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

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ABSTRACT

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

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 10198 (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 <1mm slice protocols. Mortality, spirometry and demographic data were sourced from the COPDGene database.

For our study, all 10198 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 \geq 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 \geq 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 COPD-Gene 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 \geq 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 \geq 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 neversmokers. 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 $(0, 1-2 \text{ and } \ge 3 \text{ obstructed segments})$ 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 | | |
| Concerns and an all home of an annual second s | | | | | | | | |

Cox proportional nazard regression models. *Adjusted for age, gender, race, BMI, smoking status, packyears, FEV, %, emphysema (~950HU%), airway wall thickness (Pi10), scanner model. *Including all variables from the adjusted model except FEV, 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.

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