ORIGINAL ARTICLE

Prevalence and Risk Factors of GERD among Stable COPD Patients

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ARTICLE INFO

Article history:
Received 22 January 2022
Received in revised form
16 September 2022
Accepted 8 December 2022
Available online 30 January 2023

Keywords:
Chronic respiratory diseases,
COPD,
GERD,
Prevalence.

Cite this as:
Hafiz M, Yunus F, Suryamin M, *et al*. Prevalence and Risk Factors of GERD among Stable COPD Patients. *J Respi* 2023; 9: 1–6.

ABSTRACT

Introduction: Gastroesophageal reflux disease (GERD) is one of the most common causes of a chronic cough and is a potential risk factor for chronic obstructive pulmonary disease (COPD) exacerbation. This study aimed to determine the prevalence of GERD in COPD patients.

Methods: This was a cross-sectional study involving 40 stable COPD patients recruited from outpatient asthma and COPD clinics at Persahabatan National Respiratory Referral Hospital, Jakarta, from May to November 2018. COPD was defined as having a ratio of post-bronchodilator $FEV_1/FVC < 0.7$ and no abnormality on a chest X-ray except emphysematous. Diagnosis of GERD was based on oesophageal mucosal lining break surrounding the distal esophageal sphincter through esophagogastroduodenoscopy (EGD). Asthma patients with known esophageal diseases such as cancer, achalasia, and active peptic ulcer and patients who had used proton pump inhibitors in the last 15 days were excluded.

Results: Patients were divided into GERD (+) (16/40, 40%) and GERD (-) (24/40, 60%). Subjects were predominantly elderly (25/40, 62.5%) and had a smoking history (36/40, 90%). Exacerbation and COPD assessment test (CAT) score was significantly associated with GERD ($p < 0.05$). No significant difference regarding age, sex, Brinkman Index, lung function, and body mass index (BMI) was found between groups. However, the GERD (+) group showed a slightly higher BMI and more severe airflow obstruction.

Conclusion: The prevalence of GERD in COPD patients found in this study was as high as 40%. A cohort study and preventive strategy of GERD in COPD should be studied further.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading diseases accompanied by surging incidence, morbidity, and mortality across the globe.[1] The World Health Organization (WHO) suggested that at least three million people die due to COPD each year, and it is estimated that in the year 2030, it will become the third leading cause of death. Among the adult population, the prevalence of COPD increases significantly over forty years old.[2] Gastroesophageal reflux disease (GERD) has been considered one of the leading causes of respiratory symptoms, such as a cough. Studies have revealed that it is commonly associated with COPD patients as one of the comorbidities that can aggravate symptoms and thus lead to an exacerbation.

GERD can cause uncomfortable sensations, including heartburn, regurgitation, and a metallic sensation in the mouth. It has been regarded as one of the most noticeable diagnoses in clinical settings, with an estimated prevalence of 13-21% in the general population. Patients with chronic respiratory symptoms, including obstructive and restrictive pulmonary disease, have a higher prevalence of GERD than other disease entities. Moreover, upper respiratory symptoms are frequent among patients with GERD. The direct correlation between GERD and pulmonary diseases or symptoms is still unclear. Although studies and research have been completed in this particular interest, regarding

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Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v9-I.1.2023.1-6

the association between GERD and COPD, many areas are still unclear about the impact of these two diseases. Experts have expressed that to be sure of GERD, they must look directly into the gastrointestinal tract. Therefore, esophagogastroduodenoscopy (EGD) is deemed to be the gold standard. However, as a symptomatic diagnosis is simple and readily applicable in clinical practice, most studies have investigated the prevalence of GERD in COPD patients using questionnaires, and some have used 24-hour pH monitoring.[3,4]

This study aimed to determine the prevalence of GERD in stable COPD patients.[5,6] To our knowledge, only one previous study used EGD to determine GERD in COPD patients. Lee, *et al*. (2015) in South Korea from 2006-2010 retrospectively searched for subjects with gastrointestinal symptoms and established COPD then underwent EGD.[6] They found that the prevalence of esophagitis was 30%. Most other studies used questionnaires, hence the results might be overestimated. GERD prevalence in Asia is generally lower than in Europe or America. This may be due to lifestyle and obesity levels. In Indonesia, Lelosutan, *et al*. (2001) performed EGD on 127 subjects and found that 22.8% had GERD.[7] Syam, *et al*. (2015) found an increased prevalence of GERD from 5.7% in 1997 to 25.1% in 2002.[8] The prevalence of GERD in moderate persistent asthma studied by Susanto, *et al*. (2009) at Persahabatan National Respiratory Referral Hospital in 2005 found 50% (18/36) of patients had GERD.[9]

METHODS

Subjects were outclinic COPD patients aged ≥ 40 years old who met the inclusion criteria and had given their permission to undergo EGD. Subjects were recruited consecutively from outpatient asthma and COPD clinics at Persahabatan National Respiratory Referral Hospital, Jakarta, from May to November 2018.

COPD was defined as having a ratio of $FEV_1/FVC < 0.7$ in postbronchodilator spirometry using the GOLD diagnosis criteria. Episodes of exacerbation were identified by recorded emergency visits and hospitalization, then received systemic corticosteroids and inhaled beta-2 agonists at least three days during one year prior to this study. Patients were diagnosed with COPD and used respiratory medications (ICS + LABA, LAMA, SABA) three years before this study. Patients with an abnormality impacting lung function, such as old tuberculosis scars, bronchiectasis, pulmonary fibrosis on a chest X-ray, and those with known esophageal disease such as malignancy, a previous history of upper gastrointestinal (UGI) surgery or achalasia, were excluded from this study. All patients were not on proton pump inhibitors (PPI) for at least 15 days.

Exacerbation was defined as hospitalization or emergency room (ER) visits, receiving systemic corticosteroids, and inhaling beta-2 agonists for at least three days. The diagnosis of GERD was based on the mucosal break on the esophageal lining surrounding the lower esophageal sphincter (LES) through EGD examination, with Los Angeles criteria to determine the grade by an endoscopy specialist in the Division of Gastroenterology, which was performed within six months of the postbronchodilator spirometry.[6,9–14]

This was a cross-sectional study with ethical clearance from the Ethics Committee of Universitas Indonesia and Persahabatan National Respiratory Referral Hospital (No. 31 KEPK-RSUPP/07/2017), and informed consent was obtained from all patients. Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 23 (IBM Co, Armonk, NY, USA). Characteristics of patients expressed by using mean ± sd, median (interquartile range) and percentages. Independent sample T-test for parametric variables, Chi-Square, and Mann-Whitney tests for nan-parametric variables were used to compare GERD and non-GERD in stable COPD patients. Statistical significance was accepted for p-value < 0.05.

RESULTS

We recruited 52 COPD patients, but only 40 patients underwent EGD. Nine patients were intolerable for EGD due to heart failure, and three withdrew their consent. The prevalence of GERD in COPD patients was 40% (16/40), higher than in general patients with dyspepsia in Jakarta. The clinical characteristics and comparisons according to the presence or absence of GERD are shown in Table 1. Subjects were predominantly elderly (25/40, 62.5%) and male (36/40, 90%). There was no significant difference between GERD-positive and negative patients regarding age, sex, Brinkman Index, and BMI $p > 0.05$. Subjects with severe Brinkman Index had a slightly higher prevalence of GERD but were not statistically significant. However, the GERD-positive patients had more frequent exacerbation than the non-GERD patients ($p < 0.001$). COPD assessment test (CAT) and MMRC Modified Medical Research Council (MMRC) score were higher in the GERD group, showing that the patient had more symptoms and dyspnea score, which was statistically significant.

Table 1. Clinical characteristics of patients with COPD according to the presence or absence of GERD

Variable	Total (n=40)	GERD (+) (n=16)	GERD (-) (n=24)	p-value
Age	63.76 ± 8	64.06 ± 6	63.5 ± 9	0.836
Male/female	36/4	14/2	22/2	0.531
BMI	22.1 ± 4.5	23.07 ± 1	21.46 ± 5	0.279
Smoker/ex	36 (90)	15 (37)	21 (52.5)	0.531
Exacerbation	1.75 ± 1.6	2.38 ± 0.8	1.33 ± 0.7	< 0.001
MRC	2.33 ± 0.8	2.56 ± 0.8	2.17 ± 0.8	0.141
CAT score	14.95 ± 5	19.8 ± 4.4	11.7 ± 2.5	
Brinkman Index				
Mild-moderate	22	6 (17)	16 (45)	< 0.001
Severe	14	10 (28)	4 (11)	
COPD Group A	2 (5)	(-)	2 (5)	> 0.05
Group B	7 (17.5)	2 (5)	5 (12.5)	
Group C	14 (35)	2 (5)	12 (30)	
GroupD	17 (42.5)	12 (30)	5 (12.5)	

Values are presented as mean ± sd. BMI = body mass index; MRC = medical research council; CAT = COPD assessment test

EGD findings mostly revealed erosive gastritis with various grades, gastric ulcers, and other conditions such as hiatal hernias and diverticulitis. Malignant changes such as Barett's esophagus were not found. Interestingly enough, candidiasis esophagus, which is usually found in the immunocompromised patient, was found in six patients. A tissue biopsy was performed on each disorder during EGD. Non-active chronic gastritis was found in most cases, with only duodenitis and polyp gaster found in two other patients.

Table 2. EGD findings and pathologic examination of patients with COPD according to the presence or absence of GERD

Variable	Total (n=40)	GERD (+) (n=16)	GERD (-) (n=24)
EGD findings			
Gastric ulcer	9 (22.5)	7 (17.5)	2 (5)
Candidiasis	6 (15)	5 (12.5)	1 (2.5)
Erosive gastritis	32 (80)	16 (40)	16 (40)
Other findings	16 (40)	8 (20)	8 (20)
Pathologic exam			
Chronic gastritis	23 (57.5)	15 (37.5)	8 (20)
Duodenitis	1 (2.5)	1 (2.5)	0
Gastric polyp	1 (2.5)	1 (2.5)	0

Values are presented as percentage

Table 3. Postbronchodilator spirometry in patients with COPD according to presence or absence of GERD

Variable	Total (n=40)	GERD(+) (n=16)	GERD (-) (n=24)	p-value
FVC (L)	1.97 ± 0.6	1.87 ± 0.5	2.03 ± 0.6	
FVC (%)	67 ± 18	62.69 ± 2	71.25 ± 16	
FEV1 (L)	1.0 ± 0.9	0.96 ± 0.4	1.11 ± 0.4	
FEV_1(%)	47.8 ± 19	43.06 ± 18	51.08 ± 20	
FEV_1/FVC	50.9 ± 11	48.25 ± 10	52.75 ± 11	$p > 0.05$
GOLD				
≥ 80	4 (10)	-	4 (17)	
≥ 50 - < 80	12 (30)	3 (19)	9 (37.5)	
≥ 30 - < 50	15 (37.5)	8 (50)	7 (30)	
< 30	9 (22.5)	5 (32)	4 (17)	

Values are presented as mean ± SD. FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; GOLD = global obstructive lung disease

Table 4. Medication history in patients with COPD according to the presence or absence of GERD

Variable	GERD (+) (n=16)	GERD (-) (n=24)	Total (n=40)	OR	p-value	CI (95%)
ICS + LABA	13 (43)	17 (57)	30	1.784	0.459	(0.385 - 8.267)
LAMA	15 (43)	20 (57)	35	3.00	0.347	(0.303 - 29.263)
SABA	11 (38)	18 (62)	29	1.235	0.773	(0.295 – 5.181)

Values are presented as percentage. OR = Chi-Square; CI = confidence interval

Post-bronchodilator spirometry revealed no statistical difference between the two groups, although GERD positive had a lower lung function than GERD negative (Table 3). Based on the GOLD criteria of airflow limitation, the largest proportion of patients with GERD positive had severe airflow limitation, followed by moderate and very severe, although this showed no statistical difference. Most of the COPD patients that came to the clinic were in group D. Therefore, they had already used a triple-drug combination consisting of LAMA and ICS + LABA. There was no significant difference between the two groups regarding the use of inhalation medication for COPD ($p > 0.05$) (Table 4).

DISCUSSION

This study aimed to determine the prevalence of GERD in stable COPD patients. This study is important because there is no data yet on this population in Indonesia. GERD has been recognized to cause a chronic cough, and the relationship between COPD symptoms and exacerbation has been revealed. The prevalence of GERD among COPD patients in this study was 40% (16/40), which was higher compared to general patients with dyspepsia, which was 22-25%. Generally, the prevalence of GERD in Asia is lower than in western countries. Dent, *et al.* (2014) reported that it was 15-20% in America and Europe, but <5% in Asia.[5] Indonesians tend to eat spicy food, which may contribute to this finding. Moreover, obesity and a westernized diet may have a role in the increasing prevalence of GERD.[8,10]

Many modalities may be used to diagnose GERD, such as questionnaires, 24-hour pH monitoring, and EGD. Questionnaires may overestimate the prevalence of GERD. Lin, *et al.* (2015) used Mayo gastro-oesophageal reflux questionnaires (GORQ) and found that 53.6% (59/110) of COPD patients had GERD.[13] They also used 24-hour pH monitoring and found that 62% of COPD patients had a pH lower than 4. Lee, *et al.* (2015) retrospectively searched medical records for COPD patients with dyspepsia syndrome and found that 30% had a mucosal break or reflux esophagitis.[6] This study did not find any *Helicobacter pylori*, similar to the study in Jakarta, which showed that only around 3% of patients had dyspepsia syndrome caused by *H. pylori*.[6,9,12–15]

In this study, smoking did not show a statistical difference. This might be due to the small sample and the fact that most patients were current or former smokers. Other studies found a connection between smoking and GERD. Theoretically, nicotine may reduce lower esophageal tones. Advanced age is another known risk factor for GERD, and this study showed similar results. Other studies showed that those with a higher BMI tend to have GERD more frequently due to the flattening in the diaphragm musculature, which may cause reflux. In this study, there was no statistical difference between both groups.

Regarding sex, several studies showed different results. One study showed that females are more prone to GERD, but another showed no difference between the two groups. In this study, most of the samples were male, hence there was no difference between the two groups. Theoretically, females have more fat and a higher BMI, thus making them more prone to GERD, but fewer smoke and have COPD.[13,15–17]

This study found the exacerbation rate twice higher in GERD groups and was statistically significant. Exacerbation of COPD, commonly treated with systemic corticosteroid, has been known to have a deleterious effect, such as an increase in esophageal acid contact times and a reduction in LES pressure, which will lead to repeated reflux. It is difficult to determine whether GERD directly affects exacerbation, or merely coexists in patients who experience frequent exacerbations.[14,16–18]

Almost all patients in this study used LAMA (tiotropium) daily, and some previous studies had conflicting results. This is because one study by Lee, *et al.* (2015) in South Korea showed that anticholinergic decreased the risk of GERD.[6] However, Broers et al. (2018) reported that the relative risk of GERD increased with inhaled anticholinergic use.[18] Indeed, anticholinergic drugs reduce LES tone, but they also suppress a cough that may promote reflux and exacerbation. Thus, using anticholinergic may benefit more patients with chronic bronchitis than emphysema phenotype. Another widely used drug was ICS + LABA, which contains a steroid, and has been known to alter esophageal motility and reduce LES tone. Relevant to that theory, this study showed that using ICS + LABA is associated with an increased risk of GERD. A similar result from Broers, *et al.* (2018) reported an increased prevalence of GERD.[16] In another study, the effect of medication was not statistically significant or hard to evaluate, because COPD patients were treated with multiple medications other than lung conditions.[18,19] In this study, patients had been diagnosed with COPD and used inhaled medications three years before this evaluation. Our hospital is a tertiary referral hospital for pulmonary disease, but we could not retrieve oral medication data, such as theophylline and oral corticosteroid before the patients were referred to our hospital. This is particularly due to no data connection between the health center in Indonesia and widely used pulverized drugs into capsules for which we did not know the ingredients. Medications such as theophylline and inhaled beta-2 agonists may decrease LES and could facilitate GERD.

Regarding lung function, this study measured post-bronchodilator spirometry in the patients before performing EGD within six months, but we could not find any association ($p > 0.05$) between the severity of airway obstruction with the occurrence of GERD. Even Khamitov, *et al.* (2021) failed to find any association between lung function and GERD.[14] A study from Özdemir, *et al.* (2017) in Pakistan found a tendency to report GERD symptoms with more advanced COPD in those with $FEV_1 < 50\%$.[20] In one study with a prospective cohort using a GERD questionnaire, the

symptoms were compared between 100 COPD patients and 150 controls. In both studies, patients but not controls reported that respiratory symptoms were more common with heartburn and regurgitation.[13,15,18–20]

This study had several limitations. The samples were small and mostly had advanced COPD. Moreover, the distribution of sex was unbalanced, but we still managed to obtain important data in a limited resource setting. There may be recall bias because we obtained data from interviewing patients and family regarding the symptoms, but we managed to obtain exacerbation rate from medical records. The use of EGD is the strength of this study because we directly analyzed the mucosal changes in the esophageal lining as a proof of reflux occurrence, and to our knowledge this is the first study in Indonesia regarding this issue. Patients with previous UGI conditions and chest X-ray abnormalities other than emphysematous lung were excluded.

In conclusion, the prevalence of GERD as a comorbid in COPD patients is high, because the patients had more symptoms and exacerbation rates. Therefore, it should be getting attention from physicians. Well-designed prospective studies and preventive measures should be performed to address this issue.

CONCLUSION

Early awareness and management of comorbidities in COPD patients are important to improve quality of life and alleviate symptoms. The prevalence of GERD in this study was higher than in the population with dyspepsia symptoms. Exacerbation rate, dyspnea score, and daily symptoms were significantly higher than patients without GERD. This pilot study prompts further research with larger samples and better study designs.

Acknowledgments

The main author would like to thank Prof. Faisal, Dr. Maulana, and Dr. Fahmi for their dedication, willingness, and support in completing this study. The main author's wife and three beautiful children for being the eternal flame. For the patients included in this study, we hope they all live well and healthily.

Conflict of Interest

The authors declared there is no conflict of interest.

Funding

This study was self-funded by the main author.

Authors' Contributions

Designed the study and drafted the manuscript: MH and FY. Collected data and performed background literature review: MH and MS. Performed statistical analysis: MH. Supervised results and discussion: FY, MFA and AW. All authors reviewed and approved the final version of the manuscript.

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