International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Impact of Airway-Occluding Mucus Plugs on Mortality in Patients with COPD According to Disease Severity: A Subset Analysis of Data From COPDGene

Paola Rogliani[1], Luigino Calzetta[2]

[1]Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome "Tor Vergata", Rome, Italy; [2]Respiratory Disease and Lung Function Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy

Correspondence: Paola Rogliani, Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome "Tor Vergata", Via Montpellier 1, Rome, 00133, Italy, Tel +39 06 2090 4656, Email paola.rogliani@uniroma2.it

Background: Chronic mucus hypersecretion (CMH) in chronic obstructive pulmonary disease (COPD) is associated with severe outcomes, but its impact on mortality across COPD stages is not well understood. This study evaluated the risk of mortality according to mucus plugs and COPD severity.

Methods: A subset analysis was performed using secondary unadjusted data from published figures of a study on the COPDGene cohort. Data on mortality rates and mucus plug scores were extracted and classified by the GOLD stages. The mortality risk was calculated based on the number of mucus plugs occluding lung segments and GOLD stage, using calibration curves and best-fitting non-linear regression curve analysis.

Results: The risk of all-cause mortality was significantly increased for GOLD stage 1 patients with ≥1 occluded lung segments (1.48, 95% CI 1.10–1.86; P<0.01) compared to those with no occlusions. Patients with GOLD stage 1 and ≥3 occluded lung segments had a significantly higher mortality risk (1.89, 95% CI 1.43–2.36; P<0.001). No increased mortality risk resulted for patients with 1–2 occluded lung segments and those at GOLD stage 2–4. The number needed to harm analysis indicated that 6 patients with ≥3 occluded segments at GOLD stage 1 were required to observe one death, compared to 26 patients at GOLD stage 4.

Conclusion: The significant mortality risk associated with multiple mucus-plugged segments at GOLD stage 1 supports the potential benefit of thiol-based mucolytic therapy. Targeted interventions to reduce mucus plugs could be crucial in improving survival outcomes for early-stage COPD patients.

Keywords: COPD, mucus plugs, mortality risk, GOLD stages, mucolytic therapy

Introduction

Chronic mucus hypersecretion (CMH) in chronic obstructive pulmonary disease (COPD) is associated with a decline in forced expiratory volume in the 1st second (FEV_1), increased risk for pulmonary infections, elevated frequencies of exacerbations and hospitalizations, and reduced health-related quality of life (QoL).[1,2] CMH is due to altered activity of goblet and submucosal gland cells as well as decreased elimination of mucus due to altered mucociliary clearance.[2]

Evidence from a large observational retrospective analysis of prospectively collected data of 4363 patients with a diagnosis of COPD in the Genetic Epidemiology of COPD (COPDGene, https://copdgene.org) cohort indicates that 40.7% of participants had mucus plugs in one or more medium- to large-sized bronchi according to chest computed tomography (CT) scan.[3] Among the analyzed patients, 40.6% died in a median follow-up of 9.5 years, with the presence of mucus plugs occluding airways being significantly associated with higher risk of all-cause mortality.[3]

Indeed, the quantitative risk analysis was performed accordingly to the number of airways occluded by mucus. However, it was not matched with the severity of disease. In fact, the mortality rate, and not the risk, by chronic

Received: 20 November 2024
Accepted: 21 March 2025
Published: 26 March 2025

obstructive lung disease (GOLD) stage and mucus plug score were only qualitatively reported in the primary publication (Figure S1A and B).[3] The absence of a detailed analysis of mortality risk in relation to both the extent of airway occlusion by mucus and disease severity is a missed opportunity to comprehensively evaluate the impact of mucus in COPD patients, even at early stages of the disease.

In this respect, it has been demonstrated that CMH is a pivotal treatable trait (TT) with thiol-based drugs in COPD, that chronic sputum production is significantly associated with COPD and is consistently reported across all stages of the disease, from mild to very-severe patients, with a prevalence around 30%.[4–6] Current international recommendations are proposing increasing interest in the management of mucus hypersecretion with mucolytic agents for the treatment of COPD, even at early stages of the disease and in subjects with chronic bronchitis.[7] Effectively, mucolytic therapy may improve symptoms and QoL while also reducing the risk of exacerbations and hospitalization in COPD patients.[8–13]

Intriguingly, CMH is also significantly reported with a prevalence of 20% in early COPD patients, who are individuals under 50 years of age with >10 pack-years of tobacco consumption with one or more of the following conditions: FEV_1/forced vital capacity ratio less than the lower limit of normal and/or chest CT abnormalities and/or accelerated FEV_1 decline.[14]

The impact of pharmacological treatment on mortality in COPD is a highly relevant topic, as highlighted by the last GOLD document.[7] Therefore, characterizing a TT such as CMH in relation to mortality and disease severity may provide further support in the use of mucolytic agents in COPD.

The aim of this study was to perform a subset analysis of results obtained from the COPDGene study, as published by Diaz et al.[3] As independent researchers without access to the COPDGene database, we extracted data from the primary article by Diaz et al.[3] This analysis seeks to determine the risk of mortality in COPD patients associated with the presence of airway-occluding mucus plugs at specific levels of COPD severity, namely GOLD stage 1 (mild COPD), GOLD stage 2 (moderate COPD), GOLD stage 3 (severe COPD), and GOLD stage 4 (very severe COPD).

Materials and Methods

Data Extraction

Unadjusted data were extracted from Figure S1, which reports data adapted from the study published in JAMA by Diaz et al.[3] Specifically, the percentage for all-cause mortality rates and participant counts were obtained by GOLD stage and mucus plug score from Figure S1C and D, respectively.

The severity of COPD was classified according to the level of airflow limitation as defined by the GOLD stages: GOLD 1: post-bronchodilator (PB) FEV_1 ≥80% predicted; GOLD 2: 50%≤ PB FEV_1 <80% predicted; GOLD 3: 30%≤ PB FEV_1 <50% predicted; GOLD 3: PB FEV_1 30%≤ predicted.[7] The mucus plug score identified the number of lung segments with mucus plugs, defined as a CT opacity that completely occluded the lumen of a medium-to-large-sized airways.[3]

Outcomes

The primary outcome was the risk of all-cause mortality based on GOLD stage and the number of lung segments with mucus plugs. The secondary outcomes were the strength of association between all-cause mortality based on GOLD stage and the number of lung segments with mucus plugs, as well as the number needed to harm (NNH).

Data Analysis

Color images in Figure S1A and B were converted from RGB to 8-bit grayscale using Heckbert's median-cut color quantization algorithm to quantify the luminance of each cell and the corresponding specific scales. Figure S1C and D show the converted to 8-bit grayscale, reporting all-cause mortality and participants by GOLD stage and mucus plug score. The RGB-to-grayscale conversion was a procedure necessary to optimize image classification and data extraction.[15] Data from scales were assessed at 20%, 40%, 60%, and 80% for all-cause mortality rate and at 5%, 10%, 15%, 20%, and 25% for the percentage of participants. The luminance levels ranged from 0 (black) and 255 (white), with intermediate values representing shades of gray.

The correspondence of scale luminance with the above reported percentages was used to build specific calibration curves that allowed to calculate the percentages of all-cause mortality rate and participants according to GOLD stage and the number of lung segments with mucus plugs. The number of patients at each GOLD stage was provided in the primary publication (GOLD 1, n = 766; GOLD 2, n = 1887; GOLD 3, n = 1127; GOLD 4, n = 583).[3]

Using data from the calibration curves, along with the number of participants for each GOLD stage and the total number of patients, it was possible to calculate the exact number of participants for each cell based on GOLD stage and the number of lung segments with mucus plugs. These values were then used to determine the exact number of deceased and surviving patients for each cell according to GOLD stage and the number of lung segments with mucus plugs. This allowed for the calculation of the risk of all-cause mortality based on the GOLD stage for patients with ≥1, 1–2, and ≥3 lung segments with mucus plugs compared to those without mucus plugs in the lung segments. The risk of all-cause mortality was also analyzed via a best-fitting non-linear regression curve analysis to assess whether there is a trend in the risk of death related to the severity of COPD and the number of lung segments with mucus plugs.[16]

The strength of association between all-cause mortality based on the GOLD stage and the number of lung segments with mucus plugs, as well as the NNH, were also calculated as previously described.[17–19] Detailed information is available in the supplementary data.

Software and Statistical Significance

ImageJ software was used to extract data from the Figures;[20] GraphPad Prism (CA, US) software was used to build the calibration curves, calculate the risk of all-cause mortality, the strength of association, and NNH, and to perform the best-fitting non-linear regression curve analysis. Data are generally reported as mean and 95% confidence interval; the best-fitting non-linear regression models were graphed reporting the 95% confidence bands, which indicate the likely location of the true curves. The level of statistical significance was set at $P<0.05$.[16]

Results

Calibration Curves and Extracted Data

The calibration curves used to calculate the percentages of all-cause mortality rate and participants according to the levels of luminance of the respective scales are presented in Figure 1A and B, respectively. Both the calibration curves fit parabolic equations, characterized by a very high goodness of fit as indicated by the R^2 values. The percentages of all-cause mortality rate and participants, according to GOLD stage and the number of lung segments with mucus plugs, are shown in Figure 1C and D, respectively.

Risk of All-Cause Mortality Based on the GOLD Stage and the Number of Lung Segments with Mucus Plugs

The overall unadjusted analysis indicated that the risk of all-cause mortality was significant at GOLD stage 1 and 3 ($P<0.01$ and $P<0.001$, respectively) and that the GOLD stage was inversely related to the risk of all-cause mortality. The unadjusted analysis performed according to the number of lung segments with mucus plugs showed that when 1 or 2 segments are occluded by mucus plugs, there is no significant increased risk of all-cause mortality at GOLD stage 1, 2, and 4. When ≥3 lung segments are occluded by mucus plugs, the risk of all-cause mortality is significantly increased at GOLD stage 1 ($P<0.001$) and is also reported at GOLD stage 3 ($P<0.01$), showing an inverse relationship with the GOLD stage. Detailed information on the unadjusted risk of all-cause mortality based on GOLD stage and the number of lung segments occluded by mucus plugs is reported in Table 1.

The overall best-fitting non-linear regression curve analysis of the risk of all-cause mortality confirmed a significant inverse relationship with the GOLD stage following a hyperbolic trend (R^2 0.85), with a significantly increased risk of death at GOLD stage 1 ($P<0.01$) (Figure 2A). For participants with 1 or 2 segments occluded by mucus plugs, no significant trend was detected ($P>0.05$) (Figure 2B). However, in participants with ≥3 segments occluded by mucus plugs, the significant inverse hyperbolic trend with GOLD stage (R^2 0.95) was confirmed, with the risk of all-cause mortality significantly increased at GOLD stage 1 ($P<0.001$) (Figure 2C). Detailed information on the significant best-

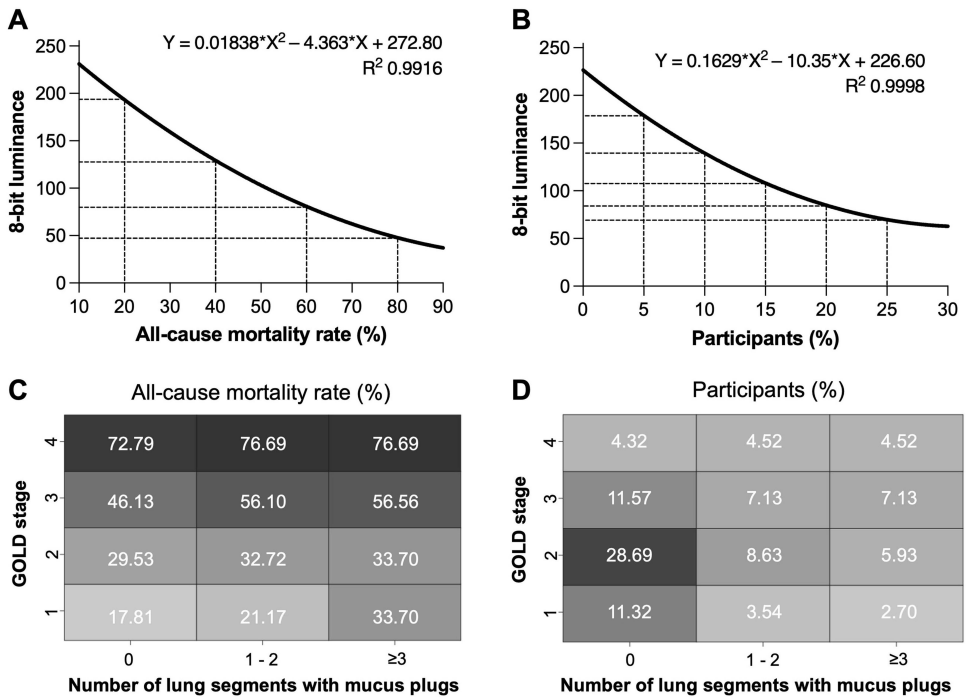

Figure 1 Calibration curves with equations and R^2 values for the percentages of all-cause mortality rate (**A**) and participants (**B**) according to the levels of 8-bit luminance; percentages of all-cause mortality rate (**C**) and participants (**D**), according to GOLD stage and the number of lung segments with mucus plugs.

fitting non-linear regression hyperbolic models describing the risk of all-cause mortality by GOLD stage and the number of lung segments with mucus plugs is provided in the supplementary data. Table 2 presents the predicted risk of all-cause mortality based on GOLD stage and the number of lung segments with mucus plugs vs participants without mucus plugs derived from the best-fitting non-linear regression models.

The evidence resulting from the best-fitting non-linear regression curve analysis was supported by the analysis of the strength of association. A moderate association was found at GOLD stage 1 between all-cause mortality and participants with ≥1 occluded lung segments. A strong association was consistently observed at GOLD stage 1 in participants with ≥3 occluded lung segments.

The NNH analysis, reported in Table 3, indicates the worst-case scenario at GOLD stage 1 in participants with ≥3 occluded lung segments, where 6 patients were required to observe one death, compared to 26 patients at GOLD stage 4.

Discussion

The findings of this study underscore the significant impact of GOLD stage and the number of lung segments occluded by mucus plugs on all-cause mortality in COPD patients. The overall best-fitting non-linear regression curve analysis

Table 1 Unadjusted Risk of All-Cause Mortality Based on GOLD Stage and the Number of Lung Segments With Mucus Plugs vs Participants Without Mucus Plugs. Values Reported as Mean and 95% CI

GOLD 4	1.05 (0.95–1.17)	1.05 (0.94–1.19)	1.05 (0.94–1.19)
GOLD 3	1.22 (1.09–1.37)***	1.21 (1.06–1.39)**	1.22 (1.07–1.40)**
GOLD 2	1.22 (0.98–1.29)	1.10 (0.93–1.30)	1.14 (0.93–1.37)
GOLD 1	1.49 (1.13–1.95)**	1.20 (0.84–1.70)	1.90 (1.38–2.58)***
	Overall: ≥1 lung segments with mucus plugs	1–2 lung segments with mucus plugs	≥3 lung segments with mucus plugs

Notes: ** P<0.01 and *** P<0.001 vs lung segments without mucus plugs. 95% CI: 95% confidence interval.

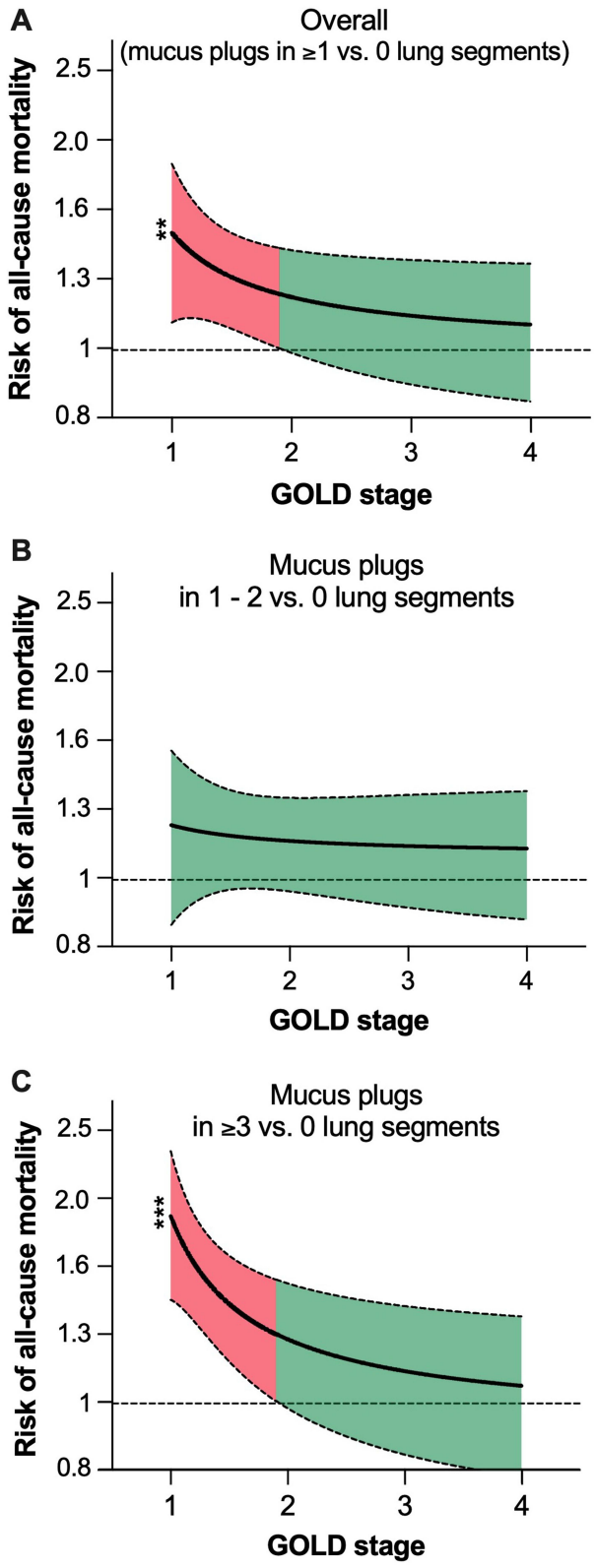

Figure 2 Best-fitting non-linear regression curve analysis of the risk of all-cause mortality by GOLD stage according to ≥1 occluded lung segments (**A**), 1–2 occluded lung segments (**B**), and ≥3 occluded lung segments (**C**). The average best-fitting non-linear regression models are graphed reporting the 95% confidence bands, which indicate the likely location of the true curves. ** P<0.01 and *** P<0.001 vs lung segments without mucus plugs.

https://doi.org/10.2147/COPD.S504065

Table 2 Predicted Risk of All-Cause Mortality Based on GOLD Stage and the Number of Lung Segments With Mucus Plugs vs Participants Without Mucus Plugs Derived From the Best-Fitting Non-Linear Regression Models. Values Reported as Mean and 95% CI

GOLD 4	1.09 (0.84–1.34)	1.11 (0.88–1.35)	1.06 (0.78–1.35)
GOLD 3	1.12 (0.89–1.35)	1.12 (0.91–1.33)	1.12 (0.84–1.39)
GOLD 2	1.20 (0.99–1.40)	1.14 (0.96–1.32)	1.24 (0.98–1.50)
GOLD 1	1.48 (1.10–1.86)**	1.20 (0.86–1.54)	1.89 (1.43–2.36)***
	Overall: ≥1 lung segments with mucus plugs	1–2 lung segments with mucus plugs	≥3 lung segments with mucus plugs

Notes: ** P<0.01 and *** P<0.001 vs lung segments without mucus plugs. 95% CI: 95% confidence interval.

Table 3 NNH Values for the All-Cause Mortality Based on GOLD Stage and the Number of Lung Segments With Mucus Plugs. Values Reported as Mean and 95% CI

GOLD 4	26 (9 - ∞)	26 (8 - ∞)	26 (8 - ∞)
GOLD 3	10 (6–23)	10 (6–36)	10 (6–29)
GOLD 2	28 (12 - ∞)	33 (12 - ∞)	25 (10 - ∞)
GOLD 1	12 (7–37)	28 (9 – ∞)	6 (4–12)
	Overall: ≥1 lung segments with mucus plugs	1–2 lung segments with mucus plugs	≥3 lung segments with mucus plugs

Notes: 95% CI: 95% confidence interval; NNH: number needed to harm.

reveals a moderately increased risk of all-cause mortality at GOLD stage 1 for COPD patients with at least one lung segment occluded by mucus plugs. In examining the role of mucus plugs, our results show that the presence of 1 or 2 occluded lung segments has not relevant impact on the risk of all-cause mortality according to the GOLD stage. This suggests that a low number of occluded segments might not sufficiently impair lung homeostasis to influence mortality risk appreciably.[21] However, the situation changes dramatically when ≥3 lung segments are occluded. At this threshold, the risk of all-cause mortality rises significantly and becomes strong at GOLD stage 1, reinforcing the inverse relationship between the severity of GOLD stage and all-cause mortality risk. This suggests that early stages of COPD, as defined by the GOLD classification, are critical in influencing all-cause mortality risk, particularly in patients with CMH and multiple mucus-plugged lung segments.

This evidence has important clinical relevance because patients at GOLD stage 1 have a lower mortality rate than those with more severe COPD.[3] However, this low prevalence of mortality may mask an increased risk of death for patients with lung segments occluded by mucus plugs compared to those without mucus plugs. This is a typical condition in which, when an event rate is low, the relative distribution of risk estimates may be highly skewed, potentially masking significant risks in a specific population.[22] Indeed, this finding represents the main scientific added value that did not emerge in the initial analysis by Diaz et al.[3]

Another study[23] found that the mortality rate, rather than the risk of mortality, was associated with a high mucus score, but it did not provide information about the severity of COPD. Additionally, even a recent sophisticated artificial intelligence-based analysis of automated mucus quantification on chest CT scans, which explored the association with mortality in the full cohort of all Phase 1 COPDGene participants, did not provide models to assess the risk of mortality according to the severity of COPD, but only for patients across GOLD stages 1–4.[24] This evidence further corroborates the novelty of our analysis, which addresses a critical gap in the current literature.

Producing such important clinical evidence by extracting data from Figures in previously published study[3] may initially seem speculative or imprecise. However, it is important to highlight the robust scientific basis supporting graphical data extraction methods. When performed with suitable software,[20] such as that used to interpret the Figure in

the original article by Diaz et al,[3] this approach has been shown to ensure high accuracy and enable reliable interrater consistency.[25,26] These methods are particularly valuable when primary data, such as patient-level data from resources like the COPDGene database, are restricted to study investigators and not available to independent researchers. In such cases, Figure-based data extraction serves as a validated and effective strategy for generating reproducible results in clinical research.

In this regard, our study provides additional evidence, marking an important advancement beyond the primary analysis conducted by Diaz et al.[3] The NNH analysis identified the most unfavorable case at GOLD stage 1 in COPD patients with ≥3 occluded lung segments, reporting a worrying NNH value of 6. This means that for every only 6 mild COPD patients with ≥3 lung segments occluded by mucus plugs, one died. This value is particularly striking compared to very severe COPD patients, where 26 patients with ≥3 lung segments occluded by mucus plugs were necessary to report one death. Although there are no established rules for what constitutes an acceptable NNH, considering the severity of the outcome "mortality", pragmatically an NNH value <10 can be generally regarded as concerning.[27] Indeed, this highlights the urgent need for targeted interventions in these patients to mitigate the elevated risk of mortality.

The potential benefit of mucolytic therapy, particularly with thiol-based drugs, should be considered as part of these targeted interventions. Thiol-based mucolytics break the disulfide bonds linking mucin proteins by donating electrons to the thiol groups of cysteine residues in mucin monomers. This process leads to the depolymerization of mucin oligomers, altering the rheology of mucin-rich secretions. As a result, the elasticity and viscosity of the mucus are reduced, making it easier to expel from the lungs.[28] By reducing mucus plugs, thiol-based mucolytics may help prevent the occlusion of lung segments, thereby reducing the risk of all-cause mortality, especially in patients with mild COPD (GOLD stage 1) who have multiple occluded lung segments.

In the era of TT approach, where CMH is recognized as a pivotal trait in COPD,[6,29] and considering that mortality has been suggested as a potential outcome for the pharmacological treatment of COPD,[30] addressing mucus hypersecretion in patients with a hypersecretory phenotype may offer both pharmacological and clinical rationale.[2] The currently recommended thiol-based mucolytics in COPD include carbocysteine, erdosteine, and N-acetylcysteine.[7] Regular treatment with carbocysteine and N-acetylcysteine has been shown to reduce the risk of exacerbation only in patients not receiving inhaled corticosteroids (ICS). Erdosteine, however, has demonstrated a significant effect against exacerbation regardless of concurrent ICS treatment.[8,9,31–33] As prodrug, erdosteine contains two blocked thiol groups which are stable in the stomach acid environment and become available only after first-pass metabolism, this accounting for the very good safety profile of erdosteine.[34,35] Additionally, erdosteine has been proven to potentiate the effectiveness of antibiotics.[34] This is particularly important as COPD exacerbations are often caused by bacterial infections, which require antibiotics and corticosteroid therapy.[36,37] Furthermore, ICS-containing treatment are frequently prescribed in COPD management, with data from routine clinical practice indicating that 50–80% of COPD patients are prescribed with ICS.[38]

Considering that increased mortality is associated with exacerbations even in COPD patients with mild lung function impairment, thiol-based mucolytics, particularly erdosteine, may counteract the risk of mortality by both reducing the risk of mild exacerbation and decreasing CMH.[39] However, it is yet to be investigated whether the increased risk of death in patients with mild COPD and multiple occluding mucus plugs is primarily due to the higher mortality risk associated with COPD exacerbations.[3] Identifying the TT CMH in early-stage COPD could be pivotal as part of a broader precision medicine strategy. In any case, it remains unclear whether mitigating this TT with thiol-based mucolytic therapy in early-stage COPD might also reduce the risk of mortality, as the efficacy of these therapies in reducing mucus plugs is currently unproven and requires further investigation.

Assessing the impact of thiol-based mucolytic agents on a rare event such as mortality presents significant challenges, particularly due the need for a very large population size when employing classic frequentist inference. This limitation may be addressed by utilizing Bayesian inference, which is well-suited for modeling uncertainty, an essential aspect when predicting rare events that often necessitate data extrapolation. The Bayesian statistical approach allows for a substantial reduction in the required population size, providing a reliable assessment of rare events without dependence on p-values.[40]

The limitation of this study is that it is a subset analysis of secondary data extracted from published Figures of a study on the COPDGene cohort, which has already been analyzed.[3] Additionally, the data were not adjusted for critical

variables such as smoking status, body mass index (BMI), and comorbidities. As independent researchers not affiliated with the COPDGene study consortium, we do not have direct access to patient-level data.[41] Consequently, we could not adjust data for age, sex, race and ethnicity, BMI, pack-years smoked, current smoking status, FEV_1, and CT measures of emphysema and airway disease, as performed in the primary publication.[3] Therefore, the extraction and use of unadjusted data may have led to an inflated effect size in the assessment of the risk of all-cause mortality reported in Table 1 of our study, similar to the difference between unadjusted and adjusted hazard ratios reported by Diaz et al[3,42] The unadjusted nature of data may also have introduced potential bias especially for outcomes with small effect sizes; thus, caution is warranted when interpreting results originating from unadjusted analysis.[43]

The consequent risk of Type I error is particularly important when outcomes result in a small effect size, especially during large-N replication stage. This is evident in our detection of the risk of all-cause mortality at GOLD stage 2 to 4, where we reported risk values between 1.05 and 1.22.[44] These values fall within the range of a small effect size for measures of risk of rare events, thereby increasing the probability of theoretical false positive.[44,45] Conversely, the significant risk values detected at GOLD stage 1 were greater and thus less likely to be affected by Type I error.[44,45]

To address this matter, we aimed to reduce the risk of Type I error by performing a best-fitting non-linear regression curve analysis, a procedure shown to be effective in mitigating the risk of obtaining false positive results, particularly for binary data such as mortality.[42] In fact, when adjustment is not possible, balancing in regression models can alleviate the limitations of unadjusted analyses.[42] Notably, applying the best-fitting non-linear regression model abolished the significance observed at GOLD stage 2 to 4, reinforcing the concern regarding Type I error in the unadjusted analysis.

Therefore, the predicted values resulting from the best-fitting non-linear regression models, as reported in Figure 2 and Table 2 of this study, should be considered the main results of our research depicting the impact of airway-occluding mucus plugs on mortality in patients with COPD, according to disease severity, in a real COPD population.

In this way, our study represents a significant advancement compared to the analysis performed by Diaz et al in the primary publication.[3] Although it is a subset analysis, our regression models provide an in-depth and Type I error-free evaluation of mortality risk in COPD, offering important insights into the importance of effect sizes as supported by Gene V. Glass and Jacob Cohen, two of the most influential statistician-researchers of the past half-century.[46] Despite employing robust statistical approach, such as the NNH analysis and regression models, our findings are based on the specific COPDGene cohort. We recognize that this may limit their generalizability to broader populations, highlighting the necessity for further research in diverse COPD populations to validate and enhance the applicability of our results.

Concluding, the analysis of secondary unadjusted data from published Figures of the COPDGene study emphasizes the importance of early detection and intervention in COPD patients, particularly those with CMH. The significant increase in all-cause mortality risk at GOLD stage 1 in patients with multiple mucus-plugged lung segments suggests that even early-stage COPD should not be underestimated. Implementing effective pharmacological strategies to reduce mucus plugs could potentially improve survival outcomes in these patients. Further research is needed to explore therapeutic approaches aimed at reducing mucus plugging and to validate these findings across diverse COPD populations with varying levels of disease severity.[47]

Funding

This article was not funded.

Disclosure

PR has participated as a faculty member and advisor in scientific meetings and was a consultant sponsored by Recipharm and Zambon. PR also participated as a lecturer and advisor in scientific meetings and courses under the sponsorship of AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Novartis and Sanofi. She also reports that her department was funded by Boehringer Ingelheim, Chiesi Farmaceutici, Novartis, and Zambon. LC has participated as an advisor in scientific meetings and courses sponsored by Zambon and was a consultant for Recipharm and Zambon.

References

1. Beeh KM, Burgel PR, Franssen FME, et al. How do dual long-acting bronchodilators prevent exacerbations of chronic obstructive pulmonary disease? *Am J Respir Crit Care Med*. 2017;196(2):139–149. doi:10.1164/rccm.201609-1794CI
2. Shah BK, Singh B, Wang Y, Xie S, Wang C. Mucus hypersecretion in chronic obstructive pulmonary disease and its treatment. *Mediators Inflamm*. 2023;2023:1–15. doi:10.1155/2023/8840594
3. Diaz AA, Orejas JL, Grumley S, et al. Airway-occluding mucus plugs and mortality in patients with chronic obstructive pulmonary disease. *JAMA*. 2023;329. doi:10.1001/jama.2023.2065
4. Sarwar MR, McDonald VM, Abramson MJ, Paul E, George J. Treatable traits in an English cohort: prevalence and predictors of future decline in lung function and quality of life in COPD. *ERJ Open Res*. 2021;7. doi:10.1183/23120541.00934-2020
5. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016;47(2):410–419. doi:10.1183/13993003.01359-2015
6. McDonald VM, Fingleton J, Agusti A, et al. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: treatable traits down under international workshop report. *Eur Respir J*. 2019;53(5):1802058. doi:10.1183/13993003.02058-2018
7. GOLD, 2025 GOLD report - global initiative for chronic obstructive lung disease – GOLD. 2025. Available from: https://goldcopd.org/wp-content/uploads/2024/11/GOLD-2025-Report-v1.0-15Nov2024_WMV.pdf. Accessed December 30, 2024.
8. Cazzola M, Calzetta L, Page C, et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. *Eur Respir Rev*. 2015;24(137):451–461. doi:10.1183/16000617.00002215
9. Rogliani P, Matera MG, Page C, Puxeddu E, Cazzola M, Calzetta L. Efficacy and safety profile of mucolytic/antioxidant agents in chronic obstructive pulmonary disease: a comparative analysis across erdosteine, carbocysteine, and N-acetylcysteine. *Respir Res*. 2019;20(1). doi:10.1186/s12931-019-1078-y
10. Cazzola M, Rogliani P, Calzetta L, Hanania NA, Matera MG. Impact of mucolytic agents on COPD exacerbations: a pair-wise and network meta-analysis. *COPD*. 2017;14. doi:10.1080/15412555.2017.1347918
11. Rogliani P, Manzetti GM, Gholamalishahi S, Cazzola M, Calzetta L. Impact of N-acetylcysteine on mucus hypersecretion in the airways: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2024;19:2347–2360. doi:10.2147/COPD.S474512
12. Cazzola M, Calzetta L, Page C, Rogliani P, Matera MG. Impact of erdosteine on chronic bronchitis and COPD: a meta-analysis. *Pulm Pharmacol Ther*. 2018;48:185–194. doi:10.1016/j.pupt.2017.11.009
13. Papi A, Alfano F, Bigoni T, et al. N-acetylcysteine treatment in chronic obstructive pulmonary disease (COPD) and chronic bronchitis/pre-COPD: distinct meta-analyses. *Arch Bronconeumol*. 2024;60(5):269–278. doi:10.1016/J.ARBRES.2024.03.010
14. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prevalence, characteristics, and prognosis of early chronic obstructive pulmonary disease the Copenhagen general population study. *Am J Respir Crit Care Med*. 2020;201(6):671–680. doi:10.1164/rccm.201908-1644OC
15. Güneş A, Kalkan H, Durmuş E. Optimizing the color-to-grayscale conversion for image classification. *Signal Image Video Process*. 2016;10(5):853–860. doi:10.1007/s11760-015-0828-7
16. Motulsky H, Christopoulos A. *Fitting Models to Biological Data Using Linear and Nonlinear Regression: A Practical Guide to Curve Fitting*. Oxford: Oxford University Press; 2004.
17. Rogliani P, Cazzola M, Calzetta L. Cardiovascular disease in chronic respiratory disorders and beyond. *J Am Coll Cardiol*. 2019;73(17):2178–2180. doi:10.1016/J.JACC.2018.11.068
18. Rogliani P, Laitano R, Ora J, Beasley R, Calzetta L. Strength of association between comorbidities and asthma: a meta-analysis. *Eur Respir Rev*. 2023;32. doi:10.1183/16000617.0202-2022
19. Calzetta L, Aiello M, Frizzelli A, Rogliani P, Chetta A. Dexamethasone in patients hospitalized with COVID-19: whether, when and to whom. *J Clin Med*. 2021;10(8):1607. doi:10.3390/jcm10081607
20. Abràmoff MD, Magalhães PJ, Ram SJ. Image processing with ImageJ. *Biophotonics Int*. 2004;11:36–42.
21. Lloyd CM, Marsland BJ. Lung homeostasis: influence of age, microbes, and the immune system. *Immunity*. 2017;46(4):549–561. doi:10.1016/j.immuni.2017.04.005
22. Cook NR. Quantifying the added value of new biomarkers: how and how not. *Diagn Progn Res*. 2018;2(1). doi:10.1186/s41512-018-0037-2
23. Tanabe N, Shimizu K, Shima H, et al. Computed tomography mucus plugs and airway tree structure in patients with chronic obstructive pulmonary disease: associations with airflow limitation, health-related Independence and mortality. *Respirology*. 2024;29. doi:10.1111/RESP.14776
24. van der Veer T, Andrinopoulou ER, Braunstahl GJ, et al. Association between automatic AI-based quantification of airway-occlusive mucus plugs and all-cause mortality in patients with COPD. *Thorax*. 2025;80. doi:10.1136/THORAX-2024-221928
25. Troscianko J, Stevens M. Image calibration and analysis toolbox - a free software suite for objectively measuring reflectance, colour and pattern. *Methods Ecol Evol*. 2015;6(11):1320–1331. doi:10.1111/2041-210X.12439
26. Jelicic Kadic A, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. *J Clin Epidemiol*. 2016;74:119–123. doi:10.1016/j.jclinepi.2016.01.002
27. Andrade C. The numbers needed to treat and harm (NNT, NNH) statistics: what they tell us and what they do not. *J Clin Psychiatry*. 2015;76. doi:10.4088/JCP.15f09870
28. Cazzola M, Calzetta L, Page C, Rogliani P, Matera MG. Thiol-based drugs in pulmonary medicine: much more than mucolytics. *Trends Pharmacol Sci*. 2019;40(7):452–463. doi:10.1016/j.tips.2019.04.015
29. Papi A, Faner R, Pavord I, et al. From treatable traits to GETomics in airway disease: moving towards clinical practice. *Eur Respir Rev*. 2024;33(171):230143. doi:10.1183/16000617.0143-2023
30. Maniscalco M, Calzetta L, Rogliani P, Cazzola M. Reducing the risk of death - a possible outcome in COPD patients. *Expert Rev Clin Pharmacol*. 2024. doi:10.1080/17512433.2024.2408272
31. Dal Negro RW, Wedzicha JA, Iversen M, et al. Effect of erdosteine on the rate and duration of COPD exacerbations: the RESTORE study. *Eur Respir J*. 2017;50(4):1700711. doi:10.1183/13993003.00711-2017
32. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2019;2019. doi:10.1002/14651858.CD001287.pub6

33. Calverley PMA, Page C, Dal Negro RW, et al. Effect of erdosteine on COPD exacerbations in COPD patients with moderate airflow limitation. *Int J COPD*. 2019;14. doi:10.2147/COPD.S221852
34. Dal Negro R, Pozzi E, Cella SG. Erdosteine: drug exhibiting polypharmacy for the treatment of respiratory diseases. *Pulm Pharmacol Ther*. 2018;53:80–85. doi:10.1016/j.pupt.2018.10.005
35. De Giovanni L, Fregnan GB, Rabitti C, et al. Lack of gastric adverse effects of erdosteine in rats and men - PubMed. *Int J Clin Pharmacol*. 1991;29:269–273.
36. Celli BR, Fabbri LM, Aaron SD, et al. An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome proposal. *Am J Respir Crit Care Med*. 2021;204(11):1251–1258. doi:10.1164/rccm.202108-1819PP
37. Viniol C, Vogelmeier CF. Exacerbations of COPD. *Eur Respir Rev*. 2018;27(147):170103. doi:10.1183/16000617.0103-2017
38. Quint JK, Ariel A, Barnes PJ. Rational use of inhaled corticosteroids for the treatment of COPD. *NPJ Prim Care Respir Med*. 2023;33. doi:10.1038/s41533-023-00347-6
39. Fortis S, Wan ES, Kunisaki K, et al. Increased mortality associated with frequent exacerbations in COPD patients with mild-to-moderate lung function impairment, and smokers with normal spirometry. *Respir Med X*. 2021;3. doi:10.1016/j.yrmex.2020.100025
40. Straub D, Papaioannou I, Betz W. Bayesian analysis of rare events. *J Comput Phys*. 2016;314. doi:10.1016/j.jcp.2016.03.018
41. COPDGene | COPD Foundation, (n.d.). Available from: https://www.copdfoundation.org/Research/Research-Projects-and-Consortia/COPDGene.aspx. Accessed July 23, 2024.
42. Ciolino JD, Martin RH, Zhao W, Jauch EC, Hill MD, Palesch YY. Covariate imbalance and adjustment for logistic regression analysis of clinical trial data. *J Biopharm Stat*. 2013;23(6):1383–1402. doi:10.1080/10543406.2013.834912
43. Markham JL, Richardson T, Stephens JR, Gay JC, Hall M. Essential concepts for reducing bias in observational studies. *Hosp Pediatr*. 2023;13(8):E234–E239. doi:10.1542/hpeds.2023-007116
44. Wilson BM, Harris CR, Wixted JT. Theoretical false positive psychology. *Psychon Bull Rev*. 2022;29(5):1751–1775. doi:10.3758/s13423-022-02098-w
45. Olivier J, May WL, Bell ML. Relative effect sizes for measures of risk. *Commun Stat Theory Methods*. 2017;46. doi:10.1080/03610926.2015.1134575
46. Sullivan GM, Feinn R. Using effect size—or why the P value is not enough. *J Grad Med Educ*. 2012;4. doi:10.4300/jgme-d-12-00156.1
47. Calzetta L, Ritondo BL, Zappa MC, et al. The impact of long-acting muscarinic antagonists on mucus hypersecretion and cough in chronic obstructive pulmonary disease: a systematic review. *Eur Respir Rev*. 2022;31. doi:10.1183/16000617.0196-2021