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Asthma and severity of 2009 novel H1N1 influenza: A population-based case-control study

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Abstract

Background—Asthma has been shown to be associated with an increased risk of the 2009 novel H1N1 influenza (H1N1) infection among children. However, little is known about the role of asthma in severity of H1N1 infection.

Objective—To determine the association between asthma and other atopic conditions and severity of H1N1 infection.

Patients and Methods—We conducted a population-based case-control study. Cases were all Olmsted County, MN residents admitted to the hospital within a week of a positive test for H1N1. Controls who had a positive H1N1 but were not admitted to hospital were individually matched to cases with regard to birthday, gender, clinic registration date, diagnostic method, and calendar month of influenza testing. Asthma was ascertained using predetermined criteria. Data were fit to conditional logistic regression models.

Results—There were 46 eligible individuals admitted to hospitals with H1N1 infection during the study period. Ninety-seven controls were individually matched to their corresponding cases. Among cases, 23 (50%) were male and 29 (63.0%) were Caucasians. The median age at hospitalization was 20.7 years. Twenty-five (54.4%) cases had asthma before the date of hospitalization, compared to 33 (34.0%) controls (matched OR: 2.31; 95% CI, 1.13–4.73; $p=0.02$). This association approached statistical significance after adjusting for all pertinent covariates (adjusted matched OR: 2.55; 95% CI, 0.98–6.64; $p=0.055$).

Conclusion—Asthma may be associated with severe H1N1 infection. In addition to timely influenza vaccination for asthmatics, consideration for prophylactic treatment for unimmunized asthmatics with significant exposure to influenza and immunized asthmatics with early flu-like symptoms should be given.

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Keywords

H1N1; severity; asthma; atopy; risk; epidemiology

INTRODUCTION

In April of 2009, the Centers for Disease Control and Prevention (CDC) reported the first cases of H1N1 in California. Shortly thereafter, the virus had spread throughout the world. As of July 25, 2010, WHO had reported more than 214 countries affected by H1N1 influenza with more than 18,000 deaths worldwide.¹ Individuals with asthma and other atopic conditions (i.e. atopic dermatitis and/or allergic rhinitis) have been reported to have suboptimal innate and adaptive immune functions against microbial agents.^{2–11} Indeed, previous studies showed that people with asthma had increased risk of microbial infections than those without asthma.^{12–20} A recent prospective study that compared rates of H1N1 infection between children with and without asthma showed that children with asthma had a higher risk of H1N1 infection during the second peak of the pandemic than non-asthmatics.²¹

Several reports from different countries identified asthma as the single most common comorbid condition among hospitalized individuals with H1N1 infection, with rates of asthma ranging from 10% to 32%.^{22–25} However, these studies did not include concurrent control groups for their investigations. Thus, although it provides circumstantial evidence, it is still unknown whether asthma increases severity of H1N1 infection. No population-based case-control study has been conducted to determine the association between asthma and severity of H1N1 infection using predetermined criteria for asthma (instead of self-report or ICD-9 codes).

We hypothesized that individuals with asthma have more severe H1N1 infections than individuals without asthma. To test this hypothesis, we conducted a population-based nested case-control study using all residents of Olmsted County, MN, who were admitted to the hospital after developing community-acquired H1N1 influenza during the study period (6/1/2009 to 11/30/2009) and their matched controls. During this period, CDC reported that almost all (98%) positive influenza A cases were due to H1N1 influenza.²⁶ Also, as a secondary aim, we determined which subgroup of asthmatics developed severe H1N1 influenza infection. This information will be helpful for determining the extent to which asthma status affects the severity of influenza caused by an emerging influenza strain, such as the new avian influenza A (H7N9) virus.

METHODS

The Institutional Review Boards at both Mayo Clinic and Olmsted County Medical Center approved this study.

Study design

We designed the study as a population-based case-control study comparing the frequency of asthma between patients admitted to the hospital with H1N1 infection (cases) and their

matched H1N1-infected non-hospitalized controls. Severe H1N1 influenza was defined as hospitalization with H1N1. The study period was between June 1, 2009, to November 30, 2009, during the second wave of the 2009 H1N1 influenza pandemic.²⁷ Controls were individually matched to the corresponding cases by birthday, gender, first clinic registration date, and calendar month for the test for influenza.

Study setting

Study subjects were residents of Olmsted County, MN. According to the 2010 U.S. Census, the population of Olmsted County was 144,248 with preponderance of whites.²⁸ Despite a higher proportion of healthcare workers, the population of Olmsted County has a demographic distribution similar to the upper Midwest.^{29,30} Olmsted County, MN, has unique epidemiologic advantages for retrospective case-control studies. The health care environment is self-contained (two medical centers provide medical care to more than 95% of all residents). In addition, medical records of all residents of Olmsted County, MN, are linked and available for approved medical research under the auspices of the Rochester Epidemiology Project, which has been continuously funded for 40 years by the NIH.^{31,32}

Study population

Eligibility criteria—Residents of Olmsted County, MN, of all ages and both genders with a positive test for influenza A from a respiratory source (nares, nasopharyngeal swab, and throat swab or bronchioalveolar lavage) during the study period were eligible for the study. During the H1N1 pandemic, the diagnostic tests for influenza used in Olmsted County were real-time RT-PCR or commercial influenza rapid test. To ensure community exposure for H1N1, if an individual was tested for influenza after being discharged from the hospital, the testing date must be 2 or more days from the date of hospital discharge. If an individual was tested for influenza after being admitted to the hospital, the testing date had to be no more than 2 days after the date of hospital admission. If an individual was discharged from the hospital without influenza and then readmitted and tested for H1N1, there must be at least 2 days between the two hospitalizations.

Exclusion criteria—The exclusion criteria included: 1) non -Olmsted County residency at the time of the test for influenza, 2) insufficient information on medical records to determine the exposure status (asthma or other atopic conditions), or 3) no research authorization for using patients' medical records for research. Additional exclusion criteria included clinical conditions which made ascertainment of asthma status difficult. These conditions included: 1) pulmonary function tests that showed FEV₁ to be consistently below 50% predicted or diminished diffusion capacity, 2) tracheobronchial foreign body at or about the incidence date of asthma, 3) wheezing occurring only in response to anesthesia or medications, 4) bullous emphysema or pulmonary fibrosis on chest radiograph, 5) PiZZ alpha₁-antitrypsin, 6) cystic fibrosis, or 7) other major chest disease such as severe kyphoscoliosis or bronchiectasis.

Identification of cases and controls

Case ascertainment: Severe H1N1 influenza (cases) was defined as hospitalization with H1N1. Cases were all Olmsted County, MN, residents who were hospitalized with H1N1

infection. Hospital admission could occur within 7 days of a positive test result for influenza A during the study period. For individuals tested for influenza after being admitted to the hospital, the test must be performed within the first 48 hours of hospitalization. During the study period, cases from Mayo Clinic were prospectively identified and ascertained by the Infection Prevention and Control Unit of Mayo Clinic, based on clinical and laboratorial evidence of H1N1 infection. We recorded the date of the first positive influenza A test and the date of hospital admission (the index date for hospital admission).

Identification of controls: From the microbiology databases at both Mayo Clinic and Olmsted Medical Center, we selected a random sample of controls having a positive test for influenza A from each institution but who had not been admitted to hospitals using individual matching (1:3 matching). The matching criteria included gender, birthday (within 6 months for patients younger than 18 years and within 1 year for patients 18 years and older), H1N1 test date within 1 month, and clinic registration date within 1 year. Although we intended to identify three controls per case, due to the difficulty of finding controls who met the individual matching criteria, the number of control per case varied from one to three resulting in unbalanced matching.

Ascertainment of exposure status (i.e., asthma status)—Asthma status of cases and controls was ascertained using predetermined criteria delineated in Table 1, which has been extensively used in epidemiologic research for asthma and was found to be highly reliable.³³ Definite and probable asthma were included in the analysis, since most probable asthmatics become definite over time.^{34,35} In order to ascertain temporal relationship between the exposure (asthma status) and outcome (H1N1 related hospitalization), the incidence dates of asthma (i.e., the date when one met the criteria for asthma) in all study subjects were recorded. Since H1N1-related hospitalization could be due to exacerbation of asthma (instead of H1N1 infection), we defined hospital admission due to asthma exacerbation instead of H1N1 infection alone as the use of systemic corticosteroids given at index date of hospitalization or during the hospital admission.

Other variables—We collected the following information from the medical records: sociodemographic variables, asthma severity at index date based on medication use (use of inhaled corticosteroids), history of medical visits related to asthma exacerbations in the 6 months prior to H1N1 index date (i.e., a proxy measure of asthma control status), other atopic conditions (atopic dermatitis and/or allergic rhinitis), comorbid conditions associated with influenza complications,³⁶ smoking status (either active or passive exposure), 2008–2009 seasonal influenza vaccine, and antibiotic use within 1 week prior to the testing date for H1N1.

Data analysis

The primary aim of analysis was to determine whether asthma status was associated with H1N1-related hospitalization by fitting data to conditional logistic regression models taking into account matching. The data was summarized with descriptive statistics, including counts and percentages for categorical variables or medians for continuous variables. We characterized the study subjects and assessed similarity between cases and their

corresponding controls. We conducted univariate analyses to identify all pertinent covariates and confounders. For categorical variables, the 2-sample chi-square test was used to compare the distribution of a variable of interest between cases and controls. For discrete or continuous variables, we used the Wilcoxon rank sum test to compare medians. Conditional logistic regression models were used to estimate the matched OR and their corresponding 95% CI for the association between asthma or other atopic conditions and risk of H1N1-related hospitalization. We performed multivariate analysis to adjust the main results for all pertinent covariates. All analyses were carried out with the JMP statistical software package (Version 9.0.1; SAS Institute, Inc, Cary, NC) and STATA (Version 11; StataCorp LP, College Station, TX).

RESULTS

Study subjects

Characteristics of the subjects are summarized in Table 2. We initially identified 54 patients who were admitted to hospitals with H1N1 infection during the study period. Among these 54 patients, 46 cases were eligible and 8 were excluded (4 cases did not provide research authorization, and 4 cases met other exclusion criteria). From the pool of eligible controls, 97 subjects who were individually matched to cases were eligible and available for this study. Of the 46 cases, 23 (50.0%) were male and 29 (63.0%) were Caucasians. The median age at H1N1 index date was 20.7 (IQR 7.4–47.4), and 25 (54.3%) were younger than 18 years. There were no differences in ethnicity between cases and controls. Four cases received oseltamivir prior to H1N1 index date (8.7%), compared to none in the control group. One individual in the group of cases died during his H1N1-related hospitalization. The estimated sensitivity of RT-PCR for H1N1 in respiratory specimens was 99.3% and the specificity 92.3%.³⁷ For the influenza rapid tests used in Olmsted County during the H1N1 outbreak, a recent study in the pediatric population estimated a sensitivity of 62% and a specificity of 99%.³⁸

Asthma and severity of H1N1 infection (hospitalization with H1N1 influenza)

The summary of the association between asthma and H1N1-related hospitalization is shown in Tables 3 to 6. Asthma was the single most common comorbid condition found among cases and controls. Twenty-five (54.4%) of the 46 cases had asthma before the H1N1 index date, compared to 33 (34.0%) of the 99 control subjects (OR; 2.59; 95% CI, 1.10–6.09; $p=0.02$). In the multivariate model adjusted for comorbid conditions and history of previous smoking exposure, the association between asthma and H1N1-related hospitalization approached statistical significance (adjusted OR: 2.54; 95% CI 0.98–6.64; $p=0.055$).

In the subgroup analysis among asthmatics alone, there was no association between the current use of inhaled corticosteroids at index date of hospitalization and the risk of H1N1-related hospitalization (OR: 0.68; 95% CI 0.22–2.10; $p = 0.50$). However, H1N1-related hospitalization was strongly associated to wheezing at the index date of hospital admission (OR: 14.85; 95% CI, 4.10–53.82; $p < 0.001$) as well as to a burst course of systemic corticosteroid therapy administered at index date of hospital admission (surrogate for asthma exacerbation) (OR: 5.57; 95% CI 1.75–17.70; $p=0.003$). H1N1-related hospitalization was

also associated to previous history of sick visits due to asthma symptoms (OR: 4.07; 95% CI, 1.08–15.37; $p=0.031$) and previous history of one or more burst courses of systemic corticosteroids in the 6 months prior to the index date of hospital admission. (OR: 4.40; 95% CI, 1.27–15.15; $p=0.015$).

In the subgroup analysis among hospitalized individuals with asthma ($n=25$), the administration of a burst course of systemic corticosteroids at index date of hospitalization was not associated with the median duration of hospitalization (2 days for both groups, $p=0.241$), ICU admission rate (10.0% among non-receivers vs. 40.0% among receivers, $p=0.102$), the frequency of diagnosis of pneumonia (30.0% among non-receivers vs. 33.3% among receivers, $p=0.861$), and the frequency of antibiotic use (70.0% among non-receivers vs. 66.7% among receivers, $p=0.861$). In addition, among hospitalized subjects, there were no differences in the median duration of illness at index date of hospitalization, duration of hospitalization, frequency of antibiotic use, or frequency of diagnosis of pneumonia between individuals with and without asthma.

Other variables and H1N1-related hospitalization

Among the 46 cases, atopic dermatitis and/or allergic rhinitis were present in 19 (41.3%), compared to 46 (47.4%) among the 99 matched controls. This association was not statistically significant (OR: 0.80; 95% CI, 0.37–1.71; $p=0.56$). The presence of one or more comorbid conditions was associated with H1N1-related hospitalization infection (OR: 6.52; 95% CI, 2.12–20.09; $p=0.001$). The history of previous smoking exposure was also associated with the risk of H1N1-related hospitalization (OR: 2.98; 95% CI, 1.02–8.71; $p=0.046$). Neither the educational level nor the history of prior 2008–09 seasonal influenza vaccine was associated with the risk of H1N1-related hospitalization. Only one individual in the control group and none among the cases received the H1N1 vaccine prior to H1N1 index date.

DISCUSSION

Our study results show a potential impact of asthma status on the risk of H1N1-related hospitalizations; taking into consideration all matching variables, other comorbid conditions, and previous smoking exposure.

Our study is the first population-based case-control study which assessed the potential association between asthma and severity of H1N1 infection. The initial matched analysis showed a significant association between asthma and H1N1 (matched OR: 2.59; 95% CI, 1.10–6.09; $p=0.02$) taking into account all matching variables (age, gender, season, duration of follow up, institution, and H1N1 test positivity, access to health care). However, when the data were fitted to a multivariate model to control additional covariates (comorbidities and previous smoking exposure), the results approached statistical significance, most likely due to a limited statistical power (i.e., type II error). Post-study calculation showed only 25% power (type II error: 0.75) to detect the effect size observed based on the sample size studied. H1N1-related treatments (oseltamivir) or vaccinations did not seem to impact the likelihood of hospitalizations, given the small number of subjects treated or vaccinated against H1N1 infection. Susceptibility bias stemming from other factors is also less likely,

given the matching between cases and controls for the aforementioned pertinent variables. Identification and ascertainment of cases were prospectively performed independent of asthma status and the intent of the current study. Detection bias arising from different medical care-seeking behavior or different H1N1 ascertainment method between individuals with and without atopic conditions could happen. However, our controls were selected from the pool of those who had a positive test for influenza at the same time as their matched cases, and they were also matched by diagnostic method, minimizing the possibility of this bias. In our study, asthmatics appear to be significantly overrepresented among controls compared to the general population,^{39–41} probably due to increased care-seeking behavior. Therefore, the association between asthma and the risk of severe H1N1 infection might be undermined in our study.

The influence of asthma on H1N1-related hospitalization could be due to asthma exacerbation triggered by H1N1, given the significant association between the burst courses of systemic corticosteroid treatment at index date of hospitalization and the risk of hospital admission. However, when we examined the relationship between a burst course of systemic corticosteroids and other severity measures for H1N1 infection (i.e. duration of hospitalization, ICU admission rate, frequency of pneumonia, and antibiotic use), it did not significantly influence these disease severity measures for H1N1 infection. Moreover, recent studies suggested that H1N1 infection is unlikely to affect asthma control status during the H1N1.^{21,42} Taken together, given the difficulty to discern temporality and nature of asthma exacerbation, we postulate that both severity of H1N1 infection and asthma exacerbation are likely to be responsible for increased hospitalization among asthmatics, especially those with poorly controlled asthma at the time of exposure to H1N1 infection.

During the H1N1 influenza pandemic, two independent studies conducted in the U.S. and Australia-New Zealand showed that the majority of individuals (73%) who developed severe H1N1 influenza (i.e., admitted to inpatient floor or ICU) had underlying chronic conditions.^{24,43} Among those conditions, asthma as the single most common comorbid condition among patients admitted to inpatient floor or ICU (28% and 32.7% in the U.S. and Australia-New Zealand studies, respectively). Similarly, asthma was the most common chronic condition among cases in our study. Other studies corroborated these results.^{22–24,43,44} These studies, however, have a significant limitation of not having a concurrent control group to compare rates of influenza infection or asthma ascertainment based on self-report or ICD-9 codes. In a recent prospective study conducted in children, asthma was associated with the risk of H1N1 infection and H1N1 infection increased severity of cold symptoms compared to other viruses.²¹ This study, however, was not specifically designed to evaluate the risk for H1N1-related hospitalization.

The mechanisms for the potential influence of asthma on the severity of H1N1 infection need to be investigated. Immunosuppression due to the use of inhaled corticosteroids is unlikely to account for the association since it did not show an increased risk of lung infections in asthmatics,⁴⁵ although it was shown in patients with COPD.^{46,47} Several studies showed evidence of impairments of the innate and acquired immunity among asthmatics.^{8,10,11,48,49} These impairments could compromise the host's ability to clear microbial organisms (viruses or bacteria) from the airways, increasing the risk of invasive

infection. A recent study showed severe influenza was associated to increased virus-specific CD4⁺ T cells in blood and increased concentration of CD8 lymphocytes in the lung, suggesting immune dysregulation in the lymphocytic response to H1N1 might contribute to the severity of H1N1 infection.⁵⁰ Alternatively, previous studies showed that influenza infection could increase the risk of bacterial pneumonia through excessive expression of negative immune regulators (e.g., IL-10).^{51,52} However, whether or not asthma affects those immunologic mechanisms needs to be determined.

The main strengths of our study include the epidemiologic advantages, including the self-contained healthcare environment and the linkage of medical records for research among healthcare providers in our study setting, which facilitates the reliable ascertainment of asthma and H1N1-related hospitalization. Our study had a population-based design, which should minimize selection bias. Controls were randomly identified from the same sampling frame as cases minimizing detection bias. Finally, this study allowed an opportunity to study the effect of a new influenza strain in a population with no prior immunity to the infecting strain.

Our study has inherent limitations due to its retrospective design. We did not include clinical tests or biomarkers for severity of H1N1. However, hospitalization has been used in clinical studies as a proxy measure for severity of illness, especially in infectious diseases. Not all pertinent variables (e.g., allergy sensitization) were available for this study. This limitation is likely to be subject to a non-differential misclassification bias. Our data abstractors were not blinded, which could introduce performance bias. However, the ascertainment criteria for asthma were specific and objective, which should minimize this bias.^{33,53}

In conclusion, individuals with asthma, especially those with poorly controlled asthma, may have more severe H1N1 infection than non-asthmatics. In addition to timely influenza vaccination for asthmatics, consideration for prophylactic treatment for unimmunized asthmatics with significant exposure to influenza and immunized asthmatics with early flu-like symptoms should be given.

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Abbreviations

CDC	Centers for Disease Control and Prevention
COPD	Chronic Obstructive Pulmonary Disease
FEV1	Forced expiratory volume in one second
FVC	Forced Vital Capacity
H1N1	2009 novel H1N1 influenza
HRV	Human Rhinovirus

ICU	Intensive Care Unit
NIH	National Institutes of Health
OR	Odds Ratio
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
WHO	World Health Organization

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Table 1

Definition of asthma in medical records

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present; and they were considered to have *probable* asthma if only the first two conditions were present:

- 1** History of cough, dyspnea, and/or wheezing or history of cough and/or dyspnea plus wheezing on examination,
- 2** Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and
- 3** Two or more of the following:
 - Sleep disturbance by nocturnal cough and wheeze
 - Nonsmoker (14 yrs. or older)
 - Nasal polyps
 - Blood eosinophilia higher than 300/uL
 - Positive wheal and flare skin tests or elevated serum IgE
 - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing one FEV1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV1 of higher 70% predicted or methacholine challenge test showing 20% or greater decrease in FEV1
 - Favorable clinical response to bronchodilator

Table 2

Sociodemographic and clinical characteristics of patients with H1N1-related hospitalization and their matched control subjects

	Controls (N=97)	Cases (N=46)	OR (95%CI), p-value
Age at case's index date (years)			
Median (IQR)	19.0 (5.9–41.2)	20.7 (7.4–47.4)	-
Age group, n (%)			
Younger than 18 years	46 (47.4)	21 (45.7)	-
Age 18 years or older	51 (52.6)	25 (54.3)	-
Gender, n (%)			
Male	41 (42.3)	23 (50.0)	-
Female	56 (57.7)	23 (50.0)	-
Detection Method			
PCR	90 (92.8)	42 (91.3)	-
Rapid antigen test detection	7 (7.2)	4 (8.7)	-
Time of illness prior to index date of hospitalization (days)			
Median (IQR)	2 (1–4)	3 (1–7)	$\hat{\tau}$ p = 0.130
Ethnicity, n (%)			
Non-Caucasians	19 (19.6)	13 (28.3)	Referent
Caucasians	66 (68.0)	29 (63.0)	0.65 (0.26–1.65), 0.369
Unknown	12 (12.4)	4 (8.7)	0.54 (0.14–2.11), 0.374
*Educational status, n (%)			
High school or less	14 (14.4)	10 (21.8)	Referent
Education higher than high school	32 (33.0)	7 (15.2)	0.50 (0.16–1.56), 0.230
Unknown	51 (52.6)	29 (63.0)	1.98 (0.46–8.49), 0.360
History of receiving the 2008–09 seasonal influenza vaccine, n (%)			
No	42 (43.3)	26 (56.5)	Referent
Yes	55 (56.7)	20 (43.5)	0.52 (0.24–1.14), 0.103
**History of smoking exposure, n (%)			
No	67 (69.1)	26 (56.5)	Referent
Yes	17 (17.5)	16 (34.8)	2.98 (1.02–8.71), 0.046
Unknown	13 (13.4)	4 (8.7)	0.93 (0.21–4.15), 0.921
***Comorbid conditions other than asthma prior to index date, n (%)			See results below
Neuromuscular disorders	4 (4.1)	6 (13.0)	-
Hemoglobinopathies	0 (0.0)	1 (2.2)	-
Cardiac disease	6 (6.2)	6 (13.0)	-
Chronic pulmonary disease	1 (1.0)	4 (8.7)	-
Chronic renal disease	2 (2.1)	3 (6.5)	-
Endocrine/metabolic conditions	10 (10.3)	13 (28.3)	-

	Controls (N=97)	Cases (N=46)	OR (95%CI), p-value
Autoimmune/immunosuppressive treatment	3 (3.1)	1 (1.0)	-
Hepatic disease	1 (1.0)	0 (0.0)	-
Cancer	1 (1.0)	6 (13.0)	-
Comorbid conditions other than asthma prior to index date, n (%)			
None	76 (78.35)	23 (50.0)	Referent
Any	21 (21.65)	23 (50.0)	6.52 (2.12–20.09), 0.001

* For children, parent's educational status was used.

** For children <15 years, smoking exposure was passive smoking; for subjects ≥15 years, smoking exposure included active smoking. Smoking exposure included past history of smoking or active smoking at H1N1 index date.

*** Comorbid conditions were not mutually exclusive because subjects could have more than one condition.

[†] Wilcoxon rank sum test was used to compare medians.

Table 3

Adjusted OR for the association between asthma and the risk of H1N1-related hospitalization

History of Asthma prior to index date	Controls N=97 (%)	Cases N=46 (%)	Unadjusted OR (95% CI), p-value	[‡] Adjusted OR (95% CI), p-value
No	64 (66.0)	21 (45.6)	Referent	Referent
Yes	33 (34.0)	25 (54.4)	2.59 (1.10–6.09), 0.029	2.55 (0.98–6.64), 0.055

[‡]OR was based on matched analysis adjusted for comorbid conditions and previous smoking exposure in the multivariate model.

Table 4

Sub-group analyses of asthmatic patients diagnosed prior to index date of hospitalization

	Control (N=33)	Cases (N=25)	[‡] OR (95%CI), p-value
Current use of inhaled corticosteroids at index date of hospitalization n (%)			
No	21 (63.6)	18 (72.0)	Referent
Yes	12 (36.4)	7 (28.0)	0.68 (0.22–2.10), 0.502
History of sick visits related to asthma in the 6 months prior to the index date of hospitalization, n (%)			
No	28 (84.9)	14 (60.9)	Referent
Yes	5 (15.1)	11 (39.1)	4.40 (1.27–15.15), 0.015
Burst of systemic steroids in the 6 months prior to index date of hospitalization, n (%)			
No	29 (87.9)	16 (64.0)	Referent
Yes	4 (12.1)	9 (36.0)	4.07 (1.08–15.37), 0.031
Wheezing at index date of hospitalization, n (%)			
No	26 (78.8)	5 (20.0)	Referent
Yes	7 (21.2)	20 (80.0)	14.85 (4.10–53.82), <0.001
Systemic steroids given at index date of hospitalization, n (%)			
No	26 (78.8)	10 (40.0)	Referent
Yes	7 (21.2)	15 (60.0)	5.57 (1.75–17.70), 0.003

[‡]OR was based on unmatched analysis.

Table 5

Sub-group analyses of hospitalized patients

	Non-asthmatics N=21	Asthmatics N=25	[‡] OR (95%CI), p-value
Median duration of hospitalization (IQR)	2 (1–3)	2 (1–3.5)	[†] p = 0.337
Diagnosis of pneumonia during hospitalization, n (%)			
No	15 (71.4)	17 (68.0)	Referent
Yes	6 (28.6)	8 (32.0)	1.17 (0.33–4.17), 0.801
Use of antibacterials during hospitalization, n (%)			
No	9 (42.9)	8 (32.0)	Referent
Yes	12 (57.1)	17 (68.0)	1.59 (0.48–5.32), 0.447
ICU admission during hospitalization, n (%)			
No	18 (85.7)	18 (72.0)	Referent
Yes	3 (14.3)	7 (28.0)	2.33 (0.52–10.48), 0.261

[‡]OR was based on unmatched analysis.[†]Wilcoxon rank sum test was used to compare medians.