Disease Activity Influences Cardiovascular Risk Reclassification Based on Carotid Ultrasound in Patients with Psoriatic Arthritis

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Running title: Cardiovascular risk reclassification in PsA

Abstract

Objective. Since the addition of carotid ultrasound into composite cardiovascular risk (CVR) scores has been found effective for identifying patients with inflammatory arthritis and high CVR, we aimed to determine if its use would facilitate the reclassification of patients with psoriatic arthritis (PsA) into the very-high-risk SCORE (Systematic Coronary Risk Evaluation) category and whether this might be related to disease features.

Methods. Cross-sectional study involving 206 patients who fulfilled CASPAR criteria for PsA and 197 controls. We assessed lipid profile, SCORE, disease activity measurements, and the presence of carotid plaques and carotid intima-media thickness by ultrasonography. A multivariable regression analysis, adjusted for classic CVR factors, was performed to evaluate if the risk of reclassification could be explained by disease-related features and to assess the most parsimonious combination of risk reclassification predictors.

Results. Forty-seven percent of patients were reclassified into a very-high SCORE risk category after carotid ultrasound compared to 26% of controls (p=0.000). Patients included in the low-risk SCORE category were those who were more commonly reclassified (30% vs. 14%, p=0.002). The DAPSA score was associated with reclassification (beta coefficient 1.10 [95%CI 1.02-1.19], p=0.019) after adjusting for age and traditional CVR factors. A model containing SCORE plus age, statin use, and DAPSA score yielded the highest discriminatory accuracy compared to the SCORE alone model (AUC 0.863 [95%CI 0.789-0.936] vs. 0.716 [95%CI 0.668-0.764], p=0.000).

Conclusions. PsA patients are more frequently reclassified into the very-high SCORE risk category following carotid ultrasound assessment than controls. This was independently explained by the disease activity.

Key Indexing Terms: Psoriatic Arthritis, Carotid Plaques, Cardiovascular Risk Score.

Introduction

There is growing evidence that psoriatic arthritis (PsA) patients have a higher cardiovascular disease burden than the general population (1). Exposure to an increased inflammation load is associated with a higher prevalence of atherosclerosis in these individuals (2). Previous studies have reported that this occurred independently of traditional cardiovascular risk factors and correlated with PsA disease duration and increased inflammatory markers (3,4). Moreover, PsA patients lacking traditional cardiovascular risk factors were found to have the more commonly observed subclinical atherosclerosis, manifested by a higher frequency of endothelial dysfunction, greater carotid intima-media wall thickness (cIMT), and a higher frequency of carotid plaques than healthy controls (5,6). Additionally, increased cIMT independently correlated with parameters of disease activity and conventional risk factors of atherosclerosis in PsA patients (7). This is of great relevance, since the presence of carotid atherosclerosis was associated with an increased risk of experiencing future cardiovascular events in patients with PsA (8).

Prediction score algorithms for cardiovascular disease, such as the Framingham Risk Score and the Systematic Coronary Risk Evaluation (SCORE), were reported to be of limited value in correctly identifying high-cardiovascular risk PsA patients (7,9). This implies that such risk charts do not correctly identify patients who might benefit from intensive management of cardiovascular risk factors. For this reason, the search for non-invasive tools that would facilitate the identification of very high cardiovascular risk PsA patients is of great relevance. In this regard, the reclassification of individuals included in the moderate or low categories, based on the SCORE, into the very high cardiovascular risk category using carotid ultrasound has been reported in patients with systemic lupus erythematosus (10) and rheumatoid arthritis (11,12).

According to the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (13), carotid artery plaque assessment using ultrasound has gained support as a way of reclassifying those patients for whom the SCORE is thought to underestimate the actual cardiovascular risk. However, there is still limited data available to define a candidate profile for this evaluation, the cost-effectiveness of which would be greater. Taking this into account, we aimed to determine if the use of carotid ultrasound would facilitate the reclassification of patients with PsA into the very high cardiovascular risk SCORE category and whether this could be related to characteristics assessed in the daily clinical practice, particularly those related to disease features.

Methods

Study participants

This was a cross-sectional study that included 206 patients with PsA and 179 controls. All of them were 18 years old or older, had a clinical diagnosis of PsA, and were enrolled based upon the international Classification of Psoriatic Arthritis (CASPAR) study (14). They had been diagnosed by rheumatologists and were periodically followed-up at rheumatology outpatient clinics. For the purpose of inclusion in the present study, PsA disease duration had to be ≥1 year. Although long-term anti-TNF-α therapy has been found to improve aortic stiffness and cIMT progression in patients with PsA (15,16), those undergoing anti-TNF-α, IL-17 inhibitors or other biological therapies were not excluded from the present study. Likewise, since glucocorticoids are often used in the management of PsA, patients taking prednisone were not excluded. The controls (n=179) were community-based, recruited by general practitioners in primary health centers of the Cantabria region. Controls with family history of any inflammatory or autoimmune rheumatic diseases were excluded. None of the patients and controls had established cardiovascular disease. Diabetes mellitus patients were included when target organ damage was not present. The study protocol was

approved by the Institutional Review Committee at Hospital Marqués de Valdecilla in Santander, Spain, and all subjects provided informed written consent (Approval Number: 2016.052).

Assessments and data collection

Surveys in PsA patients and controls were performed to assess cardiovascular risk factors and medication. Hypertension was defined as a systolic or a diastolic blood pressure higher than140 and 90 mmHg, respectively. Dyslipidemia was defined if one of the following factors was present: total cholesterol > 200 mg/dl, triglycerides > 150 mg/dl, HDL-cholesterol < 40 mg/dl in men or < 50 mg/dl in women, or LDL-cholesterol > 130 mg/dl. At the time of assessment, all patients were evaluated using two clinical measures of disease activity: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)(17) and the Disease Activity Index for Psoriatic Arthritis (DAPSA) (18). In addition, a functional status index (Bath Ankylosing Spondylitis Functional Index [BASFI]) (19), a patient life impact measure (PsA Impact of Disease Score [PsAID]) (20), two cutaneous indexes (Psoriasis Area and Severity Index score [PASI] and Psoriasis Global Assessment [PGA]) (21), and the Nail Psoriasis Severity Index (NAPSI) were used to assess the severity of nail psoriasis (22). Furthermore, high-sensitivity C-reactive protein (hsCRP) was assessed, and standard techniques were used to measure serum lipids.

Carotid ultrasound assessment

Carotid ultrasound was performed to determine cIMT in the common carotid artery and to detect focal plaques in the extracranial carotid tree both in patients with PsA and in controls (12,23). A commercially available scanner, Mylab 70, Esaote (Genoa, Italy) equipped with a 7-12 MHz linear transducer and an automated software-guided radiofrequency technique — Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland) — was used for this purpose. Based on the Mannheim consensus, plaque criteria in the accessible extracranial carotid tree

(common carotid artery, bulb and internal carotid artery) were defined as follows: a focal protrusion in the lumen measuring at least cIMT >1.5 mm; a protrusion at least 50 % greater than the surrounding cIMT; or an arterial lumen encroaching >0.5 mm (24).

Statistical analysis

Patients and controls with carotid plaques based on ultrasound assessment were reclassified into very-high SCORE risk category. Subjects without plaques were maintained in their original SCORE category. cIMT was not used to determine reclassification because according to current guidelines (25) cIMT is not considered an unequivocal CVD on imaging. Univariate differences between reclassified and non-reclassified patients were assessed through T Student, U Mann-Whitney, Chi squared or Fisher Exact tests according to normal distribution or the number of subjects. Logistic regression analysis adjusted for the variables with a p value below 0.20 in the univariate analysis was performed to assess the relation between PsA disease-related data and the presence of reclassification. An all-sets logistic regression model was constructed to describe the most parsimonious combination of risk reclassification predictors according to Akaike Information Criteria, Schwarz Bayesian Criterion, the area under the curve, and Hosmer-Lemeshow goodness-of-fit. For characteristics associated with reclassification and that were included in the predictive model, sensitivity versus false positive frequency (1-specificity) was analyzed utilizing receiver-operating characteristic curves (ROC). To determine the optimal cutoff value of baseline characteristics in predicting reclassification, we calculated the Youden index using the following formula: sensitivity + specificity – 1, with the maximum obtained value corresponding to the optimal cut-off point. To estimate the increase in prediction accuracy between models, we used logistic regression to calculate the ROC curves and the area under the receiver-operator characteristic curves (AUC). The SCORE AUC was thus considered the reference and was compared to the other model when adding PsA-related data (age, statins use and DAPSA score). A

comparison of ROC curves to test the statistical significance of the difference between the areas under two dependent ROC curves (derived from the same cases) was conducted using the method of DeLong *et al*. (26). Reclassification differences between models were studied through the net reclassification index (NRI) and integrated discrimination improvement (IDI) as previously described (27). Similarly, calibration of the models was calculated using the Hosmer-Lemeshow goodness-of-fit test by grouping individuals on the basis of deciles (28,29). All the analyses used a 5% two-sided significance level and were performed using SPSS software, version 24 (IBM, Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

Results

Demographic, laboratory and disease-related data

A total of 206 PsA patients and 179 sex-matched controls with a mean ± SD age of 45 ± 8 and 41± 9 years, respectively, were included in this study. Demographic and disease-related characteristics of the participants are shown in **Table 1**. Body mass index (26.9 ± 5.8 vs. 25.4 ± 4.2; p=0.010) and waist circumference (94 ± 15 vs. 91 ± 15 cm, p=0.048) were higher in PsA patients than controls. Differences between patients and controls in the prevalence of traditional cardiovascular risk factors were also observed. In this regard, patients were more commonly hypertensive (37% vs. 12%, p=0.000), smokers (28% vs.18%, p=0.017) and diabetic (10% vs. 2%, p=0.002). A lipid profile assessment revealed lower levels of total cholesterol (0.006) and LDL-cholesterol (0.023) in patients compared to controls. The median PsA disease duration was 4.6 years (interquartile range -IQR- 2.0-10.9). Psoriasis was present in 73% of patients at the time of the study and 10% were positive for HLA-B27. An extended version of **Table 1** is available as **Supplementary Table 1** with the online version of this article.

Regarding carotid ultrasound assessment, 49% of the PsA patients had carotid plaques compared to 26% of controls (p=0.000). The average cIMT in patients and controls was 0.679 ± 0.165 mm and 0.606 ± 0.116 mm, respectively (p=0.000).

SCORE risk category reclassification after carotid sonography

Following SCORE risk chart stratification, 101 (49%) patients and 139 (78%) controls were included in the low cardiovascular risk category. In contrast, none of the controls and only 8 (4%) patients fulfilled the definition for very high cardiovascular risk when the risk charts were applied (**Table 2**). Interestingly, carotid ultrasound assessments revealed a significantly higher frequency of reclassification in PsA patients compared to controls (47% vs. 26%, p=0.000). In this regard, 30 of the 101 patients (30%) and 19 of the 139 controls (14%) who fulfilled the definition for low cardiovascular risk, according to the SCORE risk charts, had carotid plaques; consequently, they were reclassified into the very-high risk category (30% vs. 14%, p=0.000). Fifty-four of 78 patients (69%) and 18 of 28 controls (64%) (p=0.54) included in the moderate-risk SCORE category had carotid plaques and, consequently, were also reclassified into the very high cardiovascular risk category. Similarly, 12 of 19 PsA patients (63%) and 10 of 12 controls (83%) included in the high cardiovascular risk SCORE category prior to carotid ultrasound assessment were reclassified into the very high-risk category once that this test was performed (p=0.42) (**Table 2**).

Similar results were obtained when analyses were performed separating patients according to current anti-TNF alpha therapy or not. In this regard, both groups disclosed a higher probability of being reclassified compared to controls (**Supplementary Table 2**).

Differences between reclassified and non-reclassified patients into very high cardiovascular risk categories after carotid ultrasound assessment

Several differences in the recorded characteristics of PsA patients who were reclassified following the carotid ultrasound assessment and those who were not reclassified were observed (**Table 3**). In this regard, reclassified patients were older (57 ± 9 years vs. 50 ± 13 years, p=0.000), and more commonly had hypertension (54% vs. 22 %, p=0.000) and obesity (28% vs. 14%, p=0.011).

As expected, PsA patients who were reclassified following a carotid ultrasound had greater cIMT than those who were not reclassified (0.725 ± 157 mm vs. 0.638 ± 0.162 mm, p=0.000). Interestingly, neither laboratory parameters related to the lipid profile nor CRP values revealed any differences between reclassified and non-reclassified patients with the exception of total cholesterol (197 ± 36 mg/dl vs. 179 ± 40 mg/dl, p=0.001) and LDL-cholesterol (116 ± 35 mg/dl vs. 106 ± 34 mg/dl, p=0.032), which were lower in reclassified patients.

Regarding PsA-related features, some differences were also observed between these two groups of patients. Those with peripheral polyarthritis were more commonly reclassified following a carotid ultrasound assessment than the other patients. In addition, disease duration was found to be higher in the reclassified patients (5.7 [IQR 2.2-12.5] years vs. 4.1 [IQR 1.4-8.0] years, p=0.023). However, this association was lost after adjusting for age and traditional cardiovascular risk factors. The DAPSA score, both as a continuous (6.10 [0.05-15.10] vs. 1.92 [0.00-10.01], p=0.056) and categorical measure (low, moderate or high activity vs. remission), was found to be higher in reclassified patients in the univariate analysis. Moreover, DAPSA score differences were still present when this relation was constructed after adjusting for confounding factors. In this regard, DAPSA's positive relation with reclassification yielded a statistically significant association (beta coefficient 1.10 [95%cCI 1.02-1.19], p=0.019) after the multivariable analysis. Multivariable regression analysis also confirmed the aforementioned results using DAPSA as a categorical (low, moderate or high activity vs. remission) and ordinal (moderate and high activity, or low activity vs. remission) variable. Patients with moderate or high activity, according to their DAPSA score at the

time of assessment, exhibited a higher probability of being reclassified compared to the remaining patients (beta coef. 15.09 [95%CI 1.69-135.08], p=0.015). An extended version of **Table 3** is available as **Supplementary Table 3** in the online version of this article.

Predictive model for reclassifying patients into the very high cardiovascular risk category following a carotid ultrasound assessment

A predictive model was constructed only for those patients with PsA who had been included in the low and moderate risk SCORE categories prior to a carotid ultrasound assessment. These variables conjointly represented the most parsimonious model capable of predicting the reclassification of patients with PsA into the very high cardiovascular-risk category (**Table 4**): age, use of statins, and DAPSA score. Moreover, an age exceeding 48 years and a DAPSA score equal to or higher than 5 were the cut-offs among the continuous variables that reached the highest Youden indices.

Table 5 represents the discrimination, re-classification and calibration assessment of the model using clinical data (age, statins use, and DAPSA score) versus the reference SCORE model. The SCORE, which included traditional CV risk factors, showed a statistically significant discrimination of reclassification (AUC 0.716 [95%CI 0.668-0.764]). However, the AUC of the model, which contained SCORE plus age, statin use, and the DAPSA score, was found to have higher discrimination (0.863 [95%CI 0.789-0.936]), p=0.000) (**Figure 1**). The addition of clinically related data represented a significant change in NRI vs. the SCORE reference model (NRI 0.65 [95%CI 0.38-0.92], p=0.000). Similarly, IDI was significantly higher in this model compared to that of the SCORE reference (0.46 [95%CI 0.36-0.56], p=0.000). Model calibration (through a Hosmer-Lemeshow chi2 test) was found to be optimal in the final model (0.89).

Discussion

A carotid ultrasound is a non-invasive well-validated and reproducible procedure for quantifying the burden of subclinical vascular disease and determining cardiovascular disease risk. Using this technique we can measure the cIMT and identify the presence of carotid plaques, which are surrogate markers for atherosclerotic disease. In the present study we observed not only that use of a carotid ultrasound allowed us to reclassify nearly half of the PsA patients, but also that disease activity influenced reclassification, regardless of traditional cardiovascular risk factors. In this sense, tools that are commonly utilized in clinical practice proved useful for identifying PsA patients who would benefit from a complementary cardiovascular assessment.

Reclassification of cardiovascular risk using carotid ultrasound in PsA has previously been reported. In a recent study of 102 patients (30), 70.6% had intermediate-cardiovascular risk, 25.5% high cardiovascular risk, and 3.9% very high cardiovascular risk according to the SCORE risk charts. Of these, 26.5% were upgraded and reclassified into the very high risk category due to the presence of carotid plaques. However, this study lacked any comparison of reclassification between PsA patients and healthy individuals. Moreover, the study did not provide information on determinants of this reclassification. In another cross-sectional multicenter descriptive study from the same group, 30.8% of the 176 PsA patients assessed by SCORE risk charts were subsequently reclassified as having very high risk following carotid ultrasound evaluation (31). Subclinical atherosclerosis was associated with age and dyslipidemia, but not with other traditional cardiovascular risk factors. Axial disease was associated with reclassification in patients with moderate-cardiovascular risk (31). Similarly, in a series of 226 patients with PsA, Eder *et al.* observed that 56.1% of the patients in the Framingham Risk Score-based low to intermediate risk groups had carotid plaques. Interestingly, 55.9% of the patients from the intermediate risk category were reclassified into an ultrasound-based high-risk category, while 47.1% of the patients in the low-risk category were reclassified into a higher ultrasound-based risk group (32).

The DAPSA score has been validated for its use in PsA. In both trials and observational studies, it has proven to be sensitive to change, showing good correlation with ultrasound-assessed synovitis (18). Several reports have demonstrated that disease activity, as determined by this score or by other biomarkers, is responsible for the accelerated atherogenesis observed in PsA patients (3,33,34). Our findings, which support the contention that DAPSA is independently related to reclassification, reinforce the importance of disease activity and disease duration as key factors in the development of accelerated atherosclerosis in PsA patients. A recent prospective study has shown that patients achieving MDA were associated with lower risk of subclinical atherosclerosis progression (35). Furthermore, when we established a predictive model on the probability of being reclassified, we found that the DAPSA score, when combined with age and statins treatment, was capable of explaining such a reclassification. Our findings were in agreement with a recent report by our group involving patients with systemic lupus erythematosus (10). In this study, we found that disease-related factors - such as disease duration, a score of disease damage and complement serum levels - were capable of explaining such a reclassification in systemic lupus erythematosus patients, independently of traditional cardiovascular factors. These findings reinforce the pivotal role of disease activity in chronic inflammatory conditions as a major factor leading to cardiovascular risk reclassification.

We do not have an exact explanation for the fact that other PsA disease related scores were not related to reclassification. In this sense, BASDAI index and cutaneous psoriasis scores did not reveal any differences between reclassified and non-reclassified patients. We believe that this was probably related to a low prevalence of spinal involvement and mild skin involvement in our cohort. Moreover, the disease duration in our patients was relatively short. This fact may have influenced that disease duration in our study were not related to reclassification after adjustment. We also believe that the fact that statins use was associated with reclassification may reflect a marker of high underlying CV risk in these reclassified patients instead of a causative effect.

PsA may involve peripheral joints, axial joints or both. However, polyarthritis is commonly observed during the disease course. Certainly the polyarthritis pattern is the most common, and it is frequently associated with higher disease activity (36). In our study, the peripheral polyarthritis PsA pattern was more commonly associated with reclassification than were other PsA patterns.

In our study we found that both discrimination through AUC, which reflects the ability of a prognostic model to correctly identify clinical status, and reclassification with NRI were significantly higher in the model containing clinically related data compared to the SCORE model. The capacity of the SCORE model to predict clinical cardiovascular events in the general population is potent and has been widely demonstrated. In fact, improvements in risk prediction and classification beyond SCORE, such as by adding novel risk markers, including imaging techniques and biomarkers, have been modest. In our study on PsA patients, the contribution of SCORE data to a prediction model of reclassification was also great. However, we were able to identify novel markers (age, statins use and DAPSA score) with a significant incremental predictive value for the presence of reclassification in PsA.

A limitation of our study was that controls were not age-matched. However, this difference was not found to be excessive (mean difference of 4 years), and it is known that the SCORE model used age as a time variable and not as a risk factor. Moreover, it has previously been shown that regardless of matching, identical results are obtained when multivariable regression analysis is applied to epidemiological case-control studies (37). Consequently, we feel that the multivariate analysis performed in our study was capable of dealing with potential confounders. In addition, patients in our cohort had significantly lower CRP serum levels compared to controls. We believe that this is because a large majority of the patients were on biological treatment. Nevertheless, we do not believe that this issue affected the results of our study. Another limitation was that currently it is unknown if reclassified PsA patients experience a higher number of CV events. Moreover, the reduction of CVD risk in patients treated with lipid- or blood pressure-lowering drugs because of

reclassification with, for example, carotid ultrasound remains to be demonstrated. However, current guidelines (25) recommend additional risk factor assessment if such risk factors improve risk classification by calculation of a NRI, and if the assessment is feasible in daily practice. We believe, therefore, that this is the case of our study, in which NRI was proved to be statistically significant.

In conclusion, our results indicate that reclassification of cardiovascular risk following carotid ultrasound assessment in patients with PsA is independently associated with disease activity. This fact supports the need for active management of the disease in order to reduce the inflammatory burden, in a dual strategy to prevent not only disability but also the risk of cardiovascular events.

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Table 1. Demographic data of 206 psoriatic arthritis patients and 179 controls.

	Controls=179	Psoriatic arthritis=206	p
Demographics			
Male, n (%)	90 (50)	91 (44)	0.23
Age, years	41 ± 9	45 ± 8	**0.000**
BMI, mg/cm2	25.4 ± 4.2	26.9 ± 5.8	**0.010**
Waist circumference, cm	91 ± 15	94 ± 15	**0.048**
Systolic pressure, mmHg	121 ± 13	129 ± 18	**0.000**
Diastolic pressure, mmHg	76 ± 9	77 ± 11	0.237
Comorbidity			
Hypertension, n (%)	21 (12)	76 (37)	**0.000**
Dyslipidemia, n (%)	106 (59)	114 (55)	0.48
Current smoking, n (%)	32 (18)	58 (28)	**0.017**
Diabetes, n (%)	4 (2)	21 (10)	**0.002**
BMI > 30, n (%)	25 (14)	42 (20)	**0.020**
Laboratory data			
ESR, mm/1st h	5 (2-9)	6 (3-12)	**0.002**
hsCRP, mg/l	0.8 (0.5-2.0)	0.3 (0.1-0.8)	**0.006**
Cholesterol, mg/dl	199 ± 34	189 ± 30	**0.006**
Triglycerides, mg/dl	103 ± 56	102 ± 52	0.83
LDL-cholesterol, mg/dl	119 ± 31	111 ± 34	**0.023**
HDL-cholesterol, mg/dl	59 ± 17	57 ± 17	0.27
Atherogenic index	3.62 ± 1.06	3.94 ± 5.89	0.49
Psoriatic arthritis-related data			
Type of psoriatic arthritis			
Peripheral oligoarthritis		19 (9)	
Peripheral polyarthritis		124 (60)	
Spondylitis		30 (15)	
Mixed		30 (15)	
Disease duration, years		4.6 (2.0-10.9)	
Psoriasis at the time of the study, n (%)		151 (73)	
HLA-B27 positive, n (%)		20 (10)	
Family history of PsA, n (%)		69 (33)	
BASDAI, total score		2.2 (0.0-4.7)	
BASDAI >4, n (%)		31 (15)	
BASFI, total score		0 (0-3)	
PsAID, total score		1-0 (0.0-2.9)	
DAPSA, total score		4.2 (0.1-13.0)	
BSA, total score		0.75 (0.00-2.05)	
PASI, total score		0.45 (0.00-2.00)	
NAPSI, total score		0.0 (0.0-3.1)	
PGA, total score		0 (0-1)	
Axial symptoms, n (%)		70 (34)	

Peripheral symptoms, n (%)		150 (73)	
Hip symptoms, n (%)		44 (21)	
Enthesitis, n (%)		78 (38)	
Uveitis, n (%)		13 (6)	
Dactylitis, n (%)		51 (25)	
Inflammatory bowel disease, n (%)		14 (7)	
Sacroiliitis on MRI, n (%)		26 (13)	
Syndesmophytes in axial x-ray, n (%)		7 (3)	
Current NSAIDs, n (%)		162 (79)	
Current prednisone, n (%)		85 (41)	
DMARDs, n (%)		154 (75)	
Methotrexate, n (%)		139 (67)	
Anti TNF-therapy, n (%)		87 (42)	
Carotid intima media assessment			
Carotid plaque, n (%)	47 (26)	100 (49)	**0.000**
bilateral, n (%)	20 (11)	56 (27)	**0.000**
cIMT, mm	0.606 ± 0.116	0.679 ± 0.165	**0.000**

Data represent mean ± SD or median (IQR) when data were not normally distributed.
BMI: body mass index; CRP: C-reactive protein; LDL: low-density lipoprotein.
DMARD: disease-modifying antirheumatic drug.
HDL: high-density lipoprotein; hsCRP: high-sensitivity C-reactive protein.
cIMT, carotid intima media thickness; BASFI: Bath Ankylosing Spondylitis Functional Index.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
NAPSI: Nail Psoriasis Severity Index; BSA: Body Surface Area.
PGA: Psoriasis Global Assessment; PsAID: PsA Impact of Disease Score.
DAPSA: Disease Activity in PSoriatic Arthritis.

Table 2. SCORE risk category reclassification after carotid ultrasound assessment.

		SCORE Risk Category after Carotid Ultrasound Assessment					
Initial SCORE risk category		Low	Moderate	High	Very high	% patients reclassified	p*
Controls							
Low	139	120	0	0	19	13.7%	
Moderate	28	0	10	0	18	64,3%	
High	12	0	0	2	10	83.3%	
Very High	0	0	0	0	0	-	
	179	120	10	2	47	26.3%	
Psoriatic arthritis patients							
Low	101	71	0	0	30	29.7%	**0.002**
Moderate	78	0	24	0	54	69.2%	0.54
High	19	0	0	7	12	63.2%	0.42
Very High	8	0	0	0	8	-	
	206	71	24	7	104	46.6%	**0.000**

SCORE: Systematic Coronary Risk Evaluation.

*p values refer to the comparison between patients and controls for each SCORE category and for the total of both populations.

Table 3. Differences between reclassified and non-reclassified PsA patients into the very high cardiovascular risk category following carotid ultrasound assessment.

	Reclassification into Very High Risk after Carotid Ultrasound			Adjusted Model	
	No (n = 109)	Yes (n = 97)	p	OR (95% CI)	p
cIMT, carotid intima media thickness, mm	0.638 ± 0.162	0.725 ± 157	**0.000**		
Demographics					
Men, n (%)	44 (40)	47 (48)	0.24		
Age, years	50 ± 13	57 ± 9	**0.000**		
BMI, mg/cm2	27.7 ± 6.8	27.9 ± 6.6	0.89		
Waist circumference, cm	94 ± 15	94 ± 20	0.91		
Systolic pressure, mmHg	137 ± 22	136 ± 19	0.74		
Diastolic pressure, mmHg	79 ± 13	80 ± 11	0.63		
Comorbidity					
Hypertension, n (%)	24 (22)	52 (54)	**0.000**		
Dyslipidemia, n (%)	64 (59)	50 (52)	0.15		
Current smoking, n (%)	30 (28)	28 (29)	0.83		
Diabetes, n (%)	7 (6)	14 (14)	0.058		
BMI > 30, n (%)	15 (14)	27 (28)	**0.011**		
Statins, n (%)	32 (29)	80 (82)	**0.000**		
Laboratory data					
ESR, mm/1st h	7 (4-13)	5 (3-11)	0.94		
hsCRP, mg/l	0.3 (0.1-0.8)	0.2 (0.1-0.7)	0.19		
Cholesterol, mg/dl	197 ± 36	179 ± 40	**0.001**		
Triglycerides, mg/dl	96 ± 39	108 ± 62	0.10		
LDL-cholesterol, mg/dl	116 ± 35	106 ± 34	**0.032**		
HDL-cholesterol, mg/dl	58 ± 17	55 ± 17	0.32		

Atherogenic index	3.37 (2.73-4.12)	3.62 (2.89-4.41)	0.68		
Psoriatic arthritis-related data					
Type of psoriatic arthritis					
Peripheral oligoarthritis	14 (13)	5 (5)			
Peripheral polyarthritis	55 (50)	69 (71)	**0.001**		
Spondylitis	15 (14)	15 (15)			
Mixed	24 (22)	6 (6)			
Disease duration, years	4.1 (1.4-8.0)	5.7 (2.2-12.5)	**0.023**	1.00 (0.97-1.02)	0.77
Psoriasis at the time of the study, n (%)	76 (70)	75 (77)	0.093	1.66 (0.65-4.25)	0.30
HLA-B27 positive, n (%)	17 (16)	3 (3)	**0.004**	0.17 (0.03-1.06)	0.058
Positive family history of PsA, n (%)	40 (37)	29 (30)	0.23	0.76 (0.29-1.96)	0.56
BASDAI, total score	2.65 (0.00-5.70)	1.4 (0.0-3.8)	0.21	0.92 (0.74-1.13)	0.41
BASDAI >4, n (%)	19 (17)	12 (12)	0.19	0.54 (0.16-1.84)	0.33
BASFI, total score	0.3 (0.0-3.5)	0.0 (0.0-2.1)	0.40	0.88 (0.70-1.11)	0.27
PsAID, total score	1.0 (0.0-3.2)	1.0 (0.0-2.0)	0.11	1.03 (0.77-1.37)	.87
DAPSA, total score	1.92 (0.00-10.01)	6.10 (0.05-15.10)	0.056	**1.10 (1.02-1.19)**	**0.019**
Remission, n (%)	35 (32)	23 (24)	**0.049**	-	-
Low, moderate or high activity, n (%)	23 (21)	32 (33)		**3.22 (1.05-9.90)**	**0.041**
DAPSA, total score					
Remission, n (%)	35 (32)	23 (24)	0.14	-	-
Low activity, n (%)	13 (12)	17 (18)		1.50 (0.42-5.37)	0.53
Moderate or high activity, n (%)	10 (9)	15 (15)		**15.09 (1.69-135.08)**	**0.015**
BSA, total score	0.5 (0.0-2.9)	0.9 (0.0-2.0)	0.30	0.79 (0.52-1.22)	0.29
PASI, total score	0.8 (0.0-2.1)	0.2 (0.02.0)	0.30	0.73 (0.51-1.04)	0.73
Low	42 (39)	44 (45)	0.27	-	-
Moderate and severe	6 (6)	2 (2)		0.10 (0.01-1.48)	0.094
NAPSI, total score	0 (0-3)	0 (0-4)	0.43	1.08 (0.93-1.26)	0.45
log PGA, total score	0.37 ± 0.88	0.42 ± 0.64	0.82	180 (0.57-5.70)	0.32

Axial symptoms, n (%)	44 (40)	26 (13)	**0.046**	0.86 (0.36-2.07)	0.74
Peripheral symptoms, n (%)	83 (76)	67 (33)	0.31	0.57 (0.22-7.85)	0.23
Hip symptoms, n (%)	29 (27)	15 (7)	0.053	0.38 (0.14-1.07)	0.067
Enthesitis, n (%)	47 (43)	31 (15)	0.14	0.93 (0.39-2.º14)	0.87
Uveitis, n (%)	8 (7)	5 (2)	0.54	0.75 (0.17-3.39)	0.75
Dactylitis, n (%)	28 (26)	23 (11)	0.79	1.30 (0.47-3.58)	0.61
Inflammatory bowel disease, n (%)	8 (7)	6 (3)	0.80	0.63 (0.15-2.60)	0.63
Sacroiliitis on MRI, n (%)	17 (16)	9 (4)	0.21	0.74 (0.21-2.61)	0.64
Sacroiliitis in x-ray grade				0.69 (0.20-2.39)	0.69
Grade I, n (%)	55 (50)	47 (48)	0.62	-	-
Grade >= II, n (%)	16 (15)	11 11)		0.72 (0.21-2.51)	0.60
Syndesmophytes in axial x-ray, n (%)	4 (4)	3 (3)	0.99	0.52 (0.08-3.34)	0.49
Current NSAIDs, n (%)	91 (83)	71 (73)	0.12	0.45 (0.17-1.20)	0.11
Current prednisone, n (%)	44 (40)	41 (42)	0.59	1.02 (0.45-6.74)	0.96
DMARDs, n (%)	78 (72)	76 (37)	0.11	2.32 (0.87-6.24)	0.095
Methotrexate, n (%)	71 (65)	68 (70)	0.30	1.25 (0.52-3.03)	0.62
Anti TNF-therapy, n (%)	50 (46)	37 (38)	0.32	1.41 (0.57-3.52)	0.63

Data represent mean ± SD or median (IQR) when data were not normally distributed.

BMI: body mass index; CRP: C-reactive protein; LDL: low-density lipoprotein; hsCRP: high-sensitivity C-reactive protein

DMARD: disease-modifying antirheumatic drug; HDL: high-density lipoprotein; ANA: antinuclear antibodies.

cIMT, carotid intima media thickness; NAPSI: Nail Psoriasis Severity Index; BSA: Body Surface Area.

DAPSA: Disease Activity in PSoriatic Arthritis; PGA: Psoriasis Global Assessment.

BASDAI: Bath Ankylosing Spondylitis Disease Activity; BASFI: Bath Ankylosing Spondylitis Functional Index.

Adjusted model for age, hypertension, dyslipidemia, diabetes, obesity and statins.

Table 4. All the logistic regression model subsets for the prediction of reclassification in patients with PsA included in the low and moderate cardiovascular risk category according to the SCORE prior to carotid ultrasound assessment.

Variables	OR (95% CI)	p	Optimal Cut-off	Sensitivity, %	Specificity, %
Age, years	1.12 (1.03-1.21)	**0.006**	48	81	59
Statins treatment	90 (14-573)	**0.000**			
DAPSA	1.13 (1.02-1.25)	**0.024**	5	60	63
Pseudo R2	0.562				
AIC	53				
BIC	62				
AUC	0.932				
Sensitivity	93.8%				
Specificity	84.6%				
pfitHL	0.996				

Values in bold face are statistically significant. AIC: Akaike information criterion; BIC: Schwarz Bayesian criterion
AUC: area under the curve; pfitHL: Hosmer-Lemeshow goodness-of-fit
DAPSA: Disease Activity in PSoriatic Arthritis

Table 5. Discrimination, re-classification and calibration assessment of SCORE versus model adding clinical data.

	SCORE	SCORE + clinical data	p
Reclassification in patients with SCORE <5%			
Discrimination			
AUC	0.716 (0.668-0.764)	**0.863 (0.789-0.936)**	**0.000**
Re-classification			
NRI	-	**0.65 (0.38-0.92)**	**0.000**
IDI	-	**0.46 (0.36-0.56)**	**0.000**
Calibration			
H-L test	0.000		0.890

SCORE: Systematic Coronary Risk Evaluation; PsA clinical data: age, statins use and DAPSA score.

AUC: area under the curve; NRI: net reclassification index; IDI: integrated discrimination improvement.

'p' values in AUC rows represent the comparison of the second model with the first one (SCORE model), which is considered the reference. NRI and IDI are expressed as their values (95% confidence interval) and p value; NRI and IDI are compared using the SCORE model as the reference.

'p' value in H-L test expresses the p value of the Hosmer-Lemeshow chi2 statistical test.

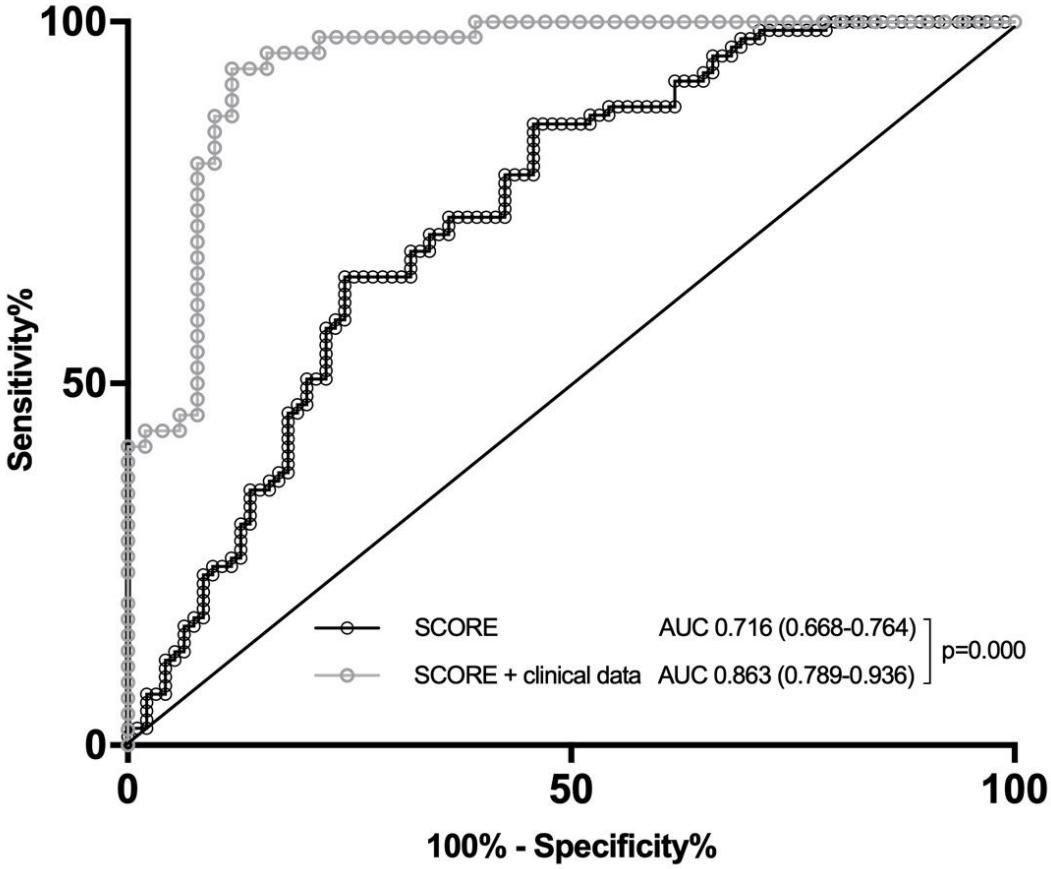

Figure 1. The receiver-operator characteristic (ROC) curves and the area under the receiver-operator characteristic curves (AUC) for reclassification of both the SCORE model vs. SCORE model plus clinical data (age, statins use and DAPSA score).