Underestimation of Risk of Carotid Subclinical Atherosclerosis by Cardiovascular Risk Scores in Patients with Psoriatic Arthritis

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ABSTRACT. ***Objective.*** To test the performances of established cardiovascular (CV) risk scores in discriminating subclinical atherosclerosis (SCA) in patients with psoriatic arthritis.

Methods. These scores were calculated: Framingham risk score (FRS), QRISK2, Systematic COronary Risk Evaluation (SCORE), 10-year atherosclerotic cardiovascular disease risk algorithm (ASCVD) from the American College of Cardiology and the American Heart Association, and the European League Against Rheumatism (EULAR)–recommended modified versions (by 1.5 multiplication factor, m-). Carotid intima-media thickness > 0.9 mm and/or the presence of plaque determined by ultrasound were classified as SCA+.

Results. We recruited 146 patients [49.4 ± 10.2 yrs, male: 90 (61.6%)], of whom 142/137/128/118 patients were eligible to calculate FRS/QRISK2/SCORE/ASCVD. Further, 62 (42.5%) patients were SCA+ and were significantly older, with higher systolic blood pressure and higher low-density lipoprotein cholesterol (all $p < 0.05$). All CV risk scores were significantly higher in patients with SCA+ [FRS: 7.8 (3.9–16.5) vs 2.7 (1.1–7.8), $p < 0.001$; QRISK2: 5.5 (3.1–10.2) vs 2.9 (1.2–6.3), $p < 0.001$; SCORE: 1 (0–2) vs 0 (0–1), $p < 0.001$; ASCVD: 5.6 (2.6–12.4) vs 3.4 (1.4–6.1), $p = 0.001$]. The Hosmer-Lemeshow test revealed moderate goodness of fit for the 4 CV scores (p ranged from 0.087 to 0.686). However, of the patients with SCA+, those identified as high risk were only 44.1% (by FRS > 10%), 1.8% (QRISK2 > 20%), 10.9% (SCORE > 5%), and 43.6% (ASCVD > 7.5%). By applying the EULAR multiplication factor, 50.8%/14.3%/14.5%/54.5% of the patients with SCA+ were identified as high risk by m-FRS/m-QRISK2/m-SCORE/m-ASCVD, respectively. EULAR modification increased the sensitivity of FRS and ASCVD in discriminating SCA+ from 44% to 51%, and 44% to 55%, respectively.

Conclusion. All CV risk scores underestimated the SCA+ risk. EULAR–recommended modification improved the sensitivity of FRS and ASCVD only to a moderate level. (First Release November 15 2017; J Rheumatol 2018;45:218–26; doi:10.3899/jrheum.170025)

Key Indexing Terms:
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Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with increased prevalence of cardiovascular (CV) diseases and related mortality[1,2,3]. The increased risk was estimated to be similar to rheumatoid arthritis (RA)[4]. A recent metaanalysis revealed that the CV morbidity was increased by 43% in patients with PsA, compared with the general population[5]. Subclinical atherosclerosis (SCA), which is a good surrogate endpoint for CV disease in the general population[6,7] and in patients with RA[8,9,10], is also more common in patients with PsA[11,12]. The higher prevalence of traditional CV risk factors in patients with PsA probably contributed to the increased risk[3,13]. Nevertheless, abnormally increased carotid intima-media thickness (IMT) was observed in PsA patients without CV events or classic CV disease risk factors when compared with matched controls[14]. Moreover, uncontrolled low-grade inflammation also accounts for the 24% increased risk of major adverse CV events in patients with PsA who were not prescribed a disease-modifying antirheumatic drug (DMARD) compared with control subjects in a population-based cohort study[1]. Nonsteroidal antiinflammatory drugs and glucocorticoid are commonly prescribed drugs in the treatment of PsA; both are associated with increased CV risks[15]. Thus, stratification of CV risks is more complicated in patients with PsA.

In the general population, certain predictive scores were developed to estimate CV risks. The Framingham risk score (FRS)[16], QRISK2[17], Systematic COronary Risk Evaluation (SCORE)[18], and the 10-year atherosclerotic CV disease risk algorithm (ASCVD)[19] from the American College of Cardiology and the American Heart Association (ACC/AHA) are among the most widely used CV risk scores. In RA, these risk scores generally underestimated the risk of CV events[20] or SCA[21,22,23,24]. A 1.5 multiplication factor for the risk scores is recommended by the European League Against Rheumatism (EULAR) in patients with RA who fulfill 2 out of 3 of the following criteria: disease duration > 10 years; rheumatoid factor and/or anticyclic citrullinated peptide positivity; and presence of extraarticular manifestations[25]. However, the performance was still unsatisfactory with this modification[21,22,23,26].

In PsA, similar data are scarce. Ernste, *et al*[27] and Eder, *et al*[28] suggested that FRS underestimated the risk of CV events and SCA in PsA, respectively. Gulati and colleagues found that SCORE could not explain the increased prevalence of established CV diseases in patients with PsA compared with the general population[29]. Comprehensive evaluation and comparison of the risk scores in patients with PsA is lacking. Moreover, because the increased CV risk in PsA was estimated to be similar to RA[4], it would be important to ascertain whether the multiplication factor of 1.5 should be introduced to patients with PsA to refine CV risk assessment.

In our study, we aimed to evaluate the performance of FRS, QRISK2, SCORE, and ASCVD in discriminating carotid SCA in patients with PsA. We also tested whether introducing the multiplication factor of 1.5 could improve their performance.

MATERIALS AND METHODS

Patients. Data from 162 patients with PsA who fulfilled the Classification for Psoriatic Arthritis criteria[30] and who underwent carotid ultrasound were retrieved in our study. There were 93 patients who participated in a previous cohort study[11,31], and 69 patients were enrolled in an ongoing prospective study aiming to assess the effect of treat-to-target in the prevention of atherosclerosis progression (trial registration no.: NCT02232321). In these 2 studies, patients with established CV diseases (e.g., myocardial infarction, angina, stroke, transient ischemic attack, etc.) or clinically significant renal disease (serum creatinine level > 270 mol/l) were excluded. There were 16 patients excluded because of a lack of information for calculating at least 1 CV risk score. There were 146 patients (79 and 67 from the 2 studies, respectively) who were finally included in the analysis. Ethics approval was obtained from the Ethics Committee of The Chinese University of Hong Kong–New Territories East Cluster Hospitals (reference number: CRE-2012.478), and written informed consent was obtained from all participants according to the Declaration of Helsinki.

Clinical interview. Pain, as well as physicians' and patients' global assessments, were evaluated using a 100-point visual analog scale, where 0 indicated excellent well-being and 100 indicated feeling extremely unwell. Physical examination included the number of tender and swollen joints using the 68 tender/66 swollen joint count, the presence of dactylitis, and the number of permanently deformed joints. The Health Assessment Questionnaire was used to evaluate physical function, and the psoriasis area and severity index was used to assess the extent of skin involvement[32]. Overall disease activity was assessed using disease activity in psoriatic arthritis (DAPSA)[33], and patients were considered as being in remission (REM, DAPSA ≤ 4), or having low (LDA, > 4 DAPSA ≤ 4), moderate (MDA, > 14 DAPSA ≤ 28), or high (HAD, DAPSA > 28) disease activity[34]. Anthropometric measurements including height, weight, and 2 consecutive blood pressure (BP) readings in sitting position were also recorded. Body mass index (BMI) was calculated. Other data obtained from patients with PsA through the interview and chart review included smoking habits, history of diabetes, hypertension, and hypercholesterolemia. Drug history was retrieved from case notes or obtained during the clinical assessment. All patients were interviewed and examined using standardized data collection instruments. Checks were done for complete blood count, liver and renal function, erythrocyte sedimentation rate, C-reactive protein (CRP), fasting blood glucose, and lipid profile [total cholesterol (TC), high density lipoprotein-cholesterol, low density lipoprotein-cholesterol (LDL), and triglycerides (TGC)].

Carotid atherosclerosis. Carotid IMT was measured at 6 carotid arterial segments using a high-resolution B-mode ultrasound machine (iE33, Philips) by an experienced cardiologist (QS) as previously described[35,36]. Briefly, duplex carotid ultrasound was performed using an 11-MHz linear vascular probe. The IMT was measured offline in the distal common carotid artery (the arterial segment 1 cm proximal to the carotid bulb), bulb, and proximal internal carotid artery (the arterial segment 1 cm distal to the carotid bifurcation) using dedicated software (QLab 6.0, Philips), and was analyzed by the same investigator, who was blinded to all clinical information. The IMT values of 6 arterial segments were measured, the maximum of which were calculated for further analysis. Plaque was defined as a localized thickening > 1.2 mm[11,36,37]. Our study involved a single ultrasonographer and a single reader. The intraclass correlation coefficient for the mean of the site-specific IMT values was 0.97[11,35]. Patients with maximum IMT > 0.9 mm and/or the presence of plaque were classified as SCA+[21,22].

Risk score calculation. FRS was calculated for Framingham 10-year risk of general CV disease[16]. QRISK2 was calculated by the QRISK2-2016 risk calculator[17]. SCORE was calculated by the interactive software HeartScore Risk Calculator 1.0[18], developed by the European Society of Cardiology.

There are no charts designed for Asians; however, because the Chinese population in general has a lower CV risk[38,39], the European low-risk chart was adopted. ASCVD risk estimator was used to calculate atherosclerotic CV disease risk[19]. EULAR modified scores (multiplied by 1.5) were calculated for all risk scores and labeled with the prefix "m-". Patients with FRS > 10%[24], QRISK2 > 20%[22], SCORE > 5%[22], and ASCVD > 7.5%[22] were considered as having high CV risks according to the CV risk scores.

Statistical analysis. Results are expressed as mean ± SD or median (interquartile range) as appropriate. Comparisons between 2 groups were assessed using the Student t test or Mann-Whitney U test for continuous variables, and chi-square test for categorical variables. The receiver-operating characteristic (ROC) curve was used to evaluate the performance of CV risk scores in discriminating carotid atherosclerosis. Cutoff values of the CV risk scores with best combined sensitivity and specificity were determined according to the Youden index. The Hosmer-Lemeshow test was applied to assess the goodness of fit for the observed and expected SCA case numbers estimated by the CV risk scores. Multivariate logistic regression was used to identify the independent risk factor for carotid atherosclerosis in patients with PsA. All traditional CV risk factors with $p < 0.1$ in the univariate analysis were included in the multivariate analysis as potential confounding factors. All statistical analyses were conducted using IBM SPSS Statistics Version 22. A minimal level of significance of $p < 0.05$ was used.

RESULTS

Patients' characteristics and CV risk scores. There were 146 patients with PsA [90 male (61.6%), mean ± SD age: 49.4 ± 10.2 yrs] included. Median disease duration was 7 years and ranged from 1 month to 40 years. There were 7 (4.8%) patients in REM, 64 (43.8%) with LDA, 52 (35.6%) with MDA, and 23 (15.8%) with HDA. Traditional CV risk factors were common: 54 (37.0%) patients were overweight (BMI ≥ 25 kg/m^2) and 25 (17.1%) patients were obese (BMI ≥ 30 kg/m^2); 42 patients (28.8%) were current or ever smokers; and 64 (43.8%), 19 (13.0%), and 17 (11.6%) had hypertension, diabetes, and dyslipidemia, respectively. Overall, 116 patients (79.5%) had at least 1 of these traditional risk factors. Data for 142, 137, 128, and 118 patients were available to calculate FRS, QRISK2, SCORE, and ASCVD, respectively. The following patients were classified as having high CV risk: 42 (29.6%) by FRS, 2 (1.5%) by QRISK2, 6 (4.7%) by SCORE, and 35 (29.7%) by ASCVD. More details of the patients' characteristics were shown in Table 1.

SCA and CV risk scores. The mean IMT of the 6 sites was 0.70 ± 0.12 mm, and maximum IMT was 0.85 ± 0.18 mm. Respectively, 8 patients (5.5%) and 42 (28.8%) had mean and maximum IMT > 0.9 mm. Thirty-three (22.6%) patients had at least 1 carotid plaque. There were 62 (42.5%) patients defined as SCA+ with maximum IMT > 0.9 mm and/or the presence of plaque. The patients with SCA+ were significantly older (53.3 ± 9.0 vs 47.0 ± 10.2 years, $p < 0.001$), had higher systolic BP (137 ± 25 vs 129 ± 17 mmHg, $p = 0.018$), TC (5.3 ± 0.9 vs 4.9 ± 0.9 mmol/l, $p = 0.007$), and LDL levels (3.2 ± 0.8 vs 2.9 ± 0.8 mmol/l, $p = 0.015$). There was a trend suggesting increased TGC and fasting glucose levels in patients with SCA+ (Table 2). All CV risk scores were significantly higher in patients with SCA+ ($p \leq 0.001$, Table 2). The cases of diabetes and dyslipidemia were higher in patients with SCA– but the difference between SCA+ and SCA– was not significant (Table 2). The areas under the ROC curve (AUROC) for discriminating SCA+ were 0.72 (95% CI 0.63–0.80, $p < 0.001$) for FRS, 0.69 (0.60–0.77, $p < 0.001$) for QRISK2, 0.67 (0.58–0.77; $p = 0.001$) for SCORE, and 0.67 (0.58–0.77; $p = 0.001$) for ASCVD (Figure 1). The

Table 1. Clinical characteristics of all patients. Values are median (interquartile range) or mean ± SD unless otherwise specified.

Variables	All Patients, n = 146
Male, n (%)	90 (61.6)
Age, yrs	49.4 ± 10.2
PsA characteristics	
PsA disease duration, yrs	7.0 (3.2–13.0)
Tender joint count, 0–68	3 (0–7)
Swollen joint count, 0–66	1 (0–2)
Damaged joint count, 0–68	2 (0–5)
VAS pain, 0–100	40 (20–60)
PtGA, 0–100	50 (30–60)
PGA, 0–100	20 (10–40)
PASI, 0–72	3.5 (1.0–8.6)
HAQ, 0–3	0.38 (0–0.88)
ESR, mm/h	22 (11–37)
CRP, mg/dl	0.4 (0.2–1.2)
DAPSA, 0–164	14.9 (9.0–21.2)
PsA medication, n (%)	
NSAID	71 (49.0)
Steroid	10 (6.9)
Synthetic DMARD	68 (46.9)
Biologic DMARD	10 (6.9)
CV risk factors	
BMI, kg/m^2	26.1 ± 4.9
Ever smoker, n (%)	42 (28.8)
Systolic BP, mmHg	132 ± 21
Diastolic BP, mmHg	82 ± 12
Total cholesterol, mmol/l	5.1 ± 0.9
HDL cholesterol, mmol/l	1.5 ± 0.5
LDL cholesterol, mmol/l	3.0 ± 0.8
Triglycerides, mmol/l	1.5 ± 0.9
Fasting glucose, mmol/l	5.4 ± 1.2
Hypertension, n (%)	64 (43.8)
Diabetes, n (%)	19 (13.0)
Dyslipidemia, n (%)	17 (11.6)
CV risk scores*, n (%)	
FRS	5.0 (1.6–12.0)
QRISK2	3.8 (1.6–8.5)
SCORE	1 (0–1)
ASCVD	4.4 (1.9–9.8)

*Available in 142, 137, 128, and 118 patients for FRS, QRISK2, SCORE, and ASCVD, respectively. PsA: psoriatic arthritis; VAS: visual analog scale; PtGA: patient's global assessment; PGA: physician's global assessment; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; CV: cardiovascular; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FRS: Framingham risk score; SCORE: Systematic COronary Risk Evaluation; ASCVD: atherosclerotic cardiovascular disease risk algorithm.

Table 2. Clinical characteristics of patients with and without subclinical atherosclerosis. Values are median (interquartile range) or mean ± SD unless otherwise specified.

	SCA–, n = 84	SCA+, n = 62	p
Male, n (%)	49 (58.3)	41 (66.1)	0.338
Age, yrs	47.0 ± 10.2	53.3 ± 9.0	< 0.001
PsA characteristics			
PsA disease duration, yrs	8.2 (3.0–13.3)	5.9 (3.4–11.3)	0.606
Tender joint count, 0–68	2 (0–6)	5 (1–8)	0.148
Swollen joint count, 0–66	1 (0–2)	1 (0–2)	0.687
Damaged joint count, 0–68	1 (0–5)	2 (0–6)	0.624
VAS pain, 0–100	40 (20–60)	50 (30–70)	0.388
PtGA, 0–100	50 (30–60)	50 (40–70)	0.113
PGA, 0–100	20 (10–35)	30 (10–40)	0.112
PASI, 0–72	3.5 (1.4–8.4)	3.4 (1.0–8.7)	0.768
HAQ, 0–3	0.38 (0–0.88)	0.31 (0–0.88)	0.874
ESR, mm/h	20 (10–37)	25 (13–37)	0.327
CRP, mg/dl	0.4 (0.2–1.2)	0.4 (0.1–1.3)	0.946
DAPSA, 0–164	14.2 (8.2–20.2)	16.4 (9.4–21.5)	0.182
PsA medication, n (%)			
NSAID	44 (53.0)	27 (43.5)	0.259
Steroid	6 (7.1)	4 (6.5)	0.870
Synthetic DMARD	41 (49.4)	27 (43.5)	0.485
Biologic DMARD	5 (6.0)	5 (8.1)	0.631
CV risk factors			
BMI, kg/m^2	26.3 ± 5.2	25.8 ± 4.5	0.496
Ever smoker, n (%)	21 (25.0)	21 (33.9)	0.242
Systolic BP, mmHg	129 ± 17	137 ± 25	0.018
Diastolic BP, mmHg	81 ± 12	83 ± 11	0.372
Total cholesterol, mmol/l	4.9 ± 0.9	5.3 ± 0.9	0.007
HDL cholesterol, mmol/l	1.5 ± 0.5	1.5 ± 0.4	0.939
LDL cholesterol, mmol/l	2.9 ± 0.8	3.2 ± 0.8	0.015
Triglycerides, mmol/l	1.4 ± 0.9	1.6 ± 1.0	0.084
Fasting glucose, mmol/l	5.2 ± 0.9	5.6 ± 1.5	0.068
Hypertension, n (%)	36 (42.9)	28 (45.2)	0.782
Diabetes, n (%)	11 (13.1)	8 (12.9)	0.973
Dyslipidemia, n (%)	10 (11.9)	7 (11.3)	0.909
CV risk scores*, n (%)			
FRS	2.7 (1.1–7.8)	7.8 (3.9–16.5)	< 0.001
QRISK2	2.9 (1.2–6.3)	5.5 (3.1–10.2)	< 0.001
SCORE	0 (0–1)	1 (0–2)	< 0.001
ASCVD	3.4 (1.4–6.1)	5.6 (2.6–12.4)	0.001

*Total number of SCA± patients with available scores: 83/59, 81/56, 73/55, and 63/55, for FRS, QRISK2, SCORE, and ASCVD, respectively. PsA: psoriatic arthritis; SCA: subclinical atherosclerosis; VAS: visual analog scale; PtGA: patient's global assessment; PGA: physician's global assessment; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; CV: cardiovascular; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; FRS: Framingham risk score; SCORE: Systematic COronary Risk Evaluation; ASCVD: atherosclerotic cardiovascular disease risk algorithm.

Hosmer-Lemeshow test revealed moderate goodness of fit for the 4 CV scores (p ranging from 0.087 to 0.686, Figure 2). Sensitivity and specificity of the cutoff values with the highest Youden index was shown in Table 3.

By applying the preset cutoff values, 44.1%, 1.8%, 10.9%, and 43.6% of the patients with SCA+ were identified as high risk by FRS, QRISK2, SCORE, and ASCVD, respectively (Figure 3). There were 19.3% and 17.5% of patients with SCA– also classified as high risk by FRS and ASCVD.

EULAR modification of the CV risk scores. While the 1.5 multiplication factor was introduced to the risk scores, 50.8%, 14.3%, 14.5%, and 54.5% of the patients with SCA+ were identified as high risk by m-FRS, m-QRISK2, m-SCORE, and m-ASCVD, respectively (Figure 3). The patients with SCA– who were classified as high risk also increased to 30.1% (m-FRS), 7.4% (m-QRISK2), 4.1% (m-SCORE), and 36.5% (m-ASCVD). Sensitivity and specificity of the modified cutoff values were shown in Table 3.

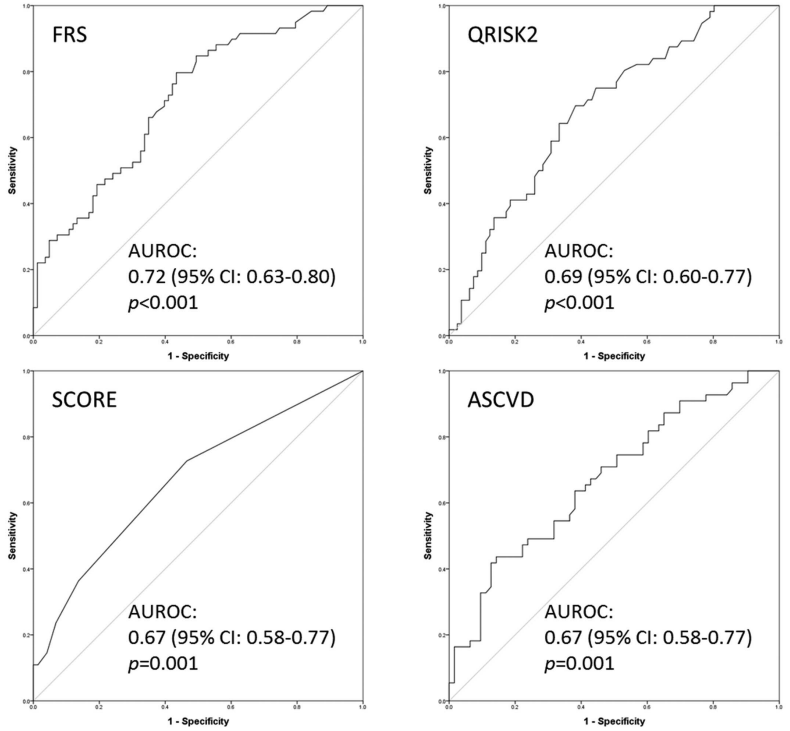

Figure 1. Receiver-operating characteristic curve of the risk scores in discriminating subclinical atherosclerosis. AUROC: area under receiver-operating characteristic curve; FRS: Framingham risk score; SCORE: Systematic COronary Risk Evaluation; ASCVD: atherosclerotic cardiovascular disease risk algorithm.

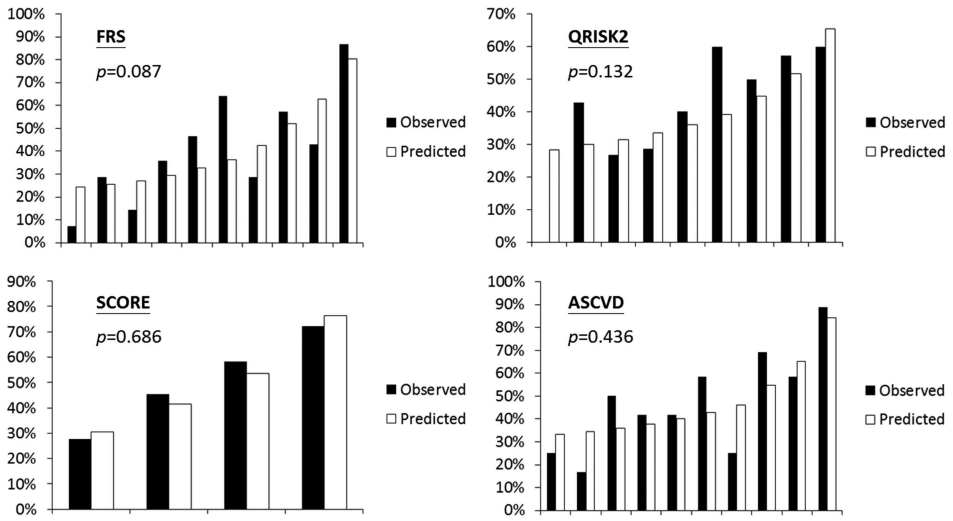

Figure 2. Hosmer-Lemeshow test for the goodness of fit for the observed and expected risk of subclinical atherosclerosis by the risk scores. FRS: Framingham risk score; SCORE: Systematic COronary Risk Evaluation; ASCVD: atherosclerotic cardiovascular disease risk algorithm.

Independent predictors for SCA among traditional CV risk factors. Age, systolic BP, LDL, TGC, and fasting glucose were included in a multivariate logistic regression model to identify the independent predictors for SCA+. Older age (OR 1.090, 95% CI 1.044–1.138; p < 0.001) and higher LDL level (OR 1.899, 95% CI 1.160–3.108; p = 0.011) were found to be independently associated with SCA+. None of the 4 CV risk scores were independently associated with SCA+ if they were also included in the regression model.

Table 3. Sensitivity and specificity of preset and modified cutoffs for risk scores, and cutoffs with highest overall accuracy. Values are %.

Risk Scores	Cutoff	Sensitivity	Specificity
Highest Youden index			
FRS	3.7	79.7	56.6
QRISK2	3.8	69.6	61.7
SCORE	0.5	72.7	53.4
ASCVD	8.3	43.6	85.7
Preset			
FRS	10	44.1	80.7
QRISK2	20	1.8	98.8
SCORE	5	10.9	98.6
ASCVD	7.5	43.6	82.5
Modified			
m-FRS	10	50.8	69.9
m-QRISK2	20	14.3	93.8
m-SCORE	5	14.5	95.9
m-ASCVD	7.5	54.5	65.1

FRS: Framingham risk score; SCORE: Systematic COronary Risk Evaluation; ASCVD: atherosclerotic cardiovascular disease risk algorithm; m-: modified.

DISCUSSION

This is the first study, to our knowledge, that comprehensively evaluated the performance of established CV risk assessment tools in patients with PsA. Our results suggested that all 4 CV risk assessment tools, including FRS, QRISK2, SCORE, and ASCVD, exhibited moderate discrimination between PsA patients with or without carotid SCA. However, the preset cutoff values of all scores underestimated the risk of SCA. The 1.5 multiplication factor only led to a modest improvement in their performance.

All the CV risk scores were calculated mainly based on traditional CV risk factors, and were developed for the CV risk stratification in the general population. Patients with PsA had higher prevalence of SCA compared with controls even after adjustment of the traditional CV risk factors[11]. It is not unexpected that the risk scores would underestimate the CV risk in patients with PsA. In RA, although 1 study suggested that QRISK2 may have overestimated the CV risk[20], most studies found CV risk was underestimated by FRS[20,22,24], SCORE[20,21,22,23,26], or ASCVD[22,24]. In PsA, FRS[27,28] and SCORE[29] had also been reported to underestimate CV risk. In our study, PsA patients with SCA had significantly higher CV risks evaluated by all 4 CV risk assessment tools ($p \leq 0.001$). All scores had moderate discriminating abilities in SCA (AUROC ranged from 0.67 to 0.72), and moderate goodness of fit by the Hosmer-Lemeshow test ($p > 0.05$). However, by applying the preset cutoff values (FRS > 10%, QRISK2 > 20%, SCORE > 5%, ASCVD > 7.5%), 55.9%, 98.2%, 89.1, and 56.4% of the patients with SCA+ were classified as "low risk" according to FRS, QRISK2, SCORE, and ASCVD, respectively. This discrepancy between the moderate discriminating abilities of the 4 scores (as continuous variables) and poor calibrating abilities of the cutoff values could be explained by the threshold selection. As shown in Table 3, the cutoff values with best accuracy (highest Youden index) were much lower in FRS, QRISK2, and SCORE compared with the preset ones. Only the preset cutoff value for ASCVD was close to the cutoff value with best accuracy.

For CV risk management in RA, EULAR recommends applying a multiplication factor of 1.5 to SCORE in selected patients to enhance the risk estimates[25]. However, the improvement of risk assessment by such modification appeared to be suboptimal[21,22,23,26]. Based on the knowledge that patients with PsA had similar CV risk compared to patients with RA[4], we also tested whether the multiplication factor would improve the performance of the scores for the first time. By adopting the multiplication factor, although the sensitivity of the various CV assessment tools increased by 6.7% to 12.5%, a significant proportion of patients with SCA+ were still misclassified as having "low risk" (over 45% by m-FRS and m-ASCVD, and over 85% by m-QRISK2 and m-SCORE, Figure 3). This result is not surprising because adopting the multiplication factor of 1.5 is the same as lowering the cutoff values to 6.7%, 13.3%, 3.3%, and 5% for FRS, QRISK2, SCORE, and ASCVD, respectively. Those are still not close to the cutoffs with best accuracy.

A possible explanation for the underestimation of the SCA risk is chronic inflammation in patients with PsA. Low-grade inflammation may account for almost a quarter of the increased CV risk in patients with PsA who were not prescribed DMARD[1], and systemic therapy significantly decreased the CV risk in patients with psoriatic disease[15]. The inflammatory process is believed to enhance the expression of adhesion molecules, and promote endothelial cell dysfunction and smooth muscle cell proliferation, leading to atherosclerotic plaque formation[40]. Proinflammatory cytokines also play a role in plaque remodeling and fibrous cap thinning, increasing plaque vulnerability[40]. Targeted antiinflammatory therapy by blocking tumor necrosis factor halted, or even reversed the progression of IMT in patients with inflammatory arthritis[41]. While atherosclerosis is an inflammatory disease[40,42], most CV risk scores do not include inflammatory biomarkers. Among all 4 CV risk assessment tools, only RA is included as one of the CV risk factors in QRISK2. Assuming patients with PsA had similar CV risk compared to patients with RA, we had recalculated the CV risk by marking this question as "yes" in our PsA cohort, and the performance was similar (AUROC changed from 0.685 to 0.687, detailed data not shown). The Reynolds Risk Score (RRS) includes high-sensitivity CRP as one of the CV risk factors[43,44]. Because RRS is limited to nondiabetic subjects and only 90 patients with PsA in our cohort provided adequate data to calculate RRS, we did not include RRS in the main analysis. However, the discriminating ability of RRS in SCA was even lower than any other risk scores [AUROC: 0.66 (0.54–0.77); $p = 0.010$].

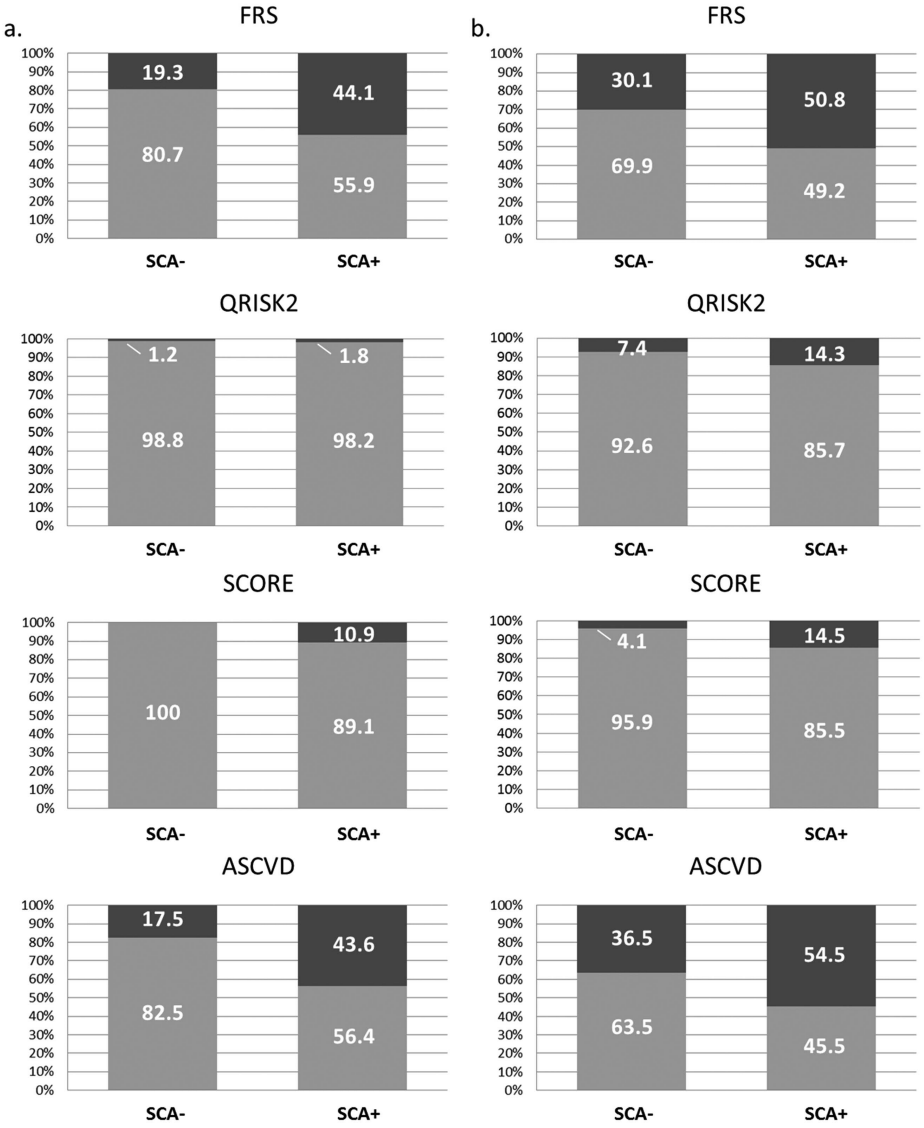

Figure 3. Original risk scores and EULAR modified risk scores in discriminating subclinical atherosclerosis using the preset cutoffs. (A) Original risk scores. (B) EULAR modified risk scores. Dark grey: high risk; Light grey: low risk. High risk: FRS > 10%, QRISK2 > 20%, SCORE > 5%, and ASCVD > 7.5%. SCA: subclinical atherosclerosis; FRS: Framingham risk score; SCORE: Systematic COronary Risk Evaluation; ASCVD: atherosclerotic cardiovascular disease risk algorithm; EULAR: European League Against Rheumatism.

To overcome this problem, some authors suggested lowering the threshold for high CV risk in patients with RA[22,24]. Dessein, *et al* demonstrated that FRS and SCORE effectively estimated the presence of carotid plaques in patients with RA at very low threshold values of 7.3%–10.8%, and 0.5%–1.5%, respectively[45]. According to our results, it would be more important to improve the AUROC to increase the overall predictive accuracy. Arts, *et al*[26] tried to incorporate RA disease activity (if 28-joint Disease Activity Score > 5.1) into the SCORE; however, the adapted SCORE algorithm did not provide sufficient improvement in CV risk prediction in patients with RA. Nevertheless, the usefulness of a similar adaptation of the SCORE algorithm in PsA would need to be addressed in future large cohort studies.

The strength of our study was the comprehensive CV risk assessment and ultrasonographic evaluation. We had thoroughly evaluated 6 sites of carotid arteries by a single investigator, which ensured the identification of SCA. Our study also has a few limitations. First, the risk scores were originally developed in American or European communities; therefore, the CV risk calculated may be overestimated or underestimated because of differences in ethnicity. Second, our results may not be applicable to patients with PsA from

other ethnic backgrounds. Third, the outcome of our study is only a surrogate of clinical CV events. The performance of the risk scores in predicting CV events should be evaluated in future prospective studies. Fourth, our sample size is small; further validation is necessary to consolidate the conclusion. Nonetheless, the correlation of SCA and high CV risk is well recognized. In studies based on the general population, the 10-year risk of coronary heart disease ranged from 11% to 25% in patients with carotid plaque or increased IMT, while in patients without SCA, it ranged only from 1% to 8%[6,46,47,48]. Fourth, the addition of carotid IMT measurements to the risk stratification may be modest[49], and plaque may be more robust in predicting CV events[50]. Nevertheless, in a subgroup analysis considering only patients with carotid plaque as SCA+, the results were generally similar (AUROC ranged from 0.626 to 0.664, p ranged from 0.026 to 0.004; over half the patients with SCA+ were missed by FRS > 10% and ASCVD > 7.5%, and over 80% were missed by QRISK2 > 20% and SCORE > 5%). Finally, carotid plaque burden and vulnerability were not assessed in our study.

FRS, QRISK2, SCORE, and ASCVD may underestimate the risk of SCA in patients with PsA. The 1.5 multiplication factor provided limited improvement in the performance of these CV risk assessment tools. Disease-specific CV risk prediction algorithms should be developed.

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