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The Association between Asthma and Invasive Pneumococcal Disease: A Nationwide Study in Korea

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The purpose of this study was to investigate the association between asthma and invasive pneumococcal disease (IPD) in Korea. A retrospective population-based cohort study was conducted using the Korean Health Insurance Review and Assessment database 2010-2011. The subjects included 935,106 (2010) and 952,295 (2011), of whom 398 (2010) and 428 (2011) patients with IPD were identified. There was significant difference in the prevalence of IPD in patients with and without asthma (0.07% vs. 0.02% in 2010 and 0.08% vs. 0.01% in 2011; $P < 0.001$). After adjusting for age and gender, patients with asthma showed over a three-fold increased risk of IPD compared with patients without asthma (adjusted odds ratio [aOR] 3.90, 95% confidence interval [CI] 3.02-5.03 in 2010 / aOR, 5.44; 95% CI, 4.10-7.22 in 2011; $P < 0.001$). These findings were also significant in children (aOR, 2.08; 95% CI, 1.25-3.45 in 2010; $P = 0.005$ / aOR, 3.26; 95% CI, 1.74-6.11 in 2011; $P < 0.001$). Although diabetes mellitus was also significantly associated with IPD, relatively low ORs compared with those of asthma were noted (aOR, 1.85; 95% CI, 1.35-2.54 in 2010 / aOR, 2.40; 95% CI, 1.78-3.24 in 2011; $P < 0.001$). Both children and adults with asthma are at increased risk of developing IPD.

Keywords: Asthma; Invasive Pneumococcal Disease; Diabetes Mellitus

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a Gram-positive diplococcus that causes a variety of diseases in both children and adults. Invasive pneumococcal disease (IPD) includes meningitis, sepsis, and complicated pneumonia, and is a major cause of morbidity and mortality worldwide, particularly among patients with certain underlying illnesses (1). In Korea, although population-based incidence data of IPD is not available, several retrospective multicenter studies reported epidemiology and clinical features of IPD (2-4). In a study including children and adults, 168 cases of IPD were identified, and 54.8% of patients have underlying conditions which 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended (2). A pediatric multicenter study showed that the proportion of *S. pneumoniae* among invasive bacterial infections was 21.9% (1996-2000), 24.1% (2001-2005), and 23.2% (2006-2010) in children (3, 4).

Asthma is a clinical condition that is now considered to be a risk factor for the development of IPD. Recently, it is recommended to administer pneumococcal vaccines for children with asthma aged < 71 months who are treated with high-dose oral corticosteroids in the Advisory Committee on Immunization Practices (ACIP), and Korean guideline (5-7). Furthermore, the ACIP recommends pneumococcal polysaccharide vaccination for adults aged < 65 yr with chronic lung diseases such as asthma, chronic obstructive lung disease (COPD), and emphysema (8). There have been limited studies regarding asthma and the risk of IPD (9-11).

Talbot et al. (9) demonstrated that both children and adults with asthma had over a two-fold increased risk of IPD compared to those without asthma (aOR, 2.4; 95% CI, 1.9-3.1), and patients with high-risk asthma had a high chance of developing IPD (aOR, 2.6; 95% CI, 2.0-3.5). Juhn et al. (10) reported that adults with asthma had a more than six times higher risk of IPD and pneumococcal pneumonia than those without asthma. Another study conducted in Finnish adults also found that asthma was an independent risk factor for IPD, with the highest rates in high-risk asthma (OR, 12.3; 95% CI, 5.4-28.0) compared to low-risk asthma (OR, 2.8; 95% CI, 2.1-3.6) (11). In contrast, another study using data from the US Veteran's Administration Health Care system found that patients with COPD had an increased risk of hospitalization for pneumococcal pneumonia, but this relationship has not been shown in asthma (12). However, population-based study for asthma as a risk factor for pneumococcal infection including both adults and children is scarce.

In this study, we conducted a nationwide population-based study using a database from the Korean Health Insurance Review and Assessment (HIRA) Service to evaluate an association between asthma and IPD in Korean adults and children.

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MATERIALS AND METHODS

Study population

The databases of the Korean HIRA from January 2010 to December 2011 were analyzed. HIRA is a compulsory health insurance system covering the entire Korean population, and all medical reimbursement records are included in the database. As a result, the HIRA database is a useful source of nationwide epidemiologic data.

Patients with asthma as a principal or secondary diagnosis were identified by searching for codes of the International Classification of Diseases, Tenth Revision (ICD-10). Codes used to identify asthma patients were J30, J82, J450, J451, J459, J460, J461, J468, and J469. The differential diagnosis of asthma and COPD in older patients is difficult, thus patients under 65 yr were included in this study to maximize exclusion of confounding factors (9, 11). Patients with diabetes mellitus (DM), using codes of E10 through E14, were also identified to compare to patients with asthma as a risk factor for pneumococcal infection.

Ascertainment of IPD cases

IPD is defined as an acute illness associated with the isolation of *S. pneumoniae* from normally sterile body fluids such as blood, cerebrospinal fluid, pleural fluid, and joint fluid. In our study, IPD cases were identified by searching for ICD-10 codes of pneumococcal sepsis (A403), meningitis (G001), pericarditis (I301), pneumonia (J13), and arthritis (M001).

Study design

A retrospective population-based cohort study was constructed, and healthcare utilization data was analyzed. Patients were categorized into two groups such as children and adolescents (aged less than 18 yr of old) and adults (aged between 19 and 65 yr of old).

Data analysis

Prevalence of IPD was provided along with its number of patients using Korean insurance claim database of HIRA for each of 2010 and 2011 yr. An association of IPD prevalence with asthma, as well as with DM, was examined using chi-square test. The relationship of prevalence between IPD and asthma or DM was analyzed. Crude odds ratios (OR) and its 95% confidence interval (CI) for IPD with asthma, and also with DM, were obtained. As a multivariate analysis, multiple logistic regression analysis was performed to adjust age and sex. Statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA). All reported *P* values are two-tailed and a *P* value less than 0.05 is considered as the minimum level of statistical significance.

Ethics statement

This study protocol was approved by the institutional review board of Konkuk University Medical Center, Seoul, Korea (IRB No. KUH1090025). Informed consent was waived by the board.

RESULTS

A total of 935,106 patients in 2010 and 952,295 patients in 2011 were included in this study. From them, a total of 398 (2010) and 428 (2011) patients with IPD were identified, representing 42.6 (2010) and 44.9 (2011) cases per 100,000 persons in the HIRA database. Of these, 323 (2010) and 371 (2011) patients had asthma. There was a significant difference in the IPD prevalence between patients with and without asthma: 0.07% vs. 0.02% in 2010 and 0.08% vs. 0.01% in 2011 ($P < 0.001$) (Table 1). A significant difference in IPD prevalence in patients with and without asthma was also found in both age groups: 0.05% vs. 0.01% in the adult group ($P < 0.001$ in both 2010 and 2011) and 0.11% vs. 0.03% ($P < 0.001$ in 2010) and 0.13% vs. 0.02% ($P < 0.001$ in 2011) in the children and adolescents group.

After adjusting for age and gender effects in multivariate analysis, patients with asthma had an increased risk of IPD, with aORs of 3.90 (95% CI, 3.02-5.03; $P < 0.001$) in 2010 and 5.44 (95% CI, 4.10-7.22; $P < 0.001$) in 2011 compared with the patients without asthma (Table 2). While DM was also significantly associated with IPD, relatively low ORs were observed (aOR, 1.85; 95% CI, 1.35-2.54; $P < 0.001$ in 2010, while aOR, 2.40; 95% CI, 1.78-3.24; $P < 0.001$ in 2011).

In the adults group, asthma was significantly associated with IPD, having aORs of 3.60 (95% CI, 2.66-4.87; $P < 0.001$) in 2010 and 4.88 (95% CI, 3.53-6.74; $P < 0.001$) in 2011. DM was significantly associated with IPD in 2011 (aOR, 1.77; 95% CI, 1.29-2.41; $P < 0.001$), but it was not associated with IPD in 2010 (aOR, 1.34; 95% CI, 0.96-1.86; $P = 0.083$).

In children under 19 yr of age, asthma was also associated with an increased risk of IPD, with aORs of 2.08 (95% CI, 1.25-3.45; $P = 0.005$) in 2010 and 3.26 (95% CI, 1.74-6.11; $P < 0.001$) in 2011. However, DM was not a risk factor for IPD in both year

Table 1. Comparison of presence of invasive pneumococcal disease in patients with asthma and diabetes mellitus

Diseases	2010		2011	
	IPD (n = 398)	Non-IPD (n = 934,708)	IPD (n = 428)	Non-IPD (n = 951,867)
Asthma				
Yes	323* (0.07)	466,971 (99.93)	371* (0.08)	481,784 (99.92)
No	75 (0.02)	467,737 (99.98)	57 (0.01)	471,083 (99.99)
DM				
Yes	53† (0.05)	98,633 (99.95)	64‡ (0.06)	104,705 (99.94)
No	345 (0.04)	836,075 (99.96)	364 (0.04)	847,162 (99.96)

Values provided are number of cases (%). *$P < 0.001$ compared with patients without asthma; †$P = 0.073$ compared with patients without DM; ‡$P = 0.009$ compared with patients without DM. IPD, invasive pneumococcal disease; DM, diabetes mellitus.

Table 2. Results of multivariate analysis of asthma and diabetes mellitus for invasive pneumococcal disease

Variables	2010		2011	
	cOR (95% CI)	aOR (95% CI)	cOR (95% CI)	aOR (95% CI)
Total				
Asthma	4.31* (3.36-5.55)	3.90* (3.02-5.03)	6.35* (4.81-8.39)	5.44* (4.10-7.22)
DM	1.30 (0.98-1.74)	1.85† (1.35-2.54)	1.42§ (1.09-1.86)	2.40† (1.78-3.24)
0-18 yr				
Asthma	3.37* (2.07-5.48)	2.08‡ (1.25-3.45)	6.37* (3.47-11.71)	3.26* (1.74-6.11)
DM	0.78 (0.11-5.54)	1.12 (0.16-7.99)	1.41 (0.35-5.68)	2.33 (0.58-9.44)
19-65 yr				
Asthma	3.68* (2.72-4.97)	3.60* (2.66-4.87)	4.97* (3.60-6.86)	4.88* (3.53-6.74)
DM	2.01† (1.48-2.75)	1.34 (0.96-1.86)	2.28† (1.71-3.05)	1.77† (1.29-2.41)

By multivariate logistic regression analysis adjusting patient's age and sex. *$P < 0.001$ compared with patients without asthma; †$P < 0.001$ compared with patients without DM; ‡$P = 0.005$ compared with patients without asthma; §$P = 0.009$ compared with patients without DM. cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval; DM, diabetes mellitus.

of 2010 (aOR, 1.12; 95% CI, 0.16-7.99; $P = 0.914$) and 2011 (aOR, 2.33; 95% CI, 0.58-9.44, $P = 0.236$).

DISCUSSION

Among the subjects of our study, individuals with asthma had over a three-fold increased risk of IPD after adjustment for age and gender (aOR, 3.90; 95% CI, 3.02-5.03; $P < 0.001$ in 2010, while aOR, 5.44; 95% CI, 4.10-7.22; $P < 0.001$ in 2011). Significant association was also observed in children and adolescents (aOR, 2.08; 95% CI, 1.25-3.45; $P = 0.005$ in 2010, while aOR, 3.26; 95% CI, 1.74-6.11; $P < 0.001$ in 2011). This implies that asthma was associated with a risk of developing IPD in both children and adults. Relatively low ORs were also observed in patients with DM in whom pneumococcal vaccination had been recommended (aOR, 1.85; 95% CI, 1.35-2.54; $P < 0.001$ in 2010, while aOR, 2.40; 95% CI, 1.78-3.24; $P < 0.001$ in 2011).

While there are a number of studies that have described effect of clinical risk factors such as COPD, immunosuppression, and chronic liver and renal disease in patients with IPD (13-15), there is limited data on the association of asthma with IPD (9-12). Since then the first report was published in 2005 by Talbot et al. (9), further studies were carried out in the US and Finland. The US study, which included subjects aged 2-49 yr in Tennessee Medicaid recipients, showed that patients with asthma are at increased risk of IPD, with aOR of 2.4 (95% CI, 1.9-3.1) for IPD compared to controls without asthma (9). This risk was greater in patients with high-risk asthma with more severe disease requiring medication or frequent hospital admissions (4.2 episodes/10,000 persons with high-risk asthma vs. 2.3 episodes/10,000 persons with low-risk asthma vs. 1.2 episodes/10,000 persons without asthma). The Finnish study included adults aged 18-49 yr and reported similar results with previous studies (11). It found that asthma was an independent risk factor for IPD (7.1% of patients with IPD and 2.5% of controls had asthma; 6.0% of patients with IPD and 2.4% of controls had low-risk asthma; 1.1% of patients with IPD and 0.1% of controls had high-risk asthma, respectively). They also reported an increased risk of IPD, with the highest rates in high-risk asthma (OR, 12.3; 95% CI, 5.4-28.0) compared to low-risk asthma (OR, 2.8; 95% CI, 2.1-3.6). In another US study using a retrospective case-control design was conducted in adults in Rochester, Minnesota, USA between 1964 and 1983, the pre-pneumococcal vaccine era (10). That study showed that serious pneumococcal disease was associated with asthma among adults (aOR, 6.7; 95% CI, 1.6-27.3; $P = 0.01$), whereas the association was not significant among children (aOR, 0.4; 95% CI, 0.05-3.42; $P = 0.40$), likely due to the small number of cases. However, a study using data from the US Veteran's Administration Health Care System found that patients with COPD had an increased risk of hospitalization for pneumococcal pneumonia, but those with asthma did not (12).

Even though there has been limited investigation regarding the association between asthma and IPD in children, some authors recently analyzed pneumococcal infections in children with chronic underlying diseases including asthma (14, 16). A Danish study reported that adjusted risk rate ratio of IPD in children with asthma was 1.1 (95% CI, 0.7-1.6) (14). However, the US pediatric study found that, even if not receiving corticosteroid therapy, children with asthma developed pneumococcal pneumonia more often than children without risk factors (65% vs. 31%; $P < 0.05$) (16).

Differences of findings among these studies may be related to the different data sources, study populations including races and age, outcomes, and analytical methods employed (11).

In our study, we restricted our study population aged 0-65 yr to exclude patients with COPD and demonstrated that patients with asthma had over a 3-5 times increased risk of IPD, which is consistent with the previous studies. Although lower ORs were observed in children compared to adults, asthma was also associated with the risk of developing IPD in children. Since there were insufficient data to evaluate asthma as a risk factor for developing IPD in children, further studies examining pediatric patients with asthma are necessary.

In patients with asthma, several pathological alterations in

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the airways could be associated with an increased risk for IPD. Remodeling of the respiratory tract due to chronic inflammation, which is characteristic of the disease, is accompanied by impaired mucociliary bronchial clearance, increased production of sputum, and airway obstruction (1, 11, 17). These respiratory structural abnormalities can be served as a focus for viral infections, which might predispose a patient to development of invasive bacterial infections (1, 11, 18, 19). Patients with asthma can also be at risk for colonization with *S. pneumoniae* and, when the bacteria is present, are at greater risk of occurrence and exacerbation of IPD (9, 10, 20). Moreover, long-term treatment with corticosteroids may be associated with increased risk for pneumococcal disease because of their immunosuppressive action (1, 11, 21, 22). A recent study reported that inhaled corticosteroids were associated with colonization of *S. pneumoniae*; thus inhaled and oral corticosteroids might increase the risk for the development of pneumococcal disease in patients with asthma (21). Finally, impaired innate and adaptive immunity may play a role in developing pneumococcal infection (1). An increased risk of serious pneumococcal diseases in patients with atopic conditions other than asthma was demonstrated in studies by Jung et al. (23). Although these conditions are not accompanied by airway inflammation or remodeling, they share immunological mechanisms similar to those of asthma. Polymeric immunoglobulin receptor (plgR), a pneumococcal specific human receptor for pneumococcal choline binding protein A (CbpA) that causes transcytosis of *S. pneumoniae* across epithelial cells, has been understood to increase in patients with asthma via production of IL-4 (24, 25). De Schutter et al. (26) found that bronchial bacterial infection is associated with persistent wheezing in young children; and *S. pneumoniae* is one of the common pathogens in preschoolers with persistent wheezing. Therefore, a defective immunologic mechanism may be associated with increased pneumococcal disease in patients with asthma.

After widespread use of 7-valent pneumococcal conjugate vaccine (PCV7), IPD cases attributable to all pneumococcal serotypes decreased by 45% (from 24.4 to 13.5 cases per 100,000 population), and PCV7-serotypes decreased by 94% (from 1,535 to 1.0 cases per 100,000 population) in all age groups in the US (27). Even if pneumococcal vaccination is targeted towards children and high-risk individuals, it was not recommended for patients with asthma in the Centers for Disease Control and Prevention (CDC) guidelines published in 2000, because asthma was not considered a possible risk factor for the development of IPD in children and adults (28). The ACIP and Korean guidelines recommend pneumococcal conjugate vaccination for children with asthma aged < 71 months if they are treated with prolonged high-dose oral corticosteroids and for adults aged < 65 yr with asthma (without mention of any definition of severity or treatment) (5-8). Moreover, they recommend a single dose of 13-valent pneumococcal conjugate vaccine (PCV13) and PPSV23 after completing all recommended doses of PCV13 for children with chronic medical conditions aged 6-18 yr. These medical conditions are considered to increase the risk of IPD and include sickle cell disease, asplenia, HIV infection, other immunocompromising conditions, cochlear implantations or cerebrospinal fluid leaks. Children not receiving prolonged high-dose oral corticosteroids and children with asthma aged > 6 yr are excluded. However, previous studies have demonstrated that patients with mild asthma, even if not receiving corticosteroid therapy, were more likely to develop IPD than healthy controls (9-11, 14, 16). In our study, it is also found that both children and adults with asthma were at greater risk of developing IPD compared to those with DM. Some reports suggest that broadening recommendations regarding vaccinations to include patients with asthma should be considered (11, 29). Since there are limited data available for the role of pneumococcal vaccination in asthma, further studies are required to evaluate the burden of pneumococcal disease and immune responses of pneumococcal vaccination in patients with asthma.

The strength of this study was large population and robustness of the database used. We evaluated the association between asthma and IPD in children and adults, using population-based data in a nationwide health care system setting.

However, retrospective nature of study design is a limitation. Although a broad category of codes to identify IPD was used, it was possible to miss mild IPD cases. We also did not include other confounding factors such as previous pneumococcal vaccination status, coexisting conditions, smoking, corticosteroid use, previous antibiotics use, and socioeconomic status. In addition, we did not compare the association between IPD and asthma according to severity of asthma.

In conclusion, asthma is associated with a risk of developing IPD in both children and adults. Further studies are needed to elucidate the association between asthma and IPD, and the effectiveness of pneumococcal vaccination in patients with asthma.

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DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceived and designed the study: Choung JT, Park YM. Ana-

lyzed the data: Kwak BO, Choung JT, Park YM. Wrote the first draft of the manuscript: Kwak BO. Wrote the paper: Kwak BO, Choung JT, Park YM. ICMJE criteria for authorship read and met: Kwak BO, Choung JT, Park YM. Agree with manuscript results and conclusions: Kwak BO, Choung JT, Park YM. Reviewed and approved the final version of the manuscript: Kwak BO, Choung JT, Park YM.

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