

2026.6.13

Utilization of CT scan in COPD

Speaker

Hyun Woo Lee

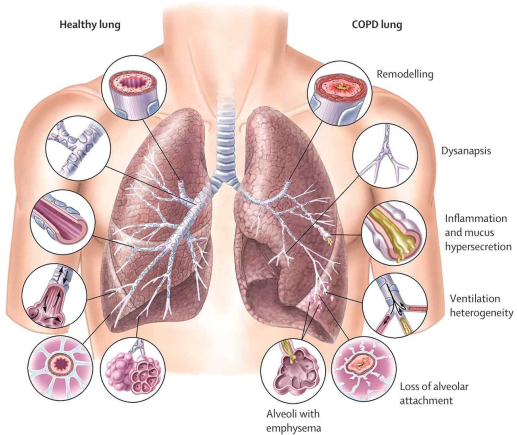
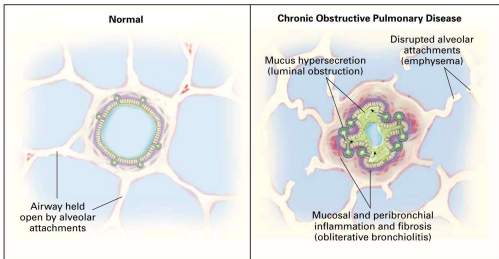
(Seoul National University College of Medicine,
Seoul Metropolitan Government Boramae Medical Center)

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Pathophysiology of COPD



Why should CT be performed in COPD?

Use of CT in Stable COPD

Figure 2.14

Differential Diagnosis

- Frequent exacerbations with excessive cough with sputum production, raising concern for bronchiectasis or atypical infection
- Symptoms out of proportion to disease severity based on lung function testing or refractory to medical management

Lung Volume Reduction

- Endobronchial valve therapy may be a therapeutic option for patients if they demonstrate postbronchodilator FEV1 between 15% to 45% and evidence of hyperinflation
- Lung volume reduction surgery may be a therapeutic option for patients with hyperinflation, severe upper lobe predominant emphysema and low exercise capacity after pulmonary rehabilitation

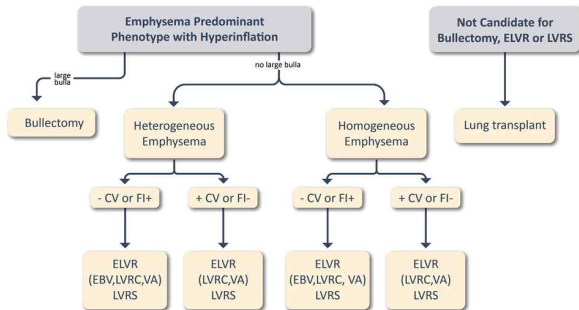
Lung Cancer Screening

- Annual low-dose CT scan is recommended for lung cancer screening in patients with COPD due to smoking according to recommendations for the general population

Different strategy according to emphysema

Surgical and Interventional Therapies in Advanced Emphysema

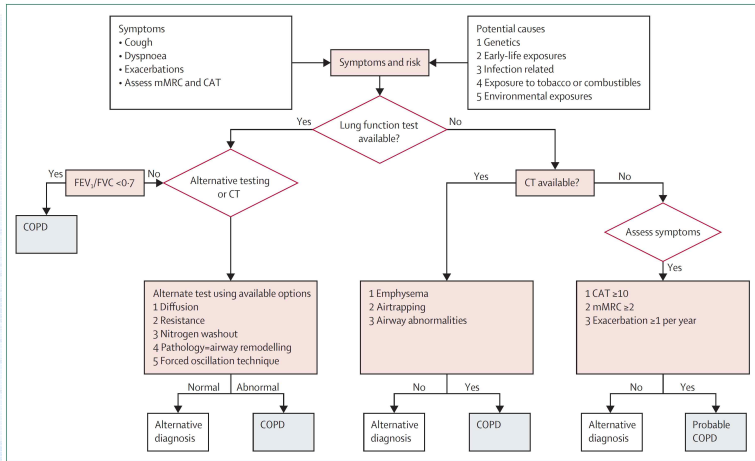
Figure 3.23



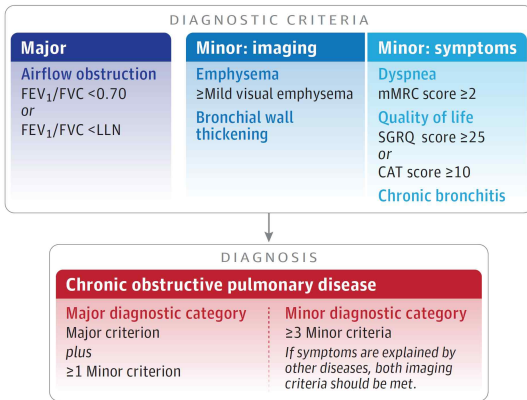
Note: not all therapies are clinically available in all countries. Long term ELVR outcomes or direct comparisons to LVRS are unknown.

Definition of abbreviations: CV, collateral ventilation measure by Chartis; FI + fissure integrity > 90% by HRCT; FI-, fissure integrity < 90% by HRCT; ELVR, Endoscopic Lung Volume Reduction, EBV, Endobronchial Valve; VA, Vapor Ablation; LVRC, Lung Volume Reduction Coil; LVRS, Lung Volume Reduction Surgery. Modified from Vogelmeier, AJRCCM, 2017.

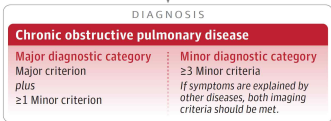
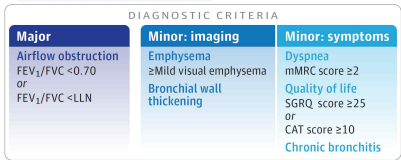
Proposed diagnostic algorithm for COPD



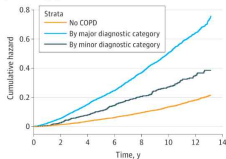
Diagnostic schema using major and minor criteria



Diagnostic schema using major and minor criteria

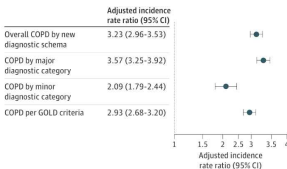


A Multivariable cumulative hazards plot of all-cause mortality by COPD category



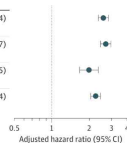
No. at risk	0	2	4	6	8	10	12	14
No COPD	4721	4183	3986	3612	3276	2932	1820	
By major diagnostic category	3884	3495	3100	2626	2160	1763	1015	
By minor diagnostic category	811	670	598	517	423	354	201	

C Adjusted incidence rate ratio for exacerbations



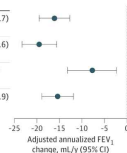
B Adjusted hazard ratio for all-cause mortality by COPD category

	Adjusted hazard ratio (95% CI)
Overall COPD by new diagnostic schema	2.58 (2.35-2.84)
COPD by major diagnostic category	2.70 (2.45-2.97)
COPD by minor diagnostic category	1.98 (1.67-2.35)
COPD per GOLD criteria	2.24 (2.05-2.44)



D Adjusted annualized change in FEV₁

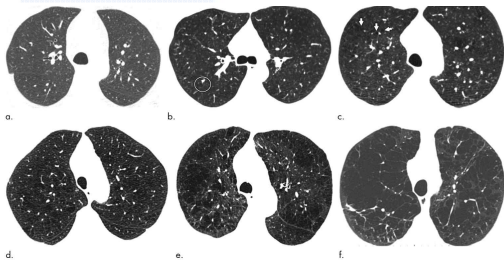
	Adjusted annualized FEV ₁ change, mL/y (95% CI)
Overall COPD by new diagnostic schema	-16.1 (-19.5 to -12.7)
COPD by major diagnostic category	-19.5 (-23.3 to -15.6)
COPD by minor diagnostic category	-7.7 (-13.2 to -2.3)
COPD per GOLD criteria	-15.4 (-18.9 to -11.9)



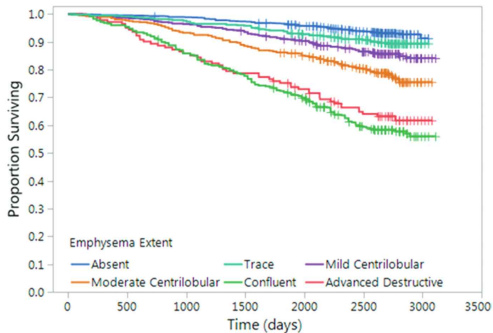
Visual assessment for severity of emphysema

Grade	% of Lung Zone Involved	CT Appearance
Absent	None	No low-attenuation foci
Trace	< 0.5%	A few scattered centrilobular low-attenuation foci
Mild	0.5% – 5%	Multiple centrilobular foci scattered throughout the lung zone
Moderate	> 5% (non-confluent)	Widespread low-attenuation areas throughout the lung zone Lesions begin to merge
Confluent	Large areas (no threshold)	Individual centrilobular lesions coalesce into large confluent areas of destruction + Vascular structures partially lost
Advanced Destructive (ADE)	Extensive (no threshold)	Widespread confluent destruction with marked distortion of pulmonary vascular architecture -> Mimic panlobular emphysema

Prognosis according to severity of emphysema



(a) No emphysema; (b) Trace centrilobular emphysema;
(c) mild centrilobular emphysema; (d) moderate centrilobular emphysema;
(e) Confluent emphysema; (f) Advanced destructive emphysema with vascular distortion



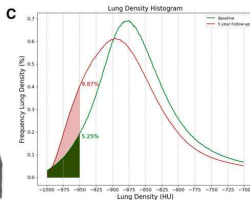
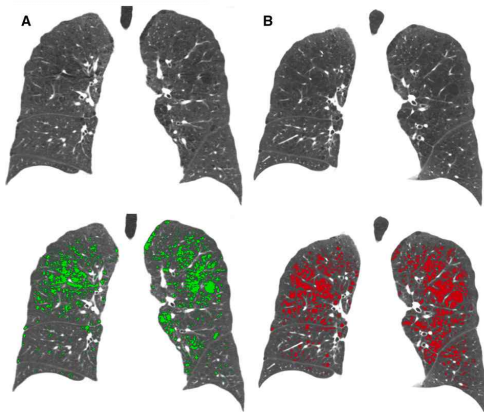
Progression according to visual severity

- **Increasing visual grade of parenchymal emphysema** at baseline CT was generally associated with an **increasing rate of progression of emphysema**.

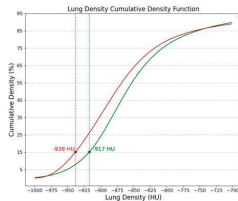
Table 6: Longitudinal Change in Volume-adjusted Lung Density, Stratified according to Presence or Absence of COPD and according to Parenchymal Emphysema Grades

Parenchymal Emphysema Grade	COPD (<i>n</i> = 1655)		No COPD (<i>n</i> = 2511)	
	Mean Change (g/L)	<i>P</i> Value	Mean Change (g/L)	<i>P</i> Value
Absent	-0.3 (-1.5, 1.0)	.64	-0.3 (-1.0, 0.4)	.42
Trace	-2.4 (-3.7, -1.1)	<.001	-1.8 (-2.8, -0.9)	<.001
Mild	-4.6 (-5.7, -3.5)	<.001	-3.6 (-4.7, -2.6)	<.001
Moderate	-6.7 (-7.7, -5.6)	<.001	-3.1 (-4.7, -1.5)	<.001
Confluent	-6.4 (-7.6, -5.2)	<.001	-4.0 (-8.1, 0.2)	.06
ADE	-6.2 (-8.0, -4.5)	<.001	-17.6 (-35.9, 0.8)	.06

Assessment of emphysema by CT densitometry



LAA-950% (=Emphysema index)
(Percentage of low-attenuation area below -950 HU)



Perc15 (=PD15)
(15th percentile of lung attenuation)

CT metrics of emphysema

Metric	Abbreviation	Definition	Strengths	Weaknesses
Percent emphysema	LAA ₋₉₅₀	Lung voxels with CT attenuation ≤ -950 HU as a percentage of total lung voxels	<ul style="list-style-type: none"> Well-validated Intuitively interpretable Widely used in cross-sectional studies Predictive of events 	<ul style="list-style-type: none"> Skewed distribution More complex to evaluate longitudinally Sensitive to variation in lung volume, CT dose and reconstruction kernel
15th Percentile lung attenuation	Perc15 (also denoted as PD15)	CT attenuation at the 15th percentile point of the cumulative CT histogram	<ul style="list-style-type: none"> In an idealized setting, it can provide a measure of physical lung density Can be adjusted for inspired lung volume More normal distribution and, therefore, potentially more robust for longitudinal analysis 	<ul style="list-style-type: none"> Less well evaluated in cross-sectional studies Sensitive to variation in lung volume, CT dose and reconstruction kernel
Volume-adjusted lung density	VALD _{PERC15} (also denoted as volume-adjusted Perc15 in lung density units)	Perc15 lung attenuation, converted to lung density, and adjusted for inspired lung volume based on predicted or observed lung volume	<ul style="list-style-type: none"> Has been used for longitudinal analysis in several large studies, including as endpoint in clinical trials of AAT 	<ul style="list-style-type: none"> Increased lung volume due to airflow obstruction and/or emphysema may reduce VALD_{PERC15}

Advantage of CT densitometry over FEV1

Limitation of FEV1

- Does not directly reflect emphysema itself
- Weak correlation between emphysema and airflow limitation
- Confounded by comorbidities such as cardiovascular disease and osteoporosis
- Emphysema present in 43% of smokers without airflow obstruction
- Changes in FEV1 and lung density progress largely independently

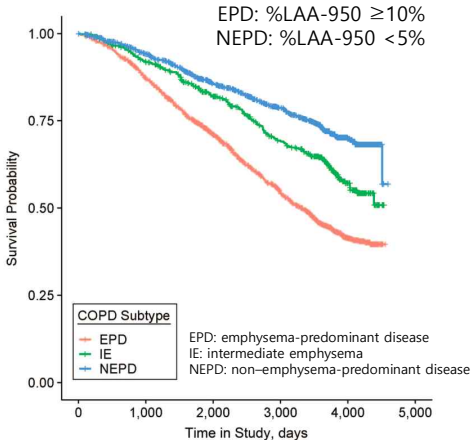
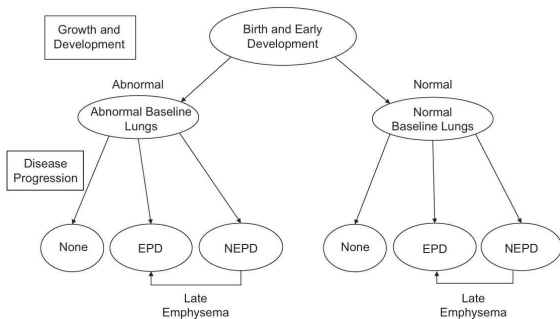
Advantages of CT densitometry

- **Directly correlates** with pathological emphysema
- **Superior reproducibility** over FEV1 (ICC 0.99)
- **Validated** as diagnostic, prognostic, and monitoring biomarker
- Used as a **primary endpoint** in clinical trials (RAPID trial)
- **More sensitive detection** of treatment effects over FEV1 (signal-to-noise ratio 3.2 vs 1.3)

Heterogenous prognosis according to emphysema

Original Contribution

Heterogeneity and Progression of Chronic Obstructive Pulmonary Disease: Emphysema-Predominant and Non-Emphysema-Predominant Disease

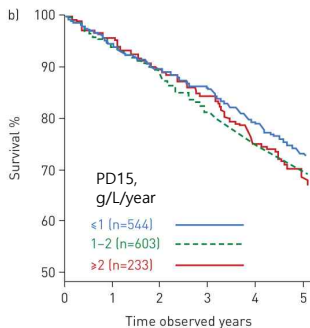


Worse prognosis due to emphysema progression

Markers of disease activity in COPD:
an 8-year mortality study in the
ECLIPSE cohort

	1-year change/event (n=2097)			3-year change/event (n=1555)		
	Subjects [#] n	HR (95% CI)	p-value	Subjects [#] n	HR (95% CI)	p-value
COPD hospitalisation						
No	1770	Reference group		1064	Reference group	
Yes	308	1.65 (1.34–2.02)	<0.001	487	1.95 (1.59–2.39)	<0.001
Frequent exacerbations[†]						
No frequent exacerbations all years	1460	Reference group		1320	Reference group	
Frequent exacerbations all years	618	1.30 (1.09–1.54)	0.003	175	1.63 (1.27–2.10)	<0.001
Health status (SGRQ)						
≥4 units improvement	675	0.94 (0.76–1.17)	0.606	444	0.96 (0.72–1.28)	0.796
–4–4 units change	630	Reference group		405	Reference group	
≥4 units worse	526	1.37 (1.11–1.69)	0.004	538	1.58 (1.23–2.03)	<0.001
FEV₁ decline* mL·year⁻¹						
Per 20 mL·year ⁻¹ increment	1916	1.01 (1.00–1.02)	0.044	1555	1.14 (1.09–1.19)	<0.001
BODE index						
Improved	520	0.84 (0.67–1.07)	0.157	244	0.76 (0.54–1.08)	0.126
No change	623	Reference group		409	Reference group	
Worse	576	1.27 (1.02–1.58)	0.032	565	1.52 (1.17–1.97)	0.002
Persistent inflammation						
No markers	431	Reference group		§	§	
One marker	768	1.32 (1.03–1.71)	0.030			
>2 markers	220	1.68 (1.08–2.61)	0.016			
Emphysema PD15 decline* g·L⁻¹·year⁻¹						
Per 1 g·L ⁻¹ ·year ⁻¹ increment	1556	1.00 (0.99–1.01)	0.078	1380	1.12 (1.00–1.24)	0.046

Emphysema change

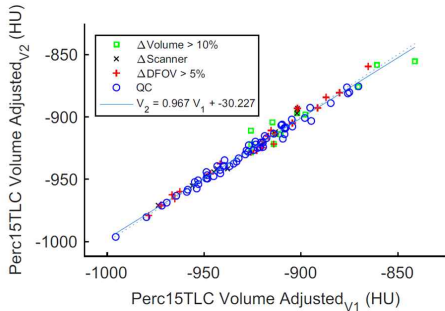
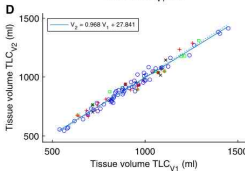
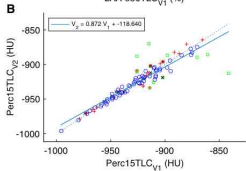
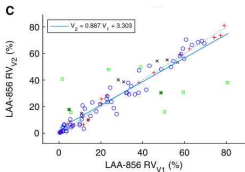
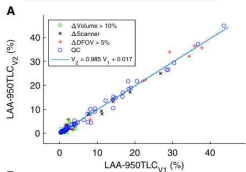


Repeatability of VALDperc15

Repeatability of Pulmonary Quantitative Computed Tomography Measurements in Chronic Obstructive Pulmonary Disease

Amin Motahari¹, R. Graham Barr^{3,4}, MeilAn K. Han⁵, Wayne H. Anderson⁷, Igor Barjaktarevic⁹, Eugene R. Bleeker¹⁰, Alejandro P. Comellas², Christopher B. Cooper^{11,12}, David J. Couper⁸, Nadia N. Hansel¹³, Richard E. Kanner¹⁴, Ella A. Kazerooni⁶, David A. Lynch¹⁶, Fernando J. Martinez¹⁷, John D. Newell, Jr.^{1,18}, Joyce D. Schroeder¹⁵, Benjamin M. Smith^{3,4,19}, Prescott G. Woodruff²⁰, and Eric A. Hoffman^{1,2,18}, for the SPIROMICS Group

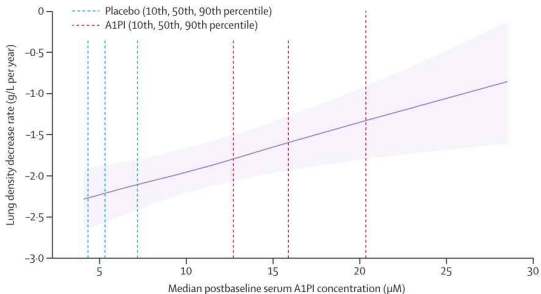
All repeatability study participants underwent repeat CT scanning 2–6 weeks after the baseline CT scan.



Longitudinal change of VALDperc15

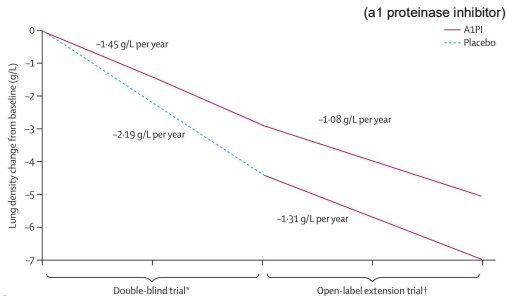
Intravenous augmentation treatment and lung density in severe α 1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial

Kenneth R Chapman, Jonathan G W Burdon, Eeva Piitulainen, Robert A Sandhaus, Niels Seersholm, James M Stocks, Berend C Stoel, Liping Huang, Zhenheng Yao, Jonathan M Edelman, Noel G McElvaney, on behalf of the RAPID Trial Study Group*



- HU is transformed to g/dL

Slow progression of emphysema



Longitudinal change of LAA-950

npj | digital medicine

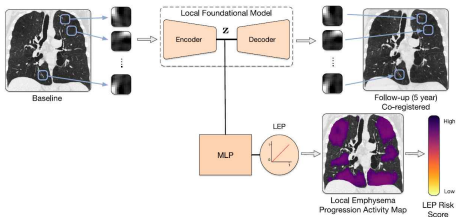
Published in partnership with Seoul National University Bundang Hospital

Article



<https://doi.org/10.1038/s41746-025-01917-3>

Emphysema progression risk in COPD using a localized foundational model of density evolution



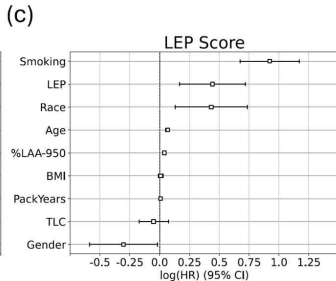
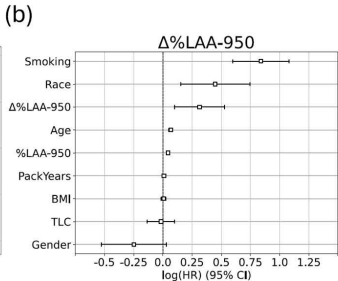
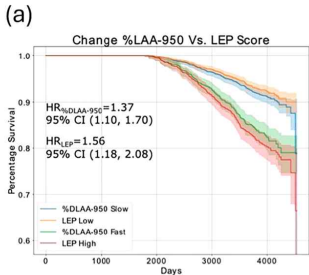
Definition of **Local Emphysema Progression (LEP)**
: > -950 HU at baseline to a value of ≤ -950 HU at 5-year follow-up co-registered CT scan

Foundational -> Pre-trained (by big data)

Local emphysema progression -> Not global assessment

Risk of mortality by emphysema progression

Adjusted Cox regression model for mortality



Sources of variation in CT densitometry

Source of Variation	Approach to Mitigation
Scanner related	
Calibration	Regular calibration
Image noise	Regular phantom measurements to detect scanner deviations from their nominal behavior
Beam hardening	Standardized, consistent protocol (slice thickness, reconstruction algorithm) Avoid substantial metal artifacts (e.g., scoliosis rods)
Patient related	
Inspired lung volume	Technologist is trained to coach the patient in breath holding to maximal inspiration, using standardized breathing instructions. Rehearse breath hold at least once before scan. Consider adjusting lung density measurement for inspired lung volume. Consider excluding scans with >10% change in inspired lung volume
Motion artifact	Emphasize importance of breath holding during scan
Current smoking	Consider exclusion of current smokers or stratify for smoking status. Consider exclusion of those who change smoking status during study. Consider exclusion of individuals who have not smoked <1 yr
COPD exacerbation	Avoid scanning within 4–6 wk of exacerbation
Analysis software	
Segmentation/airway removal	Use consistent analysis software throughout the study

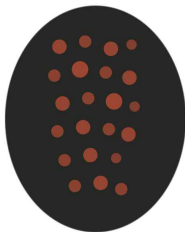
Recommendations for use of CT densitometry

CT technique	Technique is based on QIBA CT lung densitometry profile. Use same CT scanner (or same make and model) and consistent breath-hold instructions for baseline and follow-up examinations.
Patient selection	Eligibility criteria will depend on the specifics of the trial but could include either visual identification of emphysema using the Fleischner criteria and/or LAA ₋₉₅₀ greater than a specified threshold (typically 5%). Either exclude individuals who currently smoke or stratify analysis by smoking status. Expand visit windows to avoid CT scans during current COPD exacerbations.
CT interval	The interval between CT scans should range from 12 to 24 mo, with shorter intervals (6–12 mo) considered for high-risk populations or adaptive trial designs requiring frequent anchoring.
Treatment efficacy CT metric	Longitudinal evaluation uses volume-adjusted lung density (sponge model) using measured (e.g., baseline) lung volume.
Statistical adjustment factors	Potential adjustment factors may include lung volume differences (if sponge model is not used), scanner make and model, smoking status, sex, age, height, body mass index, image field of view, and image noise measurement.

QIBA= Quantitative Imaging Biomarkers Alliance

Limitation of CT densitometry

CT densitometry tells us only how much the lung is destroyed, not how it is destroyed.

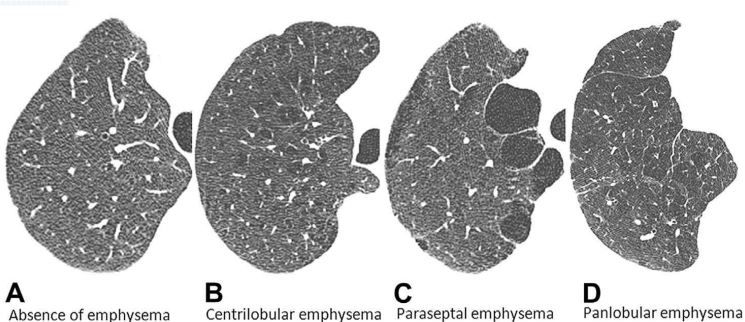


Uniform
distribution

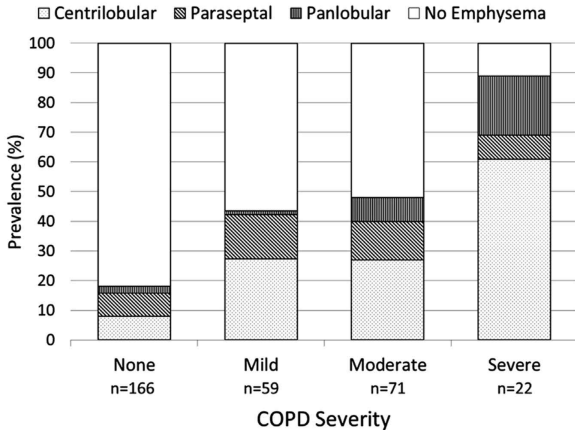
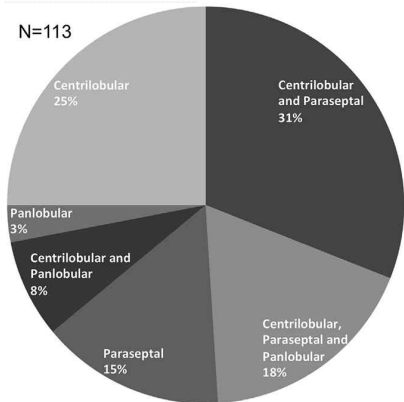
Various pathologic subtypes of emphysema

Pulmonary Emphysema Subtypes on Computed Tomography: The MESA COPD Study

Benjamin M. Smith, MD, MS,^{a,b} John H. M. Austin, MD,^c John D. Newell Jr, MD,^d Belinda M. D'Souza, MD,^c
Anna Rozenshtein, MD,^c Eric A. Hoffman, PhD,^d Firas Ahmed, MD, MPH,^c R. Graham Barr, MD, DrPH^{a,b}



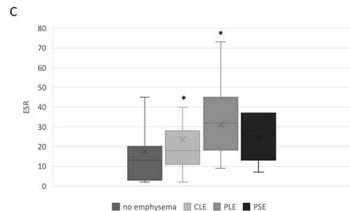
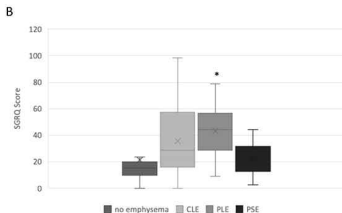
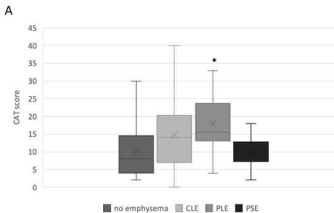
Different severity with pathologic subtypes



Different impact by pathologic subtypes

Original Research

Panlobular emphysema is associated with COPD disease severity: A study of emphysema subtype by computed tomography



CLE: centrilobular emphysema
PLE: panlobular emphysema
PSE: paraseptal emphysema

Different predominant lobar distribution

Category

Upper Lobe Predominant

Lower Lobe Predominant

Etiology

COPD- 'The Blue Bloater'

COPD- 'The Pink Puffer'

CT Pattern

Lung Function

LVRS / BLVR

Airway Disease

Prognosis



362-868; Lancet
Engl J Med. 2003;
Eu

104-910;
5-2335;
16:18-23.

Upper vs. Lower lobe emphysema

Lobar Emphysema Distribution Is Associated With 5-Year Radiological Disease Progression

Adel Boueiz, MD; Yale Chang, PhD; Michael H. Cho, MD, MPH; George R. Washko, MD; Raul San José Estépar, PhD; Russell P. Bowler, MD; James D. Crapo, MD; Dawn L. DeMeo, MD, MPH; Jennifer G. Dy, PhD; Edwin K. Silverman, MD, PhD; Peter J. Castaldi, MD; for the COPDgene Investigators

- COPDgene cohort
- After removing poorly clustered observations, unsupervised random forest clustering was done.

Characteristic	Minimal Emphysema Cluster (n = 1,312)	Upper Lobe-Predominant Cluster (n = 905)	Lower Lobe-Predominant Cluster (n = 796)	P Value (All Groups Omnibus Test)	P Value (Upper-Lobe Predominant vs Lower-Lobe Predominant)
Demographics					
Age, y	53.20 (49.18-59.26)	59.30 (52.50-66.30)	64.00 (57.40-69.83)	< .001	< .001
Male sex, %	36.36	53.37	58.92	< .001	.07
Non-Hispanic whites, %	48.63	61.44	83.67	< .001	< .001
BMI	29.69 (25.91-33.71)	26.64 (23.17-30.33)	28.03 (24.21-32.55)	< .001	< .001
Smoking history (pack-years)	35.80 (24.08-47.10)	43.90 (33.00-61.30)	45.00 (32.68-63.00)	< .001	1.00
Current smoking, %	75.15	57.79	40.83	< .001	< .001
Spirometry					
FEV ₁ , % predicted	86.45 (74.80-97.80)	71.70 (52.90-87.00)	65.80 (39.40-86.20)	< .001	< .001
FEV ₁ /FVC	0.79 (0.74-0.83)	0.64 (0.51-0.72)	0.59 (0.41-0.74)	< .001	.73
Bronchodilator, % responsiveness (%)	16.86	24.81	27.33	< .001	.78

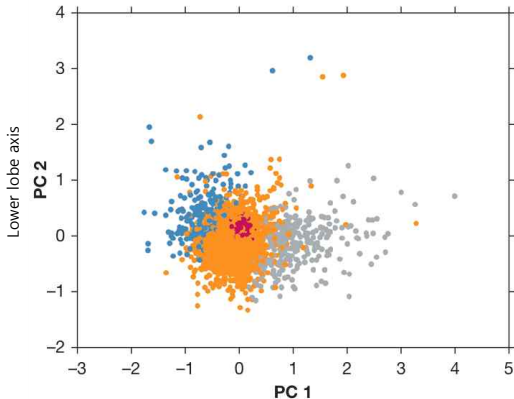
Upper vs. Lower lobe emphysema

• Upper lobe

- ✓ Baseline: Younger / Higher current smoker / Higher lung function
- ✓ 5Y FU: **More emphysema (LAA) progression / Worse gas trapping / Worse mMRC score**

Upper Lobe-Predominant Cluster vs Lower Lobe-Predominant Cluster	Univariate Model			Multivariate Model 1 ^a			Multivariate Model 2 ^b		
	Beta	SE	P Value	Beta	SE	P Value	Beta	SE	P Value
Change of total emphysema between visit 1 and visit 2, % LAA-950/y	0.19	0.05	< .001	0.14	0.05	0.002	0.15	0.04	< .001
Change of % gas trapping between visit 1 and visit 2, %/y	0.48	0.19	.01	0.47	0.18	0.007	0.50	0.16	.002
Change of FEV ₁ between visit 1 and visit 2, mL/y	-9.00	4.62	.05	-3.51	3.78	0.35	-2.57	4.24	.59
Change of FEV ₁ between visit 1 and visit 2, % predicted/y	-0.16	0.15	.29	-0.19	0.15	0.23	-0.11	0.14	.42
Change of 6-min walk distance between visit 1 and visit 2, ft	56.00	22.84	.01	22.89	25.73	0.37	-2.03	29.21	.95
Change of SGRQ score between visit 1 and visit 2	-0.42	0.79	.59	0.35	0.97	0.72	0.77	0.95	.42
Change of mMRC dyspnea score between visit 1 and visit 2	0.21	0.13	.10	0.36	0.13	0.008	0.42	0.14	.002

Limitation of lobar classification



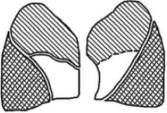
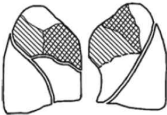
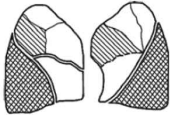
On PCA visualization,

- 1) Subjects spread along a severity continuum rather than forming distinct distribution-based clusters
- 2) Majority of subjects were unassigned

Group	N
Minimal emphysema cluster (red)	1,312
Upper lobe-predominant cluster (gray)	905
Lower lobe-predominant cluster (blue)	796
Unassigned (Orange)	6,197

Defining emphysema heterogeneity

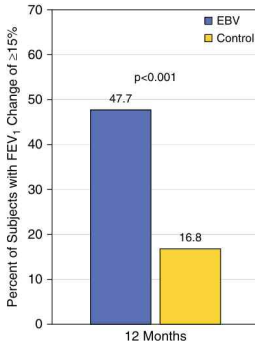
- **No golden standard** for assessing heterogeneity of emphysema

Lobar heterogeneity index	Intralobar heterogeneity index	Segmental heterogeneity index
		
<p><u>Region of interest: lobe</u> Region of comparison: ipsilateral lobe*</p>	<p><u>Region of interest: segment</u> Region of comparison: most diseased segment within respective lobe</p>	<p><u>Region of interest: segment</u> Region of comparison: ipsilateral lobe*</p>
<p>*If the region of interest is associated with an upper lobe, the region of comparison is the lower lobe. If the region of interest is associated with a lower lobe, the region of comparison is the upper lobe. If the region of interest is associated with the right middle lobe or the lingula, the region of comparison is the more diseased of the upper or lower lobe.</p>		

EBV in heterogeneous emphysema

A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)

- Quantitative threshold (LIBERATE trial):
 - 1) Target lobe destruction score ($\%LAA < -910 \text{ HU}$) $>50\%$
 - 2) Absolute difference in destruction score between the target lobe and the **ipsilateral lobe of ≥ 15 percentage points.**
- Zephyr EBV in patients with **heterogeneous emphysema** and no collateral ventilation improves **FEV₁, exercise tolerance, dyspnea, and QoL** at ≥ 12 months.



Issues in defining emphysema heterogeneity

- Discrepant proportion of homogeneous emphysema

Frequency of homogeneous emphysema in GOLD stage III/IV patients using a 15% heterogeneity threshold

		Frequency of homogeneous emphysema, %			
		emphysema is not heterogeneous at lobar level ^a	emphysema is not heterogeneous at segmental level ^b	emphysema is not heterogeneous within a lobe ^c	emphysema is truly homogeneous ^d
Upper lobe	Left	47	33	43	15
	Right	44	29	25	9
	Both	33	21	13	3
Middle lobe/lingula	Left	53	33	56	23
	Right	51	36	65	20
	Both	35	19	34	6
Lower lobe	Left	84	70	9	9
	Right	87	68	3	2
	Both	79	57	2	2
Entire lung	Left				1
	Right				0
	Both				0

$$\text{Heterogeneity index} = \frac{\text{tissue destruction of region of interest}}{\text{tissue destruction of region of comparison}}$$

HI = Heterogeneity index.

^aLobar HI <1.15.

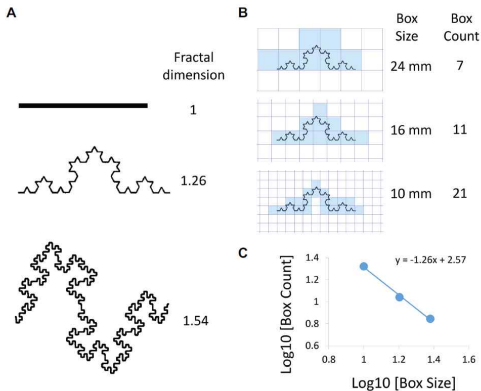
^bSegmental HI <1.15 for all segments in the lobe of interest.

^cIntralobar HI <1.15 for all segments in the lobe of interest.

^dLobar HI <1.15; segmental HI <1.15; intralobar HI <1.15.

Fractal dimension, *FD*

- Emphysema diffusely distributed vs. clustered into large confluent lesions

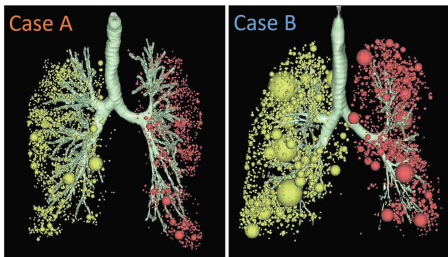


Box → Emphysema

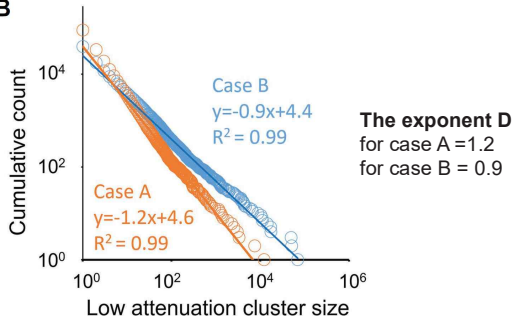
Power law exponent, D

- D is not the same as FD of emphysematous clusters, but it is a useful index to characterize the spatial pattern.

A



B



Power-law exponent D =
the negative slope of the regression lines

Clinical Implication of *D* value

D value	Cluster pattern	Implication
Larger	Many small clusters, uniform distribution	Mild/early destruction
Smaller	Few dominant large clusters	Severe/advanced destruction

Previous studies

Results

Hwang et al. Eur Radiol 2019

Low D independently associated with **increased mortality**

Shimizu et al. Thorax 2020

Low D associated with shorter time to **exacerbation**

Tanabe et al. AJRCCM 2011

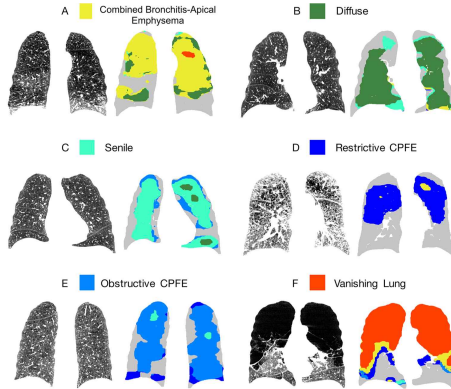
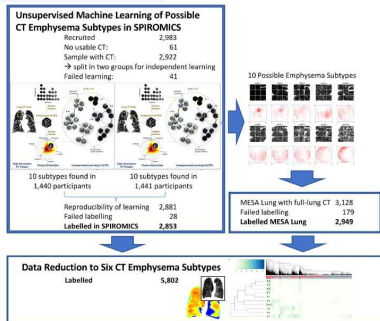
D decreases further after exacerbation, suggesting exacerbations accelerate parenchymal destruction

ML-based subtypes of emphysema

Chronic obstructive pulmonary disease

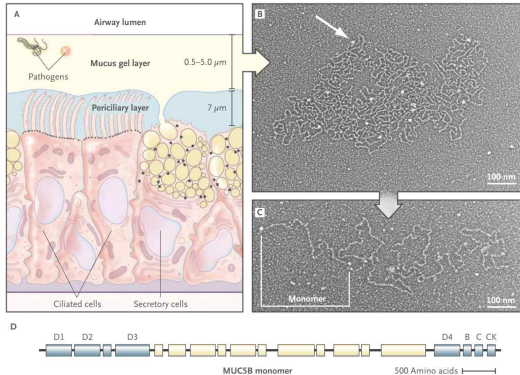
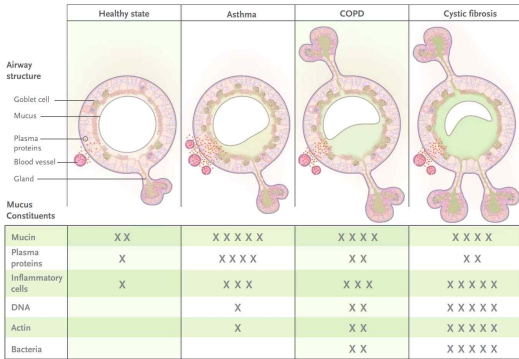
Original research

Pulmonary emphysema subtypes defined by unsupervised machine learning on CT scans

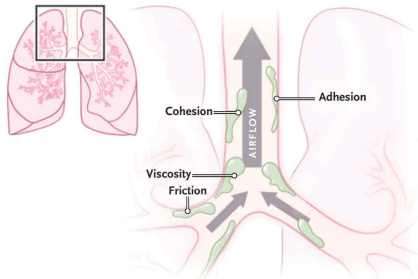
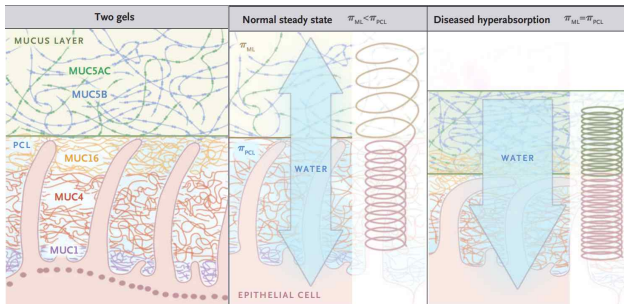


Mortality risk: F > A > B

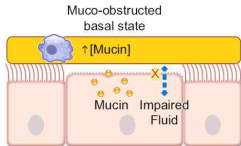
Mucus characteristics of COPD



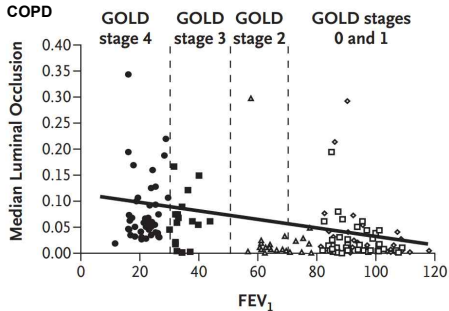
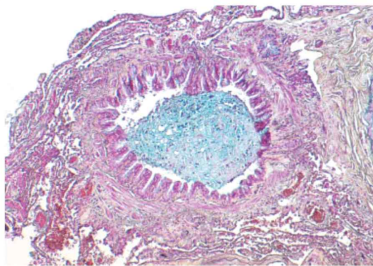
Formation of mucus plug



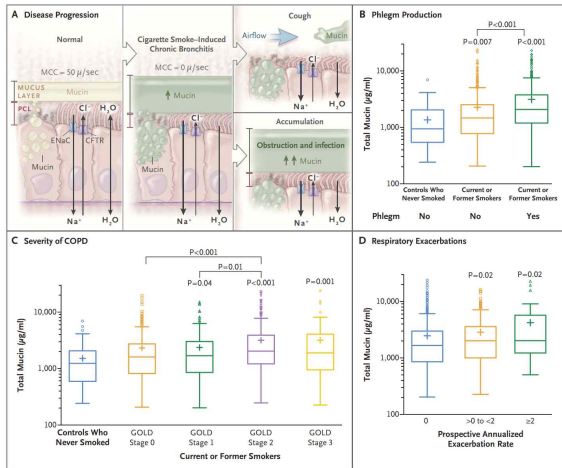
Mucus plug impairs lung function



Chronic injury produces a **muco-obstructed epithelium with impaired fluid secretion**



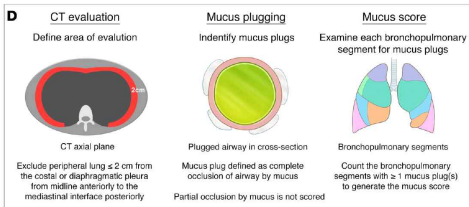
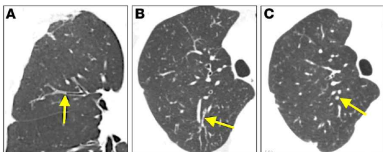
Mucin level and COPD progression



Mucus plug score calculation in asthma

JCI The Journal of Clinical Investigation

Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction



- Asthma and control subjects
- SARP1/2 baseline scan -> SARP3 Rescan (mean 5.2yr)

CT Mucus Scoring Method (Dunican Score)

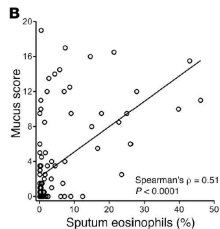
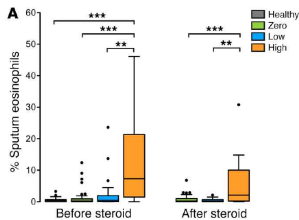
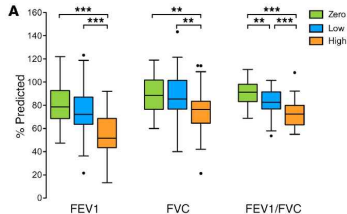
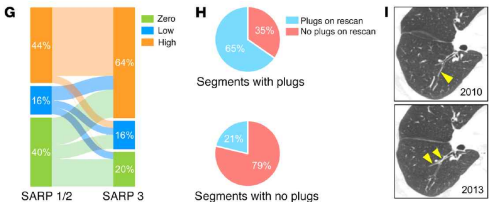
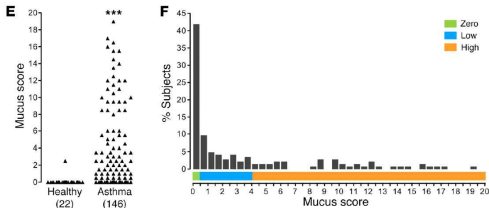
- ✓ MDCT scans scored by 5 thoracic radiologists (2 randomly assigned per scan, scores averaged)
- ✓ **20 bronchopulmonary segments** systematically assessed
- ✓ Peripheral airways **within 2 cm of pleura excluded**
- ✓ Mucus plug **defined as complete occlusion of a bronchus** (partial occlusion not scored)
- ✓ Each segment scored 0 or 1 → summed → total score 0–20
- ✓ Plugs identified as intraluminal opacities contiguous with patent airway lumen across sequential CT slices, less radiodense than adjacent vessels
- ✓ Between-rater ICC = 0.80; within-rater ICC = 0.99

Mucus plug, lung function, and eosinophil

Zero: score = 0

Low: score 0.5–3.5

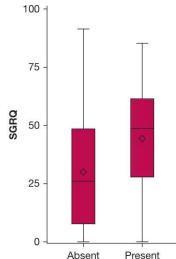
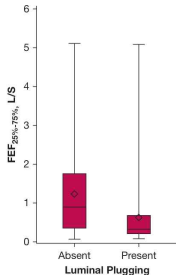
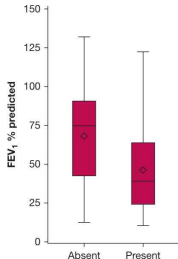
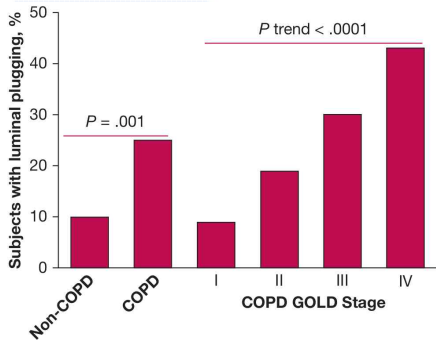
High: score ≥ 4 (based on median score of mucus-present group)



Mucus plug and lung function, QoL

Luminal Plugging on Chest CT Scan

Association With Lung Function, Quality of Life, and COPD Clinical Phenotypes



Mucus plug and FEV1, SGRQ, Emphysema

Luminal Plugging	FEV ₁ % Predicted	Log FEF _{25%-75%} (L/s)	SGRQ
Absent	Ref	Ref	Ref
Present	-6.1 (2.1), .004	-0.11 (0.06), .08	4.9 (2.4), .04

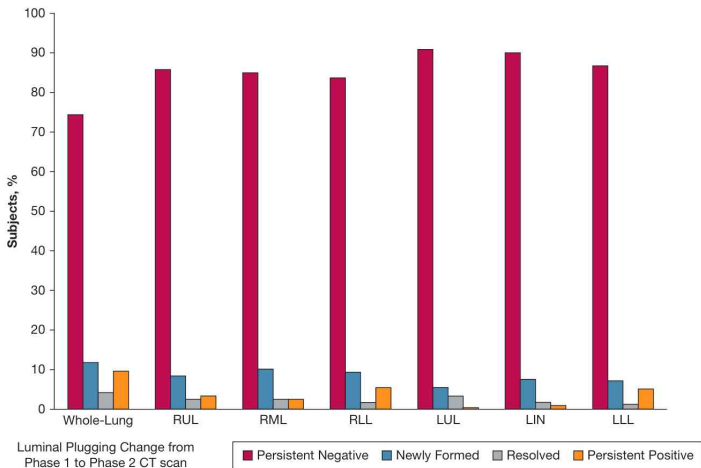
Adjusted for age, sex, race, BMI, current smoking status, smoking pack-years history, asthma, CT scan identified bronchiectasis, and CT measures of emphysema and airway wall thickness

Model		Log Emphysema on CT Scan	Emphysema \geq 5% on CT Scan (Yes/No)	Chronic Bronchitis
Model 1				
Luminal plugging	Absent	Ref	Ref	Ref
	Present	0.43 (0.16), .007	2.06 (1.09-3.90), .02	1.68 (0.95-2.97), .07
Model 2				
Luminal plugging	Absent	Ref	Ref	Ref
		0.21 (0.14), .14	1.52 (0.76-3.07), .24	1.55 (0.87-2.76), .14

Model 1: Adjusted for age, sex, race, BMI, current smoking status, smoking pack-years history, asthma, CT scan-identified bronchiectasis, and CT scan measures of emphysema and airway wall thickness

Model 2: Model 1 + FEV1

Longitudinal change of luminal mucus plug



Factors associated with mucus plugging

Review Article

From mucus plugging to airway dilatation in chronic airway diseases:
A perspective on the contribution of the airway microbiome and
inflammation

	Asthma	Ref	COPD	Ref
Inflammation	<u>Blood and sputum eosinophil,</u> FeNO, IL-13, IL-5, blood total IgE and <i>Af</i> sIgE. Sputum neutrophil count in smokers with asthma	1,3,18 26	<u>Sputum neutrophil count</u>	2
Lung function	Lower FEV ₁	1,17,20	Lower FEV ₁	2,29
Lung function decline	FEV ₁ decline	17	FEV ₁ decline	34
Airway structure	Central airway wall thickening and lower total airway count on CT.	3,92	Lower total airway count	29
Exacerbations	Exacerbation frequency	17–19	Exacerbation frequency	2,31–33
Physical function			Lower 6-min walk distance and lower oxygen saturation.	2
Prognosis			Loss of health-related independence and mortality.	27,29

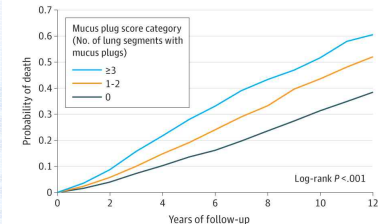
Mucus plug as surrogate for COPD mortality

JAMA | Original Investigation

Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease

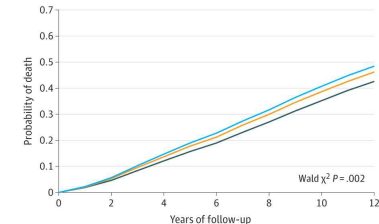
- COPDgene cohort
- 4363 Participants who smoked with mucus plug scores

A Unadjusted probability of death by mucus plug score



No. at risk							
Mucus plug score	0	2337	2126	1860	1587	1339	792
1-2	953	859	763	643	526	411	237
≥3	825	730	613	481	372	299	167

B Adjusted probability of death by mucus plug score



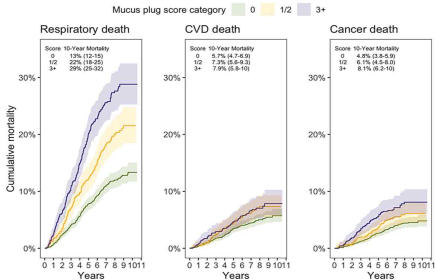
No. at risk							
Mucus plug score	0	2337	2126	1860	1587	1339	792
1-2	953	859	763	643	526	411	237
≥3	825	730	613	481	372	299	167

Mucus plug as surrogate for COPD mortality

Table 2. Association Between Mucus Plug Score and All-Cause Mortality in Participants With COPD

	No.	Mucus plug score (No. of lung segments with mucus plugs)				
		0 (n = 2585)	1-2 (n = 953)	≥3 (n = 825)		
Mortality rate, % (95% CI)		34.0 (32.2-35.8)	46.7 (43.5-49.9)	54.1 (50.7-57.4)		
Unadjusted mortality rate difference, % (95% CI)			1-2 vs 0: 12.7 (9.1-16.4)	≥3 vs 0: 20.1 (16.2-24.0)		
Model		HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value
Unadjusted model	4363	1 [Reference]	1.51 (1.34-1.69)	<.001	1.98 (1.76-2.22)	<.001
Adjusted model ^a	4166	1 [Reference]	1.15 (1.02-1.29)	.02	1.24 (1.10-1.41)	<.001
Plus coronary artery disease ^b	4166	1 [Reference]	1.16 (1.03-1.30)	.02	1.26 (1.11-1.43)	<.001
Plus chronic bronchitis ^c	4166	1 [Reference]	1.15 (1.02-1.30)	.02	1.25 (1.10-1.42)	<.001
Plus current asthma ^d	4166	1 [Reference]	1.15 (1.02-1.30)	.02	1.25 (1.10-1.41)	<.001
Plus exacerbations per year ^e	3759	1 [Reference]	1.10 (0.96-1.25)	.17	1.20 (1.05-1.38)	.008
Plus BODE index ^f	4060	1 [Reference]	1.14 (1.01-1.29)	.03	1.21 (1.06-1.37)	.004

Mucus plug and cause-specific mortality



- Respiratory mortality**

- ✓ Score 1/2: aHR 1.13 (95% CI 0.91–1.41), P=0.300
- ✓ **Score ≥ 3** : aHR 1.36 (95% CI 1.10–1.69), P=0.005

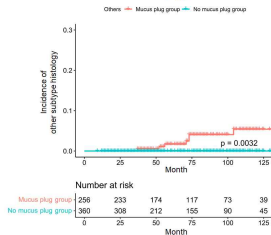
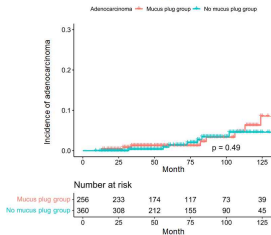
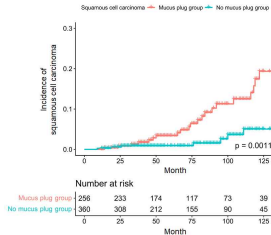
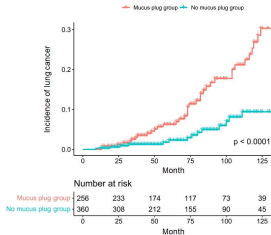
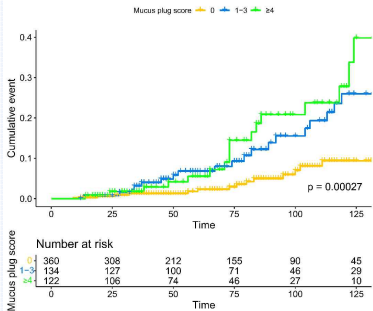
- Cardiovascular mortality**

- ✓ Score 1/2: aHR 1.35 (95% CI 0.96–1.91), P=0.089
- ✓ **Score ≥ 3** : aHR 1.27 (95% CI 0.87–1.85), P=0.210

Cause of Death	Mucus Plug Score Category										
	0 (n = 2,297)			1/2 (n = 833)				3+ (n = 734)			
	Events	Competing Events	HR (95% CI)	Events	Competing Events	HR (95% CI)	P Value	Events	Competing Events	HR (95% CI)	P Value
Model 1: respiratory	271	125	Ref.	159	48	1.13 (0.91-1.41)	0.270	191	50	1.36 (1.10-1.69)	0.005
Model 2: cardiovascular	114	282	Ref.	56	151	1.35 (0.96-1.91)	0.089	50	191	1.27 (0.87-1.85)	0.210
Model 3: cancer	98	298	Ref.	47	160	1.26 (0.85-1.88)	0.250	54	187	1.8 (1.23-2.63)	0.002

Mucus plug and lung cancer incidence

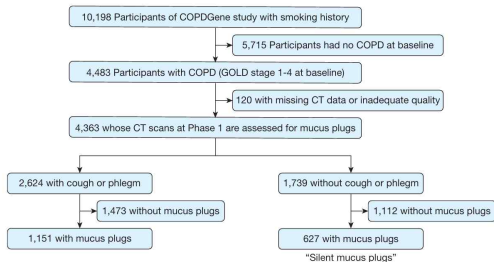
Mucus plug and lung cancer incidence in patients with COPD



With vs. without mucus plug-related symptoms

[COPD Original Research]

Silent Airway Mucus Plugs in COPD and Clinical Implications



Risk factors for silent mucus plugs compared to symptomatic mucus plugs

Covariate	OR (95% CI)	P Value
Age	1.02 (1.01-1.04)	.004
Female sex (vs male)	1.4 (1.12-1.74)	.003
Black race (vs non-Hispanic White)	1.93 (1.44-2.59)	< .001
BMI	0.99 (0.97-1.01)	.45
Active tobacco use (vs previously smoked)	0.35 (0.27-0.45)	< .001
Pack-y	0.997 (0.993-1.001)	.193
History of congestive heart failure	1.18 (0.7-1.97)	.533
History of asthma	0.69 (0.54-0.88)	.003

Values from a multivariable logistic regression model are shown.

Clinical Importance of silent mucus plug

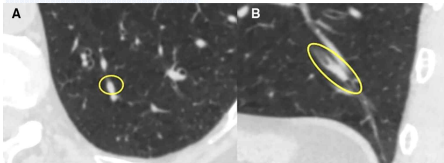
Among those without cough or phlegm,

Outcome	Mucus Plug Score Category (No. of Lung Segments With Mucus Plugs)			
	1-2 vs 0		≥ 3 vs 0	
	Mean Difference (95% CI)	P Value	Mean Difference (95% CI)	P Value
Linear regression models				
6-min walk distance, m	-35.88 (-50.17 to -21.58)	< .001	-61.48 (-78.61 to -44.35)	< .001
Resting SpO ₂ , %	-0.88 (-1.25 to -0.51)	< .001	-0.68 (-1.13 to -0.23)	.003
SGRQ total score	6.48 (4.22 to 8.75)	< .001	10.2 (7.46 to 12.93)	< .001
SGRQ impact score	5.48 (3.42 to 7.53)	< .001	9.01 (6.53 to 11.49)	< .001
SGRQ activity score	8.31 (4.94 to 11.69)	< .001	12.51 (8.43 to 16.58)	< .001
Postbronchodilator FEV ₁ /FVC	-0.05 (-0.07 to -0.04)	< .001	-0.08 (-0.1 to -0.07)	< .001
Postbronchodilator FEV ₁ % predicted	-9.79 (-12.38 to -7.21)	< .001	-16.21 (-19.33 to -13.09)	< .001
Emphysema, % lung volume	4.16 (2.66 to 5.66)	< .001	5.34 (3.52 to 7.17)	< .001
Airway wall thickness (Pi10), mm	0.22 (0.15 to 0.28)	< .001	0.39 (0.31 to 0.47)	< .001
Small airways disease, % lung volume	4.16 (2.72 to 5.6)	< .001	6.53 (4.77 to 8.29)	< .001
Logistic regression models				
Had COPD exacerbation requiring hospitalization in the past 12 mo	1.79 (1.14 to 2.76)	.0101	2.26 (1.38 to 3.62)	< .001

Mucus plug and future exacerbation

ORIGINAL ARTICLE

Airway Mucus Plugs on Chest Computed Tomography Are Associated with Exacerbations in Chronic Obstructive Pulmonary Disease



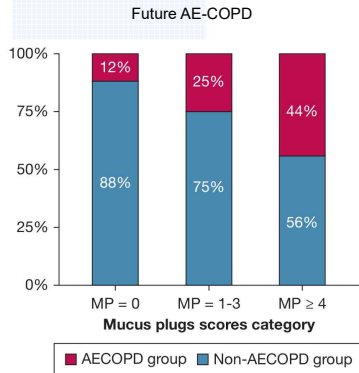
Characteristic	COPDGene (N = 3,250)	ECLIPSE (N = 1,716)
Age, yr	63.7 ± 8.4	63.3 ± 7.1
Sex		
Male	1,784 (54.9%)	1,094 (63.7%)
Female	1,466 (45.1%)	622 (36.2%)
European ancestry	2,580 (79.4%)	1,680 (97.9%)
BMI	28.2 ± 6.2	26.4 ± 5.6
Current smoker	1,245 (38.3%)	638 (37.2%)
Pack-years of smoking	52.9 ± 27.2	49.1 ± 27.3
Exacerbation in 1 yr before enrollment	1,257 (38.7%)	782 (45.6%)
Chronic bronchitis	894 (27.5%)	560 (32.6%)
FEV ₁ , L	1.45 ± 0.62	1.34 ± 0.52
FEV ₁ , % predicted	50.6 ± 17.8	48.3 ± 15.8
Percent emphysema on CT*	13.5 ± 12.9	17.8 ± 12.1
Pi10 [†]	2.73 ± 0.56	3.95 ± 0.20
Years of follow-up	8.1 ± 4.3	2.7 ± 0.7
Total prospective acute exacerbations	4.9 ± 7.4	3.4 ± 3.8
Mucus plug score	1.4 ± 2.5	1.6 ± 2.6

	COPDGene			ECLIPSE		
	0	1–2	≥3	0	1–2	≥3
No. of patients	1,808	753	689	926	373	417
Moderate to severe AEs	Ref.	1.070 (1.048–1.093)	1.145 (1.098–1.195)	Ref.	1.056 (1.019–1.094)	1.115 (1.039–1.197)
Severe AEs	Ref.	1.045 (1.008–1.084)	1.092 (1.016–1.175)	Ref.	1.169 (1.072–1.273)	1.365 (1.15–1.622)

Mucus plug and future exacerbation

Association Between Airway Mucus Plugs and Risk of Moderate-to-Severe Exacerbations in Patients With COPD

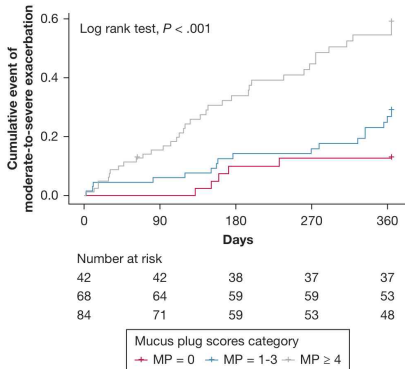
Results From a Chinese Prospective Cohort Study



IRR for annual moderate-to-severe exacerbation rate

Characteristics	Estimate	Adjusted IRR (95% CI)	P Value
Sex			
Female	ref.	NA	NA
Male	0.56	1.75 (0.44-9.09)	.452
Age	0.01	1.01 (0.98-1.04)	.467
BMI	0.01	1.00 (0.92-1.08)	.999
Smoking status			
Does not smoke	ref.	NA	NA
Previously smoked	0.27	1.31 (0.51-3.96)	.595
Currently smokes	-0.27	0.77 (0.27-2.48)	.627
History of severe AECOPD			
Nonsevere AECOPD	ref.	NA	NA
≥ 1 severe AECOPD	0.68	1.98 (1.15-3.34)	.012
FEV ₁ % predicted	-0.01	0.99 (0.98-1.01)	.225
MP score (per 1-unit score increase)	0.08	1.08 (1.01-1.16)	.028

Mucus plug and future exacerbation

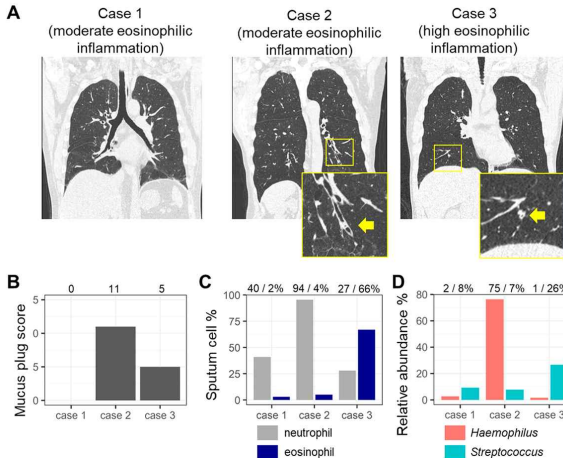


HR for moderate-to-severe exacerbation event

Outcome	Adjusted HR (95% CI)	P Value	Overall P Value
Model 1^a			
MP scores category			< .001
0	Ref.		
1-3	2.16 (0.78-5.98)	.137	
≥ 4	5.02 (1.84-13.75)	.002	
Model 2^a			
MP scores category			< .001
0	0.46 (0.17-1.28)	.137	
1-3	Ref.		
≥ 4	2.32 (1.25-4.33)	.008	

^aAdjustment for age, sex, BMI, smoking status, history of severe exacerbations, and FEV₁ % predicted. HR = hazard ratio; MP = mucus plug; Ref. = reference.

Mucus plug & Microbiome

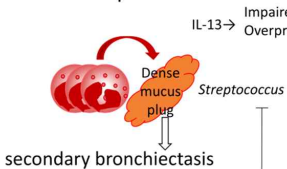


Microbiome associated with airway inflammation

	Effects on inflammation	Ref
Bacteria		
Phylum Firmicutes, genus <i>Streptococcus</i>	Positively associated with eosinophilic inflammation	5,80,81
Phylum Bacteroidetes, genus <i>Porphyromonas</i>	Negatively associated with eosinophilic inflammation	4,93
Phylum Fusobacteria	Positively associated with neutrophilic inflammation	93,94
Phylum Proteobacteria, genus <i>Haemophilus</i>	Positively associated with neutrophilic inflammation	67,74–77
Bacterial products		
Butylate	Suppress eosinophilic inflammation	69,70
Indole-3-acetic acid (produced by genus <i>Lactobacillus</i> , belonging to Firmicutes)	Suppress neutrophilic inflammation	95

Mucus plug & Inflammatory cell & Microbiome

A. Severe eosinophilic

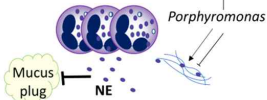


B. Mixed granulocytic

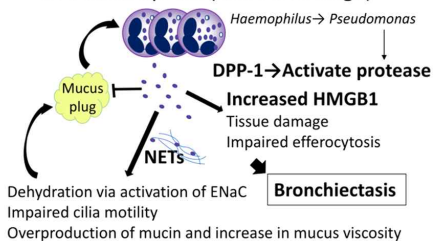
Impaired cilia motility
Overproduction of mucin and increase in mucus viscosity



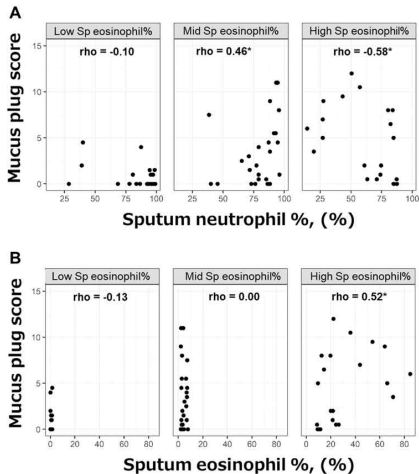
C-1. Neutrophilic (early stage)



C-2. Neutrophilic (advanced stage)

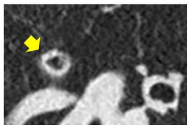


Role of eosinophilic inflammation in mucus plug

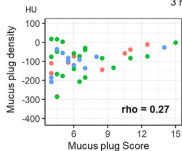
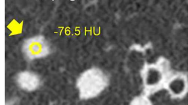


Eosinophilic inflammation & mucus plug features

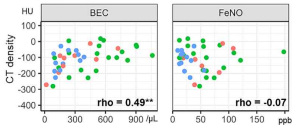
Measurement of CT density



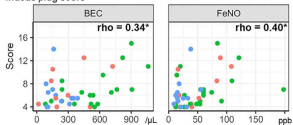
Mucus plug



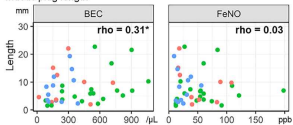
Mucus plug density



Mucus plug score



Mucus plug length



ACO asthma COPD

MP, BEC and clinical features

TABLE 1 Association of type 2 inflammation (Th2i) and mucus plug (MP) phenotypes with lung function, quality of life, and history of exacerbations in participants with COPD from the COPDGene and ECLIPSE cohorts

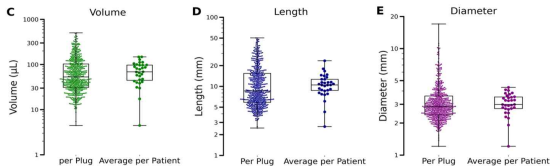
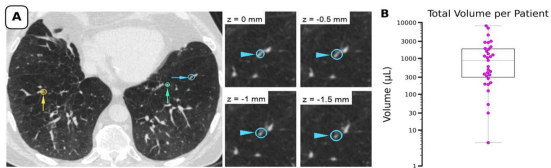
Outcome	Phenotype ^a					
	MP 0, Th2i ⁻	MP 1-2, Th2i ⁻	MP ≥3, Th2i ⁻	MP 0, Th2i ⁺	MP 1-2, Th2i ⁺	MP ≥3, Th2i ⁺
Adjusted least squares mean FEV₁ L (95% CI)						
COPDGene	1.38 (1.35-1.42)	1.31 (1.26-1.35)	1.21* (1.14-1.28)	1.34 (1.27-1.40)	1.31 (1.23-1.39)	1.23 (1.13-1.34)
ECLIPSE	1.39 (1.35-1.42)	1.31 (1.26-1.36)	1.24* (1.19-1.30)	1.47 (1.40-1.53)	1.39 (1.29-1.49)	1.24* (1.17-1.31)
Adjusted least squares mean SGRQ total score (95% CI)						
COPDGene	35.8 (34.2-37.3)	38.8 (36.9-40.8)	41.0* (37.9-44.0)	38.6 (35.7-41.5)	40.5 (37.1-43.9)	37.2 (32.8-41.7)
ECLIPSE	47.8 (46.3-49.4)	51.0 (48.6-53.3)	53.7* (51.1-56.2)	45.9 (42.7-49.1)	47.9 (43.2-52.6)	50.9 (47.3-54.4)
Adjusted least squares mean SGRQ symptom score (95% CI)						
COPDGene	38.3 (36.4-40.2)	41.7 (39.4-44.0)	43.9 (40.2-47.6)	41.1 (37.6-44.6)	44.1 (40.0-48.2)	44.0 (38.6-49.4)
ECLIPSE	57.2 (55.5-58.8)	61.8 (59.3-64.3)	64.1* (61.4-66.7)	53.3 (49.9-56.8)	61.1 (56.0-66.1)	63.0 (59.3-66.8)
History of ≥1 exacerbation OR (95% CI)						
COPDGene	Reference	1.31 (0.96-1.80)	1.98 (1.29-3.05)	1.34 (0.88-2.05)	1.71 (1.07-2.73)	2.79 (1.57-4.98)
ECLIPSE	Reference	1.20 (0.88-1.64)	1.64 (1.17-2.28)	1.03 (0.69-1.53)	1.19 (0.69-2.05)	2.28 (1.47-3.54)

Th2i⁻ (BEC <300/μL); Th2i⁺ (BEC ≥300/μL)

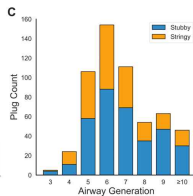
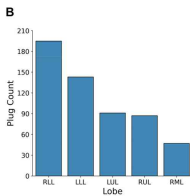
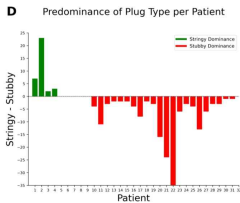
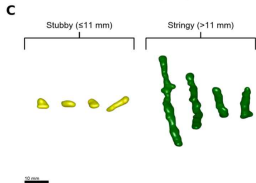
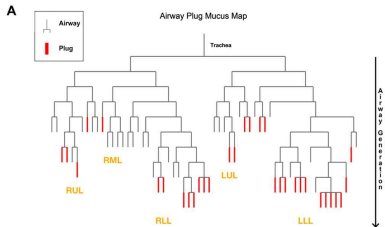
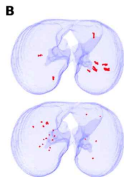
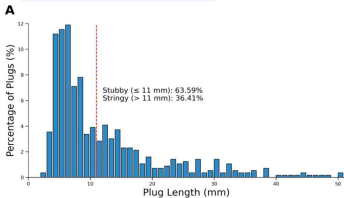
Heterogeneous mucus plug in size and shape

Mucus plugs in chronic obstructive pulmonary disease are heterogeneous in size and shape and occur in relatively large airways

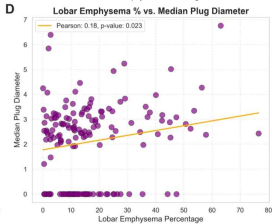
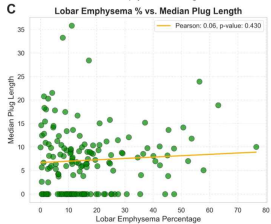
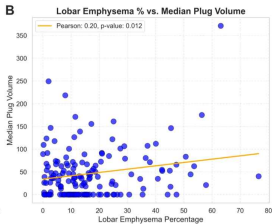
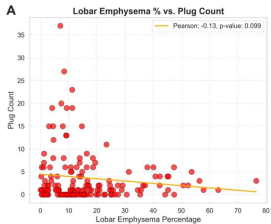
- Complete occlusion of a bronchus, irrespective of generation or size



Heterogeneous distribution of mucus plug



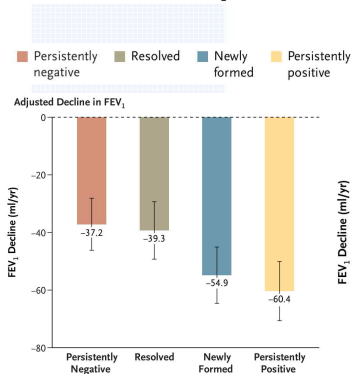
Emphysema and mucus plug



- Higher lobar emphysema (%)
 - ✓ Fewer mucus plugs per lobe
 - ✓ Greater individual plug diameter and volume
- Mucus plug length is independent of emphysema severity

Longitudinal change of mucus plugs and smoking

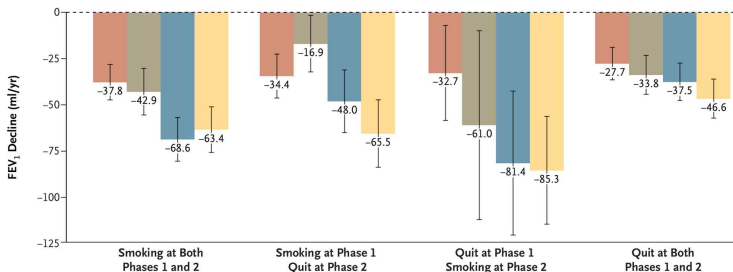
Longitudinal Changes in Airway Mucus Plugs and FEV₁ in COPD



Phase 1-2 interval: mean 5yr

Interaction with smoking status

- Persistently positive + continued smoking: steepest FEV₁ decline
- Resolved + smoking cessation: least FEV₁ decline



Airway-related CT parameters in COPD

- Small airway disease (dysfunction): e.g., PRM^{fSAD}, ND-E/I ratio
- Airway remodeling: e.g., Pi10, Pi Slope
- Mechanically affected lung: e.g., MAL₂, Jacobian determinant

Review

trd
Tuberculosis & Respiratory Diseases

Imaging in Chronic Obstructive Pulmonary Disease: Ready for Prime Time?

<https://doi.org/10.4046/trd.2025.0202>

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SEOUL NATIONAL UNIVERSITY HOSPITAL

Tuberc Respir Dis (Seoul). 2026 Apr;89(2):143-153.

Emphysema

- Emphysema assessment will be essential for COPD diagnosis and prognostic evaluation (survival)
- LAA-950% and Perc15 serve as well-established metrics for emphysema extent, while **VALDperc15** is favored for longitudinal monitoring.
- Comprehensive emphysema evaluation requires assessment of severity (0.5%/5%/confluent/vascular distortion), pathologic subtype (CLE/PLE/PSE), lobar distribution (Upper/Lower), **spatial heterogeneity**, and **D value**.

Mucus plug

- Mucus plug score independently predicts lung function impairment, FEV1 decline, exacerbation, mortality, and lung cancer incidence.
- **Neutrophilic inflammation** appears to dominate mucus plug formation in COPD, though eosinophils contribute independently. The dominant inflammatory pathway may be modulated by the airway microbiome.
- **Mucus plug pheno/endotyping** is evolving → Greater emphysema extent associates with fewer but larger plugs (increased volume, length, and diameter).





Thank you for your attention