [CI], 5.3 years – 7.4 years). Kaplan-Meier curves were created to assess survival differences between CT subtypes, and statistical significance in survival was assessed with log-rank tests. All analyses were carried out using R v3.4.4 (using the packages of lmer4, survival, and ggplot2 function in R to get appropriate updated citation). Adjustments with false discovery rate (FDR) were used to account for multiple statistical comparisons. An FDR of less than or equal to 0.05 was considered to be statistically significant.

e-Figure 1.



e-Figure 2.



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e-Table 1.

	Airway Predominant (Groups 3 and 4)	Emphysema Predominant (Groups 6, 7, 8)	p - value
n	1242	1068	
Age_at_Enrollment (mean (sd))	58.0 (9.1)	65.9 (7.6)	<0.001
Female (%)	568 (45.7)	558 (52.2)	0.002
Race (Non-Hispanic White/African American) (%)	809/433 (65.1/34.9)	886/182 (83.0/17.0)	<0.001
BMI (mean (sd))	30.6 (6.4)	26.2 (5.2)	<0.001
Current smoker (%)	754 (60.7)	244 (22.8)	<0.001
Pack-years of smoking (mean (sd))	40.6 (22.9)	55.5 (27.2)	<0.001
PRMfSAD (mean (sd))	13.4 (9.8)	32.4 (9.9)	<0.001
Emphysema at 15th Percentile (mean (sd))	-899.7 (27.1)	-957.0 (16.6)	<0.001
Percent Emphysema at -950 HU (mean (sd))	1.4 (1.3)	21.7 (11.8)	<0.001
Upper Lobe Percent Emphysema at -950HU (mean (sd))	1.6 (1.5)	23.9 (13.9)	<0.001
Lower Lobe Percent Emphysema at -950HU (mean (sd))	1.2 (1.3)	18.2 (12.3)	<0.001
Upper Lobe/Lower Lobe Emphysema Ratio (mean (sd))	1.5 (0.9)	1.9 (2.0)	0.005
Adjusted Lung Density (mean (sd))	97.5 (21.6)	51.4 (19.3)	<0.001
Pi10 (mean (sd))	2.7 (0.7)	2.6 (0.5)	0.001
FEV1 % predicted (mean (sd))	77.0 (19.9)	46.2 (22.3)	<0.001
FEV1/FVC (mean (sd))	0.7 (0.1)	0.4 (0.1)	<0.001
FVC% predicted (mean (sd))	84.7 (17.3)	77.5 (21.2)	<0.001
Bronchodilator Responsiveness (Yes, %)	343 (28.0)	338 (31.7)	0.054
GOLD Spirometry Grade at Enrollment (N, %)			<0.001
PRISm	222 (17.9)	10 (0.9)	
0	439 (35.3)	28 (2.6)	
1	84 (6.8)	72 (6.7)	
2	396 (31.9)	285 (26.7)	
3	88 (7.1)	386 (36.1)	
4	13 (1.0)	287 (26.9)	
Resting Oxygen Saturation (mean (sd))	96.4 (2.5)	94.0 (4.0)	<0.001
Six minute walk distance (mean (sd))	1354.7 (384.1)	1135.3 (401.3)	<0.001
SGRQ Total Score (mean (sd))	27.9 (22.7)	42.4 (20.5)	<0.001
Exacerbation Frequency per year (mean (sd))	0.4 (0.9)	0.8 (1.2)	<0.001
Survival Rate	airway	emphysema	<0.001
One Year Follow-Up	94.22719	92.52049	
Two Year Follow-Up	93.48231	90.26639	
Three Year Follow-Up	92.17877	85.7582	
Four Year Follow-Up	90.96834	78.58607	
Five Year Follow-Up	89.57169	72.7459	