Original Research

Association of Mucus Plugging and Body Mass Index in Patients With Advanced COPD GOLD 3/4 With Emphysema

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***Running Head*: Association of Mucus Plugging and BMI in Emphysema**

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Abstract

Background

COPD is classified by its clinical phenotypes—chronic bronchitis and emphysema. A CT-based mucus plug score (MPS) was recently identified as a biomarker to subgroup COPD patients with increased airway mucus plugs. While not necessarily linked to more pronounced symptoms or structural lung changes, mucus plugs are associated with increased mortality. Interestingly, a higher MPS seems to be associated with a lower body mass index (BMI), likewise associated with increased mortality. This study aims to characterize patients with advanced lung emphysema presenting for lung volume reduction therapy with a special focus on mucus plug occurrence.

Material and Methods

This retrospective, monocentric study assessed MPS in advanced COPD (GOLD III/IV) and emphysema patients evaluated for lung volume reduction therapy at Charité-Universitätsmedizin Berlin. CT scans were analyzed for mucus plugging, and clinical data were obtained from the Lung Emphysema Registry (www.lungenemphysemregister.de).

Results

A total of 127 CT scans were assessed for MPS. About 50% had no mucus plugs (score = 0), 25% had an intermediate burden (score 1–2), and 25% had a high burden (score ≥3). Higher MPS correlated with lower BMI, more pronounced emphysema, and worse lung function, including forced expiratory volume in 1 second, vital capacity, and diffusing capacity of carbon monoxide. Residual volume, pCO2, the 6-minute walk test, and quality-of-life parameters were unaffected. Multivariate regression analysis found a strong association between mucus plugs and BMI, showing that a decrease in BMI was associated with a higher mucus burden ($p<0.001$; coefficient of -1.584).

Interpretation

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This study supports an association between high MPS and BMI in a vulnerable subgroup of advanced COPD patients. Further research is needed to understand the pathophysiology and consequences of mucus plugs, aiming for individualized risk assessments and treatment strategies.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition with increasing prevalence and significant morbidity and mortality, making it one of the leading causes of death worldwide [1]. Patients are frequently classified into clinical COPD phenotypes: emphysema and chronic bronchitis. In lung emphysema, chronic respiratory tract inflammation leads to remodeling and thickening of the airway walls, particularly in the small airways. The resulting airflow trapping in the alveoli worsens during expiration, and the ensuing hyperinflation impairs breathing mechanics, causing dyspnea and exercise intolerance [2–5]. In chronic bronchitis, excessive mucus production—resulting from an increase in goblet cell number and dysplasia, expansion of submucosal glands, mucus dysfunction, and impaired mucociliary clearance—results in chronic cough and excessive expectoration [2,6–9]. Recently, focus has been directed towards mucus plugs observed on computed tomography (CT) of the chest, which completely occlude the airway lumen, as a potential imaging biomarker. Mucus plugs can be found in up to 57% of COPD patients and are associated with worse lung function, a lower 6-minute walk distance, and may even be present without eliciting symptoms [10,11]. Although higher emphysema scores and an increased number of mucus plugs are independently associated with impaired lung function, there may be a significant overlap between the two COPD phenotypes. This is particularly relevant, as a higher mucus plug burden has been associated with increased mortality [10,12]. Emerging evidence suggests that mucus plug burden is a valuable imaging biomarker for risk assessment in COPD patients. Impact of mucus burden in patients with advanced COPD and clinically leading lung emphysema was previously underestimated, even though mucus plug are present in patients with COPD in 25%-76% [10]. Recent publications drastically underlined that patients with COPD and high mucus burden had worse functional outcome and increased mortality without eliciting more symptoms. Additionally, a lower body mass index, a simple clinical parameter to assess body adiposity, seemed to be associated with a higher mucus burden[10–12].

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Interestingly, a lower BMI has been associated with increased mortality in COPD patients, as well[13].

Among COPD patients undergoing endoscopic lung volume reduction therapy with valves (ELVR), despite advanced lung emphysema, there might be a subgroup with mucus plugging that is particularly vulnerable and has a worse overall prognosis.

The aim of this study was to investigate the presence of mucus plugging and its impact on patients with lung emphysema presenting for ELVR. Therefore, we evaluated mucus plugs on CT scans of the thorax and linked it with baseline characteristics, such as BMI, lung function parameters, exercise capacity and quality of life parameters in this well-defined cohort of lung emphysema patients.

Material and Methods

Data Acquisition

Data were obtained from patients with advanced COPD who presented for evaluation of lung volume reduction therapy at Charité – Universitätsmedizin Berlin. Patients were assessed according to the standards of the lung emphysema registry. The lung emphysema registry (www.lungenemphysemregister.de) is a German national open-label, non-interventional, multicenter trial. Study approval was obtained from the local ethics committee (A2/149/17 and EA1/136/13), and all patients provided informed consent. Data were acquired from individual patient files and via REDCap electronic data capture tools managed by CAPNetz [14].

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria, as defined by the lung emphysema registry standards, were described in detail previously and are presented in table 1 [15–19]. Patients with advanced COPD (GOLD stages III and IV), a forced expiratory volume in 1 second (FEV_1) of <50%, and a residual volume (RV) of >150% were included. There were no restrictions regarding diffusing

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capacity for carbon monoxide (DLCO), and the 6-minute walk test (6-MWT) had to be <450 m. All patients were required to be non-smokers for at least three months, as documented by a carboxyhemoglobin (COHb) level of <2%. Mild hypercapnia (pCO_2 <55 mmHg) was acceptable; otherwise, patients were evaluated for non-invasive ventilation therapy. Additionally, all patients received optimal medical treatment for their COPD and participated in a structured exercise program for respiratory diseases either before or after lung volume reduction therapy. Patient symptoms had to be primarily attributed to lung emphysema, with dyspnea as the lead symptom and without chronic cough and sputum production.

Study population

Patients included in this study were evaluated at Charité – Universitätsmedizin Berlin for interventional or surgical treatment of advanced COPD and subsequently underwent therapy. Eligibility and treatment recommendations were determined by the local emphysema board, a multidisciplinary team comprising interventional pulmonologists, thoracic surgeons, and radiologists.

Evaluation procedure

Patients underwent a standardized evaluation procedure. To calculate the BMI, the patient´s weight in kilograms was divided by the square of their height in meters (kg/m^2). Lung function parameters were measured using spirometry, body plethysmography, and diffusion tests (Power Cube+, Ganshorn Medizin Electronic GmbH, Niederlauer, Germany). A 6-MWT, capillary blood gas analysis, measurement of HbCO, and echocardiography were also performed. Baseline symptom burden was assessed using the COPD Assessment Test (CAT) and the modified Medical Research Council Dyspnoea Scale (mMRC. All patients received a CT scan of the thorax in inspiration without contrast media, along with a software-based quantification of emphysema destruction per lobe and an assessment of fissure integrity with StratX (PulmonX Inc., Redwood City, CA, USA). To quantify emphysematous destruction, the number of low-density voxels (≤ –950 Hounsfield units) was summed to calculate the

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emphysema score for each lung lobe. In most cases, lung volume reduction therapy targets the lobe with the highest emphysema score. Accordingly, this target lobe is documented in the REDCap database, along with the heterogeneity index, which quantifies the difference in emphysema scores between the target lobe and its adjacent lobe. To evaluate collateral ventilation per lobe with the Chartis® assessment system (PulmonX Inc., Redwood City, CA, USA), all patients with intermediate fissure integrity underwent bronchoscopy under procedural sedation with propofol and midazolam, either using high-frequency jet ventilation or while breathing spontaneously [20–22].

Assessment of mucus plug score

A retrospective analysis of all baseline CT scans was performed by two expert radiologists (AP and TE with 5 and >15 years of experience) to assess mucus plug burden. For each case, mucus plug burden was quantified using a broncho-pulmonary scoring system previously described by Dunican et al. [10,23]. Soft-tissue thin-slice reconstructions were evaluated using the multiplanar reconstruction tool of the clinical imaging viewer (Visage® 7 version 7,.2, Visage Imaging GmbH Berlin, Germany). A lung window with (level -550 HU, width 1600 HU) was used.

One point was scored for every pulmonary segment with at least one mucus plug, resulting in a maximum score of 20 points. A mucus plug was defined as an opacification that completely occludes the airway. In the most peripheral two centimeters of lung parenchyma the bronchial diameter was too small to detect mucus plugs. CT scans were categorized by mucus plug score as suggested by Diaz et al.: 0, 1, 2, and ≥3.

An example of a typical mucus plug is shown in figure A-C. For visualization of concomitant emphysema the corresponding areas are coded in red in the lower half of the figure D-F.

Statistical Analysis

Categorical variables were summarized using absolute and relative frequencies for each level. Continuous variables were reported as means and standard deviations. Comparisons between

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subgroups, defined by patient characteristics, were conducted using analysis of variance (ANOVA), followed by independent samples t-tests for pairwise comparisons and chi-quadrat test. Interrater reliability was calculated with Cronbach´s alpha. To examine the relationship between an ordinal outcome and independent variables, an ordinal logistic regression analysis was performed. Two separate ordinal logistic regression models were constructed. The first included the covariates: gender, age, BMI, emphysema in the target lobe (%), FEV_1 (%), and 6-MWT (m). The second model excluded emphysema and included: gender, age, BMI, FEV_1 (%), and 6-MWT (m). As no adjustment for multiple comparisons was applied, all p-values should be considered exploratory. Statistical analyses were conducted using SPSS software (version 24.0.0.0; IBM, Armonk, NY, USA).

Results

Patient characteristics

Table 2 displays patient parameters of 127 patients who underwent ELVR. In 66 cases mucus plug score was 0, in 31 cases an intermediate mucus plug score of one or two and in the remaining 29 cases a mucus plug score of ≥3 was detected *(s. figure 2)*. All patients had COPD GOLD III/IV (GOLD III n=38 (31%) vs, GOLD IV n=87 (69%)). Patients with a mucus plug score of 0 had a GOLD III stage in 42% and GOLD IV in 58%. With increasing mucus plug score more patients had a GOLD IV airflow obstruction with only 14% GOLD III and 86% GOLD IV in case of a mucus plug score ≥3 (p=0.014).

Age range was comparable among the groups. With increasing mucus burden body mass index decreased. (p<0.001). Significant differences in gender distribution with an almost similar distribution in patients with a mucus plug score of one to two and ≥3. However, patients with a mucus plug score of 0 were in 25% female and 75% male, respectively (p=0.002).

Interobserver variability

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To determine interobserver variability of the 20 CT scans that were independently scored by two experienced thoracic radiologists Cronbach´s alpha was calculated. It showed and excellent agreement between the two radiologists with an alpha of 0.955.

Emphysema Score

Emphysema score of the target lobe and difference and heterogeneity index between the target lobe and its adjacent lobe did increase with increasing mucus plug score (p=0.005 and p=0.029 respectively), as displayed in table 2.

Lung function test parameters, pCO2 and 6-MWT

Table 2 shows statistically significant differences in FEV1 (relative, p=0.023; absolute, p<0.001), VC (absolute, p<0.001) and DLCO (absolute and relative, p<0.001) with increasing mucus burden. No difference in relative VC, absolute and relative RV, pCO2 and 6-MWT was noted between the groups.

Quality of life parameters

No association of CAT score or mMRC with increasing mucus plug burden was detected (see table 2).

Additional parameters

In regard to COPD exacerbations over the past 12 months there was no difference between the groups. When comparing the GOLD stages of the three groups, patients with more mucus plugs had more advanced GOLD stages (p=0.014), as presented in table 2.

BMI, emphysema, lung function and mucus burden

To detect associations between mucus burden and patient characteristics we examined a logistic ordinal regression model and included the following variables: Age, gender, BMI, emphysema in target lobe (%), FEV1 (%),6-MWT (m), as shown in table 3. A statistically significant association between mucus burden and BMI was detected, showing that a decrease in BMI was associated with a higher mucus burden (p<0.001; Coefficient of -1.584).

BMI, lung function and mucus burden

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To account for a possible interaction between emphysema and BMI we repeated the logistic ordinal regression model excluding emphysema in the target lobe, as shown in table 4. The statistically significant association between mucus burden and BMI remained, showing that a decrease in BMI was associated with a higher mucus burden ($p<0.001$; Coefficient of -1.724).

Discussion

This is a novel analysis focusing on the impact of mucus burden in patients with advanced COPD and lung emphysema, a highly symptomatic and vulnerable patient population. Our results showed that patients with higher mucus plug score had worse pulmonary function parameters, more advanced lung emphysema on lung emphysema quantification, without affecting life quality parameters. Interestingly, a decrease in BMI was associated with a higher mucus burden.

A strong association between lower FEV1 and lower BMI in COPD patients—linked to increased mortality—has been previously described [24]. In our analysis, we observed an association between mucus burden and BMI in the regression models, both with and without adjustment for the emphysema score of the target lobe. Multiple mechanisms have been suggested for this relationship, including increased resting energy expenditure, non-respiratory skeletal muscle atrophy due to reduced peripheral oxygen supply, and systemic inflammation [25–28]. Furthermore, the recent publication by Diaz et al. reported an overall decline in lung function parameters, higher emphysema scores, and lower BMI with increasing mucus burden, along with a higher risk of mortality in patients with a high mucus burden [12]. Our study similarly demonstrates a decline in lung function parameters and BMI with increasing mucus burden in a cohort of patients with very advanced lung emphysema. Importantly, our results also reveal a novel finding: a strong association between BMI and mucus burden, both of which serve as indicators of increased mortality in COPD.

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The mucus plug score is a helpful and reproducible radiological biomarker in quantifying mucus plugs in medium to large sized airways demonstrated by an almost perfect agreement in our analysis, which is in line with previous publications [10,23]. In our study, the distribution of mucus burden was similar to that reported by Diaz et al. from the COPD Gene Study cohort: approximately 50% of cases exhibited low mucus plug scores (0), about 25% showed intermediate scores (1–2), and roughly 25% demonstrated high scores (≥3). In the COPD Gene Study, around 40% of patients were active smokers [12]. In contrast, among subjects from the SPIROMICS cohort reported by Dunican et al., a very high mucus plug score (MPS ≥5) was observed in 50–60% of patients with severe COPD (GOLD III/IV). Notably, in the SPIROMICS cohort, 17.8% of patients with GOLD IV and 30.1% of those with GOLD III were current smokers. Dunican et al. also found that higher MPS was associated with smoking and that mucus plugs and lung emphysema had a similar impact on airflow obstruction (FEV1) and resting hypoxemia [10]. In the mucus plug study by Dunican et al., 400 patients with COPD across all GOLD stages and 20 never-smokers were included. Although the majority of cases were COPD GOLD III (51%) and IV (15%), the remaining 34% comprised patients with COPD GOLD I and II [10]. Similarly, the larger patient cohort from Diaz et al. (n = 4363) included all stages of COPD irrespective of clinical phenotype—specifically, 72% of patients had COPD GOLD I and II, 20% had GOLD III, and 8% had GOLD IV [12]. In contrast, our study population consisted exclusively of non-smokers with advanced COPD (GOLD III–IV) and the clinical subtype of lung emphysema, with approximately one-third of patients having COPD GOLD III and two-thirds having COPD GOLD IV. Dunican et al. report a higher degree of mucus plugging than Diaz, whose findings align with ours. It remains unclear whether the lower mucus plugging observed in our study is due to the inclusion of only non-smokers or a selection bias, as we included only patients with clinically predominant lung emphysema.

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Furthermore, more advanced stages of COPD in our study were associated with overall worse lung function parameters compared to those reported in other studies. Consistent with previous publications, a higher mucus burden was strongly correlated with lower FEV1, VC, and DLCO [10,12]. Notably, no differences in RV were observed among the three groups, even though both the emphysema score in the target lobe and the heterogeneity index increased with a higher mucus burden. This suggests that quantitative emphysema measures may more precisely characterize differences in patients with advanced COPD and lung emphysema than RV alone. The data showed a higher heterogeneity index in patients with greater mucus burden. While the underlying reason is not entirely clear, this finding likely reflects more extensive emphysema and more severely impaired lung function in this patient group. Additionally, there were no differences in the 6-minute walk test (6-MWT) and pCO2 between the groups in our study. While previous studies have demonstrated an association between mucus burden and six-minute walk test (6-MWT) performance, our data did not replicate these findings. The most likely explanation is that our study population consisted exclusively of patients with very advanced stages of COPD, potentially limiting the variability in exercise capacity[12,23].

Symptoms reported by the CAT score and mMRC were comparable in all three groups, highlighting the observation that an increase in mucus plugs does not correlate with an increase in mucus burden [11].

These findings suggest that the mucus plug score should be used to evaluate patients with advanced lung emphysema presenting for lung volume reduction therapy for individual risk stratification. Additionally, our results support that these patients might benefit from airway clearance techniques and inhaled mucokinetic or mucolytic therapies such as hypertonic saline or novel reducing agents that are currently in clinical testing for COPD [29,30].

The main limitations of this study are its retrospective monocentric design and the relatively small sample size. However, by focusing exclusively on patients with advanced COPD and

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lung emphysema, the study provides a detailed overview of mucus burden in this specific patient group. Unfortunately, our data does not show to what extent mucus plugs influence lung volume reduction therapies, such endoscopic lung volume reduction therapy with valves. More research is needed to elucidate these questions.

This study demonstrates that high mucus burden is present in patients with advanced lung emphysema—a subgroup of patients with COPD in which its impact may have been previously underestimated. Our data also corroborate previous findings that mucus plugs are associated with worse lung function parameters due to increased airflow obstruction. Notably, this is the first study to link a higher mucus plug score with a lower BMI. This observation is particularly relevant given recent findings associating higher mucus burden with increased mortality, and that lower FEV1 and lower BMI are both independent risk factors for mortality in COPD patients. Furthermore, it highlights the heterogeneity of COPD and the significant overlap between lung emphysema and chronic bronchitis, two clinical entities once considered distinct. These findings underscore the need to explore novel treatment strategies to target mucus plugging for personalized, risk-stratified management of patients with advanced COPD and lung emphysema. Our results also raise the question of whether mucus burden should be routinely evaluated in all patients with advanced COPD and lung emphysema presenting for lung volume reduction therapy.

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ChatGPT (OpenAI) was used to assist with language refinement and grammar to improve the readability of the manuscript. AI was not used to generate content. The authors reviewed and approved all AI-assisted content.

Statement of Ethics

The research presented in this article was conducted according to the standards of the World Medical Association Declaration of Helsinki and the appropriate guidelines for human studies. All data were derived from prospective open-label clinical studies in our institution which were approved by the Ethics Committee of the Charité Universitätsmedizin Berlin, Germany (EA2/149/17 and EA1/136/13). All patients consented to participation. Inability to sign the consent form was an exclusion criterion.

Conflict of interest

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Data Availability Statement

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Data can be made available on request to the corresponding author.

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References

1. Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet*. 2022;400(10356):921-972. doi:10.1016/S0140-6736(22)01273-9

2. Hogg JC, Chu F, Utokaparch S, et al. The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2004;350(26):2645-2653. doi:10.1056/NEJMoa032158

3. Agustí A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2019;381(13):1248-1256. doi:10.1056/NEJMra1900475

4. Booth S, Hsieh A, Mostaco-Guidolin L, et al. A Single-Cell Atlas of Small Airway Disease in Chronic Obstructive Pulmonary Disease: A Cross-Sectional Study. *Am J Respir Crit Care Med*. 2023;208(4):472-486. doi:10.1164/rccm.202303-0534OC

5. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. 2011;365(17):1567-1575. doi:10.1056/NEJMoa1106955

6. Innes AL, Woodruff PG, Ferrando RE, et al. Epithelial mucin stores are increased in the large airways of smokers with airflow obstruction. *Chest*. 2006;130(4):1102-1108. doi:10.1378/chest.130.4.1102

7. Leopold PL, O'Mahony MJ, Lian XJ, Tilley AE, Harvey BG, Crystal RG. Smoking is associated with shortened airway cilia. *PLoS One*. 2009;4(12):e8157. doi:10.1371/journal.pone.0008157

8. Verra F, Escudier E, Lebargy F, Bernaudin JF, De Crémoux H, Bignon J. Ciliary abnormalities in bronchial epithelium of smokers, ex-smokers, and nonsmokers. *Am J Respir Crit Care Med*. 1995;151(3 Pt 1):630-634. doi:10.1164/ajrccm/151.3_Pt_1.630

9. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med*. 2010;363(23):2233-2247. doi:10.1056/NEJMra0910061

10. 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(8):957-968. doi:10.1164/rccm.202006-2248OC

Published online October 3, 2025 https://doi.org/10.15326/jcopdf.2025.0617

11. Mettler SK, Nath HP, Grumley S, et al. Silent Airway Mucus Plugs in COPD and Clinical Implications. *Chest*. Published online November 25, 2023:S0012-3692(23)05825-7. doi:10.1016/j.chest.2023.11.033

12. Diaz AA, Orejas JL, Grumley S, et al. Airway-Occluding Mucus Plugs and Mortality in Patients With Chronic Obstructive Pulmonary Disease. *JAMA*. 2023;329(21):1832-1839. doi:10.1001/jama.2023.2065

13. Divo MJ, Cabrera C, Casanova C, et al. Comorbidity Distribution, Clinical Expression and Survival in COPD Patients with Different Body Mass Index. *Chronic Obstr Pulm Dis*. 2014;1(2):229-238. doi:10.15326/jcopdf.1.2.2014.0117

14. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208

15. Lenga P, Grah C, Ruwwe-Glösenkamp C, et al. Endoscopic Lung Volume Reduction with One-Way Valves in Patients with Severe Chronic Obstructive Pulmonary Disease with Hypercapnia. *Respiration*. Published online 2022. doi:10.1159/000524996

16. Thomas Sgarbossa, Pavlina Lenga, Franz Stanzel, et al. Assessment of efficacy and safety of endoscopic lung volume reduction with one-way valves in patients with a very low FEV_1. *erjor*. Published online January 1, 2023:00190-02023. doi:10.1183/23120541.00190-2023

17. Lenga P, Ruwwe-Glösenkamp C, Grah C, et al. Endoscopic lung volume reduction with endobronchial valves in very low D (LCO) patients: results from the German Registry - Lungenemphysemregister e.V. *ERJ Open Res*. 2021;7(1):00449-02020. doi:10.1183/23120541.00449-2020

18. Saccomanno J, Hübner R, Lenga P, Gloesenkamp C, Suttorp N, Witzenrath M. *Vergleich Der Chartismessung Unter Spontanatmung Und Hochfrequenz-Jet-Ventilation Zur Evaluation Einer Kollateralventilation Vor Endoskopischer Lungenvolumenreduktion*. Vol 74.; 2020. doi:10.1055/s-0039-3403240

19. Saccomanno J, Kilic L, Sgarbossa T, et al. Clinical Improvements after Endoscopic Lung Volume Reduction with Valves in Patients with advanced Emphysema and a 6-Minute-Walk-Test ≤140 m at Baseline. *erjor*. Published online January 1, 2024:00410-02024. doi:10.1183/23120541.00410-2024

Published online October 3, 2025 https://doi.org/10.15326/jcopdf.2025.0617

20. Saccomanno J, Hübner RH, Witzenrath M, et al. Bronchoscopic Measurement of Collateral Ventilation: State of the Art. *Respiration*. Published online 2023. doi:10.1159/000528419

21. Saccomanno J, Sgarbossa T, Pappe E, et al. VT20 Method for Chartis® Assessment of Collateral Ventilation with Flexible Bronchoscopy Under Procedural Sedation. *erjor*. Published online January 1, 2024:00945-02023. doi:10.1183/23120541.00945-2023

22. Koster TD, Klooster K, McNamara H, et al. An adjusted and time-saving method to measure collateral ventilation with Chartis. *ERJ Open Res*. 2021;7(3):00191-02021. doi:10.1183/23120541.00191-2021

23. Dunican EM, Elicker BM, Gierada DS, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest*. 2018;128(3):997-1009. doi:10.1172/JCI95693

24. Wada H, Ikeda A, Maruyama K, et al. Low BMI and weight loss aggravate COPD mortality in men, findings from a large prospective cohort: the JACC study. *Sci Rep*. 2021;11(1):1531. doi:10.1038/s41598-020-79860-4

25. Sergi G, Coin A, Marin S, et al. Body composition and resting energy expenditure in elderly male patients with chronic obstructive pulmonary disease. *Respir Med*. 2006;100(11):1918-1924. doi:10.1016/j.rmed.2006.03.008

26. Wagner PD. Possible mechanisms underlying the development of cachexia in COPD. *Eur Respir J*. 2008;31(3):492-501. doi:10.1183/09031936.00074807

27. Agustí AGN, Sauleda J, Miralles C, et al. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166(4):485-489. doi:10.1164/rccm.2108013

28. Agustí AGN, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21(2):347-360. doi:10.1183/09031936.03.00405703

29. Mall MA. Unplugging Mucus in Cystic Fibrosis and Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. 2016;13 Suppl 2:S177-185. doi:10.1513/AnnalsATS.201509-641KV

Published online October 3, 2025 https://doi.org/10.15326/jcopdf.2025.0617

30. Addante A, Raymond W, Gitlin I, et al. A novel thiol-saccharide mucolytic for the treatment of muco-obstructive lung diseases. *Eur Respir J.* 2023;61(5). doi:10.1183/13993003.02022-2022

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Inclusion Criteria of the German Lung Emphysema Registry e.V.

Table 1: Inclusion Criteria

Criteria	Specification
FEV_1	< 50% of predicted value
RV	> 150% of predicted value
DLCO	No restriction
6-MWT	< 450 meters
Smoking Status	Non-smoker ≥ 3 months; confirmed by COHb < 2%
pCO_2	< 55 mmHg (mild hypercapnia allowed)

FEV1: Forced expiratory capacity in the first second. RV: Residual Volume. DLCO: Diffusing capacity of the lungs for carbon monoxide. pCO2: Partial pressure of carbon dioxide. 6-MWT: 6 Minute Walk Test.

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Table 2: Patient Characteristics

	MPS 0	MPS 1+2	MPS ≥3	p
Baseline CT (n)	66	31	30	
Mucus Plug Score (n)	0.0 ± 0.0	1.4 ± 0.5	5.4 ± 3.3	**<0.001**
Age (years)	66.5 ± 6.8	65.9 ± 6.4	64.1 ± 7.9	0.340
Sex, n (%)				
Male	49 (75)	15 (48%)	12 (41)	
Female	17 (25)	16 (52)	17 (59)	**0.002**
Body Mass Index	26.3 ± 3.0	21.8 ± 0.8	18.1 ± 1.9	**<0.001**
Emphysema score target lobe, %	42.4 ± 11.7	43.8 ± 11.2	51.5 ± 12.1	**0.005**
Heterogeneity index, %	13.7 ± 10.4	12.3 ± 9.9	19.9 ± 14.2	**0.029**
FEV1, L	0.8 ± 0.3	0.7 ± 0.2	0.6 ± 0.2	**<0.001**
FEV1, %	28.1 ± 7.5	25.3 ± 7.1	23.8 ± 7.2	**0.023**
VC IN, L	2.3 ± 0.7	1.9 ± 0.5	1.8 ± 0.7	**<0.001**
VC IN, %	59.7 ± 12.7	57.4 ± 13.8	52.2 ± 15.0	0.053
RV, L	5.1 ± 1.2	5.1 ± 1.2	4.8 ± 1.1	0.541
RV, %	215.1 ± 47.8	225.1 ± 42.5	222.5 ± 49.4	0.573
DLCO SB in mmol/min/kPa	3.2 ± 1.6	2.1 ± 0.8	1.9 ± 0.8	**<0.001**
DLCO SB, %	35.0 ± 14.8	26.1 ± 9.2	22.7 ± 9.3	**<0.001**
pCO2, mmHg	39.5 ± 5.4	40.1 ± 11.4	42.1 ± 6.7	0.326
6-MWT, m	219.8 ± 105.4	262.2 ± 98.7	221.8 ± 104.0	0.167
CAT Score, points	25.1 ± 6.2	25.4 ± 6.2	27.5 ± 6.2	0.236
mMRC, points	3.2 ± 0.8	3.2 ± 0.7	3.4 ± 0.8	0.579
GOLD Stage				
Stage III	27 (42)	7 (23)	4 (14)	

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Stage IV	38 (58)	24 (77)	25 (86)	**0.014**
Exacerbations (n)	1.8 ± 1.4	1.4 ± 2.0	2.0 ± 2.0	0.409

CT – Computed Tomography, MPS – Mucus Plug Score, FEV1: Forced expiratory capacity in the first second. L: Liters. RV: Residual volume. DLCO: Diffusing capacity of the lungs for carbon monoxide. pCO2: Partial pressure of carbon dioxide. 6-MWT: 6 Minute Walk Test. CAT: COPD Assessment Test (CAT) Score. mMRC: Modified Medical Research Council. Data represented as mean ± SD. Highlighted p-value indicates statistically significant results.

Missing data: Sex (2 missing), age (3 missing), BMI (1 missing), emphysema score (16 missing), heterogeneity index (16 missing) FEV1, L (2 missing), FEV1, % (2 missing), VC IN, L (4 missing), VC IN, % (4 missing), RV, L (3 missing), RV, % (3 missing), DLCO SB in mmol/min/kPa (8 missing), DLCO SB, % (5 missing), pCO2, mmHg (12 missing), 6-MWT, m (9 missing), CAT Score, points (8 missing), mMRC, points (8 missing), GOLD Stage (2 missing)

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Table 3: Multivariable logistic analysis for mucus plugs including emphysema

Variables	Coefficient	Std. Error	p-value	Wald	95% CI	
Gender	-0.018	0.711	0.980	0.001	-1.734	1.411
Age	-0.049	0.058	0.396	0.720	-0.162	0.064
Body Mass Index	-1.584	0.294	**<0.001**	28.930	-2.161	-1.007
Emphysema in target lobe, %	0.000	0.028	0.994	0.000	-0.056	0.056
FEV1, %	0.023	0.057	0.682	0.167	-0.088	0.135
6-MWT, m	0.003	0.004	0.477	0.505	-0.005	0.011
n	103					

FEV1: Forced expiratory capacity in the first second. 6-MWT: 6-minute walk test

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Table 4: Multivariable logistic analysis for mucus plugs excluding emphysema

Variables	Coefficient	Std. Error	p-value	Wald	95% CI	
Gender	-0.149	0.706	0.832	0.045	-1.532	1.234
Age	-0.032	0.049	0.832	0.426	-0.129	0.064
Body Mass Index	-1.724	0.305	**<0.001**	32.039	-2.321	-1.127
FEV1, %	0.046	0.052	0.377	0.780	-0.057	0.149
6-MWT, m	0.003	0.004	0.447	0.577	-0.005	0.011
n	114					

FEV1: Forced expiratory capacity in the first second. 6-MWT: 6-minute walk test

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Figure 1:

Patient with advanced COPD. Multiplanar reconstruction (A: parasagittal, B paracoronal, C paratransversal orientation with orientation cubes in the left lower corner of each image) in 1mm slice thickness in a lung window (center -500 HE, width 1500 HE). The yellow bar in each image indicates the length of 5 cm. The mucus plug is outlined by yellow arrows in each image.

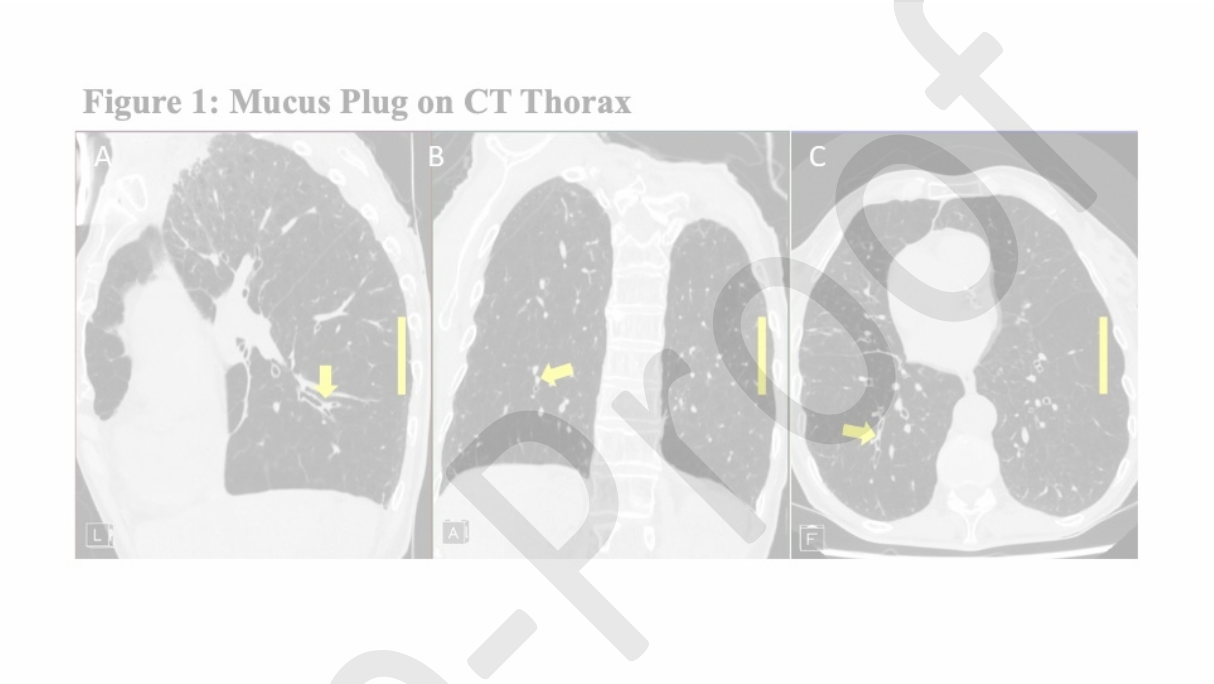

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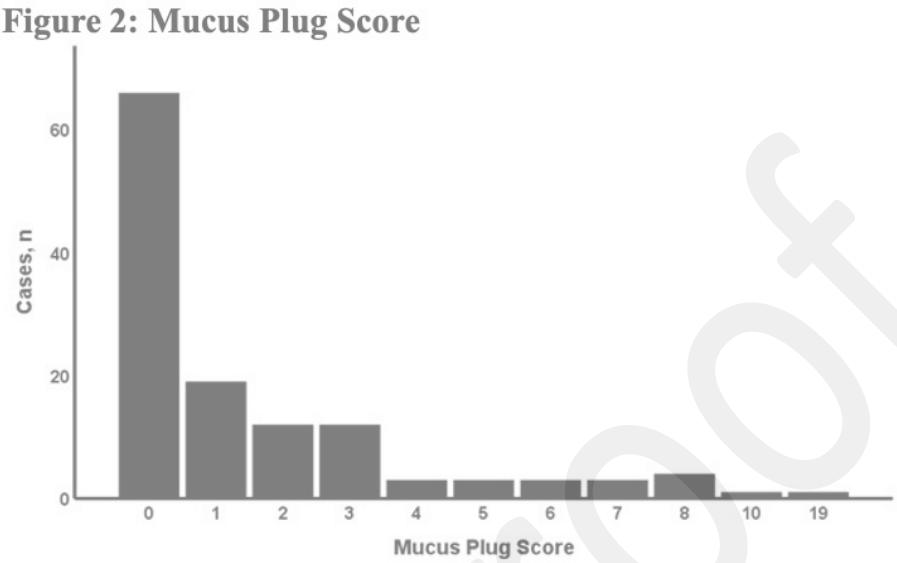
Figure 2:

Frequency of mucus plug score in patients with advanced COPD GOLD III/IV and emphysema



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