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Risk factors of asthma exacerbation based on asthma severity: a nationwide population-based observational study in South Korea

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ABSTRACT

Objectives Asthma exacerbation, associated with many risks factors, can reflect management failure. However, little is known about how risk factors are associated with exacerbation, according to asthma severity. We aimed to investigate differences in risk factors in patients with different asthma severity and evaluate whether risk factors differed between frequent exacerbators and patients with single exacerbation.

Design Nationwide population-based observational study.

Setting Korean National Sample Cohort database.

Participants We included 22 130 adults with asthma diagnoses more than twice (ICD-10 (International Classification of Diseases, Tenth revision) codes J45 and J46) and one prescription for asthma medication from 2010 to 2011.

Outcome measures Asthma exacerbation was defined as having a corticosteroid (CS) burst characterised by a prescription of high-dose oral CS for ≥3 days or one systemic CS injection, hospitalisation or emergency department visit.

Results Among severities, history of CS bursts was significantly associated with exacerbation. In mild and moderate asthma, exacerbation was significantly associated with age ≥45 years, being female, gastro-oesophageal reflux disease and chronic rhinitis. High medication possession ratio (MPR≥50%), compared with low MPR (<20%) showed adjusted ORs of 0.828 (95% CI 0.707 to 0.971) and 0.362 (0.185 to 0.708) in moderate and severe asthma, respectively. In severe asthma, compared with mild asthma, only allergic rhinitis and history of hospitalisation were strongly associated with exacerbation. When comparing frequent exacerbators to patients with single exacerbation, age ≥45 years, atopic dermatitis, anxiety and history of CS burst were significant risk factors in mild and moderate asthma, whereas no risk factors were significant in severe asthma.

Conclusions Different associations between risk factors and asthma exacerbations based on asthma severity suggest that patients with mild asthma require greater attention to their age and comorbidities, whereas those with severe asthma require greater attention to hospitalisation history and drug adherence.

Strengths and limitations of this study

► This is the first study to identify differences in risk factors of asthma exacerbation according to asthma severity.
► This is a nationwide population-based observational study that included representative South Korean population of approximately 1 million people between 2010 and 2011.
► Our study is subject to potential for inaccuracy of coding and incompleteness of records in claims data.

INTRODUCTION

Asthma affects an estimated 235 million people worldwide and contributes to substantial health and economic burdens.[1 2] As asthma control, being one of the most feasible and effective therapeutic strategies, becomes more important, its evidence base becomes well established, and much of it can be delivered at a primary care level.[3 4] However, although asthma management has focused on achieving clinical control and reducing the future risk of exacerbations, some countries, including Korea, the USA and the Slovak Republic, reported hospital admission rates greater than twice the Organization for Economic Co-operation and Development average, indicating a failure of preventive care in established asthma cases.[5 6]

To establish and implement an asthma control strategy, it is important to evaluate the risk factors of poor control and frequent exacerbation. Guidelines for the management of asthma recommend that clinicians evaluate patients for history of asthma exacerbations and the presence of chronic comorbid conditions, as treating those conditions may improve asthma management.[4 7] Periodic assessments of asthma severity and control

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are recommended because they include the extent of current impairment and future risk of asthma exacerbations.[7] Previous studies have reported that adherence to medication should be monitored to achieve asthma control.[8–11] However, little is known about differences in the risk factors of exacerbation of asthma with different severities, although a cross-sectional study reported that asthma-related healthcare utilisation and direct costs increased depending on the severity.[12] In addition, while mild asthma is predominant in clinical settings and may be accompanied by chronic conditions,[12] previous studies included cases of severe or persistent asthma, resulting in limited interpretations of these studies.[8 9 13]

The purposes of this study were to investigate differences in the risk factors associated with asthma exacerbation in patients with different severities of asthma and to evaluate whether the risk factors of patients who developed a single asthma exacerbation differed from those of patients who had frequent exacerbations, providing more comprehensive information that can contribute to evidence-based guidelines to clinicians and professional organisations.

SUBJECTS AND METHODS

Database
This study used the National Sample Cohort data from the National Health Insurance Service (NHIS-NSC) in South Korea. South Korea has a compulsory universal health insurance system that includes medical reimbursement records for the entire Korean population.[14] The NHIS uses a systematic sampling approach to randomly select a representative database of approximately 1 million people from 2002 to 2013, 2% of total Korean population.[15] These data are 12-year cohort data and include age, sex, socioeconomic variables such as the income rank and disability, diagnoses, details of medical treatment and health examinations.[16]
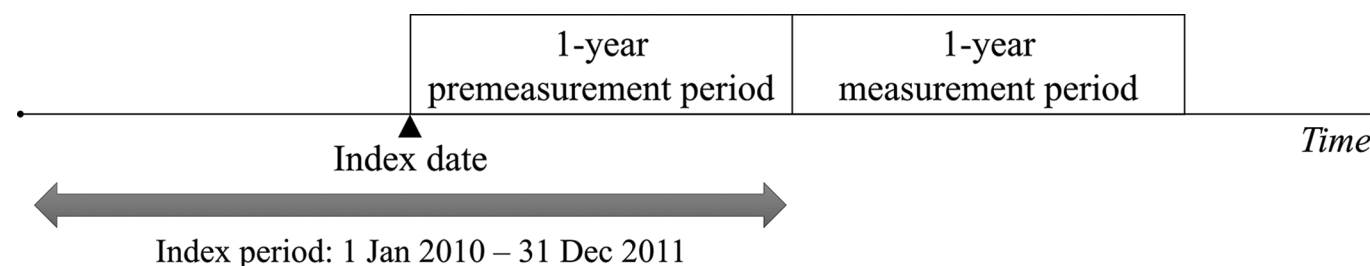
Study design
We conducted an observational study to assess the risk factors of asthma exacerbation. For patients satisfying the inclusion criteria, the index date was defined as the date of the first asthma diagnosis between 1 January 2010

and 31 December 2011, which was considered the index period. We defined the first year after the index date as the premeasurement period and the next year as the measurement period (figure 1). The risk factors of the study subjects, with the exception of adherence to medication, were assessed in the premeasurement period. Adherence to medication was assessed in the measurement period to account for cases where the time gap between the premeasurement period and the exacerbation was too long for the adherence to be reflected in the exacerbation. All personal identifying information of the included patients was anonymous; therefore, informed consent for this study was waived by the institutional review board.

Selection of study subjects
Patients were included in this study if they (1) received an asthma diagnosis as a primary or secondary diagnosis coded according to the International Classification of Disease, Tenth Revision (ICD-10 codes J45 and J46) more than twice between 1 January 2010 and 31 December 2011; (2) had at least one prescription for more than one of the following asthma medications between 1 January 2010 and 31 December 2011: inhaled corticosteroids (ICSs), inhaled long-acting ß2-agonists (LABAs), an ICS and a LABA combined in a single inhaler (ICS/LABA), inhaled short-acting ß2-agonists, oral leukotriene antagonists, xanthine derivatives, mast cell stabilisers and systemic corticosteroids (CSs); (3) were ≥20 years of age. The Global Initiatives for Asthma (GINA) suggests a stepwise approach to asthma management depending on age: children aged ≤5 years, children aged 6–11 years, adolescents and adults.[4] In NHIS-NSC data, age is presented in the intervals of 5 years; we included only patients aged ≥20 years. According to a report from GINA and the Global Initiative for Chronic Obstructive Lung Disease, the patients with diagnoses and/or features of both asthma and chronic obstructive pulmonary disease (COPD) experience frequent exacerbations and a more rapid decline in lung function than those with asthma or COPD alone.[17] As patients with asthma and COPD might differ from the patients with asthma we aimed to study, we excluded patients if they had a diagnosis of

Figure 1 Observational study design. The index date was defined as the date within the index period when the patient was diagnosed with asthma for the first time. The 1-year period from the index date was defined as the premeasurement period, in which asthma severity and risk factors except the medication possession ratio (MPR) were measured. The following 1-year period was defined as the measurement period, in which the MPR and the outcome of this study, asthma exacerbation, were measured.
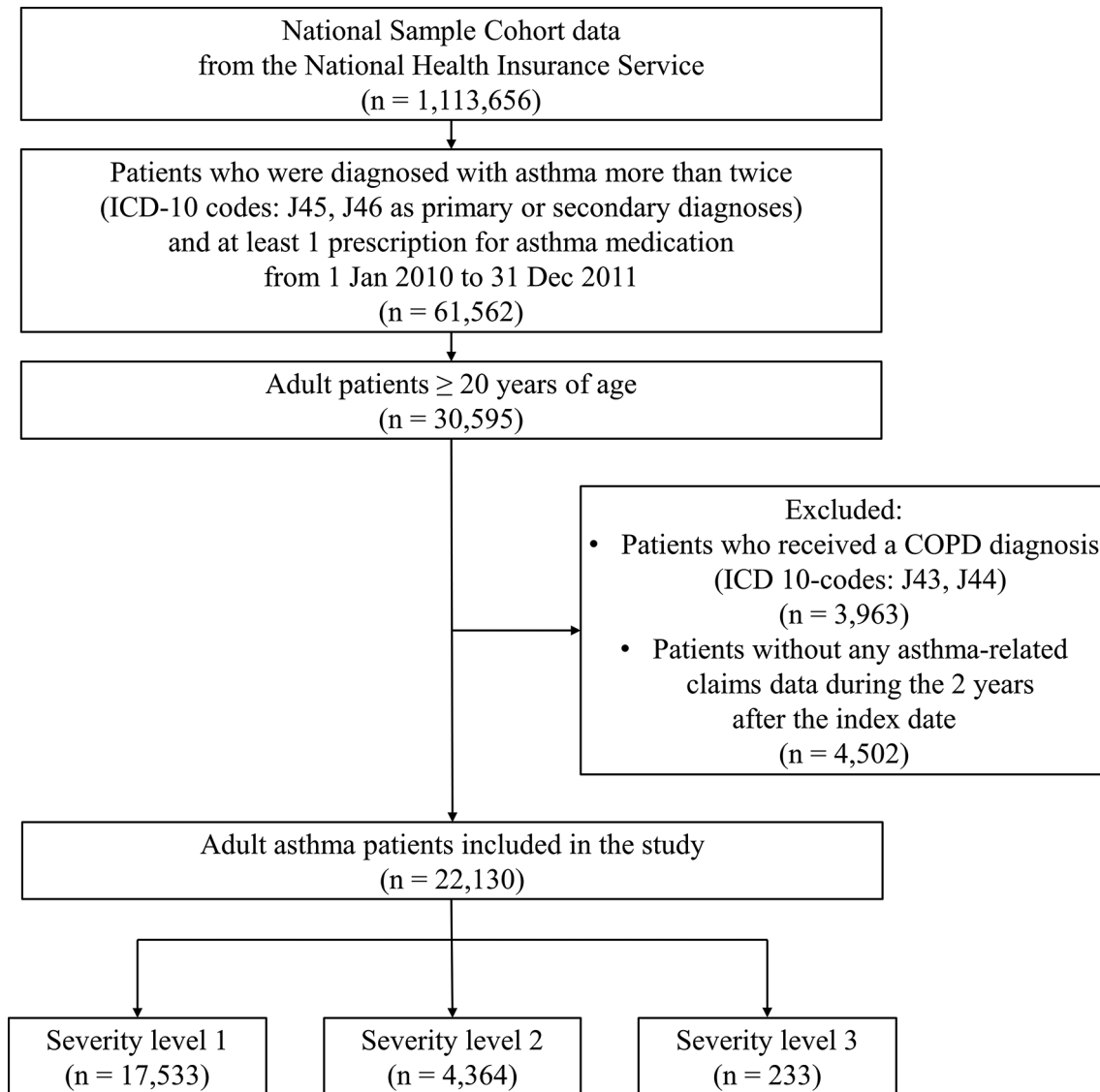
Figure 2 Study flow chart. COPD, chronic obstructive pulmonary disease; ICD, International Classification of Diseases, 10th revision.

COPD (ICD-10 codes J43 and J44) in the premeasurement period. Patients without any claims during the 2 years after the index date were excluded because the risk factors and asthma exacerbation could not be assessed. A study flow chart is presented in figure 2.

Assessment of asthma severity level

Asthma severity level was assessed on the basis of the patient's medication use as recommended by GINA. According to the guideline, mild asthma is well controlled with low-dose ICS, while moderate asthma is controlled by low-dose ICS/LABA. Severe asthma requires high-dose ICS/LABA, and tiotropium or low-dose oral CS (OCS) can be added as a controller.[4] However, there is a limitation in clearly distinguishing whether the recorded dosage of ICS/LABA is low-dose or high-dose in NHIS-NSC. As the prescription unit is recorded as a canister or tablet, it is difficult to determine the actual prescribed dose of ICS/LABA. Therefore, in our study, the asthma severity was

operationalised on the basis of the definition of severity by the GINA guideline and a previous study that analysed claims data with its definition of asthma severity.[12] Three mutually exclusive severity levels were defined according to patient's prescribed medication with a primary or secondary diagnosis of asthma during the premeasurement period. Patient was defined as level 3 (severe) if prescribed with an ICS/LABA single inhaler of various intensity (from low dose to high dose) and received at least one prescription of tiotropium or low-dose OCS. A low-dose OCS was defined as a prednisolone equivalent of ≤7.5 mg/day for at least 2 weeks.[4] The patient who was prescribed with a low-dose or high-dose ICS/LABA single inhaler but was not prescribed with tiotropium or low-dose OCS was defined as level 2 (moderate). The patient was defined as level 1 (mild) if prescribed with at least one asthma medication, with the exception of an ICS/LABA single inhaler, a low-dose OCS and tiotropium.

Risk factor measures

In previous studies, age, sex and history of exacerbation were reported to be associated with asthma-related healthcare utilisation.[8 9 18] Various comorbidities including gastro-oesophageal reflux disease (GERD), allergic or chronic rhinitis, chronic sinusitis, atopic dermatitis, psychiatric disorders, particularly anxiety and depression and obesity were reported in patients with asthma and may affect asthma control and outcomes.[9 19–23] To assess the association between these risk factors and asthma exacerbation, we evaluated each risk factor in the premeasurement period. The comorbidities were determined by the presence of the following ICD-10 codes as primary or secondary diagnosis: GERD (K21), allergic rhinitis (J30), chronic rhinitis (J31), chronic sinusitis (J32), atopic dermatitis (L20), depression (F32 and F33), anxiety (F40 and F41) and obesity (E66). Although smoking status is an important factor associated with predicting the future risk of asthma exacerbation, the NHIS-NSC does not provide the information on smoking status, so we could not evaluate the smoking history of the study population.

Good adherence to medication tended to be associated with a lower risk of asthma exacerbations.[10 24] We evaluated the medication possession ratio (MPR) as a measure of adherence, which was the number of days of medication supplied divided by the number of days between the first and the last refill.[25] The MPR was calculated for the period from the beginning of the measurement period to the day before the first exacerbation to reflect adherence just before the asthma exacerbation. If the days of supply exceeded 365, the total number of covered days was considered to be 365. Based on a previous study, the MPR was divided into low, medium and high categories: low adherence was defined as <20% adherent, medium adherence as 20%–49% adherent and high adherence as ≥50% adherent.[24]

Outcome measures

The primary outcome was asthma exacerbation during the measurement period. Based on a previous study,[26] systemic CSs for asthma, asthma-specific hospital admissions and asthma-specific emergency department (ED) visits are recommended core outcomes for classifying asthma exacerbation in observational studies. In order to be distinguished as an exacerbation in adult/adolescent populations, systemic CSs, including high-dose OCS defined as a prednisolone equivalent of ≥30 mg/day in a previous study,[12] should be prescribed for at least 3 days.[26] Therefore, an asthma exacerbation was defined as the occurrence of at least one of three of the following events: CS bursts, hospitalisations or ED visits with asthma as a primary or secondary diagnosis. A CS burst was defined as receiving a prescription for high-dose OCS for at least 3 days or one systemic CS injection. If CS burst occurred with an ED visit or hospitalisation, it was defined as an ED visit or hospitalisation, respectively, to ensure that the ED visit or hospitalisation was asthma-related.

Statistical analysis

In this analysis, we classified patients into mutually exclusive groups based on the asthma severity level (1, 2 or 3) in the premeasurement period. First, we examined and compared the risk factors among asthma severity groups using the χ^2 test. Second, to estimate the association between the risk factors and asthma exacerbations, we constructed multivariable logistic regression model and reported adjusted ORs with 95% CIs. Additionally, we performed a subgroup analysis to examine the risk factors of a higher frequency of exacerbation. In each asthma severity group, risk factors for patients with two or more exacerbations were evaluated; patients with only one exacerbation were used as the reference and patients with no exacerbations were excluded. All tests were two-sided, with a significance level of 0.05. All data transformations and statistical analyses were conducted using SAS V.9.4 for Windows (SAS Institute).

RESULTS

Patient characteristics according to asthma severity

Of the 22 130 patients with asthma included in this study, 79.2% (17 533), 19.7% (4364) and 1.05% (223) of patients were classified with a severity of level 1, 2 and 3, respectively. Patient demographics, comorbidities, history of exacerbation and MPR differed among severities (table 1). The proportion of patients ≥65 years of age was the highest in level 3, while the proportion of patients 20–44 years of age was the lowest in level 3. There was a slight predominance of female patients among severities. Patients with a higher severity level were more likely to have comorbidities including GERD (P=0.0021), chronic sinusitis (P=0.0002), depression (P<0.0001) and anxiety (P=0.0222). In particular, depression was more than twice as frequent among level 3 patients as level 1 patients (17.6% vs 7.25%). Obesity was also found to be more prevalent in patients with higher asthma severity (P=0.0173), although only a few patients had obesity. 43.94% of the study subjects experienced CS burst, 1.46% experienced ED visits and 3.77% experienced hospitalisation in the premeasurement period. Patients with increased severity were more likely to have history of each type of exacerbation. For example, 3.4% (601/17 533) of level 1 patients had a history of hospitalisation in the premeasurement period, compared with 4.7% (207/4364) of level 2 and 11.6% (27/233) of level 3 patients in the same period. The overall MPR during the measurement period was low: 85.5% of all patients had an MPR<20%. More than 90% (16 075/17 533) of level 1 patients had a low MPR (<20%), while 23.1% of level 2 (1006/4364) and 31.8% of level 3 (74/233) patients had a high MPR (≥50%).

Risk factors associated with asthma exacerbation according to severity

In a multivariable logistic regression model, age greater than 45 years showed a significant association with asthma exacerbations for asthma severity of level 1 and 2, but not

Table 1 Patient demographics, comorbidities, history of exacerbation and MPR according to asthma severity

Variable*	Total	Level 1 (mild)	Level 2 (moderate)	Level 3 (severe)	P value†
Total number of patients	22 130	17 533 (79.23)	4364 (19.72)	232 (1.05)	
Age group					
20–44	7088 (32.03)	5615 (32.03)	1426 (32.68)	47 (20.17)	<0.0001
45–64	8629 (38.99)	6731 (38.39)	1809 (41.45)	89 (38.2)	
≥65	6413 (28.98)	5187 (29.58)	1129 (25.87)	97 (41.63)	
Sex					
Female	14 572 (65.85)	11 658 (66.49)	2749 (62.99)	165 (70.82)	<0.0001
Comorbidities‡					
GERD	7399 (33.43)	5846 (33.34)	1450 (33.23)	103 (44.21)	0.0021
Allergic rhinitis	17 302 (78.18)	13 698 (78.13)	3419 (78.35)	185 (79.4)	0.8599
Chronic rhinitis	1834 (8.29)	1457 (8.31)	351 (8.04)	26 (11.16)	0.2367
Chronic sinusitis	2933 (13.25)	2248 (12.82)	641 (14.69)	44 (18.88)	0.0002
Atopic dermatitis	869 (3.93)	668 (3.81)	187 (4.29)	14 (6.01)	0.0909
Depression	1601 (7.23)	1271 (7.25)	289 (6.62)	41 (17.6)	<0.0001
Anxiety	3240 (14.64)	2606 (14.86)	591 (13.54)	43 (18.45)	0.0222
Obesity	34 (0.15)	24 (0.14)	8 (0.18)	2 (0.86)	0.0173
History of exacerbation‡					
CS bursts	9724 (43.94)	7608 (43.39)	1981 (45.39)	135 (57.94)	<0.0001
ED visits	323 (1.46)	205 (1.17)	110 (2.52)	8 (3.43)	<0.0001
Hospitalisations	835 (3.77)	601 (3.43)	207 (4.74)	27 (11.59)	<0.0001
MPR§					
MPR<20%	18 910 (85.45)	16 075 (91.68)	2712 (62.14)	123 (52.79)	<0.0001
20%≤MPR<50%	1330 (6.01)	648 (3.7)	646 (14.8)	36 (15.45)	
MPR≥50%	1890 (8.54)	810 (4.62)	1006 (23.05)	74 (31.76)	

*Data are expressed as number (%) unless otherwise specified.
†The P value was calculated using the χ^2 test for categorical variables.
‡Patients overlapped in each category.
§The MPR was calculated in the measurement period, whereas age group, sex, comorbidities and history of exacerbation were evaluated in the premeasurement period.
CS, corticosteroid; ED, emergency department; GERD, gastro-oesophageal reflux disease; MPR, medication possession ratio.

in level 3 (table 2). In particular, when compared with the patients aged 20–44 years, patients aged ≥65 years showed nearly doubled risk of exacerbation, showing an adjusted ORs of 1.890 (95% CI 1.733 to 2.062) and 1.905 (1.594 to 2.277) in level 2 and 3, respectively. Female sex was a significant risk factor in patients with a severity of level 1 or 2, but not level 3. Asthma exacerbations were associated with comorbidities including GERD, allergic rhinitis, chronic rhinitis, chronic sinusitis, depression and anxiety in level 1 patients (all P<0.05). However, as disease severity increased, the association between asthma exacerbation and comorbidities became insignificant, and only allergic rhinitis showed a significant association with asthma exacerbation in level 3 patients, showing adjusted OR of 2.476 (1.163 to 5.273). History of asthma exacerbations showed a significant association with asthma exacerbations. CS bursts showed adjusted ORs of 3.060 (2.868 to 3.264), 3.344 (2.938 to 3.808) and 2.269 (1.261 to 4.083) in level 1, 2 and 3, respectively.

Hospitalisations showed a significant association with adjusted OR of 3.253 (1.105 to 9.576) in level 3, whereas ED visits showed no significance across all severity groups. The MPR was not significantly associated with asthma exacerbation in level 1 patients. However, an MPR ≥50% was associated with a decrease in asthma exacerbation, showing adjusted ORs of 0.828 (0.707 to 0.971) and 0.362 (0.185 to 0.708) in level 2 and 3 patients, respectively.

Risk factors associated with frequent asthma exacerbation according to severity

The subgroup analysis of risk factors associated with frequent asthma exacerbation included 7105, 1885 and 125 patients of severity levels 1, 2 and 3, respectively, with at least 1 exacerbation in the measurement period (table 3). Age greater than 45 years, atopic dermatitis, anxiety and history of CS bursts were significantly associated with frequent exacerbation in level 1 and 2 patients. Similar to the results in table 2, an MPR between 20%

Table 2 Multivariable logistic regression model of risk factors associated with asthma exacerbation according to asthma severity

Variable	Level 1 (n=17 533)			Level 2 (n=4364)			Level 3 (n=233)		
	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Age group									
20–44	1	Reference		1	Reference		1	Reference	
45–64	1.691	1.562 to 1.830	<0.0001	1.583	1.356 to 1.848	<0.0001	1.994	0.884 to 4.497	0.0961
≥65	1.890	1.733 to 2.062	<0.0001	1.905	1.594 to 2.277	<0.0001	1.852	0.817 to 4.200	0.1400
Sex									
Female	1.122	1.048 to 1.201	0.0010	1.156	1.011 to 1.323	0.0346	1.054	0.538 to 2.065	0.8780
Comorbidities (presence)									
GERD	1.278	1.193 to 1.369	<0.0001	1.227	1.068 to 1.411	0.0039	0.658	0.363 to 1.193	0.1682
Allergic rhinitis	1.129	1.042 to 1.223	0.0030	1.147	0.974 to 1.351	0.0999	2.476	1.163 to 5.273	0.0187
Chronic rhinitis	1.211	1.079 to 1.360	0.0012	1.364	1.076 to 1.730	0.0104	2.173	0.805 to 5.870	0.1258
Chronic sinusitis	1.147	1.041 to 1.263	0.0054	1.197	0.995 to 1.439	0.0560	0.513	0.237 to 1.111	0.0905
Atopic dermatitis	1.143	0.969 to 1.348	0.1131	1.170	0.854 to 1.604	0.3278	0.827	0.242 to 2.821	0.7610
Depression	1.157	1.020 to 1.312	0.0231	1.183	0.907 to 1.541	0.2147	1.870	0.847 to 4.128	0.1212
Anxiety	1.211	1.104 to 1.329	<0.0001	1.128	0.929 to 1.370	0.2246	0.963	0.431 to 2.151	0.9273
Obesity	0.800	0.336 to 1.903	0.6137	0.939	0.220 to 4.009	0.9322	0.575	0.031 to 10.773	0.7112
History of exacerbation (presence)									
CS bursts	3.060	2.868 to 3.264	<0.0001	3.344	2.938 to 3.808	<0.0001	2.269	1.261 to 4.083	0.0062
ED visits	1.083	0.801 to 1.466	0.6039	1.250	0.811 to 1.926	0.3119	1.331	0.210 to 8.421	0.7612
Hospitalisations	1.384	1.157 to 1.655	0.0004	1.142	0.830 to 1.572	0.4150	3.253	1.105 to 9.576	0.0322
MPR*									
MPR<20%	1	Reference		1	Reference		1	Reference	
20%≤MPR<50%	1.040	0.878 to 1.231	0.6507	0.652	0.538 to 0.790	<0.0001	0.632	0.277 to 1.441	0.2752
MPR≥50%	1.147	0.985 to 1.335	0.0768	0.828	0.707 to 0.971	0.0202	0.362	0.185 to 0.708	0.0030

Bold results are statistically significant.

*The MPR was calculated in the measurement period, whereas age group, sex, comorbidities and history of exacerbation were evaluated in the premeasurement period.

CS, corticosteroid; ED, emergency department; GERD, gastro-oesophageal reflux disease; MPR, medication possession ratio.

Table 3 Multivariable logistic regression model of risk factors associated with frequent asthma exacerbations (≥2 vs 1 exacerbation) according to asthma severity

Variable	Level 1 (n=7105)			Level 2 (n=1885)			Level 3 (n=125)		
	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Age group									
20–44	1	Reference		1	Reference		1	Reference	
45–64	**1.677**	**1.477 to 1.903**	**<0.0001**	**1.447**	**1.141 to 1.834**	**0.0023**	1.213	0.336 to 4.386	0.7680
≥65	**2.170**	**1.892 to 2.489**	**<0.0001**	**2.247**	**1.713 to 2.947**	**<0.0001**	1.009	0.271 to 3.751	0.9896
Sex									
Female	1.046	0.940 to 1.164	0.4069	0.993	0.808 to 1.221	0.9499	0.566	0.179 to 1.793	0.3333
Comorbidities (presence)									
GERD	1.108	0.999 to 1.230	0.0526	0.969	0.788 to 1.191	0.7616	0.800	0.318 to 2.017	0.6366
Allergic rhinitis	**1.250**	**1.104 to 1.415**	**0.0004**	1.198	0.930 to 1.544	0.1628	0.233	0.044 to 1.237	0.0872
Chronic rhinitis	1.037	0.874 to 1.231	0.6731	1.061	0.760 to 1.480	0.7285	0.752	0.217 to 2.607	0.6537
Chronic sinusitis	1.069	0.925 to 1.236	0.3642	0.975	0.746 to 1.273	0.8502	0.946	0.286 to 3.129	0.9269
Atopic dermatitis	**1.310**	**1.020 to 1.681**	**0.0343**	**1.900**	**1.153 to 3.131**	**0.0118**	3.745	0.337 to 41.637	0.2826
Depression	**1.307**	**1.086 to 1.574**	**0.0047**	1.087	0.746 to 1.583	0.6639	1.937	0.560 to 6.695	0.2961
Anxiety	**1.169**	**1.020 to 1.340**	**0.0253**	**1.425**	**1.071 to 1.896**	**0.0151**	0.634	0.210 to 1.909	0.4172
Obesity	2.428	0.490 to 12.044	0.2775	1.408	0.141 to 14.024	0.7706	<0.001	<0.001->999.999	0.9863
History of exacerbation (presence)									
CS bursts	**2.053**	**1.856 to 2.270**	**<0.0001**	**2.020**	**1.653 to 2.468**	**<0.0001**	2.468	0.926 to 6.583	0.0710
ED visits	0.874	0.568 to 1.345	0.5409	1.012	0.556 to 1.841	0.9687	0.702	0.067 to 7.350	0.7678
Hospitalisations	**1.462**	**1.134 to 1.886**	**0.0034**	1.160	0.742 to 1.812	0.5149	0.626	0.157 to 2.495	0.5063
MPR*									
MPR<20%	1	Reference		1	Reference		1	Reference	
20%≤MPR<50%	**1.532**	**1.172 to 2.002**	**0.0018**	**0.718**	**0.530 to 0.972**	**0.0318**	0.464	0.140 to 1.536	0.2087
MPR≥50%	1.156	0.918 to 1.456	0.2177	0.960	0.755 to 1.221	0.7398	0.706	0.230 to 2.170	0.5435

Bold results are statistically significant.
*The MPR was calculated in the measurement period, whereas age group, sex, comorbidities and history of exacerbation were evaluated in the premeasurement period.
CS, corticosteroid; ED, emergency department; GERD, gastro-oesophageal reflux disease; MPR, medication possession ratio.

and 50% was associated with less frequent exacerbation compared with an MPR<20% in level 2 patients, whereas an MPR≥50% did not show a significant association. In level 3, which consisted of a small number of patients, no risk factors showed any significant association with frequent asthma exacerbation.

DISCUSSION

This study found that the association between each risk factor and asthma exacerbation differed according to asthma severity. The risk of exacerbation was associated with age ≥45 years in patients with mild and moderate asthma, but not in those with severe asthma. An MPR>50% was associated with a decrease in asthma exacerbation in patients with moderate and severe asthma. Comorbidities including GERD, allergic or chronic rhinitis, chronic sinusitis, depression and anxiety were associated with exacerbation in patients with mild asthma, and GERD and chronic rhinitis were associated with exacerbation in patient with moderate asthma, while only allergic rhinitis was associated with exacerbation in patients with severe asthma. History of CS bursts was a risk factor for future exacerbation across all severities, and history of hospitalisation was strongly associated with exacerbation in patients with severe asthma. We also found that frequent exacerbations were associated with age ≥45 years, atopic dermatitis, anxiety and history of CS bursts in patients with mild and moderate asthma; in contrast, no risk factors showed significant association with frequent exacerbations in patients with severe asthma.

A previous observational study of the utilisation and costs of severe uncontrolled asthma (SUA) reported that age, sex, comorbidities and history of exacerbation were associated with asthma utilisation in SUA compared with non-SUA.[9] However, the study only included patients with persistent asthma, and the definition used for persistent asthma could be inconsistent with persistent asthma in a clinical setting. The study used the Health Effectiveness Data and Information Set (HEDIS) persistent asthma criteria, where patients were included if they met the criteria every year for two consecutive years. However, it might be more appropriate to define persistent asthma with three or more consecutive years of HEDIS criteria, including both ED visits and hospitalisations as markers of persistent asthma.[27] A descriptive study of asthma-related healthcare utilisation and direct costs in Korea included patients with varying severities of asthma.[12] However, due to its cross-sectional design with 1 year of data, the study population was followed up for less than 1 year, which was not long enough to observe time-dependent relationships between asthma severity and exacerbation or to account for the risk factors of exacerbation. A previous study analysing the risk factors of asthma-related healthcare use found that higher age, being female, chronic asthma, medication compliance and history of exacerbation were independent risk factors for increased asthma-related healthcare use.[8] However, as the study included only 736

patients from tertiary hospitals in South Korea, the study could not represent the general asthma patient population, considering only 5% of asthma patients are reported to be managed in tertiary hospitals.[28] Most previous studies reported an association between each risk factor and asthma exacerbation,[21–24 29–32] but no previous observational studies have been performed to comprehensively investigate all of the risk factors included in our study.

To our knowledge, this is the first population-based observational study focusing on the difference in association between risk factors and asthma exacerbation according to severity. In agreement with previous studies,[9 19] we found that a history of exacerbation and comorbidities including GERD, allergic or chronic rhinitis, sinusitis, atopic dermatitis, depression and anxiety were more prevalent in severe asthma. Among them, allergic rhinitis and history of CS burst or hospitalisation were significantly associated with asthma exacerbation, whereas good adherence was associated with reduced risk of asthma exacerbation. However, patients with severe asthma showed no significant relationship between their disease severity and comorbidities excluding allergic rhinitis compared with those with mild or moderate asthma. Despite 44% of severe asthma patients having GERD, the association between severe asthma and GERD was insignificant, which is in line with the fact that anti-reflux therapy had little effect on asthma control in severe asthma.[33] In addition, a previous study has reported high prevalence of undiagnosed psychiatric morbidity in difficult asthmatics,[34] which might explain the lack of significant findings between anxiety or depression and exacerbation in moderate or severe asthma. Another explanation is that anxiety or depression may be less likely to be associated with asthma exacerbation in moderate or severe asthma patients, as suggested by a meta-analysis that did not find a benefit of psychological interventions on asthma outcomes.[35] A small number of patients with each comorbidity may also explain the insignificant results in cases of severe asthma.

In addition, patients of 45–65 years of age and ≥65 years of age accounted for 39% and 29% of the study population, respectively, which was similar to a previous study in South Korea.[28] Compared with other countries,[36 37] our study population was relatively older, which can be partly explained by the fact that Korean adults and children have an average age of asthma onset later than that of other populations.[38] However, higher age did not have a significant association with exacerbation in severe asthma, even though the proportion of the elderly was higher. Therefore, these results could suggest that patients with severe asthma were more likely to experience exacerbations regardless of their age or comorbidities, while patients with mild or moderate asthma were likely to experience exacerbations due to the risk factors. High adherence was associated with a decrease in asthma exacerbation in patients with moderate or severe asthma, but not in those with mild asthma, indicating that low adherence became an important risk factor of asthma exacerbation as severity

increased. Considering that more than half of patients with moderate or severe asthma reported an MPR<20%, the current management of adherence to asthma medication in Korea was suboptimal. In fact, a previous study reported that the average adherence to asthma medication was 30%–70%.[39 40]

Another finding was that risk factors for frequent exacerbation were different according to asthma severity. Two observational studies reported risk factors associated with frequent ED visits,[32 41] but the effect of each risk factor based on asthma severity was unknown. Our analysis found that the comorbidities, including allergic rhinitis, atopic dermatitis and anxiety, and history of CS burst were associated with frequent exacerbation in patients with mild and moderate asthma, while no risk factors were significant in severe asthma, possibly resulting from only 125 patients of severe asthma having one or more exacerbations in the measurement period. Although it was difficult to obtain significant results in severe asthma, our results could support the importance of managing risk factors of frequent exacerbation in mild and moderate asthma.

Our study had several strengths. First, use of the NSC database can yield representative results and overcome the limitations of previous study that recruited a small number of patients only from tertiary hospitals.[8 15] Second, as we analysed the risk factors of asthma exacerbation according to asthma severity, our segmented results suggested that the association between the risk factors and exacerbation should not be overlooked in patients with mild and moderate asthma, even though a lower proportion of them had the risk factors, compared with patients with severe asthma. Third, our study demonstrated that there were different associations between adherence to medication and risk of exacerbation according to asthma severity. The association reported in previous studies was inconsistent, partly due to differences in study designs and included patients.[42–45] Our study showed that poor adherence in moderate and severe asthma patients was more associated with exacerbation than that in mild asthma, thus providing a basis for the importance of managing adherence with increasing asthma severity.

Some potential limitations should be considered when interpreting our findings. First, as the measurements of comorbidities and exacerbations were based on the diagnoses in claims data, there is the potential for inaccuracies in coding and incompleteness of records. However, previous studies have validated ICD-10 code-based definitions for diabetes and acute myocardial infarction (AMI), which were compared with medical records reviews, demonstrating positive predictive values of 72.3% to 87.2% for diabetes and >70% for AMI.[46 47] Second, due to our definition of severity, patients prescribed with medium- to high-dose ICS/LABA, who would have been classified as having severe asthma according to GINA recommendations, were classified as having moderate asthma in our analysis. In addition, mild, moderate and severe asthma should be assessed retrospectively from the

treatment required to control symptoms.[4] However, due to the lack of clinical records in the database, we could not identify patient's daytime asthma symptoms, night waking and activity limitations, which are necessary in determining whether asthma was well controlled. Consequently, the severity of mild or moderate asthma defined in our study could be higher than that of the GINA recommendations. Third, residual confounding may exist due to the observational nature of this study. Several variables that could affect the outcomes were not fully captured in the database, including smoking status, spirometry data, education, socioeconomic factors and the proper use of controller or reliever medication.

CONCLUSIONS

This study suggests that there were different associations between asthma exacerbation and the risk factors of age, sex, comorbidities, history of exacerbation and adherence according to asthma severity. In patients with mild and moderate asthma, the management of the risk of exacerbation should consider their age, sex, history of exacerbation and comorbidities including GERD and chronic rhinitis. With increasing asthma severity, the risk of exacerbation should be carefully managed by considering allergic rhinitis, history of exacerbation and adherence to medication. Given the struggle clinicians have had to manage asthma and prevent exacerbations, professional organisations must address the relevant risk factors and intensify evidence-based guidelines.

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