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ORIGINAL RESEARCH

Medical Utilization and Cost in Patients with Overlap Syndrome of Chronic Obstructive Pulmonary Disease and Asthma

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Abstract

Background: Little information is available regarding medical utilization and cost in patients with overlap syndrome of chronic obstructive pulmonary disease (COPD) and asthma. The purpose of this study is to analyze medical utilization and cost in patients with overlap syndrome and to compare them to COPD patients without asthma. **Methods:** Using the 2009 Korean National Health Insurance (NHI) database, COPD patients were identified. Medical utilization and costs were also analyzed. **Results:** Of a total of 185,147 patients identified with COPD, 101,004 patients were classified with overlap syndrome of COPD and asthma and 84,143 patients with COPD without asthma. In 2009, the percentages of emergency room visits, admissions, and intensive care unit admissions were 14.6%, 30.5%, and 0.5%, respectively, in the patients with overlap syndrome group and 5.0%, 14.1%, and 0.2%, respectively, in the COPD patients without asthma group ($p < 0.05$ for all comparisons). The cost of medical utilization was 790 ± 71 US dollars per person and $3,373 \pm 4,628$ dollars per person for outpatient and inpatient services, respectively, in the patients with overlap syndrome and 413 ± 512 and $3,010 \pm 5,013$, respectively, in the COPD patients without asthma ($p < 0.05$ for all comparisons). Multiple linear regression showed that age, sex, overlap syndrome, hospitalization in the last year, low socioeconomic status, and type of hospital use were significant factors affecting medical utilization and cost. **Conclusions:** In patients with overlap syndrome, both medical utilization and cost were higher than in COPD patients without asthma.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation. However, some patients with COPD show significant reversibility of airflow limitation, which is one of the archetypal characteristics of asthma. These patients can be considered as having an overlap syndrome of COPD and asthma. Although the exact definition remains unclear, overlap syndrome can be recognized by the coexistence of increased variability of airflow in a patient with incompletely reversible airway obstruction (1, 2).

Previous studies showed that there are many patients who showed features of overlap and these patients showed different clinical characteristics compared with non-overlap patients. Hardin et al. (3) showed that patients with overlap syndrome represent an important clinical population, with a poorer health-related quality of life. Hoppers et al. (4) showed that COPD patients with AHR showed increased risk of exacerbation. Shaya et al. (5) suggested that patients with an overlap of COPD and asthma show greater morbidity

Keywords: chronic obstructive pulmonary disease, asthma, overlap syndrome, medical utilization, medical cost

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and used more medical services. However, despite these previous studies, little information is available regarding the medical utilization and cost of patients with overlap syndrome.

South Korea has a compulsory universal health insurance system that includes medical reimbursement records for entire the Korean population. The National Health Insurance (NHI) reimbursement database provides a unique and advantageous mechanism for evaluating the nationwide magnitude of an illness and the consequent health care use (6, 7).

The purposes of this study were: (1) to analyze the medical utilization and costs of patients with overlap syndrome, and (2) to compare medical utilization and cost between overlap syndrome and COPD without asthma in a nationwide study through the use of the NHI data for Korea.

Methods

Study design

In our present study, we utilized the 2009 databases of the South Korean NHI. We identified patients with COPD as a principal or secondary diagnosis by searching for codes of the International Classification of Diseases-, Tenth Revision (ICD-10) and medication use information. A COPD patient was defined by the following criteria: 1) age greater than 40 years; 2) ICD-10 codes for COPD or emphysema (J42.x–J44.x, except J430); 3) use of more than one drug for COPD at least twice per year [long-acting muscarinic antagonist (LAMA), long-acting beta-2 agonist (LABA), inhaled corticosteroids (ICS), ICS plus LABA (ICS+LABA), short-acting muscarinic antagonist (SAMA), short-acting beta-2 agonist (SABA), or theophylline]. An asthma patient was defined by the following criteria: 1) ICD-10 codes for asthma (J45.x–J46); 2) use of more than one drug for asthma at least twice per year [LAMA, LABA, ICS, ICS+LABA, SAMA, SABA, theophylline, leukotriene antagonist (LTRA), systemic corticosteroids, or systemic beta agonist]. A patient was defined as having an overlap of COPD and asthma by meeting both sets of these criteria.

Patients with more than one reimbursement per year due to cancer (ICD-10: C00.x–C97.x), renal failure (N17.x–N19.x), and/or cerebrovascular disease (I60.x–I69.x) were excluded from this study because it was difficult to distinguish the enormous expenses reimbursed for treatment of these diseases from those of COPD-related medical services.

For patients who were defined as having COPD, medical utilization and cost were analyzed during one calendar year (2009). For all utilization and costs during the year, analysis was confined to COPD-related utilization and cost. Medical utilization and costs were excluded for analysis if they were not considered to be COPD-related, even when patients who were defined as having COPD used the medical service. For utilization and cost of medication, only COPD-related medications

[LAMA, LABA, ICS, ICS+LABA, SAMA, SABA, theophylline, LTRA, SABA plus SAMA (SABA+SAMA), oral corticosteroid (OCS), systemic beta agonist, mucolytics, antitussive agent, and non-steroidal respiratory anti-inflammatory inhalant] were analyzed. For outpatient services, analysis was confined to visits when the principal or secondary diagnosis was COPD (J42.x–J44.x, except J430). For inpatient services, analysis was confined to admission when the principal or secondary diagnosis was COPD (J42.x–J44.x, except J430) or a COPD-related disease (pneumonia: J12.x–J17.x, pulmonary thromboembolism: I26, I26.0, and I26.9, dyspnea: R06.0, or acute respiratory distress syndrome: J80).

Data regarding age, sex, co-morbidity, hospitalizations, emergency room (ER) visits, intensive care unit (ICU) admissions, medical costs, and medication use were collected. For co-morbidity, the prevalence of 10 diseases [ischemic heart disease, osteoporosis, depressive disorder, arthritis, diabetes mellitus (DM), pneumothorax, congestive heart failure (CHF), hypertension, anemia, and metabolic syndrome] were analyzed using ICD-10 codes.

The number of days that a particular service was used (“used days”) was analyzed separately for outpatient and inpatient services. Used days for the outpatient service was analyzed only for patients who had used the outpatient service, while the used days for the inpatient service was analyzed only for patients who had used the inpatient service. Total used days were analyzed for all patients who used either outpatient or inpatient services.

All costs are presented in US dollars (USD) with an exchange rate of 1 USD equaling 1152 Korean won (exchange rate on July 20, 2012).

The National Evidence-Based Healthcare Collaborating Agency Ethics Committee of Korea approved the present study (PIRB11-022). The requirement for informed consent from the patients studied was waived by the ethical review board.

Statistical analysis

Differences between groups were assessed using the chi-squared test for categorical variables, and the Student's *t*-test for continuous variables. Multiple linear regression analysis was performed to find factors affecting medical cost. The dependent variable was log-transformed in linear regression analysis as usually healthcare utilization variables are right-skewed (i.e. distributed with a long and heavy right tail). All tests were two-sided, and *p*-values < 0.05 were considered statistically significant. Data are expressed as mean ± standard deviation (SD). All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics

A total of 185,147 COPD patients were identified during the relevant period. Of these, 101,004 (54.6%) were also

compatible with criteria of asthma and 84,143 (45.4%) were not. Comparisons were made between the two groups (overlap syndrome vs. COPD without asthma; Table 1). The mean age in the overlap syndrome group was 69.7 ± 10.7 vs. 70.3 ± 10.5 years for the COPD without asthma group ($p < 0.001$) and the percentage of male

patients was 67.3% vs. 57.6%, respectively ($p < 0.001$). The percentages of ER visits, admissions, and ICU admissions were significantly higher in the overlap syndrome group than in the COPD without asthma group ($p < 0.001$).

Computed tomography (CT) scans and pulmonary function tests (PFTs) were more frequently performed

Table 1. Patient characteristics

Characteristics	Overlap syndrome (n = 101,004)	COPD without asthma (n = 84,143)	p-value
Males (%)	68,025 (67.3%)	48,464 (57.6%)	<0.001
Mean age, years	69.7 ± 10.7	70.3 ± 10.5	<0.001
Number of patients in each age group (%)			
40–49 years	4,345 (4.3%)	3,784 (4.5%)	
50–59 years	12,498 (12.4%)	9,450 (11.2%)	
60–69 years	28,237 (28.0%)	22,376 (26.6%)	
70–79 years	39,405 (39.0%)	32,658 (38.8%)	
>80 years	16,519 (16.4%)	15,875 (18.9%)	
Medical aid [#]	17,643 (17.5%)	12,965 (15.4%)	<0.001
Type of hospital use			
Primary	44,379 (43.9%)	57,192 (68.0%)	
Secondary	9,676 (9.6%)	6,117 (7.3%)	
Tertiary	46,583 (46.1%)	20,834 (24.8%)	
Hospitalizations [†]	30,807 (30.5%)	11,884 (14.1%)	<0.001
ICU care [†]	477 (0.5%)	158 (0.2%)	<0.001
ER visits [†]	14,733 (14.6%)	4,222 (5.0%)	<0.001
Mean number of visits	1.5 ± 1.0	1.2 ± 0.5	<0.001
Number of patients in each group (%)			
0 visit	86,271 (85.4%)	79,921 (95.0%)	
1–2 visits	13,243 (13.1%)	4,090 (4.9%)	
3–4 visits	1,203 (1.2%)	122 (0.1%)	
>5 visits	287 (0.3%)	10 (0.0%)	
Chest X-rays	21,092 (20.9%)	17,538 (20.8%)	0.836
Chest CTs	791 (0.8%)	409 (0.5%)	<0.001
PFTs	41,931 (41.5%)	15,321 (18.2%)	<0.001
Hospitalizations in the last year [*]	14,637 (14.5%)	5,105 (6.1%)	<0.001
Co-morbidity			
Ischemic heart disease	9,053 (9.0%)	7,100 (8.4%)	<0.001
Osteoporosis	5,267 (5.2%)	3,650 (4.3%)	<0.001
Depressive disorder	2,080 (2.1%)	1,316 (1.6%)	<0.001
Arthritis	3,484 (3.4%)	3,658 (4.3%)	<0.001
Diabetes mellitus	13,540 (13.4%)	10,926 (13.0%)	0.008
Pneumothorax	1,271 (1.3%)	527 (0.6%)	<0.001
Congestive heart failure	5,542 (5.5%)	4,813 (5.7%)	0.029
Hypertension	30,020 (29.7%)	24,186 (28.7%)	<0.001
Anemia	1,643 (1.6%)	1,365 (1.6%)	0.940
Metabolic syndrome	6,686 (6.6%)	5,483 (6.5%)	0.720

Data are expressed as the mean $\pm$ SD or the number of patients (with percentage in parentheses).

[#]Patients with low socioeconomic status were covered by medical aid in Korea. Medical cost was covered by government for patients with medical aid.

[†]Number of patients who were hospitalized, cared for in the ICU, and visited the ER in the year 2009.

^{*}Number of patients who were hospitalized in the year 2008.

ER = emergency room; CT = computed tomography; PFT = pulmonary function test.

in the overlap syndrome group that the COPD without asthma group during the study period. The percentage of hospital admissions in the overlap syndrome group during the previous year (2008) was significantly higher than that of the COPD without asthma group ($p < 0.001$). The prevalences of ischemic heart disease, osteoporosis, depressive disorder, DM, pneumothorax, and hypertension were significantly higher in the overlap syndrome group than the COPD without asthma group (all $p < 0.001$ except for $p = 0.008$ for DM). On the other hand, the prevalence of arthritis and CHF was significantly higher in the COPD without asthma group than the overlap syndrome group ($p < 0.001$ and $p = 0.029$, respectively).

Medical cost and used days per person during 2009 were also analyzed (Table 2). The cost of outpatient and inpatient services per person were significantly higher in the overlap syndrome group than the COPD without asthma group ($p < 0.001$). Moreover, the number of outpatient clinic visits, admission days, and total used days were significantly higher in the overlap syndrome group ($p < 0.001$).

In addition, total cost of all medical utilization of COPD patients and the proportion of medical utilization were analyzed (Table 3). The total cost of inpatient services and outpatient services were higher in the overlap syndrome group than the COPD without asthma group.

The frequency of medication use was also analyzed, which showed that ICS, ICS+LABA, LAMA, LTRA, OCS, SAMA, SABA, SAMA+SABA, systemic beta agonist, and theophylline were used more frequently in the overlap syndrome group than the COPD without asthma group ($p < 0.001$; Table 4).

The total cost of medication was higher in the overlap syndrome group than the COPD without asthma group (Table 5). The total cost of each medication was also higher in the overlap syndrome group than the COPD without asthma group. The mean cost of each medication per person was also significantly higher in the overlap syndrome group than the COPD without asthma group ($p < 0.001$) with the exception of LAMA and LABA.

Table 2. Healthcare utilization of COPD patients[†]

	Overlap syndrome	COPD without asthma	<i>p</i> -value
Cost of all medical utilization (USD)			
Cost of outpatient services	790 ± 71	413 ± 512	<0.001
Cost of inpatient services	3,373 ± 4,628	3,010 ± 5,013	<0.001
Total cost	1,807 ± 3,096	829 ± 2,215	<0.001
Used days			
Outpatient services	9.2 ± 9.76	7.4 ± 8.11	<0.001
Inpatient services	25.44 ± 34.74	23.19 ± 36.41	<0.001
Total used days	16.81 ± 24.56	10.5 ± 17.46	<0.001

Data are expressed as the mean ± SD.

[†]Costs or used days per person. Costs and used days are restricted to COPD-related ones.

Table 3. Total cost in the USD of all medical utilization of COPD patients and the proportion of medical utilization.

	Overlap syndrome		COPD without asthma	
	Sum	%	Sum	%
Outpatient services				
Medical examination	3,569,931	4.55%	1,482,296	4.36%
Radiologic examination	1,045,169	1.33%	481,453	1.42%
Medication	63,767,200	81.20%	25,919,388	76.32%
Others	10,028,548	12.91%	6,078,520	17.90%
Total cost	78,527,082	100.00%	33,961,656	100.00%
Inpatient services				
Medical examination	18,974,697	18.03%	6,082,634	16.69%
Radiologic examination	3,941,917	3.74%	1,489,646	4.09%
Medication	28,680,165	27.25%	9,365,771	25.70%
Others	53,662,667	50.98%	19,508,004	53.53%
Total cost	105,259,446	100.00%	36,446,055	100.00%
Total				
Medical examination	22,544,628	12.27%	7,564,930	10.74%
Radiologic examination	4,987,129	2.71%	1,971,099	2.80%
Medication	92,447,366	50.30%	35,285,159	50.11%
Others	63,807,405	34.72%	25,586,523	36.34%
Total cost	183,786,528	100.00%	70,407,710	100.00%

Medical examination includes all examinations (which includes laboratory examination, pulmonary function test, and echocardiography) except radiological examinations.

Multiple linear regression was performed in order to find factors affecting medical costs (Table 6) and used days (Table 7). Age, sex, overlap syndrome, and hospitalization in the last year were used for analysis. All these variables were significant factors affecting medical costs and used days ($p < 0.001$). Of three categorical variables

Table 4. The frequency of medication use.

Medication	Overlap syndrome		COPD without asthma		<i>p</i> -value
	n	(%)	n	(%)	
ICS	16,271	16.1%	2,994	3.6%	<0.001
ICS+LABA	50,963	50.5%	6,480	7.7%	<0.001
LAMA	39,782	39.4%	14,877	17.7%	<0.001
LABA	83	0.1%	51	0.1%	0.086
LTRA	30,690	30.4%	3,380	4.0%	<0.001
OCS	36,631	36.3%	13,485	16.0%	<0.001
SAMA	22,702	22.5%	6,364	7.6%	<0.001
SABA	41,817	41.4%	11,570	13.8%	<0.001
SABA+SAMA	3,245	3.2%	1,330	1.6%	<0.001
Systemic beta agonist	49,107	48.6%	36,815	43.8%	<0.001
Theophylline	81,683	80.9%	63,826	75.9%	<0.001

LAMA = long-acting muscarinic antagonist; LABA = long-acting beta-2 agonist; ICS = inhaled corticosteroids; ICS+LABA = ICS plus LABA; LTRA = leukotriene antagonist; OCS = oral corticosteroids; SAMA = short-acting muscarinic antagonist; SABA = short-acting beta-2 agonist; SABA+SAMA = SABA plus SAMA.

Table 5. Cost of medication (USD)

Medication	Overlap syndrome			COPD without asthma			p-value [†]
	n	Total cost	Cost per person	n	Total cost	Cost per person	
ICS	16,260	733,065	45 ± 81	2,991	80,768	27 ± 58	<0.001
ICS+LABA	50,893	12,579,822	247 ± 188	6,471	1,146,991	177 ± 167	<0.001
LAMA	39,754	10,886,969	274 ± 347	14,862	4,013,086	270 ± 406	0.308
LABA	83	6,354	77 ± 64	51	5,415	106 ± 70	0.013
LTRA	30,652	5,521,407	180 ± 167	3,376	316,137	94 ± 127	<0.001
OCS	36,588	224,819	6 ± 17	13,472	55,144	4 ± 13	<0.001
SAMA	22,689	558,096	25 ± 57	6,360	111,408	18 ± 40	<0.001
SABA	41,772	713,180	17 ± 34	11,558	130,579	11 ± 152	<0.001
SABA+SAMA	3,244	157,000	48 ± 65	1,330	49,372	37 ± 51	<0.001
Systemic beta agonist	49,066	1,758,055	36 ± 56	36,791	861,244	23 ± 46	<0.001
Theophylline	81,621	3,404,787	42 ± 44	63,789	1,518,381	24 ± 35	<0.001

[†]The p-value applies to the comparison of cost per person.

Data are expressed as the mean ± SD.

LAMA = long-acting muscarinic antagonist; LABA = long-acting beta-2 agonist; ICS = inhaled corticosteroids; ICS+LABA = ICS plus LABA; LTRA = leukotriene antagonist; OCS = oral corticosteroids; SAMA = short-acting muscarinic antagonist; SABA = short-acting beta-2 agonist; SABA+SAMA = SABA plus SAMA.

(male gender, overlap syndrome, and hospitalization in the last year), hospitalization in the last year was the most powerful factor affecting medical costs and used days, followed by overlap syndrome.

Discussion

In this nationwide study, we used Korean NHI data to analyze medical utilization and costs for patients with overlap syndrome and to compare medical utilization and cost between patients with overlap syndrome and COPD without asthma. Medical utilization and costs in the patients with overlap syndrome are higher than in COPD patients without asthma. To our knowledge, this is the largest report (n = 185,147) to date of the medical utilization and costs associated with overlap syndrome.

Shaya et al. (5) found through the analysis of Medicaid data that patients with overlap of COPD and asthma used more medical services and had a higher cost burden than patients with COPD without asthma. However, there were some limitations to this earlier study. First, as Medicaid is largely used by low-income populations and

female patients, caution is needed in applying these data to the general COPD patient populations. In our current study, however, the data comes from a nationwide registry, which covers the entire South Korean population regardless of age, sex, and income. Second, Medicaid data do not contain the actual costs for each type of service, unlike the Korean NHI data, which contain much more detailed information. Korean NHI data also contain medication information of not only tertiary hospital but also all primary care clinics. We have for the first time therefore described the frequency of medication use in COPD patients in a nationwide manner and our analyses represent a real world clinical picture of COPD management.

Previous studies have shown that overlap syndrome is more severe and has a poorer prognosis than COPD without asthma. Kauppi et al. (8) showed that overlap syndrome of COPD and asthma is a strong predictor of low quality of life than COPD without asthma. Diaz-Guzman et al. (9) reported that patients with coexisting COPD and asthma have a higher risk of obstruction on spirometry and a higher risk of death during follow-up.

Table 6. Multiple linear regression analysis of factors affecting medical cost

Variable	Unadjusted			Adjusted		
	β	exp (β)	p-value	β	exp (β)	p-value
Age (year)	0.015	1.015	<0.001	0.012	1.012	<0.001
Male gender	0.530	1.699	<0.001	0.276	1.317	<0.001
Overlap syndrome	1.082	2.951	<0.001	0.645	1.907	<0.001
Hospitalization in the last year	1.319	3.740	<0.001	0.753	2.122	<0.001
Medical aid [†]	0.613	1.845	<0.001	0.474	1.605	<0.001
Type of hospital use	0.790	2.204	<0.001	0.568	1.764	<0.001

[†]Patients with low socioeconomic status were covered by medical aid in Korea. Medical cost was covered by government for patients with medical aid.

Table 7. Multiple linear regression analysis of factors affecting used days

Variable	Unadjusted			Adjusted		
	β	exp (β)	p -value	β	exp (β)	p -value
Age (year)	0.012	1.012	<0.001	0.011	1.011	<0.001
Male gender	0.176	1.192	<0.001	0.120	1.127	<0.001
Overlap syndrome	0.456	1.578	<0.001	0.323	1.381	<0.001
Hospitalization in the last year	0.824	2.280	<0.001	0.579	1.785	<0.001
Medical aid*	0.437	1.548	<0.001	0.348	1.416	<0.001
Type of hospital use	0.598	1.818	<0.001	0.274	1.315	<0.001

*Patients with low socioeconomic status were covered by medical aid in Korea. Medical cost was covered by government for patients with medical aid.

Hardin et al. (3) also showed that patients with overlap syndrome demonstrated a poorer disease-related quality of life, were more likely to have had a severe COPD exacerbation in the past year, and were more likely to experience frequent exacerbations (odds ratio 3.55). They also showed, using chest CT scan data, that patients with overlap syndrome demonstrated greater gas-trapping. These findings are consistent with those of our current study. We show in our present analysis that patients with overlap syndrome use more medical services, take more medication, and have more hospitalizations. The calculated mean used days of medical services were also significantly higher in the overlap syndrome group than the COPD without asthma group. Bronchodilator medication including LAMA or ICS+LABA was also more frequently used in patients with overlap syndrome. Moreover, by multivariate analysis, we find that overlap syndrome is an independent factor for increasing medical cost and utilization.

In this study, the incidence of overlap syndrome was high (54.6% among COPD patients). Few previous studies have specifically investigated the incidence of this syndrome. The prevalence of overlap syndrome was determined to be 46% among COPD patients in the combined cohort of general pulmonary and asthma clinic patients (10). The prevalence of overlap was 43% in the previous study using Medicaid data (5). In an UPLIFT trial, nearly 66% of COPD patients improved their forced expiratory volume in 1 second (FEV₁) by more than 15% after receiving 80 µg ipratropium and 400 µg of salbutamol (11). More studies regarding on the exact incidence of overlap syndrome among COPD patients are needed.

The incidence of co-morbidity was significantly different between our two patient groups. This is the first study to show the difference in co-morbidity incidence between overlap syndrome and COPD without asthma. Increased co-morbidity was more frequently seen in the overlap syndrome group, suggesting that patients with overlap syndrome not only have more severe COPD disease but also other co-morbidity diseases. Accordingly, increased morbidity may have contributed to the greater utilization of the medical services and increased costs in these patients, compared with COPD patients without asthma.

We further find that the pattern of medication for COPD is different between the overlap syndrome and COPD without asthma groups. Overall, almost all medication was used more frequently in patients with overlap syndrome. Of these, ICS+LABA and LTRA were used much more frequently in overlap syndrome patients than those with COPD without asthma. This finding is of some interest as there has been no previous report on the pattern of medication for overlap syndrome compared to COPD without asthma. Both ICS+LABA and LTRA are well-known medications for asthma and it is therefore reasonable to expect that these medications will be used more frequently in patients with overlap syndrome.

Although LTRA is not primary choice for asthma in guideline, it can be added to inhaler. We guess that the reason of high percentage of LTRA (30.4%) in overlap group may be because of disease severity. Patients with overlap syndrome of asthma and COPD may have incomplete airway obstruction. From the point of view of asthma, not fully reversible airway obstruction means that asthma is not treated enough. Thus, adding LTRA can be considered for these patients. The explanation of high percentage of use of oral corticosteroid is also same. However, in spite of more frequent medication use, patients with overlap syndrome both visited the ER and were admitted more frequently. These results suggest that the severity of the disease is much greater in patients with overlap syndrome.

There may be some factors that could be driving up cost and utilization in the overlap group. In our study, the percentage of male is significantly higher in overlap group. Smoking is well known risk factor for poor outcome in COPD. Current smoker showed rapid decline of FEV₁ (12) and higher mortality (13). Although there is no data regarding smoking status in this study, smoking rate is much higher in men than woman in Korea (41.8% vs 5.5%, men vs women, age over 40) (14). Considering smoking factor, male gender can contribute to poor outcome in overlap group in this study. Low socioeconomic status is also known factor for poor outcome in COPD (15). In our study, the percentage of medical aid is also higher in overlap group. Thus, low socioeconomic status may have contributed higher medical cost and

utilization. However, in spite of this, multivariate analysis showed that overlap syndrome is still independent factor for increasing medical cost and utilization after adjusting other confounders. Further study regarding the factors increasing cost and utilization in patients with overlap syndrome is needed.

There are some limitations to our present study. First, there was no PFT data in this study. Thus, no patients considered to have COPD were definitely diagnosed through measurement of FEV₁/forced vital capacity (FVC) ratio. Furthermore, the diagnosis of overlap syndrome was not proven by PFT. Although the exact definition remains unclear, overlap syndrome can be recognized by the coexistence of increased variability of airflow (positive in provocation or bronchodilator response test) in a patient with incompletely reversible airway obstruction (post bronchodilator FEV₁/FVC < 0.7) (1,2). However, no data regarding bronchodilator response or provocation tests were available for our analyses. Second, there were no data on smoking history and environmental or occupational exposure. Thus, the cause of COPD is unknown in the patients enrolled in this study. Third, data regarding medication use in this study could be biased by the definition of COPD or asthma. We used both the ICD-10 codes and the medication prescribed for the definition of disease. Thus, the results pertaining to different medication use may come from the definition of the disease itself. However, most medications overlapped in the definition of COPD or asthma. Moreover, use of "at least one" particular medication was a criterion we used for disease definition. In fact, many patients enrolled in this study used many medications for both COPD or asthma. Thus, the bias by definition of disease by medication seems to be small. Fourth, enroll criteria for medication use may result in selection bias. Patients whose symptom was very mild may be missed in this study. However, this criterion can increase accuracy of diagnosis because use medication can exclude false positive patient. Patients who were diagnosed as COPD only by ICD code without history of medication may not be real COPD patients. Fifth, LAMA, which was not yet recommended in asthma guideline, was included in the medication criteria in asthma. However, previous studies (16–18) showed that LAMA can be effective in asthma treatment and physicians may have used LAMA in asthma treatment. Thus, including LAMA in asthma medication may be appropriate.

Conclusions

In conclusion, analysis of the NHI database in Korea shows that patients with overlap syndrome use medical services more frequently and thus place a higher cost burden on the health system than COPD patients without asthma. Further study on patients with overlap syndrome of COPD and asthma is needed. In order to obtain more precise and qualified data, study using

pulmonary function test or mass medical prescriptions surveillance is needed.

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Declaration of Interest Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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