International Journal of Chronic Obstructive Pulmonary Disease Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Relationship Between Changes in Inhalation Treatment Level and Exacerbation of Chronic Obstructive Pulmonary Disease: Nationwide the Health Insurance and Assessment Service Database

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

Yong Suk Jo[1,2]
Kwang Ha Yoo[3]
Yong Bum Park[1,2]
Chin Kook Rhee[4]
Ki Suck Jung[2,5]
Seung Hun Jang[2,5]
Ji Young Park[2,5]
Youlim Kim[2,6]
Bo Yeon Kim[7]
Sang In Ahn[7]
Yon U Jo[7]
Yong Il Hwang[2,5]

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea; [2]Lung Research Institute of Hallym University College of Medicine, Chuncheon, South Korea; [3]Department of Internal Medicine, Division of Pulmonary and Allergy Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea; [4]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [5]Department of Pulmonary, Allergy and Critical Care Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea; [6]Department of Pulmonary, Allergy and Critical Care Medicine, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon-Si, Gangwon-Do, Korea; [7]Health Insurance Review & Assessment Service, Wonju, Republic of Korea

Correspondence: Yong Il Hwang
Tel +82-31-380-3715
Fax +82-31-380-3973
Email hyicyk@hallym.or.kr

Background and Objective: Maintaining adequacy in chronic obstructive pulmonary disease (COPD) care is essential to sustain an adequate level of care. We aimed to assess the current status of COPD quality control and the influence of inhaler changes on disease-related health care utilization.

Methods: The Health Insurance Review and Assessment Service (HIRA) nationwide database for reimbursed insurance claims from all medical institutions in South Korea from May 2014 to April 2017 was investigated. COPD care quality was assessed by the performance rate of spirometry, the percentage of persistent visit patients and patients prescribed a bronchodilator. The number of severe exacerbations was evaluated.

Results: A total of 68,942 COPD patients were included for 3 years of longitudinal analyses. The overall spirometry enforcement rate was just over 50%, the percentage of regular follow-up patients was over 85%, and bronchodilators were prescribed to over 80% of the patients. COPD-related hospitalization or ER visit rates were 16.6%, 15.3%, and 17.8% for three consequent assessments, respectively. Inhaler changes were analyzed between the first and second assessments: 57.1% were maintained, 0.4% were changed to another class, 9% were escalated, and 5.2% were de-escalated. Only in the escalated group, especially those who changed from the mono to dual inhaler and dual to triple inhaler, had fewer hospitalizations or ER visits.

Conclusion: Adequacy of COPD care status was not that high considering the low-enforcement rate of spirometry, but most patients were prescribed a bronchodilator and regularly followed up. Those who escalated inhaler treatment experienced less health care utilization.

Keywords: COPD, population-based, quality assessment, inhaler, health care utilization

Background

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of death worldwide, with a prevalence of 5.6% in 2015, and this is expected to increase further to 7.8% by 2030.[1] The worldwide prevalence of COPD has been estimated to be 7.5–10%.[2] In South Korea, COPD occurs in 13.6% and 30.5% of adults aged over 40 and 65 years, respectively.[3] These rates exceed the worldwide prevalence.

COPD is not only a chronic inflammatory airway disease characterized by fixed airflow limitation and chronic respiratory symptoms, such as cough, sputum, and progressive dyspnea, but it is also regarded as a systemic problem accompanied by

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/COPD.S248616

multiple comorbidities.[4] Disease severity and the presence of frequent exacerbation and accompanied comorbidities may all contribute to adverse clinical outcomes and determine the economic and social costs of COPD.[5] As the number of COPD patients has increased in Korea, the cost of COPD-related medication per person has also increased, from $138.4 in 2008 to $216.6 in 2013, a 56.5% increase over 6 years.[6]

COPD is a chronic disease and ambulatory care–sensitive condition. Treatment of patients with COPD is mainly based on inhaled LABA or LAMA either alone or in combination, ICS/LABA, and ICS/LABA/LAMA combination.[7,8] Considerable health care utilization due to exacerbation can be avoidable, and medical expenses can be saved by high-quality care. To achieve this goal, it is important to sustain adequate level of quality in assessment and treatment. However, the Organization for Economic Cooperation and Development (OECD) reported that COPD-related hospitalization occurred in 214.2 patients per 100,000 in South Korea, which is higher than the OECD average of 189.8 patients per 100,000.[9]

There have been lack of nationwide studies regarding the quality of COPD care assessment and even less related longitudinal studies. South Korea implemented a unique, compulsory health insurance system called National Health Insurance (NHI) in 1998 that covers 97% of the population in South Korea, the remaining 3% of which is covered by the Medical Aid Program.[10] All health care institutions in South Korea claim medical expenses through the Health Insurance Review and Assessment Service (HIRA). This agency evaluates the adequacy of claimed medical expenses and approves insurance reimbursements from the NHI service. The HIRA collects clinical information of patients provided by physicians for insurance claims, and so almost all patients diagnosed with COPD in the nation can be identified in the HIRA database. The HIRA database complies with patient data privacy regulations. Furthermore, a COPD quality assessment program was launched in 2014 to identify the current status of and improve COPD care.

In this study, we analyzed the HIRA database to assess adequacy of COPD care status, and the association between changes in inhaler and health care utilization, including hospitalization and emergency room (ER) visits, representing an exacerbation of COPD in South Korea.

Methods

Data Source and Subjects

The first COPD quality assessment program in South Korea was from May 2014 to April 2015, and the evaluation has been conducted every year during the same period. We analyzed all medical information and the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) provided by the HIRA database. Medical institutions that did not treat any COPD patients during the 3-year analysis period were excluded. Inclusion criteria were: (1) age >40 years; (2) ICD-10 code for COPD (J43 or J44) as the primary or first secondary diagnosis; (3) use of COPD medication prescribed by an outpatient clinic more than twice per year; (4) or history of admission with taking systemic steroid and at least once of prescription of COPD medication in an outpatient clinic; (5) patients whose 3 years of COPD quality assessment data were all confirmed.

The study was exempted from the informed consent requirement because of its retrospective nature and anonymity of patient personal information, and was approved by the Institutional Review Board of the Kangdong Sacred Heart Hospital (approval number KANGDONG 2019–07-014).

Assessment of COPD Care Quality

Evaluation of COPD management adequacy consists of an evaluation index and a monitoring index. The evaluation index is composed of the performance rate of spirometry at least once, the percentage of persistent visit patients, defined as patients who visited the same medical institution more than three times, and the percentage of patients prescribed bronchodilator during the assessment period. The monitoring index includes the rate of hospital admission or ER visits due to COPD, which is regarded as an exacerbation event. We also examined changes in the prescription of COPD medication depending on each assessment and considering the time lag between the effects of treatment change and its influence on the clinical outcome. In addition, we analyzed the association of the exacerbation events at the third assessment with the change in medication between the first and second phases.

Statistical Analysis

We calculated the performance rate for spirometry, the percentage of persistent visit patients, the prescription rate for COPD medication, and the rate of hospital admission and ER visit. We also analyzed the number of hospital admissions and ER visits according to the category of inhaler treatment

for COPD. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

In the first year of the COPD quality assessment program, a total of 68,942 patients were included. Table 1 shows the demographics and COPD medication profiles of the patients. Males were the predominant sex (55,145 subjects, 80%), and the majority (86.5%) of the patients were aged over 60 years. In the primary assessment, COPD medication prescriptions were mostly for long-acting muscarinic receptor antagonist (LAMA) monotherapy (26.6%), followed by a combination of inhaled corticosteroid (ICS), long-acting β2 adrenergic receptor agonist, and LAMA (24.5%), and a combination of ICS and LABA (20.1%). At the second and third assessments, triple combination of ICS/LABA/LAMA was prescribed more than LAMA monotherapy (24.6% vs 22.6% and 22.7% vs 17.8%, respectively) Although prescription of LABA/LAMA gradually increased for more than four times through three assessments (4% at the first to 17.1% at third assessment), it was lower in all three assessments compared to ICS/LABA/LAMA (Figure 1).

Adequacy of COPD Care

The overall spirometry enforcement rate was 53.6%, 52.4%, and 53.9%, and the proportion of regular follow-up patients was 87.8%, 89.8%, and 85.4%, respectively, in each of three assessments. Bronchodilator inhalers were prescribed in 87.0%, 86.4%, and 80.9% of the patients, from the first to third evaluation (p for trend <0.001).

COPD-related hospital admission occurred in 11,099 (16.1%), 10,449 (15.2%), and 12,169 (17.6%) of patients, and ER visits occurred in 5585 (8.1%), 3319 (4.8%), and 6891 (10%) of patients, sequentially, until the third assessment. Hospitalization and ER visits together accounted for 11,393 (16.6%), 10,607 (15.3%), and 12,287 (17.8%) of patients from the first to third assessment. Regarding the COPD drug used, triple inhaler use corresponded to the most frequent hospitalization or ER visit (Figure 2).

Table 1 Baseline Characteristics of Primary Assessment of COPD Quality of Care

	Features	Number	%
Gender	Male	55,145	80.0
	Female	13,798	20.0
Age group	40–49 years	1422	2.1
	50–59 years	7866	11.4
	60–69 years	19,868	28.8
	70–79 years	28,335	41.1
	80–89 years	10,768	15.6
	≥90 years	684	1.0
Medication	LABA	8621	12.5
	LAMA	42,391	61.5
	Methylxanthine	44,313	64.3
	ICS	37,811	54.8
	PDE4 inhibitor	2822	4.1
Total		68,943	100

Abbreviations: ICS, inhaled corticosteroid; LABA, long acting beta$_2$ receptor agonist; LAMA, long acting muscarinic receptor agonist; PDE4, phosphodiesterase 4.

Inhaler Medication Changes and Health Care Utilization

Changes in inhaler medication between the first and second assessments are presented in Figure 3. A total of 39,330 (57.1%) patients maintained the same level of inhalation treatment (eg, from LAMA to LAMA), 280 (0.4%) changed to another combination of inhalation drug but were neither escalated nor de-escalated (eg, from LABA to LAMA and from ICS/LABA to LABA/LAMA), 6172 (9%) were escalated (eg, from LAMA to LABA/LAMA, ICS/LABA, or ICS/LABA/LAMA), and 3545 (5.2%) were de-escalated (eg, from ICS/LABA/LAMA to LABA/LAMA, ICS/LAMA, or LAMA).

Health care utilization by the status of change in inhaler treatment is presented in Figure 4. When comparing between the patients who maintained the same level of inhaler treatment versus those who changed to another class, the rate of COPD-related hospital admission or ER visit was 5716 (14.5%) versus 25 (8.9%) at second assessment, and 7037 (17.9%) versus 35 (12.5%) at third assessment, respectively. COPD-related hospital admission or ER visit for those who were prescribed escalated inhaler treatment versus de-escalated inhaler treatment occurred in 1332 (21.6%) versus 507 (14.3%) patients at second assessment, and 1183 (19.2%) versus 658 (18.6%) at third assessment, respectively. Hospitalization or ER visits according to the details of the inhaler change can be seen in Figure 5. Health care-related use decreased for patients in the escalation group who changed from the mono inhaler (LAMA or LABA) to dual inhaler (LABA/LAMA or ICS/LABA), and from the dual to triple inhaler (ICS/LABA/LAMA), but increased in those escalated from mono bronchodilator to triple inhaler. All patients in the

de-escalation group encountered increased hospitalization or ER visit.

In detail, among the escalation group, those patients who changed from LABA or LAMA to ICS/LABA or triple inhaler, from ICS/LABA to triple inhaler, and from LABA/LAMA to triple inhaler resulted in a decrement of exacerbation but those who switched from LABA or LAMA to LABA/LAMA were associated with an increased exacerbation risk. In comparison, all patients in the de-escalation group showed increased exacerbation, except for those who changed from ICS/LABA to LAMA, for whom the exacerbation risk remained similar before and after the change.

Discussion

We reported the nationwide COPD quality assessment data over 3 years in South Korea. Our sample included 68,942 patients. Over 80% of patients were prescribed bronchodilator-containing inhalers, but only slightly above 50% of the patients were evaluated by spirometry during the 3-year evaluation. Between the first and second assessments, 57.1% of patients were maintained on the same class of inhaler, 0.4% changed to another class of inhaler but were neither escalated nor de-escalated, 9% were escalated, and 5.2% were de-escalated. Patients who were maintained, changed, and de-escalated of inhalers experienced more hospitalization or ER visit at third assessment than the two prior assessments. Only the escalation group experienced less hospitalization or ER visit between the first to third assessments.

Although the proportion of bronchodilator prescribed in all patients included in the third assessment increased 76.9%, from 67.9% in the first and 71.2% in the second assessment, respectively, it was lower compared with the prescription rate, which exceeded 80% throughout the three consecutive rounds in this study. We selected only patients whose quality of care data for COPD for 3 years were available, and overt, more severe COPD patients who need to visit hospital regularly might be over-represented in our study. However, the spirometry enforcement rate was as low as 50%. Spirometry-derived fixed airflow limitation is critical for diagnosing COPD and, also for monitoring, follow-up of treatment response, and detection of rapid lung function decline. Nationwide COPD quality care assessments are conducted in all medical institutions where medical expenses for COPD patients are claimed. While 80% of the health care facilities that claimed medical expenses for COPD patients were primary care institutions, which may not be equipped with proper spirometry or other diagnostic modalities, the number of patients was about one-third of the total. Considering the inhaler prescription rate decreased through 3 consecutive years, and the enforcement rate of spirometry was only about 50%, it suggests that proper treatment for COPD is not achieved in South Korea.

Patients whose inhaler was maintained, changed to another class, or de-escalated between the first and second assessments experienced more exacerbation, but exacerbation were alleviated in the escalation group. A more detailed analysis of the change in inhaler showed that patients who

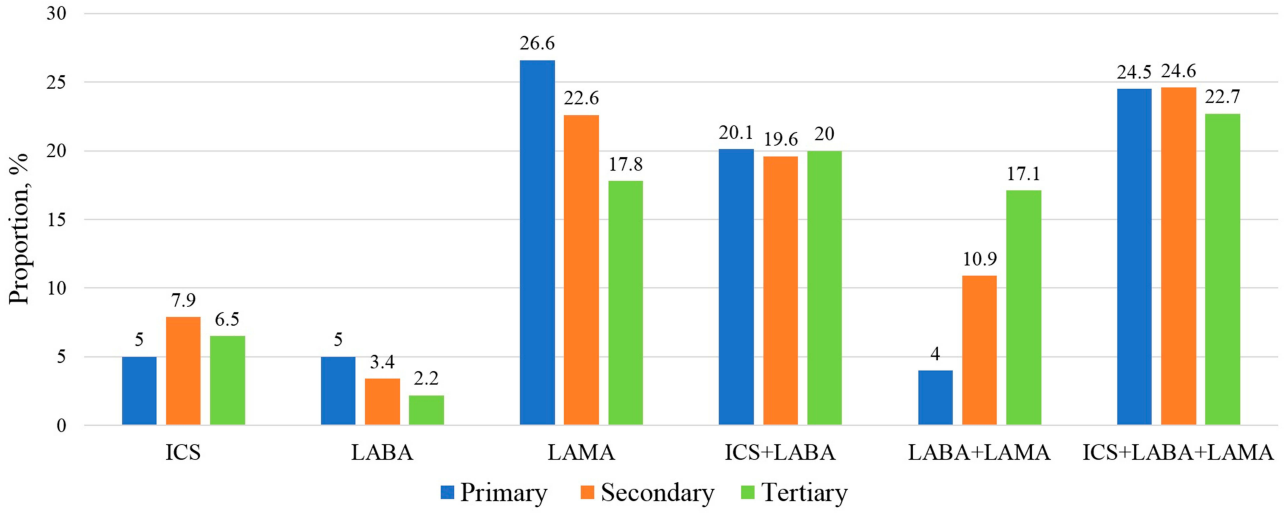

Figure 1 Proportion of COPD medication in each assessment.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β2 receptor agonist; LAMA, long-acting muscarinic receptor agonist.

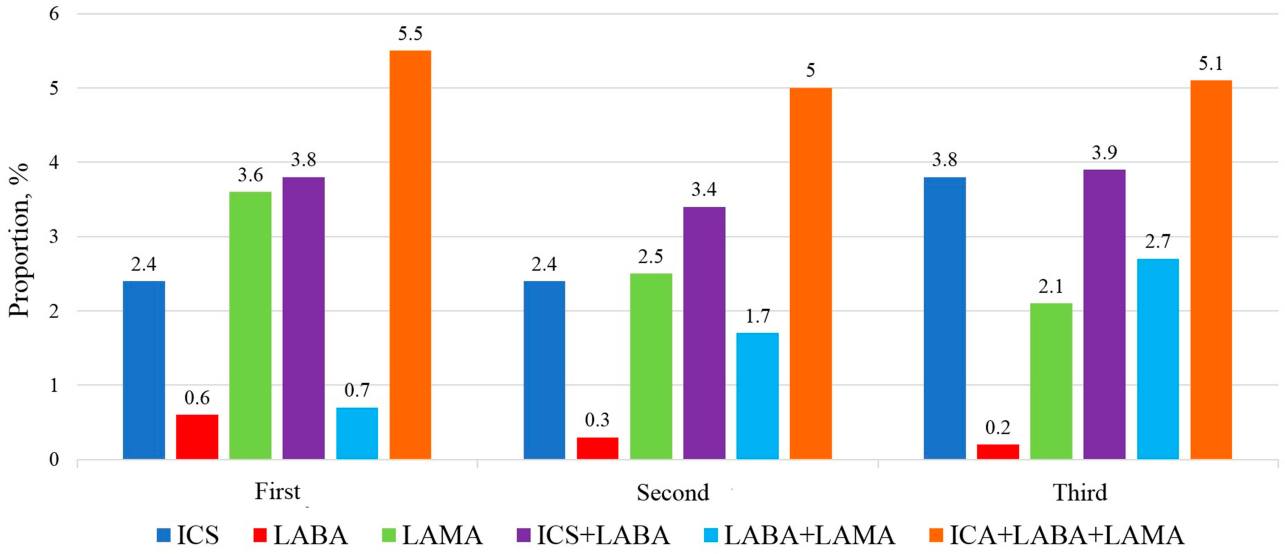

Figure 2 Hospital admission and emergency room visit according to inhaler use for each three assessments.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β2 receptor agonist; LAMA, long-acting muscarinic receptor agonist.

First	Second	N	%
LABA	LABA	1356	2.0
	LAMA	34	0.0
	ICS+LABA	133	0.2
	LABA+LAMA	691	1.0
	ICS+LABA+LAMA	146	0.2
LAMA	LABA	41	0.1
	LAMA	9593	13.9
	ICS+LABA	126	0.2
	LABA+LAMA	1778	2.6
	ICS+LABA+LAMA	1436	2.1
ICS+LABA	LABA	119	0.2
	LAMA	107	0.2
	ICS+LABA	7581	11.0
	LABA+LAMA	170	0.2
	ICS+LABA+LAMA	1438	2.1
LABA+LAMA	LABA	182	0.3
	LAMA	215	0.3
	ICS+LABA	35	0.1
	LABA+LAMA	2050	3.0
	ICS+LABA+LAMA	424	0.6
ICS+LABA+LAMA	LABA	55	0.1
	LAMA	913	1.3
	ICS+LABA	1109	1.6
	LABA+LAMA	845	1.2
	ICS+LABA+LAMA	18750	27.2

Figure 3 Changes of inhaler treatment between first and second assessment.

switched from the mono to dual inhaler and dual to triple inhaler exhibited little exacerbation. Unusually, patients who switched from mono bronchodilator to triple inhaler had greater exacerbation compared with the previous assessment. This trend might be explained by the underestimation of patients who need ICS but did not use ICS initially, and this

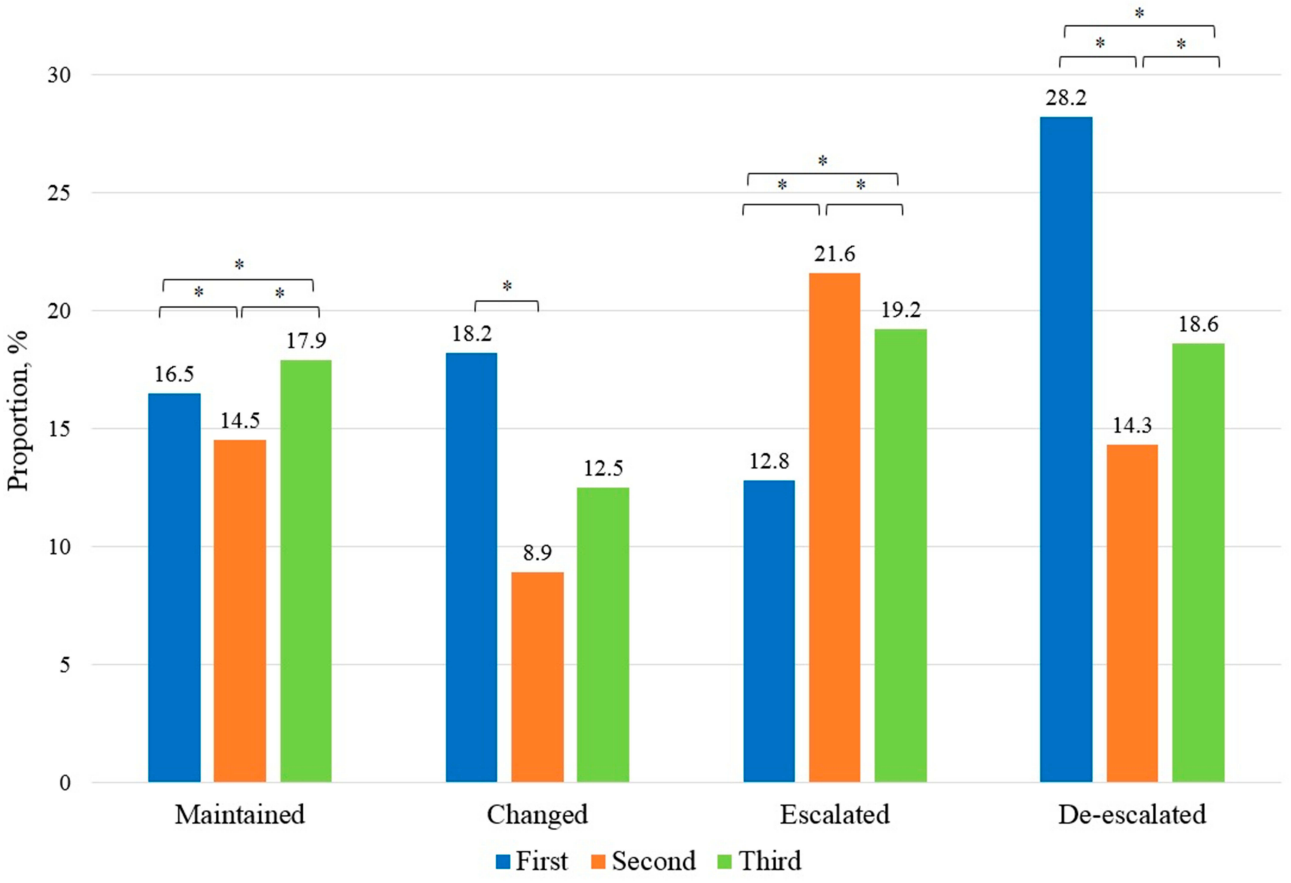

Figure 4 COPD-related hospitalization or ER visit according to changes in inhaler treatment between first and second assessments. *, <0.001.

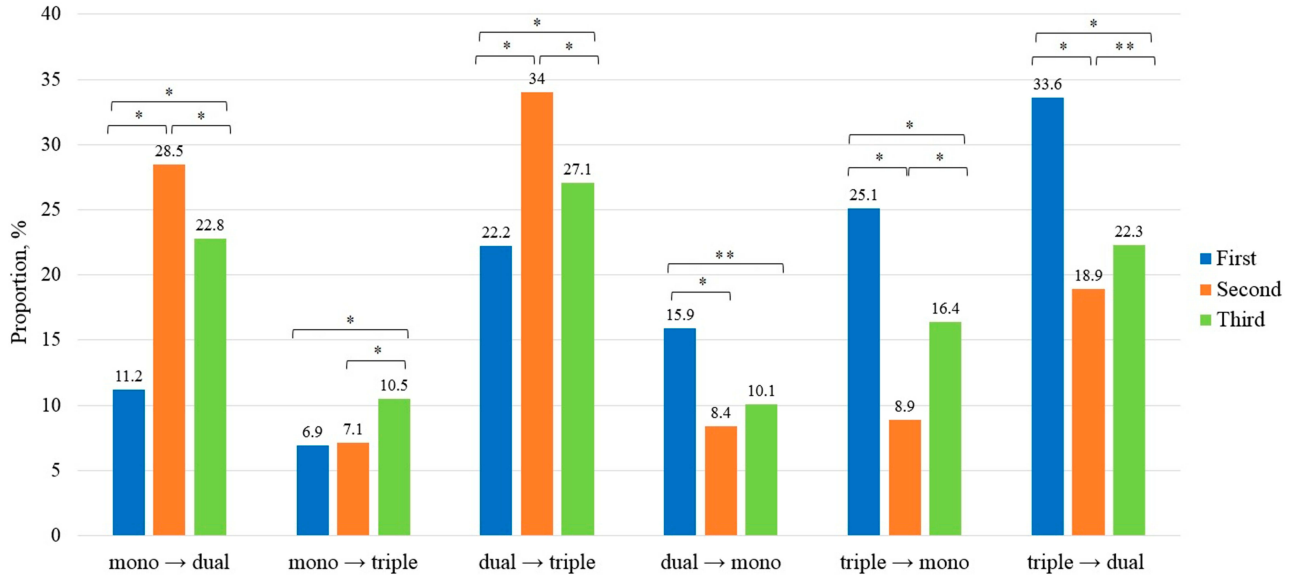

Figure 5 Hospitalization or ER visit focused on escalation and de-escalation group. Mono includes LAMA or LABA; dual includes ICS/LABA or LABA/LAMA; triple denotes ICS/LABA/LAMA. *, <0.001; **, <0.01.

led to more exacerbation, or it might have been escalated improperly. That is, it is possible that the triple inhaler was prescribed to patients who may not be sensitive to ICS. Currently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend ICS treatment for patients with a blood eosinophil count ≥300 cells/μL or history of asthma as initial pharmacological treatment as well as add-on during maintenance treatment.[11] This is in line with the flow of the importance of phenotype-based pharmacotherapy in COPD, especially with regard to the use of ICS.[12] The Korean clinical practice guideline for COPD classify patients into three groups (Group Ga, Na and Da) according to FEV_1, severity of respiratory symptom and exacerbation history. ICS/LABA recommended as initial inhaler regimen to group Da patients who considered as asthma overlap or have elevated blood eosinophil.[13] However, discrepancies between guidelines suggested best practice and real clinical field always exist. Data on COPD primary care in Switzerland reported inadequate overuse of ICS in mild to moderate COPD.[14] This situation represents a major quality control problem in patients with COPD.

We assessed inhaler changes between 2014 and 2015 and analyzed its impact on exacerbation in 2016. Patients who adequately escalated from the mono to dual inhaler or dual to triple inhaler led to decreased exacerbation. However, the escalation from the mono to triple inhaler was rather associated with increased exacerbation. It is difficult to interpret this, but there are possible explanations for this result. Lack of biomarkers for stratification of COPD patients who might be benefitted by ICS and difficulty on identification of asthma-COPD overlap would be contributed. That is, the increased exacerbation on escalation group from the mono to triple inhaler could be because ICS was applied to patients who do not need ICS.

For the de-escalation group, patients who experienced less exacerbation in 2015 compared with the previous year were prescribed a de-escalated inhaler, and this led to increased exacerbation in 2016. Except for those who changed from ICS/LABA to LAMA, for whom the exacerbation took place similarly before and after the change which is in line with a randomized, controlled trial, which the proportion of patients experienced exacerbation in the LAMA group did not differ from that in the LAMA plus ICS/LABA (62.8% vs 60%).[15] In the case of de-escalation from the dual to mono inhaler, exacerbation slightly increased compared to the previous year, but may not have a clinical significance because this exacerbation rate was similar to that of the mono inhaler users in the escalation group in 2014.

Interestingly, patients escalated from LABA or LAMA to LABA/LAMA experienced more exacerbation, but de-escalation from LABA/LAMA to LABA or LAMA increased exacerbation paradoxically. This observation contrasts with the fact that LABA/LAMA is known to reduce exacerbation risk compared with LAMA alone.[16,17] Misclassifying patients who need ICS for escalation but are changed to LABA/LAMA may be the one of possible explanation of these findings.

To date, there has been a lack of nationwide data on the adequacy of COPD management and little research on the relevance of health care utilization for drug changes. In this context, our study is meaningful in that it is one of the few studies performed in a Korean population to assess the status of COPD quality of care and influence of inhaler changes on disease-related health care utilization. However, this study has several limitations. First, this is an observational retrospective study, and the HIRA database does not include any information on the COPD control status, severity of dyspnea, and spirometry result on each patient. Second, several biases in counting health care utilization may be present because we used the ICD-10 code as the primary or first secondary diagnosis at each hospitalization or ER visit. Third, considering the relatively low proportion of patients undergoing spirometry, the COPD diagnosis itself may be questionable. However, several studies have used the identical COPD definition to that used here, and so the potential for diagnosis inaccuracy might not be that problematic.[18–20] Lastly, although we included patients whose 3 years of COPD case quality assessment data were available, the lack of data consistency through the three time points may not reflect sufficiently personalized diagnostic and therapeutic approach to COPD.

Conclusion

We analyzed the South Korean national insurance claim database for 3 years, which includes almost all patients (~97%) in the nation. Analysis of these nationwide data revealed the current status of COPD care and the relationship between changes in inhaler treatment and health care utilization representing exacerbation. Adequately escalated inhaler treatment could reduce further exacerbation, and caution should be taken when de-escalating treatment. To improve and achieve an appropriate quality of care in patients with COPD, integrated management, including education of the disease, rehabilitation, and an action

plan for exacerbation signs, will be needed, and institutional and economic support is required.

Abbreviations

COPD, chronic obstructive pulmonary disease; ER, emergency room; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HIRA, Health Insurance Review and Assessment Service; ICS, inhaled corticosteroid; LABA, long-acting β2 receptor agonist; LAMA, long-acting muscarinic receptor agonist; NHI, National Health Insurance.

Ethical Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of the Kangdong Sacred Heart Hospital (approval number KANGDONG 2019-07-014).

Acknowledgment

This study was supported by the Joint Project on Quality Assessment Research on the Health Insurance Review and Assessment Service.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

References

1. Mathers CD, Loncar D, Samet J. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442. doi:10.1371/journal.pmed.0030442
2. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J*. 2006;28(3):523–532. doi:10.1183/09031936.06.00124605
3. Korean Statistical Information Service (KOSIS). 2016. Available from: http://kosis.kr/eng/. Accessed August 1, 2019.
4. Cavailles A, Brinchault-Rabin G, Dixmier A, et al. Comorbidities of COPD. *Eur Respir Rev*. 2013;22(130):454–475. doi:10.1183/09059180.00008612
5. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet*. 2007;370(9589):765–773. doi:10.1016/S0140-6736(07)61380-4
6. Lee J, Lee JH, Kim JA, Rhee CK. Trend of cost and utilization of COPD medication in Korea. *Int J Chron Obstruct Pulmon Dis*. 2017;12:27–33. doi:10.2147/COPD.S121687
7. Fuso L, Mores N, Valente S, Malerba M, Montuschi P. Long-acting beta-agonists and their association with inhaled corticosteroids in COPD. *Curr Med Chem*. 2013;20(12):1477–1495. doi:10.2174/0929867311320120003
8. Montuschi P, Macagno F, Valente S, Fuso L. Inhaled muscarinic acetylcholine receptor antagonists for treatment of COPD. *Curr Med Chem*. 2013;20(12):1464–1476. doi:10.2174/0929867311320120002
9. OECD. Health statistics; 2017. Available from: http://www.oecd.org/els/health-systems/health-data.htm/. Accessed July 20, 2019.
10. Kim DS. Introduction: health of the health care system in Korea. *Soc Work Public Health*. 2010;25(2):127–141. doi:10.1080/19371910903070333
11. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2019. Available from: http://www.goldcopd.org/. Accessed Feb 15, 2019.
12. Montuschi P, Malerba M, Macis G, Mores N, Santini G. Triple inhaled therapy for chronic obstructive pulmonary disease. *Drug Discov Today*. 2016;21(11):1820–1827. doi:10.1016/j.drudis.2016.07.009
13. Park YB, Rhee CK, Yoon HK, et al. Revised (2018) COPD clinical practice guideline of the Korean Academy of Tuberculosis and Respiratory Disease: a summary. *Tuberc Respir Dis (Seoul)*. 2018;81(4):261–273. doi:10.4046/trd.2018.0029
14. Steurer-Stey C, Dallalana K, Jungi M, Rosemann T. Management of chronic obstructive pulmonary disease in Swiss primary care: room for improvement. *Qual Prim Care*. 2012;20(5):365–373.
15. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone–salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2007;146(8):545–555. doi:10.7326/0003-4819-146-8-200704170-00152
16. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med*. 2013;1(3):199–209. doi:10.1016/S2213-2600(13)70052-3
17. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6(5):337–344. doi:10.1016/S2213-2600(18)30102-4
18. Kim J, Rhee CK, Yoo KH, et al. The health care burden of high grade chronic obstructive pulmonary disease in Korea: analysis of the Korean health insurance review and assessment service data. *Int J Chron Obstruct Pulmon Dis*. 2013;8:561–568. doi:10.2147/COPD.S48577
19. Kim J, Kim K, Kim Y, et al. The association between inhaled long-acting bronchodilators and less in-hospital care in newly-diagnosed COPD patients. *Respir Med*. 2014;108(1):153–161. doi:10.1016/j.rmed.2013.08.003
20. Rhee CK, Yoon HK, Yoo KH, et al. Medical utilization and cost in patients with overlap syndrome of chronic obstructive pulmonary disease and asthma. *Copd*. 2014;11(2):163–170. doi:10.3109/15412555.2013.831061