Atherosclerosis 226 (2013) 263–268

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

# Risk of myocardial infarction in patients with rhinosinusitis

Wen-Rui Hao [a], Hui-Wen Lin [b,c], Pin-Zhir Chao [d], Chin-Wen Wu [e], Tze-Hsun Yen [e], Ju-Chi Liu [a], Tsan-Hon Liou [e,f,*]

[a] Department of Cardiovascular Medicine, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
[b] Department of Mathematics, Soochow University, Taipei, Taiwan
[c] Evidence-Based Medicine Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[d] Department of Otolaryngology, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
[e] Department of Physical Medicine and Rehabilitation, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
[f] Graduate Institute of Injury Prevention, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

*Article history:*
Received 1 March 2012
Received in revised form
22 October 2012
Accepted 23 October 2012
Available online 2 November 2012

*Keywords:*
MI
Rhinosinusitis
Risk factors
Incidence
Epidemiology

ABSTRACT

Research has indicated that inflammation promote all phases of atherosclerosis. The current study tested the hypothesis that rhinosinusitis is a risk marker for myocardial infarction (MI). Data on the general population were obtained from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005). The study cohort comprised patients who had received a recorded diagnosis of rhinosinusitis ($N = 52{,}930$) between January 1, 2004 and December 31, 2004. The comparison group consisted of patients who had not received a rhinosinusitis diagnosis, and who were matched for age and sex with the study group at a ratio of 4 controls to 1 study patient (1:4) ($N = 211{,}720$). Each patient's condition was followed using database entries until the end of 2006. Cox proportional hazard regressions were used to evaluate the 3-year MI-free survival rates, after adjusting for known confounding factors. We found that patients with rhinosinusitis were more likely than the control group to have MI, after adjusting for potential confounders [adjusted hazard ratio (HR), 1.84; 95% confidence interval (CI), 1.44 ~ 2.40]. Of the total 264 650 patients, 290 experienced MI during the 3-year follow-up period, including 8 acute sinusitis patients, 77 chronic sinusitis patients, and 205 control patients. The incidence rate of MI was 6.19 (95% CI 5.01–7.65) per 10,000 person-years for rhinosinusitis patients, compared to 3.51 (95% CI, 3.06–4.02) for the control patients. From this study, rhinosinusitis may be associated with MI. Further research in this important area of public health is warranted.



## 1. Introduction

Rhinosinusitis is defined as inflammation of the mucosa of the nose and paranasal sinuses characterized by 2 or more symptoms [1]. The manifestation of rhinosinusitis includes post-nasal drip, nasal blockage, mucopurulent nasal discharge, and facial pain associated with affected sinuses. According to a study, 3 in every 1000 people have rhinosinusitis in the United States each year [2]. The condition has become one of the major causes of out-patient clinic visits, and results in a substantial loss in working time and usage of medical resources [3]. Bacteria and viruses are 2 common etiologic factors in rhinosinusitis, followed by local anatomic or systemic factors (asthma, cystic fibrosis, allergy, and so on). The pathogens of infectious rhinosinusitis are usually multi-microbial, such as *Streptococcus pneumonia, Haemophilus influenza*, and rhinovirus, which are the predominant organisms in afflicted patients. Medical treatment comprises major therapy of rhinosinusitis and often includes a regimen of broad spectrum antibiotics [4]. Minimal invasive functional endoscopic surgery is rarely used and is reserved for refractory chronic rhinosinusitis [5].

Myocardial infarction (MI) constitutes a major disease worldwide. By 2025, according to a recent study, cardiovascular mortality on a global scale will exceed that of every other major disease, including trauma, infection, and cancers [6,7]. Because of its severity and high mortality, great efforts have been made to combat the disease. The Framingham Heart Study revealed the typical risk factors for atherosclerosis, and health care practitioners have attempted to reduce these conventional risk factors to prevent MI [8]. However, certain studies have shown that atherosclerosis cannot be explained purely by the conventional risk factors.

* Corresponding author. Graduate Institute of Injury Prevention, Taipei Medical University, 250 Wu-Hsing St., Taipei 110, Taiwan. Tel.: +886 2 2249 0088x1600; fax: +886 2 2248 0577.
*E-mail address:* peter_liou@s.tmu.edu.tw (T.-H. Liou).

0021-9150/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosis.2012.10.058

One study revealed that only 50% of the risk of atherosclerosis can be explained by conventional and established risk factors [9]. This finding stimulated further research to identify further risk factors for atherosclerosis, and several new emerging risk factors have been reported [10]. In addition, infection may participate in the process of atherosclerosis [11,12].

In a study by Rochat, rhinosinusitis and ischemic stroke were shown to be associated [13]. Our previous epidemiological study also found that people with rhinosinusitis were more likely to suffer from stroke than those without this condition [14]. The correlation between rhinosinusitis and MI, another prevalent cardiovascular disease, had not yet fully explored. However, researchers have linked infection in general as a risk factor to various atherosclerotic diseases, including acute MI [15,16]. The present study examined whether a relationship between rhinosinusitis and MI could be confirmed, in which case we would propose a new risk marker for MI.

## 2. Methods

### 2.1. Study design and study population

Our study samples were obtained from Taiwan's Longitudinal Health Insurance Database 2005 (LHID2005), which is available to researchers interested in observing longitudinal changes in medical utilization. Taiwan's National Health Insurance (NHI) program provides health insurance to more than 99% of the country's population, with over 25 million enrollees [17]. The LHID2005 contains the entire claims data of 1,000,000 beneficiaries, randomly sampled from the 25.68 million beneficiaries listed with the Registry for Beneficiaries in the NHI's Research Database (NHIRD). The claim files contain details on ambulatory care, inpatient care, pharmacy use, date of service, ICD-9-CM (International Classification of Diseases) diagnostic codes, and claimed medical expenses. The procedure of sampling was described in detail elsewhere [16,17].

We selected from the ambulatory care claims data patients who had received a diagnosis of rhinosinusitis with the ICD-9-CM codes of 461 (acute sinusitis) or 473 (chronic sinusitis) between January 1, 2004, and December 31, 2004. Patients who had been identified as having at least 2 previous ICD-9-CM diagnoses of rhinosinusitis were included. Patients younger than 18 years were excluded, as were those who had MI before having rhinosinusitis. The comparison controls were selected blinded to outcome by SAS package program. For each patient with rhinosinusitis, four persons were selected randomly by the computer software for comparison. In our comparison cohort, patients who had been diagnosed as having rhinosinusitis in 2004–2006 or having rhinosinusitis before 2004 were excluded. We randomly stratified the selected 211,720 subjects (four for every patient in the study cohort) matched with those in the study cohort in terms of age (18–45, 46–65 and >65 years) and entry year. The entry date of comparison cohort was assigned their first out-patient visit during entry year. Our cohorts comprised 52,930 patients with rhinosinusitis and 211,720 controls. Each case was followed up from the patient's entry date until either the occurrence of MI (ICD-9-CM codes 410 and 412) or for a follow-up period of up to 3 years, or until the end of the study period on December 31, 2006.

### 2.2. Statistical analysis

After matching patients from the 2 cohorts for age and sex, we used Pearson's Chi-squared tests or Fisher's exact test to compare the differences between the 2 groups. The results are shown in Table 1. We then calculated the 3-year MI hazard ratio using Cox's regression model [18] to examine differences in the risk of MI between the 2 cohorts, after adjusting for patients' age, sex, geographic region, and urbanization level, as well as for the comorbidities of diabetes mellitus (DM), hypertension, hyperlipidemia, COPD (chronic obstructive pulmonary disease), CAD (coronary artery disease), asthma and cancer. Urbanization was stratified into 3 levels. All 359 cities or towns in Taiwan had already been stratified into 7 levels according to the standards published by National Health Research Institute, with level 1 referring to "most urbanized" and level 7 referring to "least urbanized." For our study, levels 1 and 2 were combined into a single group, referred to as urban; levels 3 and 4 were combined into a single group, referred to as suburban; and the remaining three levels (5, 6, and 7) were combined into a single group, referred to as rural.

To meet the proportional hazards assumption, each dichotomous variable in the model was checked for proportionality by investigative diagnostic log–log survival plots. Confidence intervals for incidence rates were evaluated according to a common application of Poisson confidence intervals using the R package. A Kaplan–Meier plot for different conditions associated with patient survival, and the nonparametric log-rank test, were used to compare the survival distributions of the 2 cohorts. All data

**Table 1**
Baseline variables for sinusitis patients and patients in the comparison cohort, 2004 ($N = 264,650$).

| Baseline variables | Sinusitis patients $n = 52930$ | | Comparison patients $n = 211720$ | | $p$ value |
|---|---|---|---|---|---|
| | Total no. | % | Total No. | % | |
| Age (years) | | | | | |
| 18–45 | 36472 | 68.9 | 145888 | 68.9 | |
| 45–65 | 13385 | 25.3 | 53540 | 25.3 | |
| >65 | 3073 | 5.8 | 12292 | 5.8 | |
| Gender | | | | | |
| Male | 21261 | 40.2 | 85044 | 40.2 | |
| Female | 31669 | 59.8 | 126676 | 59.8 | |
| Monthly income | | | | | <0.001 |
| 0 | 12296 | 23.2 | 48988 | 23.1 | |
| NT$1–16,000 | 5784 | 10.9 | 28833 | 13.6 | |
| NT$16,001–26,000 | 19594 | 37.0 | 81319 | 38.4 | |
| ≥ NT$26,001 | 15256 | 28.8 | 52580 | 24.8 | |
| Urbanization level | | | | | <0.001 |
| Urban | 33667 | 63.6 | 127259 | 60.1 | |
| Suburban | 14588 | 27.6 | 61870 | 29.2 | |
| Rural | 4675 | 8.8 | 22591 | 10.7 | |
| Geographic region | | | | | <0.001 |
| Northern | 25792 | 48.7 | 103369 | 48.8 | |
| Central | 13119 | 24.8 | 47950 | 22.6 | |
| Southern | 13213 | 25.0 | 55510 | 26.2 | |
| Eastern | 806 | 1.5 | 4891 | 2.3 | |
| Cancer diseases | | | | | 0.008 |
| Yes | 874 | 1.7 | 3158 | 1.5 | |
| No | 52056 | 98.3 | 208562 | 98.5 | |
| Diabetes mellitus | | | | | 0.336 |
| Yes | 2667 | 5.0 | 10453 | 4.9 | |
| No | 50263 | 95.0 | 201267 | 95.1 | |
| Hypertension | | | | | <0.001 |
| Yes | 6030 | 11.4 | 21974 | 10.4 | |
| No | 46900 | 88.6 | 189746 | 89.6 | |
| Hyperlipidemia | | | | | <0.001 |
| Yes | 4008 | 7.6 | 12074 | 5.7 | |
| No | 48922 | 92.4 | 199646 | 94.3 | |
| COPD | | | | | <0.001 |
| Yes | 2351 | 4.4 | 5399 | 2.6 | |
| No | 50579 | 95.6 | 206321 | 97.4 | |
| CAD | | | | | <0.001 |
| Yes | 2123 | 4.0 | 6691 | 3.2 | |
| No | 50807 | 96.0 | 205029 | 96.8 | |
| Asthma | | | | | <0.001 |
| Yes | 2389 | 4.5 | 4220 | 2.0 | |
| No | 50541 | 95.5 | 207500 | 98.0 | |