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Proximal and distal gastro-oesophageal reflux in COPD and bronchiectasis

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Summary at a Glance:

The prevalence of gastro-oesophageal reflux in adults with chronic obstructive pulmonary disease or bronchiectasis is twice as high compared to the individuals without lung disease. The findings of this observational study suggest that gastro-oesophageal reflux is a common co-morbidity across the disease spectrum in adults with these lung conditions.

ABSTRACT

Background and objective: The aims of this observational study were to (1) examine the prevalence of symptomatic and clinically silent proximal and distal **gastro-oesophageal reflux** (GOR) in adults with COPD or bronchiectasis, (2) the presence of gastric aspiration and (3) to explore the possible clinical significance of this co-morbidity in these conditions.

Methods: 27 participants with COPD, 27 with bronchiectasis and 17 control subjects completed reflux symptom evaluation and dual-channel 24hr oesophageal pH monitoring.

In those with lung disease, pepsin levels in sputum samples were measured using ELISA, with disease severity (lung function and high resolution computed tomography) also measured.

Results: The prevalence of GOR in COPD was 37%; in bronchiectasis was 40% and in control subjects was 18% ($p=0.005$). Of those diagnosed with GOR, clinically silent reflux was detected in 20% of participants with COPD and 42% with bronchiectasis. While pepsin was found in 33% of COPD and 26% of bronchiectasis participants, the presence of pepsin in sputum was not related to a diagnosis of GOR based on oesophageal pH monitoring in either condition. Neither a diagnosis of GOR nor the presence of pepsin was associated with increased severity of lung disease in COPD or bronchiectasis.

Conclusions: The prevalence of GOR in COPD or bronchiectasis is twice that of the control population, and the diagnosis could not be based on symptoms alone. Pepsin was

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detected in sputum in COPD and bronchiectasis, suggesting a possible role of pulmonary aspiration which requires further exploration.

Key words: bronchiectasis, chronic obstructive pulmonary disease, gastro-oesophageal reflux, quality of life

Short title: Gastric reflux in chronic lung disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and bronchiectasis unrelated to cystic fibrosis (CF) are chronic respiratory conditions.¹⁻³ Their clinical presentations may be complicated by co-morbidities, including gastro-oesophageal reflux (GOR).^{3,4} GOR is prevalent in several lung disorders, including asthma,⁵ cystic fibrosis^{6,7} and pulmonary fibrosis,⁸ with the hypothesis that reflux is a risk factor for microaspiration and reflex bronchospasm and may contribute to lung disease severity.^{4,9} In COPD, the prevalence of GOR is estimated between 17 - 76%.^{8,10-17} In studies using ambulatory 24hr oesophageal pH monitoring, the extent of proximal acid reflux, the surrogate marker of microaspiration^{18,19} has been predominantly measured in patients with severe COPD.^{8,12,16} Few studies have used 24hr pH monitoring in bronchiectasis,^{8,16,20,21} with the largest reporting distal GOR in patients with Mycobacterium-associated bronchiectasis.²¹ The prevalence of proximal and distal GOR in patients with well defined COPD or bronchiectasis is unknown.

Oesophageal pH monitoring detects acid reflux from the stomach into the oesophagus, but the extent of reflux within the hypopharynx and the airway is not measured. The detection of pepsin in saliva, tracheal aspirates or bronchoalveolar lavage fluid has been proposed as

a surrogate marker for reflux aspiration.^{7,22-25} However, analysis of pepsin in airway samples in COPD or bronchiectasis has not been undertaken and its connection to proximal reflux events is unknown.

Exploration of the significance of GOR in COPD and bronchiectasis has produced disparate results. In COPD, GOR appears to have a minimal impact on lung function.^{10-13,26} In contrast, distal reflux has been linked to extensive bronchiectasis and bronchiolitis,²¹ while symptoms of acid regurgitation have been related to reduced lung function in bronchiectasis.²⁷ The relationship between GOR, pulmonary aspiration and markers of disease severity requires further clarification.

The aims of our study were 1) to determine the prevalence of proximal and distal GOR in patients with COPD or bronchiectasis compared with a control population, 2) to quantify the levels of pepsin in sputum samples in COPD or bronchiectasis using an indirect sandwich enzyme-linked immunosorbent assay (ELISA) and 3) to explore the relationship between GOR and aspiration on lung disease severity.

METHODS

Subjects

A prospective, observational study was conducted of patients with COPD or bronchiectasis who attended respiratory outpatient clinics of Alfred Health between

September 2005 and May 2007. A diagnosis of COPD was confirmed according to the GOLD criteria,²⁸ with bronchiectasis confirmed by high resolution computed tomography (HRCT).²⁹ Consecutive patients who met the eligibility criteria and were clinically stable were invited to participate. Participants were excluded if they had both COPD *and* bronchiectasis, a diagnosis of asthma,³⁰ CF, interstitial lung disease, known oesophageal varices/strictures and orthopaedic, cognitive or geographical limitations to participation. Recruited participants prescribed anti-reflux medication (Histamine-2 Receptor Antagonists and Proton Pump Inhibitors) ceased their reflux medication seven days prior to the study, while antacids were stopped the day before the study.^{31,32} Control participants were consecutively recruited within and outside the study centre by advertisement, with no history of smoking, respiratory disease, GOR symptoms or prescription of respiratory or anti-reflux medication. All participants gave written informed consent with the study approved by the administering institution's ethical review board (Alfred Health 106/05).

Protocol

A structured reflux symptom questionnaire was completed by all participants with a score of ≥ 4 indicative of clinical reflux symptoms.³³ Ambulatory 24hr oesophageal pH monitoring was used to measure gastro-oesophageal reflux³¹. Following calibration, the distal antimony probe was positioned 5cm above the lower oesophageal sphincter, using the pH step up method^{34,35} with the proximal probe 15cm above the distal probe. After 24hrs of monitoring, the principle GOR parameters measured were number of reflux episodes, fraction of reflux time (reflux index) for the 24hrs and the DeMeester score (distal only)³¹. The clinical definition of GOR in this study was a DeMeester score

(composite of distal reflux) $>14.72^{36}$ while proximal reflux was defined by proximal oesophageal $\text{pH}<4$ for $>0.9\%$ of the total study time.³⁷ Symptomatic GOR was described by these parameters and a symptom score of ≥ 4 .³³

Sputum samples were collected at four intervals over the 24hr period (immediately upon waking, mid morning, mid afternoon and prior to sleeping), each obtained prior to meals or one hour post-prandial, with samples frozen prior to processing. Due to secretion viscosity, sputum supernatants were prepared by centrifugation (10 minutes, 2850rpm) within 4hrs of collection, with aliquots stored at -80°C until batch analysis.^{19,38} A locally developed ELISA, based on a monospecific antibody to porcine pepsin was developed to measure pepsin concentrations,^{22,23,39} with each assay performed in duplicate with enzyme controls. Captured pepsin was detected by biotinylated goat anti-pepsin antibody followed by incubation with Streptavidin Horse-Radish Peroxidase. Enzymatic color development was carried out using a substrate. The assay was performed by one individual, blinded to GOR diagnostic status, with a lower limit of detection of 1.953ng/ml.

Clinical evaluation in COPD and bronchiectasis

Spirometry, completed within the 24hr study period at the same time of day for each participant, was used to measure disease severity in all participants. The extent and severity of bronchiectasis was scored using the modified HRCT scoring³⁰ by an independent radiologist blinded to GOR diagnostic status.

Data management and sample size calculation

Data analysis was performed using Statistical Package for Social Sciences (SPSS version 15.0). Based on results from a previous study¹⁰ with a prevalence of 20% of GOR in normal subjects and 62% in subjects with COPD, 27 participants with COPD and 27 with bronchiectasis were required (power 0.80; two-sided alpha 0.05). Data are presented as mean (SD) or median (IQR). Comparison between groups was performed using χ^2 Test, Mann Whitney *U* test or Kruskal Wallis test with Bonferroni's correction for multiple comparisons. Alpha was set at 0.05 unless otherwise stated.

RESULTS

Over the recruitment period, 341 patients with COPD and 136 with bronchiectasis were screened (Figure 1). A total of 244 did not meet the inclusion criteria while a further 180 declined to participate. Overall, 27 participants with COPD and 27 with bronchiectasis were included. Aside from a higher proportion of males with COPD agreeing to participate compared to non-participants ($p < 0.001$), there were no significant differences in lung function, prior prescription of anti-reflux medication or symptom scores³⁴ between participants versus non-participants with COPD or bronchiectasis. A total of 17 control participants were also enrolled.

The severity of bronchiectasis was predominantly mild ($n=15$) to moderate ($n=12$), with most participants (74%) demonstrating involvement of at least six bronchopulmonary segments.²⁹ The majority of participants with COPD were classified as moderate ($n=12$) or

severe (n=10) disease severity.²⁸ Seventeen participants with COPD (63%) and 16 with bronchiectasis (53%) were prescribed anti-reflux therapy prior to the study. The demographics of all participants are summarised in Table 1. Control participants were younger (25 – 70 years) ($p<0.0001$), had higher FEV₁% predicted ($p<0.0001$) and fewer individuals with symptoms scores ≥ 4 compared to those with lung disease ($p=0.03$).

GOR data

Three control participants (18%) met the diagnostic criteria for GOR, all of whom were asymptomatic with distal reflux only. In COPD, the prevalence was 37% (n=10), of whom 2 participants demonstrated clinically silent reflux. Those with a symptom score ≥ 4 were more likely to be diagnosed with reflux ($p=0.018$). Of those 10 participants, 8 had distal reflux only and 2 had both proximal and distal reflux. A higher proportion of those with GOR had mild to moderate COPD compared to severe disease (n=9[90%] vs 1[10%], $p=0.003$).

In bronchiectasis, the prevalence of GOR was 40% (n=12), of whom 5 participants demonstrated clinically silent reflux. Diagnostic status of GOR did not influence the proportion of participants with bronchiectasis with a symptom score ≥ 4 ($p=0.879$). Of these 12 participants, 7 had distal reflux only, 3 had proximal and distal reflux and 2 had proximal reflux only. In bronchiectasis, 7(58%) of those with GOR had mild bronchiectasis, while 5(42%) had moderate to severe disease ($p=0.43$). The proportion of participants with lung disease diagnosed with GOR was greater compared to controls ($p=0.005$). The pattern of GOR in each group is outlined in Table 2.

One participant was unable to provide an adequate sputum quantity for analysis, while 2 participants with bronchiectasis declined to collect samples. A total of 158 samples of supernatant sputum from 48 participants were analysed. Overall, 16 participants (7 with bronchiectasis, 9 with COPD) had detectable pepsin in at least one sputum sample. In COPD, the median(IQR) pepsin concentration in sputum was 2.84(4.05)ng/ml while in bronchiectasis, the concentration was 3.48(4.18)ng/ml.

The proportion of participants with pepsin in sputum who were diagnosed with GOR compared those without GOR were similar in COPD (n=8[31%] vs 1[4%], p=0.087) and in bronchiectasis (n=3[11%] vs 4[14%], p=0.823). There was no association between pepsin concentration and distal or proximal reflux indices in COPD or bronchiectasis. The presence or absence of pepsin did not influence FEV₁ or FVC % predicted in COPD or bronchiectasis.

Clinical impact of GOR

In COPD, those with GOR had a higher FEV₁ and FVC % predicted (p<0.01); in bronchiectasis, neither the radiological severity (extent or severity of bronchiectasis on HRCT) nor physiological severity (spirometry) differed in those diagnosed with GOR compared to those without (Figure 2). A retrospective power calculation suggested that a total of 312 patients with bronchiectasis and 107 patients with COPD per GOR diagnostic group would be required to detect a 10% difference in FEV₁ % predicted, with a probability of 0.8.

DISCUSSION

This study demonstrates that the prevalence of distal and proximal GOR in patients with COPD or bronchiectasis is twice as high as the control population included in this study. The clinical usefulness of this questionnaire for GOR symptom screening appeared to be limited to those with COPD. Pepsin was detected in sputum in COPD and bronchiectasis, suggesting that aspiration of gastric contents can occur, irrespective of a formal diagnosis of GOR. Finally, neither a diagnosis of GOR nor the presence of pepsin in sputum was associated with an increased severity of lung disease in our sample of patients.

The prevalence of GOR in COPD and bronchiectasis is consistent with earlier reports and any disparity may be due to the differences in disease severity of included participants. A higher prevalence has been reported in individuals with advanced COPD (62%)^{8,10,12,16} and bronchiectasis (75%).^{8,16} With a recent study demonstrating a similar prevalence of 78% of patients with mild to moderate COPD in a developing country¹⁷, our results further confirm that proximal and distal reflux in both patient populations is not confined to those advanced disease, but also present in mild to moderate COPD and bronchiectasis.

One limitation was the large proportion of individuals with COPD or bronchiectasis who met the eligibility criteria but declined to participate. The primary reason for refusal was the study's invasive nature, which may have biased the sample towards individuals with GOR. However, the lack of difference in lung function, symptom scores and use of anti-reflux medication between participants and non-participants, as well as the consistency in

prevalence reported from previous studies suggests that our results may provide a reliable estimate.

The prevalence of GOR in the control subjects was similar to prior reports of the normal population⁴⁰ using oesophageal pH monitoring⁴¹ and is one of few studying control subjects contemporaneously¹⁰. Attempts to age-match controls were limited by the inherent difficulty of recruiting for an invasive study. Some pH monitoring studies suggest that age is unlikely to influence the pattern of reflux events⁴¹⁻⁴⁴ while others indicate that reflux is more prevalent in males and increases with age.⁴⁵ Although the prevalence of GOR in the healthy volunteers in our study was comparable to previous descriptions,⁴³ the dominance of males with COPD and the older age of those with respiratory disease may have influenced these results and requires further clarification. Furthermore, exploration of the links between GOR and other pathophysiological factors, including respiratory mechanics and coughing, which is associated with GOR,⁴⁶ in COPD and bronchiectasis is warranted.

Diagnosis of GOR in the absence of typical reflux symptoms in bronchiectasis is not a novel observation.^{20,21} This suggests that 24hr oesophageal pH monitoring continues to be a valuable tool for diagnostic confirmation. In contrast, the proportion of participants with symptomatic reflux in COPD was slightly higher than in previous reports, ranging between 19% and 76%.^{8,10,16,17} This symptom questionnaire may be of clinical value for detecting symptomatic reflux in the COPD population, but this should be confirmed in a larger sample.

Meeting the diagnostic criteria for GOR was not a prerequisite for pepsin to be detected in sputum samples in this study. While a strong relationship between pepsin concentrations and GOR is evident in individuals with chronic cough and laryngopharyngeal reflux,^{18,46,47} detectable pepsin in airway samples in the context of normal GOR indices has been previously observed in individuals with lung disease.^{18,19,23-25} Brief, isolated events which could be aspirated may be insufficiently frequent to contribute to the DeMeester score or proximal RI, our criteria defining GOR. The lack of association between proximal reflux events and detected pepsin may also be due to the few participants (7 of 54) with proximal reflux. As the first study to concurrently measure oesophageal pH monitoring and pepsin in sputum in COPD and bronchiectasis, these findings reinforce the need for definitive markers of pulmonary microaspiration. In addition, alkaline reflux events were not assessed in our study. Further studies using oesophageal impedance monitoring to detect weakly acidic and non-acid reflux^{24,25} may provide a more reliable evaluation of all reflux events and their contribution to pulmonary aspiration in these populations.

Neither a diagnosis of GOR nor the presence of pepsin in sputum was associated with reduced lung function in COPD or bronchiectasis. While this lack of relationship is consistent with previous reports in these populations^{10-14,21} and in lung transplant recipients,^{23,25} this study may be inadequately powered to provide definitive conclusions. Examining the clinical impact of GOR on disease severity may be more accurately assessed using consecutive measures of lung function over a longer time frame. Recent studies demonstrated a significant relationship between reflux symptoms and the

frequency of acute exacerbations of COPD;^{48,49} this may provide an ideal reflection of the clinical significance of GOR. The lack of difference in severity and extent of bronchiectasis on HRCT in our study contrasts with two earlier reports,^{21,27} and may be attributed to the few patients experiencing proximal reflux. Recent studies of pepsin concentrations and airway cytokines demonstrated positive correlations in respiratory conditions;^{24,25,50} these biological markers may be more reliable in assessing the effect of pulmonary microaspiration on lung disease severity. The presence of pepsin in easily obtainable airway samples is encouraging and suggests this marker may have a greater role in clinical practice.

In conclusion, an increased prevalence of distal and proximal GOR was demonstrated in a group of individuals with well defined COPD or bronchiectasis and appears not to be confined to those with severe lung disease. Pepsin was detectable in an easily obtainable sputum sample. However, the detection of pepsin in sputum did not always align with a diagnosis of GOR. With some patients asymptomatic for GOR, the index of clinical suspicion of GOR may be high in both lung conditions. The clinical impact of reflux and pulmonary microaspiration on lung disease severity requires further evaluation.

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Table 1: Demographics and clinical characteristics

	COPD	Bronchiectasis	Control
	n=27	n=27	n=17
Male / Female	21 / 6*	13 / 14	7 / 10
Age (years)	67.7 (7.7)	53.7 (14.0)	36.6 (15.1)‡
BMI (kg/m ²)	26.9 (4.7)	26.6 (5.8)	24.8 (3.5)
FEV ₁ % predicted	47.2 (17.4)#	73.9 (23.4)	96.0 (8.8)‡
FVC % predicted	87.7 (24.5)	89.4 (20.2)	98.9 (12.4)
Symptom score ≥ 4 †	13 (48%)	18 (60%)	3 (18%)†

Data are n (%), mean (SD) or median (IQR)

COPD = Chronic obstructive pulmonary disease; BMI = Body Mass Index; FEV₁ = Forced expiratory volume in one second; FVC = Forced vital capacity‡Control versus

Bronchiectasis and COPD p<0.0001; †Control versus COPD and Bronchiectasis p<0.05;

*COPD versus Bronchiectasis and controls p<0.001; #COPD versus Bronchiectasis p<0.05

Table 2: Pattern of gastro-oesophageal reflux in lung disease and controls, based on oesophageal pH monitoring

	COPD	Bronchiectasis	Control
Symptomatic for GOR	n=8 (80%)	n=7 (58%)	n=0 (0%)
GOR*	10 (37%)	12 (40%)	3 (18%)
Distal GOR	8 (80%)	7 (26%)	3 (18%)
Distal and proximal GOR	2 (20%)	3 (11%)	0 (0%)
Proximal GOR	0 (0%)	2 (7%)	0 (0%)

Data are n (%)

COPD = Chronic obstructive pulmonary disease; GOR = Gastro-oesophageal reflux

GOR* = Diagnosis of gastro-oesophageal reflux based on DeMeester score > 14.72

Figure legends

Figure 1 Selection tree for participants with COPD or bronchiectasis

Figure 2 - Differences in FEV₁ and FVC % predicted in a) COPD and b) bronchiectasis according to diagnostic status of GOR

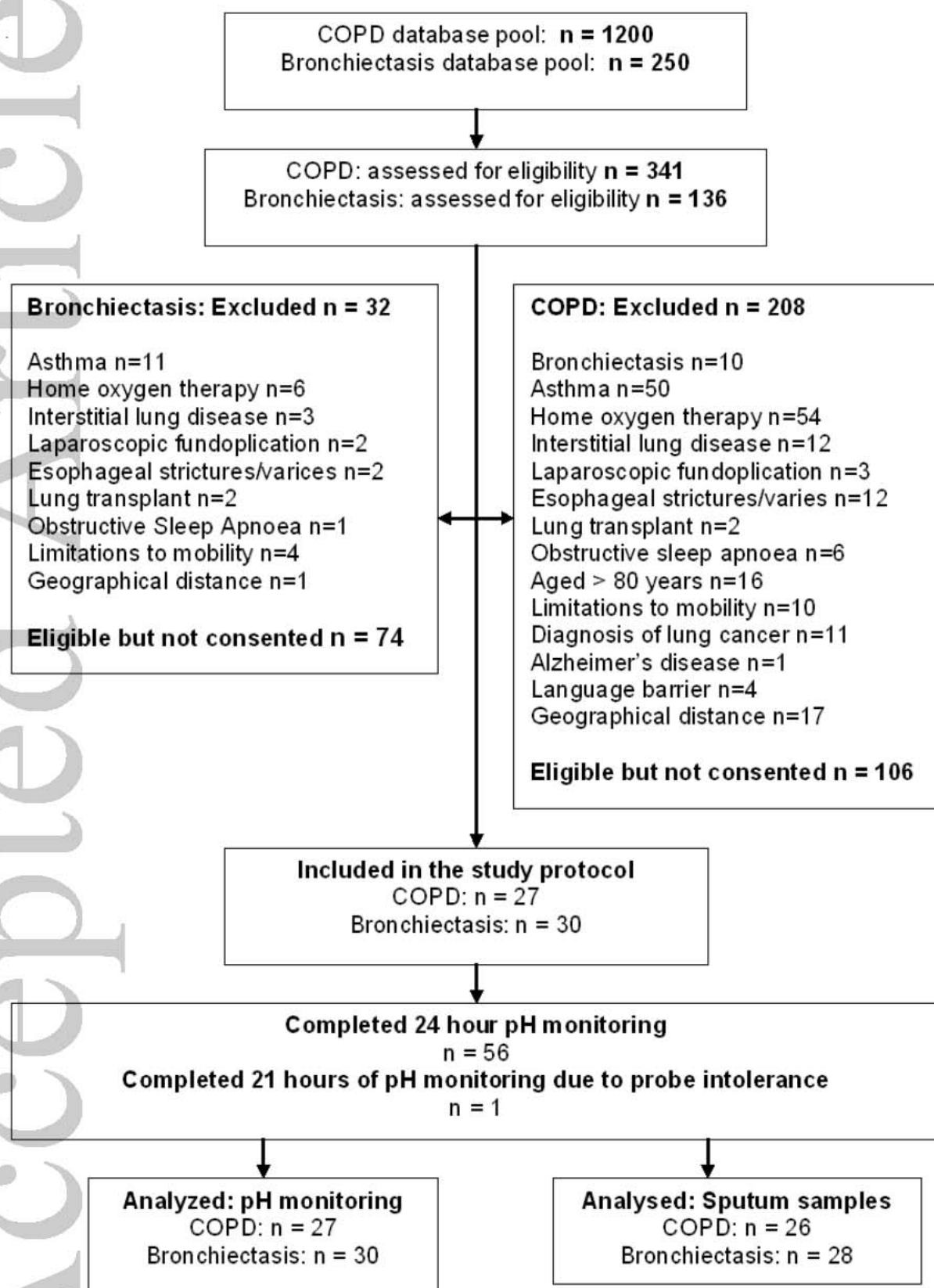


Figure 1.TIF

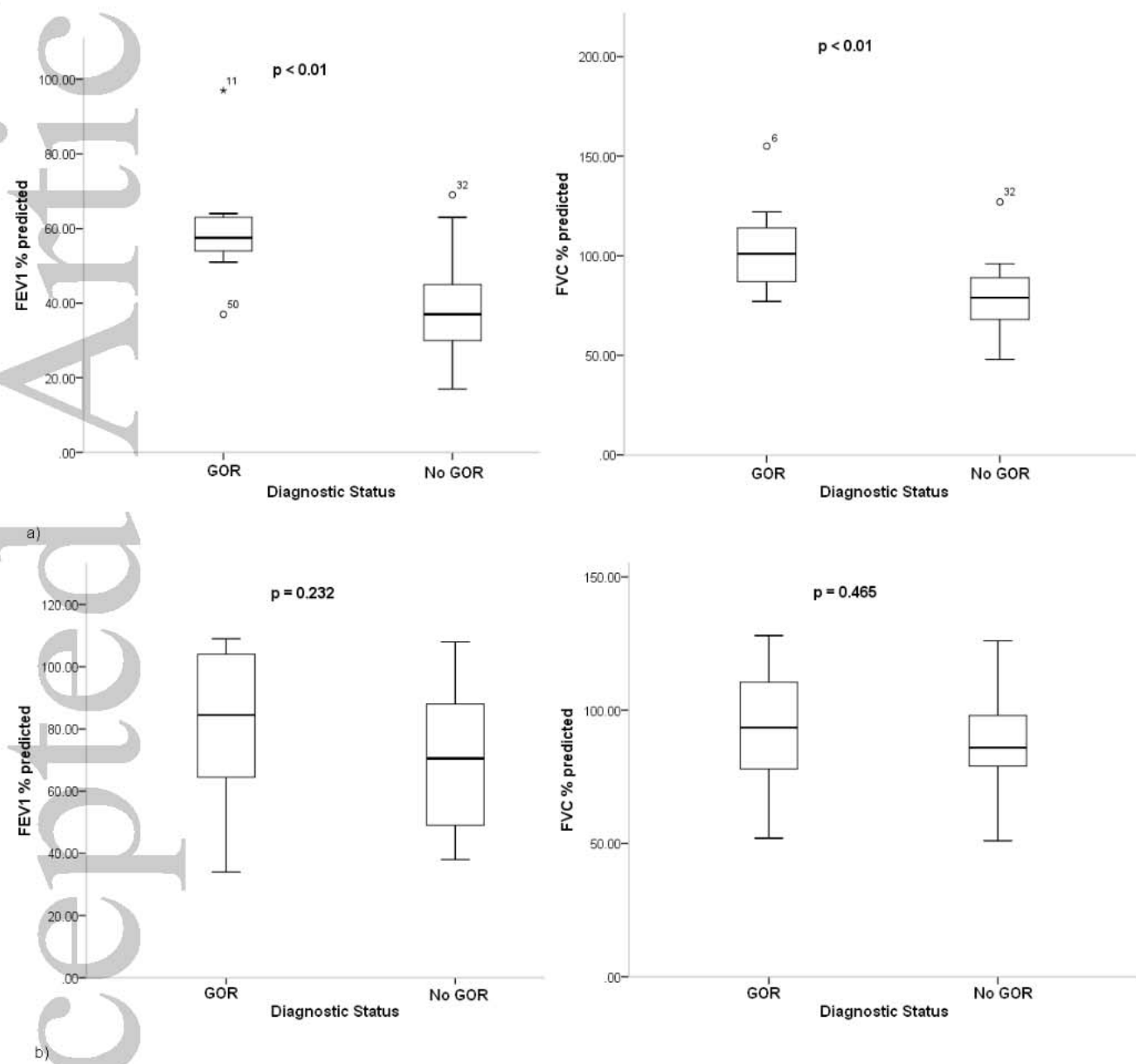


Figure 2.TIF