Using Novel CT analysis to describe the contribution and distribution of emphysema and Small Airways Disease in COPD

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Author contributions

All authors contributed substantially to the study design and the writing of the manuscript. KO, KG, HB, AF, SH, MK, SP, JS, KS and TW collected or generated the data. KO, KG, KP, KS and TW analysed or interpreted the data. KO had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Abstract

Rationale: Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation, caused by emphysema and small airways disease (SAD). CT, coupled with image analysis enables the quantification of these abnormalities, however the optimum method for doing so has not been determined.

Objectives: This study aims to compare two CT quantitative analysis techniques, disease probability measure (DPM), and parametric response mapping (PRM) and assess their relationship with specific physiological measures of SAD.

Methods: Subjects with mild-moderate COPD, never smokers and healthy ex-smokers were recruited. Each had airway oscillometry and multiple breath nitrogen washout, measuring peripheral airway resistance (R5-R19), peripheral airway reactance (AX) and acinar airway inhomogeneity (S_{acin}). Subjects also had an inspiratory and expiratory chest CT, with DPM and PRM analysis performed by co-registering images and classifying each voxel as normal, emphysema (DPM_{Emph}/PRM_{Emph}) or non-emphysematous gas trapping related to SAD ($DPM_{GasTrap}$/$PRM_{GasTrap}$).

Results: 38 COPD subjects, 18 never smokers and 23 healthy ex-smokers were recruited. There were strong associations between DPM and PRM analysis when measuring gas trapping (rho=0.87, $p<0.001$) and emphysema (rho=0.99, $p<0.001$). DPM assigned significantly more voxels as emphysema and gas trapped compared to PRM ($p<0.001$). Both techniques showed significantly greater emphysema and gas trapping in COPD subjects compared to never smokers and ex-smokers ($p<0.001$). All CT measures had significant associations with peripheral airway resistance and reactance, with $DPM_{GasTrap}$ having the strongest independent association with R5-R19 ($\beta=0.42$, $p=0.001$) and AX ($\beta=0.41$, $p=0.001$). Emphysema measures had the strongest associations with S_{acin} ($\beta=0.35$-0.38).

Conclusions: These results provides further validation for the use of DPM/PRM analysis in COPD by demonstrating significant relationships with specific physiological measures of SAD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterised by airflow limitation, caused by a combination of parenchymal destruction and small airways disease(1). The quantity and distribution of these pathologies play important roles in the disease and may contribute to the variable clinical phenotypes that exist(2). Computed tomography (CT) can be used to image these pathological changes, with quantitative analysis techniques having the potential to detect regional distribution of disease, subtle changes in early disease and possibly the ability to track response to therapy beyond what physiological tests offer.(3).

Emphysema is relatively simple to detect as low attenuation areas on CT and quantitative thresholding methods have been validated against histopathological specimens(4, 5). Measuring small airways disease is more complex, as the small airways are beyond the resolution of CT scanners. Gas trapping on expiratory CT can be used as a surrogate marker of small airways disease, although this is not specific and can be influenced by emphysema. More recently, co-registration techniques, such as parametric response mapping (PRM)(6) and disease probability measure (DPM)(7) have been developed, where individual voxels are registered between the inspiratory and expiratory CT and labelled as emphysema, non-emphysematous gas trapping or normal. The main difference between these is that PRM uses fixed attenuation thresholds, whereas DPM uses an alternative method based on the continuous distribution of Hounsfield unit (HU) values between inspiration and expiration CT to assess the probability of each voxel belonging to each tissue sub-type(7). Although PRM analysis is currently the more established technique, with studies showing associations with lung function(8) and decline in FEV1(9), there is a lack of thorough validation, with most studies comparing them to non-specific measures of pulmonary function.

There is currently no gold standard for detecting small airways disease, with all methods having limitations(10). This provides significant challenges when trying to validate CT measures of small

airways disease, with most studies simply assessing them against clinical and basic physiological characteristics. More specific physiological tests of small airways dysfunction include the forced oscillation technique (FOT) and multiple breath nitrogen washout. FOT allows the measurement of change in resistance with frequency (R5-R19), a marker of peripheral airways resistance(11) and measurement of reactance at low frequencies (AX), which has also been suggested to reflect the properties of the peripheral airways(10, 11). The MBNW test measures the ventilation heterogeneity in in the acinar region (S_{acin}), an indicator of structural changes in this region potentially resulting from pathology in the small airways(12).

This study aims to compare DPM and PRM CT analysis and provide further validation for their use in COPD subjects by assessing the relationship with detailed pulmonary function tests, including FOT and MBNW.

Materials and Methods

Subjects with mild-moderate COPD, healthy ex-smokers and never smokers were recruited into this study performed at the University hospital Southampton. COPD subjects were recruited from a combination of sources, including an established research database of COPD subjects, contact by clinicians involved or aware of the study within the hospital and other local health care facilities and through subjects responding to study adverts/posters. Never smokers and healthy ex-smokers were recruited from either a healthy volunteer's research database held within the University hospital Southampton or through subjects responding to study adverts/posters. COPD subjects had an FEV1/FVC of <0.7 and an FEV1 of ≥50% predicted, while healthy ex and never smokers had normal lung function. COPD and healthy ex-smokers had at least a ten-pack year history but had quit at least 6 months ago, while never smokers were defined by a minimal smoking history (<2 pack years). Exclusion criteria included a history of other pulmonary disease, long-term antibiotics/steroids or an

exacerbation within the month prior to recruitment. All subjects gave written consent and the study was approved by the South Central C Research Ethics committee (REC number 15/SC/0528).

CT scanning and image analysis

Subjects underwent volumetric CT scans of the chest in full inspiration and maximum expiration using a Siemens Sensation 64 scanner. The imaging protocol followed standardised guidelines and consisted of; slice thickness 0.75mm, slice separation 0.5mm, tube voltage 120KV, effective mAs 90mAs, collimation 0.6mm and a pitch of 1. Images reconstructed with the B35 kernel were used for image analysis. Breathing instructions for optimum lung volume acquisition were followed(13–15).

CT analyses were performed by an ISO-certified core laboratory, VIDA Diagnostics, Inc. (Coralville, IA, USA), using the DPM approach (figure 1)(7). Inspiratory and expiratory scans were registered using a nonlinear registration algorithm. For each registered voxel pair, two exponential probability decay functions, $p_{loss}(x)$ and $p_{trap}(x)$ were used to determine the continuous probabilities of structural loss and gas trapping, respectively. Structural loss probability was calculated based on the concentration of tissue ($t_{in}(x)$) as indicated by the CT inspiration intensity value. Gas trapping probability was calculated based on the difference in tissue concentrations between expiration and inspiration ($\Delta_t(x)$) in a way that scales inversely with $t_{in}(x)$. The ultimate classifications of normal (DPM_{Normal}), non-emphysematous gas trapping ($DPM_{GasTrap}$), and emphysema (DPM_{Emph}) were determined based on the maximal product of the probabilities as follows:

$$DPM(x) = \begin{cases} \mathrm{DPM_{Normal}} \text{ if} & (1 - p_{loss}(x)) \cdot (1 - p_{trap}(x)) \quad \text{is maximal} \\ \mathrm{DPM_{GasTrap}} \text{ if} & (1 - p_{loss}(x)) \cdot p_{trap}(x) \quad \text{is maximal} \\ \mathrm{DPM_{Emph}} \text{ if} & p_{loss}(x) \cdot p_{trap}(x) \quad \text{is maximal} \end{cases}$$

Figure 1, part D shows the three resulting classification regions on a 2D probability plot of gas trapping versus structural loss. Under this scheme, voxels with <50% probability of gas trapping and <50% probability of structural loss are classified as normal (DPM_{Normal}), voxels with >50% probability of gas trapping and <50% probability of structural loss are classified as non-emphysematous gas trapping ($DPM_{GasTrap}$) and voxels with >50% structural loss and >50% gas trapping are classified as emphysema

(DPM_{Emph}). Voxels with >50% structural loss and <50% gas trapping are labelled as DPM_{Emph} if the sum of those probabilities is>100%, otherwise they are labelled as normal. The rationale for this being that emphysematous tissue is presumed to exhibit both structural loss and gas trapping characteristics, but heightened certainty of structural loss is allowed to compensate for a lack of certainty of gas trapping in order to still warrant the DPM_{Emph} label.

The precise numerical definitions of $p_{loss}(x)$ and $p_{trap}(x)$ were determined using CT inspiration and expiration image pairs from a training set of subjects with various stages of COPD in the COPDGene and SPIROMICS studies. The various function parameters were optimized as to give the strongest Pearson correlation coefficient for the final DPM disease classification with standard pulmonary function and clinical measurements (FEV_1, six minute walk distance, and St. George's Respiratory Questionnaire score) (data not shown).

PRM analysis was also performed on these co-registered images with voxels labelled as normal (PRM_{Normal}), emphysema (PRM_{Emph}) or non-emphysematous gas trapped ($PRM_{GasTrap}$) according to the fixed thresholds, -950HU and -856HU(6).

Pulmonary Function

All lung function tests were performed during the same study visit. Pre-bronchodilator, single breath diffusion was performed as per guidelines, with percent-predicted carbon monoxide transfer coefficient calculated (TLCO%). 400mcg of salbutamol was administered using an inhaler and spacer device. Following this the tidal breathing tests, MBNW and oscillometry were performed before plethysmography and spirometry, with subjects allowed sufficient recovery time between testing. For MBNW, subjects breathed in 100% oxygen, maintaining a tidal volume of 1L for more than 6 turnovers in order to obtain S_{acin} values generated by the software Spiroware 3.1.6®, Exhalyzer D, Eco Medics(16). At least two measurements were obtained and the mean reported. The multifrequency airwave oscillometry system tremoFlo C-100; THORASYS, measured impedance during tidal breathing of at least 30 seconds, with three repeatable tests achieved and the mean reported(17).

Plethysmography was performed as per guidelines to give measurements for residual volume/total lung capacity ratio (RV/TLC) and percent predicted residual volume (%RV). Spirometry was performed as per guidelines(18), giving measurements for FEV1%, FEV1/FVC and FEF75-25%. .

Statistical Analysis

Analysis was performed using SPSS version 24. The differences in demographic, physiological, and CT parameters between groups were tested using the Kruskal-Wallis test. Simple univariate associations were tested using spearman's correlations. Multivariable analysis was performed by combining each of the CT parameters in turn with demographic variables (age and gender) to predict each of the dependent variables. For differences between multiple groups a Bonferroni correction was applied to adjust for multiple tests. A p value <0.05 was considered statistically significant.

Results

38 COPD subjects, 18 never smokers and 23 healthy ex-smokers were recruited. Demographic and pulmonary function data are shown in table 1. Groups were well matched. As expected, never smokers and healthy ex-smokers had preserved lung function. COPD subjects had a median FEV1 of 71% predicted (IQR 26.0), with 29% belonging to GOLD group 1 and 71% belonging to GOLD group 2. R5-R19, AX and S_{acin} were all significantly higher in COPD compared to never and healthy ex-smokers ($p \leq 0.001$).

CT Analysis

Figure 2 shows an illustrative DPM-derived and PRM-derived map for three subjects (one never smoker and 2 with COPD). There was significantly more emphysema in COPD (DPM_{Emph} 10.4%, IQR 15.7 and PRM_{Emph} 4.6%, IQR 9.4) compared to never (DPM_{Emph} 1.2%, IQR 1.8 and PRM_{Emph} 0.4%, IQR 0.5) and healthy ex-smokers (DPM_{Emph} 1.4%, IQR and PRM_{Emph} 0.6%, IQR 1.3) using both techniques ($p<0.001$) (figure 3). There was also significantly more gas trapping in COPD subjects ($DPM_{GasTrap}$ 27.1%,

IQR 16.8 and $PRM_{GasTrap}$ 23.1%, IQR 18.2) compared to never ($DPM_{GasTrap}$ 13.7%, IQR 8.6 and $PRM_{GasTrap}$ 4.0%, IQR 5.9) or healthy ex-smokers ($DPM_{GasTrap}$ 16.4%, IQR 9.3 and $PRM_{GasTrap}$ 4.8%, IQR 7.5) using PRM and DPM analysis ($p<0.001$). There was however, no difference in emphysema or gas trapping between never smokers and healthy ex-smokers using either method. The two techniques showed relatively good overall consistency with one another as a median of 82.1% (IQR 11.2) of voxels were labelled the same. Much of this was driven by voxels labelled as normal, with a median of 99.3% (IQR 0.0) voxels labelled as DPM_{Normal} also being labelled as PRM_{Normal}. Voxels labelled as DPM_{Emph} were only labelled as PRM_{Emph} a median of 36.9% of (IQR 15.0) the time, with the rest being labelled as $PRM_{GasTrap}$. A median of 30.7% (IQR 31.0) voxels labelled as $DPM_{GasTrap}$ were also labelled as $PRM_{GasTrap}$, with the remainder labelled as PRM_{Normal}. As a result of this, there was significantly greater emphysema ($p<0.001$) and gas trapping ($p<0.001$) measured by DPM compared to PRM (figure 3). There were however strong associations between DPM_{Emph} and PRM_{Emph} (rho 0.99, $p<0.001$) and between $DPM_{GasTrap}$ and $PRM_{GasTrap}$ (rho 0.87, $p<0.001$) (figure 4).

Table 2 shows the associations between CT parameters and lung function. There were significant independent relationships between all CT parameters and FEV_1% (DPM_{Emph} β -0.57, CI [-0.78, -0.37], PRM_{Emph} β -0.52 CI [-0.73 to -0.32], $DPM_{GasTrap}$ β -0.56, CI [-0.78 to -0.34], $PRM_{GasTrap}$ β -0.54, CI [-0.76 to -0.32]). There were also significant relationships between all CT parameters and FEV1/FVC, $FEF_{75-25\%}$, TLCO% and RV/TLC. Associations were broadly similar between these CT and lung function measures, although emphysema tended to have stronger associations with TLCO% than gas trapping (DPM_{Emph} β -0.54, CI [-0.75 to -0.34], PRM_{Emph} β -0.55, CI [-0.75 to -0.35], $DPM_{GastTrap}$ β -0.34, CI [-0.57 to -0.10], $PRM_{GastTrap}$ β -0.40, CI [-0.64 to -0.17]). All CT parameters had independent associations with R5-R19 and AX, with the strongest of these being with $DPM_{GasTrap}$ (R5-R19 $DPM_{GastTrap}$ β 0.42, CI [0.19 to 0.66] and AX $DPM_{GastTrap}$ β 0.41, CI [0.19 to 0.64]). All CT measures, apart from $DPM_{GasTrap}$, had significant associations with S_{acin}, with emphysema measures showing the strongest relationships (DPM_{Emph} β 0.38, CI [0.16 to 0.60], PRM_{Emph} β 0.35, CI [0.13 to 0.57])

To understand whether level of lung inflation on CT influenced these results, we compared TLC and RV measured using plethysmography and CT. There were strong associations between TLC measured using CT and plethysmography (rho 0.90, $p<0.001$) and for RV (rho 0.84, $p<0.001$). When adding the ratio of level of lung inflation on CT at TLC (calculated by dividing CT inspiratory volume/TLC) and RV (calculated by dividing CT expiratory volume/RV) into the regression models, broadly similar results were seen (supplementary data).

Discussion

Emphysema and small airways disease are key pathological features of COPD, meaning it is vital that accurate methods for discriminating them are available. We used a novel CT analysis method, DPM, as well as PRM to determine these, finding that even within this relatively mild cohort of COPD subjects there was significantly more emphysema and small airways disease compared to never or healthy ex-smokers. For the first time, we compared these CT parameters with specific physiological measures of small airways disease, measured using FOT and MBNW, showing significant associations and thereby providing further validation for their use.

DPM and PRM are image analysis techniques that co-register inspiratory and expiratory CT scans to identify voxels representing normal tissue, emphysema and non-emphysematous gas trapping secondary to small airways disease. One previous study has utilised both of these methods and in common with our results showed significantly more emphysema and gas trapping in COPD subjects compared to controls(7). To provide further validation for these, we assessed their performance against in-depth measures of pulmonary physiology. As with previous studies we found significant associations between CT-derived emphysema and gas trapping and FEV_1%, $FEF_{75-25\%}$, TLCO% and RV/TLC(7, 19, 20). R5-R19 and AX, measured using FOT, reflect peripheral airway resistance and reactance with prior studies showing increased values in COPD(21–23). Both emphysema and gas trapping, measured using either DPM or PRM, had independent associations with R5-R19 and AX,

278 although associations were strongest for DPM gas trapping. This is in contrast to a study in healthy
279 individuals, which showed small airways resistance had an inverse relationship with PRM gas trapping,
280 but not emphysema, while airway reactance did not show associations with either measure(24). The
281 cause for this discrepancy is unknown although the study populations were different as we included
282 COPD subjects and in addition, the direction of the relationships was as expected in our study. No
283 other studies have assessed the relationships between CT image analysis and R5-R19 and AX in COPD
284 subjects. S_{acin}, measured using MBNW, measures ventilation inhomogeneity, with a previous
285 histopathological study suggesting it reflects acinar structural changes predominantly due to
286 emphysema(25). To the best of our knowledge this is the first study comparing imaging with this
287 measure and our findings would support this, as associations were strongest for emphysema. These
288 results therefore provide further evidence for the use of both DPM and PRM in accurately measuring
289 emphysema and small airways disease in COPD. It is however, important to point out that acquisition
290 between the CT and physiological techniques are different. CT measures are volumetric measures and
291 are derived from manoeuvres at TLC and RV, while FOT and MBNW are measured during tidal
292 breathing. The pressure signals from which these FOT indices are derived may not reach beyond
293 closed-off airways and thus may not measure all facets of small airways disease. Thus, incorporating
294 imaging can improve understanding of early structural changes and compliment FOT and MBNW
295 pulmonary data. Further studies can also advance the understanding with comparisons of
296 physiological, imaging and histological measurements of small airways disease.

297 We also sought to compare DPM with PRM measurements(6). PRM uses fixed attenuation thresholds
298 to classify each voxel as emphysematous or gas trapped while DPM uses variable attenuation
299 thresholds based on probability mapping. We found strong associations between the two techniques
300 and found they were relatively consistent, especially when labelling voxels as normal. DPM did
301 however, assign significantly more voxels as emphysematous and gas trapped than PRM. This is
302 consistent with the previous work by Kirby et al(7) and together suggests that DPM may be more

sensitive at detecting subtle changes in lung structure. An alternative explanation for this may be that DPM is overly sensitive, especially when measuring gas trapping as higher amounts were found in control subjects. Although both DPM and PRM had significant associations with specific measures of small airways disease (R5-R19 and AX), DPM gas trapping had the strongest association, while other associations with lung function were broadly similar. This is the first study to compare both CT techniques against these in-depth pulmonary function tests and provides some evidence to suggest that DPM may be superior at measuring small airways disease in COPD. This may be because using variable attenuation thresholds is less influenced by scanner or respiratory effort variability and therefore offers greater potential future application as a research and clinical tool. This however is conjecture and it must be noted that the difference in results between the two techniques were small and therefore may have limited practical significance. Unlike PRM, DPM assumes that most emphysematous voxels will exhibit both structural loss and a degree of gas trapping. There is however a risk that DPM incorrectly assigns a voxel as normal when there is emphysema present but only limited probability of gas trapping. This is overcome by allowing a voxel to be labelled as emphysematous where there is a heightened probability of structural loss (sum of the probabilities of structural loss and gas trapping is >100%). Further studies are required to compare the DPM and PRM techniques, especially in more severe cohorts, multi-centre studies and in longitudinal work.

Our study has a number of strengths. Compared to many quantitative CT studies, this was a single centre study with all imaging performed on the same scanner, meaning scanner variability did not affect our results. All CT imaging was performed to an optimum protocol, allowing accurate segmentation and quantitative analysis. Particular attention was paid to standardising breath holding to ensure scans were captured at TLC and RV. In addition, none of the subjects were current smokers, which has been shown to be a potential confounder on CT analysis. Our study had a number of limitations, with the main one being the relatively small sample size of subjects. This however allowed the in-depth physiological tests to be performed. This cohort was relatively mild and so it is unknown whether similar results will be achieved with a more severe cohort. In addition to this, it must be

acknowledged that unlike in previous studies there was little difference between never smokers and healthy ex-smokers. Another limitation is the multiple comparisons made in this study, however where appropriate Bonferroni corrections were used and we found far more significant associations than would be expected by chance alone.

In conclusion, we provide further validation for the use of novel DPM and PRM CT analysis in determining emphysema and small airways disease by showing significant associations with in-depth pulmonary function tests, including FOT and MBNW techniques. Therefore, this data demonstrates that these novel imaging techniques can detect subtle changes in lung structure to provide important phenotypical insights which could in the future be utilised for clinical and drug development purposes.

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Tables

Table 1. Demographics and lung function in never smokers, ex-smokers and COPD subjects.

	Never Smoker (N=18)	Ex-smokers (N=23)	COPD (N=38)
Age (years)	63.0 (14.0)	67 (7.0)	70.5 (13.0)
Male	10 (55.6%)	13 (56.5%)	29 (76.3%)
BMI (kg/m^2)	27.5 (6.3)	27.9 (6.38)	28.3 (6.8)
Pack years	0.0 (1.6)	25.0 (22.0)	40.5 (37.2)
Pulmonary Function			
FEV1%	104.0 (24.3)	100.0 (11.0)	71.0 (26.0)
FEV1/FVC	79.0 (6.8)	78.0 (7.0)	56.5 (14.8)
FEF75-25%	106.5 (33.8)	103.0 (31.0)	34.5 (21.5)
TLCO%	95.0 (18.0)	90.0 (18.0)	72.0 (22.0)
RV%	88.0 (30.5)	84.5 (21.0)	109.0 (39.0)
RV/TLC	34.0 (7.0)	37.0 (9.8)	41.0 (11.0)
R5-R19	0.31 (0.30)	0.27 (0.43)	0.78 (0.98)
AX	4.4 (4.7)	4.4 (3.1)	11.2 (16.8)
S_{ACIN}	0.10 (0.17)	0.12 (0.08)	0.35 (0.30)

Values given as medians (IQR). Males given as number of subjects (%).
For TLCO% n=18 for never smokers, n=20 for ex-smokers and n=36 COPD subjects.
For RV% and RV/TLC ratio n=17 for never smokers, n=20 for ex-smokers and n=35 COPD subjects.
For R5-R19 and AX n=18 for never smokers, n=21 for ex-smokers and n=37 for COPD subjects.
For S_{ACIN} n=17 for never smokers, n=17 for ex-smokers and n=29 for COPD.

Table 2: Regression models assessing the relationship between CT parameters and lung function

	DPM_{Emph}	$DPM_{GasTrap}$	PRM_{Emph}	$PRM_{GasTrap}$
FEV1%				
R^2	.331	.299	.296	.284
Standardized Effect Estimate	-0.57	-0.559	-0.524	-0.54
95% CI	**-0.775 to -0.365**	**-0.778 to -0.339**	**-0.731 to -0.317**	**-0.761 to -0.319**
FEV1/FVC				
R^2	.625	.303	.591	.388
Standardized Effect Estimate	-0.742	-0.427	-0.704	-0.540
95% CI	**-0.896 to -0.588**	**-0.646 to -0.208**	**-0.862 to -0.546**	**-0.744 to -0.366**
FEF75-25%				
R^2	.471	.310	.423	.361
Standardized Effect Estimate	-0.664	-0.520	-0.609	-0.578
95% CI	**-0.846 to -0.481**	**-0.737 to -0.302**	**-0.797 to -0.421**	**-0.787 to -0.370**
TLCO%				
R^2	.393	.236	.408	.275
Standardized Effect Estimate	-0.542	-0.336	-0.549	-0.404
95% CI	**-0.746 to -0.338**	**-0.574 to -0.098**	**-0.747 to -0.351**	**-0.636 to -0.173**
RV/TLC				
R^2	.472	.555	.430	.539
Standardized Effect Estimate	0.480	0.491	0.260	0.463
95% CI	**0.293 to 0.668**	**0.306 to 0.676**	**0.065 to 0.456**	**0.277 to 0.648**
R5-R19				
R^2	.250	.288	.236	.241
Standardized Effect Estimate	0.346	0.423	0.315	0.343
95% CI	**0.114 to 0.577**	**0.187 to 0.659**	**0.085 to 0.545**	**0.101 to 0.584**
AX				
R^2	.252	.284	.248	.242
Standardized Effect Estimate	0.34	0.413	0.329	0.338
95% CI	**0.119 to 0.561**	**0.185 to 0.641**	**0.111 to 0.547**	**0.106 to 0.570**
S_{acin}				

R^2	.380	.285	.362	.318
Standardized Effect Estimate	0.380	0.192	0.348	0.277
95% CI	**0.160 to 0.601**	-0.051 to 0.436	**0.127 to 0.568**	**0.040 to 0.513**

Each of the CT parameters were combined into a regression model with demographic variables (age and gender) to predict each of the dependent variables. N = 63-76. All outcome variables were log-transformed before regression analyses.

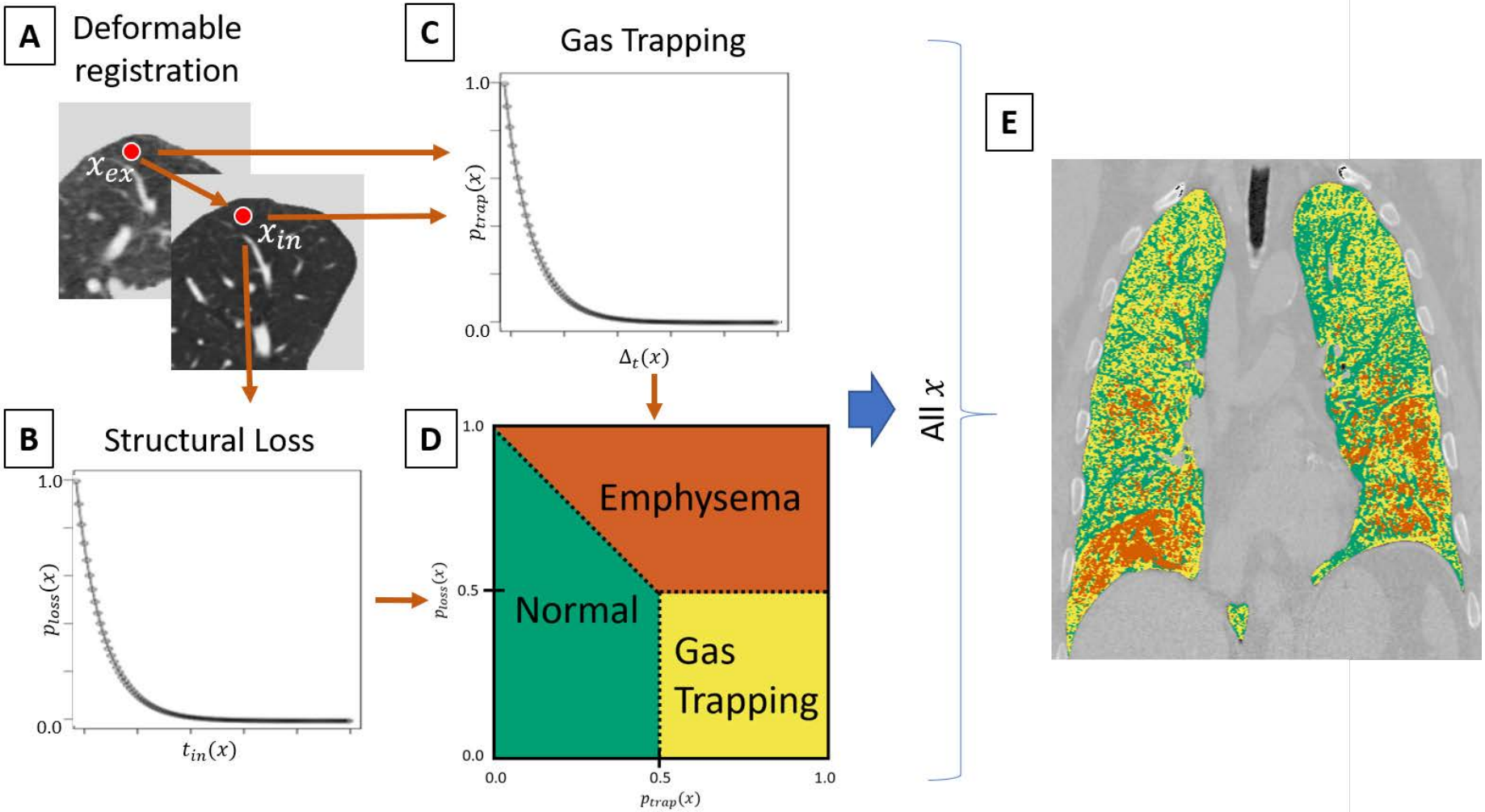
Figure Legends

Figure 1. DPM analysis methodology. CT inspiratory and expiratory images are co-registered using a non-linear registration algorithm (A). Continuous probabilities of structural loss (B) and gas trapping (C) are computed at every lung voxel pair based on co-registered inspiratory and expiratory Hounsfield unit values. Results are classified according to the maximal product of probabilities, resulting in the three classification regions (normal, non-emphysematous gas trapping, and emphysema) shown on the 2D probability plot (D). Labels are aggregated for all voxel pairs and mapped back into a volumetric representation (E).

Figure 2. DPM (1) and PRM (2) -derived maps showing normal tissue in green, non-emphysematous gas trapping in yellow and emphysema in red for three subjects (A) a healthy control subject (B) A COPD subjects with significant gas trapping and moderate emphysema (C) a COPD subject with significant emphysema.

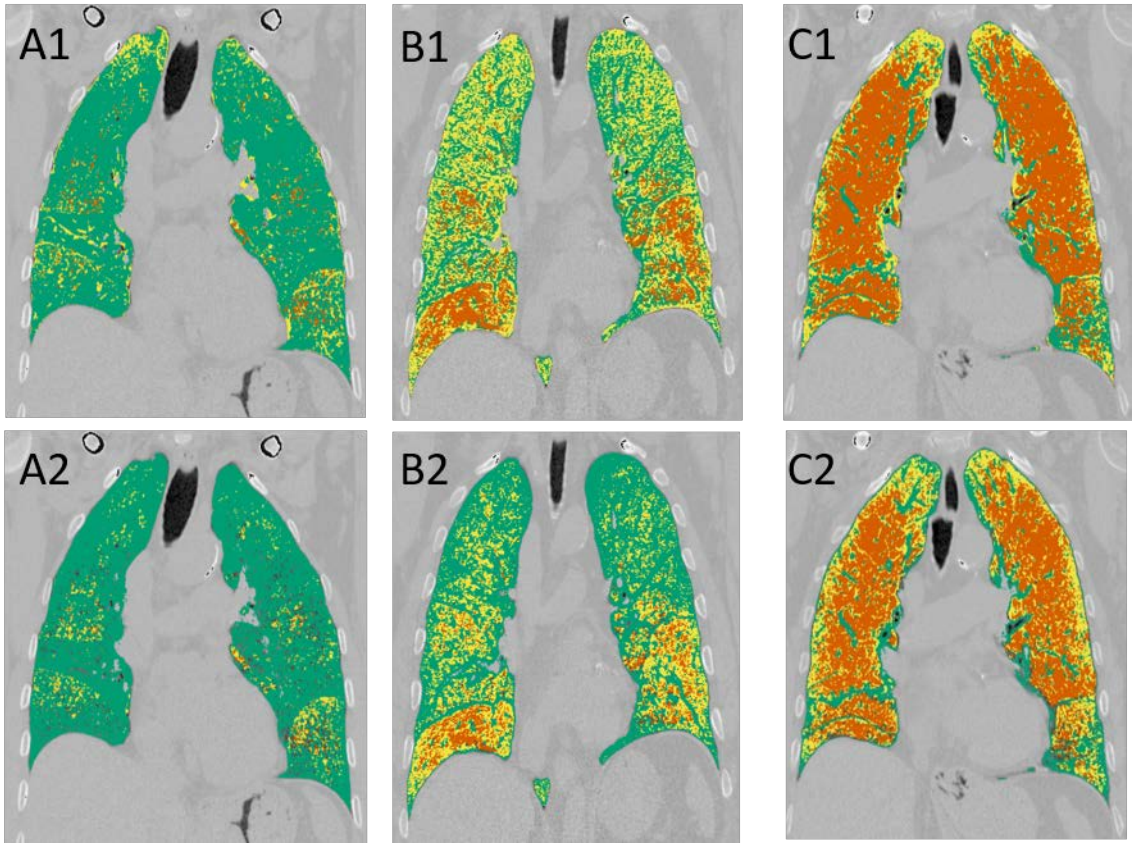
Figure 3. Quantity of emphysema and gas trapping in never smokers (NS), ex-smokers (ES) and COPD subjects using DPM and PRM techniques. (A) DPM_{normal} (B) PRM_{normal} (C) $DPM_{GasTrap}$ (D) $PRM_{GasTrap}$ (E) DPM_{Emph} (F) PRM_{Emph}. Data represents median and IQR. N=18 for never smokers, 23 for ex-smokers and 38 for COPD subjects. *$p<0.05$.

Figure 4. Scatterplots of DPM against PRM (A) Normal (B) Gas trapping (C) Emphysema.


A
Deformable registration
x_{ex}
x_{in}
B
Structural Loss
1.0
0.0
$p_{loss}(x)$
$t_{in}(x)$
C
Gas Trapping
1.0
0.0
$p_{trap}(x)$
$\Delta_t(x)$
D
1.0
0.5
0.0
$p_{loss}(x)$
Emphysema
Normal
Gas Trapping
0.0
0.5
1.0
$p_{trap}(x)$
All x
E

502

503



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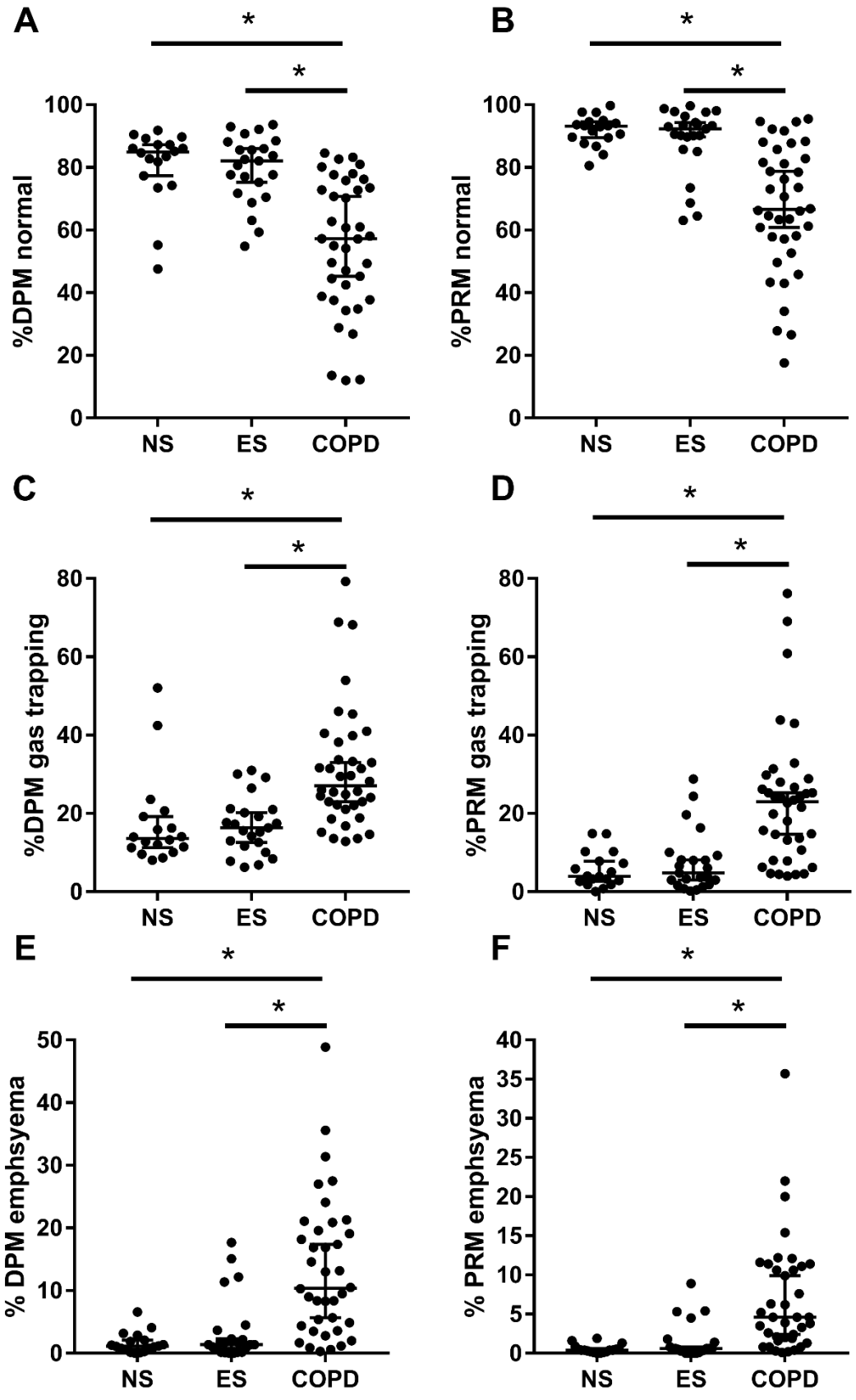
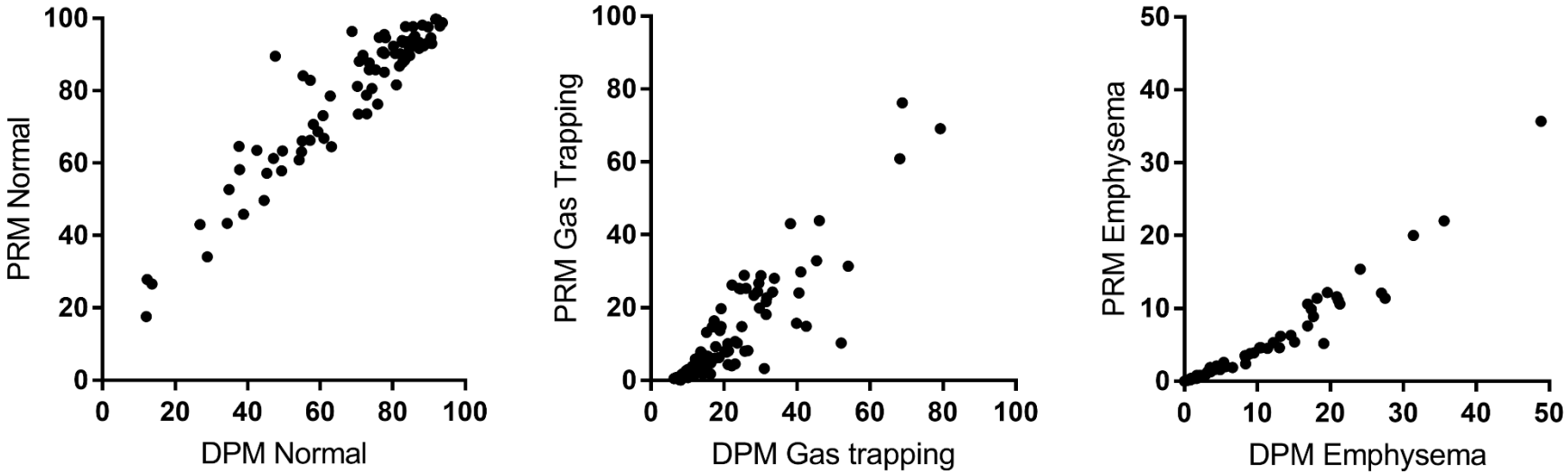

A
B
C
D
E
F
*
%DPM normal
%PRM normal
%DPM gas trapping
%PRM gas trapping
% DPM emphsyema
% PRM emphsyema
NS
ES
COPD

505


PRM Normal
DPM Normal
0
20
40
60
80
100
PRM Gas Trapping
DPM Gas trapping
PRM Emphysema
DPM Emphysema
10
30
50

506

Supplementary Table: Regression models assessing the relationship between CT parameters and lung function

	DPM_{Emph}	$DPM_{GasTrap}$	PRM_{Emph}	$PRM_{GasTrap}$
FEV1%				
R^2	.426	.351	.380	.369
Standardized Effect Estimate	-0.629	-0.553	-0.554	-0.544
95% CI	**-0.848 to -0.409**	**-0.792 to -0.314**	**-0.773 to -0.334**	**-0.767 to -0.321**
FEV1/FVC				
R^2	.621	.401	.594	.433
Standardized Effect Estimate	-0.719	-0.470	-0.666	-0.490
95% CI	**-0.897 to -0.540**	**-0.700 to -0.240**	**-0.844 to -0.489**	**-0.701 to -0.279**
FEF75-25%				
R^2	.499	.396	.452	.414
Standardized Effect Estimate	-0.662	-0.557	-0.589	-0.548
95% CI	**-0.867 to -0.457**	**-0.788 to -0.326**	**-0.795 to -0.382**	**-0.763 to -0.334**
TLCO%				
R^2	.447	.233	.450	.285
Standardized Effect Estimate	**-0.625**	**-0.320**	**-0.606**	**-0.398**
95% CI	**-0.847 to -0.404**	**-0.590 to -0.050**	**-0.819 to -0.393**	**-0.643 to -0.153**
RV/TLC				
R^2	.573	.559	.500	.589
Standardized Effect Estimate	**0.490**	**0.526**	**0.359**	**0.496**
95% CI	**0.301 to 0.679**	**0.336 to 0.716**	**0.273 to 0.648**	**0.317 to 0.676**
R5-R19				
R^2	.273	.277	.251	.250
Standardized Effect Estimate	**0.424**	**0.439**	**0.373**	**0.372**
95% CI	**0.169 to 0.679**	**0.178 to 0.699**	**0.123 to 0.623**	**0.120 to 0.623**
AX				
R^2	.276	.279	.269	.252
Standardized Effect Estimate	**0.395**	**0.411**	**0.370**	**0.339**
95% CI	**0.149 to 0.642**	**0.158 to 0.663**	**0.131 to 0.608**	**0.097 to 0.582**

S_{acin}				
R^2	.391	.262	.361	.301
Standardized Effect Estimate	0.475	0.190	0.410	0.288
95% CI	**0.223 to 0.727**	-0.083 to 0.464	**0.162 to 0.658**	**0.036 to 0.539**

Each of the CT parameters were combined into a regression model with demographic variables (age and gender) and inflation level at TLC and RV to predict each of the dependent variables. N = 63-76. All outcome variables were log-transformed before regression analyses.