Reliability of Cardiovascular Risk Calculators to Estimate Accurately the Risk of Cardiovascular Disease in Patients With Sarcoidosis

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Chronic inflammation is an independent risk factor for cardiovascular disease (CVD), but most risk calculators, including the Framingham risk score (FRS) and the American College of Cardiology (ACC)/American Heart Association (AHA) risk score do not account for it. These calculators underestimate cardiovascular risk in patients with rheumatoid arthritis and systemic lupus erythematosus. To date, how these scores perform in the estimation of CVD risk in patients with sarcoidosis has not been assessed. In this study, the FRS and the ACC/AHA risk score were calculated for a previously identified cohort of patients with incident cases of sarcoidosis in Olmsted County, Minnesota, United States, from 1989 to 2013 as well as their gender- and age-matched comparators. The standardized incidence ratio (SIR) was estimated as the ratio of the predicted and observed numbers of CVD events. All CVD events were identified by diagnosis codes and were verified by individual medical record reviews. The predicted number of CVD events among 188 cases by FRS was 11.8 and the observed number of CVD events was 34, which corresponded to an SIR of 2.88 (95% confidence interval 2.06 to 4.04). FRS underestimated the risk of CVD events in patients with sarcoidosis by gender, age and severity of sarcoidosis. The predicted number of CVD events among cases by ACC/AHA risk score was 4.6 and the observed number of CVD events was 19, corresponding to an SIR of 4.11 (95% confidence interval 2.62 to 6.44). In conclusion, the FRS and the ACC/AHA risk score underestimate the risk of CVD in patients with sarcoidosis. **(Am J Cardiol 2017;120:868–873)**

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide. Identification of subjects at high risk of developing CVD is the pivotal first step for appropriate primary interventions. Several multivariable cardiovascular (CV) risk prediction models have been developed to help identify high-risk subjects in the general population, including the Framingham risk score (FRS)[1] and the American College of Cardiology (ACC)/American Heart Association (AHA) risk score.[2] However, those tools may not accurately predict the risk of CVD in patients with chronic inflammatory disorders. Evidence of underestimation of CVD risk by those tools has been demonstrated in rheumatoid arthritis[3,4] and systemic lupus erythematosus.[5] It is unknown how these CV risk models perform in patients with other chronic systemic inflammatory diseases. This study aimed to assess the accuracy of the FRS and the ACC/AHA risk score for the prediction of CVD events in a cohort of patients with incident sarcoidosis in Olmsted County, Minnesota, United States.[6]

Methods

This study utilized a previously identified retrospective population-based cohort of patients with incident sarcoidosis in Olmsted County, Minnesota, from 1989 to 2013. Methods and baseline clinical characteristics of the cohort have been described in detail elsewhere.[6] In brief, potential cases were identified from the medical record-linkage system of the Rochester Epidemiology Project using diagnosis codes related to sarcoid, sarcoidosis, and noncaseating granuloma. The Rochester Epidemiology Project medical record-linkage system provides a comprehensive access to both inpatient and outpatient medical records of all residents of Olmsted County, Minnesota, seeking medical care from all local providers (Mayo Clinic, Olmsted Medical Center, and its affiliated hospitals, local nursing homes, and the few private practitioners). The system allows identification of essentially all clinically recognized cases of sarcoidosis in the community.[7]

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Medical records of those potential cases were individually reviewed. Inclusion in the cohort required a diagnosis of sarcoidosis made by health-care providers supported by presence of noncaseating granuloma on biopsy, radiologic characteristics of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other granulomatous diseases. The sole exception to the requirement of histopathologic confirmation was stage 1 pulmonary sarcoidosis that required only the presence of a symmetric enlargement of bilateral hilar lymph nodes on an imaging study without any other identifiable causes. Isolated extrathoracic sarcoidosis was also included after excluding other causes of granulomatous inflammation. Prevalent cases with sarcoidosis before residency in Olmsted County were not included. For the current analysis, only patients aged 30 to 74 years, similar to the cohort used for the construction of FRS, were included. Subjects who had CVDs before the index date and subjects who took statins on the index date were excluded as those subjects were not included in the Framingham cohorts used for the development of FRS.

A comparator cohort without sarcoidosis was constructed. For each patient with sarcoidosis, 1 comparator without sarcoidosis at the time of the patient's sarcoidosis diagnosis was randomly identified from the same underlying population. The index date for comparators was the sarcoidosis incidence date of the corresponding case. Matching criteria were similar age (±3 years) and same gender.

The medical records of cases and comparators were then individually reviewed for CVD, which included coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular accident (CVA), and peripheral arterial disease (PAD). CAD included both nonfatal and fatal myocardial infarctions. Classification was based on physician diagnosis. Patients who underwent percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were also classified as CAD. The Framingham criteria for CHF were used to classify CHF.[8] CVA was defined as ischemic stroke, hemorrhagic stroke, subarachnoid hemorrhage, or death from CVA. Classification was based on physician diagnosis supported by imaging studies or cerebrospinal fluid analysis. Classification of PAD was based on a resting ankle-brachial systolic pressure index of ≤0.9.[9] Data on baseline CV risk factors necessary for the calculation of the FRS and the ACC/AHA risk score, including gender, ethnicity, height and weight, blood pressure, use of antihypertensive medications, smoking status, diabetes mellitus, cholesterol levels, and use of statins were also collected. To minimize missing data, the closest blood pressure and lipid values to the sarcoidosis incidence or index date within ±2 years and the closest height and weight values within 1 year before and 3 months after sarcoidosis the incidence or index date were used to calculate the risk scores. Follow-up was continued until death, migration, 10 years after index, or January 1, 2015 (whatever came first).

This study was approved by the Mayo Clinic and the Olmsted Medical Center Institutional Review Boards. The need for informed consent was waived.

Descriptive statistics (percentages, means, etc.) were used to summarize the characteristics of cases and comparators. Chi-square and rank-sum tests were used to examine the differences in CV risk factors between cohorts. As patients were seen in routine clinical practice without a standardized protocol for periodic assessment of dyslipidemia, the FRS was selected a priori for the primary CV risk analysis as the office-based FRS version does not require cholesterol levels. The FRS was calculated from published algorithms using lipid values where available, and the office-based version was used when lipids were not available. The ACC/AHA risk score was also calculated from published algorithms, and the risk score values were converted to the predicted number of CVD events in both groups. For patients with <10 years of follow-up, the predicted risk of CVD was adjusted proportionately. To ensure comparability, the observed CVD events were defined according to those used to develop each algorithm, the first of CAD, CHF, CVA, or PAD for FRS and of CAD or CVA for the ACC/AHA risk score. The standardized incidence ratio (SIR) was estimated as the ratio of the observed to the predicted number of CVD events. SIR 95% confidence intervals (CI) were calculated, assuming that the expected rates were fixed and the observed rates followed a Poisson distribution. An SIR of >1 indicated that the observed events were higher than predicted, meaning the predicted risk underestimated the actual risk. Conversely, an SIR of <1 indicated that the predicted risk overestimated the actual risk. A sensitivity analysis including only white patients was performed for the FRS to increase the similarity of the ethnic component to the Framingham cohorts. A p value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In the years 1989 to 2013, 218 patients with incident sarcoidosis aged 30 to 74 years and 218 gender- and age-matched comparators were identified. A total of 30 cases and 48 comparators were excluded from the analysis because of history of CVD before the sarcoidosis index date or statin use at baseline. Among the cases, all but 16 had pulmonary sarcoidosis. The majority of the cases had a stage 1 pulmonary sarcoidosis (93 cases, 54%) followed by stage 2 (50 cases, 29%) and stage 3 to 4 (29 cases, 17%). Forty-four percent of the cases also had an extrathoracic involvement by sarcoidosis. Only 14 patients required immunosuppressive therapy (9 hydroxychloroquine, 4 methotrexate, 2 other disease-modifying antirheumatic drugs, 4 antitumor necrosis factor biologics, and 2 other biologics), and 63 (34%) were treated with prednisone. Table 1 summarizes the demographics and CV risk factors of the subjects in this study.

Data needed for the calculation of the FRS were available in 186 of 188 cases and 139 of 170 comparators. The mean FRS for cases and comparators was 8.2% (SD, 7.7%) and 8.8% (SD, 9.7%), respectively. The predicted number of CVD events among cases was 11.8 and the observed number of CVD events was 34, corresponding to an SIR of 2.88 (95% CI 2.06 to 4.04). The predicted number of CVD events among comparators was 11.0 and the observed number of CVD events was 11, corresponding to an SIR of 1.00 (95% CI 0.56 to 1.81). FRS underestimated the risk of CVD events in patients with sarcoidosis across analyses by gender, age, and severity of sarcoidosis as indicated by the presence of extrathoracic disease and staging of pulmonary disease as described in Table 2. FRS