

Where borders meet: Psoriatic arthritis and the cardiovascular risk

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ABSTRACT

Objective: we aimed to estimate the long-term global cardiovascular risk (GCVR) in patients with psoriatic arthritis (PsA) and to identify factors correlated with this risk among traditional and non-traditional risk factors.

Material and method: cross-sectional observational study enrolling 45 consecutive patients with PsA without known atherosclerotic disease or heart failure, attending an outpatient rheumatology department over 12 months. Disease-related parameters (clinical phenotype, inflammation tests, type of medication), traditional cardiovascular risk factors (smoking, obesity, dyslipidemia, hypertension, diabetes) and 10-year GCVR (Framingham Heart Study online platform) were collected in all patients according to a predefined protocol.

Results: 57.77% of patients were female, with a mean age of 52.1 years; hypertension (46.66%), dyslipidemia and current smoking (20% each) were reported as main traditional cardiovascular risk factors in our cohort. 46.67% patients presented with high cardiovascular risk, 37.78% with intermediate risk, while only 15.55% with low risk. Framingham risk score correlated with coronary atherosclerosis, its sensitivity for the detection of CV risk factors being high ($p < 0.05$). However, no statistically significant correlation was identified between moderate and elevated cardiovascular risk score and lipids, DAPSA score, pain severity and body mass index ($p > 0.05$).

Conclusion: Traditional cardiovascular risk factors were reported in a significant proportion of PsA patients, but cannot entirely explain the global cardiovascular risk; additionally, more than half of patients were stratified as having high or intermediate cardiovascular risk. Different factors could interfere with 10-year cardiovascular risk.

Keywords: Psoriatic arthritis, cardiovascular risk, Framingham Risk Score

INTRODUCTION

Psoriatic arthritis (PsA) remains a multifaceted disease characterized by chronic local (synovium, entheses, skin) and systemic inflammation; it is defined by a wide range of systemic manifestations and comorbidities ranging from extra-articular, concept-related manifestations, such as uveitis and inflammatory bowel disease, to cardiovascular risk factors, metabolic syndrome and cardiovascular disease.

It is widely accepted that patients with psoriasis and PsA have a higher risk of developing cardiovascular diseases, with an increased morbidity and mortality correlating with disease activity and severity. In addition, these patients may be at increased risk for developing cardiometabolic disease

and experiencing significant cardiovascular events (coronary heart disease, cerebrovascular disease, peripheral vascular disease) (1,2,3). Higher incidence rates of comorbidities especially cardiovascular disease was reported in patients with PsA compared with the general population resulting in significantly more hospitalization for cardiovascular events. Overall, patients with PsA had a 43% higher risk for CV disease than did individuals in the general and also had a 55% higher risk for incident CV events (1-8).

The incidence and prevalence of cardiovascular risk factors among patients with rheumatoid arthritis, psoriasis and PsA have been assessed in different studies demonstrating hypertension in up to 20% cases, dyslipidemia in 10-12%, diabetes 6 to 8%

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and obesity in 4-5% of patients. The prevalence of traditional cardiovascular risk factors in PsA seems to exceed psoriasis and rheumatoid arthritis, suggesting that inflammation could have a lower impact on the cardiovascular risk in PsA than in rheumatoid arthritis (1-8).

Although the pathogenetic mechanism of cardiovascular damage in PsA is not fully understood, augmented cardiovascular risk in such patients is thought multifactorial: (i) increased prevalence of traditional cardiovascular risk factors; (ii) chronic local and systemic inflammation; (iii) early accelerated atherosclerosis with endothelial dysfunction, intima-media thickness, abnormal arterial stiffness as well as coronary artery calcification. In addition, increased levels of proinflammatory cytokines such as TNF- α , IL-17, IL-12, L-23 are able to modulate cardiovascular disease risk in PsA, including major cardiovascular events. PsA is widely characterized by a dynamic overlap between traditional cardiovascular risk factors, inflammation and accelerated atherosclerosis confirming the link between PsA and cardiovascular risk (1-8).

Overall, it seems that current risk stratification strategies based on clinical risk algorithms such as Framingham risk score or SCORE underestimate the cardiovascular risk in patients with psoriasis and PsA, since these scores do not assess the independent risk of chronic immune inflammation. Furthermore, it was suggested that PsA should be considered as an independent risk factor for cardiovascular disease (1-8).

Indeed, EULAR 2016 recommendations have recommended main points for the cardiovascular risk management in patients with inflammatory rheumatic conditions including rheumatoid arthritis and PsA, underpinning the role of optimal disease control together with non-pharmacological (smoking cessation, physical activity, healthy diet) and pharmacological management of traditional cardiovascular risk factors using statins and antihypertensives (1-8).

The current study aimed to assess long-term cardiovascular risk in patients with PsA and to identify factors correlated with this risk among traditional and non-traditional cardiovascular risk factors.

MATERIAL AND METHODS

We conducted a cross-sectional observational study in a cohort of 45 consecutive patients with PsA fulfilling the CASPAR 2006 classification criteria, who attended at least once between January 2019 and January 2020 an academic outpatient department in Nord-East Romania (Rheumatology 2, Clinical Rehabilitation Hospital in Iasi). We collected detailed information according to a standard protocol including (i) demographics; (ii) disease-related: dis-

ease duration, clinical phenotype with axial/ peripheral involvement, inflammatory makers, type of medication; and (iii) cardio-metabolic parameters: arterial hypertension, dyslipidemia (lipid profile), type II diabetes mellitus (fasting plasma glucose), obesity (body mass index, BMI), smoking.

Patients with a history of atherosclerotic heart disease and cardiac failure were not allowed in the study.

The long-term cardiovascular risk was calculated by the Global Cardiovascular Risk (GCVR) score that enables to estimate the risk of developing major adverse cardiovascular events (MACE) including fatal or non-fatal myocardial infarction, fatal or non-fatal stroke and heart failure in the next 10 years. The information required to estimate the risk comprise the following parameters: sex, age, systolic blood pressure, treatment for hypertension (yes / no), smoking (yes / no), diabetes mellitus (yes / no), as well as total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels. Patients with a probability of less than 5% were stratified as having a low risk to develop cardiovascular events; those with a GCVR between 5 and 20% for men and 5 and 10% for women were classified as intermediate risk, while the increased risk was considered higher than 20% for men and 10% for women. The GCVR score was calculated using the computer on the Framingham Heart Study online platform.

All patients were under synthetic and/or biologic anti-rheumatic drugs at the time of monitoring visit in our department.

Each study participant signed an inform consent and the study was approved by the local ethics committee.

The data collection and graphical representation were done using Microsoft Office 2010 Pack and the categorical variables were compared using the Person Chi-Square test. All statistical tests were 2-tailed and $p < 0.05$ was considered statistically significant. All statistical analysis including odds ratio (OR) were performed in IBM SPSS Statistics (Statistical Package for the Social Sciences) version 20.

RESULTS

Demographics and disease-related parameters

Table 1 summarizes the general characteristics of patients in our PsA cohort. The majority of subjects (57.8%) were females and the mean age of 52.1 ± 6.8 years (37-67 years). Up to 68.9% patients lived in rural areas and 46.7% were on medical retirement, which stands up for the major functional impairment related to PsA.

40% patients were former smokers and only 20% were current smokers at the time of the evaluation, the percentage difference being explained by the

TABLE 1. Characteristics of the study population

Variable	Psoriatic arthritis (n=45)
Age (mean ± SD)	52.1 ± 6.8
Gender (n, %)	
female	26 (57.8%)
male	19 (42.2%)
Residential status (n, %)	
urban	14 (31.1%)
rural	31 (68.9%)
Professional status (n, %)	
active	17 (37.8%)
medical retirement	21 (46.7%)
old age retirement	4 (8.9%)
other categories	3 (6.6%)
Smoking status (n, %)	
non-smoker	18 (40%)
smoker	9 (20%)
former smoker	18 (40%)

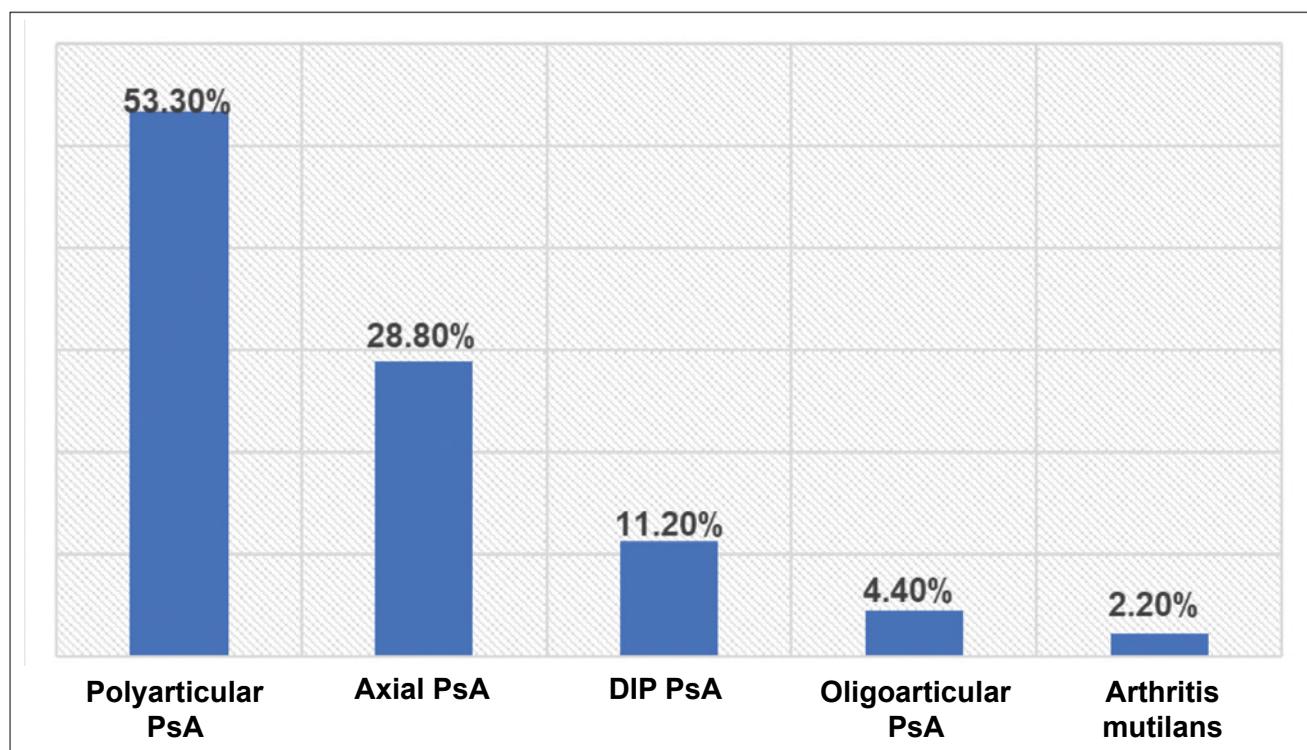
positive effect of patient education at the time of the diagnosis. Smoking is one of the factors involved in both the onset and maintenance of the disease and poorer response to treatment.

More than half (53.3%) of patients had peripheral polyarticular PsA pattern and about one third (28.9%) axial disease. The disease subtype that affects mainly the distal interphalangeal joints was reported in only 11.2% of patients, while the most severe PsA phenotype, mutilating arthritis, was diagnosed in only one patient (2.2%) (Figure 1).

TABLE 2. Disease-related parameters in the studied population

Disease-related parameters	Psoriatic arthritis (n=45)
Disease onset	
≤ 5 years	17 (37.8%)
5-10 years	17 (37.8%)
≥ 10 years	11 (24.4%)
Clinical subtype	
Polyarticular PsA	24 (53.3%)
Axial PsA	13 (28.8%)
DIP arthritis	5 (11.2%)
Oligoarthritis	2 (4.4%)
Arthritis mutilans	1 (2.2%)
Disease activity	
DAPSA	15.8 ± 7.4
ASDAS-CRP	3.3 ± 1.5
Functional impairment	
HAQ-DI	1.9 ± 0.9
BASFI	6.8 ± 1.4
Treatment	
NSAIDs	18 (40%)
Methotrexate	15 (33.3%)
Leflunomide	3 (6.6%)
Biologic therapy	24 (53.3%)

Table 2 summarizes PsA - related parameters. In 37.8% of patients, the duration of the disease was less than 5 years and between 5-10 years, which shows that the diagnosis was established relatively early in this cohort. The subgroup with peripheral arthritis showed a moderate disease activity (DAPSA=15.8±7.8) and moderate functional impairment (HAQ-DI=1.9±

**FIGURE 1.** PsA clinical subtype

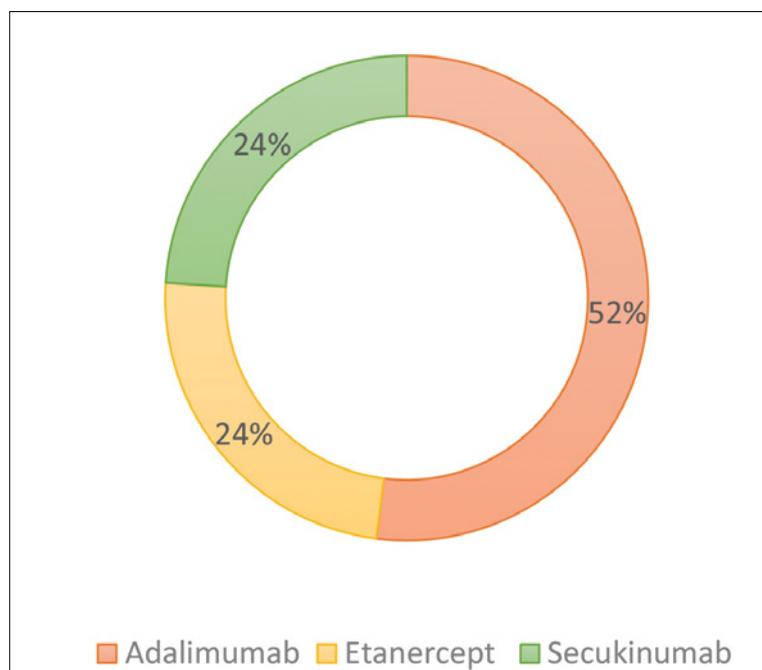


FIGURE 2. PsA distribution according to biological medication

0.9), while those with axial PsA had a highly active disease (ASDAS-CRP=3.3±1.5) with moderate to high functional impairment (BASFI=6.8±1.4).

53.3% patients were on biological treatment (52% adalimumab original and biosimilars, 24% etanercept and biosimilars, 24% secukinumab) and 33.3% of those with peripheral arthritis were on Methotrexate (Figure 2).

The mean value of CRP was 2.03 mg/dL, corresponding to a significant inflammatory status, potentially guiding an early atherosclerotic plaque formation.

TABLE 3. Comorbidities including traditional cardiovascular risk factors in the study population

Comorbidity*	Psoriatic arthritis (n=45)
Arterial hypertension	21 (46.6%)
Dyslipidemia	10 (22.2%)
Diffuse pulmonary fibrosis	8 (17.7%)
Osteoporosis	5 (11.1%)
Diabetes mellitus	6 (13.3%)
Virus B hepatitis	3 (6.6%)
Virus C hepatitis	2 (4.4%)
Hepatic cirrhosis	1 (2.2%)
Chronic obstructive pulmonary disease	1 (2.2%)
Chronic kidney disease	1 (2.2%)

*n (%), number (%) of patients

Comorbidities

Comorbidities including traditional cardiovascular risk factors were systematically analyzed in our study. Hypertension was the most common comorbidity in patients with PsA (46.6%), followed by dyslipidemia (22.2%) and diffuse pulmonary fibrosis (17.7%); conversely, we identified only one case of liver cirrhosis, chronic obstructive pulmonary disease, and chronic kidney disease (Table 3). Subgroup analysis showed that top three comorbidities in polyarticular PsA were also hypertension (45.8%), dyslipidemia (29.1%) and diffuse pulmonary fibrosis (12.3%) (Figure 3).

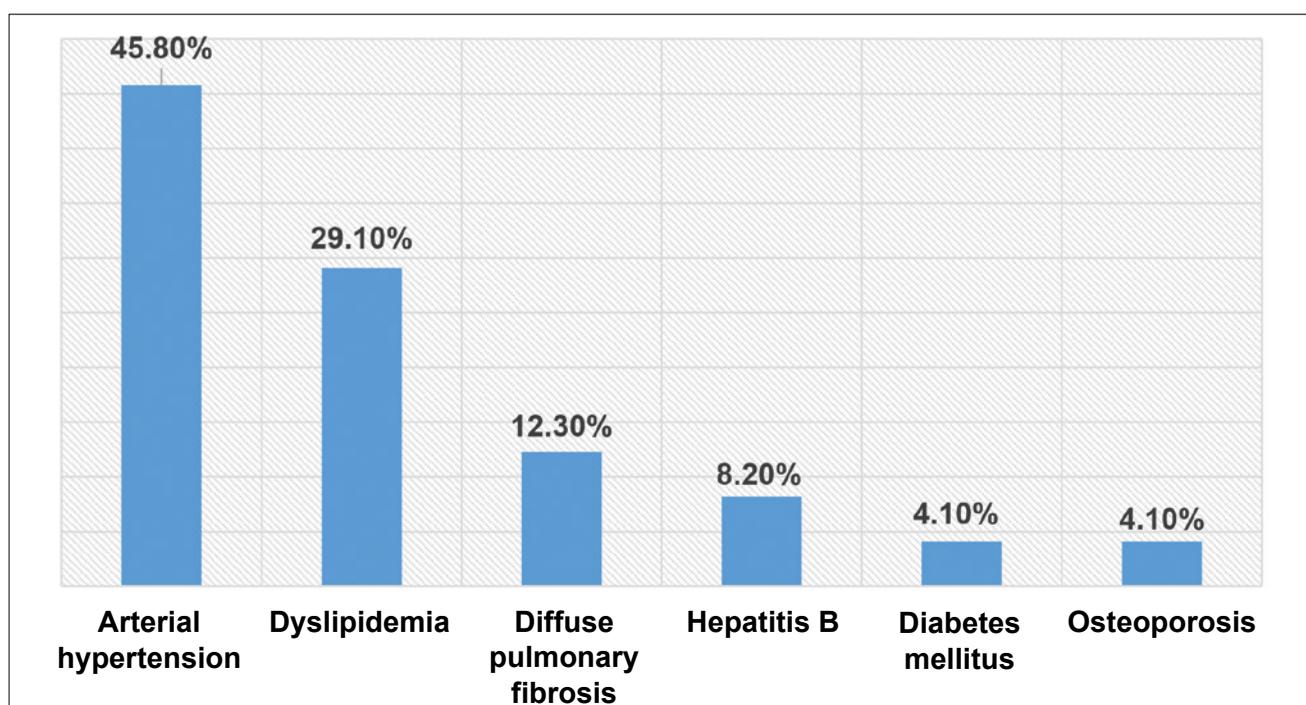


FIGURE 3. Comorbidities in polyarticular PsA

TABLE 4. Traditional cardiovascular risk factors in study population

Cardiovascular risk factors	Psoriatic arthritis n (%)	Clinical subtype				
		1	2	3	4	5
Arterial hypertension	21 (46.6%)	11 (45.8%)	6 (46.1%)	-	4 (80%)	-
Diabetes mellitus	6 (13.3%)	1 (4.1%)	4 (30.7%)	-	1 (20%)	-
Dyslipidemia	9 (20%)	7 (29.1%)	1 (7.6%)	-	1 (20%)	-
Obesity	3 (6.7%)	2 (8.3%)	1 (7.6%)	-	-	-
Smoking	9 (20%)	2 (8.3%)	5 (38.4%)	-	2 (40%)	-

Legend: 1 – symmetrical polyarticular form; 2 – spondylitic form; 3 – assymetric olygoarticular form; 4 - DIP arthritis alone; 5 – arthritis mutilans; n, number of patients

Cardiovascular risk assessment

The traditional cardiovascular risk factors recorded in our cohort were age, gender, family history of early-onset cardiovascular disease (the presence of atherosclerotic manifestations in first-degree relatives under the age of 65 for women, and under 55 for male relatives), smoking, alcohol consumption, obesity, dyslipidemia, hypertension and type II diabetes (Table 4).

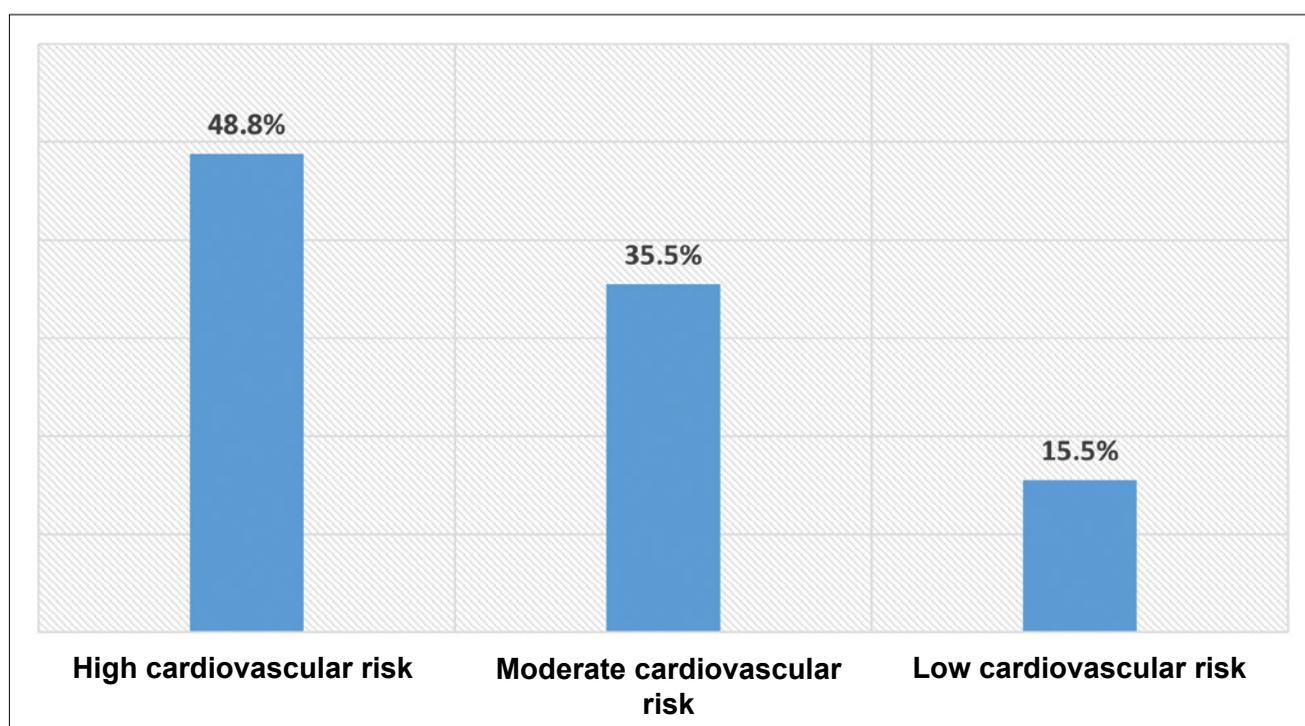
The online platform of the Framingham Heart Study (<https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/>) was used to systematically evaluate the 10-year Framingham risk score in our study. 7 (15.5%) patients had a low cardiovascular risk (<5%), 16 (35.5%) patients had an intermediate cardiovascular risk (5-20% risk for males and 5-10% for females), and 22 patients (48.8%) were classified as having an increased cardiovascular risk (>20% for male; >10% for female). Therefore, most of patients fall into the in-

termediate and high-risk groups, meaning that PsA typically associates with an increased burden of cardiovascular risk (Figure 4).

We further performed subgroup analysis based on PsA clinical subtypes and we identified the highest cardiovascular risk in patients with axial disease (18.02±11.1) compared to other clinical patterns (Table 5).

TABLE 5. Cardiovascular risk score in different PsA subtypes

Framingham Score (Range ± SD)			
PsA, n (%) 45 (100%)	Asymetric polyarticular PsA 20 (44.4%)	Spondylitic form 12 (26.6%)	Asymetric oligoarthritis/mutilans arthritis/DIP arthritis 6 (13.3%)
14.56 ± 9.45	15.4 ± 7.9	18.02 ± 11.1	17 ± 5.6

**FIGURE 4.** Cardiovascular risk stratification in the study population

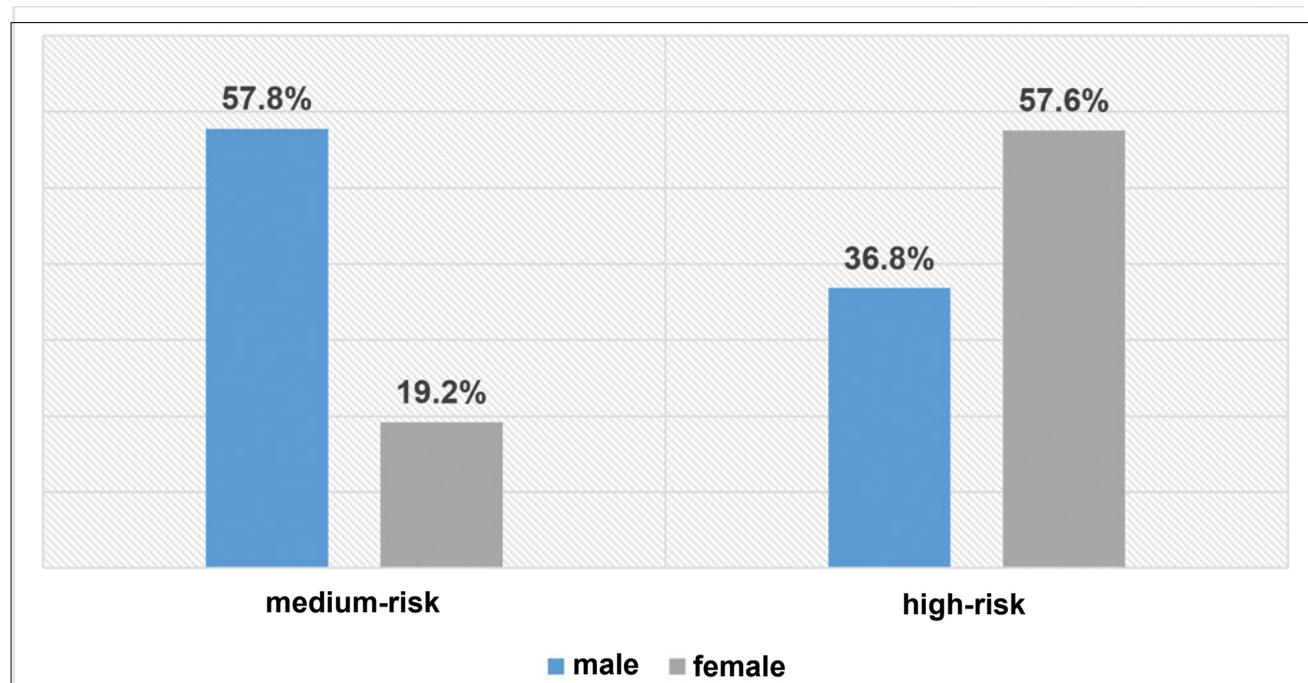


FIGURE 5. Gender differences of CV risk score in studied patients

Also, patients in the moderate and increased cardiovascular risk subgroups were stratified by gender; 57.6% of female and 36.8% of male patients had an increased cardiovascular risk ($p < 0.05$), while for the intermediate category of the risk class, we demonstrated the predominance of male patients as compared to female (57.8% vs. 19.2%) (Figure 5).

A closer look to cardiovascular risk stratification demonstrated the majority of patients presented with Framingham score of 10% or higher. Surprisingly, no association was identified between cardiovascular risk and traditional cardiovascular risk factors including clinical as well as laboratory parameters: systolic blood pressure ($p = 0.079$), serum triglycerides ($p = 0.326$), total cholesterol ($p = 0.074$), HDL-Cholesterol ($p = 0.254$), LDL-Cholesterol ($p = 0.399$) and uric acid ($p = 0.702$). Also, neither smoker status ($p = 0.165$), nor disease onset ($p = 0.449$) were associated with Framingham score results.

However, the PsA clinical subtype ($p < 0.001$), serum CRP levels ($p < 0.06$) and disease activity according to ASDAS-CRP score in the axial PsA ($p < 0.001$) were closely related to Framingham-estimated cardiovascular risk. Also, patients' diastolic blood pressure ($p = 0.001$), extraarticular manifestations (uveitis, inflammatory intestinal diseases) ($p = 0.039$) and comorbidities ($p < 0.001$) appear to affect cardiovascular morbidity and mortality in our cohort.

As most patients had a moderate-to-severe elevated Framingham score, the next step in our statistical analysis was to investigate which parameters could influence this risk stratification. Therefore, we demonstrated a statistically significant association for serum uric acid ($p < 0.014$), ASDAS-CRP disease activity ($p < 0.001$) and the CRP concentration ($p < 0.014$).

However, no statistically significant correlation was identified between moderate and elevated cardiovascular risk score and lipid parameters (triglycerides, $p = 0.291$; total cholesterol, $p = 0.125$; HDL-cholesterol, $p = 0.319$), disease activity in those with polyarticular form (DAPSA, $p = 0.124$), pain severity ($p = 0.558$) and BMI ($p = 0.316$).

DISCUSSION

It is widely accepted that traditional cardiovascular risk factors (e.g. hypertension, obesity, dyslipidemia, diabetes, metabolic syndrome) and cardiovascular disease are commonly described in PsA (9), the risk of developing acute myocardial infarction, cerebrovascular disease and heart failure being 68%, 22% and 31%, respectively, compared to the general population (10). Moreover, the increased cardiovascular morbidity and mortality in PsA significantly correlates with disease activity and severity, and is even higher than cardiovascular risk described in rheumatoid arthritis (1-8). Different studies have also reported a raised frequency of subclinical atherosclerotic coronary disease, with increased mean intima-media thickness as well as up to 3 times increased risk to develop carotid plaques versus general population, as surrogate biomarkers of cardiovascular disease (1-8). Interestingly, the incidence and prevalence of cardiovascular risk factors among patients with rheumatoid arthritis, psoriasis and psoriatic arthritis seems to be higher in PsA (1-8). Besides, higher incidence rates of comorbidities, especially cardiovascular disease, are reported in patients with PsA compared with the general population (1-8).

We aimed to estimate the burden of cardiovascular disease in PsA by using the classical Framingham risk score and to identify factors that could influence this risk apart from known traditional cardiovascular risk factors. Thus, we examined the association of PsA with comorbidities including traditional risk factors for cardiovascular disease. Overall, the majority of patients in our cohort had at least one comorbidity, up to a maximum of four comorbidities per individual: more than one comorbidities were reported in 66.5% cases, while in 2.2% we described four concomitant comorbidities/ risk factors.

Traditional cardiovascular risk factors, comprising not only individual variables such as smoking, type 2 diabetes, obesity, hypertension, dyslipidemia, but also the composite metabolic syndrome, were identified in several studies based on psoriasis and PsA population, their presence being clearly attested in the vast majority of patients. In a Spanish population study, the prevalence of classic cardiovascular risk factors and metabolic syndrome were higher among patients with PsA, compared to patients with other chronic inflammatory arthritis (11).

Up to 68.8% of our PsA patients were overweight (68.8%), while grade I abdominal obesity was identified in a lower percentage (6.6%) and none presented with moderate (grade II) to severe (grade III) obesity. Although only several studies focused on body mass index in PsA, clearly the excess fat is able to increase cardiovascular risk and is considered an important risk factor for worsening psoriasis (12). In addition, about half (46.6%) of patients had the blood pressure slightly higher as compared to other cohort population studies in Canada (14) or Northern Europe (13) (45.5% and 32.7%, respectively). Known to increase the oxidative damage and to promote inflammation, smoking remains a significant risk factor in PsA and pustular psoriasis irrespective of the sex; current smoking status was reported in 20% of patients and similar results were identified in other studies (15.6-21.3%) (13).

Studies revealed a large variation of clinical patterns of PsA, based on type of joint involvement: 15-78% patients had a polyarticular PsA, 16-70% an asymmetric oligoarthritis, 1-17% cases had a predominant distal interphalangeal joint involvement, 2-16% severe destructive disease (arthritis mutilans), while 2-27% account for axial PsA. Besides, overlap between periphery and axial disease is common in PsA, as joint involvement may progress; consequently, patients with an asymmetric oligoarthritis at onset may progress to symmetrical polyarthritis (15). In our analysis, the polyarticular PsA subtype was the most prevalent (53.5%), followed by the axial disease (28.9%), corresponding to data already reported.

Conflict of interest: none declared

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We have also carried out a detailed analysis of comorbidities burden according to PsA clinical subtype. The polyarticular form of PsA was associated with an increased frequency of cardiovascular risk factors, closely followed by axial disease. In the literature, studies have not identified an influence of a particular joint pattern on CV risk by studying carotid sub-clinical atherosclerosis, endothelial abnormalities and the use of echocardiography and Doppler ultrasound to identify certain changes (16).

Various cardiovascular risk scores are commonly used to estimate the cardiovascular burden in different populations, including Framingham Risk Score, SCORE (Systematic Coronary Risk Evaluation), Regicor (Registro Gironí del COR), DORICA (Dyslipidemia, Obesity, and Cardiovascular Risk). A recent paper compared cardiovascular risk scores to show which is the most useful and accurate study of cardiovascular mortality in PsA. The authors concluded that the prevalence of moderate / high CV risk varies depending on the specific score used, but the Framingham and DORICA scores were the most consistent (17). Another study compared four cardiovascular scores in APs: Framingham, ACC/AHA (American College of Cardiology/American Heart Association), SCORE and QRISK (Cardiovascular disease risk algorithm version). Framingham score was best correlated with coronary atherosclerosis, its sensitivity for the detection of cardiovascular risk factors being high (17). However, it seems that measures of cardiovascular risk that rely only on traditional measures of cardiovascular risk (such as Framingham risk score) are likely to underestimate the cardiovascular event risk of people with psoriatic disease according to a new study published online by researchers affiliated with the University of Toronto (18) as it fails to consider the independent risk conferred by the immune disease per se.

The main limitation of our study was that we did not include a comparator group and, therefore, we could not determine whether PsA is an independent risk factor for cardiovascular disease.

CONCLUSION

Traditional cardiovascular risk factors were identified in a significant percentage of patients with PsA, but cannot entirely explain the global cardiovascular risk. More than half of the study population were stratified as having a high or intermediate cardiovascular risk despite specific management with anti-rheumatic drugs.

Current cardiovascular risk stratification strategies should be a part of standard of care in patients with PsA.

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