Association between automatic AI-based quantification of airway-occlusive mucus plugs and all-cause mortality in patients with COPD

Veer, T. van der; Andrinopoulou, E.R.; Braunstahl, G.J.; Charbonnier, J.P.; Kim, V.; Latisenko, R.; ... ; Tiddens, H.

Association between automatic AI-based quantification of airway-occlusive mucus plugs and all-cause mortality in patients with COPD

Tjeerd van der Veer ,[1,2] Eleni-Rosalina Andrinopoulou,[3,4] Gert-Jan Braunstahl,[1,5] Jean Paul Charbonnier,[6] Victor Kim ,[7] Rudolfs Latisenko,[8] David A Lynch ,[9] Harm Tiddens[6,10]

[1]Respiratory Medicine, Erasmus MC, Rotterdam, Netherlands
[2]Respiratory Medicine, Leiden University Medical Center, Leiden, Netherlands
[3]Biostatistics, Erasmus Medical Center, Rotterdam, Netherlands
[4]Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands
[5]Pulmonology, Franciscus Gasthuis & Vlietland, Rotterdam, Netherlands
[6]Thirona BV, Nijmegen, Netherlands
[7]Division of Pulmonary and Critical Care Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania, USA
[8]Respiratory Medicine, Thirona BV, Nijmegen, Netherlands
[9]Medicine, National Jewish Health, Denver, Colorado, USA
[10]Pediatric Pulmonology, Erasmus Medical Center, Rotterdam, Netherlands

Correspondence to
Dr Tjeerd van der Veer; t.vanderveer@lumc.nl
Published Online First 5 December 2024

To cite: van der Veer T, Andrinopoulou E-R, Braunstahl G-J, *et al*. *Thorax* 2025;**80**:105–108.

ABSTRACT

In this cohort study involving 9399 current and former smokers from the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease study, we assessed the relationship between artificial intelligence-quantified mucus plugs on chest CTs and all-cause mortality. Our results revealed a significant positive association, particularly for those with COPD GOLD stages 1–4, with HRs of 1.18 for 1–2 mucus-obstructed bronchial segments and 1.27 for ≥3 obstructed segments. This corroborates previous visual mucus plug counting research and demonstrates the relevance of mucus plugs in COPD pathology and as a marker for risk assessment. Automated mucus plug quantification methods may provide an efficient tool for both clinical evaluations and research.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects millions worldwide, ranking as a leading cause of mortality.[1] Central to COPD pathology is mucociliary dysfunction, leading to mucus plugs that can occlude the airways.[2] Mucus plugs, detectable in CT scans of many patients with COPD, are linked to several adverse outcomes, including impaired airflow, lower oxygen levels and reduced exercise tolerance.[3] Furthermore, mucus plugs can persist for years without symptoms like cough or sputum production.[4] Finally, the presence of mucus plugs in medium-sized to large-sized airways has been associated with all-cause mortality in COPD (GOLD 1–4), through meticulous visual counting of the number of mucus-obstructed bronchial segments.[5] The investigation was carried out on a subset of the data from the Genetic Epidemiology of COPD (COPDGene) study.[6]

Our study employed an artificial intelligence (AI)-based platform (LungQ) for automated mucus quantification on chest CT scans to explore its association with mortality in the full cohort of all Phase 1 COPDGene participants, across all COPD stages including GOLD 0 and PRISm (GOLD, global initiative for chronic obstructive lung disease; PRISm, preserved ratio impaired spirometry, often considered a precursor to COPD). We hypothesised that automated quantification would confirm visual scoring findings and would provide enhanced detail and efficiency in assessing the prognostic significance of mucus plugs in COPD.

METHODS

COPDGene is a multicentre, prospective study on COPD genetics and epidemiology. It enrolled non-Hispanic black and white participants aged 45–80 with a significant smoking history (≥10 pack-years). Exclusion criteria and ethical considerations have been outlined in the original COPDGene protocol.[5] The study included 10 198 (ex-)smokers, enrolled from November 2007 to April 2011, followed up at 5 and 10 years. Data collection involved questionnaires, spirometry and standardised chest CT scans using <1 mm slice protocols. Mortality, spirometry and demographic data were sourced from the COPDGene database.

For our study, all 10 198 phase 1 ever-smoker participants were included in the analysis, meaning that COPD GOLD stage 1–4, GOLD 0 and PRISm were all included.[7] Additionally, CT scans of 107 never-smoker COPDGene controls were analysed for comparison.

Automatic mucus plug quantification was performed using the LungQ platform (Thirona, Nijmegen, The Netherlands). LungQ uses AI-based algorithms to segment the bronchial tree and identify each bronchopulmonary segment. Mucus plugs are detected throughout the lung and linked to their respective segments. The detection algorithm, trained on expert annotations, identifies full mucus obstructions with clear proximal and distal airways, providing both location and volumetric assessments. The segmentation combines seed-based and voxel-based methods, providing accurate detection and quantification of mucus plugs along the entire bronchi, including the peripheries (figure 1a).

Participants were categorised by the number of mucus-obstructed standard bronchopulmonary segments: 0, 1–2 or ≥3. Emphysema percentage was based on the lung parenchyma with attenuation below −950 Hounsfield units and airway wall thickness by taking the square root of the wall area for a hypothetical airway with a 10 mm inner perimeter (Pi10).[8]

Cox proportional hazard regression assessed the relationship between mucus plug scores categories and mortality in three models as in the study by Diaz *et al*.[5] The first model adjusted for demographics, smoking history, forced expiratory volume in 1 s, emphysema and Pi10. The second added coronary disease, chronic bronchitis, asthma and annual exacerbations. The third model consisted of the first model plus the BODE (body mass index, obstruction, dyspnea,

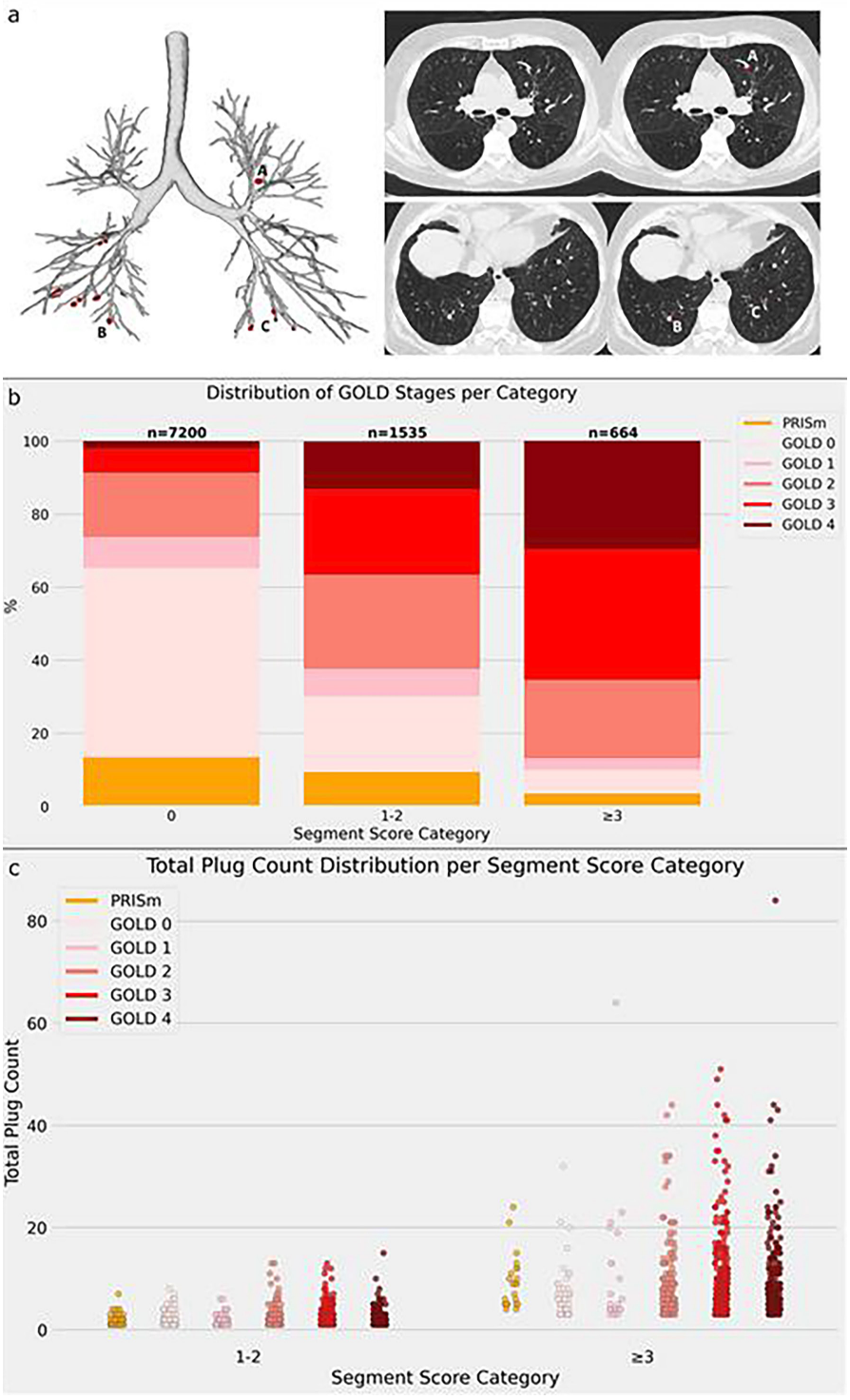

Figure 1 Mucus plug detection and GOLD class distribution. (a) LungQ reconstruction of the bronchial tree with detected mucus plugs indicated in red and the corresponding transversal CT images. (b) Distribution of participants' GOLD class for segment scores 0, 1–2 and ≥3 mucus-obstructed segment categories. (c) Scatterplot of total mucus plug counts and GOLD classes. NB. Total plug count can be >2 also at 1–2 bronchial segments affected, as multiple plugs can be found in the same segment. GOLD, global initiative for chronic obstructive lung disease—severity classification; PRISm, preserved ratio impaired spirometry.

and exercise capacity) index, the most validated COPD mortality prediction score.[9] Analyses, performed using R (V.4.3.2), considered p values <0.05 significant without adjustment for multiple testing.

RESULTS

The final cohort for analysis consisted of 9399 ever-smoker participants, after the exclusion of 799 participants due to missing CT scans (n=297), poor-quality CT scans (n=82), technical issues (n=360) or missing spirometry data (n=60). In total 4165 participants had COPD GOLD 1–4 and 5234 participants GOLD 0 and PRISm. Over a median follow-up of 3957 days, there were 2633 (28.0%) deaths. Of all participants, 7200 (76.6%) participants had a score of 0, indicating no mucus-obstructed segments, 1535 (16.3%) had 1–2 and 664 (7.1%) had 3 or more mucus-obstructed

Table 1 Participant characteristics

COPDGene phase 1 cohort (n=9399)	Mucus plug score category (No. of segments w/mucus plugs)		
Characteristics	0 (n=7200)	1–2 (n=1535)	≥3 (n=664)
Age, median (IQR), years	57.7 (51.3–65.1)	62.3 (54.5–69.0)	64.4 (57.1–70.7)
Sex			
Female	47.6%	44.7%	39.5%
Male	52.4%	55.3%	60.5%
Race and ethnicity			
Non-Hispanic white	4733 (64.3%)	1173 (75.8%)	540 (81.2%)
Non-Hispanic African American	2618 (35.7%)	376 (24.2%)	125 (18.8%)
BMI, median (IQR)	28.3 (24.7–32.6)	27.1 (23.5–31.5)	25.5 (22.3–29.4)
Current smoker, No. (%)	3901 (54.2%)	747 (48.7%)	291 (43.8%)
Pack-years of smoking, median (IQR)	37.6 (25.9–51.7)	44.0 (32.5–63.3)	47.4 (34.7–68.3)
Medical history			
Chronic bronchitis	1143 (15.9%)	414 (27.0%)	230 (34.6%)
Coronary artery disease	754 (10.5%)	197 (12.8%)	85 (12.8%)
Asthma	760 (11.4%)	247 (16.1%)	165 (24.8%)
Exacerbations/year (mean, SD)	0.28 (0.79)	0.58 (1.09)	1.02 (1.50)
COPD GOLD stage of severity			
PRISm	971 (13.5%)	145 (9.4%)	23 (3.5%)
0 (≥10 packyears with FEV_1/FVC>0.7)	3732 (51.8%)	320 (20.8%)	43 (6.5%)
1 (mild)	613 (8.5%)	115 (7.5%)	21 (3.2%)
2 (moderate)	1265 (17.6%)	396 (25.8%)	143 (21.5%)
3 (severe)	478 (6.6%)	359 (23.4%)	237 (35.7%)
4 (very severe)	141 (2.0%)	200 (13.0%)	197 (29.7%)
BODE index, median (IQR)	0 (0.0–2.0)	2 (0.0–4.0)	4 (2.0–5.0)
FEV_1, L, median (IQR)	2.41 (1.85–3.01)	1.69 (1.09–2.41)	1.16 (0.77–1.71)
FEV_1, % predicted, median (IQR)	85.3 (70.6–97.6)	62.0 (39.9–82.8)	40.5 (27.0–59.2)
Emphysema on CT, median (IQR), %	1.54 (0.45–4.85)	4.52 (1.05–16.7)	11.33 (2.90–24.15)
Airway wall thickness, median (IQR), mm	2.14 (1.84–2.53)	2.61 (2.19–3.06)	3.02 (2.58–3.46)
Total number of plugs			
Median (IQR), no.	0.0	1.0 (1.0–2.0)	7.0 (5.0–12.0)
Total plug volume (mm^3)			
Median (IQR)	0 (0–0)	39.8 (14.6–93.7)	318.1 (164.0–742.4)
Never-smokers (control group, n=107)	101 (94.4%)	5 (4.7%)	1 (0.9%)

BMI, body mass index; BODE, body mass index, obstruction, dyspnoea, and exercise capacity; COPD, chronic obstructive pulmonary disease; COPDGene, genetic epidemiology of COPD; FEV1, forced expiratory volume 1 s; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; PRISm, preserved ratio impaired spirometry.

segments. See table 1 for participant characteristics and figure 1b,c for mucus plug distribution across GOLD stages.

In the adjusted model, automated mucus plug score categories were significantly associated with all-cause mortality. HRs were 1.14 (95% CI 1.03 to 1.26) for 1–2 mucus-obstructed segments and 1.24 (95% CI 1.09 to 1.42) for 3 or more. In the second model adjusted for additional confounders HR 1.13 (95% CI 1.02 to 1.25) and HR 1.21 (95% CI 1.06 to 1.38). In the third model adjusting for the BODE index, HRs were 1.10 (95% CI 0.995 to 1.22) and 1.15 (95% CI 1.0 to 1.31), respectively (see table 2).

Among 4165 participants with COPD (GOLD stages 1–4), HRs were 1.18 (95% CI 1.05 to 1.32) for 1 or 2 obstructed segments and 1.27 (95% CI 1.10 to 1.46) for 3 or more obstructed segments. In the second model, HRs were 1.17 (95% CI 1.04 to 1.31) and 1.24 (95% CI 1.07 to 1.43) and in the third model, HRs were 1.14 (95% CI 1.02 to 1.28) and 1.22 (95% CI 1.05 to 1.41), respectively. In COPD stages (GOLD 0 and PRISm), mucus plug scores were lower and showed no significant association with mortality.

In the control group of 107 never-smokers, LungQ detected mucus plugs in 6 participants (5.6%), with 4 participants with one plug, 1 participant with three plugs in two segments and 1 subject with 4 plugs in 4 segments.

DISCUSSION

This study confirms automated mucus plug analysis in the COPDGene cohort associations with higher mortality, consistent with visual scoring methods, even when adjusting for confounders and the BODE-index. HRs for COPD stages 1–4 subgroup of 1.18 and 1.27, for 1–2 and ≥3 obstructed segments, respectively, were highly similar to those found by visual methods. No mortality association was found in non-COPD subgroups (GOLD 0 and PRISm).

LungQ detected similar mucus plug counts to Diaz *et al*, with 25.7% (1070/4165) of participants showing 1–2 obstructed segments and 14.4% (598/4165) with ≥3, reflecting both method's identification of mucus plugs in 40% of GOLD 1–4 participants. The variation in the standard bronchopulmonary segment anatomy and the algorithm's conservative design, emphasising specificity, may account for differences. The prevalence of any mucus plugs in GOLD stages 1 to 4 (18.1% up to 73.8%) is substantially higher than what was observed in the PRISM (14.7%) and GOLD 0 participants (8.9%). Furthermore, also substantially higher than what was observed in never-smokers (5.6%).

The study's strengths include the inclusion of all COPDGene phase 1 participants including 5234 participants classified as GOLD 0 and PRISm as control groups, along with 107 never-smokers. Additionally, the use of automated analysis provides consistency compared with visual methods. However, one limitation is the absence of direct validation of the automated measurement against visual scoring. Due to the exceptionally laborious nature of visual mucus plug counting, large-cohort comparison is challenging. Therefore, we have focused on evaluating the association of automated mucus plug score categories with mortality. The observational design is another limitation as it limits causal conclusions.

The three mucus score categories (0, 1–2 and ≥3 obstructed segments) were chosen for their demonstrated stratification of risk.[5] Continuous variables of total mucus plug numbers and total mucus volume are highly left-skewed, limiting their utility for the current models. The distribution of mucus across segments and quantifying the total number and volume of mucus plugs may add further relevant information, particularly for longitudinal analysis at the individual level. These aspects warrant further exploration in future studies.

Overall, the results across various COPD severities confirm the association of mucus plugs with mortality, likely mediated through inflammation, infection and ventilation/perfusion mismatch. This underscores their potential as markers of disease severity and may guide treatment interventions. Automated analysis of mucus plugs could identify high-risk subgroups by integrating patient data and

Table 2 Association between mucus plug score and all-cause mortality

COPDGene phase 1 cohort (n=9399)		Mucus plug score (No. of segments w/mucus plugs)				
	No.	0 (n=7200)	1–2 (n=1535)		≥3 (n=664)	
Deceased, n (%)		1625 (22.6)	638 (41.6)		371 (55.9)	
		HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value
Adjusted model*	9397	Reference	1.14 (1.03 to 1.26)	0.010	1.24 (1.09 to 1.42)	0.001
Adjusted model plus coronary artery disease, chronic bronchitis, current asthma and exacerbations per year	9397	Reference	1.13 (1.02 to 1.25)	0.016	1.21 (1.06 to 1.38)	0.006
Adjusted model plus BODE index†	9272	Reference	1.10 (0.995 to 1.221)	0.062	1.15 (1.001 to 1.312)	0.048
Participants with GOLD stage 1–4		Mucus plug score (No. of segments w/ mucus plugs)				
	No.	0 (n=2497)	1–2 (n=1070)		≥3 (n=598)	
Deceased, n (%)		868 (34.8)	552 (51.6)		355 (59.4)	
		HR (95% CI)	HR (95% CI)	P value	HR (95% CI)	P value
Adjusted model*	4163	Reference	1.18 (1.05 to 1.32)	0.005	1.27 (1.10 to 1.46)	0.001
Adjusted model plus coronary artery disease, chronic bronchitis, current asthma and exacerbations per year	4163	Reference	1.17 (1.04 to 1.31)	0.008	1.24 (1.07 to 1.43)	0.004
Adjusted model plus BODE index†	4068	Reference	1.14 (1.02 to 1.28)	0.027	1.22 (1.05 to 1.41)	0.008
Participants with GOLD 0 and PRISm		Mucus plug score (No. of segments w/ mucus plugs)				
	No.	0 (n=4703)	1–2 (n=465)		≥3 (n=66)	
Deceased, n (%)		757 (16.1)	86 (18.5)		16 (24.2)	
Adjusted model*	5234	Reference	1.05 (0.83 to 1.31)	0.692	1.31 (0.79 to 2.17)	0.303
Adjusted model plus coronary artery disease, chronic bronchitis, current asthma and exacerbations per year	5234	Reference	1.04 (0.83 to 1.30)	0.754	1.26 (0.76 to 2.11)	0.372
Adjusted model plus BODE index†	5204	Reference	1.04 (0.83 to 1.30)	0.738	1.24 (0.75 to 2.06)	0.412

Cox proportional hazard regression models.
*Adjusted for age, gender, race, BMI, smoking status, packyears, FEV$_1$%, emphysema (–950HU%), airway wall thickness (Pi10), scanner model.
†Including all variables from the adjusted model except FEV$_1$ and BMI plus adjustment for the BODE index (continuous). Proportional hazard assumptions were evaluated using Schoenfeld residuals.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; COPDGene, genetic epidemiology of COPD; FEV1, forced expiratory volume in 1 s; HU, Hounsfield unit.

mucus metrics, opening new opportunities for personalised risk assessment, research and therapeutic strategies in COPD.

Acknowledgements COPDGene study participants and teams.

Contributors The authors contributed to the manuscript as follows: TvdV and HT were responsible for the concept and design. All authors participated in the acquisition, analysis or interpretation of data. TvdV drafted the manuscript, and G-JB, JPC, VK, DAL and HT provided critical revisions for important intellectual content. Statistical analysis was conducted by E-RA. Administrative, technical or material support was provided by RL, JPC and DAL. HT supervised the project. RL and TvdV managed the data and created the images. No funding was received for this work.

Funding This work was supported by NHLBI grants U01 HL089897 and U01 HL089856 and by NIH contract 75N92023D00011. The COPDGene study (NCT00608764) has also been supported by the COPD Foundation through contributions made to an Industry Advisory Committee 2 that has included AstraZeneca, Bayer Pharmaceuticals, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pfizer, and Sunovion.

Competing interests TvdV: no conflicts of interest involving the work under consideration for publication, no relevant financial activities outside the submitted work, no other relationships or activities that readers could perceive to have influenced or that give the appearance of potentially influencing the current manuscript. E-RA: no conflicts of interest, no relevant financial activities or other relevant relationships or activities regarding the work under consideration. G-JB: honoraria for lectures and consultancy from GSK, AstraZeneca, Novartis and Sanofi Genzyme, as well as research grants from Sanofi Genzyme, GSK and AstraZeneca, not related to the work under consideration. JPC: employee and shareholder at Thirona. VK: no conflicts of interest, no relevant financial activities or other relevant relationships or activities regarding the work under consideration. DAL: no conflicts of interest, no relevant financial activities or other relevant relationships or activities regarding the work under consideration. HT: received in the last 3 years multiple grants from the following public and institutional grant institutions for lung structure and function research: NHMRC, NIH, CFF, ECFS, IMI and ErasmusMC Sophia Foundation; received unconditional grants for investigator-initiated research from Novartis and Insmed. Acted as consultant for Insmed, Thirona, Neupharma and Boehringer Ingelheim. Chief medical officer for Thirona since April 2022. Vice-chair and faculty for the ADVANCE course sponsored by Vertex.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the institutional review board at each participating clinical centre. The COPDGene study was approved, and all participants provided written informed consent. See also Regan, E.A., et al, Genetic Epidemiology of COPD (COPDGene) Study Design. COPD, 2010, 7(1): 32-43. Participants provided informed consent before participating in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Tjeerd van der Veer http://orcid.org/0000-0003-3085-603X
Victor Kim http://orcid.org/0000-0002-1385-1571
David A Lynch http://orcid.org/0000-0002-6329-2325

REFERENCES

1 Collaborators, G.B.D.C.R.D. Global burden of chronic respiratory diseases and risk factors, 1990-2019: an update from the Global Burden of Disease Study 2019. *E Clin Med* 2023;59:101936.
2 Boucher RC. Muco-Obstructive Lung Diseases. *N Engl J Med* 2019;380:1941–53.
3 Dunican EM, Elicker BM, Henry T, *et al*. Mucus Plugs and Emphysema in the Pathophysiology of Airflow Obstruction and Hypoxemia in Smokers. *Am J Respir Crit Care Med* 2021;203:957–68.
4 Okajima Y, Come CE, Nardelli P, *et al*. Luminal Plugging on Chest CT Scan: Association With Lung Function, Quality of Life, and COPD Clinical Phenotypes. *Chest* 2020;158:121–30.
5 Diaz AA, Orejas JL, Grumley S, *et al*. Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease. *JAMA* 2023;329:1832–9.
6 Regan EA, Hokanson JE, Murphy JR, *et al*. Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010;7:32–43.
7 Agustí A, Celli BR, Criner GJ, *et al*. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am J Respir Crit Care Med* 2023;207:819–37.
8 Grydeland TB, Dirksen A, Coxson HO, *et al*. Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking. *Eur Respir J* 2009;34:858–65.
9 Celli BR, Cote CG, Marin JM, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–12.