보건학 석사 학위논문

Evaluating quality measure of asthma treatment by HIRA with nation-wide retrospective cohort data

천식 중증도를 고려한 천식 적정성 평가 결과의 적절성 분석

2019년 2월

서울대학교 보건대학원

보건학과 보건학전공

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이 논문을 보건학 석사 학위논문으로 제출함

2018년 11월

서울대학교 대학원
보건학과 보건학전공
김 남 은

김남은의 석사 학위논문을 인준함

2018년 12월

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Abstract

Evaluating quality measure of asthma treatment by HIRA with nation-wide retrospective cohort data

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Background

The prevalence of asthma in Korea has increased, and the mortality recently got a sudden increase. However, proportion of avoidable asthma exacerbation is much higher than other OECD countries. So, in order to increase the performance and quality of asthma management by each medical institution in the country, national evaluation was made through HIRA. In this thesis, the main goal is to determine whether the asthma exacerbation would change the following year according to the evaluation results, with asthma severity considered.

Methods

With national health insurance claims data from 2013 to 2017, 83,375 patients with asthma diagnoses in ICD-10 codes (J45, J46) who passed all the exclusion criteria were identified. We used k-means clustering to identify patients according to the monthly amount of prescribed asthma medication, and finally classified patients into 4 groups. Generalized estimating equation (GEE) was used to analyze the associations of evaluation results with asthma exacerbation.

Results

The exacerbation rate in mild and severe patients were 16.4%, and 56% respectively ($P < .0001$). With multiple GEE from whole-patient model, odds ratio of asthma exacerbation was lower for patients who visited 'not good' medical institution (0.86, <.0001). However, according to the result of final subgroup analysis, it was confirmed that the risk of exacerbation of asthma patients was lowered in the institutions with evaluation 'good'. Meanwhile, asthma severity was the most important factor to exacerbation as comparing with the tertiary hospital patients.

Conclusion

Asthma patients were well classified into four different groups according to the annual pattern of the asthma medication prescription obtained from the health insurance claims database. Different treatment modalities are needed for each severity, and it is necessary to supplement the current asthma management evaluation criteria to include severity as the effect of evaluation results varies depending on the severity.

keywords : asthma, asthma exacerbation, asthma severity, evaluation, health insurance claims, HIRA, Korea

***Student Number* : 2017-26514**

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INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, and the most common known risk factors to date are allergens or irritants, weather changes and respiratory infections such as colds[1]. In Korea, the prevalence of asthma is steadily increasing from 2002 to 2013, and the prevalence rate of women was consistently higher than that of men[2]. Because asthma is a prevalent disease in developed countries, prevalence and socioeconomic burden are increasing rapidly and it is expected to continue in the future as Korea develops[3].

Asthma exacerbations can be defined in some ways, usually characterized by a steady increase in symptoms of asthma and a steady decline in lung function[1]. Asthma is a typical ambulatory care sensitive condition(ACSC) disease that can prevent worsening of disease when the outpatient treatment is effective, but the avoidable hospital admission rate in Korea is more than twice as high as the OECD average[4]. There are several risk factors for asthma exacerbation so far. First, race, socioeconomic status, genetics, smoking, air pollution, allergen, obesity, and psychological stress are indicated as a factor of exacerbation of pediatric asthma defined as medication and asthma-related hospitalization. Next, some researchers insisted factors like asthma severity, history of any hospital admission in the previous year, and the use of a combination of inhaled corticosteroid(ICS) are associated with the increase of hospital readmissions due to asthma[5]. When asthma exacerbation was defined as Hospitalization, emergency department visit, and corticosteroid(CS) burst, factors including age, sex, comorbidity, medication possession ratio were significantly associated with exacerbation. However the association was different in each severity group[6].

The Health Insurance Review and Assessment Service(HIRA), which manages health insurance and medical aid claims accounting for 96.6% of the South Korean population[7], has been in the process of optimizing the asthma medical allowance since 2013. The results of asthma management evaluation of primary medical institutions have been disclosed

officially as the result of this project. Therefore, it is possible to see whether the evaluation results would lead to less asthma exacerbation in the following year, that is, whether evaluation is being carried out properly.

However, as the degree of exacerbation varies depending on the severity, severity is also a factor that should be considered when we assess the effect of asthma management evaluation. Therefore, in considering the factors affecting asthma exacerbation, it is important to accurately reflect the effects of risk factors by properly defining and taking into account the asthma severity of the patient in the model. However, there were two problems in the previous study. First, the severity of asthma did not reflect the pattern of asthma severity in each patient because severity was calculated too simple as just average value of rank. Secondly, the magnitude of the effect of severity on exacerbations was almost unknown.

Therefore, this study aims to confirm that the asthma management evaluation results were conducted in accordance with good criteria and that the organization was reasonably classified, taking into account the severity of the asthma that was systematically and statistically classified with data provided by HIRA. Finally, the purpose of this study is to scientifically verify whether the evaluating system with quality measure of asthma treatment by HIRA actually contributes to reducing the asthma exacerbation, by improving the quality of asthma patient management.

METHODS

Data description

This study used claims data from the HIRA. This data is remotely accessible under strict guarantee of secrecy and includes data regarding the demographic information, diagnostic codes(ICD-10), prescribed and dispensed medications, and other information on medical care.

Study subjects

The HIRA has conducted asthma management adequacy evaluation for the first time from 2013, and selected and announced the appropriate institutions. The aim of this evaluation was to improve the quality of asthma management in Korea and to reduce the incidence of severe asthma. According to the report of the HIRA in 2017, since the evaluation started, various indicators of asthma management according to guidelines are increasing[8]. Therefore, because there may exist changes in medical behavior in domestic medical institutions according to the examination, the data were classified by examination order, the 1st to 3rd.

HIRA database of 5,550,035 patients who were 15 years old or older and received asthma diagnosis (J45, J46) as primary or secondary code at least once from July 1, 2013 to June 30, 2017. 4,209,588 patients for the first evaluation period (2013.07 ~ 2014.06), 4,204,360 for the second evaluation period (2014.07 ~ 2015.06), and 4,151,057 for the third evaluation period and 5,288,586 patients were present in the fourth evaluation period (2016.07 ~ 2017.06) in details. The patients may exist in duplicate for each order. We evaluated each risk factor during the first and third premeasurement period, to assess the association between these risk factors and asthma exacerbations one year later during measurement period.

Of these, 32,472, 32,203, 29,579 for each period, and totally 83,375 asthma patients were found who met all of the following criteria: (1) more than two times of outpatient clinic visits using asthma medication, or at least one hospitalization using oral/intravenous corticosteroid

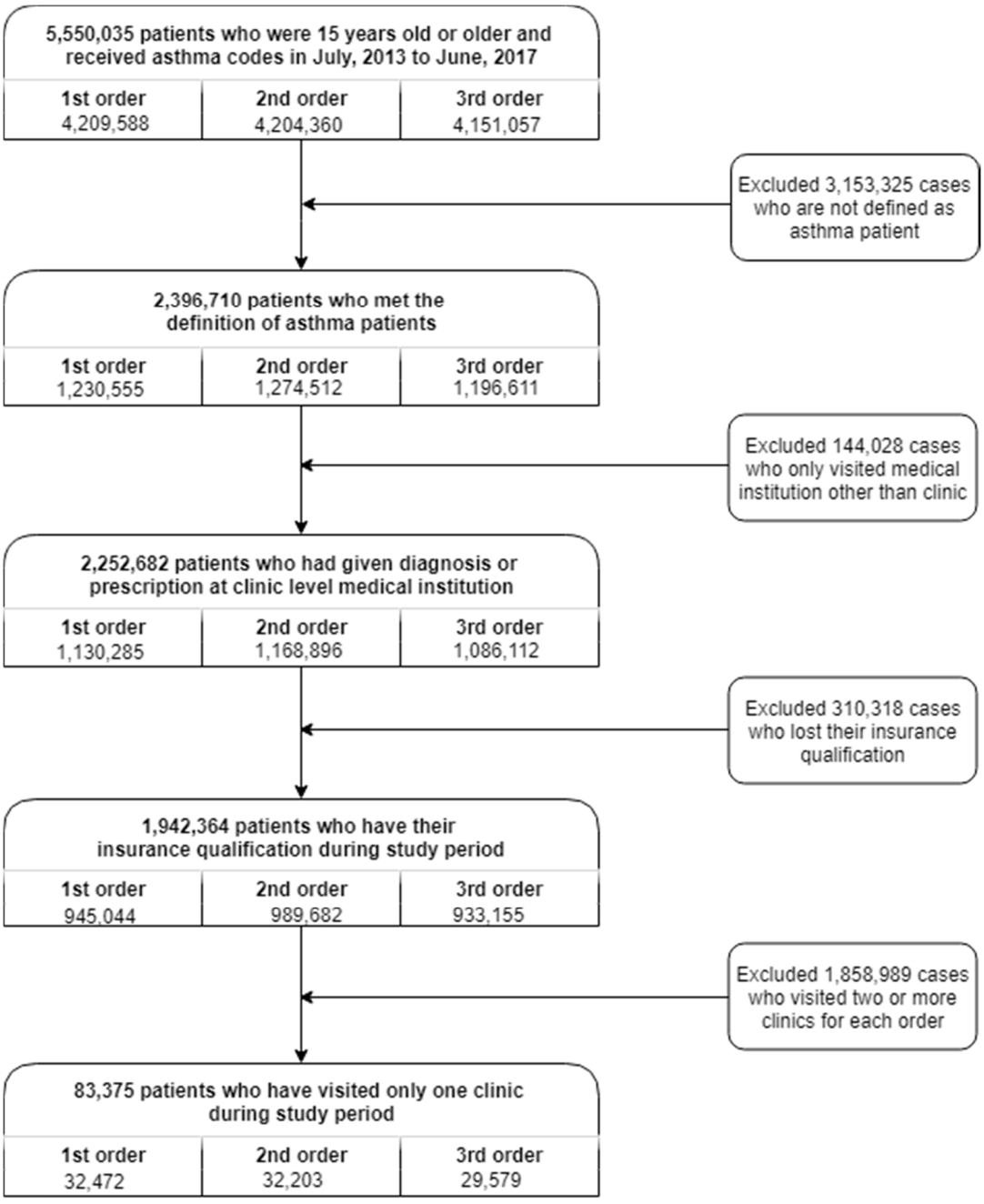
and outpatient clinic visit using asthma medication. The list of asthma medication was obtained from Global Initiative for Asthma Guidelines (Table 1)[9] (2) being diagnosed by a medical clinic (3) not having lost health insurance qualification (4) having visited only one medical clinic in one order as the evaluation is done only at primary medical institutions. (Figure 1)

Table 1: Rank of asthma medication according to the GINA guideline

Component	Type	Rank	Prescription period	Exacerbation
LTRA				
Montelukast	Oral	1	1	0
Pranlukast	Oral	1	1	0
Zafirlukast	Oral	1	1	0
Xanthine				
Aminophylline	Oral	1	1	0
Aminophylline	intravenous	1	1	0
Theophylline	Oral	1	1	0
Bamiphylline	Oral	1	1	0
Diethylaminoethyltheophylline	Oral	1	1	0
Oxtriphylline	Oral	1	1	0
doxofylline	Oral	1	1	0
LABA				
Bambuterol	Oral	1	1	0
Clenbuterol	Oral	1	1	0
Formoterol	Oral	1	1	0
Tulobuterol	patch	1	1	0

ICS				
Low-dose ICS				
Budesonide	Inhaler	1	30	0
Ciclesonide	Inhaler	1	30	0
beclomethasone	Inhaler	1	1	0
Fluticasone propionate	Inhaler	1	30	0
Medium- to high-dose ICS				
Budesonide	Inhaler	2	30	0
Fluticasone propionate	Inhaler	2	30	0
ICS/LABA				
Formoterol	Inhaler	2	30	0
Fluticasone & Vilanterol	inhaler	2	30	0
Systemic corticosteroid				
Betamethasone < 2.4mg		4	1	1
Deflazacort < 30mg		4	1	1
Dexamethasone < 3mg		4	1	1
Hydrocortisone < 80mg		4	1	1
Methylprednisolone < 16mg		4	1	1
Prednisolone < 20mg		4	1	1

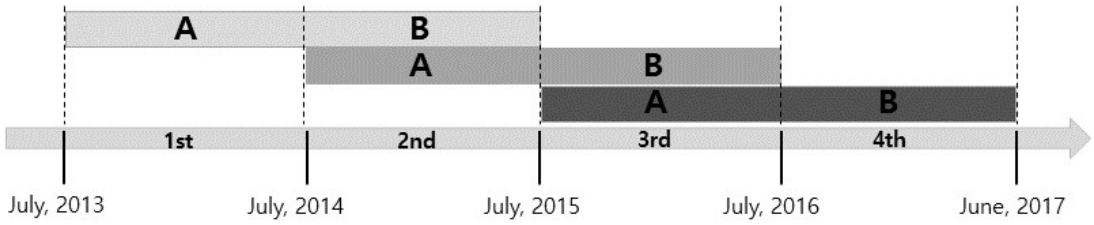
Figure 1: Flow chart of the study cohort



Study design

We conducted a retrospective cohort study to identify the risk factors of asthma exacerbation using HIRA database. We have evaluation data from the 1st to the 4th. The first year is defined as premeasurement period(A), the next year is defined as measurement period(B), and again A and B are defined through the whole period (Figure2). Risk factors including evaluation result and asthma severity for the study subjects are measured during the premeasurement period, and asthma exacerbation is measured during the measurement period. In other words, we wanted to check whether there was less asthma exacerbation in the next year(B) if the evaluation result was good(A).

Figure 2: Study design diagram



Definitions

Asthma exacerbation

Asthma exacerbation during the measurement period is the outcome. As in previous observational studies [10], systemic CS bursts for asthma is regarded as outcome in this study (i.e., more than 80mg of hydrocortisone or any other corticosteroids with each potency or SABA nebulizer treatment under J45, J46)

Evaluation of asthma medical care

Evaluation results of asthma medical care of each primary medical institutions are published with two results, good or not good. The criteria for the evaluation includes pulmonary function test execution rate, sustained visit patients' ratio, percentage of ICS prescription patients, percentage of necessary medication prescription patients, percentage of LABA without ICS prescription patients, percentage of SABA without ICS prescription patients, percentage of OCS without ICS prescription patients. The institution with a value above the median in all evaluation criteria is evaluated as good [8].

Asthma Severity

Asthma severity is calculated by using information on the prescription code of the asthma medicines and prescription days. First, we assigned rank, which is determined to each principal component code of the prescribed drug by the Global Initiative for Asthma(GINA) guidelines, as many as the prescribed number of days from the prescribed date (Table 1). The GINA guideline is as follow: rank1 with low-dose ICS, LTRA, xanthine, or LABA; rank2 with high-dose ICS, low-dose ICS/LABA; rank3 with high-dose ICS/LABA; rank4 with LAMA inhaler and low-dose oral prednisolone for long period. Then, the daily rank-sum is calculated by summing the daily ranks assigned to each order, and the average is obtained by month. Finally, the distribution of time-varying pattern of the average monthly rank of each 12-month period was obtained, and the degree of severity was classified for each pattern. At this time, the medicines prescribed for asthma exacerbations were not considered in the calculation of severity.

Total medication rank

When classifying asthma severity, it is needed to calculate the daily asthma medication rank. We can consider the yearly total rank sum of daily medication ranks as a covariate

because there can be residual effect within cluster even after considering the asthma severity clustered.

Other risk factors

First, Comprehensive Air-quality Index(CAI) is integrated air-quality index calculated by taking into account the effects of six distinct air pollutants on the human body: SO_2, O_3, CO, NO_2, $PM10$, $PM2.5$. The average CAI for each region and evaluation order was calculated and assigned to each observation. In the case of Sejong City, it was obtained and assigned by integrating with the pollution level in Chungnam because there were not many observatories in the new city of Sejong in 2013.

Second, comorbidities were considered as risk factor of asthma exacerbation. Various comorbidities were reported that they might have effect on asthma exacerbation [11]. The comorbidity variable was determined by whether or not at least one of the following ICD-10 codes exists as diagnosis: atopic dermatitis (L20), GERD (K21), chronic rhinitis (J31), allergic rhinitis (J30), chronic sinusitis (J32), depression (F32, F33), anxiety (F40, F41) and obesity (E66)[6]

Medication possession ratio (MPR) is measured to reflect the good adherence to medication which tends to reduce the risk of asthma exacerbations. It can be calculated as follows.

$$\text{MPR} = \left(\frac{\sum the\ number\ of\ days\ treatment\ precribed\ during\ the\ follow-up\ period}{follow-up\ period}\right) X\ 100$$

Follow-up period means the period from the first prescription of asthma medication to the last within premeasurement period. For observations with MPR < 20% were categorized as

“1” meaning low adherence, 20%-80% as “2”, >80% as “3” meaning high adherence. Especially, MPR “0” means that the patient had not been prescribed any asthma medication except the one for alleviating the exacerbation during the period.

Statistical analyses

Asthma Severity

The mean of the monthly rank-sum according to the use of asthma medication in each patient and the corresponding annual pattern of severity were obtained by using data from three years at the same time. In other words, first, the average rank-sum based on prescription drugs of each 12-month of all patients with a history in the year was calculated. Next, we performed k-means clustering to reflect these 12 monthly average to each dimension, K-means algorithm was executed using Euclidean distance, and k was determined to be 4 with the largest over-all R-square.

Model for Asthma exacerbation

Associations between risk factors and asthma exacerbation were analyzed with generalized estimating equation (GEE). PROC GENMOD (SAS version 6.1) was used to conduct analysis. Because outcome is binary, the logit link function was used. Among the patients, there are patients who are prescribed asthma medications every order or not, which means that individuals are repeatedly measured over time. In this case, repeated measures within patients have a first-order autoregressive (AR(1)) correlation structure according to the order of evaluation. We let Y_{ij} as 1 if there was exacerbation in i-th observation of patient j and otherwise 0, then we can define $p_{ij} = \mathrm{P}(Y_{ij} = 1|\mathrm{X}) = \mathrm{E}(Y_{ij})$ with designed matrix X. Because there may exist selection bias because there is a group that occupy a very large portion of the clusters, we performed subgroup analyses according to severity groups after executing the models with whole patients. Final model was selected by comparing odds ratio(OR), p-value and goodness of fit criteria(QIC).

Respectively, GEEs were executed in following 5 ways:

1. **Whole model**

① **Model 1**: model with whole patients, with covariates including clustered severity

$$\text{logit}(p_{ij}) = \beta_0 + \beta_1 Evaluation_{ij} + \beta_2 Severity_{ij} + \beta_3 MPR_{ij} + \beta_4 Comorbidity_{ij}$$
$$+\beta_5 Order_{ij} + \beta_6 CAI_{ij} + \beta_7 Sex_{ij} + \beta_8 Age_{ij} + Patients_j + \epsilon_{ij},$$
$$Patients_j \sim N(0, \sigma^2_{Patients})$$

② **Model 2**: model with whole patients, with covariates including total medication rank

$$\text{logit}(p_{ij}) = \beta_0 + \beta_1 Evaluation_{ij} + \beta_2 Totalrank_{ij} + \beta_3 MPR_{ij} + \beta_4 Comorbidity_{ij}$$
$$+\beta_5 Order_{ij} + \beta_6 CAI_{ij} + \beta_7 Sex_{ij} + \beta_8 Age_{ij} + Patients_j + \epsilon_{ij},$$
$$Patients_j \sim N(0, \sigma^2_{Patients})$$

③ **Model 3**: model with whole patients, with covariates including both clustered severity and total medication rank

$$\text{logit}(p_{ij}) = \beta_0 + \beta_1 Evaluation_{ij} + \beta_2 Severity_{ij} + \beta_3 Totalrank_{ij} + \beta_4 MPR_{ij}$$
$$+\beta_5 Comorbidity_{ij} + \beta_6 Order_{ij} + \beta_7 CAI_{ij} + \beta_8 Sex_{ij} + \beta_9 Age_{ij} + Patients_j + \epsilon_{ij},$$
$$Patients_j \sim N(0, \sigma^2_{Patients})$$

2. Subgroup model

① **Model 4**: 4 models with patients in each cluster, with covariates including total medication rank

$$\text{logit}(p_{ijk}) = \beta_0 + \beta_1 Evaluation_{ijk} + \beta_2 Totalrank_{ijk} + \beta_3 MPR_{ijk} + \beta_4 Comorbidity_{ijk} + \beta_5 Order_{ijk} + \beta_6 CAI_{ijk} + \beta_7 Sex_{ijk} + \beta_8 Age_{ijk} + Patients_{jk} + \epsilon_{ij},$$

$$Patients_j \sim N(0, \sigma^2_{Patients}), \qquad severity\ cluster\ k$$

② **Model 5**: 4 models with patients in each cluster, without total medication rank

$$\text{logit}(p_{ijk}) = \beta_0 + \beta_1 Evaluation_{ijk} + \beta_2 MPR_{ijk} + \beta_3 Comorbidity_{ijk} + \beta_4 Order_{ijk} + \beta_5 CAI_{ijk} + \beta_6 Sex_{ijk} + \beta_7 Age_{ijk} + Patients_{jk} + \epsilon_{ij},$$

$$Patients_j \sim N(0, \sigma^2_{Patients}), \qquad severity\ cluster\ k$$

Ethics statement

Institutional review board of Seoul National University approved this study (IRB No. E1805/003-010), and exempted informed consent.

RESULTS

Characteristics of patient

The distribution of each explanatory variable for the exacerbation of the following year is shown in Table 2. There were more proportion of male patients with exacerbation in asthma. According to the order of evaluation, there was no significant difference in asthma exacerbation. In the group without asthma exacerbation, the proportion decreased with increasing age, but the composition trend was reversed in the group with asthma exacerbation. In the case of MPR, the proportion of patients with an MPR of 0 in the group with asthma exacerbation (7.21%) was more than three times than in those without asthma exacerbations (2.29%). The rate of comorbidity with exacerbations (73.62%) was slightly lower than that without exacerbations (74.84%). In the case of CAI, there was no difference in the mean value depending on whether the exacerbation occurred, because CAI was allocated to patients by area visited.

Table 2: Frequency, proportion for categorical variable, mean value, 95% confidence interval for continuous variable, and p-values from chi-square test and t-test.

Variable	No exacerbation	With exacerbation	Total	P-value
Sex				
Male	37,842 (50.3)	10,108 (53.1)	47,950	<.0001
Female	37,381 (49.7)	8,923 (46.9)	46,304	
Age				
15-34	18,979 (25.2)	3,166 (16.6)	22,145	<.0001
35-44	15,387 (20.5)	3,642 (19.1)	19,029	
45-54	15,655 (20.8)	4,443 (23.4)	20,098	
55-64	12,011 (16)	3,642 (19.1)	15,653	
65-	13,191 (17.5)	4,138 (21.7)	17,329	
CAI	76.1 (76.0-76.1)	76.1 (76.1-76.2)		0.02

Order of evaluation				
1st	25,868 (34.4)	6,604 (34.7)	32,472	0.06
2nd	25,835 (34.3)	6,368 (33.5)	32,203	
3rd	23,520 (31.3)	6,059 (31.8)	29,579	
MPR				
0 (no history)	1,721 (2.29)	1,372 (7.2)	3,093	<.0001
1 (< 20%)	22,139 (29.4)	4,669 (24.5)	26,808	
2 (20% - 80%)	20,641 (27.4)	6,205 (32.6)	26,846	
3 (> 80%)	30,722 (40.8)	6,785 (35.7)	37,507	
Comorbidity				
Yes	18,924 (25.2)	5,021 (26.9)	23,945	0.001
No	56,299 (74.8)	14,010 (73.6)	70,309	
Total	75,223	19,031	94,254	

Clustering severity of asthma

As a result of the clustering analysis, the asthma patients were classified into four groups according to their overall severity (Figure 3). First severity group (n=76,990) is showing the lowest and stable pattern of severity and is the largest portion of all patients. The number of patients, 79,782, in the first group consists of 35.22% of the 1st order evaluation patients, 34.24% of that of 2nd order, and only 30.54% of 3rd order patients. Second severity group (n=5,759) has pattern to increase rapidly in winter peaking in January, and gradually decreasing as the weather recovers. However, it still shows the second lowest overall severity of the four groups. The third severity group (n=10,729) shows moderate and stable severity throughout the year. The last severity group (n=776) is comprised of only 776 patients but they have very high severity throughout the year. They also have peak in January and relatively low severity in summer season. Notably, the proportion of the last severity group is

the lowest in the 1st order and the highest in the 3rd order, as opposed to the first severity group (Table 3)

Figure 3: Clustered pattern of annual severity

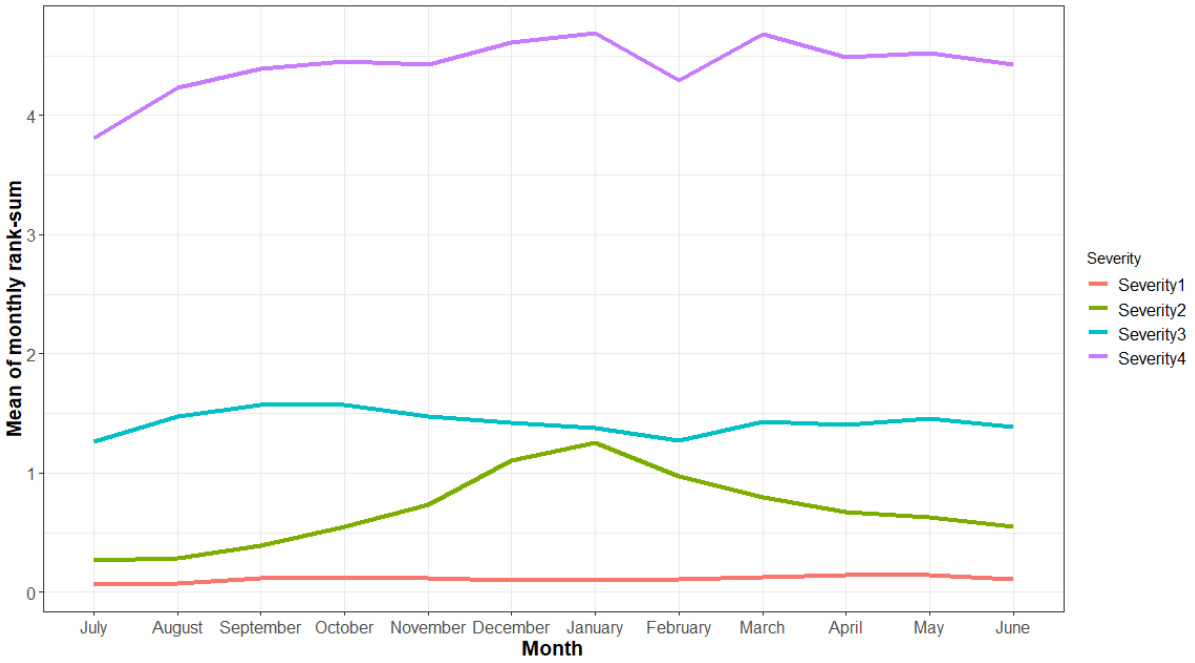


Table 3: Severity distribution according to the order of evaluation

	Severity 1	Severity 2	Severity 3	Severity 4	total
1st order	27,115(35.22)	2,007(34,85)	3,136(29.23)	214(27.58)	32,472
2nd order	26,360(34.24)	1,815(31.69)	3,752(34.97)	266(34.28)	32,203
3rd order	23,515(30.54)	1,927(33,46)	3,841(35.80)	296(38.14)	29,579
total	76,990	5,759	10,729	776	94,254

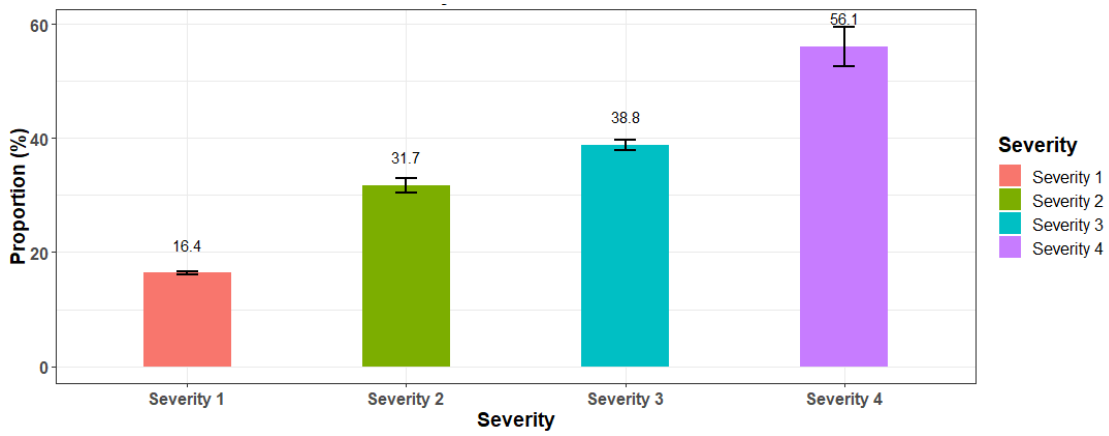
Also, the distribution of whether exacerbation occurred in the following year or not according to severity cluster is as follows. Exacerbation rate is gradually increasing as severity increases.

Table 4: Severity distribution according to exacerbation in the following year

unit: number (%)

Variable	No exacerbation	With exacerbation	Total	P-value
1	64,383 (83.6)	12,607 (16.4)	76,990	<.0001
2	3,933 (68.3)	1,826 (31.7)	5,759	
3	6,566 (61.2)	4,163 (38.8)	10,729	
4	341 (44)	435 (56)	776	
Total	75,223	19,031	94,254	

Figure 4: Exacerbation rate in each severity

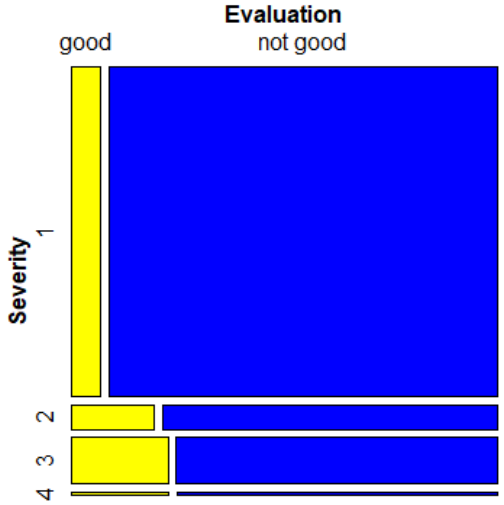


In addition, the distribution of evaluation results according to severity cluster is as follows. As we have seen above, the severity 1 group took account for the largest portion in the total. Also the proportion of visited institutions with evaluation result 'not good' is much higher than in the other severity levels. Therefore, in the following GEE analyses, subgroup analyses to correct the selection bias, which might be occurred by this, were conducted.

Table 5: Severity distribution according to evaluation result of visited clinics

	Not good visited	Good visited	Total	P-value
1	71,651 (93.1)	5,339 (6.9)	76,990	<.0001
2	4,617 (80.2)	1,142 (19.8)	5,759	
3	8,248 (76.9)	2,481 (23.1)	10,729	
4	594 (76.6)	182 (23.5)	776	
Total	85,110	9,144	94,254	

Figure 5: Mosaic plot of severity distribution according to evaluation result of visited clinics



GEE model selection and effect of evaluation

The results of GEE analyses of risk factors associated with asthma exacerbation are shown as follows. Estimated values of OR, P-values of other covariates other than severity and total rank were described only for model 1, because they are not variables we are interested in, and at the same time they represent almost the same value in all models. In subgroup analyses, total QIC can be calculated by summing up subgroup QICs.

1. Whole model

(1) Model 1: model with whole patients, with covariates including clustered severity (QIC = 89,048)

Table 6: Effect of covariates in model 1

Variable	OR	95% Lower CI	95% Upper CI	P-value
Evaluation				
Not good	0.86	0.81	0.91	<.0001
good	reference			
Severity				
2	2.23	2.08	2.39	<.0001
3	3.41	3.22	3.61	<.0001
4	6.77	5.79	7.90	<.0001
1	reference			
CAI	1.00	1.00	1.01	0.1
Sex				
Male	1.06	1.02	1.10	0.0007
Female	reference			

Age				
15- 34	0.67	0.63	0.72	<.0001
35-44	0.88	0.83	0.93	<.0001
45-54	0.98	0.93	1.04	0.56
55-64	1.03	0.98	1.10	0.25
65-	reference			
MPR				
0 (No history)	4.19	3.81	4.62	<.0001
1 (-20%)	1.54	1.47	1.63	<.0001
2 (20%-80%)	1.59	1.52	1.66	<.0001
3 (80%-)	reference			
Comorbidity				
0	0.98	0.94	1.02	0.27
1	reference			
Evaluation order				
1	1.35	1.28	1.42	<.0001
2	1.09	1.04	1.14	0.0004
3	reference			

First, air pollution indicator, CAI, didn't have a significant effect on asthma exacerbation. Also, men had more asthma exacerbation than women (P = 0.0007). Age groups less than 45 years of age had significantly less exacerbation than older people over 65 years of age (P < .0001). In the case of MPR, compared to the group with high adherence to medication over 80%, further exacerbation occurred in the group with adherence of 80% or less (P < .0001). Especially, the group with 0 MPR means that the asthma medication was not administered the year before the asthma exacerbation. So the 0 group indicates that they had not been managed in the meantime and have a large odds ratio of exacerbation as a result. Comorbidity did not have a significant difference in exacerbation (P = 0.27). Finally, asthma exacerbation was significantly decreased as the evaluation order increased (P = 0.0004).

(2) Model 2: model with whole patients, with covariates including total medication rank (QIC = 88,853)

Table 7: Effect of covariates in model 2

Variable	OR	95% Lower CI	95% Upper CI	P-value
Total rank	1.002	1.002	1.002	<.0001
Evaluation				
Not good	0.87	0.82	0.92	<.0001
good	reference			

(3) Model 3: model with whole patients, with covariates including both clustered severity and total medication rank (QIC = 88,145)

Table 8: Effect of covariates in model 3

Variable	OR	95% Lower CI	95% Upper CI	P-value
Total rank	1.002	1.002	1.002	<.0001
Evaluation				
Not good	0.90	0.85	0.96	0.0006
good	reference			
Severity				
2	1.54	1.43	1.67	<.0001
3	1.47	1.33	1.61	<.0001
4	0.44	0.33	0.58	<.0001
1	reference			

As the result, model 3 had the lowest QIC, which means goodness of fit was the best in model 3, but odds ratio of severity 4 compared with severity 1 showed less than 1. So we conducted subgroup analyses to control the possible selection bias.

2. Subgroup model

(1) Model 4: 4 models with patients in each cluster, with covariates including total medication rank (Total QIC = 87,018)

Table 9: Effect of covariates in model 4

Cluster	Variable	OR	95% Lower CI	95% Upper CI	P-value	QIC
1	**Total rank**	1.01	1.01	1.01	<.0001	64,808
	Evaluation					
	Not good	0.91	0.84	0.99	<.0001	
	good	reference				
2	**Total rank**	1.002	1.002	1.002	<.0001	7,088
	Evaluation					
	Not good	1.08	0.94	1.25	0.26	
	good	reference				
3	**Total rank**	1.002	1.002	1.002	<.0001	14,063
	Evaluation					
	Not good	1.12	1.02	1.22	0.02	
	good	reference				
4	**Total rank**	1.002	1.002	1.002	0.01	1,059
	Evaluation					
	Not good	0.89	0.63	1.24	0.49	
	good	reference				

(2) Model 5: 4 models with patients in each cluster, without total medication rank (QIC = 88,580)

Table 10: Effect of covariates in model 5

Cluster	Variable	OR	95% Lower CI	95% Upper CI	P-value	QIC
1	**Evaluation**					66,133
	Not good	0.79	0.73	0.86	<.0001	
	good	reference				
2	**Evaluation**					7,151
	Not good	1.08	0.93	1.24	0.31	
	good	reference				
3	**Evaluation**					14,232
	Not good	1.09	1.00	1.20	0.052	
	good	reference				
4	**Evaluation**					1,064
	Not good	0.91	0.65	1.27	0.57	
	good	reference				

As the result, model 4, which reflects remaining residual effect of severity clustering and considers for selection bias of large cluster 1, had the lowest QIC in all models. In model 4, the significance of cluster 2 and 4 was larger than 0.05 but less than 0.05 in cluster 1 and 3. In addition, we can confirm that the direction of effect of the evaluation result is different for each severity group. So it can be inferred that there was a selection bias that affects the results of models 1,2, and 3, which were all because of the results of the severity 1, which includes 85.6% of the total patients. Severity 1 group had lower incidence of exacerbation in not good institution, but it is hard to estimate the exact effect of evaluation because monthly rank sum

of patients in severity 1 had mean of almost 0. In the case of severity 4, as shown in the figure 5, the number of visitors to the institutions with evaluation 'good' is too small to see the significant effect of evaluation to asthma exacerbation.

Therefore, according to the results of severity 3, in which the exacerbation occurred clearly and the number of visitors to the 'good' clinics was sufficiently secured, it was confirmed that the risk of exacerbation of asthma patients was lowered in the institutions classified as 'good' according to the evaluation.

Comparison with tertiary hospital patients

Tertiary institutions are excluded from the evaluation because they are considered to be good institutions. Also, serious patients usually visit the tertiary institutions so comparing the distribution of severity and exacerbation between primary medical institutions might give some insight into factors important for asthma exacerbation.

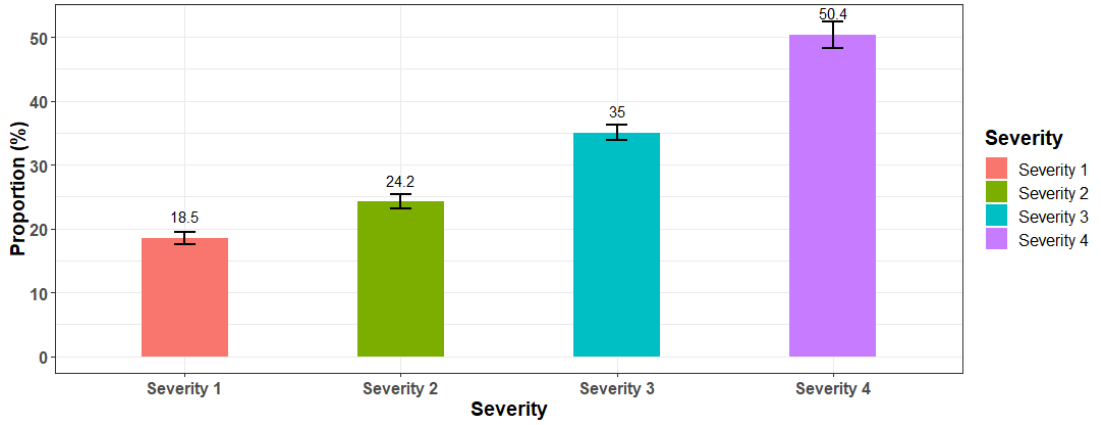
Table 11: Severity distribution according to exacerbation in the following year among tertiary hospital patients

unit: number (%)

Variable	No exacerbation	With exacerbation	Total	P-value
1	5,041 (81.5)	1,144 (18.5)	6,185	<.0001
2	4,060 (75.8)	1,297 (24.2)	5,357	
3	3,875 (65)	2,088 (35)	5,963	
4	1,086 (49.6)	1,103 (50.4)	2,189	

Total	14,062	5,632	19,694

Figure 6: Exacerbation rate in each severity among tertiary hospital patients



There were much more proportion of severe patients in tertiary hospital than in primary clinics. However, as shown in figure 6, exacerbation rate is gradually increasing as severity increases even among the tertiary institution patients like primary clinic patients, in spite of different distribution of severity among patients. which implies that the severity is the most important factor to asthma exacerbation.

DISCUSSION

We compared the magnitude of various risk factors of asthma exacerbation, including asthma severity. Retrospective cohort study of 83,375 people using the HIRA database was conducted. Our study showed that asthma severity and medicine adherence, MPR, may be important factors in asthma exacerbations.

It has already been shown that the magnitude of the effect of each risk factor on asthma exacerbation varies with subgroup analysis according to severity. In our study, we calculated the magnitude of each risk factor and the severity itself when we considered the severity as a variable in the model. All patients were clustered into four groups: severity 1 with mild severity which accounts for most of the subjects (n = 76,990), severity 2 with less mild severity with fluctuation throughout the year (n = 5,759), severity 3 with worsened severity (n = 10,729), and the last and the most severe severity 4 with the sudden increase in the severity (n = 776). In figure 3, severity 2 and 4 showed a common peak in January, and especially in the case of severity 4, it decreases in February but has the second peak in March. It is well known that seasonality and air pollution are risk factors for asthma exacerbation [12, 13], and having a peak in January can be explained by seasonality. Also, as a result of long-term monthly time-series analysis from 2000 to 2014, fine dust (PM10) was highest in March in Korea[14]. Therefore, the second peak in March for the most severe group of asthma can be deduced that the air pollution has a particularly bad effect on patients with severe asthma.

Table 6 shows that asthma exacerbation decreases as the order of evaluation progresses. This means that the quality of asthma management for preventing asthma exacerbation and alleviating asthma severity may be improved due to various incentives, penalties, or consciousness of the evaluation itself. Therefore, it is not possible to judge the validity of the evaluation from this paper, but it can be meaningful that the management of asthma is improved by the evaluation. According to the report from HIRA, as the order increases, evaluation indicators such as the rate of pulmonary function test, rate of ongoing visits, and

ratio of ICS prescribers are improving[8]. Therefore, it is necessary to estimate the magnitude of the effect on the asthma exacerbation by including the evaluation result of each institution in the model.

According to this study asthma patients' exacerbation depends on the evaluation results. According to the result of severity 3, it can be judged that the evaluation result shows that the exacerbation of the patient who visited clinic with good evaluation is lowered. However, in cases of severity 1 and 4, a more in-depth approach is needed. Severity 1 is considered to be able to distinguish the exact difference by establishing confounding variables that can correct the characteristics of the patients of the good / not good hospitals. In addition, severity 4 is difficult to judge whether (1) the characteristics of the patients are different, or (2) the results are not significant because sample is small, or (3) the current classification criteria is not appropriate in severity 4, so it is necessary to secure additional variable.

Our study had several strength and potential limitations. First, the quantitative and statistical analysis of clustering the asthma severity pattern is a meaningful approach. We calculated asthma severity by ranks from GINA guideline and grouped asthma patients according to the rank-sum values unlike the previous studies which utilize only the clinical findings and the hospital data [7, 15, 16]. Since these data are more accurate but difficult to access and data for many patients is not usually available, it is important to calculate asthma severity using health claim data from HIRA or National Health Insurance Service (NHIS). Also, the individual effect is considered in statistical model as a random variable, so the characteristics of each patient could be considered using the three-year data with repetition.

However, for the first limitation, there is a possibility of incomplete coding accuracy and recording because the measurement of asthma medication, diagnosis and exacerbation is based on the diagnoses of claims data. However previous study of the validity of health claims data using ICD-10 codes for acute myocardial infarction showed a positive predictive

value of over 70% compared to medical records. Second, all the confounding factors may not have been included in the model and this can lead to residual confounding because this is observational study. Many variables that could affect results, including smoking status, medical records, socioeconomic status, were not fully available in the HIRA database.

In conclusion, severity also had a significant effect on asthma exacerbation, and the monthly pattern of severity classification was also as it was previously known. It was also found that medication adherence is important for prevention of asthma exacerbation. Even in the patients who visited tertiary hospitals have patterns of increasing exacerbation rate as severity increases, so it is considered necessary to supplement the management evaluation criteria by newly establishing the severity level in the current criteria. For example, the medical staff should fill in the severity of asthma diagnosis or medicine prescription.

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국문 초록

천식 중증도를 고려한 천식 적정성 평가 결과의 적절성 분석

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연구 배경

한국에서 천식 유병률은 꾸준히 증가하고 있으나 피할 수 있는 천식악화는 OECD 평균에 비해 훨씬 높게 나타난다. 따라서 의료기관에서의 천식 관리의 질에 대한 국가적 평가가 이루어지고 있다. 이러한 관점에서 본 연구는 천식 중증도를 고려하였을 때 의료기관의 천식 관리 평가 결과에 따라 그 다음해의 천식 악화 여부가 달라지는지를 보아, 천식 관리 평가가 적절하게 이루어지고 있는지 확인하는 데 목적을 갖는다.

연구 방법

본 연구는 전국인구기반의 후향적 코호트 연구로, ICD-10 코드 상 천식으로 진단되었으며 모든 제외 기준을 통과한 83,375 명의 환자가 포함되었다. 3 년에

걸친 평가 기간의 자료를 사용하였으며, 천식 약제 랭크에 따른 중증도를 사용하여, k-평균 클러스터링을 거쳐 환자를 4 개의 군집으로 나누었다. 일반화추정방정식(GEE)를 통해 천식 악화와 그 요인의 관계를 살펴보았다.

연구 결과

천식 환자 중 가장 경증과 가장 중증의 환자들의 악화율은 각각 16.4%, 56%로 나타났다 (P < .0001). 전체모형에서 다중일반화추정방정식에 따르면, 비양호기관 방문 환자의 악화의 오즈는 양호기관 방문 환자들보다 낮게 나타났다 (0.86, <.0001). 그러나 최종적인 하위 그룹 분석 결과에 따르면 양호 기관 방문 환자의 천식 악화의 오즈가 비양호 기관 방문 환자에 비해 낮게 나타났다. 한편 상급의료기관의 결과와 비교하였을 때 천식 악화의 가장 큰 요인은 천식 중증도로 나타났다.

결론

천식환자는 건강보험청구데이터로부터 얻을 수 있는 천식 약제 정보를 통해 구한 연간 중증도 패턴으로 잘 분류되었다. 결론적으로 환자의 중증도 별로 다른 치료 방식이 필요하며, 평가 결과의 효과가 천식 중증도에 따라 다름에 따라 현재 천식 관리 평가 기준에 천식 중증도 항목을 고려하는 것이 요구된다.

주요어 **: 천식, 천식 악화, 천식 중증도, 천식적정성평가, 건강보험청구, 건강보험심사평가원, 대한민국, 국내**
학번 : 2017-26514