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

Patompong Ungprasert, MD, MS^{1,2,*}, Eric L. Matteson, MD, MPH^{1,3}, and Cynthia S. Crowson, MS^{1,4}

¹Division of Rheumatology, Department of Internal Medicine, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA ²Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand ³Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA ⁴Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic College of Medicine and Science, Rochester, MN 55905, USA

Abstract

Chronic inflammation is an independent risk factor for cardiovascular disease (CVD) but most risk calculators including Framingham risk score (FRS) and American College of Cardiology (ACC)/American Heart Association (AHA) risk score do not account for it. These calculators underestimate cardiovascular (CV) risk in patients with rheumatoid arthritis and systemic lupus erythematosus. To date, how these scores perform in estimation of CVD risk in patients with sarcoidosis has not been assessed. In this study, FRS and 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 sex and age-matched comparators. The standardized incidence ratio (SIR) was estimated as the ratio of the predicted and observed number of CVD events. All CVD events were identified by diagnosis codes and verified by individual medical record review. The predicted number of CVD events among 188 cases by FRS was 11.8 and the observed number of CVD events was 34, which corresponding to an SIR of 2.88 (95% CI, 2.06 – 4.04). FRS underestimated the risk of CVD events in patients with sarcoidosis by sex, 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% CI, 2.62 – 6.44). In conclusion, FRS and ACC/AHA risk score underestimate the risk of CVD among patients with sarcoidosis.

*Corresponding author; P.U.: P.Ungprasert@gmail.com, Division of Rheumatology, Mayo Clinic, 200 First avenue SW, Rochester, MN 55905, USA, Tel 507-284-8450; Fax 507-284-0564.

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Keywords

Cardiovascular Risk Calculators; Epidemiology; Inflammation

Introduction

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide. Identification of individuals 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 individuals 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 risk of CVD among patients with chronic inflammatory disorders. Evidence of underestimation of CVD risk by those tools has been demonstrated in rheumatoid arthritis (RA)^{3,4} and systemic lupus erythematosus (SLE).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 ACC/AHA risk score for prediction of CVD events in a cohort of patients with incident sarcoidosis in Olmsted County, Minnesota (MN), United States.⁶

Methods

This study utilized a previously identified retrospective population-based cohort of patients with incident sarcoidosis in Olmsted County, MN from 1989 to 2013. Methodology 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 (REP) using diagnosis codes related to sarcoid, sarcoidosis and non-caseating granuloma. The REP medical record-linkage system provides comprehensive access to both inpatient and outpatient medical records of all residents of Olmsted County, MN 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

Medical records of those potential cases were individually reviewed. Inclusion in the cohort required a diagnosis of sarcoidosis made by healthcare providers supported by presence of non-caseating granuloma on biopsy, radiologic characteristics of intrathoracic sarcoidosis, compatible clinical presentation and exclusion of other granulomatous diseases. The sole exception to the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only the presence of symmetric enlargement of bilateral hilar lymph nodes on imaging study without any other identifiable etiologies. Isolated extra-thoracic sarcoidosis was also included after excluding other causes of granulomatous inflammation. Prevalent cases with sarcoidosis prior to residency in Olmsted County were not included. For the current analysis, only patients aged 30 to 74 years, similar to the cohort used for construction of FRS, were included. Subjects who had CVD before index date and

subjects who took statins on 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 sarcoidosis patient, 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 sex.

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 infarction (MI). Classification was based on physician diagnosis. Patients who underwent percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were also classified as CAD. 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 resting ankle-brachial systolic pressure index of less than or equal to 0.9.⁹ Data on baseline cardiovascular risk factors necessary for calculation FRS and ACC/AHA risk score including sex, ethnicity, height/weight, blood pressure, use of anti-hypertensive 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/index date within ± 2 years and the closest height/weight values within 1 year before and 3 months after sarcoidosis incidence/index date were used to calculate the risk scores. Followup 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 differences in CV risk factors between cohorts. As patients were seen in routine clinical practice without a standardized protocol for periodic assessment of dyslipidemia, FRS was selected a priori for the primary CV risk analysis as the office-based FRS version does not require cholesterol levels. FRS was calculated from published algorithms using lipid values where available and the office-based version was used when lipids were not available. 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 FRA and of CAD or CVA for ACC/AHA risk score. The standardized incidence ratio (SIR) was estimated as the ratio of the observed to predicted number of CVD events. SIR 95 % confidence intervals (CI) were calculated assuming that the expected rates are fixed and the observed rates followed a Poisson

distribution. An SIR >1 indicated the observed events were higher than predicted meaning the predicted risk underestimated actual risk. Conversely, SIR <1 indicated the predicted risk overestimated the actual risk. Sensitivity analysis including only White patients was performed for 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, NC, USA) 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 between 30 and 74 years and 218 sex and age-matched comparators were identified. A total of 30 cases and 48 comparators were excluded from the analysis due to history of CVD prior to sarcoidosis index date or statin use at baseline. Among cases, all but 16 cases had pulmonary sarcoidosis. The majority of them had stage 1 pulmonary sarcoidosis (93 cases, 54%) followed by stage 2 (50 cases, 29%) and stage 3–4 (29 cases, 17%). 44% of cases also had extra-thoracic involvement by sarcoidosis. Only 14 patients required immunosuppressive therapy (9 hydroxychloroquine, 4 methotrexate, 2 other disease modifying anti-rheumatic drugs, 4 anti-tumor necrosis factor biologics and 2 other biologics) and 63 (34%) were treated with prednisone. Table 1 summarizes the demographics and CV risk factors of subjects in this study.

Data needed for calculation of FRS were available in 186 out of 188 cases and 139 out of 170 comparators. Mean FRS for cases and comparators was 8.2% (standard deviation [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 – 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 – 1.81). FRS underestimated the risk of CVD events in patients with sarcoidosis across analyses by sex, age and severity of sarcoidosis as indicated by the presence of extra-thoracic disease and staging of pulmonary disease as described in table 2. FRS also underestimated the risk of CVD events across quintiles of predicted risk among cases as demonstrated in figure 1. Sensitivity analysis including only White patients demonstrated unchanged results with an SIR of 2.89 (95% CI, 2.02–4.13). There was no evidence of a trend over calendar years in the rate of CVD events among patients with sarcoidosis (p=0.95).

The CV risk was also calculated using the ACC/AHA risk score. Since this model is designed for persons age 40–79 years, only subjects aged 40 – 74 years were included. Because of missing data on lipids, the ACC/AHA risk score could be computed for 118 cases and 85 comparators. The predicted number of CVD events among cases was 4.6 and the observed number of CVD events was 19, corresponding to an SIR of 4.11 (95% CI, 2.62 – 6.44). The predicted number of CVD events among comparators was 5.4 and the observed number of CVD events was 6, corresponding to an SIR of 1.12 (95% CI, 0.50 – 2.49).

Discussion

The current study is the first population-based study using comprehensive individual medical record review to investigate the performance of FRS and ACC/AHA risk score among patients with sarcoidosis. Both FRS and ACC/AHA risk score underestimated the risk of CVD events by about 3-fold and 4-fold, respectively. The FRS substantially underestimates the risk of CVD for both sexes, all age groups and across the severity of sarcoidosis, as indicated by the presence of extra-thoracic disease and staging of pulmonary sarcoidosis. The definition of CVD outcome for FRS and ACC/AHA risk score is different. FRS includes CAD, CHF, CVA and PAD while ACC/AHA risk score includes only CAD and CVA. The difference in outcome definition may explain the difference in the magnitude of SIR between the 2 tools.

The findings from this study suggest that the poor performance of FRS extends beyond RA and SLE to other chronic inflammatory disorders. Several in vitro studies have demonstrated that chronic inflammation plays an important role in the pathogenesis of atherosclerosis and CVD. Among the processes that lead to accelerated atherosclerosis are inflammatory cytokines such as interleukin-1 and tumor necrosis factor which are known to induce expression of vascular adhesion molecule-1 in endothelial cells, resulting in adhesion and invasion of monocytes to vascular endothelium and tunica intima.¹⁰ Subsequently, monocytes internalize and oxidize lipoprotein particles, leading to deposition of cholesterol in the arterial wall. In addition, chronic inflammation can jeopardize the stability of atherosclerotic plaque through the production of matrix metalloproteinases that could degrade extracellular matrix constituents by activated leukocytes.¹¹ In addition, an association between increased incidence of CVD and chronic inflammatory disorders has been observed in several epidemiologic studies.^{12–14} Chronic inflammation is not accounted for in either FRS or ACC/AHA risk score, which could be the explanation for the underestimation of the CVD risk in patients with these diseases.

The attempts to add C-reactive protein (CRP) to FRS failed to significantly improve its ability to predict CVD events in general population.¹⁵ It is unlikely that adding CRP to the risk calculator will increase its accuracy for patients with sarcoidosis, as CRP is not a good marker for inflammation in sarcoidosis.¹⁶ The current cohort could not be used to evaluate the performance of FRS that incorporate CRP into the model¹⁵ or model that includes CRP (such as Reynolds CVD risk score^{17, 18}). This is a retrospective study, and CRP was not systematically obtained and was available in only minority of subjects. Prospective cohort studies using a standard protocol for obtaining inflammatory markers would be needed to assess the clinical utility of adding them to CV risk assessment models in patients with these diseases.

Another factor that might influence development of CVD is glucocorticoids, the most commonly used medication among patients with sarcoidosis.^{19, 20} Use of glucocorticoids is associated with increased risk of several CV risk factors such as diabetes mellitus and dyslipidemia and could increase the risk of CVD.^{21, 22} Medications are not included in either the FRS or ACC/AHA risk score.

CVD risk calculators have been developed to help clinician identify patients at high risk of CVD for appropriate preventive strategies. For example, the 2013 ACC/AHA guideline recommends moderate or high intensity statin therapy for adults between 40 and 75 years of age whose 10-year CVD risk is $\geq 7.5\%$.²³ The United States Preventative Services Task Force recommends low dose aspirin for primary CVD prevention in adults 50 to 75 years of age whose 10-year CVD risk is $\geq 10\%$.²⁴ The results of this study suggest that FRS and ACC/AHA risk score are not reliable tools to predict CVD events in patients with sarcoidosis and would falsely classify some patients with high CVD risk as having low risk, resulting in missed opportunity for appropriate interventions aimed at primary CVD prevention. This may also be true for other chronic systemic autoimmune inflammatory conditions, but further studies are required to confirm the generalizability of the observations.

Recent studies have suggested that the rate of mortality associated with sarcoidosis is increasing.^{25, 26} However, we found no evidence of increased mortality among patients with sarcoidosis in our cohort compared to the general population or of time trends in mortality among patients with sarcoidosis.⁶ Furthermore, we found no evidence of an increase in the occurrence of CVD events among patients with sarcoidosis and CVD event rates in the general population have decreased over time. Therefore, CVD would probably not be the underlying cause of the possible increase in mortality associated with sarcoidosis.

The major strength of this study is the population-based design that reflects the true spectrum of the disease in the community, unlike hospital-based cohorts that are at risk of selection bias of only more severe cases. The diagnosis of both sarcoidosis and CVD, as well as baseline CV risk factors, were individually verified by medical record review which minimized the likelihood of misclassification from coding error. The long duration of follow-up allows capture of events that occurred long after index date. This is of particular significance for study of CVD events, as these may occur years after the diagnosis of sarcoidosis is established.

The major limitations of the study are inherent to its retrospective design. Clinical information and laboratory investigations were not prospectively obtained and recorded according to a defined protocol. Thus, some of the pertinent data were not available and precluded certain analyses such as evaluation of risk assessment tools with CRP. Generalizability of the performance of the risk scores in this cohort to other populations may be limited as clinical manifestation of sarcoidosis and baseline risk of CVD vary among ethnic groups^{27–30} and the population of Olmsted County is predominately of Northern European ancestry. It is possible that the calculators may perform even worse among Blacks with sarcoidosis as they tend to have a more severe disease and, thus, more inflammatory burden and exposure to glucocorticoid.²⁹ In addition, Olmsted County has a higher proportion of healthcare workers who may have a better access to healthcare service, resulting in a different pattern of presentations for both sarcoidosis and CVD. Finally, the small sample size of our cohort and the small number of CVD events is a limitation. However, we were able to demonstrate a statistically significant difference despite this.

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Figure 1. Comparison of observed and predicted 10 year risk of CVD according to quintiles of predicted risk obtained from the Framingham risk score. The observed risk was obtained using Kaplan-Meier methods.

Table 1

Demographics and baseline cardiovascular risk factors of cases with sarcoidosis and comparators without sarcoidosis

Variable	Cases (N=188)	Comparators (N=170)	p value
Age at diagnosis/index date (years) (SD)	46.8 ± 10.2	45.9 ± 10.2	0.37
Age group (years)			0.79
30-39	54 (29%)	54 (32%)	
40-54	96 (51%)	85 (50%)	
55-74	38 (20%)	31 (18%)	
Females	98 (52%)	84 (49%)	0.61
White	165 (90%)	160 (95%)	0.03
Black	11 (6%)	2 (1%)	
Asian	3 (2%)	0 (0%)	
Native American	1 (1%)	0 (0%)	
Other	4 (2%)	7 (4%)	
Missing	4	1	
Median index year (Q1, Q3)	2002 (1994, 2008)	2002 (1994, 2008)	0.96
Median length of follow-up (Q1, Q3)	8.9 (5.0, 10.0)	10.0 (5.4, 10.0)	N.A.
Smoking status at diagnosis/index date			<0.001
Never	115 (62%)	67 (42%)	
Ex-smoker	43 (23%)	33 (21%)	
Current smoker	28 (15%)	60 (38%)	
Missing	2	10	
Obesity (measured within 1 year before to 3 months after index date) *			0.002
Yes	80 (45%)	27 (26%)	
No	96 (55%)	75 (74%)	
Missing	12	68	
Mean systolic blood pressure measured within 2 year before or after index date (mmHg) (SD)	124.9 ± 17.2	123.8 ± 16.3	0.53
Mean diastolic blood pressure measured within 2 year before or after index date in (mmHg) (SD)	77.2 ± 11.2	80.3 ± 57.4	0.12
Hypertension	44 (23%)	33 (19%)	0.36
Anti-hypertensive medication use	40 (21%)	31 (18%)	0.49
Mean cholesterol level mg/dL) (SD)			
Total cholesterol	197.7 ± 37.3	202.0 ± 37.8	0.23
Low density lipoprotein	116.6 ± 32.2	121.2 ± 31.2	0.31
High density lipoprotein	48.9 ± 16.2	52.2 ± 15.7	0.05

Variable	Cases (N=188)	Comparators (N=170)	p value
Triglyceride	149.9 ± 105.2	130.7 ± 67.9	0.30
Presence of diabetes mellitus	16 (9%)	9 (5%)	0.23

* Obesity defined as body mass index of ≥ 30 kg/m²

SD, standard deviation; N.A., not applicable; mg, milligram; kg, kilogram; dL deciliter

Table 2
Comparison of observed and predicted cardiovascular disease risk in patients with sarcoidosis

Group	N	Observed CV events	Predicted CV events	Standardized incidence ratio	p-value	p-value for difference between groups
Cases	186	34	11.8	2.88 (2.06, 4.04)	<0.001	0.002
Comparators	139	11	11.0	1.00 (0.56, 1.81)	0.99	
Cases only						
Female	98	19	4.9	3.84 (2.45, 6.02)	<0.001	0.10
Male	88	15	6.8	2.19 (1.32, 3.64)	0.002	
Age (years)						0.19
30-39	53	5	1.3	3.72 (1.55, 8.93)	0.003	
40-54	95	18	4.8	3.74 (2.36, 5.93)	<0.001	
55-74	38	11	5.6	1.95 (1.08, 3.53)	0.026	
No extra-thoracic involvement	106	19	7.2	2.63 (1.68, 4.12)	<0.001	0.51
Extra-thoracic involvement	80	15	4.6	3.29 (1.98, 5.46)	<0.001	
Stage 1	93	11	5.1	2.15 (1.19, 3.89)	0.011	0.20
Stage 2	49	13	2.9	4.41 (2.56, 7.59)	<0.001	
Stage 3-4	29	7	2.7	2.58 (1.23, 5.40)	0.012	