Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

ASSESSING MUCUS PLUGS ON CT

The computed tomography (CT) mucus plug assessment was conducted between September 2018 and April 2022, following a method described in the main text. The readers who scored mucus plugs comprised thoracic radiologists, physicians, and a pulmonologist, and they entered their scores into a centralized collection form on the Redcap platform. Before scoring study participants' CT scans, the readers underwent training, which consisted of identifying a variety of mucus plugs on a set of typical CT images, scoring a training set of CT scans to learn the scoring system, and scoring a sample set of 20 CT scans to verify the inter-reader agreement.

MEASURING AIRWAY LUMEN SIZE ON CT

We used CT data from 39 participants to measure the airway luminal sizes. The meaurements were taken with in-house open source software Slicer (www. Slicer.org) by an analysist with experience in lung imaging, using a method previously described.[1] The right upper lobe segment was selected (see eFigure 2 below) , and measurements were taken from the segmental bronchus (designated as 3rd generation) to the 6th or 7th generation bronchus. Sixth and 7th airway generations are typically at approximately a distance of 2 cm out of the pleura (note that the distance from the last airway generation deemed for mucus plugging assessment and the costal and diaphragmatic edges of the lung was judged by eye, and not objectively measured). One to two airway measurements were taken in each generation. After placing a point in the center of the lumen, the software provided the airway measurements, including airway lumen radii. The measurements of airway lumen radii were averaged per generation, providing measurements for the approximate range of airway sizes surveyed for mucus plugging. The approximate airway lumen diameter range was from ~2 mm (7th airway generation) to 10 mm (3rd airway generation).

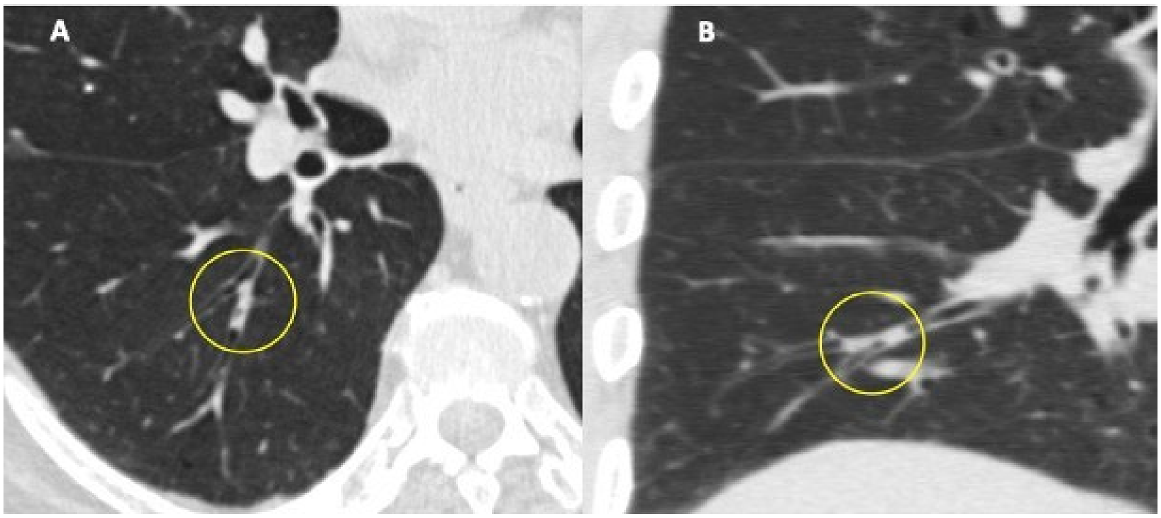
CLINICAL ASSESSMENT

The **B**ody mass index, **O**bstruction, **D**yspnea, and **E**xercise (BODE) mortality risk score for each participant was calculated.[2] BODE is comprised of four factors, body mass index, forced expiratory volume in one second (FEV_1), dyspnea, and six-minute walk distance. Dyspnea was rated with the modified Medical Research Council (mMRC) Scale (range, 0-4). Six-minute walk distance was measured using a standard protocol.[3] The participants were asked about a history of asthma with the questions, “Have you had asthma?” and “Do you still have it?” If the participant responded yes to both questions, then we considered the participant had a history of current asthma. Exacerbations after enrollment were ascertained with the Longitudinal Follow-up program of COPDGene.[4] In this program, the participants were asked to report their exacerbations every 6 months by telephone contact and web-based surveys. An exacerbation was defined as an increase or new onset of respiratory symptoms (cough, phlegm, dyspnea) treated with antibiotics and/or systemic corticosteroids.[5] Symptoms were quantified by answers to questions in a respiratory questionnaire modified from the Epidemiology Standardization Project questionnaire (American Thoracic Society–Division of Lung Diseases [ATS-DLD]-78).[6]

STATISTICAL ANALYSIS

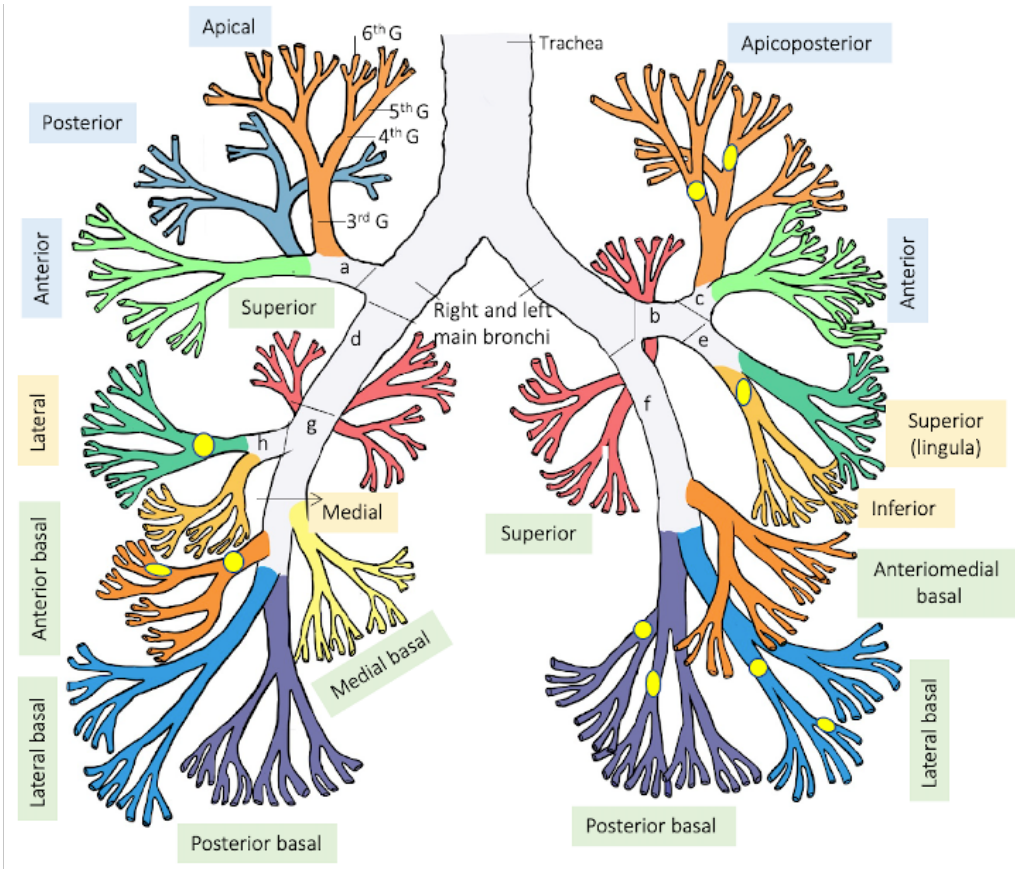
The inter-reader agreement for mucus plug score was evaluated with intra-class correlation coefficients using the mean scores of participating readers. We used two-way mixed effect models to compute intra-class correlation coefficients.[7] The association between mucus plugs and all-cause mortality was assessed with Cox proportional hazard regression analysis. The *a priori* multivariable model included age, sex, race, BMI, pack-years, smoking status (current vs. former), postbronchodilator FEV_1, and CT measures of airway wall thickness and emphysema as potential confounders. Additionally, the adjusted model described above included subsequent adjustment as follows:
-Adjusted model plus coronary artery disease
-Adjusted model plus coronary artery disease plus chronic bronchitis
-Adjusted model plus coronary artery disease plus chronic bronchitis plus history of current asthma
-Adjusted model plus coronary artery disease plus chronic bronchitis plus history of current asthma plus the number of exacerbations/year.

Finally, we included the BODE index to the adjusted model described above except FEV_1 and BMI. The FEV_1 and BMI were excluded because those variables are part of the BODE index. The model with BODE index did not include coronary artery disease, chronic bronchitis, history of current asthma, and the number of exacerbations/year. The probabilities of death used to perform the right panel plot of Figure 2 of the main text are computed by averaging the estimated survival curves for the observations within each mucus plug score category, using the covariates of the adjusted model described above with the direct adjusted survival feature of SAS.[8] A statistician (WW) conducted the analyses using the SAS 9.4 (SAS Institute, Cary, NC) software.



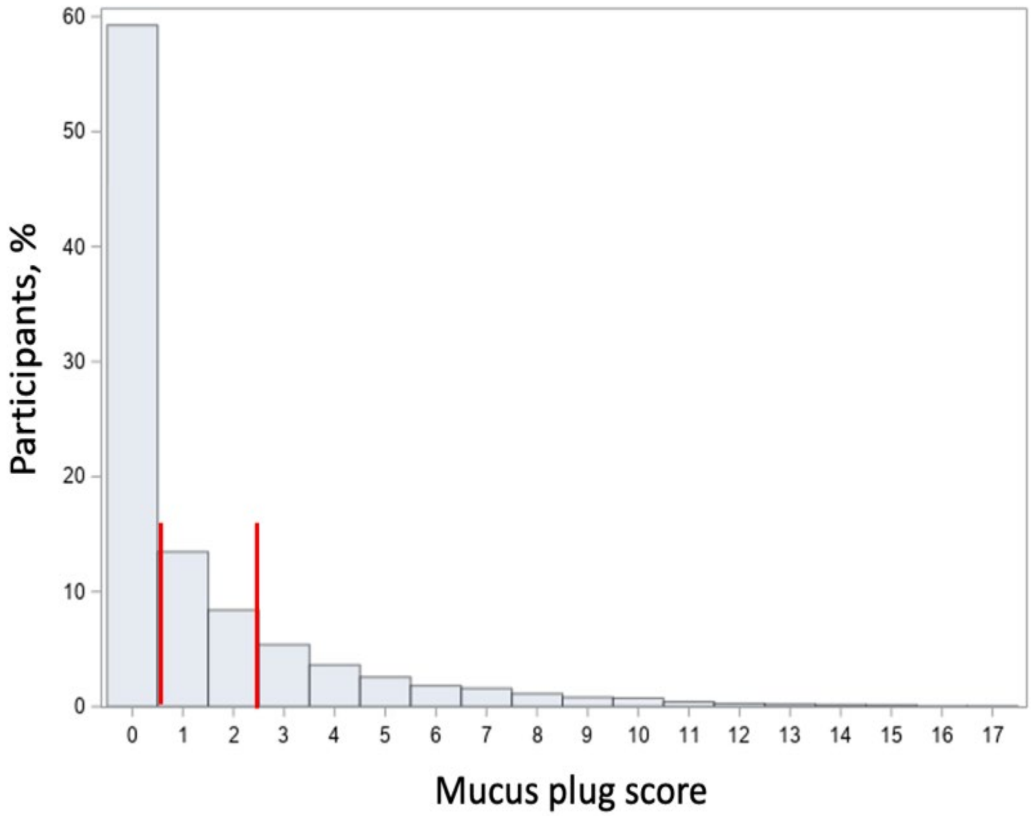
eFigure 1 Computed Tomography (CT) Sections Showing Airways Completely Occluded with Mucus Plugs (Yellow Circles).

CT axial (**A**) and coronal (**B**) sections of the right lower lobe are from two participants with Chronic Obstructive Pulmonary Disease.



eFigure 2 Illustration of the Mucus Plug Score. The score is based on counting the number of lung segments with mucus plugs completely blocking middle-to-large-sized airways (i.e., ~2-10 mm-lumen diameter) on computed tomography scans. Readers recorded the number of lung segments with mucus plugs in each lobe, with the lingula as a separate lobe. The score ranges from 0 (no mucus plugs seen in any lung segments) to 18 (all lung segments with mucus plugs). The employed bronchial nomenclature consists of 18 lung segments (right lung: 3, 2, and 5 lung segments in the upper, middle, and lower lobes, respectively; left lung: 2, 2, and 4 lung segments in the upper lobe, lingula, and lower lobe, respectively). Mucus plugs (yellow dots) are present in different airway generations of several lung segments, yielding a score of 6 (i.e., one lung segment with plugs in each of the following: right middle lobe, right lower lobe, left upper lobe, and lingula, and two lung segments with mucus plugs in the left lower lobe).

Designations: right upper lobe lung segments: apical, posterior, and anterior (labels with light blue background); right middle lobe lung segments: lateral, medial (labels with yellow background); right lower lobe lung segments: superior, medial basal, anterior basal, lateral basal, and posterior basal (labels with light green background); left upper lobe lung segments: apicoposterior, anterior (labels with light blue background); lingula lung segments: superior, inferior (labels with yellow background); left lower lobe lung segments: superior, anteromedial basal, lateral basal, and posterior basal (labels with light green background). Airway generations (G) are depicted in the right apical lung segment): 3rd G, (also termed segmental), 4th G (also termed sub-segmental), 5th G (also termed sub-sub-segmental), and 6th G.
a = right upper lobe bronchus; b = left upper lobe bronchus; c = superior division bronchus of the left upper lobe; d = intermediate bronchus; e = lingular bronchus; f = left lower lobe bronchus; g = right lower lobe bronchus; h = right middle lobe bronchus. Bronchial nomenclature based on Netter's Atlas of Human Anatomy.[9] Designations of airway generations have been previously reported.[10] Bronchial tree scheme by Anastasia Payá-Mora adapted from Netter's Atlas of Human Anatomy.[9]



eFigure 3 Distribution of Mucus Plug Scores in 4,363 Participants with Chronic Obstructive Pulmonary Disease.

Red lines indicate cut off points used to categorize the mucus plugs scores: 0, 1-2, and ≥3 lung segments with mucus plugs.

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eAppendix

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COPDGene Phase 3

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