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Risk Factors for Severe Exacerbation Occurrence Among Patients with Chronic Obstructive Pulmonary Disease with Bilevel Positive Airway Pressure Therapy: A Retrospective Claims Analysis

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B.S., University of California San Diego, 2016.

Thesis Committee Chair: Victoria Pak, Ph.D.

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Title: Risk Factors for Severe Exacerbation Occurrence Among Patients with Chronic Obstructive Pulmonary Disease with Bilevel Positive Airway Pressure Therapy: A Retrospective Claims Analysis

By Daniela Tellez

Background: Chronic obstructive pulmonary disease (COPD) exacerbations constitute a major public health and economic burden. COPD imposes heterogeneity across disease severity and treatment pathways, so exacerbation predictors may vary in subset COPD populations. Bilevel positive airway pressure (PAP) therapy reduces work of breathing and improves gas exchange in patients with COPD. Risk factors for severe exacerbations among patients with COPD using bilevel PAP therapy have not been well described. The aim of this study was to identify risk factors for severe exacerbation occurrence among COPD patients on bilevel PAP therapy.

Methods: A retrospective cohort analysis was performed on administrative claims data from patients with COPD who received a bilevel PAP device claim between 2015 and 2020. Patients were tracked 1 year prior to bilevel PAP initiation (baseline), and 1 year post bilevel PAP initiation (follow-up), for a total of 2 years per patient. A modified Poisson regression model was built to identify predictors for severe exacerbation occurrence in the year following bilevel PAP initiation. Relative risks for significant predictors were then estimated, which included baseline comorbidities and demographic factors.

Results: A total of 26,465 patients with COPD and a bilevel PAP device claim were included in the analysis (mean age 61.5±10.1 SD, 46.1% female). Most patients (90.66%) had comorbid obstructive sleep apnea (OSA). Data showed that 11.52% patients experienced one or more severe exacerbations during baseline, while 6.68% did during follow-up. Severe exacerbation occurrence at baseline was associated with a nearly quintupled increased risk for severe exacerbation occurrence at follow-up [RR, 4.86; 95% CI (4.39, 5.37), *P* value <.0001]. Moreover, a diagnosis of OSA was associated with decreased risk of severe exacerbation occurrence [RR, 0.77; 95% CI (0.69, 0.86), *P* value <.0001], likely because bilevel PAP was treating apnea events and may have helped to alleviate COPD symptoms.

Conclusion: Preventing severe exacerbations from first occurring may prevent future severe exacerbations among these patients. Importantly, findings showed that treating OSA with bilevel PAP among patients with COPD was significantly associated with reduced exacerbation risk, which may encourage screening and treatment of sleep apnea in the COPD population.

Keywords: COPD, bilevel PAP, exacerbation, overlap syndrome, OSA, claims.

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Table of Contents

Chapter 1: Background Literature Review

Burden of COPD

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States (US), and its prevalence is expected to rise due in part to smoking behaviors, environmental pollution, and an increasing aging population[1]. It is estimated that the prevalence of COPD will reach 11.6% of the US population in 2050[2], with projections higher for low- and middle-income countries[3]. COPD represents an immense public health and economic burden, causing 3.3 million deaths in 2019, 74.4 million disability-adjusted life years[4], and close to $50 billion dollars in healthcare spending costs in the US[5]. Exacerbations in COPD represent the greatest portion of these costs, both from a payer and patient perspective[6]. Up to 50% of patients with COPD experience an exacerbation every year, and exacerbation frequency tends to increase with more severe disease[7]. Exacerbations represent an enormous added burden in cost for hospital systems and payers, and a significantly worsened prognosis[8] and quality of life for patients[9]. COPD is part of Centers for Medicare and Medicaid Services' (CMS) Hospital Reduced Readmissions Program (HRRP), which aims to reduce hospital readmissions by improving communications and care coordination in discharge plans[10]. Reduction and prevention of COPD-related exacerbations is essential to alleviate burden both at large public health scale and individual patient level.

Problem Statement

Non-invasive ventilation (NIV) is a ventilatory support therapy delivered through a mask interface which is a first-line treatment for acute hypercapnic respiratory failure[11] and is known to reduce hospital length of stay and improve mortality in acute COPD exacerbations[12]. However,

the role of NIV in non-acute settings for patients with COPD remains uncertain in clinical practice, despite the high prevalence and burden of COPD. There are clinical implementation gaps in the care management and care continuum for patients, especially in the use of bilevel positive airway pressure (PAP) therapy, which is a form of at-home NIV for patients with COPD. Bilevel PAP works by reducing work of breathing, enhancing lung tidal volume, and unloading of respiratory muscles in patients with COPD[13], and it enables the correction of gas exchange abnormalities, which in turn improves health-related quality of life, sleep quality, and hospital readmission risk[14-16]. There is a need to better characterize patients with COPD who are receiving bilevel PAP therapy in the US in terms of comorbidity profile, demographics, and payer coverage. Given the heterogeneity of phenotypes and care management pathways for COPD, it is important to investigate if patients with COPD who are on a bilevel PAP device as a subset population have similar or different risk factors for future exacerbations as COPD patients overall. Furthermore, the role that bilevel PAP therapy may offer in terms of benefit for exacerbation occurrence risk to patients that have been prescribed this type of therapy should be discerned, even as if the therapy was intended to treat comorbid obstructive sleep apnea (OSA) or COPD symptoms.

COPD Pathophysiology

COPD is characterized by airflow limitation that is not fully reversible and inflammation that often leads to tissue destruction and structural changes in the lungs[17]. Symptoms include cough, shortness of breath, sputum production, and wheezing, all of which may progress over time if not properly treated[18]. The most common cause for COPD diagnoses is cigarette smoking, but long-term exposure to pollutants and occupational toxins, as well as genetics, influence increased risk of COPD development. There are two main conditions associated with COPD:

chronic bronchitis and emphysema, which can occur simultaneously and may vary with disease severity[19,20]. Disease severity is categorized into 4 stages according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[21]. Stages 3 and 4 are indicative of severely reduced lung function through low levels of forced expiratory volume (FEV_1) and are thus used to describe patients with later-stage and severe COPD. A prominent symptom in COPD is poor gas exchange and ventilation from reduced lung function and obstructed airways, which can lead to increased levels of CO_2 in the blood, a condition known as hypercapnia ($PaCO_2 \geq 45mmHg$)[22]. Hypercapnia is usually observed in severe COPD patients, with reported prevalence rates between 30% to 50% among GOLD stages 3 and 4[23], and it is associated with worsened health outcomes, quality of life[24], and COPD-related mortality[25]. COPD is a remarkably heterogeneous disease and it has proven difficult to characterize disease progression and exacerbation risk for all patients with COPD[26].

COPD-related exacerbations, especially those requiring hospitalizations, are a leading driver in healthcare utilization costs and are strongly linked to mortality, reduced health-related quality of life, and worsened disease prognosis for patients[27]. There are several studies that describe risk factors and exposures associated with COPD exacerbations[28], but there is an opportunity to tailor research for subset populations of COPD patients given the striking differences in phenotypes, severity, and therapeutic profiles across the disease spectrum.

Indications for Bilevel PAP in COPD

Bilevel PAP is indicated for the treatment of respiratory insufficiency[29] by providing pressure support through a mask interface during sleep. A higher set pressure is delivered during inhalation (inspiratory positive airway pressure, IPAP) and a lower set pressure is delivered during

exhalation (expiratory positive airway pressure, EPAP); hence the term bilevel for the two set pressures. Bilevel PAP devices can be equipped with or without a backup rate that provides artificial breaths in case respiratory effort ceases[30,31]. CMS has termed bilevel PAP devices as respiratory assist devices (RAD) under their payer guidelines in order to differentiate them from home mechanical ventilator (HMV) devices, which are more complex and equipped with various therapy modes indicated for chronic respiratory failure with hypoventilation[32]. HMV devices are significantly more expensive to purchase and more expensive to maintain, yet they are prescribed at a higher rate than RAD devices.

The indications and clinical guidelines of NIV for COPD (including bilevel PAP therapy) specify the coexistence of hypercapnia and chronic respiratory failure in the diagnostic or phenotypic profile of the patient with COPD. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend NIV for hypercapnic COPD exacerbations[11], and long-term nocturnal NIV for chronic stable hypercapnic COPD[33]. There is not enough available evidence on the effect of bilevel PAP therapy in COPD patients who do not have chronic stable hypercapnia or chronic respiratory failure[34]. Nevertheless, it is important to consider the subset of patients that are on bilevel PAP therapy for other reasons, most prominently comorbid sleep apnea. Vasquez et al. showed that the vast majority of COPD patients are not on any form of home-based NIV therapy, with only 7.5% receiving home NIV therapy (either CPAP, bilevel PAP or HMV) and of those, only 1.5% receiving bilevel PAP[15]. The low proportion of bilevel PAP use may be influenced by the lack of certainty in recommendations for home NIV in COPD in US clinical practice, lack of awareness of potential benefits[35], and lasting impressions from negative or mixed evidence from randomized controlled trials (RCTs) [35-38]. Kulkarni and colleagues

highlighted the existence of significant implementation gaps in bilevel PAP prescriptions due to CMS and other payer policies that establish regulatory barriers and financial disincentives,[34] which make it more cumbersome for both physicians and patients to prescribe and obtain a bilevel PAP device. Additionally, there are no standard clinical procedures in COPD care that assess or screen for a patient's need for home-based bilevel PAP therapy[34]. The complex CMS reimbursement policy for bilevel PAP devices, or RADs, (Healthcare Common Procedure Coding System (HCPCS) codes E0470 and E0471), as well as the need for in-hospital titrations, have made bilevel PAP accessibility very limited, even among patients who fall under the recommended use for stable hypercapnic COPD [39]. HMVs (HCPCS E0466), as mentioned previously, provide life supporting NIV therapy at a significant cost increase compared to bilevel PAP, yet are reimbursed by CMS at higher rates than bilevel PAP devices, leading to increased healthcare utilization and costs[40,41] partly because HMVs are included in the frequent and substantial servicing payment category under CMS[40]. These payer qualification criteria have been deemed outdated and detrimental to meeting patient needs[35], and providers and researchers have called out for improved advocacy efforts in this area[40].

Clinical Evidence of Bilevel PAP in COPD

Home-based bilevel PAP therapy for COPD patients is still highly debated despite robust clinical evidence that favors patient health outcomes. Three important RCTs conducted in the last 10 years[42-44] supported the use of home-based bilevel PAP for COPD through the improvement of $PaCO_2$, survival, cost-effectiveness and COPD-related hospital readmissions. Most of these RCTs excluded sleep apnea patients to isolate the benefit of home NIV/bilevel PAP therapy in COPD, particularly in reducing hypercapnia and improving ventilation. Nonetheless, other well

conducted RCTs [36-38] failed to show improvement of health outcomes or clear benefits of bilevel PAP therapy in COPD patients. One hypothesis for these neutral findings is that pressure settings in the bilevel devices were inadequate [39]. High-intensity NIV, or higher target pressures through bilevel PAP therapy, are thought to provide better efficacy, but no prospective high-intensity NIV studies using bilevel devices have been conducted in the US. However, Galli and colleagues ran an observational US-based retrospective study showing benefit of home bilevel PAP therapy after hospital discharge in event-free survival and hospital readmission[45]. These mixed findings further fuel contention in reimbursement, coverage, and standard of care for bilevel PAP prescriptions among patients with COPD. Thus, there are opportunities to better understand and describe the COPD population that has been prescribed a bilevel device in routine clinical practice as shown by administrative claims data. More clinical evidence and clinical practice applications are needed to build a stronger argument to influence policy and payers for a change in the reimbursement and accessibility paths for bilevel PAP therapy/RAD devices not only to save significant healthcare costs, but more importantly to improve health outcomes in severe COPD and provide patients the therapy that they need at the right time. Despite the low proportion of bilevel PAP usage among COPD patients, there is a need to better understand which COPD patients are receiving bilevel PAP in the US in terms of comorbidity profile, demographics, and payer coverage. Due to the high prevalence of comorbid sleep apnea among COPD patients, it's important to understand and investigate what risk factors for future exacerbation are similar to or different from the exacerbation risk factors for COPD patients without sleep apnea but who are receiving bilevel PAP therapy, as well as COPD patients in general.

This analysis accounts for patients on a bilevel PAP therapy device and examines those with a documented COPD diagnosis to uncover the demographic and comorbid profile of this patient population and identify predictors for severe exacerbation risk after bilevel PAP therapy initiation. The included COPD diagnoses may or may not include hypercapnia and respiratory failure patients, which presents both strengths and limitations. In terms of the former, findings will inform risk factors for non-acute patient settings, and in the latter, it is difficult to discern whether therapy was being appropriately prescribed per clinical guidelines or if it was targeted to reduce hypercapnia in these patients.

PAP Therapy for OSA and Overlap Syndrome

Sleep disordered breathing encompasses two main types of sleep apnea (obstructive and central) and nocturnal hypoventilation. In the case of obstructive sleep apnea (OSA), breathing pauses occur during sleep due to a physical obstruction of the upper airway. On the other hand, central sleep apnea (CSA) occurs when there is a lack of effort to breath due neurological pathophysiology[46]. Nocturnal hypoventilation is prevalent among hypercapnic patients with COPD and has been found to be associated with worsened daytime hypercapnia and mortality[38,47]. Comorbid OSA is common among COPD patients (overlap syndrome), with prevalence estimates range up to 43%[48]. The COPD-OSA overlap syndrome has been described as a disease "greater than the sum of its parts"[49] due to its amplified inflammatory and oxidative stress pathways pronounced by prolonged nocturnal hypoxemia caused by apneic events from sleep apnea and reduced ventilation from COPD. This overlap in pathophysiology of each condition creates a systemic issue that has been associated with increased incidence of cardiovascular disease[49]. However, even COPD patients who do not have sleep disordered

breathing experience sleep difficulties and excessive daytime sleepiness that may be caused by COPD symptoms like sputum and wheezing[49]. Patients with overlap syndrome have been shown to have higher levels of $PaCO_2$, which signifies the interaction of OSA with COPD in developing hypercapnia, and other physiological changes during sleep in patients with COPD that may lead to a predisposition of CO_2 accumulation both nighttime and daytime[35]. The recommended treatment for overlap patients is often determined by the predominant phenotype they exhibit[50]. PAP therapy (used as a continuous or auto-adjusting pressure) has been shown to help alleviate COPD symptoms like work of breathing and daytime gas exchange[34] and studies have also suggested that NIV reduces hyperinflation, improves ventilation-perfusion matching, hypoventilation and daytime hypercapnia[51-53]. Sterling and colleagues recently showed that PAP adherence in COPD-OSA overlap was associated with a reduction in all-cause hospitalizations and acute exacerbations[54]. This may enforce the finding that PAP therapy adds benefit for COPD exacerbations and healthcare even in circumstances where bilevel PAP is prescribed to treat the comorbid sleep apnea and/or nocturnal hypoventilation rather than COPD. Many studies of home NIV for COPD have excluded patients with OSA or not assessed for comorbid sleep apnea, therefore it is important that more studies investigating the impact of bilevel PAP on health outcomes consider the reality and prevalence of OSA in patients with COPD.

Furthermore, leveraging telemonitoring and digital health approaches to optimize treatment in longer term care can positively influence the prevention of future exacerbations and enables personalized care by adjusting patients' ventilatory needs over time. From a public health perspective, efforts may be directed towards value-based care and programs aiming to reduce COPD exacerbations and readmissions. However, it is paramount to include an

intentionally equitable approach when designing exacerbation reduction programs through telemonitoring by funding and providing incentives for care in underserved populations. For example, the recent Medicare coverage implementation for remote patient monitoring may be considered an asset in these programs and benefit the accessibility to home bilevel PAP therapy for patients with COPD. However, there are still disparities in accessibility to remote monitoring among disadvantaged populations like uninsured patients and areas where broadband or Wi-Fi are not available.

COPD Exacerbation Risk Factors

A recent review by Hogea et al. provides a thorough assessment of risk factors for COPD exacerbations identified in published literature[28], the most predominant being prior exacerbations, respiratory infections often caused by external exposures, and seasonal variations. In retrospective observational studies, patients with moderate and severe exacerbations in the year prior to an observed event have 2 to 8 times the odds of experiencing future exacerbations[55,56]. This highlights the worsened prognosis and lasting impact of an exacerbation event, and the importance of exacerbation prevention efforts. In terms of comorbidities, risk factors have included asthma, cardiovascular disease (heart failure), bronchiectasis, gastroesophageal reflux disease (GERD), mental health disorders (e.g., depression and anxiety), pulmonary embolism, diabetes, OSA, skeletal muscle weakness, and chronic kidney disease. It is vital to identify how risk factors may vary based on patient phenotypes, treatment approaches, and social determinants of health given the complex heterogeneity of COPD. Identification of risk factors associated with exacerbation occurrence, especially exacerbations requiring hospitalization, among COPD patients who are on a bilevel PAP

device will be essential and informative for treatment and care management programs, which in turn may help alleviate a significant public health strain.

Rationale for the Research Question

Reimbursement and coverage policies often dictate the accessibility and utilization of bilevel PAP therapy for patients with COPD in the US, which may blind practitioners and researchers from the real-world benefits this therapy may provide across the heterogeneity of the disease. Previous retrospective claims data studies have been conducted to model hospitalization risk of COPD patients who use NIV devices including continuous positive airway pressure (CPAP), HMV, and bilevel PAP, compared to those on medication only[15]. However, there are no studies focused on COPD patients exclusively on a bilevel PAP device. Given the unique reimbursement requirements for these devices among COPD patients, this study will be informative in describing the real-world US population receiving this type of ventilation therapy and in identifying which risk factors are associated with exacerbations. Additionally, no retrospective cohort studies have estimated the relative risk of exacerbation occurrence through regression modeling. This represents an interesting opportunity as odds ratios tend to overestimate event occurrence in cohort studies.

This study focused on COPD patients who were prescribed a bilevel PAP device in the US for at-home use between 2015 and 2020. The study objective was to identify risk factors in terms of comorbidities, medications, and demographic characteristics for severe exacerbations. The description of real-world patients with COPD using bilevel PAP considering all comorbid conditions and available demographic factors in the US, as well as the model to identify predictors of severe exacerbation risk will be instrumental for optimized disease management. This will

make findings generalizable to the current standard clinical practice and will help inform gaps in research where patients with common comorbid conditions were excluded (i.e., sleep apnea).

This analysis will inform future studies on the impact and importance of the patient profile, treatment, and timing of bilevel PAP therapy initiation in COPD patients in the US, in order to better understand optimal conditions to treat COPD with the right therapy, at the right time. It is important to investigate clinical benefits and improvement in health outcomes among COPD patients on a bilevel device in a real-world setting, in order to advocate for a focus on the clinical circumstances and provide optimal care for COPD patients. This analysis will also serve as US specific real-world evidence on the use, practicality, and benefit of home NIV using bilevel PAP for COPD, which has previously been seen only in European research studies. These findings may be insightful in guiding prevention and public health efforts to reduce the burden of COPD related exacerbations by targeting comorbid conditions that should be treated and controlled. As well as adding direction to health equity measures in COPD screening, diagnosis, and treatment.

Chapter 2: Journal Article Manuscript

Background

Chronic obstructive pulmonary disease (COPD) is a heterogenous condition associated with increased mortality, healthcare utilization, and public health burden[4,5]. It is estimated that 10.1% of people over 40 years of age have COPD worldwide, and prevalence is projected to increase with an aging population[57,58]. COPD exacerbations make up the greatest portion of costs in COPD-related expenditures[6], and risk factors for exacerbation have not been clearly distinguished[59-61], in part due to the multimorbidity and systemic heterogeneity of patients with COPD[62]. Bilevel positive airway pressure therapy (PAP) is a mode of noninvasive ventilation (NIV) commonly used for ventilatory support in sleep apnea and acute respiratory failure[63,64], and it's been demonstrated to reduce hospital length of stay and improve mortality in acute COPD exacerbations[12]. The American Thoracic Society (ATS) and European Respiratory Society (ERS) clinical guidelines recommend nocturnal bilevel PAP for hypercapnic chronic respiratory failure patients with COPD[11,33], but there is substantial lingering uncertainty about the clinical benefits of home-based NIV treatment for patients with COPD due to mixed results from randomized controlled trials (RCTs) and lack of US specific data.

In the US, about 7.5% of patients with COPD use any form of home NIV devices, and only 1.5% are on bilevel PAP therapy[15]. The low proportion of bilevel PAP use may be influenced by the lack of certainty in recommendations for home NIV in COPD expressed in clinical guidelines, and by the complexities of the Centers for Medicare and Medicaid Services' (CMS) reimbursement policy for bilevel PAP devices[29]. Kulkarni and colleagues have highlighted significant implementation gaps established by CMS and other payer policies that bring about regulatory barriers and financial disincentives, making it cumbersome for both physicians to

prescribe and patients to obtain a bilevel PAP device[34]. Additionally, there are no standard clinical procedures in COPD care that assess or screen for a patient's need for home-based bilevel PAP therapy[34]. Bilevel PAP accessibility is thus very limited, even among patients who fall under the recommended use for stable hypercapnia in severe COPD[39], and there are opportunities to describe and understand the real-world use of bilevel PAP in patients with COPD. There is a need to provide clinical and economic evidence to support the initiation and maintenance of bilevel PAP use in the US, and to consequently promote better access to bilevel therapy for patients with COPD who need ventilation assistance (with and without a back-up rate), without providing a life-support ventilator[40].

Using administrative claims data, we can identify which patients with COPD are receiving bilevel PAP and describe them in terms of comorbidity profile, medications, demographics, and payer coverage. Furthermore, identifying risk factors for exacerbations among this patient population can help guide disease management in this specific population, as patients who are already on a bilevel PAP device may have different exacerbation predictors and comorbidities than the overall COPD population. For example, comorbid sleep apnea among patients with COPD (commonly known as overlap syndrome) on bilevel PAP is expected to be highly prevalent as PAP therapy is also used to treat apneic events. Thus, it is important to investigate what comorbid conditions and medications are risk factors for future exacerbation events, and which may be protective against exacerbation occurrence among patients with COPD receiving bilevel PAP therapy. A recent review by Hogea and colleagues provides a thorough assessment of identified risk factors for COPD exacerbations in the literature[28], the most predominant being prior exacerbations, respiratory infections often caused by external exposures, and seasonal variations. In terms of

comorbidities, risk factors included asthma, cardiovascular disease, bronchiectasis, gastroesophageal reflux disease (GERD), mental health disorders (e.g., depression and anxiety), pulmonary embolism, diabetes, obstructive sleep apnea (OSA), skeletal muscle weakness, and chronic kidney disease. It is vital to identify how risk factors may vary based on patient phenotypes, therapy, medications, and social determinants of health given the complex heterogeneity of COPD. Identification of risk factors associated with exacerbations requiring hospitalizations among patients with COPD who are on a bilevel PAP device will be essential and informative for treatment and care management programs, which in turn may help alleviate a significant public health strain.

Research Question

The aim of this observational retrospective analysis of national administrative insurance claims data is to describe the demographic characteristics, healthcare utilization, and severe exacerbations (i.e., requiring hospitalization) and to identify risk factors associated with severe exacerbation occurrence in the year post bilevel PAP therapy initiation among patients with COPD. This analysis will offer a clear and recent depiction of real-world patients with COPD in the US using bilevel PAP therapy without excluding patients based on comorbidities.

Study Design and Methods

Data Source

This retrospective observational study used de-identified payer-sourced adjudicated claims data from a single cohort of patients with dispersed health plans in the US (Inovalon Insights, LLC). Inovalon's dataset is one of the largest primary sources in the US, longitudinally matching datasets containing real-world medical, pharmacy, demographic, laboratory, and clinical data. Claims are presented through International Classification of Diseases (ICD-10), Current

Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes for diagnoses, procedures, and devices billed to the patient[65,66]. The study design was reviewed by an institutional review board (Advarra, reference number Pro0004005) and deemed exempt from oversight.

Study Population

Patients that had a prescription for a bilevel PAP device (HCPCS code of E0470 or E0471, which correspond to a respiratory assist device with a bilevel pressure capability without and with a backup rate, respectively) were included. The earliest service date between January 1, 2015, and August 4, 2020 (**Figure 1**) with a bilevel PAP claim was defined as the index date. This study population was restricted to patients who have a COPD diagnosis with ICD-10 codes from J41 to J44 in the year prior to the bilevel PAP claim. Additional coding for chronic respiratory failure or blood gas conditions was not available for this analysis. Patients with a bilevel PAP index date who did not have a COPD diagnosis in the year prior to index date were excluded from analysis. Available demographic data (age, gender, region, payer), diagnosis claims, comorbid conditions, medications, and healthcare utilization data were included for all patients 1 year prior to the index date (i.e., baseline) and 1 year post index date (i.e., follow-up). Any null or unknown data fields were excluded for demographic data.

Outcomes

Severe exacerbations were defined as hospitalizations related to respiratory symptoms, as used in Mapel et al. 2021[67]. Severe exacerbation occurrence was defined as a dichotomous outcome variable where 0 related to no severe exacerbations and 1 related to 1 or more severe exacerbations experienced per patient during follow-up. The dichotomous outcome decision was

largely based on the zero-inflated distribution of the number of severe exacerbations during follow-up, but also by factoring in the usability of its interpretation and public health implications. Relative risks for the occurrence of severe exacerbation events during follow-up was estimated for significant predictors in the selected models.

Covariates

Twenty-nine comorbid conditions were included as potential risk factors. Demographic variables included age, sex, region (Northeast, Midwest, South, West), and insurance payer type (Medicare Advantage, Medicaid, commercial) at index date. Moderate and severe exacerbation occurrence at baseline were also included as covariates, defined as doctor or emergency room (ER) visits with diagnosis codes and a prescription of drugs commonly used for COPD exacerbations, and respiratory-related hospitalizations, respectively. COPD-related prescription medications were categorized as maintenance or rescue . The variables for all listed comorbidities were coded as present or absent if there was a qualifying ICD-10 diagnosis code for the condition at baseline. Obesity status was based on coded weight levels in claims data and BMI diagnosis codes: “morbidly obese” and “obese” are often (but not always) coded, “overweight” is sometimes coded, and “healthy weight” is rarely coded, and “underweight” was excluded because it is often coded incorrectly in this population. "Not categorized" patients may be obese, but do not have a code indicating it in their claims data. The level of COPD complexity defined by Mapel 2021 et al. was also included as a proxy for disease severity: high COPD complexity included serious comorbidities like tuberculosis or lung cancer, moderate COPD complexity included relevant comorbidities like pneumonia or asthma, and low COPD complexity included none of the comorbidities from high or moderate COPD rescue and maintenance medication claims were also

included as covariates. Maintenance medications included monotherapy or combination therapy of long-acting beta agonists (LABA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS), xanthine, or phosphodiesterase-4 (PDE4) medications in the year prior to index date. Rescue medications included short-acting beta agonists (SABA), and short-acting muscarinic antagonists (SAMA). Healthcare costs accounted for the estimated payment for all claims including medical and prescription, per year.

Statistical Analysis

A modified Poisson regression approach was employed to obtain estimates of the relative risks, first described by Zou and colleagues[68]. In cohort studies, direct calculation of risk rations are preferred over estimation provided by odds rations, as the latter are known to overestimate the actual risk ratios. Univariable analysis was conducted to examine the association between each available covariate and the occurrence of severe exacerbation during follow-up. Predictors identified as statistically significant in the univariate analysis were included in the model selection process. A stepwise logistic regression analysis was then used to arrive at the final model. Entry and stay criteria for model selection were 0.20 and 0.25 respectively. The selected model included only statistically significant predictors Using these selected covariates, a multivariate analysis was conducted to estimate adjusted risk ratios through the modified Poisson regression approach. Relative risk ratios are reported with 95% Confidence Intervals and *P*-values. Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4.

Results

Study Population

A total of 108,118 patients were identified as having a qualifying bilevel PAP index date and extracted from the administrative claims data. Of these, 81,183 (75.08 %) did not have a COPD

diagnosis and were excluded. An additional 470 patients who had unknown or null demographic data were excluded to enhance data completeness. The final study population included 26,465 patients with COPD with a bilevel PAP claim (**Figure 2**). **Table 1** presents the baseline demographic characteristics of the study population. Forty six percent of patients were female, and the cohort's mean (± SD) age was 61.52 ± 10.12 years old. About one-third of patients had each type of insurance, with Medicaid being slightly higher in proportion, followed by Medicare Advantage, and then Commercial. Most patients were from the South (32.35%) and Midwest (31.12%) regions, followed by West (20.38%) and Northeast (16.15%). Over half of patients were categorized as morbidly obese and had moderate COPD complexity. The most prevalent comorbidity was OSA (90.66%), which was a subset of the unspecified sleep disordered breathing code (92.66%). Other prevalent comorbidities were hypertension (87.83%), hyperlipidemia (72.42%), type 2 diabetes (54.63%), and GERD (43.48%). At the same time as the bilevel PAP index claim, 23,045 patients had a sleep apnea claim, whereas only 4,693 patients had a COPD diagnosis claim associated with the bilevel PAP claim. This may indicate that most of these patients with COPD received bilevel PAP to treat comorbid sleep apnea vs COPD symptoms. Over half of patients had ≥1 claim for a maintenance COPD medication, and 62.78% of patients had ≥1 claims for rescue medications.

Bilevel PAP Impact

Most patients did not experience any severe exacerbations during the study period, leading to a zero-inflated distribution (**Figure 3**) of severe exacerbation events. On average, unadjusted healthcare utilization costs were higher at baseline compared to follow-up, which may indicate that bilevel PAP therapy may help reduce healthcare costs. Over 11% of patients had at least 1

severe exacerbation at baseline, and only 6.68% had 1 or more severe exacerbations during follow-up. The maximum number of severe exacerbations experienced by a single patient was 11 at baseline, and 12 during follow-up. Using McNemar's test, we observed a significant difference in severe exacerbation occurrence between baseline and follow-up (t-value 24.07, *P*-value <.0001), with a reduction in outcome occurrence after initiation of bilevel PAP.

Model Assessment

All 26,465 observations were used for the model development and assessment. In the unadjusted analysis, 39 out of the 49 variables included were statistically significant in predicting severe exacerbation occurrence, considering that COPD complexity, obesity status, payer at index, region, and age were divided into categories of more than 2 levels (**Table 2**). The occurrence of a severe exacerbation at baseline was by far the strongest predictor of risk for a future exacerbation, (RR 9.12 95% CI [8.37, 9.93]). High COPD complexity, being a Medicaid beneficiary, and a pneumonia diagnosis were associated with an increased risk of severe exacerbation occurrence during follow-up (RR 7.05 95% CI [5.70, 8.74], RR 3.17 95% CI [2.78, 3.62], RR 3.14 95% CI [2.87, 3.43] respectively).

Adjusted Risk Estimates

After model selection, there were 16 variables left in the model for adjusted relative risk estimation. Parameter estimates from the selected model can be found in **Table 3**. All predictors in the selected model were statistically significant and indicated increased risk for severe exacerbation occurrence, with the exception of OSA, snoring, and morbid obesity, which yielded a protective effect against exacerbations using this model. Relative risk estimates were attenuated for all predictors in the adjusted model (**Table 4**), but occurrence of a severe

exacerbation in the year prior to bilevel remained the strongest predictor with a nearly quintupled increased risk for future severe exacerbation occurrence (RR, 4.86; 95% CI [4.39, 5.37]). Like the unadjusted model, high COPD complexity was associated with 2.28 times the risk of the outcome, and Medicaid coverage was associated with double the risk of severe exacerbation in the year post bilevel PAP index (RR, 2.28; 95% CI [1.82, 2.86], RR 2.02, 95% CI [1.78, 2.30], respectively). Moderate exacerbation occurrence was associated with 37% increased risk of a severe exacerbation (RR 1.37 95% CI [1.25, 1.49]). Comorbidities associated with increased risk included pneumonia, heart failure, anxiety, psychotic disorder, and asthma, in that order (**Table 4**). COPD maintenance and rescue medication use were both associated with approximately 23% increased risk of severe exacerbation occurrence, (RR 1.23 95% CI ([1.10, 1.37], RR 1.23 95% CI [1.08, 1.41], respectively). In terms of demographic characteristics, women were found to be at an increased risk of severe exacerbation by almost 10% compared to men, (RR 1.10 95% CI [1.00, 1.20]), and the age group of 55 to 64 years old showed a significant increased risk (RR 1.162 95% CI [1.06, 1.27]) compared to the reference category of 40 to 44 years old, but also compared to older patients who showed decreased risk in the unadjusted model. Conversely, an OSA diagnosis led to a 23% reduction in severe exacerbation risk (RR 0.77 95% CI [0.69, 0.86]), snoring was associated with 22% risk reduction (RR 0.79 95% CI [0.68, 0.90]), and morbid obesity and obesity claims both had an approximate 17% reduction in severe exacerbation risk (RR 0.83 95% CI [0.74, 0.93], RR 0.83 95% CI [0.72, 0.94], respectively). All adjusted risk ratios with a statistically significant association with severe exacerbation among patients with COPD who are prescribed bilevel PAP therapy are found in **Figure 5**.

Discussion

This analysis of administrative claims data provides a real-world understanding of risk factors associated with severe exacerbations in light of the occurrence of respiratory-related hospitalizations among patients with COPD using bilevel PAP therapy. The findings from this study showed that most patients who were prescribed bilevel PAP therapy do not have a COPD diagnosis, and that most patients with COPD who are prescribed a bilevel PAP device have comorbid sleep apnea, also commonly known as overlap syndrome. Vasquez and colleagues showed the opposing lens of this population, where most patients with COPD were found to not be on any form of PAP therapy[15].

OSA was found to have a protective effect against severe exacerbation occurrence in this patient population. This should be interpreted with caution, as it is not the pathophysiology of OSA that decreases exacerbation risk, but we believe it is rather the treatment of OSA through the bilevel PAP therapy that treats the apneas and relieves patients from COPD-related symptoms. Bilevel PAP eradicates apneic events and oxygen desaturations, allowing for better sleep quality and restoration[69], but also may help alleviate dyspnea, hypoventilation, and hypercapnia, which have been shown to be associated with increased exacerbation risk[21]. Snoring and obesity are often considered synonymous with the OSA phenotypic profile, so it is speculated that bilevel PAP therapy virtually eliminates snoring[70] as a byproduct of sleep apnea symptom improvements, and thus snoring mimics the risk reduction of OSA treatment on exacerbations. High BMI has also been linked to reduced exacerbation risk by Hunter and colleagues[71]. However, the obesity categorization in this analysis presents a limitation because the use of ICD-10 obesity claim is rarely coded for non-obese or healthy weight patients, and

healthy weight and non-categorized patients were combined and used as the reference for the regression model. There is a need for a better proxy or definition of obesity in administrative claims data.

It is likely that the bilevel device was prescribed to treat OSA (perhaps after CPAP failure or intolerance) due to the complicated CMS reimbursement pathway for bilevel device use in patients with COPD. This speculation is further reinforced by the finding that 84% of the study population had a claim for a bilevel without a back-up rate device (data not shown) that is reimbursed for severe COPD only if there is evidence of nocturnal hypoxemia and hypercapnia when sleep apnea has been ruled out[29]. In other words, according to CMS RAD guidelines, devices without a back-up rate will not be covered for patients with COPD in the presence of sleep apnea, and patients would thus be brought on to the OSA reimbursement pathway, where the same patient can qualify for a RAD device without a back-up rate coverage if there is evidence of CPAP (HCPCS E0601) intolerance or failure[72]. Despite increased costs and complexities associated with home mechanical ventilation devices (HCPCS E0466), it has been shown they are more widely prescribed for patients with COPD in place of a bilevel PAP device because the coverage and reimbursement guidelines are more convenient in clinical practice[73].

To our knowledge, this is the first study to describe risk factors for severe exacerbations in this specific population. Several studies have investigated bilevel PAP therapy on COPD but have excluded comorbid sleep apnea patients and have not been focused on describing the relative risk for severe exacerbations. Prior RCTs have shown impactful data regarding the use bilevel PAP therapy in hypercapnic patients with COPD respectively. These studies conclude that bilevel PAP therapy in this population prevented future exacerbations[44] and reduced mortality[43],

but they either excluded patients with comorbid OSA or did not include sleep apnea assessment, which is not reflective of real-world clinical practice in the US given reimbursement and clinical guidelines. Sterling and colleagues showed reduced healthcare costs in PAP adherent patients with overlap syndrome[54], which complements this study by highlighting the added benefits that adherence to bilevel PAP therapy may have on this study population.

The results from this study offer insights into how this specific COPD patient population may or may not differ in exacerbation risk factors compared to known risk factors in the general COPD population. Aligning with the available literature, severe exacerbations in the prior year were the most significant factor in predicting future exacerbations[74-78]. This emphasizes the importance of COPD treatment and care management to prevent severe exacerbations and hospitalizations in the first instance, as worsened prognosis and increased healthcare utilization tend to follow. Previously published data on COPD comorbidities associated with increased exacerbation risk were also reiterated in this analysis, including anxiety, asthma, heart failure, pneumonia, and mental disorders[56,79,80]. Comorbidities that were expected to be associated with increased exacerbation risk but did not result in statistical significance in the adjusted model for this population were diabetes, cancer, dementia, fatigue, GERD, and OSA. GERD was independently associated with severe exacerbation risk, as was cancer, except that the latter seemed to have a protective effect against exacerbation in the unadjusted model. Diabetes, dementia, fatigue, and other comorbidities that have been previously associated with COPD exacerbations[28,81-83], were not found in this model but may well be associated with increased risk for worse disease severity and prognosis, as well as all-cause hospitalizations. Another potential explanation may be related to the textbook-described COPD phenotypes of blue bloaters and

pink puffers[19], who may be more meaningfully categorized as non-emphysematous and emphysema-predominant COPD subtypes, respectively. Hersh and colleagues found that non-emphysematous patients with COPD have higher rates of diabetes[84] and in general, emphysema predominant patients have worse respiratory prognosis and may experience severe exacerbations more often than their higher BMI, non-emphysematous counterparts[85].

In terms of demographic factors associated with increased exacerbation risk, results were consistent with previous data showing women are at increased risk compared to men [86-88], which highlights the need to screen and treat women for COPD and OSA. The age category of 55 to 64 years old as a significant predictor may reflect lower adherence to medication or therapy compared to older patients[89] or perhaps a higher average number of comorbidities propagating exacerbation severity[90], but these factors were not evaluated. Finally, the increased risk associated with Medicaid as payer type is potentially attributed to lower socioeconomic status. Similarly, increased risk associated with Medicare Advantage may be related to older age, cognitive degeneration, and end stage renal disease, which have all been linked to worsened disease progression and COPD exacerbations[91,92].

Strengths

The sample size of this real-world evidence study enhances the representation of a broad spectrum patients with COPD receiving bilevel PAP therapy in standard practice in the US. The evidence presented may help guide treatment options and care management prioritization of the already complex and heterogenous COPD phenotypic and comorbidity profile.

A novel aspect in the analytic approach of this study was the relative risk estimation from a retrospective cohort study using a binomial outcome. The reporting of risk ratios may be more

informative and conservative from a public health perspective, as epidemiological and clinical research is largely grounded on the assessment of risk[68], and risk estimates are easier to interpret and apply into clinical practice. Odds ratios are often inflated and misleading when not used in a case-control study if an association between exposure and outcome exists[93,94]. Zou's use of Poisson regression used in this study has been shown to estimate relative risk consistently and efficiently in cohort studies by providing similar estimates obtained by the Mantel-Haenszel procedure[94,95].

Limitations

The nature of a retrospective claims data analysis prevents including self-reported and modifiable or behavioral factors that may be influential in COPD prognosis, such as smoking status or smoking history, environmental exposures, work environment, physical activity, alcohol or substance use, etc., which contribute to exacerbation risk. This also prevents researchers from drawing meaningful conclusions to inform public health interventions targeting behavior change at an individual, interpersonal, and policy level.

This study lacked a control group of patients with COPD who are not on bilevel PAP therapy, making it difficult to accurately interpret the impact of this therapy on the severe exacerbation risk outcome. However, only severe patients with COPD with hypercapnia or chronic respiratory failure should receive NIV therapy according to clinical guidelines, so if a control group is to be included, patients should be matched according to disease severity and other factors. Furthermore, adherence data to the bilevel PAP therapy was not included in the analysis, so it was not possible to determine whether patients were using the device long enough to provide therapeutic benefit, or if they used it at all post index date. Additionally, understanding the

prescribed and actual pressure settings in these bilevel PAP devices would help fill some gaps from RCTs that failed to show improvement in COPD health outcomes[36-38] and either excluded or overlooked sleep apnea patients, as it has been hypothesized that the lack of health improvement might have been due to inadequate pressure settings[39].

Patients were selected based on the presence of a bilevel PAP claim as a primary inclusion criterion, and patients with a COPD diagnosis claim were selected from that initial group as a secondary inclusion criterion. We found a high prevalence of comorbid OSA in this selection. However, we were not able to discern whether patients obtained the bilevel PAP claim through the PAP treatment for OSA CMS coverage guidelines (L33718) or through the RAD coverage guidelines (L33800), though we believe it is the former. Furthermore, it is hard to elucidate which disease or comorbidity is more heavily characterizing the treatment, care management, and prognosis of the patient. It would be informative to better understand what disease states and overall comorbid profiles bilevel PAP is being used for in a real-world practice by analyzing the original patient selection (n=108,118).

Interpretation

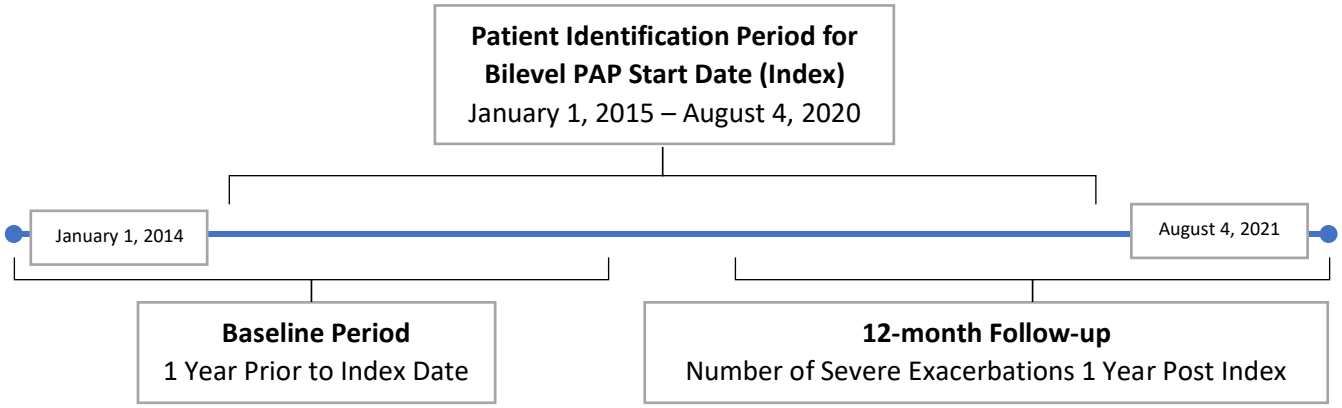
This study provides insights into the characteristics of patients with COPD who receive bilevel PAP therapy and the factors associated with severe exacerbation occurrence. The findings indicate the importance of preventing severe and moderate exacerbations from first occurring in order to prevent future severe exacerbations among patients with COPD who use bilevel PAP therapy. Key comorbidities among COPD like pneumonia, anxiety, heart failure, asthma, and psychotic disorders should be addressed in treatment management as they are associated with increased risk for severe exacerbations. Importantly, findings suggest that bilevel PAP use among

patients with COPD and OSA was significantly associated with reduced exacerbation risk. Finally, demographic factors associated with increased risk of severe exacerbations, especially females and having Medicaid or Medicare Advantage as type of health insurance, stress the need for greater health equity efforts in screening and treatment of COPD and sleep apnea.

To maximize the recognized benefits of bilevel PAP therapy for patients with COPD, future research should be focused on real-world clinical practice and incorporate acontrol group, adherence data, and analysis of therapy pressure settings. Parameters not captured in administrative claims such as lung function, physical activity, and smoking history, COPD symptoms (cough, wheezing, shortness of breath, etc.), as well as patient reported outcomes such as health-related quality of life may also be included in future studies to assess their contribution to exacerbation risk. Ultimately, combining multiple data sources through a protected method like data tokenization could enable and provide the optimal database for a thorough assessment of COPD exacerbation risk. The deeper understanding that results from this effort has the potential to help optimize access, timing, and therapeutic management of bilevel PAP for COPD in the home setting.

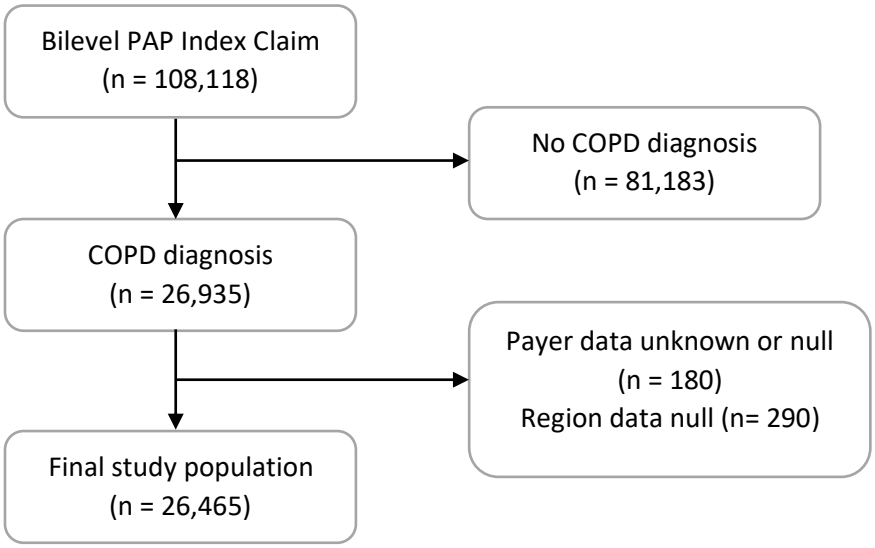
Tables and Figures

Figure 1- *Patient Identification Period*



PAP = Positive Airway Pressure

Figure 2 - *Consort Diagram*



PAP = Positive Airway Pressure

COPD = Chronic Obstructive Pulmonary Disease

Table 1] Baseline Characteristics of COPD Patients on a Bilevel PAP Device (N=26,465)

	n	Percentage
Gender		
Male	14,275	53.94
Female	12,190	46.06
Age (Mean, SD)	61.52	10.12
Age groups		
40-44 years old	930	3.51
45-54 years old	5,538	20.93
55-64 years old	11,280	42.62
65-69 years old	3,030	11.45
≥70 years old	5,687	21.49
Payer at Index		
Medicaid	9,369	35.40
Medicare Advantage	8,823	33.34
Commercial	8,273	31.26
Region		
Midwest	8,235	31.12
Northeast	4,275	16.15
South	8,561	32.35
West	5,394	20.38
COPD Complexity		
Low	7,187	27.16
Moderate	13,441	50.79
High	5,837	22.06
Obesity Status		
Not categorized	5,828	22.02
Overweight	1,132	4.28

Obese	5,917	22.36
Morbidly obese	13,588	51.34
Comorbidities		
Anxiety	8713	32.92
Asthma	9,730	36.77
Atrial fibrillation	5,280	19.95
Atrial flutter	1,121	4.24
CSA	2,013	7.61
Cancer	3,212	12.14
Cerebrovascular disease	3,667	13.86
COVID-19	2,072	7.83
CAD	11,043	41.73
Dementia	727	2.75
Depression	9,876	37.32
Fatigue	6,947	26.25
GERD	11,508	43.48
Heart failure	10,971	41.45
Hyperlipidemia	19,165	72.42
Hypertension	23,247	87.84
Insomnia	4,674	17.66
OSA	23,992	90.66
Other arrhythmia	4,944	18.68
Other mood disorders	2,571	9.71
Pneumonia	6,572	24.83
Psychotic disorders	2,629	9.93
SDB (No OSA)	531	2.01
Secondary pulmonary HTN	4,386	16.57
Snoring	4,265	16.12

Somnolence	1,433	5.41
Stroke	1,575	5.95
Type 1 diabetes	1,650	6.23
Type 2 diabetes	14,458	54.63
Diagnosis associated with bilevel PAP claim		
COPD	4,693	17.73
SDB	23,045	87.08
Medications		
Maintenance -	14,013	52.95
Rescue -	16,614	62.78
Healthcare costs		
Baseline (Mean, SD)	$ 25,301.14	$ 34,100.55
Healthcare costs		
Follow-up (Mean, SD)	$ 24,916.79	$ 32,639.67

CAD = coronary artery disease; CSA = central sleep apnea; GERD = gastroesophageal reflux disease; HTN = hypertension; OSA = obstructive sleep apnea; SDB = sleep disordered breathing; Maintenance meds = monotherapy (LABA, LAMA, ICS, PDE-4, XANTHINE) + combination therapy (LABA and LAMA, LABA and ICS, LABA, LAMA and ICS, Other combination); Rescue meds = SABA, SAMA, SABA and SAMA. Healthcare costs = total estimated payment for all claims (medical and prescription) per year.

Figure 3 - *Distribution of Severe Exacerbations at Baseline and Follow-up.*

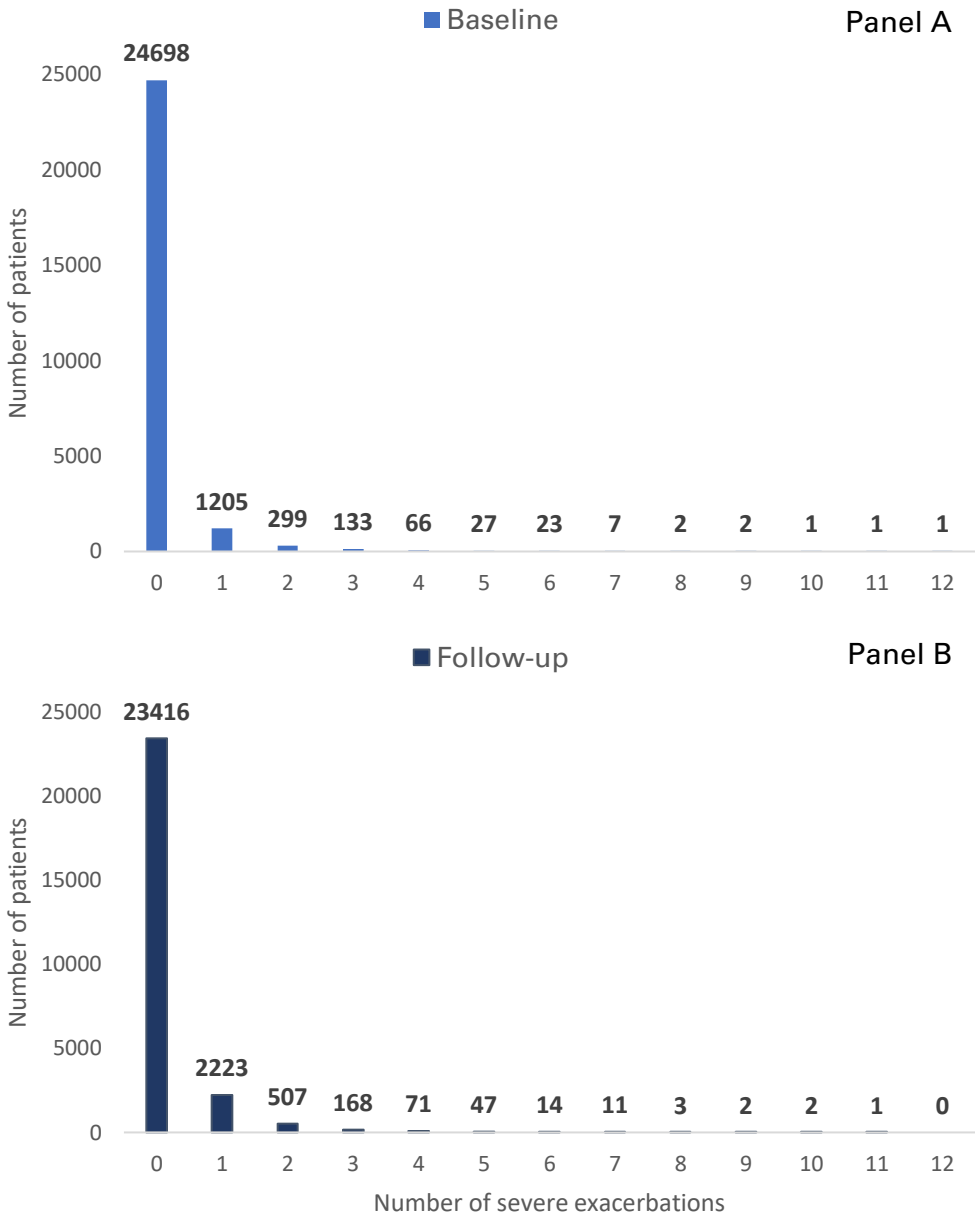


Figure 4 - *Distribution of Severe Exacerbations as a Binary Outcome*

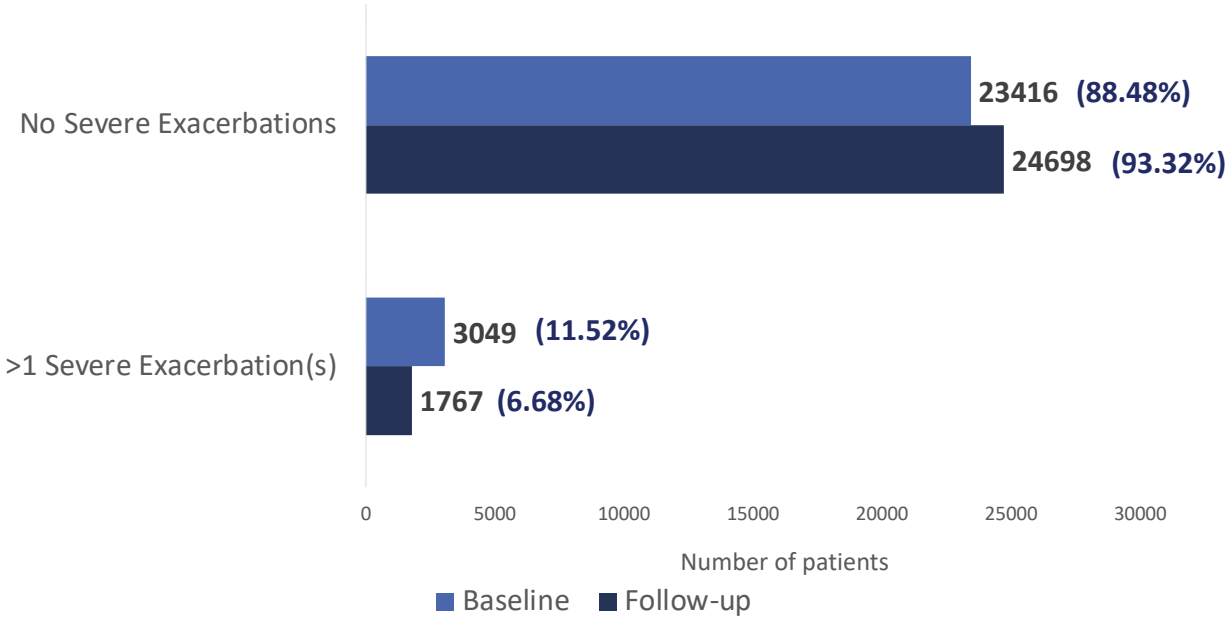


Table 2] Unadjusted Risk Ratios for Severe Exacerbation Occurrence at Follow-up.

Baseline Predictor	RR	95% CI	*P* Value
Severe exacerbation	9.12	(8.37, 9.93)	<.0001
Moderate exacerbation	2.37	(2.16, 2.59)	<.0001
Anxiety	1.94	(1.77, 2.12)	<.0001
Asthma	1.56	(1.42, 1.70)	<.0001
Arrhythmia	1.23	(1.10, 1.37)	0.0002
Atrial fibrillation	1.13	(1.01, 1.25)	0.0333
Atrial flutter†	1.20	(0.98, 1.47)	0.0820
CSA	0.57	(0.46, 0.71)	<.0001
Cancer	0.86	(0.74, 0.99)	0.0471
Cerebrovascular disease†	1.11	(0.98, 1.26)	0.0979
CAD	1.21	(1.11, 1.33)	<.0001
COVID-19	1.38	(1.19, 1.59)	<.0001
Dementia†	1.07	(0.82, 1.40)	0.6013
Depression	1.54	(1.41, 1.68)	<.0001
Fatigue†	0.94	(0.85, 1.04)	0.2223
GERD	1.36	(1.24, 1.49)	<.0001
Heart failure	1.95	(1.78, 2.13)	<.0001
Hypertension	1.41	(1.20, 1.65)	<.0001
Hyperlipidemia	0.88	(0.80, 0.97)	0.0086
Insomnia	1.16	(1.04, 1.30)	0.0097
OSA	0.41	(0.37, 0.46)	<.0001
SDB (no OSA)	1.34	(1.01, 1.76)	0.0409
Other mood disorders	1.28	(1.11, 1.46)	0.0006
Pneumonia	3.14	(2.87, 3.43)	<.0001
Psychotic disorder	1.78	(1.58, 2.01)	<.0001
Secondary pulmonary hypertension	1.55	(1.39, 1.72)	<.0001

Snoring	0.63	(0.55, 0.73)	<.0001
Somnolence	1.23	(1.03, 1.47)	0.0262
Stroke	1.31	(1.11, 1.55)	0.0018
Type 1 diabetes	1.19	(1.01, 1.42)	0.0424
Type 2 diabetes†	1.08	(0.98, 1.18)	0.1062
Female	1.69	(1.54, 1.85)	<.0001
COPD complexity (Reference: Low)			
High	7.05	(5.70, 8.74)	<.0001
Moderate	1.13	(1.03, 1.25)	0.0140
Obesity (Reference: Not categorized)			
Overweight†	1.06	(0.85, 1.33)	0.5986
Obese	0.70	(0.61, 0.81)	<.0001
Morbidly†	0.99	(0.89, 1.11)	0.9093
Payer at index (Reference: Commercial)			
Medicaid	3.17	(2.78, 3.62)	<.0001
Medicare Advantage	1.85	(1.61, 2.14)	<.0001
Medication claim			
Rescue medication	2.81	(2.49, 3.17)	<.0001
Maintenance medication	2.45	(2.21, 2.71)	<.0001
Region (Reference: South)			
Midwest	0.76	(0.68, 0.86)	<.0001
Northeast†	1.05	(0.93, 1.20)	0.4360
West	0.87	(0.77, 0.99)	0.0301
Age			
40-44 years old†	0.87	(0.67, 1.13)	0.2816
45-54 years old†	1.08	(0.97, 1.20)	0.1776
55-64 years old	1.31	(1.20, 1.43)	<.0001
65-69 years old	0.84	(0.72, 0.98)	0.0242

70 + years old	0.68	(0.60, 0.77)	<.0001

See Table 1 legend for expansion of abbreviations.

†Non-significant predictors.

Table 3] Selected Model GEE Parameter Estimates from Stepwise Regression (N=26,465)

Parameter	β Estimate	Std Error	Z Statistic	*P* Value
Intercept	-4.8525	0.1329	-36.52	<.0001
Severe exacerbation	1.5802	0.0514	30.76	<.0001
Moderate exacerbation	0.3108	0.0455	6.83	<.0001
Payer (Ref: Commercial)				
Medicaid	0.7042	0.0664	10.6	<.0001
Medicare Advantage	0.4060	0.0727	5.59	<.0001
Anxiety	0.1861	0.045	4.14	<.0001
Asthma	0.0905	0.0444	2.04	0.0414
Heart failure	0.2391	0.0466	5.13	<.0001
OSA	-0.2644	0.0571	-4.63	<.0001
Obesity (Ref: Not categorized)				
Morbidly obese	-0.1892	0.0579	-3.27	0.0011
Obese	-0.1916	0.0686	-2.79	0.0052
Overweight	0.0555	0.1048	0.53	0.5965
COPD complexity (Ref: Low)				
High	0.8232	0.116	7.09	<.0001
Moderate	0.8506	0.1108	7.68	<.0001
Pneumonia	0.3012	0.0462	6.52	<.0001
Rescue medication	0.2095	0.0688	3.05	0.0023
Maintenance medication	0.2033	0.0573	3.55	0.0004
Snoring	-0.2419	0.0705	-3.43	0.0006
Psychotic disorders	0.1524	0.0577	2.64	0.0083
Age 55 - 64	0.1497	0.045	3.33	0.0009

Female	0.0934	0.0463	2.02	0.0436

See Table 1 legend for expansion of abbreviations.

Table 4] Adjusted Risk Ratios for Severe Exacerbation Occurrence After Model Selection (N=26,465)

Baseline Predictor	RR	95% CI	*P* Value
Severe exacerbation	4.86	(4.39, 5.37)	<.0001
Moderate exacerbation	1.36	(1.25, 1.49)	<.0001
Anxiety	1.21	(1.10, 1.32)	<.0001
Asthma	1.10	(1.00, 1.19)	0.0414
Heart failure	1.27	(1.16, 1.39)	<.0001
OSA	0.77	(0.69, 0.86)	<.0001
Pneumonia	1.35	(1.23, 1.48)	<.0001
Psychotic disorder	1.17	(1.04, 1.30)	0.0083
Snoring	0.79	(0.68, 0.90)	<.0001
Female	1.10	(1.00, 1.20)	0.0436
COPD complexity (Ref: Low)			
High	2.28	(1.82, 2.86)	<.0001
Moderate	0.97	(0.89, 1.07)	0.5557
Obesity (Ref: Not categorized)			
Overweight†	1.06	(0.86, 1.30)	0.5965
Obese	0.83	(0.72, 0.94)	0.0052
Morbidly obese	0.83	(0.74, 0.93)	0.0011
Payer at Index (Ref: Commercial)			
Medicaid	2.02	(1.78, 2.30)	<.0001
Medicare Advantage	1.50	(1.30, 1.73)	<.0001
Medication Use			
Rescue COPD medication	1.23	(1.08, 1.41)	0.0023

	Maintenance COPD medication	1.23	(1.10, 1.37)	0.0004
Age				
	55-64 years old	1.16	(1.06, 1.27)	0.0009

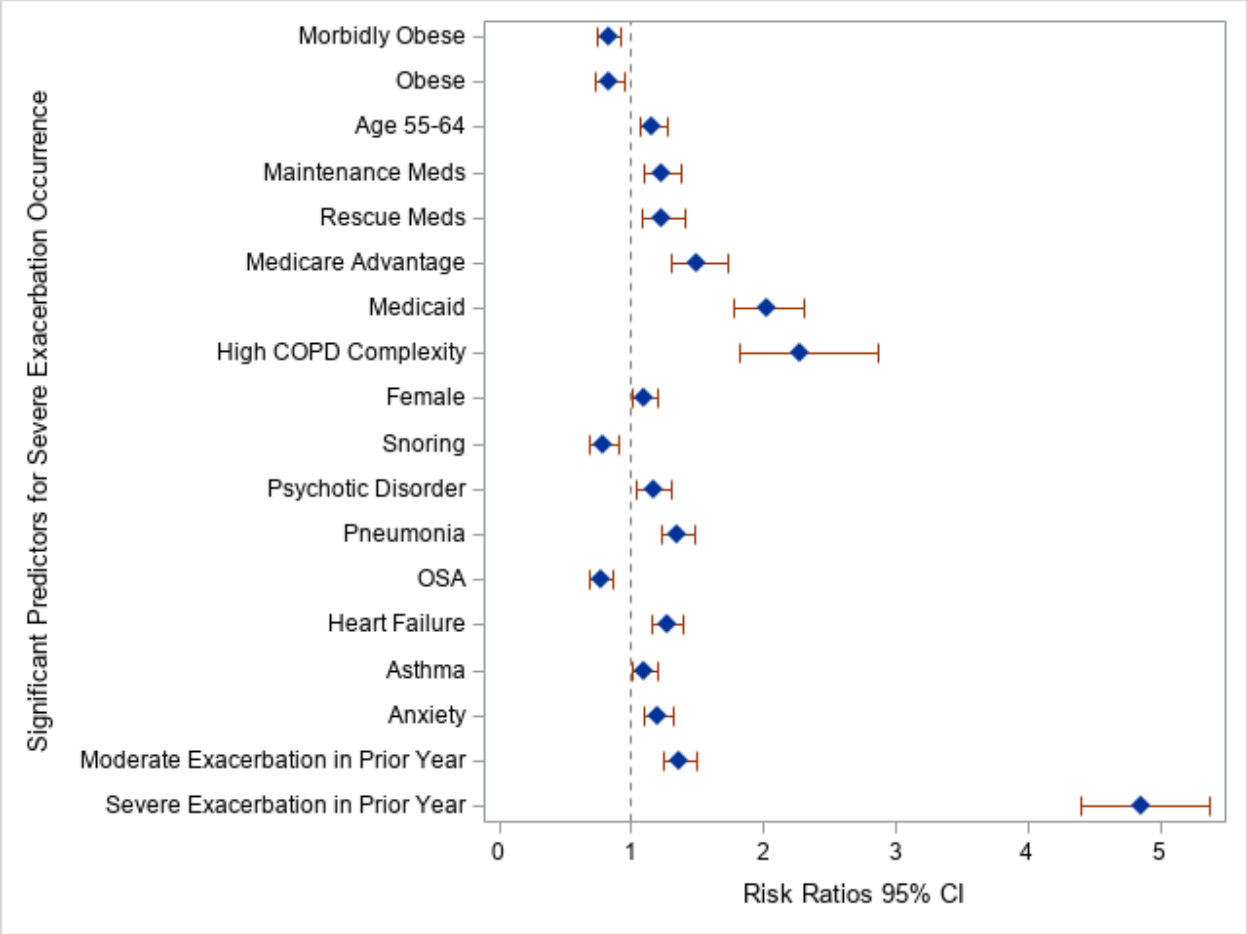
See Table 1 legend for expansion of abbreviations.

Table 5] Risk Ratios for Severe Exacerbation Occurrence in Selected Model Predictors

	Unadjusted Estimates			Adjusted Estimates		
Baseline Predictor	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Severe exacerbation	9.12	(8.37, 9.93)	<.0001	4.86	(4.39, 5.37)	<.0001
Moderate exacerbation	2.37	(2.16, 2.59)	<.0001	1.37	(1.25, 1.49)	<.0001
Anxiety	1.94	(1.77, 2.12)	<.0001	1.21	(1.10, 1.32)	<.0001
Asthma	1.56	(1.42, 1.70)	<.0001	1.10	(1.00, 1.19)	0.0414
Heart failure	1.95	(1.78, 2.13)	<.0001	1.27	(1.16, 1.39)	<.0001
OSA	0.41	(0.37, 0.46)	<.0001	0.77	(0.69, 0.86)	<.0001
Pneumonia	3.14	(2.87, 3.43)	<.0001	1.35	(1.23, 1.48)	<.0001
Psychotic disorder	1.78	(1.58, 2.01)	<.0001	1.17	(1.04, 1.30)	0.0083
Snoring	0.63	(0.55, 0.73)	<.0001	0.79	(0.68, 0.90)	<.0001
Female	1.69	(1.54, 1.85)	<.0001	1.10	(1.00, 1.20)	0.0436
COPD complexity (Ref: Low)						
High	7.05	(5.70, 8.74)	<.0001	2.28	(1.82, 2.86)	<.0001
Moderate	1.13	(1.03, 1.25)	0.0140	0.97	(0.89, 1.07)	0.5557
Obesity (Ref: Not categorized)						
Overweight†	1.06	(0.85, 1.33)	0.5986	1.06	(0.86, 1.30)	0.5965
Obese	0.70	(0.61, 0.81)	<.0001	0.83	(0.72, 0.94)	0.0052
Morbidly obese	0.99	(0.89, 1.11)	0.9093	0.83	(0.73, 0.93)	0.0011
Payer at Index (Ref: Commercial)						
Medicaid	3.17	(2.78, 3.62)	<.0001	2.02	(1.78, 2.30)	<.0001
Medicare Advantage	1.85	(1.61, 2.14)	<.0001	1.50	(1.30, 1.73)	<.0001
Medication Use						
Rescue	2.81	(2.49, 3.17)	<.0001	1.23	(1.08, 1.41)	0.0023
Maintenance	2.45	(2.21, 2.71)	<.0001	1.23	(1.10, 1.37)	0.0004

Age							
	55-64 years old	1.31	(1.20, 1.43)	<.0001	1.16	(1.06, 1.27)	0.0009

Figure 5 - *Adjusted Risk Ratios for Severe Exacerbation Occurrence*



See Table 1 legend for expansion of abbreviations.

Chapter 3: Public Health Implications

Exacerbations in severe COPD represent a major public health and economic burden in the United States and across the globe. In 2019, COPD was associated with 3.3 million deaths and 74.4 million disability-adjusted life years[4]. COPD healthcare costs totaled 50 billion USD per year in indirect morbidity and mortality costs, and direct healthcare expenditures[96], and exacerbations account for the greatest proportion of these costs[6]. Our study results emphasize the importance of preventing severe exacerbations among patients with COPD, as they are by far the greatest predictor in future occurrences. Efforts to prevent moderate exacerbations should also be reinforced through open patient-provider communications and adherence to medications and prescribed therapies. Perhaps a novel concept introduced by the findings of this study is that the treatment of OSA among COPD patients is protective against severe exacerbation occurrence as early as 1 year after bilevel PAP therapy initiation. This is an encouraging result that aligns with published literature on the health outcomes and cost benefits associated with PAP treatment in OSA and overlap syndrome patients[54,97,98]. Healthcare providers should thus screen for and treat OSA in COPD patients, and work with home medical equipment providers to encourage patients to reach and maintain long-term adherence to bilevel PAP therapy. It is also vital to recognize the influence of payers as well as coverage reimbursement guidelines in the accessibility of PAP therapy for COPD patients. Regular revision and adaptation of the coverage guidelines based on the latest clinical evidence are necessary to improve patient outcomes and reduce the public health burden.

The prevalence of comorbidities in patients with COPD is higher when compared to patients without COPD,[99], with an average of 3.7 comorbidities vs. 1.8 comorbidities in non-COPD

control patients[100]. The results of this study highlight the need for special attention to screening and treatment of comorbidities such as pneumonia, anxiety, asthma, psychotic disorders, and heart failure in patients with COPD who are treated with PAP therapy. There is a lack of clear guidance and standardized protocols for the management of patients who have COPD with multiple comorbidities[101], resulting in a high rate of underdiagnoses and treatment gaps of comorbidities in COPD[102,103]. Thus, it is important to guide efforts to define and standardize screening and treatment pathways that consider the high incidence and prevalence of multiple comorbidities in patients with COPD. Additionally, public health interventions should aim to reduce stigma surrounding mental health, including anxiety and psychotic disorders, especially among older populations[104] in hopes of encouraging patients to speak to their providers about their mental health as part of their COPD care management and general well-being.

Findings from this study also shed light on health equity issues in COPD care with increased exacerbation risk associated with sex and payer differences. Women, people over 65 years old, and low-income patients are often vulnerable and disadvantaged populations in clinical care contexts. Systemic social determinants of health affect their access to healthcare and interactions with healthcare system across logistical, stigma, education, and economic barriers. Thus, it is paramount to create awareness among these patient populations, their networks, and their healthcare providers on the higher exacerbation risk and develop mitigation options. Furthermore, public health efforts are needed to erase barriers to care that differ across demographic factors to ensure equal opportunities for care for all patients.

Future studies should include comprehensive data ecosystems that include therapy adherence data and potentially patient-reported outcomes that can be collected through

telemonitoring. The addition of these data and a control group of untreated COPD-OSA patients can help discern the impact of bilevel PAP therapy in severe exacerbation occurrence, which can inform current clinical and coverage guidelines.

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