ORIGINAL RESEARCH

Correlation of Luminal Mucus Score in Large Airways with Lung Function and Quality of Life in Severe Acute Exacerbation of COPD: A Cross-Sectional Study

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Background and Objective: Luminal mucus plugging in small airways is associated with lung function decline and death of patients with chronic obstructive pulmonary disease (COPD). However, little attention has been paid to the possible role of mucus in large airways in acute exacerbation of COPD (AECOPD). Therefore, this study aimed to explore the relationship between the luminal mucus score of large airways and other physiological parameters of severe AECOPD.

Subjects and Methods: A total of 74 AECOPD inpatients were enrolled in this cross-sectional study. All patients underwent lung function tests and bronchoscopy, and their luminal mucus was observed and scored through bronchoscopy. Four questionnaires, including the St. George Respiratory Questionnaire (SGRQ), modified Medical Research Council dyspnea scale (mMRC), COPD Assessment Test (CAT) and Exacerbation of Chronic pulmonary disease Tool (EXACT), were used to assess health-related quality of life (HRQoL).

Results: The luminal mucus score of large airways was significantly correlated with spirometry parameters and HRQoL score. Both mMRC grade and SGRQ score were significantly positively correlated with luminal mucus score (ρ=0.527, P<0.001; ρ=0.441, P<0.001, respectively). Forced expiratory flow at 25% to 75% of the FVC (FEF$_{25\%-75\%}$) and FEV$_1$% predicted, as functional measures reflecting small airway disease, were significantly negatively correlated with luminal mucus score (ρ=−0.518, P<0.001; ρ=−0.498, P<0.001, respectively). The stepwise multiple linear regression model suggested that mMRC grade and FEV$_1$% predicted could predict luminal mucus score (R^2=0.348, F=18.960, P<0.001).

Conclusion: For severe acute exacerbation of COPD, bronchoscopy-identified luminal mucus in large airways is associated with reduced lung function and worse health-related quality of life.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, luminal, mucus, bronchoscopy

Introduction

Mucus dysfunction is a major pathophysiological feature of chronic obstructive pulmonary disease (COPD), and is manifested by excessive production of mucus and luminal occlusion.[1] Mucous exudates in small airways are related to reduced lung function and increased mortality in COPD patients, as confirmed by pathological examination of isolated lung tissue.[2] In large airways (> 2 mm in diameter), it has been observed by CT that the luminal plugging is related to airflow obstruction, poor health-related quality of

life (HRQoL) and emphysema phenotype.[3] However, whether the luminal plugging identified by CT is caused by mucus or not remains to be confirmed by bronchoscopy.

Acute exacerbation of COPD (AECOPD), which is characterized by a worsening of respiratory symptoms such as dyspnea, increased sputum volume, and purulence, is the leading cause of hospitalization and death from the disease.[4] However, little attention has been paid to the possible role of the mucus in large airways in exacerbations. It was found that a bronchitis index score, determined by secretions, erythema, edema, and friability via bronchoscopy, was significantly higher in patients with chronic bronchitis than in normal subjects.[5] Therefore, we hypothesized that the luminal mucus in large airways may also be strongly correlated with traditional indices of AECOPD.

The main purpose of the present study was to explore the relationship of bronchoscopy-identified luminal mucus score (LMS) in large airways of inpatients with functional parameters which reflected the severity of AECOPD, including lung function, HRQoL score, and laboratory findings.[4] In addition, clinical indicators that could be more easily measured were tested to predict LMS in large airways, because bronchoscopy is an invasive procedure.

Subjects and Methods
Subjects
This cross-sectional study was conducted in Meizhou People's Hospital in Guangdong, China, from May 2020 to January 2021. A total of 90 inpatients clinically diagnosed with AECOPD were screened consecutively, and 74 of them were enrolled into the study. The screening process for participants is shown in Figure 1.

The inclusion criteria were as follows: (1) a postbronchodilator FEV_1/FVC ratio less than 0.7; (2) diagnosis of AECOPD, defined as:[6] two major symptoms (dyspnea, increased sputum volume or purulent sputum), or one major symptom, combined with at least one secondary symptom (wheezing, chills, fever, sore throat or cough); (3) written informed consent obtained before participating in the study. Exclusion criteria were as follows: (1) contraindication(s) existing for bronchoscopy or lung function test; (2) patients with known respiratory diseases other than COPD, including sarcoidosis, active tuberculosis, pulmonary fibrosis, cystic fibrosis, or diseases that could significantly affect clinical evaluation according to the judgment of investigators; (3) diagnosis of lung cancer, including current and recent 5-year diagnoses; (4) presence of nervous system diseases affecting the ability to expectorate; (5) lack of the ability to read and understand Mandarin.

Protocol
On the first day of admission, complete blood count, C-reactive protein (CRP), four items of coagulation (prothrombin time, activated partial thromboplastin time, thrombin time, and fibrinogen), and an electrocardiogram were completed. The HRQoL assessment,[7] including the modified Medical Research Council dyspnea scale
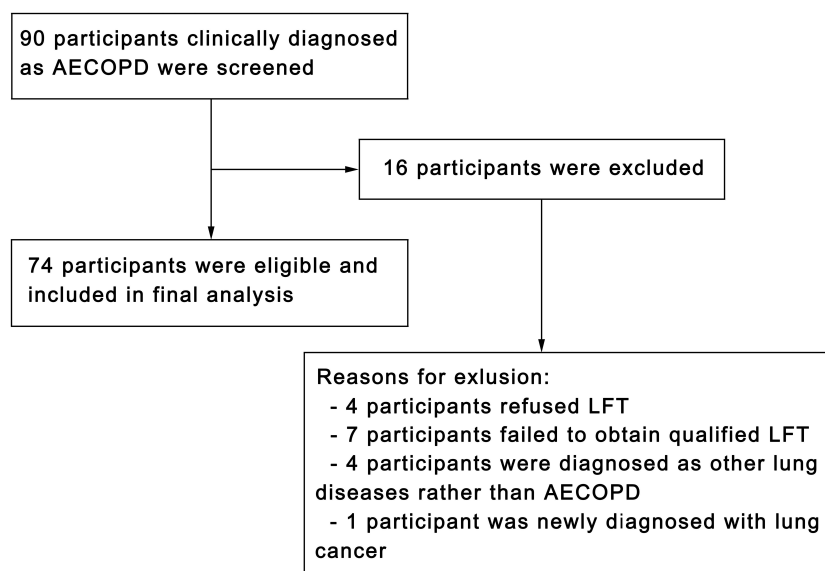

Figure 1 Flowchart of participant inclusion in the study.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; LFT, lung function test.

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(mMRC), St. George Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and EXAcerbation of Chronic pulmonary disease Tool (EXACT) questionnaires, was completed on the second day. A bronchoscopy was performed immediately after the HRQoL assessment, and a lung function test was performed within 12 to 48 hours after the bronchoscopy. The research process did not interfere with patient-management decisions. This study was registered with the Chinese Clinical Trial Registry (Registration Number: ChiCTR2000033101).

Bronchoscopy and Luminal Mucus Scoring

The bronchoscopy was performed by Yang, according to the guidance of the Chinese Medical Association.[8] The entire examination under the bronchoscope was recorded by a video processor (CV-290 EVIS LUCERA ELITE, Olympus, Tokyo, Japan). All patients were examined using the same bronchoscope (BF-Q290, Olympus, Tokyo, Japan). Patients without contraindications received intravenous midazolam for conscious sedation 10 minutes before the operation, and the total dose did not exceed 10 mg. Before the bronchoscope passed the vocal cords and was introduced to the airways, 2% lidocaine was sprayed through the working channel, and the total dose did not exceed 5mg/kg. The mucus observed under the bronchoscope was removed. Based on the clinical needs, we performed lavage and/or biopsy, and collected specimens for microbiological and/or cytological examinations. The patients' blood pressure, pulse oxygen saturation, heart rate and respiratory rate were monitored throughout operations as appropriate.

The video file was named with the corresponding subject number instead of the patient's name or other information. Zeng who was blinded to the other clinical data of the patient scored the luminal mucus based on the video. Regarding the scoring system, Thompson et al[5] proposed one involving six sites, including five lobes and the lingula. We used this scoring system with the addition of another four center airways which were involved, including the trachea, right main bronchus, left main bronchus, and right middle bronchus. The luminal mucus was scored from 0 to 3 points (0=normal, 3=severely abnormal), and thus the total LMS ranged from 0 to 30 points (Figure 2). The mucus was scored based on the most severe segment in each lobe and the lingula, and based on the most severe

section in the center airway, regardless of the airway length involved.

Lung Function Test

The lung function test was performed using an electronic spirometer (microQuark PFT, Cosmed, Rome, Italy), according to the guidance published by the American Thoracic Society and European Respiratory Society.[9] After four to six restful breaths, the patients were asked to inhale as much air as possible to total lung capacity (TLC), and then breathe out with the maximum effort for at least six seconds to the residual volume (RV); the volume of exhalation was the forced vital capacity (FVC). After inhaling 400 μg of Ventolin and then waiting for 20 minutes, spirometry was repeated. Only postbronchodilator spirometric parameters were adopted in this analysis.

Chronic Bronchitis

Chronic bronchitis was defined as productive cough present during most days or nights for at least 3 months of the year for ≥2 consecutive years. Chronic bronchitis was considered to be present when patients answered the following question positively: "Did you cough up phlegm (during most days or nights) for at least 3 months each year during the past 2 years?"[10]

Health-Related Quality of Life

Health-related quality of life (HRQoL) questionnaires were used to assess the quality of life.[7] Altogether we used four different questionnaires, including mMRC, SGRQ, CAT, and EXACT. The mMRC score is used to assess the degree of dyspnea in COPD patients, which ranged from 0 to 4 points.[11] The SGRQ score, ranging from 0 to 100 points, is widely applied to evaluate airway diseases resulting in a decline in HRQoL.[12] CAT is a validated questionnaire containing eight items to evaluate and quantify the impact of symptoms on the health status of COPD patients.[4] EXACT is used to directly measure the patient-reported symptoms of exacerbations and to conduct standardized assessment of patients' condition.[13] Subjects were asked to choose the description that best matched their symptoms, or their degree of agreement with each statement. Yang was available to provide explanations if required, but he did not give any suggestions or answers. For all four questionnaires, a higher grade or score indicated a worse quality of life.
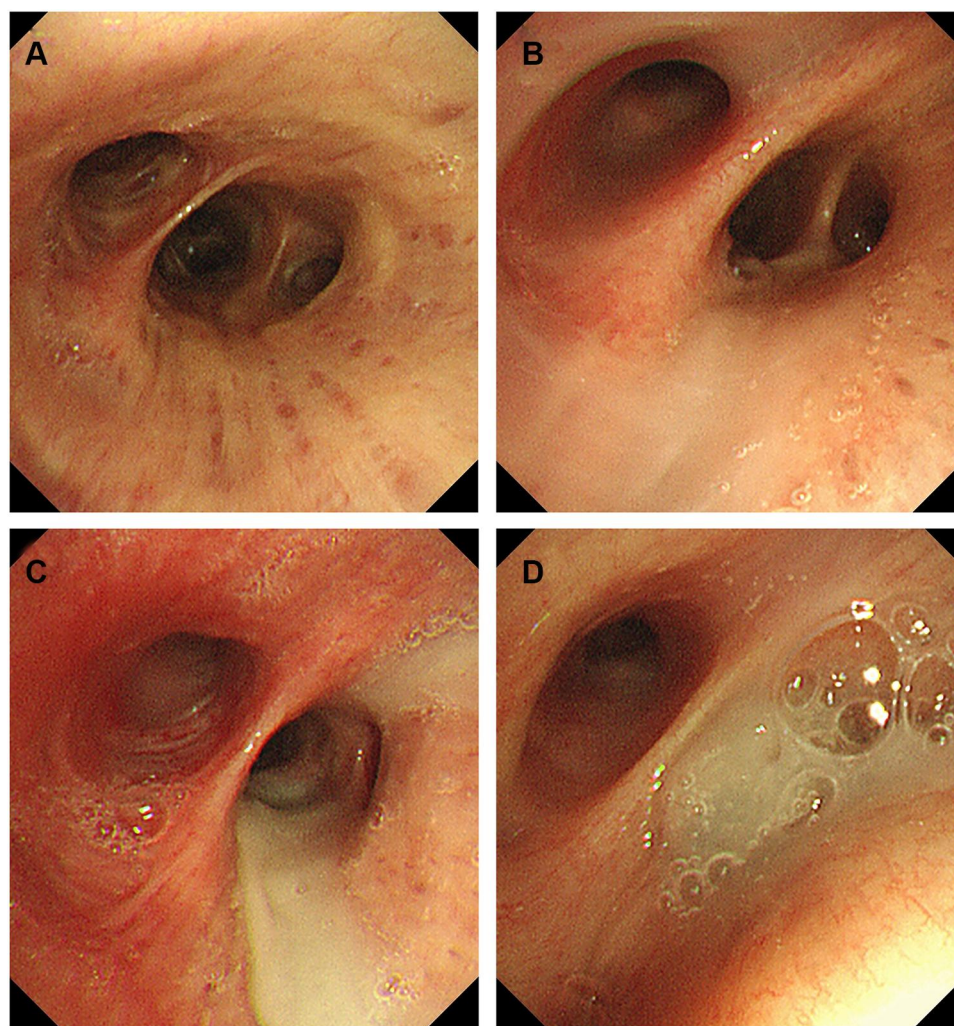
Figure 2 Bronchoscopic findings at the bronchial entrances of the right middle and lower lobe showing the luminal mucus scoring. (**A**) Score 0, normal; (**B**) score 1, strands of clear mucus; (**C**) score 2, globules of mucus; (**D**) score 3, airway occluded.

Study Size

We estimated a sample of 72 participants, calculated based on the reported prevalence of 25% of luminal mucus plug in large airways,[3] with 10% precision (95% CI). We also estimated that 20% of patients would not be able to complete bronchoscopy or lung function tests, and we therefore planned to recruit 90 subjects.

Statistical Analyses

All results were presented with descriptive data. Results were expressed by mean ± SD or median (IQR 25–75) as appropriate. Based on the data distribution, differences in parameters between the in- and excluded patients were tested by the t-test or Wilcoxon rank sum test. Spearman's rank correlation coefficient was used to

evaluate the correlation of LMS with lung function parameters, HRQoL scores, and laboratory findings; the correlation coefficient was expressed as ρ. Indicators that showed significantly correlation were used as potential covariates in the later multiple linear regression analysis. The stepwise regression algorithm was used for multiple linear regression analysis to further test the relationship between the total LMS in large airways and many other variables. Body mass index (BMI), partial pressure of carbon dioxide ($PaCO_2$), FVC, FVC % predicted, FEV_1, FEV_1% predicted, FEV_1/FVC, peak expiratory flow (PEF), forced expiratory flow at 25% to 75% of the FVC ($FEF_{25\%-75\%}$), mMRC grade, SGRQ score, CAT score, and EXACT score were included in the model as covariates. A two-sided P-value less than 0.05 was considered statistically significant. In addition, in the correlation analysis,

Bonferroni correction was applied to re-determine the α value. IBM SPSS Statistics 13.0 (IBM Corporation, Armonk, NY, USA) was used to process and analyze all data.

Ethics Statement

We carried out this study in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Meizhou People's Hospital (approval number: 2020-C-07). Written informed consent was obtained from all participants.

Results

Clinical characteristics of patients are summarized in Table 1, and show that there was no statistically significant difference between the included and excluded patients (P>0.05). Of the 74 included patients, 73 (98.7%) were male. The average age was 68.2±6.3 years. Bacterial culture of the bronchoalveolar lavage fluid (BALF) and/or sputum revealed positive findings in four patients; two patients tested positive for *Pseudomonas aeruginosa*, while the remaining two patients tested positive for *Klebsiella pneumoniae*. The serum procalcitonin (PCT) level was >0.25 μg/L in two patients. During hospitalization, none of patients died or received invasive mechanical ventilation, one patient was admitted to the ICU, and five patients received noninvasive positive pressure ventilation (NPPV). The median duration of hospital stay was 5.0 (IQR 25–75, 5.0–7.0).

The median total LMS was 15.0 (IQR 25–75, 12.0–21.0). In at least one site, 58 (78.4%) patients had luminal mucus plugging — score of 3 for the corresponding site. Results of postbronchodilator lung function are presented in Table 2. The median $FEF_{25\%-75\%}$ and FEV_1% predicted, reflecting small airway disease, were 0.42 L/sec (IQR 25–75, 0.30–0.62 L/sec) and 39.6 (IQR 25–75, 29.8–52.4), respectively.

Relationship Between Total LMS and Other Parameters

Table 3 demonstrates results of the correlation analysis of total LMS with lung function parameters and HRQoL scores (CAT, mMRC, EXACT, SGRQ). Among demographic characteristics, BMI, hospital stay, and presence of chronic bronchitis were weakly correlated with total LMS (ρ=−0.269, P=0.020; ρ=0.257, P=0.027; and ρ=0.300, P=0.009, respectively), while age and amount of smoking were not significantly correlated with total LMS.

Scores of all four questionnaires (CAT, mMRC, EXACT and SGRQ) were significantly positively correlated with total LMS, among which correlation coefficients between total LMS and scores of mMRC and SGRQ were relatively high (ρ=0.527, P<0.001; ρ=0.441, P<0.001, respectively) (Figure 3). Parameters of postbronchodilator lung function were significantly negatively correlated with total LMS, and among them, $FEF_{25\%-75\%}$ and FEV_1% predicted showed strong correlation with total LMS (ρ=−0.518, P<0.001; ρ=−0.498, P<0.001, respectively) (Figure 3). Of these laboratory findings, only $PaCO_2$ was weakly positively correlated with total LMS (ρ=0.273, P=0.018), while serum CRP levels and counts of neutrophils, lymphocytes, eosinophils showed no correlation with total LMS.

In order to reduce the risk of type I errors in the correlation analysis of multiple indicators, Bonferroni correction was used to determine a stricter α level of 0.0023 (0.05/22), which was adopted to reassess the correlations between total LMS and other parameters. At the new test level, total LMS showed significant correlation with mMRC, EXACT, SGRQ and spirometric parameters.

Relationship of LMS in Various Lobes with FEV_1% Predicted and mMRC Grade

The relationship of LMS in various lobes with FEV_1% predicted and mMRC grade is presented in Table 4. Nine lobes were examined, including the right upper lobe bronchus (RULB), right middle lobe bronchus (RMLB), right lower lobe bronchus (RLLB), left upper division bronchus (LUDB), lingular bronchus, left lower lobe bronchus (LLLB), bilateral upper lobe bronchi (RULB and LUDB), RMLB and lingular bronchus, and bilateral lower lobe bronchi (RLLB and LLLB). Except LMS in the RLLB and RULB, LMS in all other lobes was significantly and positively correlated with FEV_1% predicted. With regard to the mMRC grade, with which LMS in the all other lobes except the RLLB showed a significant correlation. At the stricter α level of 0.0027 (0.05/18), which was redetermined by Bonferroni correction, LMS in the LUDB and bilateral ULB was significantly correlated with the FEV_1% predicted; LMS in the RULB, RMLB, LUDB, lingular bronchus, RMLB and lingular bronchus, and bilateral ULB was significantly correlated with mMRC grade.

Table 1 Comparison Between Included and Excluded Patients

Characteristics	Included Patients (n=74)	Excluded Patients (n=16)	Test Statistic	P-value
Demographic factor				
Age (year)	68.2±6.3	67.8±5.6	−0.278	0.782
Sex: male (%)	73(98.7%)	15(93.8%)	0.073	0.787
BMI (kg/m^2)	19.2(17.5–21.9)	19.7(18.1–23.7)	−1.113	0.266
Smoking status				
Never-smoker	1(1.3%)	2(12.5%)	2.204	0.138
Former smoker	37(50.0%)	11(68.8%)	1.858	0.173
Current smoker [a]	36(48.6%)	3(18.7%)	3.649	0.056
Amount of smoking				
Pack-years	56.8±30.1	48.7±26.3	0.946	0.347
Bronchoscopic findings				
Luminal mucus score	15.0(12.0–21.0)	12.0(8.5–20.0)	−1.386	0.166
Quality of life				
CAT score	13.7±8.1	14.1±9.7	−0.171	0.864
mMRC grade	2.0(1.0–2.0)	2.0(1.0–3.0)	−1.124	0.261
EXACT score	15.9±8.7	17.5±8.5	−0.737	0.463
SGRQ score	49.8(38.4–63.0)	56.4(32.4–72.0)	−1.040	0.299
Complete blood count test				
White blood cell (10^9/L)	7.6(6.4–9.7)	8.3(6.6–10.3)	−0.776	0.438
Neutrophil (10^9/L)	5.1(4.1–7.0)	5.9(4.5–8.3)	−0.934	0.350
Lymphocyte (10^9/L)	1.5(1.2–1.8)	1.4(1.0–1.7)	−0.787	0.431
Eosinophil (10^9/L)	0.2(0.1–0.3)	0.2(0.0–0.3)	−0.706	0.480
Red blood cell (10^{12}/L)	4.7(4.4–5.0)	4.5(4.4–4.7)	−1.219	0.223
Hemoglobin (g/L)	144.0(135.0–152.0)	141.5(131.3–149.8)	−0.417	0.677
Arterial blood gas test				
PaCO$_2$ (mmHg)	40.5±7.0	42.1±11.1	−0.680	0.551
Lactic acid (mmol/L)	1.3(1.1–1.7)	1.2(0.9–1.6)	−0.889	0.374
Other laboratory findings				
C-reactive protein (mg/L)	2.2(1.3–10.9)	4.5(1.8–41.8)	−1.314	0.189
Albumin (g/L)	37.6±3.9	37.2±3.4	0.414	0.680
Creatinine (umol/L)	70.3(60.0–80.2)	70.7(62.3–89.1)	−0.575	0.565
Blood urea nitrogen (mmol/L)	5.7(4.4–7.3)	5.3(4.1–7.4)	−0.566	0.571
Fbrinogen (g/L)	3.6(3.1–4.6)	3.9(2.9–5.2)	−0.359	0.720
Other clinical parameters				
Hospital stay (day)	5.0(5.0–7.0)	6.0(4.3–7.8)	−0.757	0.449
ICU admission	1(1.3%)	1(6.2%)	0.073	0.787
NPPV	5(6.8%)	2(12.5%)	0.069	0.792

Notes: [a]Current smoking was defined as having smoked 100 cigarettes in one's lifetime and smoking for the 6 months before the screening. Results are expressed as mean ± SD or median (IQR 25–75) as appropriate.
Abbreviations: BMI, body mass index; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; mMRC, modified Medical Research Council dyspnea scale; EXACT, EXAcerbations of Chronic Pulmonary Disease Tool; SGRQ, St George's Respiratory Questionnaire; PaCO2, partial pressure of carbon dioxide in artery; ICU, intensive care unit; NPPV, noninvasive positive pressure ventilation.

Stepwise Multiple Regression Analysis

Stepwise multiple linear regression was performed to identify factors that could be used to predict luminal mucus. In the final regression model, mMRC score and FEV_1% predicted were significant factors (R^2=0.348, F=18.960, $P<0.001$). Results of multiple linear regression are shown in Table 5.

Table 2 Postbronchodilator Lung Function of 74 COPD Patients

Spirometric Parameters	n=74
FVC (L)	2.24±0.56
FVC % predicted	68.9±16.4
FEV_1 (L)	0.96(0.73–1.36)
FEV_1% predicted	39.6(29.8–52.4)
FEV_1≥80% predicted, n(%)	2(2.7%)
50%≤FEV_1<80% predicted, n(%)	21(28.4%)
30%≤FEV_1<50% predicted, n(%)	33(44.6%)
FEV_1<30% predicted, n(%)	18(24.3%)
FEV_1/FVC (%)	44.5(40.7–51.8)
PEF (L/sec)	2.52(1.80–3.38)
$FEF_{25\%-75\%}$ (L/sec)	0.42(0.30–0.62)

Note: Results are expressed as mean ± SD or median (IQR 25–75) as appropriate.
Abbreviations: PEF, peak expiratory flow; $FEF_{25\%-75\%}$, forced expiratory flow at 25% to 75% of the FVC.

Table 3 Relationship Between Total Luminal Mucus Score and Other Parameters

Characteristics	ρ	P-value
Age	0.069	0.559
BMI (kg/m^2)	−0.269	0.020[a]
Amount of smoking (pack-years)	0.198	0.091
Chronic bronchitis (yes)	0.300	0.009[a]
CAT score	0.313	0.007[a]
mMRC grade	0.527	<0.001[a]
EXACT score	0.426	<0.001[a]
SGRQ score	0.441	<0.001[a]
Neutrophil (10^9/L)	0.154	0.189
Lymphocyte (10^9/L)	−0.210	0.072
Eosinophil (10^9/L)	0.081	0.492
$PaCO_2$(mmHg)	0.273	0.018[a]
C-reactive protein (mg/L)	0.132	0.215
Fbrinogen (g/L)	0.059	0.619
FVC (L)	−0.437	<0.001[a]
FVC % predicted	−0.460	<0.001[a]
FEV_1 (L)	−0.502	<0.001[a]
FEV_1% predicted	−0.498	<0.001[a]
FEV_1/FVC (%)	−0.446	<0.001[a]
PEF (L/sec)	−0.455	<0.001[a]
$FEF_{25\%-75\%}$ (L/sec)	−0.518	<0.001[a]
Hospital stay (day)	0.257	0.027[a]

Note: [a]Statistical significance.
Abbreviations: BMI, body mass index; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; mMRC, modified Medical Research Council dyspnea scale; EXACT, EXAcerbations of Chronic Pulmonary Disease Tool; SGRQ, St George's Respiratory Questionnaire; PaCO2, partial pressure of carbon dioxide in artery; PEF, peak expiratory flow; $FEF_{25\%-75\%}$, forced expiratory flow at 25% to 75% of the FVC.

Discussion

The current study examined the relationship between bronchoscopy-identified LMS of inpatients and indicators reflecting the severity of AECOPD, including lung function, HRQoL assessment, and laboratory findings. Our results show that LMS was associated with reduced lung function and worse HRQoL of patients with severe AECOPD. Thus, this study provides a new perspective of luminal mucus in large airways of the disease.

There are several advantages of our research. First, previous studies mainly focused on small airways rather than large ones. Secondly, previous studies paid more attention to the airway mucus in stable COPD, while we focused on acute exacerbation, characterized by significant increased volume in sputum expectoration. Thirdly, it is generally believed that CT signs of "luminal plug" reflects "mucus plug" in large airways, but this remains to be confirmed. We took advantage of bronchoscopy to score luminal mucus and obtain direct evidence regarding this question. Last but not least, numerous clinical parameters of AECOPD, such as lung function, four different questionnaires for HRQoL, and laboratory indicators, were included in order to obtain more representative and convincing data.

We found that 78.4% of subjects with AECOPD had mucus plugging in at least one site, a higher percentage than for patients with stable COPD (25%),[3] or severe asthma (58–67%).[14,15] Besides, in patients with AECOPD, their airway mucus increased with reduced lung function, which is consistent with results of recent studies. In patients with stable COPD[3] or severe asthma,[14] CT scan-identified luminal plugging in large airways (diameter > 2 mm) was associated with lower FEV_1% predicted. It is widely acknowledged that the accumulation of mucus in small airways is closely related to the severity of COPD.[2] As a matter of fact, mucus-producing glands are
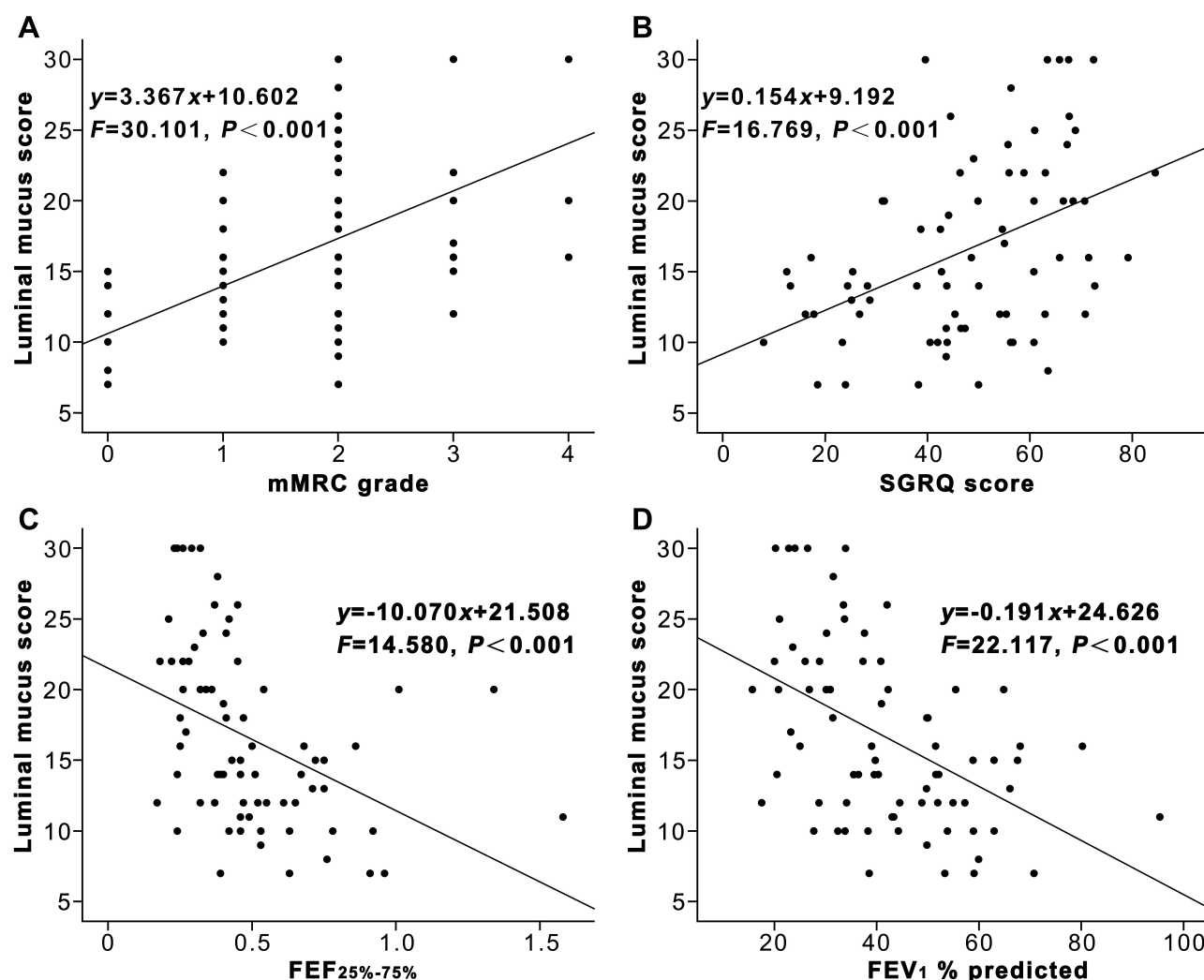
Figure 3 Correlation of total luminal mucus score with mMRC grade, SGRQ score, $FEF_{25\%-75\%}$, and $FEV_1\%$ predicted.
Note: Total luminal mucus score is significantly correlated with mMRC grade (A), SGRQ score (B), $FEF_{25\%-75\%}$ (C), and FEV_1 % predicted (D).
Abbreviations: mMRC, modified Medical Research Council dyspnea scale; SGRQ, St George's Respiratory Questionnaire; PaCO2, $FEF_{25\%-75\%}$, forced expiratory flow at 25% to 75% of the FVC.

mainly distributed in large airways,[1] and storage of mucin is significantly increased in the epithelial cells of large airways in smokers with airflow limitation.[16] In addition, some studies suggest that the mucus in some small airways contains relatively fewer cells. Therefore, this mucus could have been produced in large airways and aspirated into small airways.[17] Patients with COPD often experienced skeletal muscle dysfunction, diaphragmatic dysfunction, and impaired ciliary function,[18,19] which frequently worsen during acute exacerbations. Under combined effects of these factors, luminal mucus cannot be effectively cleared, and stays in large airways which served as a common channel for expulsion of mucus. These factors may partially explain the relationship between the LMS in

large airways and the airflow obstruction of AECOPD, but the exact mechanism remains to be elucidated.

Chronic cough and sputum production, also known as chronic bronchitis, are common symptoms and key components of COPD.[18] Studies that have focused on the potential impact of chronic bronchitis in COPD called "chronic mucus hypersecretion."[20,21] Our results showed that chronic bronchitis was weakly positively correlated with total LMS. However, in two previous studies, luminal plugging was not related to chronic cough and phlegm in stable COPD and severe asthma.[3,14] A possible explanation for these inconsistent results is that larger airways that can be observed by bronchoscopy may have more cough receptors.[22]

Table 4 Relationship of Luminal Mucus Score in Various Lobes with FEV_1% Predicted and mMRC Grade

Lobes	FEV₁% Predicted		mMRC Grade	
	ρ	*P*-value	ρ	*P*-value
RULB	−0.225	0.054	0.369	0.001[c]
RMLB	−0.308	0.008[c]	0.373	0.001[c]
RLLB	−0.169	0.150	0.176	0.134
LUDB	−0.459	<0.001[c]	0.375	0.001[c]
Lingular bronchus	−0.319	0.006[c]	0.364	0.001[c]
LLLB	−0.254	0.029[c]	0.251	0.031[c]
Bilateral ULB [a]	−0.422	<0.001[c]	0.456	<0.001[c]
RMLB and lingular bronchus	−0.340	0.003[c]	0.433	<0.001[c]
Bilateral LLB [b]	−0.245	0.036[c]	0.259	0.026[c]

Notes: [a]Bilateral ULB, including RULB and LUDB; [b]bilateral LLB, including RLLB and LLLB; [c]statistical significance.
Abbreviations: RULB, right upper lobe bronchus; RMLB, right middle lobe bronchus; RLLB, right lower lobe bronchus; LUDB, left upper division bronchus; LLLB, lower lobe bronchus; ULB, upper lobe bronchi; LLB, lower lobe bronchi; mMRC, modified Medical Research Council dyspnea scale.

COPD patients with a higher luminal mucus score in large airways has a higher SGRQ score that represented a worse HRQoL.[3] In our study, not only the SGRQ score, but also the CAT score, mMRC score and EXACT score were all significantly correlated with total LMS, further demonstrating the relationship between the mucus in large airways and HRQoL.

The correlation analysis of LMS in various lobes and the FEV_1% predicted and mMRC grade indicated that LMS in the upper lobe bronchi had a greater correlation than that in the lower lobe bronchi (Table 4). Our study cannot explain the results because numerous factors and mechanisms affected the regional distribution of ventilation and perfusion in the lung.[23] Well-designed studies are needed to explore potential effects of luminal mucus in different lobes on lung function.

Patients with exacerbation had a significantly higher CRP level and leukocyte count in the sputum than when in a stable state, and serum CRP is positively correlated with sputum leukocyte count, which suggests that the systemic inflammation of AECOPD is correlated with lower airway inflammation.[24] Nevertheless, our findings indicate that total LMS in large airways does not show significant correlation with counts of neutrophil, lymphocyte, eosinophil, fibrinogen, or CRP, and this is puzzling. Therefore, in order to reach more definitive conclusions, it will be necessary to further study the relationship between systemic inflammation, lower airway inflammation, and luminal mucus in large airways in the future.

EXACT is widely used to clinically assess the severity and duration of AECOPD,[25] and also is a sensitive, reliable tool for measuring changes in the exacerbation condition during recovery.[26] CAT scores increased significantly at exacerbation compared to those at baseline and reflected exacerbation severity as determined by lung function and exacerbation length, which indicated that the CAT provides a reliable score of exacerbation severity.[4] In our study, total LMS was significantly correlated with the CAT score and EXACT score, which suggests that total LMS may partially reflect severity of AECOPD.

Our results may have therapeutic implications. For AECOPD[27] patients undergoing tracheal intubation and children suffering acute asthma[28] with respiratory failure, bronchoscopic sputum suction showed clinical benefits. Furthermore, for the COPD patients with acute respiratory failure who were candidates for conventional mechanical ventilation because of hypercapnic encephalopathy and inability to clear copious secretions, bronchoscopic sputum suction combined with non-invasive positive pressure ventilation enabled 80% (12/15) of them to avoid tracheal intubation.[29] We found that 78.4% of inpatients had luminal mucus plugging in at least one site and also that total LMS was

Table 5 Stepwise Multiple Linear Regression Analysis for Luminal Mucus Score[a]

Variables	Coefficient (95% CI)	Standardized β	*t*-value	*P*-value	VIF
Intercept	16.724 (11.105 to 22.344)		5.934	<0.001	
mMRC	2.465 (1.065 to 3.866)	0.398	3.511	0.001[b]	1.379
FEV₁% predicted	−0.108 (−0.197 to −0.019)	−0.273	−2.410	0.019[b]	1.379

Notes: [a]R^2=0.348; *F*=18.960; *P*<0.001; [b]statistical significance; variables: BMI, CAT score, mMRC grade, EXACT score, SGRQ score, $PaCO_2$, FVC, FVC % predicted, FEV_1, FEV_1% predicted, FEV_1/FVC, PEF and $FEF_{25\%-75\%}$.
Abbreviations: β, regression coefficient; mMRC, modified Medical Research Council dyspnea scale; VIF, variance inflation factor.

proportional to $PaCO_2$, which indicates that early application of airway clearance techniques, including bronchoscopic sputum suction, might be effective for AECOPD inpatients.

Limitations

There are some limitations in our study. First of all, this was a cross-sectional study without follow-up; therefore, causal relationships could not be established and changes in parameters in stable COPD are not clear. Therefore, further cohort studies are required. Secondly, all subjects in this study were inpatients who were within the "severe" classification of acute exacerbation according to GOLD 2021,[18] thus the conclusion of this study still need to be verified in various grades of the disease. Lastly, bronchoscopy is invasive, which limits its widely clinical use for luminal mucus scoring.

Conclusion

In AECOPD inpatients, mucus frequently occludes the lumen of large airways, and LMS is significantly associated with reduced lung function and worse HRQoL. If replicated, our results suggest that LMS may be a direct indicator for evaluating the severity of AECOPD.

Abbreviations

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of COPD; SGRQ, St. George Respiratory Questionnaire; mMRC, modified Medical Research Council dyspnea scale; CAT, COPD Assessment Test; EXACT, EXAcerbation of Chronic pulmonary disease Tool; HRQoL, health-related quality of life; $FEF_{25\%-75\%}$, Forced expiratory flow at 25% to 75% of the FVC; FEV_1, forced expiratory volume in 1 second; LMS, luminal mucus score; FVC, forced vital capacity; CRP, C-reactive protein; LFT, lung function test; BMI, Body mass index; $PaCO_2$, partial pressure of carbon dioxide; PEF, peak expiratory flow; RULB, right upper lobe bronchus; RMLB, right middle lobe bronchus; RLLB, right lower lobe bronchus; LUDB, left upper division bronchus; LLLB, left lower lobe bronchus; ULB, upper lobe bronchi; LLB, lower lobe bronchi.

Data Sharing Statement

Datasets used and/or analyzed in the current study are available from the corresponding author (Qian-Yun Zhang) upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; had drafted or written, or substantially revised or critically reviewed the article; had agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agree to take responsibility and be accountable for the contents of the article.

Disclosure

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