Title: Gastroesophageal reflux disease is not associated with disease severity in patients with Mycobacterium avium complex lung infection

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Short title: GERD and MAC

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Abstract:

Background: Mycobacterium avium complex (MAC) pulmonary infection was previously associated with gastroesophageal reflux disease (GERD), although the effects of GERD on MAC outcomes remains unclear. The goal of this study was to assess the prevalence of GERD in patients with MAC pulmonary infection and its association with clinical outcomes.

Methods: This was a retrospective study of adult patients with confirmed MAC pulmonary infection who underwent ambulatory pH monitoring. Pathologic acid reflux was defined as a total distal acid exposure time ≥6%. Adjunctive esophageal tests including esophagogastroduodenoscopy, barium esophagram, and high-resolution manometry were assessed. The primary outcomes were pulmonary function testing and treatment of MAC pulmonary infection.

Results: Of 132 included patients, 35 (26.5%) had an acid exposure time ≥6%. There were no differences between patients with and without pathologic acid reflux by AET and pulmonary function tests including FEV1 absolute (1.79 vs. 1.83 L, p=0.68), FEV1% predicted (78.6 vs. 78.0%, p=0.94), FEV1/FVC% predicted (71.1 vs. 68.0%, p=0.38), or DLCO% predicted (66.0 vs. 79.0%, p=0.097). Additionally, there were no differences in MAC pulmonary infection outcomes including antimicrobial treatment, duration, or lobectomy. Findings on adjunctive esophageal testing did not associate with outcomes by pulmonary function tests or treatment of MAC pulmonary infection.

Conclusions: The prevalence of GERD in patients with MAC pulmonary infection based on ambulatory pH monitoring was 26.5%. MAC pulmonary infection with GERD was not associated with worse outcomes and further study is needed to assess the impacts of GERD on MAC pulmonary infection.

Key words: Gastroesophageal reflux disease, mycobacterium avium complex, non-tuberculous mycobacterium, bronchiectasis

Introduction:

Bronchiectasis is a chronic inflammatory lung disease characterized by cough, sputum production, and recurrent pulmonary infections with radiographic findings of dilated bronchi with and without mucus impaction.[1] The disease is hypothesized to occur through the pathway of infection, inflammation, and structural airway changes.[1, 2] Mycobacterium avium complex (MAC) encompasses multiple species of non-tuberculous mycobacterium (NTM) that can lead to pulmonary infection and complicate the clinical course of many patients with chronic structural lung disease and especially bronchiectasis.[2-6] There is a significant treatment burden for patients with bronchiectasis and MAC pulmonary disease.[6, 7]

Gastroesophageal reflux disease (GERD), defined as symptoms or complications related to reflux of gastric contents into the esophagus or more proximally, has been associated with MAC.[4, 8-10] Non-tuberculous mycobacterium are ubiquitous in the environment.[11, 12] Gastroesophageal reflux is hypothesized to lead to MAC pulmonary infection by ingestion of NTM contaminated food and water and subsequent reflux leading to microaspiration and seeding of NTM in the lungs.[8] However, this hypothesis has not been substantiated. Additionally, it is suggested that proton pump inhibitors (PPI), often used in the treatment of GERD increase the susceptibility to NTM.[13]

A complete understanding of the relationship between GERD and MAC remains unclear. Prior studies assessing GERD and MAC are limited by their small sample size and diagnosis of GERD based on clinical criteria rather than objective pH testing.[8, 14, 15] The goal of this study was to evaluate the prevalence of GERD confirmed by objective testing in patients with MAC pulmonary infection and assess its association with clinical outcomes.

Patients and Methods:

We identified adult patients aged ≥18 years old from January 2005 to April 2023 with confirmed MAC pulmonary infection who underwent ambulatory esophageal pH monitoring with catheter-based testing or wireless telemetry capsule to evaluate for GERD. This study obtained ethics approval and was deemed exempt by the institutional review board [#23-005486] on August 2, 2023. Informed consent was not required.

Mycobacterium avium complex pulmonary infection was defined according to consensus guidelines as patients meeting clinical, radiographic, and microbiologic criteria. This included presence of pulmonary symptoms (chronic cough, dyspnea) and radiographic criteria on computed tomography imaging of the chest classified as either nodular bronchiectatic or fibrocavitary disease.[6] To meet microbiologic criteria, patients were required to have a positive culture from at least two expectorated sputum samples or positive culture from one bronchial wash or lavage.[6]

All patients underwent ambulatory esophageal pH monitoring with catheter-based testing or wireless telemetry capsule while off proton pump inhibitors for at least seven days. Ambulatory pH monitoring is commonly performed at our tertiary referral center as part of the comprehensive evaluation of patients with respiratory disease including chronic cough and MAC pulmonary infection when there is concern for GERD as contributor. Catheter-based testing involved transnasal placement of a pH catheter with the pH sensor located 5 cm above the manometrically-located lower esophageal sphincter. The recording time was 24 hours. Ambulatory esophageal pH monitoring with wireless telemetry capsule was performed with the Bravo wireless pH capsule (Medtronic Inc, Shoreview, MN, USA) placed during esophagogastroduodenoscopy (EGD). The recording period was 48 hours.

Pathologic acid reflux was defined as a total acid exposure time ≥6% as per consensus guidelines.[16, 17] Patients were further stratified by AET ≥4% and <6% as this is felt to be indeterminate for GERD and by severe acid reflux defined as AET≥10%. Finally, the number of reflux events during catheter-based testing were assessed and classified as <40 (normal), 40-80 (indeterminate), and ≥80 (abnormal). Temporal association between reflux events and symptoms was assessed by the symptom index (SI), defined as the percentage of symptom episodes preceded by reflux events, and the symptom association probability (SAP), which assesses symptom association by statistical analysis. At least 4 symptom occurrences were required to calculate SI and SAP.[16, 17]

For patients who underwent EGD, the presence of erosive esophagitis according to the Los Angeles grading system and presence of hiatal hernia was recorded.[16, 17] For patients who underwent barium esophagram, the presence of reflux and hiatal hernia was recorded. If available, the extent of reflux into the distal, mid, or proximal esophagus was collected. For patients who underwent high-resolution esophageal manometry, findings were recorded according to the Chicago Classification version 3.0 as most studies were performed prior to the more recent Chicago Classification version 4.0.[18, 19]

The primary study outcomes were severity of MAC pulmonary infection assessed by pulmonary function testing (PFTs) and treatment for MAC pulmonary infection. Pulmonary function tests included the expiratory volume in the first second of a forced vital capacity maneuver (FEV1), the ratio of the FEV1 to forced vital capacity (FEV1/FVC), and the diffusing capacity for carbon monoxide (DLCO).[20] The FEV1 was collected as the absolute value and the FEV1, FEV1/FVC, and DLCO were reported as the % predicted based on persons of similar age, sex, and body composition.

Patients who underwent treatment with antimicrobials for MAC pulmonary infection were recorded as well as the treatment duration. Treatment was defined as receiving at least a 3-drug regimen including a macrolide and ethambutol. Patients who received intravenous amikacin for cavitary or severe/advanced nodular bronchiectatic disease were recorded, as well as patients with cavitary disease who required surgery with lobectomy.

Continuous variables were summarized as median, interquartile and range while categorical variables were reported as frequency and percentage. Data were compared between patients with normal and abnormal reflex test results using Kruskal-Walis test for continuous variables and Fisher's exact test for categorical variables. Abnormal reflux results were defined as AET ≥6%. Subgroup analysis was performed comparing patients with severe acid exposure time (≥10%) to patients without definitive GERD (AET<6%), by the number of reflux events (<40, ≥40 and >80, ≥80), and by findings on adjunctive esophageal testing (EGD, esophagram, high-resolution esophageal manometry). All tests were two-sided with p value <0.05 considered statistically significant. The analysis was done using R4.2.2.

Results:

One hundred thirty-two patients were included with a median (range) age 63.0 (19-81) years, 109 (82.6%) female, and median body mass index of 22.8 (14.8-45) kg/m^2. Eighty (60.6%) patients had no history of tobacco use, 51 (38.6%) were former tobacco users, and none were actively using tobacco. Mycobacterium avium complex pulmonary infection was classified as nodular/bronchiectatic in 122 (92.4%) patients and cavitary in 10 (7.6%) patients. The median duration of respiratory symptoms was 3 years (range 1-30 years) and 36 (27.5%) patients reported regular use of PPIs at the time of evaluation.

Seventy-seven (58.3%) patients underwent ambulatory esophageal pH monitoring with catheter-based testing and 55 (41.7%) with wireless telemetry capsule. Thirty-five (26.5%) patients had an AET ≥6% and 97 (73.5%) had an AET <6% (Figure 1). Thirteen (9.8%) patients had AET ≥4% and <6% and 15 (11.4%) patients had an AET≥10%. Acid exposure time was ≥6% in 20/77 (26.0%) of patients who underwent wireless telemetry capsule and 15/55 (27.3%) who underwent catheter-based testing. Of patients who underwent catheter-based testing, AET from the proximal sensor (upper esophagus) was available in 13 patients with a median (range) AET 0.0% (0.0-1.8). Patients with AET ≥6% had a shorter duration of pulmonary symptoms at GERD evaluation compared to patients with AET <6% (median 2.0 vs. 4.0 years, p=0.023). Patients reporting regular use of a PPI at GERD evaluation more often had increased AET (≥6%) on ambulatory pH monitoring compared to PPI non-users (16 [44.4%] vs. 18 [19.4%], p=0.010).

Positive indices for symptom association were rare. A positive SI (≥50%) occurred in 3/62 (4.8%) patients with cough, 3/18 (16.7%) patients with regurgitation, 1/17 (5.9%) patients with heartburn, and 5/44 (11.4%) patients with other symptoms. A positive symptom association probability (SAP) occurred in 10/34 (29.4%) patients with cough, 4/11 (36.4%) patients regurgitation, 3/12 (25%) patients heartburn, and 7/17 (41.2%) patients with other.

Sixty-one (46.2%) patients received antimicrobial treatment for MAC, the median duration of treatment was 18 months, 13 (9.8%) patients received treatment with IV amikacin, and 8 (6.3%) patients underwent surgery with lobectomy. There were no differences in pulmonary function tests (FEV1 absolute, FEV1% predicted, FEV1/FVC% predicted, DLCO% predicted) between patients with and without pathologic acid reflux by the AET (Table 1, Figure 2). There was a trend toward lower DLCO% predicted in AET≥6% although this was not statistically significant (p=0.097). Additionally, there were no differences in MAC treatment

specific outcomes including treatment with antimicrobials, duration of treatment, need for intravenous amikacin, or surgery (lobectomy) in patients with and without GERD by AET (Table 1). Of the 8 patients who underwent surgical fundoplication, all had an AET≥6%. Of the 61 patients who underwent antimicrobial treatment for MAC, repeat sputum culture results after treatment were available in 12 patients. Five (41.7%) patients had persistent positive sputum cultures for MAC, and all patients were negative of pathologic GERD on ambulatory pH monitoring with an AET <6%.

In a subgroup analysis comparing patients with severe acid exposure time (AET≥10%) to patients without gastroesophageal reflux disease (AET<6%), patients with AET≥10% had a lower DLCO% predicted (63.5 vs. 79.0, p=0.06) although this was not statistically significant and there were no differences in other PFTs or MAC specific outcomes including antimicrobial treatment, duration, IV amikacin, or surgery (lobectomy).

Patients who underwent catheter-based testing were stratified by the number of reflux events (Supplemental Table 1). Fifty-four patients had <40 reflux events, 15 patients ≥40 and <80 reflux events, and 7 patients ≥80 reflux events. There were no differences in the number of reflux events and outcomes by pulmonary function testing or MAC outcomes including antimicrobial treatment, duration, IV amikacin, or surgery (lobectomy).

One hundred two (77.3%) patients underwent EGD, 80 (60.6%) patients barium esophagram, and 58 (43.9%) patients high-resolution esophageal manometry (Table 2). There was a trend toward more patients with hiatal hernia (16 [55.2%] vs. 24 [32.9%], p=0.065) and erosive esophagitis (5 [17.8%] vs. 6 [8.2%], p=0.095) in patients with AET≥6% versus those without (Supplemental table 2). There were no differences between patients with and without AET≥6% and barium esophagram findings of hiatal hernia (9 [47.4%] vs. 19 [31.1%], p=0.27),

presence of reflux (11 [57.9%] vs. 21 [34.4%], p=0.11), or level of reflux to the lower, mid, or upper esophagus (5 [26.3%] vs. 10 [16.4%], 3 [15.8%] vs. 5 [8.2%], 3 [15.8%] vs. 6 [9.8%], p=0.28). Of patients who underwent high-resolution esophageal manometry, most patients (32, 55.2%) were normal by CCv.3.0 and there were no differences between patients with and without AET≥6% and criteria by CCv.3.0 (Supplemental Table 1, p=0.81).

Findings on EGD, esophagram, and high-resolution esophageal manometry were also assessed by PFTs and MAC specific outcomes. In patients who underwent EGD, there was a trend toward lower FEV1 absolute in patients with an endoscopically visualized hiatal hernia versus without (1.77 vs. 1.93, p=0.067). Otherwise, there were no differences in the presence of an endoscopic hiatal hernia or erosive esophagitis and PFTs. Similarly, there were no differences in patients with esophagram findings of a hiatal hernia or reflux and PFTs. When comparing patients with a normal classification on high-resolution esophageal manometry to those with abnormal classification, patients with a normal high-resolution esophageal manometry had a lower DLCO% predicted compared to those with an abnormal study (66.0 vs. 78.0, p=0.009), but no differences between other PFTs (Supplemental Table 3). There were no differences in MAC specific outcomes.

Discussion:

In this retrospective study of 132 patients with MAC pulmonary infection who underwent ambulatory esophageal pH monitoring, GERD was objectively confirmed in 26.5% of patients. When comparing patients with and without GERD, there was no difference in pulmonary function tests and MAC specific outcomes including antimicrobial treatment or lobectomy. There were no differences whether GERD was evaluated by total acid exposure time or by the number of reflux events. These findings bring into question the impact of GERD on the long-

term outcomes of patients with MAC pulmonary infection, including which patients might benefit from PPI therapy in the absence of significant GERD symptoms. Findings on adjunctive esophageal testing including esophagogastroduodenoscopy, barium esophagram, and high-resolution esophageal manometry generally did not associate with worse outcomes for MAC pulmonary infection. These tests are likely beneficial in some patients to evaluate for GERD and esophageal dysmotility, but widespread use may not be helpful in all patients.

The prevalence of GERD in patients with MAC pulmonary infection was previously estimated to be as high as 50%. In a study of 1,826 patients from the US Bronchiectasis Research Registry, 1,158 (63%) patients had NTM, and GERD was more common in patients with NTM compared to those without (51% vs. 47%, $p<0.01$). The presence of GERD was diagnosed clinically and did not require objective testing.[4] In a study of 52 patients with MAC, GERD was documented in 44% compared to 27% of control patients without MAC. Only 10 patients with MAC had objective evidence of GERD based on esophagogastroduodenoscopy (6) or esophagram (4). Patients with MAC were more likely to take antacids and have suspected aspiration events than control patients.[8] In a study of 58 patients with nodular/bronchiectatic NTM pulmonary disease, 15 (26%) patients had GERD when defined as a total acid exposure time >4%, a similar prevalence to our cohort. Most patients (73%) lacked typical GERD symptoms and there were no differences in pulmonary function tests. The study found that findings of bronchiectasis and bronchiolitis, as assessed by imaging and the number of pulmonary lobes involved, were more common in patients with GERD than without. Furthermore, patients with GERD were more likely to have a positive sputum-smear for acid fast bacilli.[15] Notably, none of the five patients in this study with a positive sputum culture for MAC after antimicrobial treatment had evidence of pathologic acid reflux. In a more recent

cohort study, GERD was associated with an increased incidence of NTM pulmonary disease with risk factors including older age and bronchiectasis.[14] The true incidence of GERD diagnosed by objective methods is likely less than previously reported with non-objective measures.

GERD has been linked to multiple pulmonary disorders including asthma, chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea, and worse outcomes after lung transplantation.[10, 21-23] Respiratory disease related to GERD is hypothesized to occur by reflex neural mechanisms from reflux or by direct damage of aspirated gastric contents.[23] Microaspiration leads to pneumonitis, increased epithelial cell permeability, stimulation of pathways promoting fibrosis, and ultimately lung fibrosis.[23] The association between GERD and bronchiectasis is well known. Patients with GERD and bronchiectasis were previously shown to have increased mortality and bronchiectasis severity measured by increased symptoms, exacerbations, hospitalizations, radiographic findings, infection, reduced quality of life and pulmonary function.[1] Treatment of GERD has demonstrated improved bronchiectasis control.[5]

The association between MAC pulmonary infection and GERD remains less clear in part due to small, retrospective studies. Pulmonary infection with non-tuberculous mycobacteria is hypothesized to occur through ingestion of contaminated food and water.[24] Presumably, gastroesophageal reflux into the proximal esophagus leads to microaspiration, often unknown to the patient and leading to seeding of NTM in the lungs. There is speculation that proton pump inhibitors increase the susceptibility to NTM by increasing the ability of these organisms to live in the gastrointestinal tract, although in vitro study has suggested these organisms are tolerant to acidic environments.[13, 24, 25]

Although GERD was not associated with worse outcomes in MAC pulmonary infection, patients with GERD were noted to have a trend towards lower DLCO and the current study may not be powered to detect an association. Potential complications of GERD include recurrent aspiration (diagnosed clinically or radiographically) or more severe bronchiectasis/bronchiolitis on imaging although this study did not assess these outcomes.[15] Given the established association between GERD and bronchiectasis and the overlapping features between bronchiectasis and MAC pulmonary infection, an association between GERD and MAC pulmonary infection seems intuitive. It remains to be seen if treatment of GERD with PPIs may lead to improved outcomes in patients with MAC pulmonary infection, and this requires further investigation. Patients with GERD exhibited a shorter duration of pulmonary symptoms at the time of evaluation, which may suggest an association between GERD and symptomatic pulmonary disease although this remains speculative.

This study did not find a significant association between adjunctive esophageal testing including barium esophagram and high-resolution esophageal manometry and study outcomes although this may be limited by sample size. We believe esophagram and high-resolution esophageal manometry remain useful tests in select patients to screen for severe esophageal dysmotility, stratify risk for GERD (i.e. absent peristalsis), evaluate anatomy (large hiatal hernia), and rule out secondary causes of regurgitation or aspiration such as disorders of esophagogastric junction opening (i.e. achalasia).

The primary limitation of this study is its retrospective design. Nevertheless, this is the largest cohort of patients with MAC pulmonary infection that assessed GERD based on objective pH testing. Other limitations include lack of symptom scores for pulmonary symptoms (cough), GERD, and esophageal dysmotility which were not available retrospectively. The extent of

radiographic involvement of MAC pulmonary infection was not assessed as performed in prior study given the focus on assessing ambulatory pH monitoring. It is difficult to understand the effect of GERD on the clinical course of MAC pulmonary disease, and this is further complicated by the fact that patients presented for GERD evaluation at varying stages of MAC pulmonary disease in this study. The presence of GERD did not correlate with lung function in this cohort. A greater reduction in lung function may predispose to MAC but it is not clearly associated with the clinical course of MAC infection. The strengths of this study include its comprehensive assessment of esophageal function in patients with MAC pulmonary infection including ambulatory esophageal pH monitoring by catheter-based testing or wireless telemetry monitoring, EGD, barium esophagram, and high-resolution esophageal manometry.

Conclusions:

In conclusion, in this large cohort of patients with MAC pulmonary infection, we found a prevalence of GERD in 26.5% of patients based on the acid exposure time from ambulatory esophageal pH monitoring. The presence of GERD was not associated with worse outcomes, which included pulmonary function tests and antimicrobial treatment. Future prospective studies may be warranted to further evaluate the association between MAC pulmonary infection and GERD, and whether GERD treatment improves long-term MAC outcomes.

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Author contributions:

All authors meet the ICMJE authorship criteria. MM and MJ made significant contributions to data collection and drafting the original manuscript. AK made significant contributions to the data analysis and interpretation and drafting the original manuscript. WB and WJ made significant contributions to the design of the work and the interpretation of data. MP, KD, and LH substantially contributed to the revision of the manuscript drafts. All authors have approved the submitted version of the manuscript and agreed to be accountable for any part of the work.

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Figure Captions:

Figure 1: Patients with mycobacterium avium complex (MAC) pulmonary infection stratified by acid exposure time (AET). Abnormal AET was defined as ≥6%. Consensus guidelines regard AET <4% as evidence against pathologic acid reflux and AET ≥4% and <6% as borderline or inconclusive.[16] Patients with AET≥6% were further stratified by severity (AET≥6% and <10% and AET≥10%).

Figure 2: Box plot demonstrating pulmonary function tests in patients with total acid exposure time <6% and ≥6%. There was no significant difference in pulmonary function tests between these groups. Small circles represent outliers. FEV1; expiratory volume in the first second of a forced vital capacity maneuver, FEV1/FVC; the ratio of the FEV1 to forced vital capacity, DLCO; diffusing capacity for carbon monoxide

Table 1: Patient demographics and outcomes in patients with MAC pulmonary disease who underwent ambulatory esophageal pH monitoring off proton pump inhibitor medications. Patients are stratified by acid exposure time. Categorical variables are described as (#, %) and continuous variables as (median, interquartile range). Treatment was defined as receiving at least a 3-drug regimen including a macrolide and ethambutol. AET; acid exposure time, MAC; mycobacterium avium complex, PFTs; pulmonary function tests, FEV1; expiratory volume in the first second of a forced vital capacity maneuver, FEV1/FVC; the ratio of the FEV1 to forced vital capacity, DLCO; diffusing capacity for carbon monoxide

Patient characteristics	AET<6%	AET≥6%	p-value
Age, years	63 (58-68)	63 (60-69)	0.59
Sex, female	83 (85.6)	26 (74.3)	0.19
Body mass index, kg/m2	22.3 (19.9-25.6)	24.7 (22.4-28.6)	0.009
MAC pattern			
Nodular/bronchiectatic	88 (90.7)	34 (97.1)	0.29
Cavitary	9 (9.3)	1 (2.9)	
PFTs			
FEV1 absolute	1.83 (1.5-2.3)	1.79 (1.3-2.3)	0.68
FEV1% predicted	78 (66.0-91.0)	78.6 (51.0-94.1)	0.94
FEV1/FVC% predicted	68 (62.7-74.1)	71.1 (61.1-79.2)	0.38
DLCO% predicted	79 (67.8-88.0)	66 (54.8-90.6)	0.097
MAC outcomes			
Antimicrobial treatment	47 (48.5)	14 (40.0)	0.43
Treatment duration, months	18 (12-30.8)	18 (13-23)	0.67
IV amikacin	10 (10.3)	3 (8.6)	1
Surgery (lobectomy)	5 (5.2)	3 (8.6)	0.44
Surgical fundoplication	0 (0.0)	8 (22.9)	<0.001

Table 2: Findings on adjunctive esophageal testing including esophagogastroduodenoscopy, barium esophagram, and high-resolution esophageal manometry in patients who underwent ambulatory reflux monitoring off proton pump inhibitor medications. Categorical variables are described as (#, %). AET; acid exposure time

Esophagogastroduodenoscopy	N=102 (77.3)
Hiatal hernia	41 (40.2)
Erosive esophagitis	
None	90 (88.2)
Los Angeles grade A	7 (6.9)
Los Angeles grade B	5 (4.9)
Esophagram	80 (60.6)
Hiatal hernia	28 (35.0)
Reflux	32 (40.0)
Level of Reflux	
Lower esophagus	15 (18.8)
Mid esophagus	8 (10.0)
Upper esophagus	9 (11.3)
High-resolution esophageal manometry by Chicago Classification version 3.0	58 (43.9)
Normal	32 (55.2)
Ineffective esophageal motility	9 (15.5)
Absent	0 (0.0)
Distal esophageal spasm	2 (3.4)

Hypercontractile esophagus	2 (3.4)
Esophagogastric junction outflow obstruction	13 (22.4)
Achalasia	0 (0.0)

Figure 1:

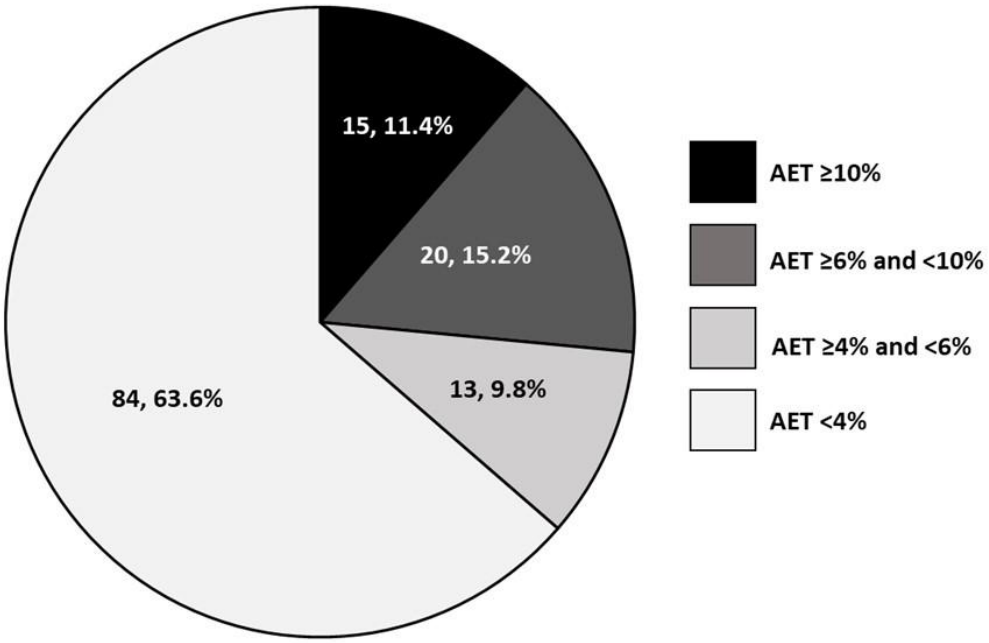
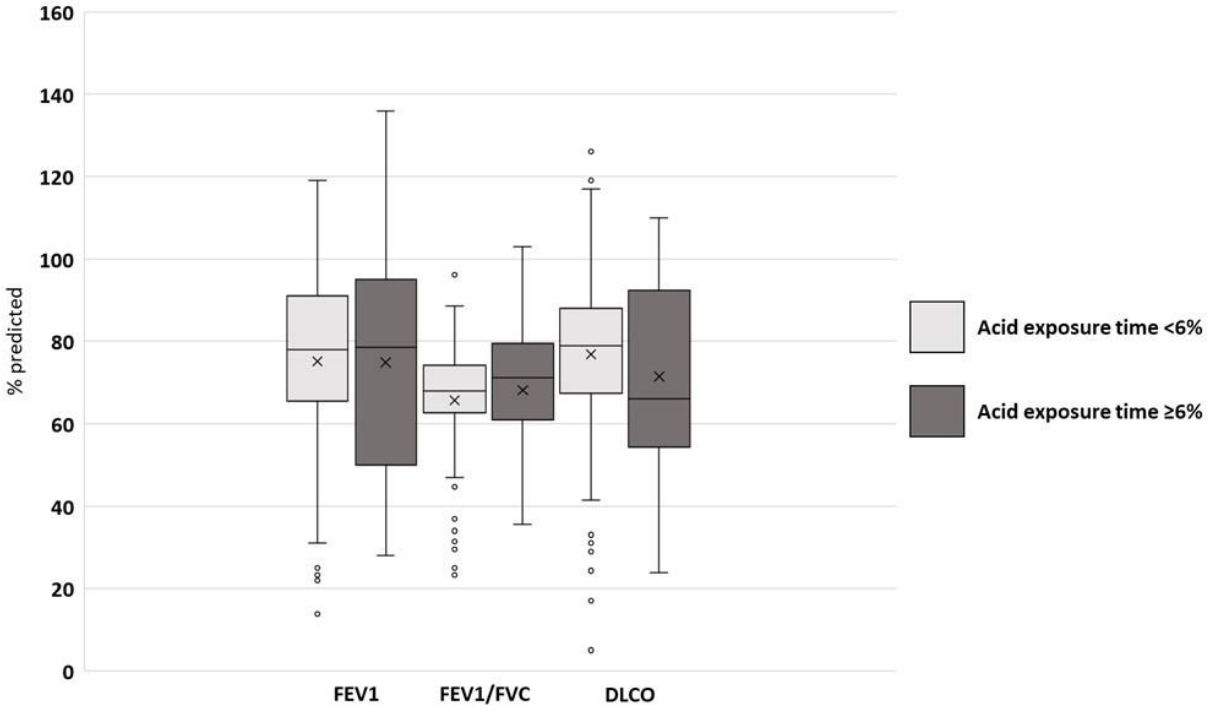


Figure 2:


160
140
120
100
80
60
40
20
0
% predicted
FEV1
FEV1/FVC
DLCO
Acid exposure time <6%
Acid exposure time ≥6%