Quantitative computed tomography and visual emphysema scores: association with lung function decline

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Multiple quantitative CT measurements reflecting different COPD-related disease features as PCA components increases the relative importance of quantitative CT when placed with visual emphysema scoring for predicting lung function decline https://bit.ly/3jIx4iS

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Abstract

Background Computed tomography (CT) visual emphysema score is a better predictor of mortality than single quantitative CT emphysema measurements in COPD, but there are numerous CT measurements that reflect COPD-related disease features. The purpose of this study was to determine if linear combinations of quantitative CT measurements by principal component analysis (PCA) have a greater association with forced expiratory volume in 1 s (FEV_1) lower limit of normal (LLN) annualised change (ΔFEV_1) than visual emphysema score in COPD.

Methods In this retrospective, longitudinal study, demographic, spirometry and CT images were acquired. CT visual emphysema score and quantitative analysis were performed; low attenuation area <950 HU (LAA_{950}) and 12 other quantitative CT measurements were investigated. PCA was used for CT feature extraction. Multiple linear regression models for baseline FEV_1 LLN and 6-year ΔFEV_1 were used to determine associations with visual emphysema score and CT measurements. A total of 725 participants were analysed (n=299 never-smokers, n=242 at-risk and n=184 COPD).

Results Quantitative CT measures (LAA_{950} and PCA components) were independently statistically significant ($p<0.05$) in predicting baseline FEV_1 LLN, whereas visual emphysema score was not statistically significant in any baseline model. When predicting 6-year ΔFEV_1, only visual emphysema score was significant ($p<0.05$) in models with LAA_{950} and PCA combination of emphysema measurements. In the model with PCA using all CT measurements predicting 6-year ΔFEV_1, visual emphysema score ($p=0.021$) along with one PCA component ($p=0.004$) were statistically significant.

Conclusions PCA with a combination of CT measurements reflecting several different COPD-related disease features independently predicted baseline lung function and increased the relative importance of quantitative CT compared with visual emphysema score for predicting lung function decline.

Introduction

COPD is characterised by irreversible airflow limitation [1] as a result of increased airflow resistance due to small airway disease and increased lung compliance due to emphysema. Emphysema affects the airspaces distal to the terminal bronchiole, and is defined as the enlargement and destruction of the alveolar walls [1]. Clinically, emphysema is evaluated by a radiologist who scores the presence and severity of the disease using computed tomography (CT) images [2, 3]. Although visual scoring of emphysema is the clinical standard, it is time consuming and there is inherent inter- and intra-observer variability [3].

Quantitative CT imaging of the lung enables automated, reproducible and objective measurements, and numerous studies have demonstrated quantitative CT measures of emphysema predict important outcomes

in COPD, such as exacerbations [4] and mortality [5]. However, a previous study that investigated the relative contributions of visual scoring and quantitative CT emphysema measurements for predicting mortality in COPD showed visual scoring outperformed the quantitative measurements [6]. It is known that visual scoring of emphysema captures several relevant morphological features, such as emphysema lesion size and distribution, in addition to overall emphysema extent, and can distinguish emphysema from small airway disease and image noise [7]. Therefore, while quantitative CT measurements are developed to characterise a single disease feature, visual scoring may be more holistic and take into consideration other information contained in the image.

In addition to CT emphysema [8], quantitative CT imaging enables many different disease features in COPD to be investigated, such as gas trapping [9], airway remodelling [10] and vascular pruning [11]. In fact, there is the potential for hundreds of measurements to be extracted using different quantitative methods. However, statistical models may be unreliable when a large number of predictors are included [12], and therefore fewer and more highly curated measurements are often considered. Principal component analysis (PCA) is an unsupervised feature extraction method that generates new, independent variables that are linear combinations of all inputted measurements [13]. PCA takes a data-driven, holistic approach to feature extraction that may be more similar to that of visual scoring of emphysema.

We hypothesise that PCA, which generates a linear combination of multiple quantitative CT measurements, will have a greater association with COPD outcomes than visual emphysema score. Therefore, the overarching objective of this study was to investigate the association of PCA linear combinations of quantitative CT measurements and visual emphysema score for predicting annualised forced expiratory volume in 1 s (FEV_1) change.

Materials and methods

Study participants

Participants from the longitudinal, multicentre Canadian Cohort Obstructive Lung Disease (CanCOLD) study cohort were evaluated [14]. Study groups (never-smokers, at-risk and COPD) were determined spirometrically as defined by the European Respiratory Society/American Thoracic Society technical standard [15]. At visit 1 (baseline visit), demographic information, spirometry and CT imaging were collected. At visit 3, which occurred 3 years after baseline, spirometry was performed. At visit 0, which occurred 3 years prior to baseline, spirometry was performed. For the participants evaluated in this study, the mean±SD time between visit 3 and visits 1 and 0 was 3.2±0.3 and 5.6±1.7 years, respectively. A flowchart detailing the selection process for analysis is shown in supplementary figure S1. Current smoking may increase lung density due to inflammation [16], therefore we excluded current smokers from our analysis. However, analysis performed with current smokers is included in the supplementary material. Our final cohort for this study was 725 participants: n=299 never-smokers, n=242 ever-smokers/at-risk and n=184 COPD.

Pulmonary function measurements

Spirometry measurements were performed according to Global Initiative for Chronic Obstructive Lung Disease criteria for measurement of FEV_1 and forced vital capacity (FVC) [17]. Lower limits of normal (LLN), which account for age, sex, ethnicity and height of subjects, were calculated using the Global Lung Function Initiative reference equations [18]. Annualised FEV_1 LLN change was calculated as the change in FEV_1 LLN between baseline and follow-up, divided by the time between baseline and follow-up (ΔFEV_1); ΔFEV_1 was calculated for the visit 3 (3-year) follow-up and between the visit 0 and visit 3 (6-year) follow-up. Annualised FEV_1 change, measured in mL per year, was calculated using the following formula:

$$\Delta FEV_1 = \frac{FEV_{1(\text{follow-up})} - FEV_{1(\text{baseline})}}{Date_{(\text{follow-up})} - Date_{(\text{baseline})}}$$

CT image acquisition

CT images were acquired according to the CanCOLD study protocol [14], from nine sites across Canada, using multislice CT scanners (⩾16 detectors) with subjects in a supine position at full-inspiration and full-expiration from the base to the apex of the lung. The CT parameters used for acquisition were: 120 kVp, 40 mAs, 0.5 s gantry rotation, 1.25 pitch and 1 mm slice thickness. The images were reconstructed using low ("b35f") and high spatial frequency (edge enhancing) reconstruction algorithms and the smallest field of view that contains both lungs.

CT image analysis

Images were scored qualitatively by two experienced chest radiologists (C.J.H. and J.A.L.) who were blinded to all subject characteristics, following the Fleischner Society glossary of terms for thoracic imaging [2]. Bronchiolitis and emphysema were visually assessed by the radiologists; however, only visual scoring of emphysema was used in this study. For scoring emphysema, the lungs were divided into six zones: upper-left and upper-right above the carina, middle-left and middle-right between the carina and inferior pulmonary veins, and lower-left and lower-right. The extent of zonal emphysema was scored on a 5-point scale: 0=no emphysema, 1=1–25% (trivial), 2=26–50% (mild), 3=51–75% (moderate) and 4=76–100% (severe–very severe) [19]. Therefore, whole lung visual emphysema scores can range from 0 to 24. The weighted κ agreement has been previously reported [19] and was considered "substantial" for emphysema (0.58 (95% CI 0.38–0.78)).

Quantitative CT image analysis was performed using commercially available VIDA software (VIDA Diagnostics, Coralville, IA, USA). A total of 13 CT measurements were extracted. Densitometry measurements included: low attenuation area $\leqslant -950$ HU on full-inspiration CT (LAA_{950}) [8], low attenuation area $\leqslant -910$ HU on full-inspiration CT (LAA_{910}) [20], low attenuation area $\leqslant -856$ HU on full-expiration CT (LAA_{856}) [9], Hounsfield units at the 15th percentile (HU_{15}) [21], mean lung density [20], and disease probability measure (DPM) emphysema and air trapping measurements [22]. Emphysema clustering was measured using the low attenuation clustering (LAC) slope [23]. Airway dimensions were measured as the average wall area percent (WA%) [24] and lumen area [25] using RB1, RB4, RB10, LB1 and LB10 airway segments. The square root of the airway wall area for a theoretical airway with 10 mm internal perimeter (Pi10) [26], total airway count (TAC) [10] and vessel volume [11] were also measured. All CT measurements were extracted from full-inspiration CT images, except LAA_{856} which was extracted from full-expiration CT images and the DPM measurements which use the registration of inspiration-to-expiration CT images for calculation.

Statistical analysis

Statistical analysis was performed using SPSS version 28.0 (IBM, Armonk, NY, USA). Descriptive statistics were analysed for demographic, pulmonary function test, and quantitative and qualitative CT imaging measurements. ANOVA with Tukey's post-hoc test was used to compare study groups. For the PCA, first highly correlated CT measurements (Pearson coefficient $|r|>0.9$) were removed for redundancy. Next, PCA analysis was performed for emphysema only (*i.e.* LAA_{950}, HU_{15}, $DPM_{emphysema}$ and LAC) and all CT measurements. PCA with a varimax rotation was performed for the all-CT measurements analysis. For dimension reduction, a threshold of eigenvalue <1 was used to determine which variables will be used for further analyses. Multiple linear regression models for baseline FEV_1 LLN and 3- and 6-year ΔFEV_1 LLN were constructed to determine the associations of visual emphysema score with quantitative CT measurements (LAA_{950}, PCA of emphysema measurements and PCA of all CT measurements), after adjusting for CT make/model, age, sex, race, pack-years, smoking status, body mass index (BMI), CT lung volume/total lung capacity, comorbidities (asthma, tuberculosis, heart disease, systemic hypertension or diabetes), use of respiratory medications (bronchodilator, inhaled steroid and oral steroid), visual emphysema score and LAA_{950}. In the models for ΔFEV_1 LLN, baseline FEV_1 LLN was included as a covariate. To account for positive skewing, our measures of qualitative and quantitative emphysema were transformed using a $\log(x+1)$ and $\log(x)$ transformation, respectively, prior to placing the variables into our multiple linear regression models. A p-value of <0.05 was used to represent statistical significance.

Results

Subject cohort and demographics

Table 1 shows subject demographics, pulmonary function, and quantitative and qualitative CT imaging measurements for all 725 subjects, stratified into study groups (n=299 never-smokers, n=242 at-risk and n=184 COPD). The COPD group had younger subjects than the other study groups ($p<0.05$) and fewer subjects of Caucasian race ($p<0.05$); however, there were no differences between study groups for sex and BMI ($p>0.05$). Pack-years increased and baseline pulmonary function measurements worsened with increasing COPD severity, as expected ($p<0.05$).

A three-dimensional reconstruction of the emphysema, airway tree and vessel segmentation for representative never-smoker, at-risk, mild COPD and moderate–severe COPD participants is shown in figure 1. It is visually apparent that as COPD disease severity increases, emphysema worsens and there are fewer visible airways and vessels in the lung. For the quantitative CT measurements, all CT measurements were statistically worse in COPD compared with the never-smokers ($p<0.05$) and at-risk participants ($p<0.05$), except for Pi10 which was not different in the at-risk group ($p>0.05$). For the qualitative CT measurements, visual emphysema score was statistically worse in COPD compared with the never-smokers

TABLE 1 Demographics, pulmonary function and imaging measurements (n=737)

	Never-smoker (n=299)	At-risk (n=242)	COPD (n=184)
Demographics			
Age, years	67±9	67±9	65±10[¶]
Female, n (%)	129 (43)	91 (38)	80 (43)
Caucasian, n (%)	287 (96)	232 (96)	174 (95)[¶]
BMI, kg·m^{-2}	27±5	28±5	28±5
Pack-years, years	0±0	24±21[#]	18±24[#,¶]
Pulmonary function			
FEV_1, L	2.79±0.77	2.74±0.72	2.26±0.74[#,¶]
FVC, L	3.75±1.05	3.76±0.98	3.89±1.14
FEV_1/FVC, %	75±6	73±6[#]	58±7[#,¶]
RV/TLC, %	38±8	38±8	43±10[#¶]
FEV_1 LLN, L	2.04±0.51	2.08±0.46	2.15±0.57[#]
FEV_1/FVC LLN, %	64.7±2.7	64.4±2.6	65.1±2.7[¶]
FEV_1 z-score	0.09±1.01	−0.19±1.01[#]	−1.41±1.09[#,¶]
Mild COPD, n (% of COPD group)	0 (0)	0 (0)	154 (84)[#,¶]
Moderate–severe COPD, n (% of COPD group)	0 (0)	0 (0)	30 (16)[#¶]
$\Delta FEV_{1(3\text{-year})}$ LLN, mL per year	−29.9±7.2	−30.7±6.8	−30.4±6.7
$\Delta FEV_{1(6\text{-year})}$ LLN, mL per year	−30.2±6.7	−30.9±6.3	−30.8±6.5
Quantitative imaging			
LAA_{856}, %	58±17	59±15	64±12[#,¶]
LAA_{910}, %	22±13	23±12	28±13[#,¶]
LAA_{950}, %	4±4	4±4	6±6[#,¶]
HU_{15}, HU	−915±21	−917±21	−926±18[#,¶]
Mean lung density, HU	−824±33	−826±31	−838±25[#,¶]
LAC	−2.00±0.25	−2.01±0.23	−1.91±0.31[#,¶]
TAC, n	213±71	206±65	152±58[#,¶]
Pi10, mm	3.95±0.16	3.98±0.16	3.98±0.17[#]
Lumen area, mm^2	20±6	22±8	18±6[#,¶]
Wall area, %	62±3	62±4	64±3[#,¶]
Vessel volume, cm^3	144±42	151±39	153±39[#]
$DPM_{air\ trapping}$, %	42±17	37±14[#]	46±15[#,¶]
$DPM_{emphysema}$, %	4±4	4±4	7±8[#,¶]
Qualitative imaging			
Visual emphysema score	0.26±0.83	0.99±1.84[#]	1.60±3.17[#,¶]

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; LLN: lower limit of normal; ΔFEV_1: FEV_1 annualised change; CT: computed tomography; LAA_{856}: low attenuation area ⩽−856 HU on full-expiration CT; LAA_{910}: low attenuation area ⩽−910 HU on full-inspiration CT; LAA_{950}: low attenuation area ⩽−950 HU on full-inspiration CT; HU_{15}: Hounsfield units associated with the 15th percentile of the CT density histogram; LAC: low attenuation cluster; TAC: total airway count; Pi10: square root of the airway wall area for a theoretical airway with 10 mm internal perimeter; DPM: disease probability measure. Significance of difference ($p<0.05$): [#]: significantly different from never-smoker group; [¶]: significantly different from at-risk group.

($p<0.05$) and at-risk participants ($p<0.05$). A histogram detailing the distribution of emphysema score across our study cohort is shown in supplementary figure S2.

Principal component analysis

A Pearson correlation heatmap showing the correlations among all quantitative CT measurements is provided in supplementary figure S3. Tables 2 and 3 show PCA component loadings of CT emphysema only measurements and all CT measurements, respectively. As shown in table 2, when only the CT emphysema measurements were considered, four CT emphysema measurements were input into a PCA after removing highly correlated measurements. One component was extracted, explaining 64.26% of the variance in data. This component was most representative of LAA_{950}, HU_{15} and $DPM_{emphysema}$, with these three measurements contributing the highest weight to the component.

When all CT measurements were considered (table 3), 10 CT measurements were input into the PCA after removing highly correlated measurements. Of these, three components explained 67.70% of the variance in data. The first component was emphysema dominant, with LAA_{950}, HU_{15} and $DPM_{emphysema}$ contributing

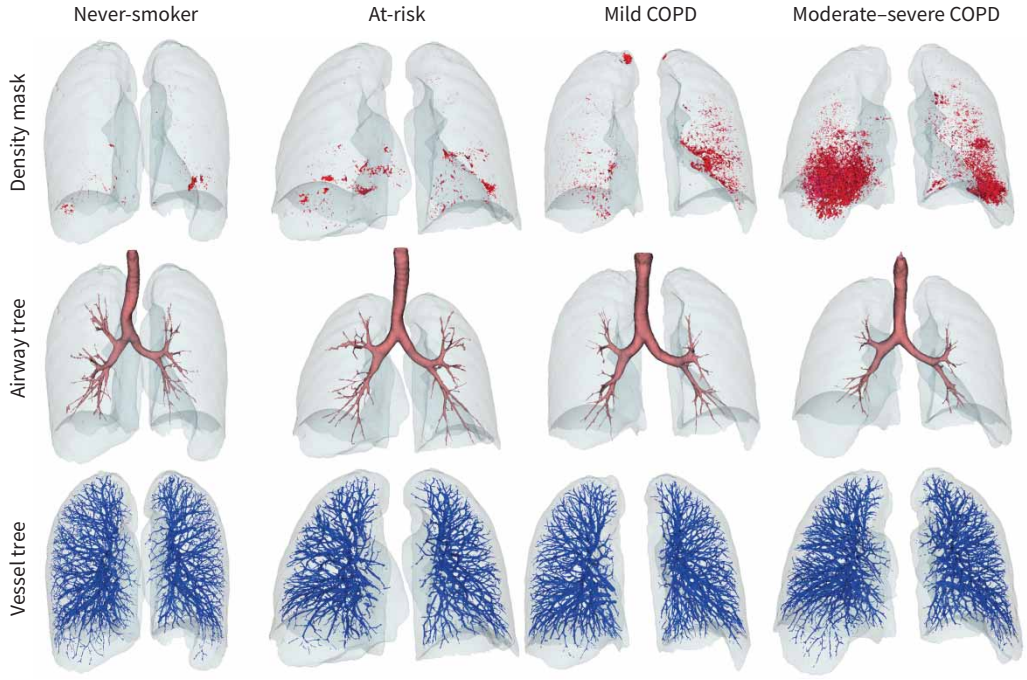

FIGURE 1 Three-dimensional coronal computed tomography (CT) reconstruction of the emphysema density mask, airway tree and vessel tree for a representative never-smoker participant (62-year-old female; FEV_1 97.8% predicted; FEV_1/FVC 0.78; LAA_{950} 0.58%; TAC 210; vessel volume 106.38 mL), an at-risk participant (67-year-old female; FEV_1 84.4% predicted; FEV_1/FVC 0.73; LAA_{950} 1.73%; TAC 177; vessel volume 124.10 mL), a mild COPD participant (49-year-old male; FEV_1 92.3% predicted; FEV_1/FVC 0.68; LAA_{950} 5.42%; TAC 151; vessel volume 212.27 mL) and a moderate–severe COPD participant (44-year-old male; FEV_1 68.9% predicted; FEV_1/FVC 0.62; LAA_{950} 7.09%; TAC 106; vessel volume 182.60 mL). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LAA_{950}: low attenuation area $\leqslant -950$ HU on full-inspiration CT; TAC: total airway count.

the highest weight. The second component was airway dominant, with TAC, lumen area and WA% contributing the highest weight. For the third component, the Pi10 measurement contributed the highest relative weight.

Multiple linear regression models for annualised FEV_1 change

Table 4 shows the various multiple linear regression models generated for baseline FEV_1 LLN and 6-year ΔFEV_1 using quantitative CT measurements and visual emphysema score, adjusted by covariates. In the first multiple linear regression model with visual emphysema score and LAA_{950} (Model 1), visual emphysema score was statistically significant in predicting 6-year ($p=0.048$) ΔFEV_1 but not baseline FEV_1 ($p>0.05$). LAA_{950} was statistically significant in predicting baseline FEV_1 ($\beta=0.293$, $p<0.001$) but not 6-year ΔFEV_1 ($p>0.05$). In the second multiple linear regression model with visual emphysema score and

TABLE 2 Computed tomography (CT) emphysema measurement principal component analysis: rotated component matrix

	Component 1 (64.26%)
LAA_{950}, %	0.931#
HU_{15}, HU	−0.875#
LAC	0.295
$DPM_{emphysema}$, %	0.922#

LAA_{950}: low attenuation area $\leqslant -950$ HU on full-inspiration CT; HU_{15}: Hounsfield units associated with the 15th percentile of the CT density histogram; LAC: low attenuation cluster; DPM: disease probability measure. #: representative quantitative CT measurements. Kaiser–Meyer–Olkin measure of sampling adequacy: 0.706; Bartlett's test of sphericity: $p<0.0001$.

TABLE 3 All quantitative computed tomography (CT) imaging measurement principal component analysis: rotated component matrix

	Component 1 (28.17%)	Component 2 (25.25%)	Component 3 (14.27%)
LAA_{950}, %	0.906#	−0.084	0.015
HU_{15}, HU	−0.870#	0.182	−0.101
LAC	0.319	0.099	−0.328
TAC, n	0.087	−0.827#	0.018
Pi10, mm	−0.031	0.418	0.711#
Lumen area, mm^2	0.107	−0.799#	0.364
Wall area, %	−0.055	0.930#	0.067
Vessel volume, cm^3	0.540	−0.164	0.590
$DPM_{air\ trapping}$, %	0.040	0.294	−0.541
$DPM_{emphysema}$, %	0.907#	−0.006	−0.159

LAA_{950}: low attenuation area ⩽ −950 HU on full-inspiration CT; HU_{15}: Hounsfield units associated with the 15th percentile of the CT density histogram; LAC: low attenuation cluster; TAC: total airway count; Pi10: square root of the airway wall area for a theoretical airway with 10 mm internal perimeter; DPM: disease probability measure. #: representative quantitative CT measurement(s). Kaiser–Meyer–Olkin measure of sampling adequacy: 0.597; Bartlett's test of sphericity: p<0.0001; rotation method: varimax with Kaiser normalisation, rotation converged in four iterations; cumulative % variance: 67.700.

the PCA component of CT emphysema only measurements (Model 2), visual emphysema score was statistically significant in predicting 6-year (p=0.027) ΔFEV_1 but not baseline FEV_1 (p>0.05). The PCA emphysema component was statistically significant in predicting baseline FEV_1 (β=0.095, p=0.043) but not ΔFEV_1 (p>0.05). In the third multiple linear regression model with visual emphysema score and the PCA component of all CT measurements (Model 3), visual emphysema score was statistically significant in predicting 6-year (p=0.021) ΔFEV_1 but not baseline FEV_1 (p>0.05). For baseline FEV_1, all three PCA components were statistically significant (p<0.03), with the Pi10 dominant PCA component having the greatest relative weight (β=0.687, p<0.001). In the models predicting 6-year ΔFEV_1, only the Pi10 dominant component was statistically significant (6-year: β= −0.108, p=0.004). Sensitivity analyses show similar results in 3-year ΔFEV_1 (supplementary table S4) and in our dataset with current smokers included (supplementary table S5).

Discussion

Here we aimed to investigate the association of linear combinations of quantitative CT measurements reflecting various disease-related features with lung function change over time. While previous COPD

TABLE 4 Multiple linear regression models for baseline forced expiratory volume in 1 s (FEV_1) and annualised change in FEV_1 (ΔFEV_1) with computed tomography (CT) measurements

	Visit 1 FEV_1 LLN, L			6-year ΔFEV_1 LLN, L per year		
	Adjusted R^2	Standardised estimate	p-value	Adjusted R^2	Standardised estimate	p-value
Model 1: Base+LAA_{950}+VES	0.097			0.531		
LAA_{950}, %		0.293	**<0.001**		−0.063	0.053
VES		−0.013	0.749		−0.058	**0.048**
Model 2: Base+emphysema QCTs+VES	0.045			0.529		
PCA emphysema component		0.088	**0.044**		−0.008	0.805
VES		0.016	0.706		−0.066	**0.027**
Model 3: Base+PCA components+VES	0.454			0.534		
PCA QCT component 1		0.242	**<0.001**		−0.043	0.208
PCA QCT component 2		0.069	**0.029**		0.006	0.831
PCA QCT component 3		0.685	**<0.001**		−0.108	**0.004**
VES		0.042	0.197		−0.069	**0.021**

LLN: lower limit of normal; LAA_{950}: low attenuation area ⩽ −950 HU on full-inspiration CT; VES: visual emphysema score; QCT: quantitative CT; PCA: principal component analysis. Base model covariates include: CT make/model, pack-years, smoking status, CT lung volume/total lung capacity, comorbidities (asthma, tuberculosis heart disease, systemic hypertension or diabetes) and use of respiratory medications (bronchodilator, inhaled steroid and oral steroid). Visit 0 FEV_1 LLN was included for 6-year ΔFEV_1 LLN. Bold indicates statistical significance (p<0.05).

imaging studies have investigated the use of PCA for feature selection [27] and cluster analysis [27, 28], to the best of our knowledge, no other studies have used PCA to generate new linear combinations of quantitative CT measurements when assessing the relative importance of quantitative and qualitative measures on longitudinal outcomes in COPD. Here we show: 1) when visual emphysema score and LAA_{950} were included in the same model, visual emphysema score was significantly associated with FEV_1 annualised change over time, but LAA_{950} was not, 2) when visual emphysema score and the PCA linear combination of CT emphysema measurements were included in the same model, visual emphysema was associated with FEV_1 annualised change but not the PCA emphysema component, and 3) when visual emphysema score and the PCA linear combination of all quantitative CT measurements were included in the same model, both visual emphysema score and PCA component were significant and independent predictors of FEV_1 annualised change.

First, we showed that visual emphysema score was a significant and independent predictor of FEV_1 annualised change, but LAA_{950} was not when included in the same multiple regression model. This finding agrees with the previous investigation showing visual emphysema score was a better predictor of mortality than LAA_{950} [6]. Due to the population-based study design of CanCOLD, the majority of CanCOLD participants have mild COPD and therefore there is low COPD-related mortality risk during the short follow-up. Therefore, in our study, we chose to use FEV_1 annualised change instead of COPD-related mortality. Taken together, these findings suggest visual emphysema score contributes independent information and may be more complex than measurements derived from simple density thresholds [7]. In another study [7], visual score could be predicted by LAA_{950}, emphysema distribution, presence/absence of gas trapping, LAC and emphysema type. Therefore, these findings suggest single quantitative CT measurements may not capture all the disease-related information that is captured by visual emphysema scoring and more complex CT measurements may be required.

Next, we used PCA analysis to investigate various emphysema-related CT measurements in combination to predict COPD progression. We showed similar results to the previous model, where visual emphysema was a significant and independent predictor of FEV_1 annualised change, but LAA_{950} was not when included in the same multiple regression model. The opposite is again shown when predicting baseline FEV_1. These results suggest that the PCA emphysema component may be a better predictor of baseline lung function than visual score. It is important to note that while the quantitative CT measurements included in the PCA (LAA_{950}, HU_{15}, $DPM_{emphysema}$ and LAC) may share conceptual or measurement-driven redundancy, we accounted for multicollinearity by removing highly correlated measurements. Furthermore, these measurements have known differences in terms of their associations with lung function and ability to predict longitudinal outcomes [29–31]. Importantly, some measurements may be more variable than others and have greater dependence on lung volume [32]. Therefore, due to the variability, several quantitative CT measurements should be considered and may be complementary. Previous studies have used multiple quantitative CT measurements that characterise similar information (lung overinflation, emphysema and airway measurements) in separate models as predictors [33] and in combination (HU_{15} regional measurements) as PCA components [34] to predict FEV_1 decline. However, to the best of our knowledge, quantitative CT measurements have not been used in combination as PCA components with visual scoring to predict lung function decline.

Finally, we showed that when using all CT measurements in combination to predict annualised lung function change, the PCA components contributed independent information from visual emphysema score. Similar results are shown in our cohort with current smokers included (supplementary table S5). Three PCA components were extracted from 10 CT measurements that included a component representative of emphysema (LAA_{950}, HU_{15} and $DPM_{emphysema}$), and two components reflecting segmental airway structural changes (TAC, lumen area and WA%) and global airway remodelling (Pi10). The first component representative of emphysema had positive coefficients for LAA_{950} and $DPM_{emphysema}$, and a negative HU_{15} coefficient, which, taken together, can be interpreted as worse emphysema. The second component had a negative coefficient for TAC and lumen area, and a positive coefficient for WA%. This may be interpreted as fewer airways, narrower segmental airway lumens and thinner walls, which are known to be associated with worse COPD [10]. For the third component, only Pi10 was selected, and increased Pi10, reflecting increased airway remodelling more globally, is well established to be associated with increased COPD severity [35]. Among the three PCA components, our results showed that the Pi10 dominant PCA component was the only PCA component that was significant in the model that included all component measurements and visual emphysema score for predicting lung function decline. This may be due to the fact that the CanCOLD population is mostly mild COPD, and it is thought that airway disease is predominant in mild COPD whereas emphysema is more apparent in those with severe COPD. Other studies have also demonstrated that CT Pi10 is a significant predictor of longitudinal lung function decline

in COPD over a 3-year [35] and 5-year follow-up [36]. Our results show that quantitative CT measures are able to predict baseline pulmonary function; however, the qualitative visual score has a comparable relative importance as quantitative measures when predicting longitudinal outcomes. This finding indicates that while quantitative CT may not yet outperform visual scoring for predicting lung function decline, it is less onerous to perform. Developing additional quantitative CT measurements that extract more information, such as texture-based radiomics or using deep learning, may provide an even more comprehensive method of evaluating the structural changes in the lung. Future studies should also focus on investigating these more composite, quantitative CT measurements in COPD patients for other outcomes, such as symptom worsening, hospitalisations/healthcare utilisation and mortality.

Identifying predictive biomarkers and developing prognostic models can provide clinicians with important information about risks of a specific end-point for their individual patients. The ultimate goal of prognostic models in clinical practice is to assist decision making regarding treatment strategy, interventions or hospital admission. Our results show that the combination of multiple predictors, from both visual and quantitative CT assessment, provided the strongest association with lung function decline and may provide a more comprehensive method of evaluation by incorporating different features of the disease.

There are limitations of our study that should be noted. The CanCOLD study is a population-based study and therefore is a relatively mild COPD cohort. Our findings cannot be generalised to more severe COPD cases. Due to the mild population and short follow-up duration, mortality and healthcare utilisation (*i.e.* hospitalisations and emergency room visits) could not be used as an outcome in our models. Future studies will focus on investigating these outcomes in CanCOLD and validation cohorts with longer follow-up duration such as COPDGene or SPIROMICS. We also note that because the cohort we investigated had relatively mild COPD, there was only a slightly greater 3- and 6-year change in FEV_1 between the never-smoker and COPD groups, but it was not statistically significant. However, previous studies have shown that while FEV_1 decline may be subtle and not statistically significant in COPD subjects compared with never-smokers, imaging measurements can more sensitively capture the structural disease changes that occur over short periods of time [37]. Therefore, our findings demonstrate that baseline CT measurements that reflect underlying lung disease can predict decline in lung function, even over short periods of time when only very subtle changes in FEV_1 are likely to occur. Long-term follow-up is, however, required to confirm these findings. Another limitation of the study was that CT images were acquired across multiple centres, with different CT systems. While a protocol was used for standardisation of image acquisition, there is still potential for variability due to different CT models, acquisition parameters and reconstruction kernels [38] to impact the quantitative measurements. Furthermore, measurements such as DPM [22] require both an inspiratory and expiratory CT image. Coaching participants to achieve the target lung volumes during image acquisition is important, since insufficient breath-hold volumes can impact the quantitative CT measurements [39]. We also acknowledge the PCA focused on only CT imaging measurements, and therefore pulmonary function tests and clinical variables were not included. A future study could explore the impact of these additional clinical/lung function variables as PCA components for predicting lung function decline. Finally, there are additional measurements, such as texture radiomics [40], regional lobular analysis [41] and parametric response mapping [42], that were not included in this study. Future work could include these measurements to explore their association with lung function decline.

In conclusion, our results show that the inclusion of multiple quantitative CT measurements reflecting different COPD-related disease features as PCA components increased the relative importance of quantitative CT compared with visual emphysema scoring for predicting lung function decline. Our results will aid in the understanding of COPD progression by showing that the inclusion of numerous CT measurements that reflect different pulmonary abnormalities as linear combinations can predict lung function decline.

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