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ORIGINAL RESEARCH

The metabolic score for insulin resistance predicts the risk of cardiovascular disease in patients with psoriatic arthritis: results from the 10-year prospective CARMA cohort

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ABSTRACT

Objective To evaluate the predictive value of the metabolic score for insulin resistance (METS-IR) in identifying patients with psoriatic arthritis (PsA) at high risk of cardiovascular (CV) events.

Methods Assessment of patients with PsA enrolled in the Spanish prospective CARdiovascular in ReuMAtology (CARMA) project. Baseline data from 500 PsA patients without a history of CV events, chronic kidney disease, diabetes mellitus or statin use at the baseline visit were analysed. Patients were prospectively followed for 10 years in rheumatology outpatient clinics at tertiary centres. The performance of the METS-IR in predicting CV events was evaluated. METS-IR was categorised into three groups: <2.25, 2.25–2.48 and >2.48.

Results Over 4788 patient-years of follow-up, 27 individuals experienced at least one CV event. The annualised incidence rate was 5.6 events per 1000 patient-years (95% CI: 3.7 to 8.2). PsA patients with CV events had significantly higher METS-IR scores than those without CV events (2.37±0.24 vs 2.26±0.19; p=0.01). In this regard, patients who had CV events were more commonly included in the METS-IR 2.25–2.48 and >2.48 categories than those without CV events (p=0.008). Adjusted regression models indicated that PsA patients with a METS-IR >2.48 at baseline had an increased risk of experiencing a CV event during the follow-up period.

Conclusions In PsA patients under close observation in rheumatology units included in the prospective CARMA project, METS-IR serves as a reliable prognostic predictor of CV.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular (CV) mortality and CV events are more common in patients with psoriatic arthritis (PsA) than in the general population.

⇒ Several studies emphasise the importance of identifying surrogate markers to detect PsA patients at high risk for CV events and CV mortality.

⇒ Metabolic syndrome, a major risk factor for CV disease incidence, CV mortality and all-cause mortality, is linked to insulin resistance and more common in patients with PsA than in the general population.

⇒ The metabolic score for insulin resistance (METS-IR) has been shown to have superior predictive capability for subclinical atherosclerosis and CV events compared with traditional insulin resistance markers.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease that affects both the joints and skin. This is a type of spondyloarthritis that leads to inflammation in the musculoskeletal system, including peripheral arthritis, spondylitis, dactylitis and enthesitis.[1 2] Patients with PsA may also exhibit extra-articular manifestations, such as uveitis or inflammatory bowel disease.[2]

Patients with PsA also have an increased risk of clinical and subclinical cardiovascular disease (CVD), mostly due to accelerated atherosclerosis.[3–7] Chronic inflammation plays a pivotal role in the pathogenesis of atherosclerosis in PsA.[3 4 7] Patients with this inflammatory arthritis often exhibit endothelial dysfunction, and early step in the atherogenesis, and subclinical atherosclerotic disease, even in the absence of traditional cardiovascular (CV) risk factors.[8 9]

A mixed retrospective and prospective cohort study using data from patients with

WHAT THIS STUDY ADDS

⇒ This study is the first to evaluate the effectiveness of METS-IR in predicting CV events in patients with PsA, followed prospectively in rheumatology units over a 10-year period.

⇒ METS-IR predicts the occurrence of CV events in patients with PsA.

⇒ PsA patients with a baseline METS-IR value exceeding 2.48 had a higher risk of developing CV events during the follow-up period.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Understanding the true risk of CV events in patients with PsA treated in referral rheumatology units is essential for developing effective health strategies and minimising CV complications.

⇒ METS-IR may improve the identification of PsA patients at high risk of CV events.

⇒ Early identification of PsA patients at high risk of CV events enables timely detection of CV complications and the implementation of appropriate measures to prevent future CV events in these patients.

rheumatoid arthritis (RA), PsA or axial spondyloarthritis (axSpA) included in the Swiss Clinical Quality Management registry showed no significant difference in the incidence and prevalence of major adverse cardiovascular events (MACE) between RA, axSpA and PsA. This suggests that systemic inflammation, rather than a specific disease, drives the increased risk of CVD.[10]

Many factors can accelerate or provide protection against CV events. For example, some studies have illustrated the effect of controlling inflammation on surrogate outcomes of CV risk. Cheng *et al* demonstrated this in their study.[11] Additionally, increased inflammatory burden has been associated with CV events, as shown by Lam *et al*.[12] More recently, Meng *et al* evaluated the incidence and risk factors of MACE in RA and PsA patients. For this purpose, they conducted a population-based retrospective cohort study involving 13 905 patients (12 233 with RA and 1672 with PsA) identified from a citywide database (2006–2015), followed until 2018. The occurrence of a first MACE was assessed, considering traditional CV risk factors, inflammatory markers and treatments. The adjusted incidence was found to be similar for RA and PsA. Systemic inflammation, as indicated by elevated erythrocyte sedimentation rate and C-reactive protein, along with glucocorticoid use, independently increased the risk of MACE in both groups. In RA, methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs) were protective against MACE; whereas, biologic disease-modifying anti-rheumatic drugs (DMARDs) were not associated with risk reduction in either condition. Based on these findings, RA and PsA patients have comparable MACE incidence. Systemic inflammation and glucocorticoid use are significant risk factors, while methotrexate and NSAIDs reduce MACE risk in RA. However, biologic DMARDs did not appear to offer CV protection in either condition.[13]

However, metabolic syndrome (MetS) appears to be more common in PsA patients than in those with RA.[14] In this regard, PsA is linked to an increased prevalence of cardiometabolic conditions, including hypertension, dyslipidaemia, diabetes, obesity and CVD, compared with the general population.[15–17] This elevated incidence and prevalence of cardiometabolic comorbidities observed in PsA is higher than in other inflammatory arthritides, such as RA and other spondyloarthritides.[15] Overall, the combination of cardiometabolic conditions along with systemic inflammation and glucocorticoid use increases the risk of CVD in these patients.[18]

MetS is a cluster of inter-related metabolic abnormalities, including central obesity, insulin resistance (IR), hypertension, dyslipidaemia (elevated triglycerides and reduced HDL cholesterol) and hyperglycaemia. MetS is a significant risk factor for CVD incidence, CV mortality and all-cause mortality.[19] This complication is influenced by chronic systemic inflammation, shared genetic factors, and lifestyle factors. Its prevalence is notably higher in individuals with PsA than in the general population.[17]

Since patients with PsA and MetS are at increased risk of developing CVD, including atherosclerosis, myocardial infarction and stroke, identifying, preventing and managing the underlying risk factors of MetS should be a key strategy in reducing the overall burden of CVD in these patients. In this regard, the European Alliance of Rheumatology Associations (EULAR) advocates for periodic CVD risk assessments, with an emphasis on the adequate control of classic cardiometabolic risk factors for CVD at least every 5 years for these individuals.[20]

IR is highly prevalent among patients with PsA.[21 22] It plays a pivotal role in the development of metabolic disorders, including type 2 diabetes, MetS and CVD. In this context, the metabolic score for insulin resistance (METS-IR) has emerged as a relatively new biomarker for estimating IR, particularly in population-based studies and clinical evaluations. METS-IR has shown a stronger correlation with all-cause and CV mortality in the US population compared with three alternative IR indices: the triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio, the triglyceride-glucose (TyG) index and the homeostatic model assessment of IR (HOMA-IR). Notably, this strong association is particularly evident in individuals younger than 65 years.[23] Higher METS-IR scores are associated with an increased likelihood of psoriasis among US adults.[24] The METS-IR index is specifically recommended as a clinical indicator for managing and treating psoriasis in women, non-obese individuals, light alcohol consumers, and those with comorbid conditions such as coronary artery disease and hyperlipidaemia, as well as in non-hypertensive and non-diabetic individuals.[24]

A recent retrospective cohort study analysed data from 1218 RA patients to assess the relationship between the METS-IR index and CVD mortality. The study used data from the National Health and Nutrition Examination Survey (NHANES) spanning 1999 to 2018. The findings revealed that increased were significantly associated with a higher risk of CVD mortality in RA patients.[25]

Considering these results in RA and recognising the importance of optimising prevention strategies by identifying PsA patients at high risk of CVD, with a focus on early detection and targeted intervention, we aimed to evaluate whether the METS-IR index could predict CVD risk in patients with PsA. For this purpose, we analysed data from the Spanish prospective CARdiovascular in RheuMAtology (CARMA) project, which included a cohort of PsA patients prospectively followed in rheumatology outpatient clinics over a 10-year period.

PATIENTS AND METHODS
Population
The CARMA project is a prospective cohort study aimed at identifying the CVD risk profile in individuals with chronic inflammatory rheumatic diseases over a 10-year period. The study included patients with ankylosing spondylitis, PsA and RA, along with a comparison cohort of individuals without inflammatory diseases. Recruitment was conducted across 67 Spanish hospitals between July 2010 and January 2012.[26] This report specifically focuses on data collected from PsA patients 10 years after the study's initiation.

The initial recruitment at baseline included 721 patients with PsA.[26] As previously reported,[26] all participants met Moll and Wright's criteria for PsA.[27] These criteria were used because, at the time the project was first discussed in 2007, the 2006 Classification Criteria for Psoriatic Arthritis (CASPAR)[28] were not yet widely adopted or used across all the centres involved in the study.

A total of 721 patients with PsA were initially recruited. For inclusion in the current analysis, patients must not have had a pre-recruitment diagnosis of diabetes mellitus, hypercholesterolaemia treated with statins, a history of CV events or chronic kidney disease. Patients with a history of CV events or chronic kidney disease are classified as high CV risk. Additionally, statins and antidiabetic medications influence the parameters of the formula used to calculate METS-IR and also impact CV risk. Regarding personal history (eg, previous events, history of diabetes) or treatments at baseline, we considered lack of information in medical records as indicator of inexistence. As a result, 221 patients were excluded from the analysis, leaving 500 patients in the final analysis.

At 10 years, information on all patients included in the initial cohort was assessed. It was obtained by consulting their medical records or by calling patients or family members directly. When it was not available, we requested information from the National Index on Mortality to assess the survival status.

The study, conducted in accordance with the principles outlined in the Declaration of Helsinki, prioritised ethical considerations. Full written informed consent was obtained from all subjects prior to their integration into the project. Approval of the study was granted by the Clinical Research Ethics Committee of Lugo, Galicia (Spain) according to protocol no. 2009/077, and in parallel, approval was requested and obtained from the Ethics Committee of each participating hospital.

Variable specifications and operative definitions
Cardiovascular events
The spectrum of CV events included diagnoses of fatal or non-fatal ischaemic heart disease, heart failure, transient ischaemic attack, stroke, or limb claudication/peripheral arterial disease, all confirmed by a doctor during the follow-up. The operational definitions for the parameters of the variables under analysis were detailed in a separate report.[26]

METS-IR
METS-IR data at recruitment were calculated as described by Zhou and Gao,[25] who conducted their study based on the initial work by Bello-Chavolla et al.[29]

$$METS-IR = \frac{In[(2 \times FPG + TG) \times BMI]}{In(HDL-C)}$$

Where FPG (fasting plasma glucose), TG (triglycerides) and HDL-C (high-density lipoprotein cholesterol) are expressed in mg/dL, and BMI (Body Mass Index) is expressed in kg/m².

Statistical analysis
Continuous variables are expressed as mean±SD. Individuals with and without CV events during follow-up were compared using the Student's t-test. Categorical variables are presented as numbers and percentages and were compared using Fisher's exact test.

The relationship between METS-IR and the first CV event was analysed using survival analysis techniques. Follow-up time was defined as the period between recruitment and the occurrence of a CV event, death from any cause, or the last follow-up. Individuals without a CV event at the end of the follow-up and patients died before their first CV event were considered censored.

Four Cox regression models were used to examine the relationship between METS-IR and CV events. Model 1 included METS-IR unadjusted. Model 2 was adjusted for age, sex and the disease duration at the time of recruitment. Model 3 included the adjustments from Model 2, plus smoking status and hypertension at recruitment. Model 4 included the adjustments from Model 3, plus treatment with NSAIDs, glucocorticoids or biological DMARDs. Results are presented as HR with 95% CI, Akaike Information Criterion (AIC) as a measure of model fitting and Gönen and Heller's K as a measure of consistence between prediction and actual events. AIC penalises the entry of new variables in the model; the lower the AIC, the better the adjustment. Gönen and Heller's K could take values between 0 (complete inconsistence) and 1 (complete consistence). The proportional hazard assumption was tested using Schoenfeld residuals.

METS-IR was categorised by Zhu and Gao[25] into three groups: <2.25, 2.25–2.48 and >2.48. In this analysis, the first category (<2.25) was used as the reference, and thus,

Table 1 Description of the 500 patients with PsA included in this analysis, showing the differences between those who had CV events and those who did not

Characteristics at recruitment	Total (n=500)	Without CV event (n=473)	With CV event (n=27)	P value
Age, years (mean±SD)	55.8±11.9	55.1±11.6	67.3±11.8	<0.001
Gender: women, n (%)	233 (46.6%)	228 (48.2%)	5 (18.5%)	0.003
Duration of the disease, years (mean±SD)	8.74±7.18	8.57±7.04	11.75±8.89	0.03
Smoking tobacco: yes, n (%)	120 (24.0%)	117 (24.7%)	3 (11.1%)	0.16
Hypertension, n (%)	103 (20.6%)	91 (19.2%)	12 (44.4%)	0.002
HAQ (median (IQR))	0.25 (0, 0.87)	0.25 (0, 0.87)	0.25 (0, 1.12)	0.74*
DAS28-ESR (mean±SD)	2.55±1.21	2.55±1.22	2.51±1.07	0.86
DAS28-CRP (mean±SD)	2.44±1.04	2.43±1.05	2.47±0.80	0.86
Treatment with steroids, n (%)	94 (18.8%)	88 (18.6%)	6 (22.2%)	0.62
Treatment with NSAID, n (%)	192 (38.4%)	180 (38.1%)	12 (44.4%)	0.55
Treatment with biological DMARD, n (%)	211 (42.2%)	202 (42.7%)	9 (33.3%)	0.42
METS-IR (mean±SD)	2.27±0.20	2.26±0.19	2.37±0.24	0.01
METS-IR: <2.25, n (%)	246 (49.2%)	240 (50.7%)	6 (22.2%)	0.008
2.25–2.48	184 (36.8%)	170 (35.9%)	14 (51.9%)	
>2.48	70 (14.0%)	63 (13.3%)	7 (25.9%)	

*Mann-Whitney U test.
CV, cardiovascular; METS-IR, metabolic score for insulin resistance; n, number; PsA, psoriatic arthritis; NSAID, non-steroidal anti-inflammatory drugs.

HR represents the multiplier effect of each of the other categories relative to individuals in the <2.25 group.

All statistical analyses were conducted using Stata 18/SE software (Stata Corp, College Station, TX, USA). Statistical significance was defined as a p value <0.05.

RESULTS

Among a cohort of 500 patients with PsA, followed for a total of 4788 patient-years (mean follow-up: 9.6 years), 27 individuals experienced at least one CV event. The annualised incidence rate was calculated at 5.6 events per 1000 patient-years, with a 95% CI ranging from 3.7 to 8.2.

A description of the 500 patients with PsA included in this analysis is shown in table 1, highlighting the differences between those who experienced CV events and those who did not. Patients who had CV events were older, had longer disease duration and were more commonly men. Hypertension was also more common among the PsA patients who suffered CV events (table 1). We detected differences neither in disease activity measures by HAQ, DAS28-ESR or DAS28-CRP nor in being treated with NSAID, glucocorticoids or biological DMARDS (table 1).

Patients with CV events had higher METS-IR than those without CV events (2.37±0.24 vs 2.26±0.19; p=0.01). When PsA were stratified in three categories as performed by Zhu and Gao[25] (<2.25, 2.25–2.48 and >2.48), significant differences between patients with and without CV events were observed. In this regard, PsA who had CV events were more commonly included in the METS-IR 2.25–2.48 and >2.48 categories than those without CV events (p=0.008) (table 1).

Deaths from other causes were treated as censored. Deaths from non-CV causes (n=14) were not associated with METS-IR in the group without CV events (online supplemental table 1). In the online supplemental table 1, we have included METS-IR at recruitment in patients died from causes other than CVD. Also, a comparison with patients without CV event alive at the end of follow-up is shown in the online supplemental table 1.

The relationship between METS-IR and CV events is shown in table 2. In this regard, three Cox regression models were used. Both in the unadjusted model (Model 1) as well as in the adjusted Model 2 (adjusted for age, sex and the disease duration at the time of recruitment), Model 3 (included the adjustments from Model 2, plus smoking status and hypertension at recruitment) and Model 4 (adjustments from Model 3, plus treatment with NSAIDs, glucocorticoids or biological DMARDs), patients included in the highest category of METS-IR—those with METS-IR greater than 2.48—had increased risk of developing CV events (table 2). Notably, the AIC was lower for Model 2, suggesting that Models 3 and 4 may involve some degree of overadjustment.

Figure 1 shows the probability of CV events according to METS-IR categories as analysed in all the models. The data indicate that patients with PsA who had a METS-IR value exceeding 2.48 at baseline had an increased risk of experiencing a CV event during the follow-up period.

**Table 2** Relationship between METS-IR and CV events

METS-IR	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
<2.25	1 (ref)	–	1 (ref)	–	1 (ref.)	–	1 (ref.)	–
2.25–2.48	3.16 (1.22, 8.23)	0.02	2.22 (0.83, 5.97)	0.11	2.06 (0.76, 5.59)	0.16	2.13 (0.77, 5.88)	0.15
>2.48	4.33 (1.45, 12.9)	0.008	3.32 (1.06, 10.4)	0.04	3.05 (0.96, 9.73)	0.05	3.10 (0.96, 9.97)	0.06
	AIC=327.1 Gönen and Heller's K=0.6454		AIC=298.0 Gönen and Heller's K=0.7742		AIC=300.9 Gönen and Heller's K=0.7726		AIC=306.2 Gönen and Heller's K=0.7720	

Model 1: unadjusted.
Model 2: adjusted for age, sex and inflammatory disease duration.
Model 3: adjusted as in Model 2 plus smoking and arterial hypertension.
Model 4: adjusted as in Model 3 plus treatment with NSAIDs, glucocorticoids or biological DMARDs.
AIC, Akaike Information Criterion; CV, cardiovascular; METS-IR, metabolic score for insulin resistance.

DISCUSSION

In this study, we present data from a large cohort of patients with PsA who participated in the Spanish prospective CARMA project, with a specific focus on CV outcomes in individuals with inflammatory arthritis. This cohort analysis includes data from 500 patients with PsA who were prospectively followed for a 10-year period after enrollment.

A major challenge in managing patients with PsA is accurately identifying those at high risk for CV events. In PsA patients closely monitored in rheumatology units as part of the prospective CARMA project, risk chart algorithms proved highly effective in distinguishing individuals at low and high CV risk. The integration of QRISK3 and SCORE2 into a comprehensive model demonstrated an optimal approach, combining the strong
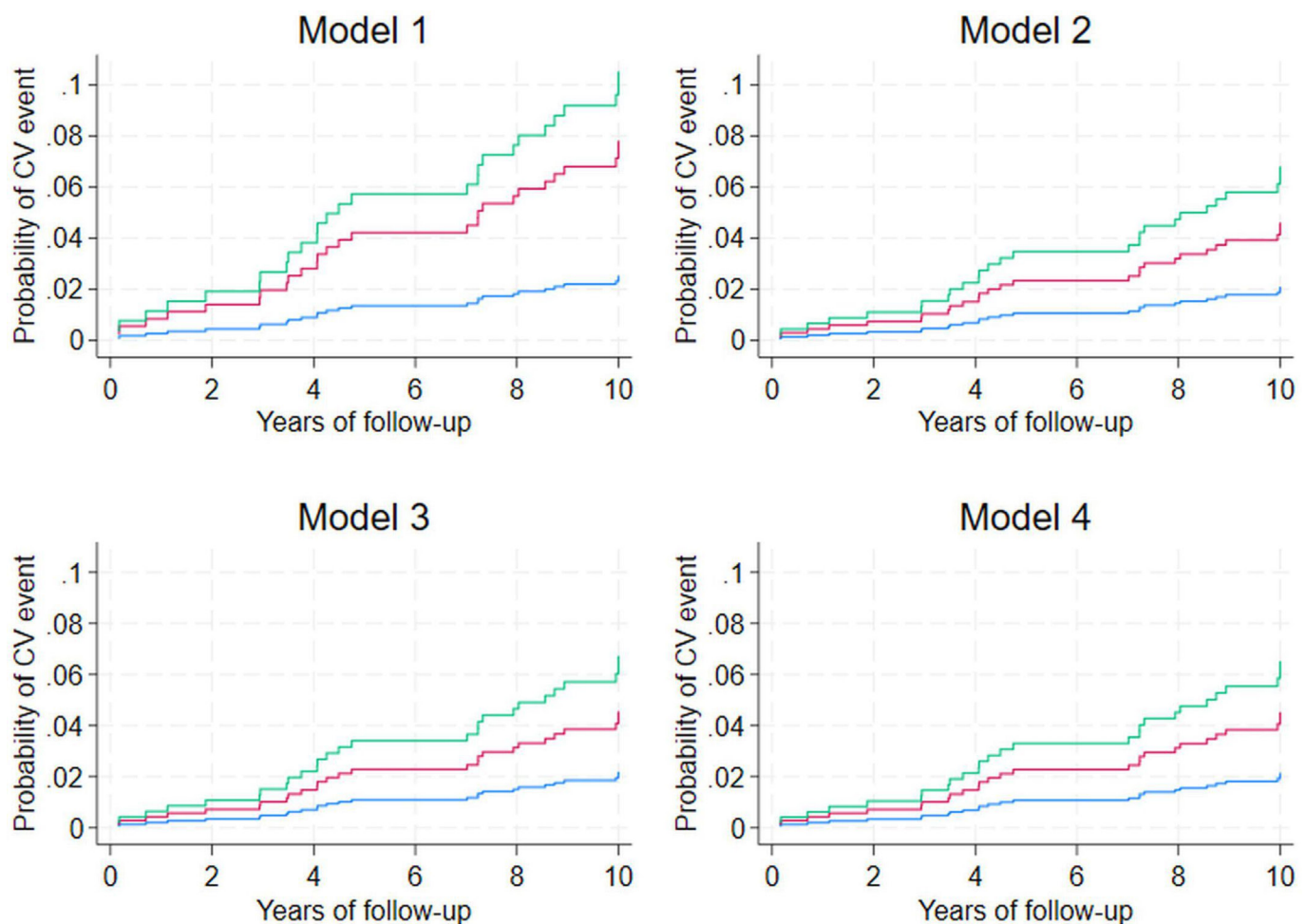
Figure 1 Probability of cardiovascular events according to categories of METS-IR. CV, cardiovascular; METS-IR, metabolic score for insulin resistance.

discriminatory power of QRISK3 with the superior calibration accuracy of SCORE2.[30] In addition to risk chart algorithms, several clinical tools are available to stratify CV risk in patients with PsA.[31] Among these, carotid ultrasound is particularly valuable as it provides detailed information on carotid intima-media thickness, as well as the presence and total area of atherosclerotic plaques. This imaging modality can complement risk chart algorithms, offering enhanced accuracy in CV risk stratification for PsA patients.[32]

Metabolic comorbidities significantly affect CV outcomes in patients with PsA.[33][34] IR, a condition closely associated with MetS and systemic inflammation, is highly prevalent in patients with PsA.[21] METS-IR showed better discrimination ability in predicting the incidence of coronary artery calcification in asymptomatic adults without CVD than the ratio TG/HDL-C and TyG index.[35] METS-IR has also shown a more significant association with all-cause and CV mortality in the US population compared with TyG index, TG/HDL-C and HOMA-IR, three IR indexes.[23] Moreover, METS-IR predicts the occurrence of major adverse CV events in patients with ischaemic cardiomyopathy and type 2 diabetes mellitus independent of established CV risk factors.[36] Furthermore, METS-IR is a reliable prognostic marker for predicting major adverse CV events in patients with premature coronary artery disease.[37] Since PsA have accelerated atherosclerosis, the use of this index may be useful to identify patients with PsA at high risk of CV events.

Our results, which demonstrate that METS-IR serves as a prognostic predictor of CV events in patients with PsA, are consistent with the findings reported by Zhou and Gao.[25] These authors studied association between the METS-IR and CVD mortality in patients with RA using data from the NHANES 1999–2018 cohort.[25] They observed that higher METS-IR scores are significantly associated with increased CVD mortality in this population. In keeping with our observation in our cohort of PsA patients, these authors found that RA patients with METS-IR >2.48 were associated with a significantly greater risk of CVD mortality than those with METS-IR ≤2.25.[25] However, there are some differences between the series of patients with RA assessed by Zhou and Gao, which used data from the NHANES,[25] and our cohort of patients with PsA. In the RA series, 56.77% were women, and 61.99% had a smoking history; whereas, in the CARMA cohort of PsA, the frequency of women and smoking was lower (46.6% and 24%, respectively). Additionally, disease duration was longer in the RA series assessed by Zhou and Gao. In contrast, in this RA series, the percentage of patients treated with glucocorticoids was lower (8.28% vs 18.8% in our cohort of PsA patients). Moreover, in the series assessed by Zhou and Gao, the mean MetS-IR was 2.38, and 33.35% had a MetS-IR greater than 2.48. In contrast, in our cohort of PsA patients, the mean MetS-IR was 2.27, and only 14% of the patients had a MetS-IR greater than 2.48.

Unlike previous studies, our research evaluated METS-IR as a predictor of CV events in patients with PsA. To the best of our knowledge, this is the first study to assess METS-IR in a cohort of PsA patients followed over a 10-year period. Our study demonstrated that METS-IR predicts the occurrence of CV events in patients with PsA. Our prospective analysis revealed that PsA patients with a baseline METS-IR value exceeding 2.48 had a higher risk of developing CV events during the follow-up period. This observation is particularly significant, because, as outlined in the Methods section, patients with a prior history of CV events, chronic kidney disease, diabetes mellitus or statin use at the time of recruitment were excluded from the assessment. These findings indicate that METS-IR could serve as a valuable tool for risk stratification and prognostic assessment in patients with PsA.

A potential limitation of this study is that it does not compare METS-IR to well-established predictive models, such as the Framingham Risk Score or SCORE, to validate its accuracy in predicting CV risk. However, the primary purpose of the present study was to determine the potential predictive value of METS-IR rather than to assess its performance relative to existing models. Further studies are needed to evaluate whether METS-IR may complement other predictive algorithms. However, it is important to note a key difference between how METS-IR was analysed in this study and how classical CV risk scales—such as Framingham, SCORE2, QRISK3 or PREVENT—are intended to be used. Traditional risk scales estimate a specific probability of developing a CV event within a predefined time frame (eg, a 3% risk over 10 years). In contrast, this study demonstrates an association between higher METS-IR values and higher CV risk without converting METS-IR values into precise percentages of risk. Consequently, a direct comparison between METS-IR and classical risk scales is not straightforward. Another potential limitation of the study was that physical activity, race, education, marital status, socioeconomic status and alcohol consumption were not included as covariates. Moreover, in our study, we did not include the Disease Activity index for PSoriatic Arthritis (DAPSA). It was first introduced in 2005. However, when the CARMA project was designed in 2007, DAPSA was not routinely used by most of the 67 participating rheumatology units to assess PsA disease activity. For this reason, it was not included in the baseline assessment of our study.

In conclusion, in PsA patients under close observation in rheumatology units included in the prospective CARMA project, METS-IR serves as a reliable prognostic predictor of CV events. Therefore, METS-IR may be considered a novel surrogate marker for identification of PsA at high risk of CVD.

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