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Original Article

The effect of rheumatoid arthritis on the risk of cerebrovascular disease and coronary artery disease in young adults

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Abstract

Background: Only a few studies have investigated the affect of rheumatoid arthritis (RA) on the risk of cerebrovascular disease (CVD)/coronary artery disease (CAD) in young adults. This study, therefore, examined the association between RA and the risk of CVD/CAD in young adults and the interaction effects between cardiovascular risk factors and RA on the risk of CVD/CAD.
Methods: Data regarding 52,840 subjects (10,568 patients with RA and 42,272 age-, sex-, urbanization-, and income-matched non-RA controls) were collected from the National Health Insurance Research Database (NHIRD) in 2006. All subjects were followed until a CVD or CAD diagnosis, or death, or December 31, 2011. The hazard ratios (HRs) of CVD/CAD were estimated using Cox proportional hazard models. The interaction effects between cardiovascular risk factors and RA on the risk of CVD/CAD were assessed using additive and multiplicative models.
Results: RA increased the risk of CVD/CAD in young adults, especially those at risk of ischemic stroke (adjusted HR, 3.48; 95% confidence interval (CI), 2.16−5.61). Even without comorbidity at baseline, patients with RA still had a 2.35-fold greater risk of CVD/CAD relative to those without RA. RA and hypertension interacted positively on the risk of CVD/CAD. The highest CVD/CAD risk was found in patients with RA and hypertension (HR, 9.08; 95% CI, 7.22−11.41) relative to subjects without RA and hypertension.
Conclusion: RA is an independent risk factor for CVD/CAD in young adults. The government should develop policies for preventing early onset hypertension to reduce the incidence of CVD/CAD among young patients with RA.

Keywords: Cerebrovascular disorders; Coronary artery disease; Hypertension; Rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is the most common inflammatory joint disease with a prevalence between 0.5% and 1.0% in industrialized countries.[1] Systemic release of pro-inflammatory cytokines (i.e., IL-1, IL-6, and TNF-α) from RA synovial tissue may promote the inflammatory process underlying atherogenesis. These cytokines either directly affect plaque progression or indirectly promote insulin resistance, dyslipidemia, prothrombotic and antifibrinolytic effects, endothelial activation and dysfunction that lead to atherosclerosis.[2,3] The cumulative evidence shows that systemic inflammation plays a key role in accelerating the development of cerebrovascular disease (CVD) and coronary artery disease (CAD) in patients with RA.[4−12] Moreover, CVD and CAD are

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the main causes of death in patients with RA, accounting for nearly 40% of their mortality.[13] Several traditional risk factors for cardiovascular disease, such as obesity, dyslipidemia, diabetes mellitus, hypertension, age, sex, and smoking, are associated with CVD/CAD, and some of these risk factors are common to patients with RA.[14−17] However, the interaction effects between RA and traditional cardiovascular disease risk factors on the risk of CVD/CAD have remained unclear. Therefore, this study explored whether RA was associated with the risk of CVD/CAD in young adults. We also investigated the interaction effects between traditional cardiovascular risk factors and RA on the risk of CVD/CAD. We analyzed data from the National Health Insurance (NHI) program, which covers more than 99% of the population in Taiwan and is one of the largest and most complete population-based datasets in the world.[18]

2. Methods

2.1. Data sources

We used the data contained in the National Health Insurance Research Database (NHIRD), managed by the NHI program, for this nationwide cohort study. The NHIRD contains data on patient demographics, disease diagnoses, and prescription records (including types of medication, time of prescription, duration of drug supply, and dosage). In this database, diseases are classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and all types of drug use are determined from dispensed prescriptions and are defined according to the Anatomical Therapeutic Chemical (ATC) Classification. Data regarding censoring due to death were obtained from the National Death Registry of Taiwan.

2.2. Study population

A total of 52,840 subjects aged less than 45 years (10,568 patients with RA and 42,272 age-, sex-, urbanization-, and income-matched non-RA controls) were enrolled from the NHIRD in 2006. Patients with RA having more than two consecutive ICD-9-CM code 714.0 diagnoses and concurrent prescriptions of RA-related medications in 2006 were recruited as our RA cohort.[19,20] RA-related medications included disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and biologics. The date of the first diagnosis of RA served as the index date for patients with RA. The index date for non-RA controls was the first day of 2006. We excluded 207 patients with RA and 150,957 non-RA subjects with CVD and CAD histories prior to the respective index dates. Each RA case was frequency matched for four controls by age, sex, urbanization, and monthly income to increase the statistical power and to control for potential confounding factors. We therefore randomly selected 42,272 non-RA controls from 10,036,255 non-RA subjects in 2006 (Fig. 1). This study was approved by the Taipei Medical University Joint Institutional Review Board (Approval No. 201411004).

2.3. Outcome assessment

The study endpoint was the new onset of CVD and CAD, including coronary heart disease, atrial fibrillation, and heart failure, during the six-year follow-up period. We defined patients with coronary heart disease (ICD-9-CM codes 410-414), atrial fibrillation (ICD-9-CM code 427.31), or heart failure (ICD-9-CM code 428) only when the disease was listed as a discharge diagnosis or was confirmed more than twice in the outpatient department. Patients with at least two outpatient visits or one hospital admission for CVD (ICD-9-CM codes 430-437, excluding 432) and who received concomitant imaging of the brain using computed tomography or magnetic resonance imaging were defined as CVD patients. Additionally, CVD patients were divided into the categories of ischemic stroke (ICD-9-CM codes 433-434, 436) and hemorrhagic stroke (ICD-9-CM codes 430-431). All subjects were followed from the index date until the occurrence of CVD/CAD, death, or December 31, 2011.

2.4. Demographic variables and comorbidities

Demographic variables in this study included age, sex, urbanization, and monthly income. In accordance with standards published by the National Health Research Institutes, 359 communities in Taiwan were stratified into seven urbanization levels. Level 1 indicated “most urbanized” and level 7 indicated “least urbanized”.[21] Urbanization levels 1 and 2 were combined and described as urban (high level of urbanization), levels 3 and 4 were combined and described as suburban (medium level of urbanization), and the remaining three levels (5, 6, and 7) were combined and described as rural (low level of urbanization).[22] The insurance premiums were calculated on the basis of the beneficiary's total income; monthly income was estimated for each person. Monthly income was divided into three levels: ≤NT$15,840, NT$15,841−25,000, and ≥NT$25,001.[23] Baseline comorbidities for each patient were hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM codes 272.0-272.4), chronic kidney disease (CKD) (ICD-9-CM codes 250.4, 274.1, 283.11, 403.1, 404.2, 404.3, 404.1, 442.1, 447.3, 580−583, 585, 587, 792.5, 642.1, and 646.2), cancer (ICD-9-CM codes 140-208), alcoholism (ICD-9-CM codes 303.0 and 303.9), peripheral vascular disease (PVD) (ICD-9-CM codes 440.20-440.24, 440.9, 443.81, 443.9, and 444.22), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 403, 416, 491−493, 495−496, 508, 515, 516, and 518), mild liver diseases (ICD-9-CM codes 571.2, 571.3, 571.5, and 573.8), and obesity (ICD-9-CM code 278.0). All comorbidities were required to have been diagnosed at least twice. Medication use included antiplatelets, anticoagulants, DMARDs, NSAIDs, glucocorticoids, and biologics.

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