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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Impact of PAP therapy on hospitalization rates in Medicare beneficiaries with COPD and coexisting OSA

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Abstract

Objective Growing evidence supports that patients with chronic obstructive pulmonary disease (COPD) and coexisting obstructive sleep apnea (OSA) have poor prognosis. This association is described as overlap syndrome. Positive airway pressure (PAP) therapy is now the preferred treatment for OSA. We hypothesized that use of PAP therapy in elderly patients with overlap syndrome would be associated with lower healthcare utilization.

Methods In this retrospective cohort study, we analyzed data from 5% national sample of fee-for-service Medicare beneficiaries with a diagnosis of COPD who were newly started on PAP therapy in 2011. We examined the effect of PAP therapy on emergency room (ER) visits and hospitalizations for all-cause and COPD-related conditions in the 1 year pre- and 1 year post-initiation of PAP therapy.

Results In year 2011, we identified 319 patients with overlap syndrome who were new users of PAP therapy. In this cohort of patients, hospitalization rates for COPD-related conditions were significantly lower in the 1 year post-initiation of PAP therapy compared to the 1-year pre-initiation period (19.4 vs 25.4%, *P* value = 0.03). However, ER visits (for any cause or COPD-related conditions) and hospitalization rates for any cause did not differ significantly in the pre- and post-initiation periods. PAP therapy was more beneficial in older adults, those with higher COPD complexity, and those with three or more comorbidities.

Conclusion Initiation of PAP therapy in elderly patients with overlap syndrome is associated with a reduction in hospitalization for COPD-related conditions, but not for all-cause hospitalizations and ER visits.

Keywords COPD · OSA · Overlap syndrome · PAP · Hospitalization and healthcare utilization

Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AHI	Apnea-Hypopnea Index
BAL	Bronchoalveolar lavage
CHF	Congestive heart failure
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
DME	Durable Medical Equipment
ER	Emergency room
HMO	Health maintenance organization
HR	Hazard ratio
ICD-9	International Classification of Diseases, Ninth Revision
OSA	Obstructive sleep apnea
PAP	Positive airway pressure

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Introduction

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are both common breathing disorders in older adults [1, 2]. Moreover, the prevalence of these

disorders increases with advancing age [1, 2]. COPD is a slowly progressive disease characterized by persistent airflow obstruction and OSA is defined as partial or total intermittent upper airway collapse resulting in hypoxemia and arousal during sleep [3].

The coexistence OSA in patient with COPD has been noted [4–7] and this association is described as the overlap syndrome [5, 8]. Recent studies have shown a higher prevalence of OSA in patients with moderate to severe COPD [4, 9], in older patients with COPD [7], and in those requiring hospitalization for COPD [7, 10]. Also, the prevalence of coexisting COPD is higher in patients with OSA compared to the general population [7, 9]. These findings have raised the possibility of a common pathophysiological link between COPD and OSA.

Patients with overlap syndrome have worse nocturnal hypoxemia [9], increased oxidative stress and systemic inflammation [11], and a higher risk of acute exacerbation of COPD (AECOPD) [10, 12]. There is increased risk of endothelial injury with the development of cardiovascular comorbidities, including arrhythmias and hypoxia-induced pulmonary vasoconstriction resulting in pulmonary hypertension and right ventricular dysfunction [9]. Patients with overlap syndrome have higher healthcare utilization [10, 12, 13] and worse survival [12–15] compared to patients with either COPD or OSA alone.

Positive airway pressure (PAP) therapy is the preferred treatment for OSA [3]. PAP therapy, especially bilevel positive airway pressure therapy, is also used effectively for acute respiratory failure following AECOPD [16]; however, only a few controlled studies have investigated the role of PAP therapy in elderly patients with stable COPD with overlap syndrome, and none were randomized controlled trails [12, 13, 15]. Marin et al., in a single-center study of overlap syndrome patients followed over a 12-year period, showed that patients not treated with PAP therapy had higher risk of AECOPD and mortality [12]. In another prospective study, COPD patients with hypoxemia and coexisting OSA showed a significantly lower risk of death with PAP therapy [13]. We examined the role of PAP therapy in stable patients with overlap syndrome using a 5% national Medicare sample of patients from 2011. We hypothesized that healthcare utilization will be decreased after initiation of PAP therapy in elderly patients with overlap syndrome.

Materials and methods

Data source

In this retrospective population-based cohort study, we used enrollment and claims data from a 5% national sample of Medicare beneficiaries from 2010 to 2012 provided by the Research Data Assistance Center [17]. The Centers for Medicare and Medicaid Services (CMS) select a random sample of 5% Medicare beneficiaries based on the eighth and ninth digits (05, 20, 45, 70, 95) of their health insurance claim number. All records were de-identified prior to analysis.

Data used in this study were from multiple files: (1) Denominator file (Medicare enrollment information and demographic data); (2) Medicare Provider Analysis and Review file (claims for hospital inpatient and skilled nursing facility stays); (3) Outpatient Standard Analytic file (hospital outpatient services); (4) 100% Physician/Supplier file (physician and other medical services); (5) Durable Medical Equipment (DME) file; and (6) Prescription Drug Event (PDE) records. This study was approved by the University of Texas Medical Branch Institutional Review Board and informed consent was not needed due to the nature of the study.

Subjects were selected for this analysis if they were identified as COPD patients in the previous year (2010) and the current year (2011); were 66 years of age or older; received PAP therapy treatment in the current (2011) but not on PAP therapy in the previous year (2010); were enrolled in Medicare Parts A and B but not in a health maintenance organization (HMO); were not a resident of a nursing facility from 1 year prior to 1 year after the index PAP treatment or until death; and resided in one of nine US geographic regions. The index PAP treatment was defined as the first PAP treatment in 2011.

A COPD patient was identified as having any of the following: (1) at least two outpatient visits (Evaluation and Management codes 99201–99205 or 99211–99215) with an encounter diagnosis of COPD [based on International Classification of Diseases, Ninth Revision (ICD-9) codes 491.x, 492.x, or 496.x] at least 30 days apart within a year; or (2) one acute care hospitalization with COPD diagnosis listed in the primary position as a discharge diagnosis; or (3) one acute care hospitalization with respiratory failure (518.81, 518.82, 518.84) listed in the primary position as a discharge diagnosis and COPD listed as the secondary diagnosis, similar to CMS methodology [17].

Initiation of PAP therapy was identified based on the Healthcare Common Procedure Coding System PAP reimbursement codes E0470, E0471, E0561, E0562, and E0601 in DME files. We used monthly claims by DME for reimbursement of PAP equipment to examine the adherence to PAP therapy for the 1 year post-initiation of PAP. In this cohort of COPD patients who began index PAP therapy in 2011, we further looked for claims with a diagnosis of OSA based on ICD-9 codes 786.03, 780.51, 780.53, 780.57, 327.20, and 327.23 [6, 18].

Variables

Medicare enrollment files were used to categorize subjects by age (66–74, 75–84, ≥ 85 years), gender, race, socioeconomic status, and nine CMS geographic regions. Low

socioeconomic status was based on whether the patient was eligible for state buy-in coverage provided by the Medicaid program for at least 1 month during the calendar year. Comorbidity was examined as an index score generated based on the number of Elixhauser comorbidities (0, 1, 2, ≥3) [19]. COPD severity was categorized as low, moderate, and high complexity as described by Mapel et al. [20]. Tobacco use was defined as ICD-9 diagnosis codes (305.1, 989.84, and V1582) in any position. In addition, we also examined for selected comorbidities including hypertension, diabetes mellitus, and congestive heart failure in patients with overlap syndrome, as previous studies have reported high prevalence of these conditions in patients with OSA and COPD [21].

Outcome

Our primary outcome of interest was to examine the impact of PAP on healthcare utilization [emergency room (ER) visits and hospitalization rate for all-cause and COPD-related conditions] in the 1 year pre- and post-initiation of PAP therapy. The secondary study outcomes include outpatient visits and use of inhaled steroids.

Statistical analysis

Characteristics were expressed as mean ± standard deviation for continuous variables and as percentages for categorical variables. The percent of patients with ER visits and hospitalizations for all-cause and for COPD-related conditions in the 1 year before and after PAP initiation was compared by the McNemar test. For any significant outcomes found in the McNemar test, we also conducted time-to-event analysis to examine the impact of PAP use on the timing of developing such an outcome. In this analysis, the index date was a year before PAP initiation in the pre-period, and in the post-period, it was the date of PAP initiation. Patients were censored at death or at 12-month follow-up. The failure rate estimated from the Kaplan-Meier method was used to show the cumulative rate of the outcome over time. To account for the cluster effect of patients, we used the robust sandwich covariance estimation for the Cox proportional hazard model. We also examined the assumption of proportion hazard through the log baseline cumulative hazard plot. We performed subgroup analyses by age groups, gender, socioeconomic status, number of comorbidities, and COPD complexity. All analyses were performed with Statistical Analysis System, version 9.4 (SAS Inc., Cary, NC). All reported P values were two-sided and P value < 0.05 was considered statistically significant.

Results

Between 2010 and 2011, we identified 319 fee-for-service Medicare patients with overlap syndrome who were new users of PAP therapy in 2011 (Fig. 1). Of these, 292 (91.5%) patients had a visit for OSA during the same year. About 66% of patients who initiated PAP therapy had DME reimbursement claims for equipment for more than 9 months during the year post-initiation.

Table 1 shows the baseline characteristics of the cohort. The mean age was 74 ± 5 years, 60.2% were male, the majority were non-Hispanic white, and 63% had three or more other comorbidities. The majority had moderate COPD complexity (57.7%) and 42.6% had used tobacco within 1 year prior to the initiation of PAP therapy. Hypertension (84%), diabetes mellitus (42%), and congestive heart failure (32%) were the most common comorbidities in these patients with overlap syndrome.

Table 2 presents the comparison of outcomes, ER visits, and hospitalization for all-cause and COPD-related reasons in the 1 year pre- and 1 year post-initiation of PAP therapy. ER

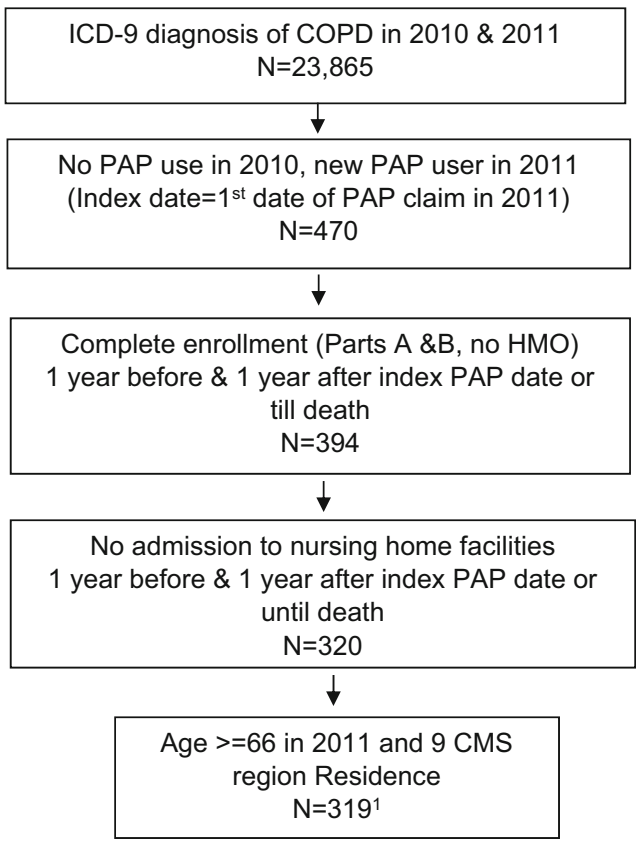

Fig. 1 Flow chart showing the cohort selection. [1]Of these 319 COPD patients who started on PAP therapy, 292 (91.5%) patients had a visit for OSA during the same year. ICD-9, International Classification of Diseases, Ninth Revision; COPD, chronic obstructive pulmonary disease; PAP, positive airway pressure; HMO, health maintenance organization; CMS, Centers for Medicare and Medicaid Services

Table 1 Baseline characteristics of patients with COPD and coexisting OSA (overlap syndrome) initiated on PAP in 2011

Characteristic	Overall (%), $N = 319$
Age in years	
66–74	173 (54.2)
75–84	135 (42.3)
≥ 85	11 (3.4)
Gender	
Female	127 (39.8)
Male	192 (60.2)
Race	
White	291 (91.2)
Black	20 (6.3)
Other	8 (2.5)
Low socioeconomic status[1]	
No	263 (82.4)
Yes	56 (17.5)
Region	
New England	9 (2.8)
Middle Atlantic	28 (8.8)
East North Central	60 (18.8)
West North Central	18 (5.6)
South Atlantic	85 (26.6)
East South Central	24 (7.5)
West South Central	39 (12.2)
Mountain	16 (5)
Pacific	40 (12.5)
Number of comorbidities[2]	
0	13 (4)
1	43 (13.5)
2	62 (19.4)
≥ 3	201 (63)
Comorbidity	
Hypertension	268 (84)
Diabetes mellitus	134 (42)
CHF	102 (32)
Anemia	72 (22.6)
Hypothyroidism	61 (19.1)
Renal failure	56 (17.5)
Obesity	56 (17.5)
Depression	31 (9.7)
Psychiatric disorder	16 (5.2)
COPD complexity[3]	
Low	83 (26.0)
Moderate	184 (57.7)
High	52 (16.3)
Tobacco use 1 year prior to initiation PAP[4]	136 (42.6)

COPD, chronic obstructive pulmonary disease; *OSA*, obstructive sleep apnea; *PAP*, positive airway pressure; *CHF*, congestive heart failure

[1] Socioeconomic status was based on whether the patient was eligible for state buy-in coverage provided by the Medicaid program for at least 1 month during the calendar year under study

[2] Comorbidities were identified using the Elixhauser Comorbidity Index (excluding COPD)

[3] COPD complexity as defined by Mapel et al. [20]

[4] Tobacco use was defined as ICD 9 diagnosis codes (305.1, 989.84, and V1582) on any position

visits for all-cause (53.9 vs 54.9%, P value = 0.77) and COPD-related reasons (16.6 vs 13.5%, P value = 0.18) were not significantly different in the 1 year pre- and 1 year post-initiation of PAP therapy. Also, hospitalization for all causes was not significantly different during the pre- and post-initiation of PAP therapy (48 vs 45.8%, P value = 0.52). However, hospitalization for COPD-related conditions was significantly lower in the 1 year post-initiation of PAP therapy (25.4 vs 19.4%, P value = 0.03). The Kaplan-Meier analysis also shows that patients with overlap syndrome had a higher risk of COPD-related hospitalizations in the 1 year pre-initiation of PAP therapy compared to the 1 year post-initiation of PAP therapy (Fig. 2). The non-proportional hazard of using of PAP therapy on the outcome of COPD hospitalization was detected through log baseline cumulative hazard plot. A Cox model with a time-dependent covariate of PAP therapy (up to 3 months and after 3 months) was conducted. During the 1-year period, the rate of COPD-related hospitalizations with use of PAP was not significantly different in the first 3 months [hazard ratio (HR) = 0.86, 95% confidence interval (CI) 0.48–1.54]. After 3 months of PAP initiation, patients had a significant lower COPD-related hospitalization rate (HR = 0.67, 95% CI 0.48–0.94). From the McNemar test (Table 2), we found that PAP reduces COPD-related hospitalization, and from the Cox model, we identified that the benefit was seen mainly after 3 months of initiating PAP.

The number of outpatient visits at 1 year pre-initiation of PAP therapy compared to 1 year post-initiation of PAP therapy did not differ (52 vs 52.4%, P value = 0.32). Of study subjects, 167 (52.4%) had complete Part D (drug benefit) enrollment during the study period. Of these 167, 71.3% were prescribed inhaled steroids (ICS, or LABA/ICS) at 1 year pre-initiation of PAP and 68.3% at 1 year post-initiation of PAP; the difference was not significant. A total of 19 (6%) of 319 patients died within a year after initiation of PAP.

Table 3 presents the outcomes by subgroups in 1 year pre- and 1 year post-initiation of PAP. PAP therapy had a nonsignificant impact on COPD-related ER visits among those who were older (≥ 75 years), were female, and had more comorbidities (≥ 3). As for COPD-related hospitalization, PAP therapy also had a nonsignificant impact for patients who were older (≥ 75 years), were male, and had more comorbidities (≥ 3). The subgroups with moderate and high COPD complexity had statistically significant reductions in COPD-related ER visits, COPD-related hospitalizations, and all-cause hospitalization.

Discussion

In this retrospective cohort study, we showed that the initiation of PAP therapy in patients with overlap syndrome was associated with a lower rate of COPD-related hospitalizations. However, hospitalizations for all cause and ER visits were not significantly different in the pre- and post-study periods. Patients with higher COPD complexity had more significant

Table 2 Outcomes in patients with overlap syndrome in 1 year pre- and 1 year post-initiation of PAP ($N = 319$)

Outcomes	One year pre-initiation of PAP	One year post-initiation of PAP	*P* values
ER visit for all cause, (*n*) %	(172) 53.9	(175) 54.9	0.77
ER visit for COPD, (*n*) %	(53) 16.6	(43) 13.5	0.18
Hospitalization for all cause, (*n*) %	(153) 48	(146) 45.8	0.52
Mean ± SD	0.97 ± 1.37	0.91 ± 1.34	
Hospitalization for COPD, (*n*) %	(81) 25.4%	(62) 19.4%	0.03
Mean ± SD	0.40 ± 0.83	0.31 ± 0.75	
Outpatient visit, (*n*) %	(166) 52%	(167) 52.4%	0.32

PAP, positive airway pressure; *ER*, emergency room; *COPD*, chronic obstructive pulmonary disease

benefit with use of PAP therapy. The majority of overlap syndrome patients had a significant comorbidity burden, as noted in previous studies [6, 12].

One possible explanation for no significant reduction in all-cause hospitalizations could be that the majority of patients with COPD are readmitted for causes other than COPD due to their high comorbidity burden. PAP therapy may reduce the risk for AECOPD but not for other causes.

Patients with overlap syndrome are at increased risk for AECOPD compared to patients with COPD alone. Complex bidirectional mechanisms have been proposed [5, 22]. Patients with COPD have hyperinflated lungs with reduced activity of respiratory muscles, which is worse in REM sleep due to hypotonia, and have blunted respiratory drive during sleep which results in worsening of nocturnal hypoxemia [5, 9, 22, 23]. In OSA, the anatomically collapsible pharyngeal airway, in combination with a sleep-induced reduced upper airway muscle tone, results in nocturnal hypoxemia. OSA may also augment vagal-mediated bronchoconstriction which leads to increased expiratory airflow resistance [22]. Patients with overlap syndrome have both upper and lower airway obstruction and a reduction in respiratory drive during sleep, which results in more pronounced nocturnal hypoxemia and appears to have a synergistic effect on nocturnal hypoxemia [5, 9, 22, 24].

Similar to patients with COPD, those with OSA have increased expression of inflammatory mediators resulting in airway and systemic inflammation [25, 26]. In a recent study [11], inflammatory mediators (including neutrophils, TNF-alpha, and IL-8) were significantly increased in the bronchoalveolar lavage (BAL) fluid from patients with overlap syndrome compared to patients with COPD alone. Investigators also found a significant correlation between nocturnal hypoxemia and airway inflammation. Also, the initiation of PAP therapy was associated with a significant reduction in markers of airway inflammation in BAL fluid. Another study has noted the beneficial effect of PAP therapy in reducing airway inflammation (documented by airway nitric oxide measurement) in OSA patients at 3 months [27].

In the current literature, PAP therapy in patients with overlap syndrome has shown to improve hypoxemia [28] and reduce systemic inflammation [11], which could be mechanisms by which the risk of AECOPD is reduced [10, 12] and survival improved [6, 12, 14]. The reduction in hypoxemia and inflammation after initiation of PAP therapy in overlap syndrome may help explain the improvement in COPD-related hospitalization rates noted here and in previous studies [10, 12]. The benefits of PAP therapy in our study are noted after 3 months, similar to a prior study showing improvement in airway inflammation [27].

Thirty-day hospital readmission after AECOPD is monitored by CMS as part of the hospital readmission reduction program which penalizes hospitals with excess readmissions.

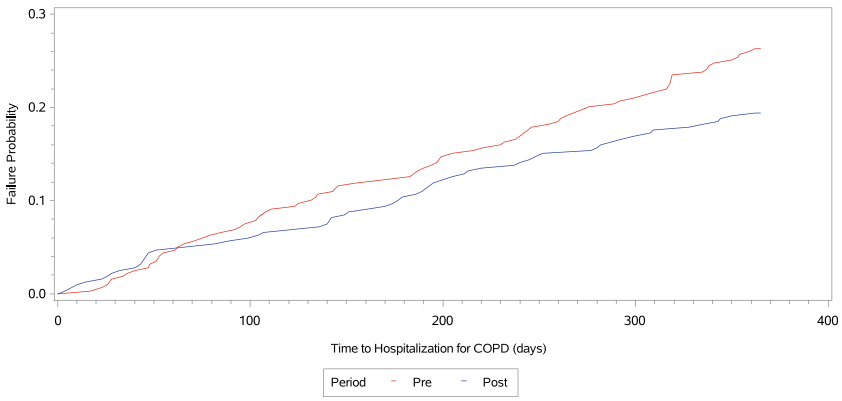

Fig. 2 COPD-related hospitalizations in patients with overlap syndrome in the 1 year pre- and 1 year post-initiation of PAP therapy. Failure rates were estimated by Kaplan-Meier method

Table 3 Pre- and post-PAP use and outcomes by subgroups in patients with overlap syndrome

		All cause			COPD-related		
		One year pre-initiation of PAP, *n* (%)	One year post-initiation of PAP, *n* (%)	*P* values[1]	One year pre-initiation of PAP, *n* (%)	One year post-initiation of PAP, *n* (%)	*P* values[1]
ER visits							
Age group	66–74 (*N* = 173)	92 (53.18)	88 (50.87)	0.59	28 (16.18)	26 (15.03)	0.71
	≥ 75 (*N* = 146)	80 (54.79)	87 (59.59)	0.33	25 (17.12)	17 (11.64)	0.13
Low socioeconomic status	Yes (*N* = 56)	39 (69.64)	37 (66.07)	0.65	14 (25.00)	12 (21.43)	0.56
	No (*N* = 263)	133 (50.57)	138 (52.47)	0.59	39 (14.83)	31 (11.79)	0.23
Number of comorbidities	< 3 (*N* = 118)	42 (35.59)	49 (41.53)	0.26	10 (8.47)	12 (10.17)	0.56
	≥ 3 (*N* = 201)	130 (64.68)	126 (62.69)	0.63	43 (21.39)	31 (15.42)	0.07
Gender	Male (*N* = 192)	97 (50.52)	102 (53.13)	0.54	26 (13.54)	23 (11.98)	0.58
	Female (*N* = 127)	75 (59.06)	73 (57.48)	0.75	27 (21.26)	20 (15.75)	0.18
COPD complexity	Low (*N* = 83)	26 (31.33)	38 (45.78)	0.04	0	5 (6.02)	–
	Moderate and high (*N* = 236)	146 (61.86)	137 (58.05)	0.29	53 (22.46)	38 (16.10)	0.04
Hospitalization							
Age group	66–74	84 (48.55)	79 (45.66)	0.51	47 (27.17)	39 (22.54)	0.19
	≥ 75	69 (47.26)	67 (45.89)	0.80	34 (23.29)	23 (15.75)	0.07
Low socioeconomic status	Yes	32 (57.14)	29 (51.79)	0.49	21 (37.50)	16 (28.57)	0.20
	No	121 (46.01)	117 (44.49)	0.69	60 (22.81)	46 (17.49)	0.07
Number of comorbidities	< 3	29 (24.58)	36 (30.51)	0.27	14 (11.86)	15 (12.71)	0.83
	≥ 3	124 (61.69)	110 (54.73)	0.11	67 (33.33)	47 (23.38)	0.007
Gender	Male	92 (47.92)	86 (44.79)	0.49	46 (23.96)	29 (15.10)	0.01
	Female	61 (48.03)	60 (47.24)	0.88	35 (27.56)	33 (25.98)	0.72
COPD complexity	Low	13 (15.66)	25 (30.12)	0.02	0	6 (7.23)	–
	Moderate and high	140 (59.32)	121 (51.27)	0.04	81 (34.32)	56 (23.73)	0.003

PAP, positive airway pressure; *ER*, emergency room; *COPD*, chronic obstructive pulmonary disease

[1] *P* values were generated from the McNemar test

These penalties can have major financial implications for safety net hospitals as most operate at a small profit margin [29]. Based on results of our study and previous evidence in the literature, early diagnosis and treatment of OSA with PAP therapy in patients with COPD may help reduce the risk of AECOPD and subsequent readmission. Any intervention that can impact re-hospitalization in the bundle payment model era is worthy of further studies.

The results of this study may have been influenced by several limitations. First, our study cohort was limited to beneficiaries aged > 66 years with Medicare Parts A and B coverage, and results may not be applicable to younger patients or patients enrolled in managed care.

Second, we used ICD-9 codes to identify patients with COPD and OSA; the use of information based on ICD-9 codes alone is problematic as a documented diagnosis does not confirm the accuracy of diagnosis. However, use of ICD-9 codes from claims data for COPD has been validated for data extraction [30]. Also, recommendations by the American Academy of Sleep Medicine for hypopnea scoring rules have changed over time and ICD-9 codes for OSA have been modified over the last decade; these changes may interfere with the accuracy of the diagnosis of OSA. We used ICD-9 codes for OSA similar to previous studies in the literature [6, 18].

Third, we did not have access to information on severity of disease, air flow limitation by spirometry for COPD, or severity of Apnea-Hypopnea Index (AHI) from previous polysomnograms for OSA. We therefore are unable to comment on the appropriateness of management and these factors may confound the risk of AECOPD and hospitalization. However, we evaluated the COPD complexity derived from administrative claims as an indirect measure of severity based on resource utilization [20].

Fourth, the use of reimbursement data to study PAP therapy only accounts for the PAP machine being prescribed and provided to patient. We did not have access to individual PAP compliance data for these patients to ensure effectiveness of therapy by correcting AHI and nocturnal hypoxemia. We used monthly claims to DME as a surrogate for adherence with PAP therapy, though this methodology has not been validated in

previous studies. Finally, given the observational design of the study, we cannot exclude unmeasured or residual confounding as a possible explanation for the observed association.

In conclusion, initiation of PAP therapy in elderly patients with overlap syndrome is associated with reduction in hospitalizations for COPD-related conditions but not for all-cause hospitalizations or for ER visits.

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Author contributions Dr. Gurinder Singh served as principal author, had full access to the data in the study, and takes full responsibility for the content of the manuscript, including accuracy of data analysis.

Dr. Amitesh Agarwal, Mr. Wei Zhang, Dr. Yong-Fang Kuo, Dr. Rizwana Sultana, and Dr. Gulshan Sharma contributed to the conception, study design, analysis, interpretation of results, drafting of manuscript, and final approval of the manuscript.

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Compliance with ethical standards

Conflict of interest Dr. Gulshan Sharma served on the advisory board of Sunovion and Mylan Pharmaceuticals. The remaining authors have no potential conflicts of interest related to the content of manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of University of Texas Medical Branch and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not needed due to the nature of the study.

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