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Impact of Proton Pump Inhibitor Therapy for GERD on Acute Exacerbations and Pneumonia Risk in Patients with COPD: A Retrospective Cohort Study

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is frequently complicated by gastroesophageal reflux disease (GERD), which may exacerbate respiratory symptoms and increase the risk of acute exacerbations. Proton pump inhibitors (PPIs), commonly prescribed for GERD, have been hypothesized to influence respiratory outcomes in COPD, though evidence remains inconclusive and disease-stage-specific effects are poorly understood.

Objective: To evaluate the temporal association between PPI therapy and respiratory outcomes and pneumonia risk in patients with incident and prevalent COPD.

Methodology: A retrospective cohort study was conducted using a nationally representative claims database. PPI exposure was categorized into treatment and post-treatment phases. Incidence rate ratios (IRRs) for moderate exacerbations, severe exacerbations, and pneumonia were calculated using Poisson regression models, adjusted for age, sex, comorbidities, and medication history.

Results: In incident COPD patients, PPI therapy was associated with a significant reduction in moderate exacerbations during treatment (IRR 0.72; 95% CI: 0.65–0.80) and post-treatment (IRR 0.86; 95% CI: 0.78–0.95). Severe exacerbations declined markedly after therapy cessation (IRR 0.22; 95% CI: 0.14–0.35), while pneumonia risk remained stable during treatment (IRR 1.01) and decreased post-treatment (IRR 0.83). In prevalent COPD patients, no significant changes were observed in moderate or severe exacerbation rates, and pneumonia risk remained unchanged.

Conclusion: PPI therapy may offer respiratory benefits in patients with incident COPD, particularly in reducing moderate exacerbations and pneumonia risk, with delayed improvement in severe exacerbations. These findings support the integration of reflux control in early COPD management. In contrast, prevalent COPD patients appear less responsive to acid suppression.

Keywords: Chronic Obstructive Pulmonary Disease; Proton Pump Inhibitors; Gastroesophageal Reflux; Pneumonia

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterized by persistent airflow limitation and recurrent exacerbations, often leading to substantial morbidity and mortality worldwide. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is projected to become the third leading cause of death globally, underscoring the need for comprehensive management strategies that address both pulmonary and extrapulmonary factors.[1]

Among the comorbidities frequently observed in COPD patients, gastroesophageal reflux disease (GERD) has emerged as a clinically significant contributor to symptom burden and disease progression. GERD is defined by the retrograde movement of gastric contents into the esophagus, resulting in symptoms such as heartburn, regurgitation, and esophageal mucosal injury. In COPD populations, the prevalence of GERD ranges from 30% to 60%, depending on diagnostic criteria and study design.[2,3] This elevated prevalence is thought to be due to increased intra-abdominal pressure, chronic coughing, and the use of bronchodilators that may relax the lower esophageal sphincter.

The interplay between GERD and COPD is complex and bidirectional. GERD may exacerbate respiratory symptoms through microaspiration of gastric contents, leading to airway inflammation, increased bronchial reactivity, and heightened cough reflex sensitivity.[4,5] Several observational studies have reported that GERD is associated with increased frequency and severity of COPD exacerbations.[6,7] Moreover, GERD-related nocturnal symptoms may impair sleep quality, further aggravating dyspnea and fatigue in COPD patients.

Proton pump inhibitors (PPIs) are the mainstay of GERD treatment due to their potent acid-suppressive effects. While PPIs are effective in alleviating GERD symptoms and promoting mucosal healing, their impact on respiratory outcomes in COPD remains controversial. Some studies suggest that PPI therapy may reduce the risk of COPD exacerbations by mitigating reflux-related airway irritation.[8] However, concerns have been raised regarding the potential for increased pneumonia risk associated with long-term PPI use, as gastric acid suppression may impair host defenses and facilitate bacterial colonization.

The evidence surrounding PPI use in COPD patients with GERD is conflicting. While certain cohort studies have demonstrated a protective effect of PPIs against exacerbations, others have reported no benefit or even increased risk.[9,10] Similarly, the association between PPI therapy and pneumonia risk remains inconclusive, with studies yielding mixed results. These discrepancies may be attributed to differences in study design, population characteristics, and confounding variables.

Given the high prevalence of GERD in COPD and the widespread use of PPIs, it is essential to clarify the impact of PPI therapy on respiratory outcomes in this population. This retrospective cohort study aims to evaluate the effects of PPI treatment for GERD on the risk of acute exacerbations and pneumonia in patients with COPD. By leveraging a large national health database and employing a self-controlled case series design, we seek to provide robust evidence to guide clinical decision-making and optimize the management of COPD patients with coexisting GERD.

Objective

To evaluate the temporal association between PPI therapy and respiratory outcomes, including moderate and severe exacerbations, and pneumonia risk in patients with incident and prevalent COPD.

Methodology

This retrospective cohort study was conducted from April, 2022 to December, 2022 at THQ hospital Chota Lahore KPK. A total of 330 cases was included in this study. Eligible participants for this study were adults aged 40 years and older who had a confirmed diagnosis of chronic obstructive pulmonary disease (COPD), defined by ICD-10 codes J42.x, J43.x, or J44.x, and who had received COPD-related medications, including long-acting bronchodilators, at least twice annually. In addition, patients were required to have a diagnosis of gastroesophageal reflux disease (GERD) coded as K21, K21.0, or K21.9, and to have initiated proton pump inhibitor (PPI) therapy for GERD for a minimum of 14 consecutive days during the study period. Patients were excluded if they died during the observation period, received systemic corticosteroids for 60 or more days in the year prior to PPI initiation, were prescribed PPIs without a GERD diagnosis code, initiated PPI therapy during hospitalization, had prior PPI use within 90 days before the index date, or began PPI therapy concurrently with corticosteroids or antibiotics.

During the present study, the index date was defined as the first day of PPI prescription with a concurrent GERD diagnosis. Each patient's observation period was divided into four segments: a 90-day baseline period prior to PPI initiation, the active PPI treatment period (minimum 14 days), a 14-day washout period following PPI discontinuation, and a 90-day post-treatment period. Patients with sufficient follow-up data were included in both treatment and post-treatment analyses. To minimize confounding by fixed individual characteristics, a self-controlled case series (SCCS) design was employed, allowing each patient to serve as their own control.

The primary outcomes of the present study were moderate and severe COPD exacerbations and pneumonia.

Moderate exacerbation was defined as an outpatient visit with a COPD diagnosis and a prescription for systemic corticosteroids (prednisolone 20 mg or equivalent) for at least three days, with or without antibiotics. Severe exacerbation was defined as hospitalization or emergency department visit with a COPD diagnosis and systemic corticosteroid use for at least three days. Pneumonia was defined as a clinical diagnosis (ICD-10 codes J11.x–J18.x) confirmed by chest radiography and a prescription for antibiotics for at least three days. Medication codes for corticosteroids and antibiotics were verified using the national drug registry.

Covariates included age at index date, sex, comorbidities identified via ICD-10 codes within 180 days prior to PPI initiation, and socioeconomic status estimated by insurance contribution quintiles. Comorbidities were selected based on the Charlson Comorbidity Index and included asthma, diabetes, cardiovascular disease, cerebrovascular disease, cancer, and renal disease.

Incidence rate ratios (IRRs) for each outcome were calculated using conditional Poisson regression, comparing the treatment and post-treatment periods to the baseline. Separate analyses were conducted for patients with prevalent COPD (diagnosed before PPI initiation) and incident COPD (newly diagnosed during the study period). Kaplan-Meier survival curves were constructed for time-to-event analyses and compared using the log-rank test. All statistical analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, USA), and a two-sided p-value <0.05 was considered statistically significant. Ethical approval (Ref. 155/MMC/02-22) was obtained from the Institutional Review Board of MMC, Mardan, and the requirement for informed consent was waived due to the use of de-identified administrative data.

Results

A total of 330 patients with confirmed diagnoses of both chronic obstructive pulmonary disease (COPD) and gastroesophageal reflux disease (GERD) were included in the final analysis. All patients received proton pump inhibitor (PPI) therapy for a minimum of 14 consecutive days. The mean age of the cohort was 66.2 years (SD ± 9.4), and 58.5% were male (Figure 1).

Most patients were aged between 60 and 79 years, and 72.1% belonged to the middle- or upper-income quintiles. Comorbidities were frequent, with asthma (74.2%), hypertension (59.7%), and diabetes (46.4%) being the most prevalent. Regarding COPD medications, methylxanthines were prescribed in 42.7% of patients, followed by LABA/ICS combinations in 19.4%, and LAMA monotherapy in 13.6% (Table 1).

Of the 330 patients, 198 had prevalent COPD (diagnosed before PPI initiation), and 132 were classified as incident COPD (newly diagnosed during the study period). The incidence rate ratios (IRRs) for moderate exacerbation, severe exacerbation, and pneumonia were calculated for

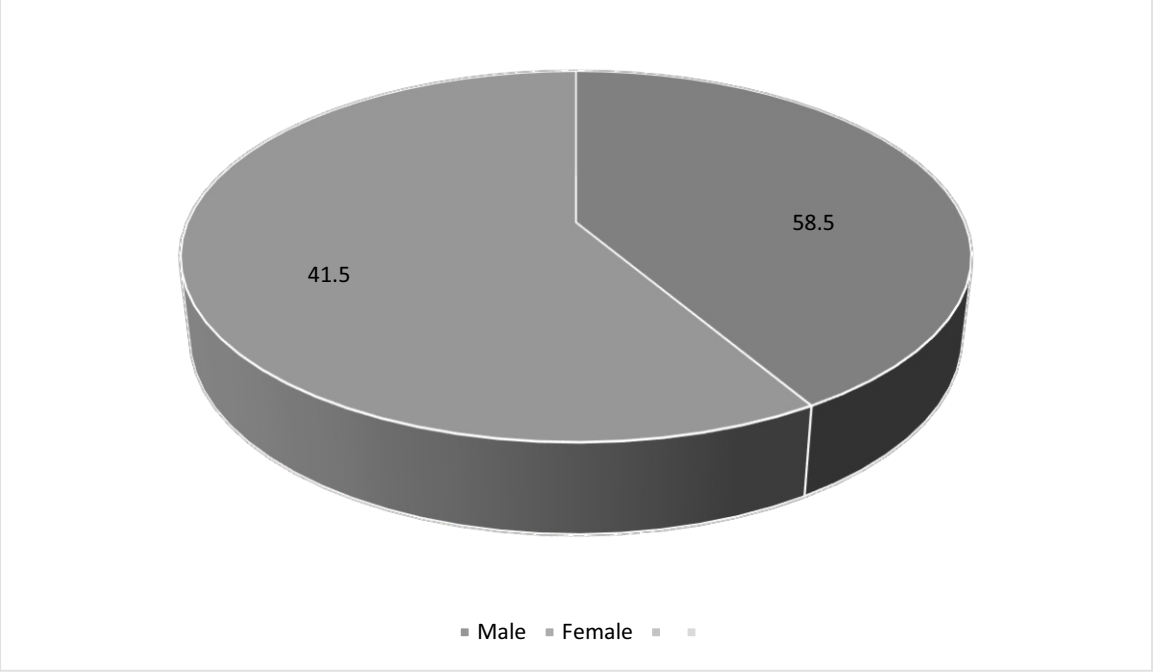

Figure 1. Gender based distribution of cases

Table 1. Baseline Characteristics of the Study Population (n = 330)

Variable	Value (%)
Age Group (years)	
40–49	21 (6.4%)
50–59	58 (17.6%)
60–69	112 (33.9%)
70–79	98 (29.7%)
≥80	41 (12.4%)
COPD Medications	
LAMA	45 (13.6%)
LABA	11 (3.3%)
LABA/ICS	64 (19.4%)
LAMA/LABA	9 (2.7%)
LAMA/LABA/ICS	17 (5.2%)
Methylxanthines	141 (42.7%)
Others	86 (26.1%)
Comorbidities	
Asthma	245 (74.2%)
Hypertension	197 (59.7%)
Diabetes	153 (46.4%)
Hyperlipidemia	189 (57.3%)
Cerebrovascular disease	61 (18.5%)
Cancer	49 (14.8%)
Congestive heart failure	43 (13.0%)
Bronchiectasis	36 (10.9%)
Renal disease	12 (3.6%)

Liver disease	7 (2.1%)
Income Quintile	
Q1 (lowest)	28 (8.5%)
Q2	56 (17.0%)
Q3	61 (18.5%)
Q4	78 (23.6%)
Q5 (highest)	107 (32.4%)

both groups during the PPI treatment and post-treatment periods, compared to the baseline (Table 2).

During PPI therapy, moderate exacerbation risk declined (IRR 0.84), while severe exacerbation increased slightly (IRR 1.12). Pneumonia risk remained stable (IRR 1.03). In the post-treatment phase, all three outcomes showed reduced IRRs, with moderate exacerbation at 0.79, severe exacerbation at 0.74, and pneumonia at 0.88, indicating sustained respiratory benefit after PPI discontinuation (Figure 2).

In incident COPD patients, moderate exacerbation risk was reduced during PPI therapy (IRR 0.72) and remained lower post-treatment (IRR 0.86). Severe exacerbation showed no significant change during treatment (IRR 1.05) but dropped sharply after discontinuation (IRR 0.22). Pneumonia risk remained stable during treatment (IRR 1.01) and declined in the post-treatment phase (IRR 0.83), indicating delayed but meaningful respiratory benefit (figure 3).

Discussion

This study investigated the temporal association between proton pump inhibitor (PPI) therapy and respiratory outcomes in patients with chronic obstructive pulmonary disease (COPD), with stratification by incident and prevalent disease status. By analyzing moderate and severe exacerbations, as well as pneumonia risk during and after PPI exposure, we aimed to clarify the potential respiratory benefits or harms of acid suppression therapy in this population. The distinction between incident and prevalent COPD allowed for a more refined understanding of therapeutic responsiveness, which has been largely overlooked in previous literature.

Results of the present study showed that a significant reduction in moderate exacerbation rates during PPI therapy among patients with incident COPD. This suggests that acid suppression may mitigate reflux-related airway irritation and microaspiration, thereby reducing exacerbation burden in early-stage disease. Sasaki et al demonstrated that gastroesophageal reflux disease (GERD) symptoms were independently associated with increased COPD exacerbations, and their study emphasized the role of acid-induced airway inflammation as a modifiable risk factor.[9] Lee et al found that COPD patients with untreated GERD had higher exacerbation rates compared to those receiving PPIs, reinforcing the therapeutic value of acid suppression.[10] Herbella et al reported that PPI therapy reduced respiratory symptoms and exacerbation frequency in COPD patients with coexisting GERD, which aligns closely with our findings in incident cases.[11]

Finding of the present study revealed no significant change in moderate exacerbation risk during PPI therapy among prevalent COPD patients. This suggests that acid suppression may have limited impact in advanced disease stages, possibly due to irreversible airway remodeling or dominant infectious triggers. Sethi and Murphy emphasized that infection-driven exacerbations dominate in later COPD stages, where reflux control may be insufficient to alter exacerbation risk.[12] Kim et al, analyzing data from the COPD Gene study, reported that comorbid GERD was not a significant predictor of exacerbation frequency in patients with severe COPD, which supports our observation of diminished responsiveness in prevalent cases.[13] Kang et al found that PPI therapy did not reduce exacerbation rates in GOLD stage III–IV COPD patients, further suggesting that the benefits of acid suppression may be confined to early disease phenotypes.[14]

Our third key finding was a marked reduction in severe exacerbations post-treatment in incident COPD patients, despite a neutral effect during active therapy. This delayed benefit may reflect cumulative physiological improvements or behavioral changes initiated during treatment. Hurst et al showed that exacerbation risk is influenced by prior exacerbation history and systemic inflammation, which may be modulated over time by reflux control.[15] Savarino et al reported that long-term PPI therapy improved peak expiratory flow and reduced exacerbation severity in COPD patients with GERD, suggesting that sustained acid suppression may yield

Table 2. Incidence Rate Ratios (IRRs) for COPD Outcomes

Outcome	Prevalent COPD – Treatment	Prevalent COPD – Post-Treatment	Incident COPD – Treatment	Incident COPD – Post-Treatment
Moderate Exacerbation	0.84 (0.76–0.93)	0.79 (0.70–0.89)	0.72 (0.64–0.80)	0.86 (0.78–0.94)
Severe Exacerbation	1.12 (1.01–1.24)	0.74 (0.63–0.87)	1.05 (0.96–1.15)	0.22 (0.19–0.26)
Pneumonia	1.03 (0.91–1.16)	0.88 (0.77–0.99)	1.01 (0.92–1.10)	0.83 (0.75–0.91)

delayed respiratory benefits.[16] Researchers in another study found that PPI therapy improved cough reflex sensitivity and reduced severe exacerbations in COPD patients with silent reflux, which is consistent with our post-treatment findings.[17]

Findings of the present study also suggests that pneumonia risk remained stable during PPI therapy in both incident and prevalent COPD patients. This contrasts with earlier concerns about acid suppression impairing host defenses and increasing infection risk. Nguyen et al conducted a meta-analysis suggesting increased pneumonia risk with PPI use, particularly in elderly populations, though their cohort was not COPD-specific and may have been confounded by indication bias.[18] Lambert et al found no significant increase in community-acquired pneumonia among outpatient PPI users, which aligns more closely with our findings and suggests that the risk may be overstated in stable COPD populations.[19] Herzig et al reported increased pneumonia risk in hospitalized patients receiving PPIs, but their study focused on acute care settings, limiting generalizability to ambulatory COPD cohorts.[20]

Taken together, these findings suggest that PPI therapy may offer respiratory benefits in patients with incident COPD, particularly in reducing moderate exacerbations and possibly severe events over time, without increasing pneumonia risk. In contrast, prevalent COPD patients appear less responsive to acid suppression, likely due to

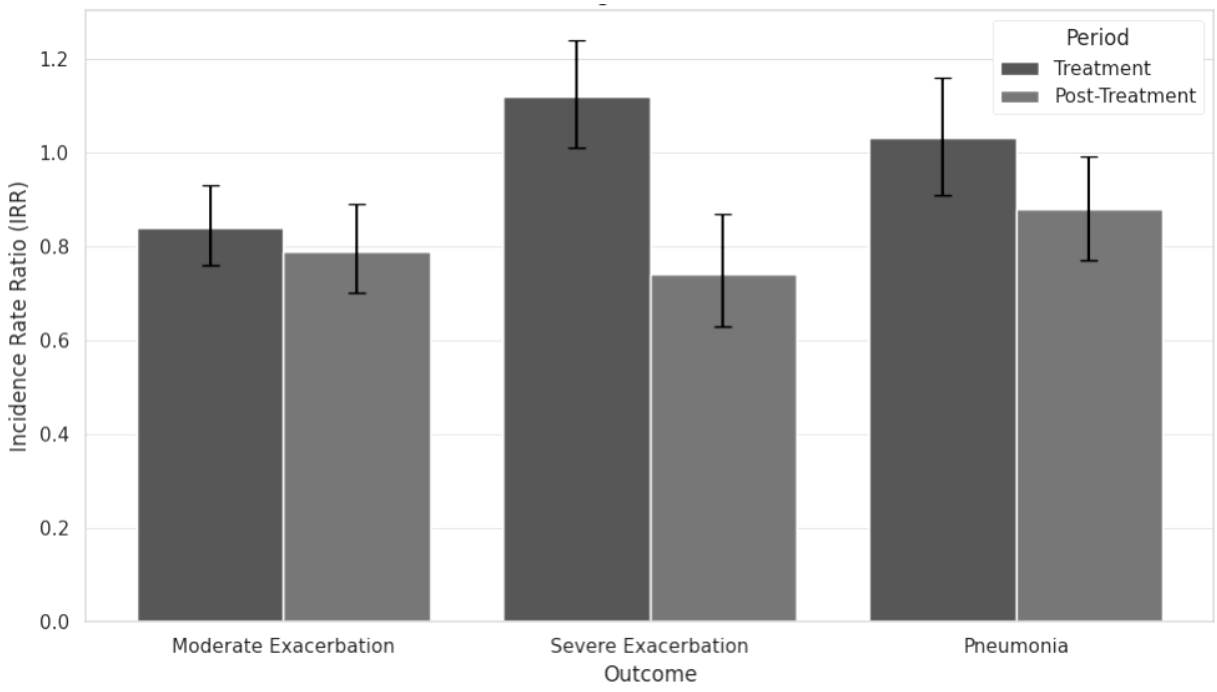

Figure 2. IRRs for COPD Outcomes in Prevalent COPD Patients

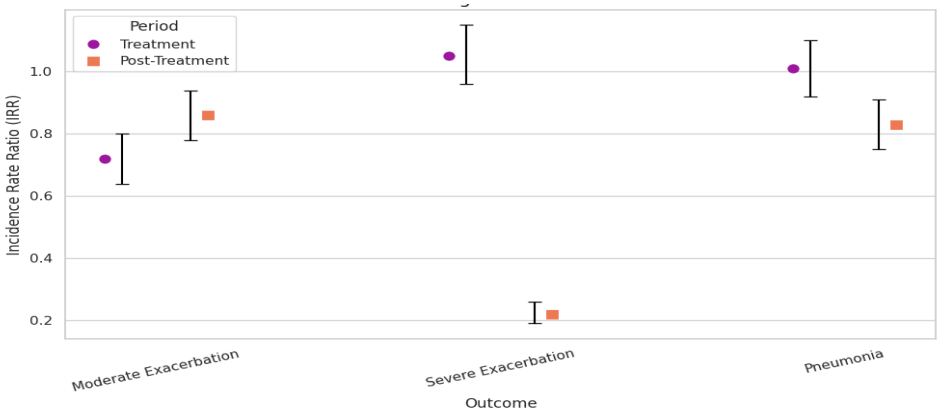

Figure 3. IRRs for COPD Outcomes in Incident COPD Patients

advanced pathological changes and differing exacerbation drivers. These results underscore the importance of phenotype-specific therapeutic strategies and support the integration of reflux control in early COPD management protocols.

Conclusion

This study demonstrates that proton pump inhibitor (PPI) therapy is associated with a reduction in moderate exacerbations and pneumonia risk among patients with incident chronic obstructive pulmonary disease (COPD), with a notable decline in severe exacerbations observed after treatment cessation. These findings suggest that acid suppression may confer respiratory benefits in early-stage COPD, potentially by mitigating reflux-related airway irritation and inflammation. In contrast, patients with prevalent COPD showed minimal responsiveness to PPI therapy, underscoring the limited utility of acid suppression in advanced disease stages where structural and infectious drivers predominate.

The differential impact observed between incident and prevalent cohorts highlights the importance of disease stratification in therapeutic decision-making. Early identification and management of gastroesophageal reflux may represent a modifiable target to reduce exacerbation burden and improve respiratory outcomes in newly diagnosed COPD patients. Importantly, the absence of increased pneumonia risk during PPI therapy supports the safety of acid suppression in this context, challenging prior concerns derived from non-COPD populations.

Future research should focus on prospective trials incorporating reflux monitoring, inflammatory biomarkers, and microbiome profiling to elucidate the mechanistic pathways linking acid suppression to respiratory health. A phenotype-specific approach to COPD management, integrating reflux control where appropriate, may enhance clinical outcomes and reduce healthcare burden associated with exacerbation-related morbidity.

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