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Original Article

Adult asthmatics increase the risk of acute coronary syndrome: A nationwide population-based cohort study ☆

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ABSTRACT

Objectives: Few studies have examined the risk of acute coronary syndrome (ACS) in asthmatics. We investigate the effects of asthma on the risk of ACS development in an Asian population.
Methods: Asthma patients aged ≥18 years were identified, and asthma-free controls were randomly selected from the general population and frequency-matched according to age, sex, index year, and baseline comorbidity by using the National Health Insurance Research Database. Both cohorts were followed up until the end of 2011 to measure the incidence of ACS. The risk of ACS was analyzed using Cox proportional hazards regression models.
Results: We observed the asthmatic patients for 97,506 person–years and followed the nonasthmatic people for 193,423 person–years. The incidence density rate of ACS increased in all groups of the asthmatic patients compared with those of the controls when the data were stratified according to sex, age, and comorbidities. The hazard ratio (HR) of ACS was 1.66-fold greater in the asthmatic cohort than in the nonasthmatic cohort, after adjusting for sex, age, and comorbidities (95% confidence interval [CI]: 1.31–2.11). The adjusted HR of developing ACS increased substantially as age and the frequency of asthmatic exacerbation and hospitalization increased.
Conclusions: Asthma is an independent risk factor of ACS, and poor control of asthma increases the risk of ACS development in a dose-dependent manner.

What is already known about this subject?

Few studies have examined the risk of acute coronary syndrome (ACS) in asthmatics. Systemic inflammation associated with acute exacerbation in addition to the presence of shared risk factors.

What does this study add?

We investigate the effects of asthma on the risk of ACS development in an Asian population. Asthma is an independent risk factor of ACS, and poor control of asthma increases the risk of ACS development in a dose-dependent manner.

1. Introduction

Acute coronary syndrome (ACS) represents a group of symptoms attributed to sudden reductions in blood flow in the coronary arteries. This syndrome, which includes unstable angina and myocardial infarction with or without ST-segment elevation, is a life-threatening disorder that leads to high morbidity and mortality despite advances in treatment [1,2]. Hypertension, diabetes, and hyperlipidemia are well-established major cardiovascular risk factors of atherosclerosis progression, which contributes to the development of ACS [3,4]. Cerebrovascular diseases and cardiovascular diseases share similar risks in the disorders of the circulatory system [5]. Studies have recently reported that chronic obstructive pulmonary disease (COPD) associated

Abbreviations: ACS, Acute coronary syndrome; COPD, chronic obstructive pulmonary disease; NHIRD, National Health Insurance Research Database; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; SABAs, short-acting beta-2 agonists; LABAs, long-acting beta-2 agonists; HRs, hazard ratios; CIs, confidence intervals; ER, emergency-room.

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with reduced lung function is a strong risk factor for cardiovascular events, independent of smoking [6,7]. This can be explained by systemic inflammation associated with acute exacerbation in addition to the presence of shared risk factors [8].

Asthma is a common chronic inflammatory disease of the airway that is characterized by airway hyperresponsiveness to irritative stimuli and reversible airflow obstruction. Asthma can cause symptoms of recurrent episodes of wheezing, breathlessness, chest tightness, and coughing [9]. As many as 300 million people of all ages and racial backgrounds are currently estimated to have asthma, and the impact of which on health-care systems, families, and patients is increasing worldwide [9]. Current asthma treatments, whether preventative or medicinal, are intended to control rather than cure the disease.

Inflammatory processes are key participants in the pathophysiology of atherosclerotic disease and hypertension [10–12]. Studies have recently detected elevated concentrations of thrombin in the sputum of asthmatic patients [13,14]. Furthermore, studies have reported that asthma is connected with prothrombotic factors and endothelial dysfunction in the development of atherothrombosis [15–17]. However, few studies have examined the risk of ACS in asthmatics [18,19]. We conducted a Taiwan-wide population-based cohort study to investigate whether the asthmatic patients increase the risk of ACS development in an Asian population.

2. Methods

2.1. Data source

We conducted a nationwide retrospective cohort study based on data obtained from the universal Taiwan National Health Insurance Research Database (NHIRD), which contains health-care claims filed between 1996 and 2011. The National Health Insurance (NHI) program covers 99.9% of the 23.74 million people in the Taiwanese population [20]. The NHIRD contains registration data on the outpatient visits, hospital admissions, prescriptions, and disease status of all insurants. The data used in this study were derived from a subdataset of the NHIRD that comprises one million randomly sampled beneficiaries enrolled in the NHI program in 2011 and contains all records on these insurants from 1996 to 2011. In this study, secondary data were analyzed after deidentification; therefore, no informed consent was required. This study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012) and the Research Ethics Committee of the National Health Research Institutes, Taiwan.

2.2. Sampled patients

Patients aged 18 years and older with newly diagnosed asthma (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] Code 493) were identified based on the 2000–2010 claims dataset, and the date of diagnosis of asthma was defined as the index date. To ensure the accuracy of asthma diagnosis, we included patients treated with inhaled corticosteroids (ICSs), inhaled short-acting beta-2 agonists (SABAs), or inhaled long-acting beta-2 agonists (LABAs) in the asthmatic cohort. Patients with ACS (ICD-9 Codes 410–411.1) or chronic ischemic heart disease (ICD-9 Code 414) before the index date were excluded. Controls were selected among people without a history of asthma, ACS, or chronic ischemic heart disease recorded in the claims dataset. The people in the nonasthmatic cohort were randomly assigned index dates as in the case of the asthmatic cohort and were frequency-matched according to age (5-year strata), sex, baseline comorbidity history of hypertension (ICD-9 Codes 401–405), diabetes (ICD-9 Code 250), hyperlipidemia (ICD-9 Code 272), stroke (ICD-9 Codes 430–438), heart failure (ICD-9 Code 428), COPD (ICD-9 Codes 490–492, 494 and 496) and smoking (ICD-9 Code 305.1), and index year at an approximate ratio of 2:1.

2.3. Diagnosis of asthma

The diagnosis of asthma in this study is based on physicians. The physicians took a history of variable respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough. The physicians conducted physical examination and may arrange a pulmonary function test including bronchodilator test or twice-daily measurements of peak expiratory flow rate over two weeks. National Health Insurance Administration can audit the diagnosis and management codes by the physicians. Several Taiwan-based studies have demonstrated the high accuracy and validity of the diagnoses in cardiology and pulmonology used here [21,22].

2.4. Main outcome

To compare the incidence of ACS between the 2 cohorts, the participants were followed from the index date until the occurrence of ACS, record termination because of death or withdrawal from the insurance system, or the end of 2011.

2.5. Statistical analysis

The differences in the distributions of sex, age, and baseline comorbidities between the asthmatic and nonasthmatic cohorts were assessed using chi-square tests and *t* tests. The incidence for ACS (per 1000 person–years) was calculated in both cohorts. The univariable and multivariable Cox proportional hazards regression analyses were used to assess the ACS risk associated with asthma, and the hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. The multivariable model was developed by controlling for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, heart failure and COPD. We further analyzed the data to assess the effect of the dose response of asthmatic exacerbation on the risk of ACS according to the number of emergency-room (ER) visits and hospitalizations required for asthma. We divided the asthmatic cohort into 4 mutually exclusive groups according to the drug-treatment status: [1] treatment with ICS; [2] treatment with ICS and inhaled SABA; [3] treatment with ICS and inhaled LABA; and [4] treatment with any above medicine and oral or IV steroids. The Kaplan–Meier analysis was used to plot the cumulative incidence, and the log-rank test was used to examine the differences between the 2 cohorts. All analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) and the Kaplan–Meier survival curve was plotted using R software (R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at $P < .05$ in 2-sided tests.

3. Results

3.1. Demographic characteristics and comorbidities of asthmatic and nonasthmatic cohorts

We analyzed 2000–2010 data on the 13,049 newly diagnosed asthmatic patients in the asthmatic cohort and 25,791 nonasthmatic people in the comparison cohort (Table 1). Both cohorts had similar sex and age distributions. The mean age (±SD) was 50.9 ± 17.4 years in the asthmatic cohort and 50.5 ± 17.5 years in the nonasthmatic cohort. Comorbidities were also similar in the asthmatic cohort and in the nonasthmatic cohort, except heart failure and smoking.

3.2. Incidence and hazard ratios of acute coronary syndrome stratified according to sex, age, and comorbidity: comparison between the asthmatic cohort and the nonasthmatic cohort

The overall incidence of ACS was 1.66-fold greater in the asthmatic cohort than in the nonasthmatic cohort (1.30 vs 0.78 per 1000 person–years), with a crude HR of 1.66 (95% CI = 1.56–1.79) (Table 2). After