Associations between gastro-oesophageal reflux, its management and exacerbations of chronic obstructive pulmonary disease

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Abstract

Aim: To determine factors, overall and by sex, associated with self-reported gastro-oesophageal reflux disease (GORD) in chronic obstructive pulmonary disease (COPD) patients, and to evaluate relationships between GORD, its modification by acid suppression medications (Proton Pump Inhibitors[PPI]/histamine-2 receptor antagonists[H2RA]) and exacerbations of COPD and mortality.

Methods: Logistic regression was used to determine factors associated with GORD; Cox proportional hazards models were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for GORD and risk of exacerbation and death.

Results: Among 2,135 COPD patients from the ECLIPSE cohort, 547 patients self-reported GORD, with female preponderance; 237 were taking PPI/H2RA. Risk factors for GORD did not differ by sex. When compared to patients who did not report GORD or use of PPI/H2RA, patients with GORD and taking PPI/H2RA had a significantly increased risk of exacerbation (HR=1.58, 95%CI=1.35-1.86); risk was also increased for patients reporting GORD only or PPI/H2RA use only (HR=1.21 [1.04-1.40] and 1.33 [1.08-1.65], respectively). Similar findings were observed for risk of hospitalised exacerbation. GORD was not associated with mortality.

Conclusion: GORD in COPD patients is highly prevalent, and risk factors did not differ by sex. Use of PPI/H2RA and self-reported GORD were associated with increased risk of moderate-to-severe and hospitalised exacerbations.

Abbreviations

BODE	Body mass index, airflow Obstruction, Dyspnea and Exercise capacity;
BMI	Body mass index
CES-D	Center for Epidemiologic Studies of Depression Scale
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue questionnaire
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
GORD	Gastro-oesophageal reflux disease
H2RA	Histamine-2 receptor antagonist
HR	Hazard ratio
mMRC	modified Medical Research Council
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PPPY	Per person per year
PPI	Proton pump inhibitor
SD	Standard deviation
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
Rx	Treatment

Introduction

It is widely accepted that co-morbidities are common in, and contribute significantly to the morbidity and mortality associated with chronic obstructive pulmonary disease (COPD) [1]. A small but significant body of literature suggests that gastro-oesophageal reflux disease (GORD) is a common co-morbidity in COPD. Two studies with prospectively collected information suggest an association between GORD and exacerbations of COPD [2,3].

Acid suppression medications are effective at reducing gastric acid production and a small randomized single-blind study suggested they may be effective in reducing exacerbations in COPD [4]; however, recent prospective studies do not support this finding [2,3].

To further elucidate the relationship between GORD, acid suppression medications and exacerbations of COPD, we analysed data from the large well characterised longitudinal Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort with the following aims: (1) to determine what factors are associated with the presence of GORD in COPD patients and whether these factors differ by sex, and (2) to evaluate the relationship between self-reported history of GORD, its modification by acid suppression medications and future exacerbations of COPD.

Methods

Study design and patients

Full details of the ECLIPSE study (SCO104960, NCT00292552) design and methods are described elsewhere [5]. In brief, clinically diagnosed COPD patients aged 40-75 years, with a smoking history ≥10 pack years, a post-bronchodilator Forced Expiratory Volume in 1 second (FEV_1) <80% of predicted value use, and a post-bronchodilator FEV_1/Forced Vital Capacity (FVC) ratio <0.7 were recruited. Baseline measurements included lung function, anthropometric factors and others, and a blood sample was collected. Patients also completed

assessments of dyspnoea (modified Medical Research Council [mMRC] Dyspnoea scale), health status (St. George's Respiratory Questionnaire for COPD patients [SGRQ-C]), fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue questionnaire [FACIT-F]) and depression (Center for Epidemiologic Studies of Depression Scale [CES-D]). Self-reported information on respiratory symptoms, medication, smoking history, occupational exposure and co-morbidities were also collected at study entry. GORD was defined by questionnaire using the following question: "Has a doctor ever told you that you had gastro-oesophageal reflux or heartburn?" Full lung function was measured on a smaller subset of 558 patients. After a baseline visit, patients were followed for a total of seven visits at three months, six months and every six months thereafter for three years.

ECLIPSE complies with the Declaration of Helsinki and Good Clinical Practice Guidelines, and has been approved by the ethics committees of the participating centres. All participants provided written informed consent.

Study outcomes

The COPD outcomes, moderate-severe exacerbations, hospitalised exacerbations, and death were reported during the three year follow-up.

Exacerbations of COPD were determined by the patients' primary clinicians or study personnel. Primary care clinicians were not given specific instructions on exacerbation diagnosis for the purposes of this study. Only exacerbations of COPD treated with antibiotics and/or systemic corticosteroids, or requiring hospitalisation were included in the analysis therefore fulfilling a health-care utilisation exacerbation definition of moderate or severe intensity. The criteria for an exacerbation used during the study follow-up were identical to those used at study baseline when collecting data from patients on the number of exacerbations they had experienced in the previous year.

Exposure variables

Self-reported history of a physician's diagnosis of GORD (referred to hereafter as self-reported GORD), treatment with acid suppression medications (proton pump inhibitor [PPI] and/or histamine-2 receptor antagonist [H2RA]) and self-reported GORD stratified by treatment with acid suppression therapy (PPI/H2RA) were used as primary exposure variables. Use of PPI and H2RA was defined as any use at the time of baseline visit.

Statistical analysis

All patients with at least 30 days of follow-up were included in the study. Only one patient withdrew from the study prior to 30 days follow-up. The individual's patient time in study started with baseline visits and was censored at end of study (day 1,060), withdrawal, or death.

Comparisons between descriptive summaries were examined using t-tests for means comparisons and chi-square tests for proportions. The incidence of exacerbations during the study period was summarised as a per-person-per-year rate with the differences between groups analysed using the nonparametric Kruskal-Wallis test.

Factors associated with self-reported GORD

Associations between GORD and possible explanatory factors were initially explored using univariable logistic regression calculating odds ratios (ORs) and 95% confidence intervals (CIs). Variables obtaining a p-value ≤0.2 were selected for inclusion in the manual stepwise model building process. For entry into and deletion from the final model, a p-value of 0.05 was used. Age (per 10 year increase), sex (male, female), exacerbations in the 12 months prior to baseline (0-1, 2+), body mass index (BMI) (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m^2), and

smoking status (past, current) were adjusted for in all multivariable models, where appropriate. Analyses were carried out for all patients combined, and by sex.

The effect of plethysmography derived lung volumes, including markers of hyper-inflation, and risk of GORD was examined in a subset of patients who completed this procedure (N=558) using univariable logistic regression analyses to estimate ORs and 95% CIs.

Two sensitivity analyses were carried out: 1) GORD case definition of self-reported history of GORD and using PPI/H2RA at baseline, and 2) restricting the analyses to only those with complete data for the adjustment factors.

GORD and time to first exacerbation and death

We evaluated risk of moderate-to-severe exacerbations, exacerbations requiring hospital admission, and all-cause mortality, as separate primary end points, by presence of GORD and treatment with PPI/H2RA using Cox proportional hazards models calculating hazard ratios (HRs) and 95% CIs. The stratification term between GORD status and PPI/H2RA included four categories: 1) no GORD and no PPI/H2RA; 2) GORD and no PPI/H2RA; 3) no GORD and use of PPI/H2RA; and, 4) GORD and use of PPI/H2RA. No GORD and no PPI/H2RA use was used as the referent category.

For all models, adjustments were made for age, sex, exacerbations in the 12 months prior to baseline, BMI, smoking status, FEV_1 (per 100ml decrease), SGRQ total score (per increase of 4 points), and white-cell count (per increase of $1x10^3/mm^3$); factors modelled previously [6]. A manual step-wise procedure for covariate selection was then followed using additionally all variables having an unconditional association with the outcome ($p \leq 0.2$).

Biomarker data were $\log_{10}$ transformed prior to all regression analyses where the normality assumption was not met. Variables with >10% missing data (fibrinogen and CCL18) were divided into quartiles, with an additional missing category included.

Two sensitivity analyses were carried out: 1) including only patients who did not report an exacerbation in the 12 months prior to enrolment, and 2) restricting the analyses to only those with complete data for the adjustment factors.

Results

Characteristics of the patients

A total of 2,135 COPD patients completed the question on history of GORD and were available for follow-up, of which 547 (26%) reported ever having been diagnosed with GORD. Amongst the patients who self-reported GORD, 237 (43%) were taking PPI/H2RA at baseline. There were an additional 127 patients who were taking PPI/H2RA but did not report a history of GORD. During the three year follow-up, 1,579 (74%) patients reported at least one exacerbation, of which, 668 (42%) required hospitalisation. A total of 201 (9%) patients died during follow-up.

Baseline characteristics of the patients overall and by GORD status are reported in Table 1. As shown, patients with GORD were more likely to be female, have a higher BMI, less impaired lung function (measured by FEV_1 percent predicted), but reported more symptoms and poorer health status and had higher levels of fibrinogen than patients without GORD. They were also more likely to have frequently exacerbated (=>2 events) in the 12 months prior to the study baseline. Patients with GORD had a lower functional residual capacity (FRC) percent predicted and higher inspiratory capacity (IC) percent predicted (Supplementary Table 1). No other lung volume measures were associated with self-reported GORD.

Moderate-severe exacerbation rate during follow-up was 1.2 (SD: 1.42) events per patient per year, and was higher in patients who self-reported a physician's diagnosis of GORD than those who did not (1.46 [SD: 1.52] versus 1.13 [SD: 1.37], respectively) (Table 1). Hospitalized exacerbation rate also differed by GORD status, but to a lesser extent (0.34 [SD: 0.73] versus 0.27 [SD: 0.63], for history of GORD yes vs. no, respectively).

Factors associated with self-reported GORD

Factors unconditionally associated with GORD for all patients, and by sex are shown in Supplementary Table 2. In a multivariable model, self-reported history of GORD was significantly more likely to be reported by females (OR=1.80, 95% CI=1.41-2.29), older patients (OR=1.20, 95% CI=1.02-1.41 per 10 year increase), overweight and obese (OR= 1.40 [1.08-1.80], and 1.48 [1.11-1.98], respectively, for 25-29.9 and 30+ kg/m^2, when compared to 18.5-24.9 kg/m^2), in patients with less impaired lung function (OR=0.95, 95% CI=0.93-0.97), poorer health status (OR=1.06, 95% CI=1.04-1.09), history of chronic wheeze (OR=1.33, 95% CI=1.05-1.68) and history of asthma (OR=1.65, 95% CI=1.29-2.12), decreasing levels of neutrophils (OR=1.02, 95% CI=1.00-1.03), and increasing levels of IL6 (OR=1.14, 95% CI=1.02-1.27) (Table 2). Although prevalence of GORD was significantly higher among females, the factors predicting GORD did not vary by sex.

Sensitivity analyses restricting the analyses to only those with complete data for the adjustment factors did not materially change the results for the whole cohort, or by sex. When the definition of GORD was restricted to include only those who reported a history of GORD and were also using PPI/H2RA at baseline, the effect of most covariates was marginally strengthened, but the overall interpretation of the models did not change for the whole cohort (N=237 cases), or by sex.

GORD and exacerbations during follow-up

Unadjusted analyses showed that for moderate-severe exacerbations, time to first exacerbation was shorter in patients with GORD compared to those without GORD ($p<0.0001$) (Figure 1A). In addition, COPD patients taking PPI/H2RA also had a shorter time to first exacerbation independent of whether or not they reported GORD ($p=0.007$ and 0.002 with GORD and no GORD, respectively) (Figures 1B and 1C). Further, patients with a self-reported history of GORD and also those treated with PPI/H2RA but no GORD had a shorter time to first hospitalised exacerbation ($p=0.02$ and 0.0003, respectively) (Figures 2A and 2C). Time to first hospitalised exacerbation did not differ by PPI/H2RA use in patients with a self-reported history of GORD (Figure 2B).

In a multivariable analysis, when compared to patients who did not report GORD or use of PPI/H2RA, the population with GORD and on medication had a significantly increased risk of exacerbation (HR=1.58 [95%CI=1.35-1.86]); the risk was also increased for patients who reported GORD only or the use of PPI/H2RA only (HR=1.21 [1.04-1.40] and 1.33 [1.08-1.65], respectively) (Table 3). Similarly, self-reported history of GORD was significantly associated with hospitalised exacerbations (HR=1.28 [95%CI=1.02-1.60]), as was use of PPI/H2RA (HR=1.45, (1.07-1.97]); however, when self-reported GORD and medication were combined, although increased, the risk was not significant (HR=1.26 [0.97-1.63]) (Table 4).

Self-reported history of GORD was not significantly associated with all-cause mortality (HR= 0.88 [95%CI=0.58-1.34], $p=0.6$), nor was the use of PPI/H2RA in GORD and non-GORD sufferers (HR = 1.36 [0.81-2.28], $p=0.2$; 0.87 [0.55-1.40], $p=0.6$, respectively).

When restricting the analysis to patients who did not exacerbate in the 12 months prior to baseline, the effect of GORD and use of PPI/H2RA was similar to the final models for moderate-severe exacerbations and hospitalised exacerbations. The results did also not materially change when restricting to patients with complete data for the adjustment factors.

Discussion

In this cohort of COPD patients, we found that self-report of GORD diagnosis or use of acid suppression medications (PPI and/or H2RA) at baseline were associated with a 20-60% increased risk of moderate-severe exacerbations and hospitalised exacerbations during the three years of follow-up. In addition, the use of PPI/H2RA in the presence of GORD also significantly increased the risk of exacerbations, but not differently from the effect of the self-reported history of GORD only or use of PPI/H2RA only. Self-reported history of GORD or use of PPI/H2RA was not associated with all-cause mortality.

Self-reported GORD was highly prevalent among patients with COPD (26%), with significantly more women than men reporting a history of GORD (31% vs 23%, respectively). Although GORD was more common in women, no specific markers of such preponderance to GORD in females were identified.

There is now information from multiple studies employing different designs to suggest the importance of GORD in COPD. Regular GORD symptoms were found to be as much as three times more prevalent in patients with COPD than the general population [7] and, smokers without COPD [8]. Despite the prominence of GORD in COPD, there is little known about the pathology of this comorbidity. Potential mechanisms include increased intra-abdominal pressure (e.g with coughing), hyper-expansion displacing the diaphragm (discussed later), increased trans-diaphragmatic pressure secondary to airflow obstruction, altered autonomic tone of the lower oesophageal sphincter (either as part of COPD, or as a consequence of medication such as salbutamol) and use of gastro-irritant medication such as steroids [9]. The relationship between GORD and COPD is complex due to varying reflux presentation, which may be proximal or distal, acidic or not, and gaseous or liquid. Moreover, due to poor correlation between GORD symptoms, endoscopic findings and pH impedance

studies, there is paucity of standardised patient-reported questionnaires that can aid clinical diagnosis or be used in clinical studies.

Similarly to findings reported from other studies, we found GORD to be more frequent in women than men [3,10,11]. In addition to these studies we explored in-depth, factors driving this differential reporting by sex but, despite having a comprehensive dataset, we did not detect any determinants of GORD that would differ by sex.

It has been suggested that GORD may be more common in patients with hyper-inflation, as a result of caudal displacement of the diaphragm [12]; however, we did not find associations between physiological indices of hyper-inflation such as residual volume and self-reported history of GORD.

The increased risk of exacerbation in GORD sufferers has been reported in other studies [2,3,13-17]. Little is known about this association, but it is thought that the relationship may be reciprocal: exacerbations with cough and hyper-expansion may result in more reflux, and/or refluxate may result in exacerbation through aspiration and/or microaspiration, and/or vagally mediated reflex cough. This is important given the impact of exacerbations in COPD and the urgent need for novel interventions to reduce the frequency and severity of exacerbations.

A hypothesis potentially explaining the risk of increased exacerbations in patients taking acid suppression medications would be that non-acidic reflux is more important in COPD, and that acid suppression medication use by reducing acid-associated symptoms may reduce patients' presentation. Non-acidic reflux may consequently be more likely to result in aspiration as protective cough reflexes are not stimulated. The COPDGene study [3] also reported an association between GORD and frequent exacerbations with and without the use of PPI drugs. This is in contrast to findings from the Copenhagen City Heart Study where acid suppression medications were not associated with risk of exacerbation in those reporting

GORD [2]. Our study showed that the presence of GORD, either as a self-reported diagnosis or as use of PPI/H2RA, is associated with an increased risk of exacerbations. Newly, we showed that COPD patients were at an increased risk of both moderate-severe and hospitalised exacerbations even if they had no report of history of GORD but were using PPI/H2RA.

As patients were not asked at recruitment about the reasons for medication prescription, it is unknown why some patients were taking PPI/H2RA in the apparent absence of GORD. It is possible that some patients may have been using PPI/H2RA for GORD without them recalling the GORD the diagnosis. It is also common practice in some countries to use PPI/H2RA in an attempt to reduce the gastro-irritant potential of steroid and non-steroidal anti-inflammatory drugs (NSAIDs) that are relevant in a population with COPD. Of the 127 patients taking PPI/H2RA and not reporting history of GORD, 11 (18%) reported taking NSAIDs.

To date there are no randomised double-blind controlled trials of interventions to reduce gastric acidity, or reflux in COPD designed to reduce exacerbations. In a 12-month, randomised, single-blind trial of lansoprazole in 100 patients, patients on active drug had a lower exacerbation frequency (0.34 versus 1.18 per year $p<0.001$) [4]. Interestingly, this study hypothesised on anti-inflammatory actions of the drug and patients with symptoms of GORD were excluded. Macrolide drugs reduce exacerbations in COPD [18] but the mechanism remains obscure: One potential mechanism is through an action on gastric motility as the drugs are motilin agonists. A lack of effectiveness of acid suppression therapy on reducing the exacerbation of COPD rate can be a result of several possibly co-occurring factors including the real lack of effect, multifactorial origins of exacerbations of COPD, and confounding by indication, whereby patients with more severe GORD are more frequently treated with acid suppression therapy.

The strengths of our study are the large and carefully characterised patient population and three years of follow-up information. The main limitation pertains to the GORD ascertainment and lack of measures specifically related to GORD. Similarly to COPDGene [3] we used a self-report of GORD diagnosis and the use of PPI/H2RA as markers of possible GORD. To date, only one study [17] has used a validated standardized questionnaire to determine history of GORD making comparisons of findings between studies difficult. The gold standards for the diagnosis of GORD are esophagogastroduodenoscopy and 24-hour esophageal pH impedance monitoring, both of which have not been measured in prospective COPD populations. The correlation between GORD symptoms, endoscopic findings, and gold-standard pH-impedance monitoring is known to be poor [9]. Larger studies are needed to clarify the significance of acid suppression medication use and COPD exacerbations in both the presence and absence of GORD.

In summary, GORD in COPD is highly prevalent and more commonly reported by women. Use of PPI/H2RA and self-reported history of GORD were associated with an increased risk of moderate-to-severe exacerbation and hospitalised exacerbations.

Table 1: Baseline characteristics of the COPD patients and summary of exacerbation of COPD during follow-up, by gastro-oesophageal reflux disease (GORD) status*

Baseline characteristic	All patients (n=2,135) Mean (SD)	GORD (Yes) (n=547) Mean (SD)	GORD (No) (n=1558) Mean (SD)	p-value
Age (years)	63.4 (7.1)	63.5 (6.9)	63.4 (7.2)	0.9
Female, n(%)	742 (34.8)	233 (42.6)	509 (32.1)	<0.0001*
GOLD Stage, n(%)				
Stage 2	943 (44.2)	285 (52.1)	658 (41.4)	<0.0001*
Stage 3	899 (42.1)	203 (37.1)	696 (43.8)	
Stage 4	293 (13.7)	59 (10.8)	234 (14.7)	
Current smoker, n(%)	772 (36.2)	191 (34.9)	581 (36.6)	0.5
Pack-years	*48.6 (27.1)*	*51.0 (28.1)*	*47.8 (26.7)*	*0.02*
Body mass index, kg/m^2, n(%)				
<18.5	108 (5.1)	17 (3.1)	91 (5.7)	<0.0001*
18.5-24.9	783 (36.7)	169 (30.9)	614 (38.7)	
25.0-29.9	760 (35.6)	211 (38.6)	549 (34.6)	
≥30	484 (22.7)	150 (27.4)	334 (21.0)	
FEV_1 (l)	1.3 (0.5)	1.4 (0.5)	1.3 (0.5)	0.1
FEV_1 (% predicted) (n=2,131)	48.2 (15.7)	50.8 (15.6)	47.4 (15.7)	<0.0001
FEV_1/FVC (%) (n=2,131)	44.7 (11.5)	46.0 (11.6)	44.3 (11.5)	0.004
Emphysema (LAA%)	17.7 (12.3)	16.5 (11.1)	18.1 (12.6)	0.02
mMRC Dyspnoea Score (2+), n(%)	1106 (53.2)	307 (57.4)	799 (51.8)	0.02
Depression (CES-D score)	11.4 (9.3)	13.2 (9.5)	10.8 (9.1)	<0.0001
Fatigue (FACIT-F score)	35.1 (10.7)	32.8 (11.0)	35.9 (10.4)	<0.0001
SGRQ Total Score	48.1 (18.3)	51.6 (17.0)	46.9 (18.6)	<0.0001
BODE Index	3.2 (2.1)	3.0 (2.1)	3.2 (2.1)	0.05
Chronic wheeze, n(%)	842 (39.4)	277 (50.6)	565 (35.6)	<0.0001
Chronic cough, n(%)	1051 (49.2)	281 (51.4)	770 (48.5)	0.2
Chronic phlegm, n(%)	1088 (51.0)	296 (54.1)	792 (49.9)	0.09
Asthma history, n(%)	489 (22.9)	182 (33.3)	307 (19.3)	<0.0001
Peptic ulcer, n(%)	218 (10.2)	114 (20.8)	104 (6.6)	<0.0001
Cardiovascular comorbidity, n(%)	713 (33.4)	186 (34.0)	527 (33.2)	0.7
Diabetes Mellitus, n(%)	213 (10.0)	62 (11.3)	151 (9.5)	0.2
Anxiety, n(%)	351 (16.4)	155 (28.3)	196 (12.3)	<0.0001
White blood cell count (109/l)	7.9 (2.3)	7.9 (2.2)	7.9 (2.3)	0.8
Fibrinogen (mg/dl)	455.1 (103.9)	468.3 (107.2)	450.5 (102.4)	0.001
hsCRP (mh/l)	6.8 (11.6)	7.0 (10.4)	6.7 (11.9)	0.5
CC-16 (ng/ml)	5.6 (3.3)	5.6 (3.3)	5.6 (3.3)	0.9
CCL-18 (ng/ml)	112.9 (43.3)	116.1 (42.8)	111.8 (43.4)	0.06
SPD (ng/ml)	135.7 (76.6)	130.1 (73.2)	137.6 (77.7)	0.05
H2RA, n(%)	65 (3.0)	43 (7.9)	22 (1.4)	<0.0001
PPI, n(%)	305 (14.3)	199 (36.4)	106 (6.7)	<0.0001
PPI and/or H2RA, n(%)	364 (17.0)	237 (43.3)	127 (8.0)	<0.0001
Any exacerbation in prior year, n(%)	1011 (47.4)	264 (48.3)	747 (47.0)	0.6
≥2 exacerbations in prior year, n(%)	466 (21.8)	140 (25.6)	326 (20.5)	0.01
Follow-up information				

Baseline characteristic	**All patients (n=2,135) Mean (SD)**	**GORD (Yes) (n=547) Mean (SD)**	**GORD (No) (n=1558) Mean (SD)**	**p-value**
Exacerbation rate (PPPY)				
Moderate-to-severe exacerbations	1.22 (1.42)	1.46 (1.52)	1.13 (1.37)	<0.0001
Requiring hospitalisation	*0.28 (0.66)*	*0.34 (0.73)*	*0.27 (0.63)*	*0.02*
Died during follow-up (%)	202 (9.5)	46 (8.4)	156 (9.8)	0.3

*Global p-value

For abbreviations, see list of abbreviations

Table 2: Factors associated with self-reported gastro-oesophageal reflux disease (GORD) in COPD patients, overall and by sex using a step-wise multivariable model

	All patients (n=1,925)		Males (n=1,339)		Females (n=718)	
Baseline characteristic	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex – *female vs male*	1.80 (1.41-2.29)	<0.0001				
Exacerbation during previous year – *2+ vs 0-1*	1.10 (0.85-1.43)	0.5	1.14 (0.82-1.59)	0.4	1.08 (0.74-1.59)	0.7
Age – *per 10 year increase*	1.20 (1.02-1.41)	0.03	1.25 (1.02-1.52)	0.03	1.28 (0.98-1.66)	0.07
Smoking status – past vs current	0.97 (0.77-1.23)	0.8	0.85 (0.64-1.13)	0.3	1.14 (0.79-1.65)	0.5
Body mass index, kg/m^2						
<18.5	0.65 (0.36-1.16)	0.003*	1.24 (0.60-2.58)	0.02*	0.30 (0.12-0.74)	0.02*
18.5-24.9	1.00		1.00		1.00	
25.0-29.9	1.40 (1.08-1.80)		1.53 (1.10-2.12)		1.17 (0.79-1.73)	
≥30	1.48 (1.11-1.98)		1.71 (1.20-2.44)		1.26 (0.81-1.96)	
FEV_1 – *per 100ml decrease*	0.95 (0.93-0.97)	<0.0001	0.94 (0.91-0.97)	<0.0001	0.95 (0.90-1.00)	0.03
SGRQ total score for *COPD* – *per increase of 4 points*	1.06 (1.04-1.09)	<0.0001	1.06 (1.03-1.10)	<0.0001	1.06 (1.02-1.10)	0.007
Neutrophils – per 1% decrease	1.02 (1.00-1.03)	0.02	-	-	-	-
Il6 – per increase of 1SD on log scale	1.14 (1.02-1.27)	0.02	-	-	-	-
Chronic wheeze – *ever vs never*	1.33 (1.05-1.68)	0.02	1.34 (1.00-1.79)	0.05	1.48 (1.02-2.14)	0.04
Asthma – *ever vs never*	1.65 (1.29-2.12)	<0.0001	1.57 (1.14-2.18)	0.006	1.89 (1.32-2.72)	0.0005

*Global p-value

For abbreviations, see list of abbreviations

Table 3: The effect of gastro-oesophageal reflux disease (GORD) stratified by the use of acid suppression medications on time to first moderate-severe exacerbation in COPD patients, adjusting for other factors. N=1,991.

Baseline characteristic	HR (95% CI)	p-value
No GORD, no acid suppression Rx	1.00	
Yes GORD, no acid suppression Rx	1.21 (1.04-1.40)	0.01
No GORD, yes acid suppression Rx	1.33 (1.08-1.65)	0.008
Yes GORD, yes acid suppression Rx	1.58 (1.35-1.86)	<0.0001
Sex – *female vs male*	1.08 (0.96-1.21)	0.2
Age – *per 10 year increase*	1.04 (0.96-1.13)	0.3
	1.08 (0.96-1.21)	0.2
Smoking status – *past vs current*		
Body mass index, kg/m^2		
<18.5	0.89 (0.70-1.13)	0.006
18.5-24.9	1.00	
25.0-29.9	0.88 (0.78-0.99)	
≥30	0.78 (0.68-0.90)	
FEV_1 – *per 100ml decrease*	1.06 (1.05-1.07)	<0.0001
SGRQ Total Score for *COPD – per increase of 4 points*	1.02 (1.01-1.03)	0.001
Exacerbation during previous year – *2+ vs 0-1*	2.04 (1.80-2.30)	<0.0001
White-cell count – *per increase of* $1x10^3/mm^3$	1.04 (1.01-1.06)	0.002
Asthma – *ever vs never*	1.12 (0.98-1.26)	0.09
Chronic wheeze – *ever vs never*	1.15 (1.02-1.29)	0.02

*Global p-value

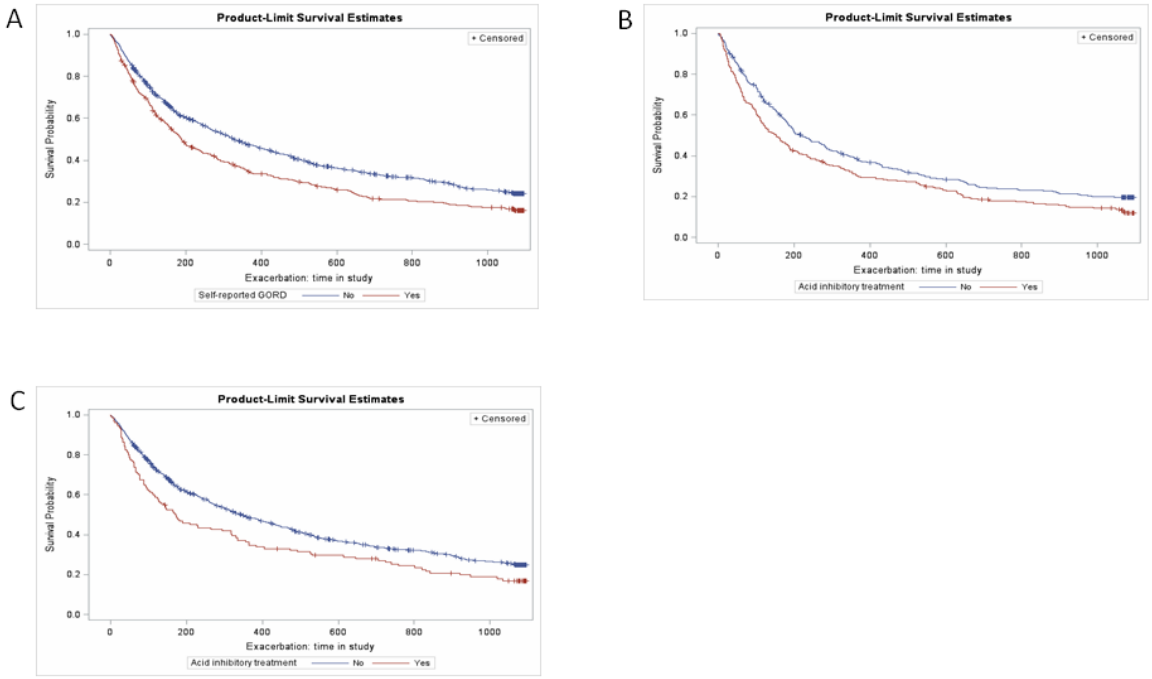
For abbreviations, see list of abbreviations

Table 4: The effect of gastro-oesophageal reflux disease (GORD) and the use of acid suppression medications on the time to first hospitalised exacerbation, adjusting for other factors. N=1,903

Baseline characteristic	HR (95% CI)	p-value
No GORD, no acid suppression Rx	1.00	
Yes GORD, no acid suppression Rx	1.28 (1.02-1.60)	0.03
No GORD, yes acid suppression Rx	1.45 (1.07-1.97)	0.02
Yes GORD, yes acid suppression tx	1.26 (0.97-1.63)	0.08
Sex – *female vs male*	0.72 (0.60-0.86)	0.0004
Age – *per 10 year increase*	1.17 (1.03-1.33)	0.02
Smoking status – *past vs current*	1.01 (0.84-1.21)	0.9
Body mass index, kg/m^2		
<18.5	1.17 (0.82-1.66)	0.01*
18.5-24.9	1.00	
25.0-29.9	0.81 (0.67-0.99)	
≥30	0.74 (0.59-0.92)	
FEV_1 – *per 100ml decrease*	1.10 (1.08-1.13)	<0.0001
SGRQ Total Score– *per increase of 4 points*	1.06 (1.04-1.08)	<0.0001
Exacerbation during previous year – *2+ vs 0-1*	1.24 (1.13-1.35)	<0.0001
		0.02
mMRC Score *2+ vs 0-1*	1.27 (1.04-1.55)	
CCL18 (quartiles)		
Q1	1.00	0.02*
Q2	1.02 (0.79-1.32)	
Q3	0.88 (0.68-1.15)	
Q4	1.27 (0.99-1.63)	
White-cell count – *per increase of* $1x10^3/mm^3$	1.06 (1.03-1.10)	0.0004
Post-high school education	0.84 (0.70-1.00)	0.05
Asthma – ever vs never	1.22 (1.01-1.47)	0.04

*Global p-value
For abbreviations, see list of abbreviations

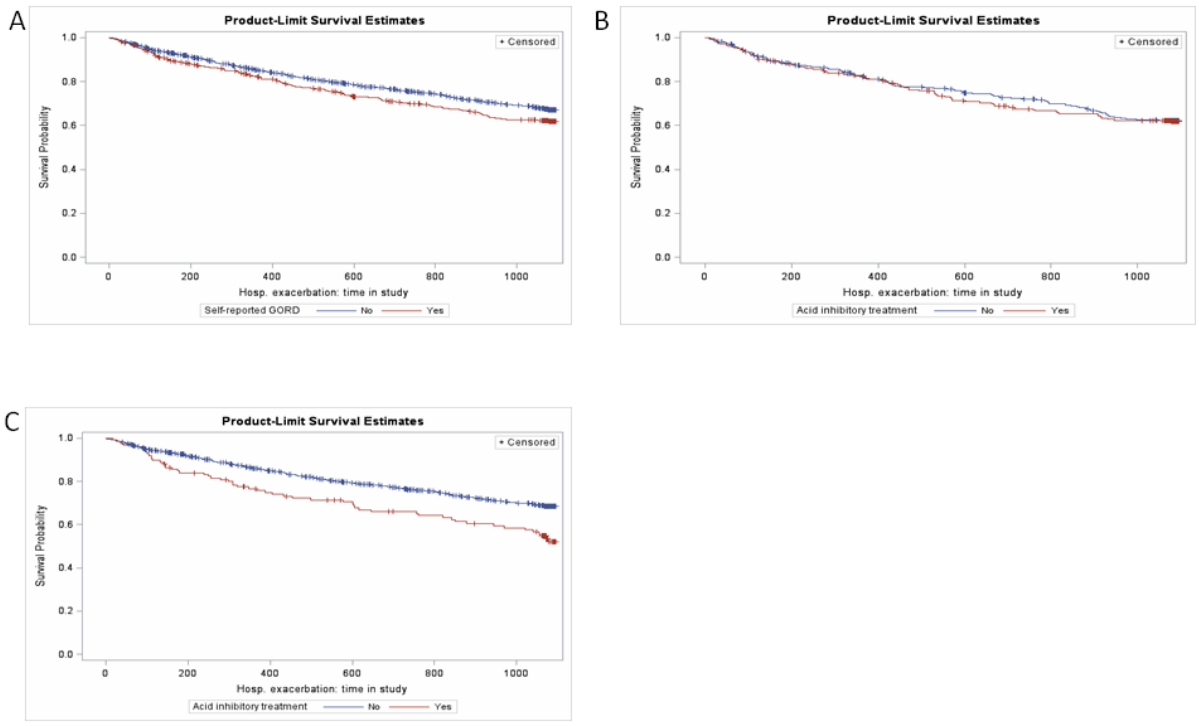
Figure 1: Kaplan-Meier Plots for time to first moderate-to-severe exacerbation in COPD, by gastro-oesophageal reflux disease (GORD) status and use of PPI and/or H2RA medications



Footnote: A) Kaplan-Meier plot for moderate-severe exacerbations, by GORD status; B) Kaplan-Meier plot for moderate-severe exacerbations in patients with GORD, by those taking PPI and/or H2RA; C) Kaplan-Meier plot for moderate-severe exacerbations in patients WITHOUT GORD, by those taking PPI and/or H2RA

For abbreviations, see list of abbreviations

Figure 2: Kaplan-Meier Plots for time to first hospitalised exacerbation in COPD, by gastro-oesophageal reflux disease (GORD) status and use of PPI and/or H2RA medications



A) Kaplan-Meier plot for hospitalised exacerbations, by GORD status; B) Kaplan-Meier plot for hospitalised exacerbations in patients with GORD, by those taking PPI and/or H2RA; C) Kaplan-Meier plot for hospitalised exacerbations in patients WITHOUT GORD, by those taking PPI and/or H2RA.

For abbreviations, see list of abbreviations

Supplementary Table 1: Lung volume measures and the risk of self-reported gastro-oesophageal reflux disease in a COPD patient population (N=558): univariable analyses

Baseline lung volume measures	OR (95% CI)	p-value
Percent predicted normal residual volume	1.00 (0.99-1.00)	0.2
Percent predicted normal total lung capacity	1.00 (0.99-1.01)	0.6
Percent predicted normal functional residual capacity	0.99 (0.99-1.00)	0.03
Slow vital capacity (L)	0.90 (0.75-1.07)	0.2
Inspiratory capacity (L)	1.09 (0.84-1.39)	0.5
Percent predicted inspiratory capacity	1.02 (1.01-1.03)	0.001

For abbreviations, see list of abbreviations

Supplementary Table 2: Odds ratios and 95% confidence intervals for factors associated with self-reported gastro-oesophageal reflux disease in a COPD patient population: univariable analyses

Baseline characteristic	All patients (n=2135)		Males (n=1,393)		Females (n=742)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Exacerbation in last 12 months (0-1, 2+)	1.33 (1.06-1.67)	0.01	1.25 (0.92-1.69)	0.2	1.33 (0.94-1.88)	0.1
mMRC Dyspnea Score (0-1, 2+)	1.26 (1.03-1.53)	0.02	1.17 (0.91-1.51)	0.2	1.41 (1.02-1.94)	0.04
Sex, female	1.57 (1.29-1.92)	<0.0001	-		-	
Body mass index, kg/m^2						
<18.5	0.68 (0.39-1.17)		1.32 (0.65-2.68)		0.29 (0.12-0.69)	
18.5-24.9	1.00	0.0001*	1.00	0.002*	1.00	0.003*
25.0-29.9	1.40 (1.11-1.76)		1.64 (1.21-2.24)		1.21 (0.84-1.75)	
≥30	1.63 (1.26-2.11)		1.86 (1.32-2.60)		1.51 (1.00-2.27)	
Age (per 10 yr increment)	1.01 (0.88-1.16)	0.9	1.02 (0.86-1.22)	0.8	1.07 (0.86-1.34)	0.5
Smoker (past vs current)	1.08 (0.88-1.32)	0.5	0.96 (0.74-1.25)	0.8	1.30 (0.94-1.80)	0.1
FEV_1, per 100ml decrease	0.99 (0.97-1.00)	0.1	0.96 (0.94-0.99)	0.002	0.98 (0.94-1.02)	0.3
FEV_1 percent predicted, per 5% predicted increment	1.07 (1.04-1.11)	<0.0001	1.07 (1.03-1.12)	0.0004	1.05 (1.00-1.10)	0.07
FEV_1/FVC (%)	1.01 (1.00-1.02)	0.004	1.01 (1.00-1.02)	0.02	1.01 (0.99-1.02)	0.4
GOLD grades						
Stage 2	1.00		1.00		1.00	
Stage 3	0.67 (0.55-0.83)	<0.0001*	0.65 (0.50-0.86)	0.002*	0.76 (0.54-1.06)	0.1*
Stage 4	0.58 (0.42-0.80)		0.60 (0.41-0.89)		0.63 (0.36-1.10)	
FVC (l)	0.98 (0.88-1.09)	0.7	1.16 (1.01-1.34)	0.04	1.08 (0.84-1.38)	0.5
SQRG Total Score per 4 unit increment	1.05 (1.03-1.07)	<0.0001	1.05 (1.02-1.07)	0.0006	1.06 (1.03-1.10)	0.0003
Fatigue (FACIT-F score)	0.98 (0.97-0.98)	<0.0001	0.98 (0.97-0.99)	0.003	0.97 (0.95-0.98)	<0.0001
Depression (CES-D score)	1.03 (1.02-1.04)	<0.0001	1.03 (1.01-1.04)	0.0004	1.02 (1.01-1.04)	0.005
Platelet count: 10 x 10^9/L increase	1.01 (1.00-1.03)	0.1	1.01 (0.99-1.02)	0.6	1.01 (0.98-1.03)	0.6
Haemoglobin per 10g/L increment	0.88 (0.82-0.95)	0.001	0.93 (0.85-1.03)	0.2	0.90 (0.78-1.03)	0.1
Neutrophils (per 1% decrease)	1.01 (1.00-1.02)	0.1	1.01 (0.99-1.02)	0.5	1.01 (0.99-1.03)	0.3
Fibrinogen (mg/dL) (quartiles)						
Q1	1.00	0.008*	1.00	0.1*	1.00	0.08*
Q2	1.11 (0.82-1.51)		1.18 (0.80-1.73)		0.97 (0.59-1.60)	
Q3	1.35 (1.00-1.82)		1.45 (1.00-2.12)		1.16 (0.70-1.90)	
Q4	1.60 (1.19-2.15)		1.49 (1.02-2.18)		1.66 (1.03-2.67)	
hsCRP (mg/L) (per 1SD increment on log scale)	1.14 (1.04-1.26)	0.007	1.10 (0.97-1.25)	0.2	1.25 (1.07-1.46)	0.006
SP-D (ng/ml) (per 1SD increment on log scale)	0.90 (0.81-0.99)	0.03	0.99 (0.87-1.13)	0.9	0.80 (0.69-0.93)	0.005
IL-6 (pg/ml) (per 1SD increment on log scale)	1.12 (1.02-1.24)	0.02	1.11 (0.98-1.26)	0.1	1.17 (0.99-1.38)	0.07
CC-18 (ng/ml) (quartiles)						
Q1	1.00	0.2*	1.00	0.8*	1.00	0.01 *
Q2	1.23 (0.91-1.67)		1.20 (0.81-1.80)		1.31 (0.81-2.11)	
Q3	1.32 (0.97-1.78)		1.05 (0.71-1.58)		1.99 (1.24-3.20)	
Q4	1.35 (1.00-1.83)		1.15 (0.77-1.70)		1.96 (1.21-3.19)	
Chronic wheeze (Y/N)	1.86 (1.53-2.26)	<0.0001	1.73 (1.34-2.23)	<0.0001	2.06 (1.50-2.83)	<0.0001
Asthma (Y/N)	2.08 (1.68-2.59)	<0.0001	1.77 (1.32-2.38)	0.0002	2.27 (1.63-3.15)	<0.0001
Chronic cough (Y/N)	1.12 (0.92-1.36)	0.2	1.22 (0.95-1.57)	0.1	1.07 (0.79-1.46)	0.7
Hypertension (Y/N)	1.22 (1.00-1.48)	0.05	1.21 (0.94-1.56)	0.1	1.22 (0.89-1.66)	0.2

*Global p-value

For abbreviations, see list of abbreviations

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Conflicts of interest
Dr Benson is contracted as a consultant to GSK.

Dr Müllerová is employed by GSK R&D and owns shares and stock options of GSK.

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