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Home oxygen therapy reduces risk of hospitalization in patients with chronic obstructive pulmonary disease: A population-based retrospective cohort study, 2005–2012

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Abstract

Objective: This study evaluated the effect of home oxygen therapy (HOT) on hospital admissions in chronic obstructive pulmonary disease (COPD) patients.

Design and setting: Using nationwide health insurance claims from 2002–2012, we conducted a longitudinal population-based retrospective cohort study.

Participants: Individuals who are 40 years or above and newly diagnosed with COPD in 2005.

Outcome measures: the primary outcome was total number of hospitalization during study period. Participants were matched using HOT propensity scores and were stratified by respiratory impairment (Grade 1: $FEV_1 \leq 25\%$ or $Pa,O_2 \leq 55mmHg$; Grade 2: $FEV_1 \leq 30\%$ or Pa,O_2 56-60mmHg; Grade 3: $FEV_1 \leq 40\%$ or Pa,O_2 61-65mmHg; No grade: FEV_1 or Pa,O_2=unknown), then a negative binomial regression analysis was performed for each group.

Results: Of the 36,761 COPD patients included in our study, 1,330 (3.6%) received HOT. In a multivariate analysis of Grade 1 patients performed prior to propensity score matching, the adjusted relative risk of hospitalization for patients who did not receive HOT was 1.27 (95% CI, 1.01–1.60). In a multivariate analysis of Grade 1 patients performed after matching, the adjusted relative risk for patients who did not receive HOT was 1.65 (95% CI, 1.25–2.18). In Grade 2 or Grade 3 patients, no statistical difference in hospital admission risk was detected. In the no grade group of patients, HOT was associated with increased risk of hospitalization.

Conclusions: HOT reduces the risk of hospital admission in COPD patients with severe hypoxemia. However, apart from these patients, HOT use is not associated with hospital

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admissions, or is more likely to admit.

Key word: home oxygen therapy, chronic obstructive pulmonary disease, hospital admission, long-term oxygen therapy

Strengths and limitations of this study

- We analyzed the association between home oxygen therapy and hospitalization for COPD patients using nationwide claims data and conducted a longitudinal population-based prospective analysis based on claims from 2005 to 2012.
- We were able to increase the homogeneity of our study sample by identifying patients who were newly diagnosed in 2005.
- We made an effort to accurately determine the net effect of HOT via propensity score matching.
- In our findings, there may be potential unmeasured variable bias because we used the data based on claims.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by progressive airflow limitation that is not fully reversible, causing disability, but is frequently undiagnosed [3]. COPD is a major cause of morbidity and mortality, acting increasingly as a substantial societal burden;[4] hence viewed as a serious public health problem in many countries throughout the world. According to the World Health Organization estimates, 80 million people have moderate to severe COPD, and three million people have died of COPD in 2005. The same estimates also predicted that it will become the fourth leading cause of death by 2030[5].

In an effort to combat COPD-related hospitalization, researchers have studied the effects of oxygen therapy. Long-term oxygen therapy (LTOT) has been shown to improve survival and quality of life as well as to stabilize pulmonary hypertension in COPD patients[6-11]. In Korea, clinical practitioners and policy-makers began to recognize the benefits of LTOT. Social welfare services for people with respiratory related disabilities in Korea are offered through respiratory impairment[12]. Home oxygen therapy is the administration of oxygen at concentrations greater than the ambient air concentration at home and the cost of such long term oxygen therapy has been included for coverage in the national health insurance system since 2006. However, ambulatory oxygen delivery systems and home ventilator service is not currently covered by the health insurance system. As the burden of COPD continues to increase, analyzing the status of health care utilization in patients with COPD is important in establishing health care plans that encourage proper management of COPD.

Yet it must be taken into account that findings on the effect of home oxygen therapy on

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hospitalization have varied. Although several studies have indicated that LTOT decreases hospital admissions[13-16], one study found no effect on hospital admissions[17]. Most studies that have found an effect of LTOT on hospital admission have detected the greatest association among severely hypoxemic COPD patients ($Pa,O_2 \leq 60$ mmHg at rest on room air)[13-16]. In moderately hypoxemic COPD patients (Pa,O_2 55–70 mmHg at rest on room air: 7.3-9.5 kPa), HOT may not reduce hospitalizations[17]. Also, regarding oxygen prescription, questions have recently been raised as hospital admission is more likely in LTOT users and medical costs are increasing due to the inappropriate use of oxygen[18].

The aim of this study was to assess the effect of HOT on hospital admissions, in which COPD patients were stratified into forced expiratory volume 1 second or arterial oxygen tension.

Methods

Data and study design

This study used 2002–2012 claims from the Korean National Health Insurance Service (KNHIS) claims database. We conducted a longitudinal population-based retrospective cohort study of newly diagnosed adult COPD patients to investigate the association between HOT and hospital admissions over a 7-year follow-up period. Participants were 40 years of age or older with newly developed COPD (codes J43.x except for J43.0 or J44.x, International Classification of Disease, 10th edition [ICD-10]). The codes of J44.x and J43.x (except for J43.0) refer to COPD or emphysema, respectively. J43.0 is McLeod's syndrome. The new

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diagnosis was confirmed by a lack of COPD-related claims in 2002–2004 and the first COPD-related claim in 2005. Presence or absence of HOT was analyzed from 2006 and onwards, and hospital admissions were analyzed from 2007 to 2012. If a patient died during the study period, we observed hospital admissions until time of death or end of study. Ethical approval for this study was granted by the institutional review board of the Graduate School of Public Health, Yonsei University, Seoul, Korea.

Study population

The total number of individuals in 2002–2012 aged 40 years or older with COPD was 1,538,711. Of these patients, 138,680 patients received their diagnosis in 2005 and were still alive in 2006. We modified the criteria which was used in Kim J. et al.'s study to define COPD patients using claims data[19]. Hence COPD was defined in the study by the following criteria: 1) age≥40-years-old; 2) ICD-10 codes for COPD (J43.x except for J43.0 and J44.x; emphysema and COPD, respectively); and 3) use of one or more COPD medications at least twice per year. Unfortunately, we could not review all of such prescriptions and thus replaced the third criteria with patients having over four outpatient visits per year due to COPD as the primary diagnosis. Since we inferred COPD diagnoses from information contained in the KNHIS claims database, we developed a process to aid in the selection of participants who actually had COPD. We excluded 101,919 patients who had fewer than four outpatient visits with COPD as the primary complaint, did not receive HOT, and did not experience a hospital admission due to COPD during 2006. Our final study sample included 36,761 patients, 1,330 who received HOT and 35,431 who did not.

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Variables

The dependent variable in this study was the total number of hospital admissions during the study period. We defined hospital admission due to COPD as the usage of inpatient medical services for more than 1 day and primary emphysema or COPD by the ICD-10 code of J43.x (except for J43.0) or J44.x.

Covariates considered included age, sex, health insurance status (national health insurance or medical aid), the Charlson comorbidity index (0, 1, or 2^{+})[20], HOT (yes, no), use of the intensive care unit (ICU) (yes, no), number of hospital admissions (0, 1, or 2^{+}), and respiratory impairment (1, 2, 3, or No grade). In Korea, The Ministry of Health and Welfare provides social welfare services to disabled person through the Welfare of Disabled Person Act. However, our government uses strict criteria for certificating a disabled person due to a lack of budget set for disabled people. According to the Welfare of Disabled Person Act, the severity of respiratory impairment is determined by 3 clinical parameters: dyspnea, FEV_1, and Pa,O_2. The Criteria corresponding to grade 1 was patients with chronic respiratory failure requiring oxygen therapy and a predicted FEV_1 of ≤25% or a resting Pa,O_2 of ≤55 mmHg (room air); the criteria corresponding to grade 2 was patients with dyspnea when walking at home and a predicted FEV_1 of ≤ 30% or Pa,O_2 of 56-60 mmHg (room air); the criteria corresponding to grade 3 was patients with dyspnea when walking at their own pace at ground level and a predicted FEV_1 of ≤40% or Pa,O_2 of 61-65 mmHg (room air). We defined the "No grade" group as patients with unknown FEV_1 or Pa,O_2. Only the comorbidity component of the Charlson comorbidity index was calculated. All of these variables were measured at the 2006 baseline.

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Statistical analysis

First, demographic characteristics of patients who received HOT and those who did not were compared; the chi-square test was used to assess categorical variables, and t-tests were used to assess continuous variables. Next, a non-parsimonious multivariable logistic regression model was used to estimate propensity scores for HOT. Propensity score matching (PSM) is a statistical matching technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict treatment reception. The PSM allows one to design and analyze an observational study so that it mimics certain characteristics of a randomized controlled trial[21]. We included the following in our propensity model: age, sex, health insurance type, Charlson comorbidity index, ICU use, number of hospital admissions in 2006, and respiratory disability grade. The c-statistic for our propensity model was 0.784. Subjects who received HOT were matched on a one-to-one basis with those who did not. Then, we stratified participants according to their respiratory disability grade, based on hypoxemic status, and evaluated the relationship between HOT and hospital admissions in each group using a negative binomial regression analysis, which was chosen due to over-dispersion. All analyses were performed using SAS v9.3.

Results

Of the 36,761 patients in our study, 1,330 (3.6%) received HOT. Prior to propensity score matching, baseline characteristics differed significantly between patients who received HOT and those who did not (Table 1). After propensity score matching, however, only the number of hospital admissions and respiratory disability grade differed between the two groups.

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Table 2 presents incidence density (ID) rates for hospital admission according to HOT usage. Prior to propensity score matching, the ID for Grade 1 ($FEV_1 \leq 25\%$ or $Pa,O_2 \leq 55$ mmHg) who received HOT was 0.60 vs. 1.01 for those who did not. However, for patients with Grade 2 or Grade 3(FEV1≤30% or Pa,O2 56-60 mmHg; FEV1≤40% or Pa,O2 61-65 mmHg) or categorized as "No grade" (FEV_1 or Pa,O_2=unknown), the ID was higher for those who received HOT than for those who did not (0.61 vs. 0.63; 0.47 vs. 0.46; and 0.34 vs. 0.05, respectively). Similar results were obtained after propensity score matching. For Grade 1 patients, the ID was lower for patients who received HOT than for those who did not (0.62 vs. 0.79), while in Grade 2/3 or No grade, the ID was higher for patients who received HOT (0.59 vs. 0.37; 0.47 vs. 0.23; and 0.34 vs. 0.07, respectively).

Table 3 presents the adjusted relative risk (RR) for hospital admission prior to propensity score matching. After controlling for all covariates, the adjusted RR for Grade 1 patients who did not receive HOT compared to the reference group (those who did receive HOT) was 1.12 (95% CI, 1.01–1.60). The RR for Grade 2 patients was 0.96, but this difference was not statistically significant. In Grade 3 or No grade, the adjusted RRs for patients who did not receive HOT were less than one (RR, 0.74; 95% CI, 0.58–0.93: RR, 0.65; 95% CI, 0.60–0.70, respectively).

After propensity score matching, the adjusted RR for Grade 1 patients who did not receive HOT was 1.65 (95% CI, 1.25–2.18); in Grade 2 patients, the adjusted RR was 1.07 (95% CI, 0.80–1.43); in Grade 3 patients, the adjusted RR was 0.72 (95% CI, 0.51–1.02); and in patients without a grade, the adjusted RR was 0.73 (95% CI, 0.62–0.86) (Table 4).

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Discussion

We found that HOT was associated with a 27% decreased risk of hospitalization in Grade 1 COPD patients ($FEV_1 \leq$ 25% or $Pa,O_2 \leq$55 mmHg) prior to propensity score matching and a 65% decreased risk after matching. However, apart from Grade 1 patients, the use of HOT did not show a statistically significant association with hospital admission prior to or after matching in Grade 2 patients. Also, in Grade 3 or No grade COPD patients ($FEV_1 \leq$ 40% or $Pa,O_2 \leq$65 mmHg; FEV_1 or Pa,O_2=unknown), HOT was associated with an increased risk of hospital admission prior to propensity score matching and in the case of No grade patients, HOT was still associated with an increased risk of admission after propensity score matching.

In Korea, HOT can be prescribed by a pulmonologist as well as an internist and a thoracic surgery specialist through only a one time test of arterial blood gas analysis; similar to the criteria that most countries use for home oxygen therapy, the indications of HOT for reimbursement are patients with Pa,O_2 less than or equal to 55mmHg or with SpO_2 less than or equal to 88%. Patients with Pa,O_2 between 56 and 60mmHg or SpO_2 below 89%, must also have congestive heart failure, polycythemia (hematocrit>55%), or pulmonary hypertension to qualify during the stable period after 3 months of internal treatment. Physicians can prescribe patients with Grade 1 or Grade 2respiratory impairment without conducting any other tests. If patients without indication of such grade receives HOT prescriptions, it means that the patient was seen by a physician under the COPD code but that the patient did not fill out the necessary form to receive an assigned grade. Hence the patient's clinical status fits the indications for HOT prescription, meaning that these patients may in actuality, have any of the grades described above, including Grade 1. Therefore, in the case of patients without a grade, the use of HOT means that the patients who use such HOT

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may have conditions that are clinically more severe than those who do not use HOT.

Our results are comparable to the findings of previous studies. Most previous studies have showed a consistent tendency in patients with severe hypoxemia (Pa,O_2<8.0 kPa) in which HOT was associated with decreased hospital admissions. However, Ringbaek et al. found that home oxygen therapy did not reduce hospitalization in patients with moderate hypoxemia (Pa,O_2>8.0 kPa)[17]. In addition, Turner et al. recently suggested that oxygen use outside the National Institute for Health and Care Excellence (NICE) guidance did not appear to prevent admissions[18]. In South Korea, although HOT is used according to NICE guidelines, HOT was not associated with decreased risk of hospital admission even in Grade 2 (Pa,O_2 56-60mmHg). In Grade 3 or No grade patients, admission to hospitals was more likely in HOT users prior to matching instead, and after matching, there was no statistically significant difference in Grade 3 patients. There are two possible explanations regarding this result. One is that because admission for exacerbation is more common in severe COPD[22] patients and in oxygen users[23], hospital admissions are more frequently expected in HOT users if patients' severity is unequal as they have more severe lung disease. The second possibility may be explained through residual confounding. Garcia-Aymerich J. et al. showed that the risks of re-admission was high in LTOT users after adjustment for severity variables such as FEV_1 or Pa,O_2[24]. The authors explained these paradoxical results using residual confounding, that the excess risk of COPD re-admission associated with medical care related factors might be partially due to confounding by indication. Our finding supports that HOT use reduces hospitalization in COPD patients with severe hypoxemia (Pa,O_2 ≤55 mmHg). However, although HOT may improve quality of life and help breathing during activities in COPD patients without severe hypoxemia, use of HOT should be considered to prevent hospital

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admissions in COPD patients with Pa,O_2>55mmHg. We need to at least conduct further research about cost-effectiveness for HOT use in these patients and then, if necessary, require modification of the criteria for HOT prescription.

This study has several limitations. First, because we used claims data, which are based on information in the KNHIS, we were not able to assess some factors that could potentially influence hospital admissions. For example, we had no data on smoking history, body mass index, health behaviors, use of systematic corticosteroids, laboratory results, etc. Second, we categorized respiratory impairment into four respiratory disability grades, as determined by FEV_1, Pa,O_2, and dyspnea. Therefore, we did not use quantitative FEV_1 or Pa,O_2 values, instead estimating a patient's hypoxemic status. Especially in the No grade group, it is possible that patients with various severities have been mixed together. The third limitation is the accuracy of our COPD diagnosis. The accuracy of diagnoses in KNHIS claims data is roughly 70%[25]. To increase accuracy, a review of all prescriptions would be required. Unfortunately, we could not perform such a review here. However, the accuracy of COPD diagnoses in this study may have been compromised. The fourth limitation involves the definition of newly diagnosed patients. In this study, newly diagnosed patients were defined as those who did not have COPD claims in 2002–2004 but did have a COPD claim in 2005. Thus, patients diagnosed prior to 2002 who did not utilize COPD-related medical services in 2002–2004 may have been included in the sample. The final limitation is related to patterns of HOT use. Although all of our study subjects used HOT in or after 2006 and we adjusted for the number of hospital admission at baseline, because of considering hypothesis in previous studies that an effect of oxygen therapy in patients who start home oxygen therapy as outpatients are less likely to be derived from a "regression to the mean phenomenon"[14], we

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did not know the duration of usage per day, whether use was continuous or non-continuous, or whether patient compliance was good.

Despite these limitations, our study has several strengths. First, we analyzed COPD patients using nationwide claims data and conducted a longitudinal population-based prospective analysis based on claims from 2005 to 2012. Our study population was relatively large and our follow-up period was relatively long compared to previous studies evaluating the association between oxygen therapy and hospitalization[1,2]. Second, we were able to increase the homogeneity of our study sample by identifying patients who were newly diagnosed in 2005. We could observe the progression of their disease over time via hospital admissions. Finally, we made an effort to accurately determine the net effect of HOT via propensity score matching.

In conclusion, HOT reduces hospital admission risk in COPD patients with severe hypoxemia. However, except for these patients, HOT use is not associated with hospital admissions, or an increase in the likeliness of hospital admission. Still, further research on cost-effectiveness of HOT in patients who does not meet the indication for HOT is needed, even in patients with Pa,O_2 56-60 mmHg who meet the indication.

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Conflicts of Interests: None of the authors have any conflicts of interest associated with this study.

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Contribution : Cho KH and Park EC carried out constructing study design, Cho KH and Nam CM carried out analyzing data, Cho KH, Park EC, and KimYS interpreted results, Kim YS was scientific advisor, Park EC guided and directed this study Cho KH and Kim TH wrote manuscript and Kim SJ and Han KT was clinical investigators.

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Table 1. Baseline characteristics of the study sample, stratified according to use of home oxygen therapy

	Pre-match (N=36,761)					Post-match (1:1, N=2,478)				
	Yes, n (%)		No, n (%)		P-value	Yes, n (%)		No, n (%)		P-value
Characteristics	1,330	(3.6)	35,431	(96.4)		1,239	(50.0)	1,239	(50.0)	
Age (years), mean (SD)	67.1	(9.6)	63.8	(12.0)	<0.0001	67.4	(9.7)	68.0	(9.9)	0.14
Sex										
Male	964	(4.7)	19,353	(95.3)	<0.0001	884	(49.2)	912	(50.8)	0.21
Female	367	(2.2)	16,078	(97.8)		355	(52.0)	327	(48.0)	
Health insurance type										
National health insurance	1,279	(3.8)	32,645	(96.2)	<0.0001	1,188	(50.5)	1,163	(49.5)	0.02
Medical aid	51	(1.8)	2,786	(98.2)		51	(40.2)	76	(59.8)	
Charlson comorbidity index*										
0	692	(6.5)	9,983	(93.5)	<0.0001	628	(48.4)	670	(51.6)	0.13
1	62	(5.7)	1,021	(94.3)		57	(47.1)	64	(52.9)	
≥2	576	(2.3)	24,427	(97.7)		554	(52.3)	505	(47.7)	
ICU use										
Yes	11	(6.9)	148	(93.1)	<0.0001	9	(39.1)	12	(60.9)	0.30
No	1,319	(3.6)	35,283	(96.4)		1,230	(50.1)	1,225	(49.9)	
Number of hospital admission										
0	1,147	(3.5)	31,923	(96.5)	<0.0001	1,067	(51.5)	1,004	(48.5)	0.002
1	127	(4.9)	2,486	(95.1)		119	(40.6)	174	(59.4)	
≥2	56	(5.2)	1,022	(94.8)		53	(46.5)	61	(53.5)	
Respiratory impairment rating										
Grade 1 (FEV_1%≤25 or Pa,O_2 ≤55 mmHg)	163	(43.2)	214	(56.8)	<0.0001	91	(43.1)	120	(56.9)	0.001
Grade 2 (FEV1%≤30 or Pa,O_2 ≤60 mmHg)	121	(35.6)	219	(64.4)		102	(55.7)	81	(44.3)	
Grade 3 (FEV1%≤40 or Pa,O_2 ≤65 mmHg)	110	(26.6)	304	(73.4)		110	(61.1)	70	(38.9)	
No Grade	936	(2.6)	34,694	(97.4)		936	(49.2)	968	(50.8)	

SD, standard deviation; ICU, intensive care unit.
*, calculated comorbidity component; subtracted age scores.

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Table 2. Incidence density for hospital admission according to use of home oxygen therapy

		Pre-match				Post-match (1:1)			
		Yes	No	Yes	No	Yes	No	Yes	No
Respiratory Impairment Rating[†]		N=1,330	N=35,431	ID[*]	ID[*]	N=1,239	N=1,239	ID[*]	ID[*]
Grade 1	Total number of hospital admission	416	748	0.60	1.01	244	319	0.62	0.79
	Person-years	694.1	743.3			390.8	406.0		
Grade 2	Total number of hospital admission	358	601	0.61	0.63	291	128	0.59	0.37
	Person-years	585.6	953.4			495.9	341.4		
Grade 3	Total number of hospital admission	245	672	0.47	0.46	245	81	0.47	0.23
	Person-years	517.8	1455.4			517.8	348.3		
No Grade	Total number of hospital admission	1409	9286	0.34	0.05	1409	322	0.34	0.07
	Person-years	4123.0	184555.3			4123.0	4837.3		

*ID, Incidence Density; calculated total number of hospital admissions divided into sum of person-years.

[†], Grade 1 was defined patients with chronic respiratory failure requiring oxygen therapy and an FEV_1 ≤25% predicted or resting Pa,O_2≤55 mmHg (room air); Grade 2 was defined patients with dyspnea when walking at home and an FEV_1 ≤ 30% predicted or Pa,O_2 56-60 mmHg (room air); Grade 3 was defined patients with dyspnea when walking at their own pace on the ground level and FEV_1 ≤40% predicted or Pa,O_2 61-65 mmHg (room air); No Grade was defined FEV_1 or Pa,O_2 unknown .

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Table 3. Relative Risk for hospital admission, stratified respiratory disability grade calculated using negative binomial regression model

Chracteristics	Relative Risk (95% CI) Grade 1		Grade 2		Grade 3		No Grade	
Age (years	1.002	(0.993-1.010)	0.992	(0.983-1.001)	1.010	(0.993-1.021)	1.006	(1.004-1.009)***
Sex								
Male	1.06	(0.87-1.29)	1.25	(0.96-1.62)	0.94	(0.75-1.18)	1.16	(1.10-1.23)***
Female	1.00		1.00		1.00		1.00	
Health insurance type								
National health insurance	1.00	(0.80-1.25)	0.94	(0.75-1.17)	0.60	(0.49-0.75)***	0.69	(0.65-0.73)***
Medical aid	1.00		1.00		1.00		1.00	
Home oxygen therapy								
Yes	1.00		1.00		1.00		1.00	
No	1.27	(1.01-1.60)*	0.96	(0.75-1.22)	0.74	(0.58-0.93)*	0.65	(0.60-0.70)***
Charlson comorbidity index†								
0	1.00		1.00		1.00		1.00	
1	0.86	(0.66-1.13)	1.00	(0.72-1.39)	0.82	(0.57-1.17)	1.00	(0.93-1.07)
≥2	1.12	(0.84-1.49)	1.11	(0.81-1.53)	0.90	(0.67-1.21)	1.11	(1.02-1.21)*
ICU use								
Yes	1.13	(0.74-1.70)	1.05	(0.42-2.59)	0.31	(0.09-1.09)	1.02	(0.82-1.27)
No	1.00		1.00		1.00		1.00	
Number of hospital admission								
0	1.00		1.00		1.00		1.00	
1	1.65	(1.29-2.11)***	1.45	(1.12-1.88)**	1.24	(0.98-1.57)	1.69	(1.58-1.81)***
≥2	1.73	(1.34-2.24)***	1.48	(1.11-1.96)**	1.65	(1.28-2.12)***	2.04	(1.88-2.21)***

*, P-value<0.05; **, P-value<0.01; ***, P-value<0.001.

Grade 1 was defined patients with chronic respiratory failure requiring oxygen therapy and an FEV_1 ≤25% predicted or resting Pa,O_2≤55 mmHg (room air); Grade 2 was defined patients with dyspnea when walking at home and an FEV_1 ≤ 30% predicted or Pa,O_2 56-60 mmHg (room air); Grade 3 was defined patients with dyspnea when walking at their own pace on the ground level and FEV_1 ≤40% predicted or Pa,O_2 61-65 mmHg (room air); No Grade was defined FEV_1 or Pa,O_2 unknown

†, calculated comorbidity component; subtracted age scores.

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Table 4. Relative risk for hospital admission after propensity score matching calculated using negative binomial regression model

	Relative Risk (95% CI)			
Characteristics	Grade 1	Grade 2	Grade 3	**No Grade**
Home oxygen therapy				
Yes	1.00	1.00	1.00	1.00
No	1.65 (1.25-2.18)***	1.07 (0.80-1.43)	0.72 (0.51-1.02)	0.73 (0.62-0.86)***

*, P-value<0.05; **, P-value<0.01; ***, P-value<0.001

Grade 1 was defined patients with chronic respiratory failure requiring oxygen therapy and an FEV_1 ≤25% predicted or resting Pa,O_2≤55 mmHg (room air); Grade 2 was defined patients with dyspnea when walking at home and an FEV_1 ≤ 30% predicted or Pa,O_2 56-60 mmHg (room air); Grade 3 was defined patients with dyspnea when walking at their own pace on the ground level and FEV_1 ≤40% predicted or Pa,O_2 61-65 mmHg (room air); No Grade was defined FEV_1 or Pa,O_2 unknown

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Home oxygen therapy reduces risk of hospitalization in patients with chronic obstructive pulmonary disease: A population-based retrospective cohort study, 2005–2012

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Home oxygen therapy reduces risk of hospitalization in patients with chronic obstructive pulmonary disease: A population-based retrospective cohort study, 2005–2012

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Abstract

Objective: This study evaluated the effect of home oxygen therapy (HOT) on hospital admissions in chronic obstructive pulmonary disease (COPD) patients.

Design and setting: Using nationwide health insurance claims from 2002–2012, we conducted a longitudinal population-based retrospective cohort study.

Participants: Individuals who are 40 years or above and newly diagnosed with COPD in 2005.

Outcome measures: the primary outcome was total number of hospitalization during study period. Participants were matched using HOT propensity scores and were stratified by respiratory impairment (Grade 1: $FEV_1 \leq 25\%$ or $Pa,O_2 \leq 55mmHg$; Grade 2: $FEV_1 \leq 30\%$ or Pa,O_2 56-60mmHg; Grade 3: $FEV_1 \leq 40\%$ or Pa,O_2 61-65mmHg; No grade: FEV_1 or Pa,O_2=unknown), then a negative binomial regression analysis was performed for each group.

Results: Of the 36,761 COPD patients included in our study, 1,330 (3.6%) received HOT. In a multivariate analysis of Grade 1 patients performed prior to propensity score matching, the adjusted relative risk of hospitalization for patients who did not receive HOT was 1.27 (95% CI, 1.01–1.60). In a multivariate analysis of Grade 1 patients performed after matching, the adjusted relative risk for patients who did not receive HOT was 1.65 (95% CI, 1.25–2.18). In Grade 2 or Grade 3 patients, no statistical difference in hospital admission risk was detected. In the no grade group of patients, HOT was associated with increased risk of hospitalization.

Conclusions: HOT reduces the risk of hospital admission in COPD patients with severe hypoxemia. However, apart from these patients, HOT use is not associated with hospital

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admissions, or is more likely to admit.

Key word: home oxygen therapy, chronic obstructive pulmonary disease, hospital admission, long-term oxygen therapy

Strengths and limitations of this study

- We analyzed the association between home oxygen therapy and hospitalization for COPD patients using nationwide claims data and conducted a longitudinal population-based prospective analysis based on claims from 2005 to 2012.
- We were able to increase the homogeneity of our study sample by identifying patients who were newly diagnosed in 2005.
- We made an effort to accurately determine the net effect of HOT via propensity score matching.
- In our findings, there may be potential unmeasured variable bias because we used the data based on claims.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by progressive airflow limitation that is not fully reversible, causing disability, but is frequently undiagnosed [1]. COPD is a major cause of morbidity and mortality, acting increasingly as a substantial societal burden;[2] hence viewed as a serious public health problem in many countries throughout the world. According to the World Health Organization estimates, 80 million people have moderate to severe COPD, and three million people have died of COPD in 2005. The same estimates also predicted that it will become the fourth leading cause of death by 2030[3].

In an effort to combat COPD-related hospitalization, researchers have studied the effects of oxygen therapy. Long-term oxygen therapy (LTOT) has been shown to improve survival and quality of life as well as to stabilize pulmonary hypertension in COPD patients[4-9]. In Korea, clinical practitioners and policy-makers began to recognize the benefits of LTOT. Social welfare services for people with respiratory related disabilities in Korea are offered through respiratory impairment[10]. Home oxygen therapy is the administration of oxygen at concentrations greater than the ambient air concentration at home and the cost of such long term oxygen therapy has been included for coverage in the national health insurance system since 2006. However, ambulatory oxygen delivery systems and home ventilator service is not currently covered by the health insurance system. As the burden of COPD continues to increase, analyzing the status of health care utilization in patients with COPD is important in establishing health care plans that encourage proper management of COPD. These issues are raised in Korea as well as in many countries which the burden of COPD is increasing, and a guideline of indication of home oxygen therapy is needed.

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Yet it must be taken into account that findings on the effect of home oxygen therapy on hospitalization have varied. Although several studies have indicated that LTOT decreases hospital admissions[11-14], one study found no effect on hospital admissions[15]. Most studies that have found an effect of LTOT on hospital admission have detected the greatest association among severely hypoxemic COPD patients ($Pa,O_2 \leq 60$ mmHg at rest on room air)[11-14]. In moderately hypoxemic COPD patients (Pa,O_2 55–70 mmHg at rest on room air: 7.3-9.5 kPa), HOT may not reduce hospitalizations[15]. Also, regarding oxygen prescription, questions have recently been raised as hospital admission is more likely in LTOT users and medical costs are increasing due to the inappropriate use of oxygen[16].

The aim of this study was to assess the effect of HOT on hospital admissions, in which COPD patients were stratified into forced expiratory volume 1 second or arterial oxygen tension, and to provide evidence about the appropriate indication of home oxygen therapy.

Methods

Data and study design

This study used 2002–2012 claims from the Korean National Health Insurance Service (KNHIS) claims database. We conducted a longitudinal population-based retrospective cohort study of newly diagnosed adult COPD patients to investigate the association between HOT and hospital admissions over a 7-year follow-up period. Participants were 40 years of age or older with newly developed COPD (codes J43.x except for J43.0 or J44.x, International Classification of Disease, 10th edition [ICD-10]). The codes of J44.x and J43.x (except for J43.0) refer to COPD or emphysema, respectively. J43.0 is McLeod's syndrome. The new

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diagnosis was confirmed by a lack of COPD-related claims in 2002–2004 and the first COPD-related claim in 2005. Presence or absence of HOT was analyzed from 2006 and onwards, and hospital admissions were analyzed from 2007 to 2012. If a patient died during the study period, we observed hospital admissions until time of death or end of study. Ethical approval for this study was granted by the institutional review board of the Graduate School of Public Health, Yonsei University, Seoul, Korea.

Study population

The total number of individuals in 2002–2012 aged 40 years or older with COPD was 1,538,711. Of these patients, 138,680 patients received their diagnosis in 2005 and were still alive in 2006. We modified the criteria which was used in Kim J. et al.'s study to define COPD patients using claims data[17]. Hence COPD was defined in the study by the following criteria: 1) age≥40-years-old; 2) ICD-10 codes for COPD (J43.x except for J43.0 and J44.x; emphysema and COPD, respectively); and 3) use of one or more COPD medications at least twice per year. Unfortunately, we could not review all of such prescriptions and thus replaced the third criteria with patients having over four outpatient visits per year due to COPD as the primary diagnosis. Since we inferred COPD diagnoses from information contained in the KNHIS claims database, we developed a process to aid in the selection of participants who actually had COPD. We excluded 101,919 patients: 1) 9,566 patients were dead in 2005; 2) 92,353 patients who had fewer than four outpatient visits with COPD as the primary complaint, did not receive HOT, and did not experience a hospital admission due to COPD during 2006. In the exclusion criteria, we arbitrary determined cut

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off points at outpatient visits were less than 4 times based on a previous study. In the previous study, the mean value of outpatient visits were 7.4 time for COPD patients in 2009. The mean value of outpatient visits was 3.2 times in 2005 in our sample. Thus we determined our cut off points by considering these points. Our final study sample included 36,761 patients, 1,330 who received HOT and 35,431 who did not.

Variables

The dependent variable in this study was the total number of hospital admissions due to COPD during the study period. We defined hospital admission due to COPD as the usage of inpatient medical services for more than 1 day and primary emphysema or COPD by the ICD-10 code of J43.x (except for J43.0) or J44.x.

Covariates considered included age, sex, health insurance status (national health insurance or medical aid), the Charlson comorbidity index (0, 1, or 2^{+})[18], HOT (yes, no), use of the intensive care unit (ICU) (yes, no), number of hospital admissions (0, 1, or 2^{+}), and respiratory impairment (1, 2, 3, or No grade). In Korea, The Ministry of Health and Welfare provides social welfare services to disabled person through the Welfare of Disabled Person Act. However, our government uses strict criteria for certificating a disabled person due to a lack of budget set for disabled people. According to the Welfare of Disabled Person Act, the severity of respiratory impairment is determined by 3 clinical parameters: dyspnea, FEV_1, and Pa,O_2. The Criteria corresponding to grade 1 was patients with chronic respiratory failure requiring oxygen therapy and a predicted FEV_1 of ≤25% or a resting Pa,O_2 of ≤55 mmHg (room air); the criteria corresponding to grade 2 was patients with dyspnea when walking at home and a predicted FEV_1 of ≤ 30% or Pa,O_2 of 56-60 mmHg (room air); the criteria

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corresponding to grade 3 was patients with dyspnea when walking at their own pace at ground level and a predicted FEV_1 of ≤40% or Pa,O_2 of 61-65 mmHg (room air). We defined the "No grade" group as patients with unknown FEV_1 or Pa,O_2. Only the comorbidity component of the Charlson comorbidity index was calculated. All of these variables were measured at the 2006 baseline.

Statistical analysis

First, demographic characteristics of patients who received HOT and those who did not were compared; the chi-square test was used to assess categorical variables, and t-tests were used to assess continuous variables. Next, a non-parsimonious multivariable logistic regression model was used to estimate propensity scores for HOT. Propensity score matching (PSM) is a statistical matching technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict treatment reception. The PSM allows one to design and analyze an observational study so that it mimics certain characteristics of a randomized controlled trial[19]. We included the following in our propensity model: age, sex, health insurance type, Charlson comorbidity index, ICU use, number of hospital admissions in 2006, and respiratory disability grade. The c-statistic for our propensity model was 0.784. Subjects who received HOT were matched on a one-to-one basis with those who did not. Then, we stratified participants according to their respiratory disability grade, based on hypoxemic status, and evaluated the relationship between HOT and hospital admissions in each group using a negative binomial regression analysis, which was chosen due to over-dispersion. All analyses were performed using SAS v9.3.

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Results

Of the 36,761 patients in our study, 1,330 (3.6%) received HOT. Prior to propensity score matching, baseline characteristics differed significantly between patients who received HOT and those who did not (Table 1). After propensity score matching, however, only the number of hospital admissions and respiratory disability grade differed between the two groups.

Table 2 presents incidence density (ID) rates for hospital admission according to HOT usage. Prior to propensity score matching, the ID for Grade 1 ($FEV_1 \leq 25\%$ or $Pa,O_2 \leq 55$ mmHg) who received HOT was 0.60 vs. 1.01 for those who did not. However, for patients with Grade 2 or Grade 3(FEV1≤30% or Pa,O2 56-60 mmHg; FEV1≤40% or Pa,O2 61-65 mmHg) or categorized as "No grade" (FEV_1 or Pa,O_2=unknown), the ID was higher for those who received HOT than for those who did not (0.61 vs. 0.63; 0.47 vs. 0.46; and 0.34 vs. 0.05, respectively). Similar results were obtained after propensity score matching. For Grade 1 patients, the ID was lower for patients who received HOT than for those who did not (0.62 vs. 0.79), while in Grade 2/3 or No grade, the ID was higher for patients who received HOT (0.59 vs. 0.37; 0.47 vs. 0.23; and 0.34 vs. 0.07, respectively).

Table 3 presents the adjusted relative risk (RR) for hospital admission prior to propensity score matching. After controlling for all covariates, the adjusted RR for Grade 1 patients who did not receive HOT compared to the reference group (those who did receive HOT) was 1.12 (95% CI, 1.01–1.60). The RR for Grade 2 patients was 0.96, but this difference was not statistically significant. In Grade 3 or No grade, the adjusted RRs for patients who did not receive HOT were less than one (RR, 0.74; 95% CI, 0.58–0.93: RR, 0.65; 95% CI, 0.60–0.70, respectively).

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After propensity score matching, the adjusted RR for Grade 1 patients who did not receive HOT was 1.65 (95% CI, 1.25–2.18); in Grade 2 patients, the adjusted RR was 1.07 (95% CI, 0.80–1.43); in Grade 3 patients, the adjusted RR was 0.72 (95% CI, 0.51–1.02); and in patients without a grade, the adjusted RR was 0.73 (95% CI, 0.62–0.86) (Table 4).

Discussion

We found that HOT was associated with a 27% decreased risk of hospitalization in Grade 1 COPD patients ($FEV_1 \leq 25\%$ or $Pa,O_2 \leq 55$ mmHg) prior to propensity score matching and a 65% decreased risk after matching. However, apart from Grade 1 patients, the use of HOT did not show a statistically significant association with hospital admission prior to or after matching in Grade 2 patients. Also, in Grade 3 or No grade COPD patients ($FEV_1 \leq 40\%$ or $Pa,O_2 \leq 65$ mmHg; FEV_1 or Pa,O_2=unknown), HOT was associated with an increased risk of hospital admission prior to propensity score matching and in the case of No grade patients, HOT was still associated with an increased risk of admission after propensity score matching.

In Korea, HOT can be prescribed by a pulmonologist as well as an internist and a thoracic surgery specialist through only a one time test of arterial blood gas analysis; similar to the criteria that most countries use for home oxygen therapy, the indications of HOT for reimbursement are patients with Pa,O_2 less than or equal to 55mmHg or with SpO_2 less than or equal to 88%. Patients with Pa,O_2 between 56 and 60mmHg or SpO_2 below 89%, must also have congestive heart failure, polycythemia (hematocrit>55%), or pulmonary hypertension to qualify during the stable period after 3 months of internal treatment. Physicians can prescribe patients with Grade 1 or Grade 2respiratory impairment without

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conducting any other tests. If patients without indication of such grade receives HOT prescriptions, it means that the patient was seen by a physician under the COPD code but that the patient did not fill out the necessary form to receive an assigned grade. Hence the patient's clinical status fits the indications for HOT prescription, meaning that these patients may in actuality, have any of the grades described above, including Grade 1. Therefore, in the case of patients without a grade, the use of HOT means that the patients who use such HOT may have conditions that are clinically more severe than those who do not use HOT.

Our results are comparable to the findings of previous studies. We could not distinguish patient's status between Pa,O_2 and FEV_1% predicted. We could only infer patients' Pa,O_2, FEV_1 or shortness of breath with respiratory impairment grade. However, for patients with $Pa,O_2 \leq$ 55 mmHg or predicted FEV_1 ≤25% of grade 1, use of HOT was associated with a reduced risk of hospital admission. Most previous studies have showed a consistent tendency in patients with severe hypoxemia (Pa,O_2<8.0 kPa) in which HOT was associated with decreased hospital admissions. However, Ringbaek et al. found that home oxygen therapy did not reduce hospitalization in patients with moderate hypoxemia (Pa,O_2>8.0 kPa)[15]. In addition, many previous studies have found that FEV_1 predicted could be a predictor of acute exacerbation hospitalization [20-22]. One recent paper suggested that oxygen use outside the National Institute for Health and Care Excellence (NICE) guidance did not appear to prevent admissions[23] and FEV_1 was the only significant predictor of readmission[16]**.** In South Korea, although HOT is used according to NICE guidelines, HOT was not associated with decreased risk of hospital admission even in Grade 2 (Pa,O_2 56-60mmHg or predicted $FEV_1 \leq$ 30%). In Grade 3 or No grade patients, admission to hospitals was more likely in HOT

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users prior to matching instead, and after matching, there was no statistically significant difference in Grade 3 patients. There are two possible explanations regarding this result. One is that because admission for exacerbation is more common in severe COPD[24] patients and in oxygen users[25], hospital admissions are more frequently expected in HOT users if patients' severity is unequal as they have more severe lung disease. The second possibility may be explained through residual confounding. Garcia-Aymerich J. et al. showed that the risks of re-admission was high in LTOT users after adjustment for severity variables such as FEV_1 or Pa,O_2[26]. The authors explained these paradoxical results using residual confounding, that the excess risk of COPD re-admission associated with medical care related factors might be partially due to confounding by indicationOur finding supports that HOT use reduces hospitalization in COPD patients with severe hypoxemia (Pa,O_2 ≤55 mmHg) and **a** predicted FEV_1 of ≤25%. However, although HOT may improve quality of life and help breathing during activities in COPD patients without severe hypoxemia, use of HOT should be considered to prevent hospital admissions in COPD patients with Pa,O_2>55mmHg or a predicted FEV_1>25% . We need to at least conduct further research about cost-effectiveness for HOT use in these patients and then, if necessary, require modification of the criteria for HOT prescription.

This study has several limitations. First, because we used claims data, which are based on information in the KNHIS, we were not able to assess some factors that could potentially influence hospital admissions. For example, we had no data on smoking history, body mass index, health behaviors, use of systematic corticosteroids, laboratory results, etc. Second, we categorized respiratory impairment into four respiratory disability grades, as determined by FEV_1, Pa,O_2, and dyspnea. Therefore, we did not use quantitative FEV_1 or Pa,O_2 values,

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instead estimating a patient's hypoxemic status. Especially in the No grade group, it is possible that patients with various severities have been mixed together. The third limitation is the accuracy of our COPD diagnosis. The accuracy of diagnoses in KNHIS claims data is roughly 70%[27]. To increase accuracy, a review of all prescriptions would be required. Unfortunately, we could not perform such a review here. However, the accuracy of COPD diagnoses in this study may have been compromised. The fourth limitation involves the definition of newly diagnosed patients. In this study, newly diagnosed patients were defined as those who did not have COPD claims in 2002–2004 but did have a COPD claim in 2005. Thus, patients diagnosed prior to 2002 who did not utilize COPD-related medical services in 2002–2004 may have been included in the sample. The final limitation is related to patterns of HOT use. Although all of our study subjects used HOT in or after 2006 and we adjusted for the number of hospital admission at baseline, because of considering hypothesis in previous studies that an effect of oxygen therapy in patients who start home oxygen therapy as outpatients are less likely to be derived from a "regression to the mean phenomenon"[12], we did not know the duration of usage per day, whether use was continuous or non-continuous, or whether patient compliance was good.

Despite these limitations, our study has several strengths. First, we analyzed COPD patients using nationwide claims data and conducted a longitudinal population-based prospective analysis based on claims from 2005 to 2012. Our study population was relatively large and our follow-up period was relatively long compared to previous studies evaluating the association between oxygen therapy and hospitalization[28,29]. Second, we were able to increase the homogeneity of our study sample by identifying patients who were newly diagnosed in 2005. We could observe the progression of their disease over time via hospital

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admissions. Finally, we made an effort to accurately determine the net effect of HOT via propensity score matching.

In conclusion, HOT reduces hospital admission risk in COPD patients with severe hypoxemia or a predicted FEV_1 of ≤25%. However, except for these patients, HOT use is not associated with hospital admissions, or an increase in the likeliness of hospital admission. Still, further research on cost-effectiveness of HOT in patients who does not meet the indication for HOT is needed, even in patients with Pa,O_2 56-60 mmHg or a predicted FEV_1 of 26-30% who meet the indication.

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Conflicts of Interests: None of the authors have any conflicts of interest associated with this study.

Contribution : Cho KH and Park EC carried out constructing study design, Cho KH and Nam CM carried out analyzing data, Cho KH, Park EC, and KimYS interpreted results, Kim YS was scientific advisor, Park EC guided and directed this study Cho KH and Kim TH wrote manuscript and Kim SJ and Han KT was clinical investigators.

Data sharing: Additional data is available by emailing the corresponding author.

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Table 1. Baseline characteristics of the study sample, stratified according to use of home oxygen therapy

	Pre-match (N=36,761)					Post-match (1:1; N=2,478)				
	Yes, n (%)		No, n (%)		P-value	Yes, n (%)		No, n (%)		P-value
Characteristics	1,330	(3.6)	35,431	(96.4)		1,239	(50.0)	1,239	(50.0)	
Age (years), mean (SD)	67.1	(9.6)	63.8	(12.0)	<0.0001	67.4	(9.7)	68.0	(9.9)	0.14
Sex										
Male	964	(4.7)	19,353	(95.3)	<0.0001	884	(49.2)	912	(50.8)	0.21
Female	367	(2.2)	16,078	(97.8)		355	(52.0)	327	(48.0)	
Health insurance type										
National health insurance	1,279	(3.8)	32,645	(96.2)	<0.0001	1,188	(50.5)	1,163	(49.5)	0.02
Medical aid	51	(1.8)	2,786	(98.2)		51	(40.2)	76	(59.8)	
Charlson comorbidity index*										
0	692	(6.5)	9,983	(93.5)	<0.0001	628	(48.4)	670	(51.6)	0.13
1	62	(5.7)	1,021	(94.3)		57	(47.1)	64	(52.9)	
≥2	576	(2.3)	24,427	(97.7)		554	(52.3)	505	(47.7)	
ICU use										
Yes	11	(6.9)	148	(93.1)	<0.0001	9	(39.1)	12	(60.9)	0.30
No	1,319	(3.6)	35,283	(96.4)		1,230	(50.1)	1,225	(49.9)	
Number of hospital admission										
0	1,147	(3.5)	31,923	(96.5)	<0.0001	1,067	(51.5)	1,004	(48.5)	0.002
1	127	(4.9)	2,486	(95.1)		119	(40.6)	174	(59.4)	
≥2	56	(5.2)	1,022	(94.8)		53	(46.5)	61	(53.5)	
Respiratory impairment rating										
Grade 1 (FEV_1%≤25 or Pa,O_2 ≤55 mmHg)	163	(43.2)	214	(56.8)	<0.0001	91	(43.1)	120	(56.9)	0.001
Grade 2 (FEV1%≤30 or Pa,O_2 ≤60 mmHg)	121	(35.6)	219	(64.4)		102	(55.7)	81	(44.3)	
Grade 3 (FEV1%≤40 or Pa,O_2 ≤65 mmHg)	110	(26.6)	304	(73.4)		110	(61.1)	70	(38.9)	
No Grade	936	(2.6)	34,694	(97.4)		936	(49.2)	968	(50.8)	

SD, standard deviation; ICU, intensive care unit.

*, calculated comorbidity component; subtracted age scores.

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Table 2. Incidence density for hospital admission according to use of home oxygen therapy

		Pre-match				Post-match (1:1)			
		Yes	No	Yes	No	Yes	No	Yes	No
Respiratory Impairment Rating[†]		N=1,330	N=35,431	ID[*]	ID[*]	N=1,239	N=1,239	ID[*]	ID[*]
Grade 1	Total number of hospital admission	416	748	0.60	1.01	244	319	0.62	0.79
	Person-years	694.1	743.3			390.8	406.0		
Grade 2	Total number of hospital admission	358	601	0.61	0.63	291	128	0.59	0.37
	Person-years	585.6	953.4			495.9	341.4		
Grade 3	Total number of hospital admission	245	672	0.47	0.46	245	81	0.47	0.23
	Person-years	517.8	1455.4			517.8	348.3		
No Grade	Total number of hospital admission	1409	9286	0.34	0.05	1409	322	0.34	0.07
	Person-years	4123.0	184555.3			4123.0	4837.3		

*ID, Incidence Density; calculated total number of hospital admissions divided into sum of person-years.

[†], Grade 1 was defined patients with chronic respiratory failure requiring oxygen therapy and an FEV_1 ≤25% predicted or resting Pa,O_2≤55 mmHg (room air); Grade 2 was defined patients with dyspnea when walking at home and an FEV_1 ≤ 30% predicted or Pa,O_2 56-60 mmHg (room air); Grade 3 was defined patients with dyspnea when walking at their own pace on the ground level and FEV_1 ≤40% predicted or Pa,O_2 61-65 mmHg (room air); No Grade was defined FEV_1 or Pa,O_2 unknown .

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Table 3. Relative Risk for hospital admission, stratified respiratory disability grade calculated using negative binomial regression model

Characteristics	Relative Risk (95% CI)							
	Grade 1		Grade 2		Grade 3		**No Grade**	
Age (years)	1.002	(0.993-1.010)	0.992	(0.983-1.001)	1.010	(0.993-1.021)	1.006	(1.004-1.009)***
Sex								
Male	1.06	(0.87-1.29)	1.25	(0.96-1.62)	0.94	(0.75-1.18)	1.16	(1.10-1.23)***
Female	1.00		1.00		1.00		1.00	
Health insurance type								
National health insurance	1.00	(0.80-1.25)	0.94	(0.75-1.17)	0.60	(0.49-0.75)***	0.69	(0.65-0.73)***
Medical aid	1.00		1.00		1.00		1.00	
Home oxygen therapy								
Yes	1.00		1.00		1.00		1.00	
No	1.27	(1.01-1.60)*	0.96	(0.75-1.22)	0.74	(0.58-0.93)*	0.65	(0.60-0.70)***
Charlson comorbidity index†								
0	1.00		1.00		1.00		1.00	
1	0.86	(0.66-1.13)	1.00	(0.72-1.39)	0.82	(0.57-1.17)	1.00	(0.93-1.07)
≥2	1.12	(0.84-1.49)	1.11	(0.81-1.53)	0.90	(0.67-1.21)	1.11	(1.02-1.21)*
ICU use								
Yes	1.13	(0.74-1.70)	1.05	(0.42-2.59)	0.31	(0.09-1.09)	1.02	(0.82-1.27)
No	1.00		1.00		1.00		1.00	
Number of hospital admission								
0	1.00		1.00		1.00		1.00	
1	1.65	(1.29-2.11)***	1.45	(1.12-1.88)**	1.24	(0.98-1.57)	1.69	(1.58-1.81)***
≥2	1.73	(1.34-2.24)***	1.48	(1.11-1.96)**	1.65	(1.28-2.12)***	2.04	(1.88-2.21)***

*, P-value<0.05; **, P-value<0.01; ***, P-value<0.001.

Grade 1 was defined patients with chronic respiratory failure requiring oxygen therapy and an FEV_1 ≤25% predicted or resting Pa,O_2≤55 mmHg (room air); Grade 2 was defined patients with dyspnea when walking at home and an FEV_1 ≤ 30% predicted or Pa,O_2 56-60 mmHg (room air); Grade 3 was defined patients with dyspnea when walking at their own pace on the ground level and FEV_1 ≤40% predicted or Pa,O_2 61-65 mmHg (room air); No Grade was defined FEV_1 or Pa,O_2 unknown

†, calculated comorbidity component; subtracted age scores.

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Table 4. Relative risk for hospital admission after propensity score matching calculated using negative binomial regression model

	Relative Risk (95% CI)			
Characteristics	Grade 1	Grade 2	Grade 3	**No Grade**
Home oxygen therapy				
Yes	1.00	1.00	1.00	1.00
No	1.65 (1.25-2.18)***	1.07 (0.80-1.43)	0.72 (0.51-1.02)	0.73 (0.62-0.86)***

*, P-value<0.05; **, P-value<0.01; ***, P-value<0.001

Grade 1 was defined patients with chronic respiratory failure requiring oxygen therapy and an FEV_1 ≤25% predicted or resting Pa,O_2≤55 mmHg (room air); Grade 2 was defined patients with dyspnea when walking at home and an FEV_1 ≤ 30% predicted or Pa,O_2 56-60 mmHg (room air); Grade 3 was defined patients with dyspnea when walking at their own pace on the ground level and FEV_1 ≤40% predicted or Pa,O_2 61-65 mmHg (room air); No Grade was defined FEV_1 or Pa,O_2 unknown

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