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ORIGINAL RESEARCH

Cardiovascular Risk Evaluation in Psoriatic Arthritis by Aortic Stiffness and the Systemic Coronary Risk Evaluation (SCORE): Results of the Prospective PSOCARD Cohort Study

Konstantinos Triantafyllias · Stefanie Liverakos · Muthuraman Muthuraman · Lorenzo Cavagna · Ioannis Parodis · Andreas Schwarting

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ABSTRACT

Introduction: Psoriatic arthritis (PsA) is associated with increased cardiovascular (CV) risk and mortality. Aortic stiffness measured by carotid-femoral pulse wave velocity (cfPWV) has been shown to predict CV risk in the general population. The present study aimed to examine cfPWV values of patients with PsA compared to healthy controls and to evaluate associations of cfPWV with patient- and disease-associated characteristics, as well as with an established traditional CV prediction score of the European Society of Cardiology (Systemic Coronary Risk Evaluation; SCORE), for the first time.

Methods: cfPWV and SCORE were evaluated in patients with PsA and healthy controls, along with clinical and laboratory disease parameters. Differences in cfPWV measurements between the two groups and associations of cfPWV with patient- and disease-associated characteristics were statistically evaluated.

Results: A total of 150 patients with PsA (PSOCARD cohort) and 88 control subjects were recruited. cfPWV was significantly higher in the PsA group compared to controls, even after adjustment for confounders ($p_{adj}=0.034$). Moreover, cfPWV was independently associated with disease duration (r = 0.304, $p=0.001$), age (rho = 0.688, $p<0.001$), systolic arterial pressure (rho = 0.351, $p<0.001$), glomerular filtration rate (inverse: rho = −0.264, $p=0.001$), and red cell distribution width, a marker of major adverse CV events (MACE) (rho = 0.190, $p=0.02$). SCORE revealed an elevated CV risk in 8.73% of

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K. Triantafyllias · S. Liverakos · A. Schwarting
Rheumatology Center Rhineland-Palatinate, Bad Kreuznach, Germany

K. Triantafyllias · A. Schwarting (✉)
Department of Internal Medicine I, Division of Rheumatology and Clinical Immunology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany
e-mail: schwarting@uni-mainz.de

M. Muthuraman
Department of Neurology, University Hospital Würzburg, Würzburg, Germany

L. Cavagna
University and IRCCS Policlinic S. Matteo Foundation, Pavia, Italy

I. Parodis
Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

I. Parodis
Department of Rheumatology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

the patients, whereas cfPWV showed increased aortic stiffness and end-organ disease in 16.00% of the same cohort.

Conclusions: In the largest cfPWV/PsA cohort examined to date, patients with PsA exhibited increased aortic stiffness compared to healthy controls. PsA duration was the most important independent disease-associated predictor of increased aortic stiffness, next to traditional CV risk factors. cfPWV measurements may help identify subclinical end-organ disease and abnormal aortic stiffness and thus assist CV risk classification in PsA.

Keywords: Aortic stiffness; Cardiovascular risk; Psoriatic arthritis; Pulse wave velocity; SCORE

Key Summary Points

Why carry out this study

Although cardiovascular (CV) disease is one of the most predominant comorbidities in patients with psoriatic arthritis (PsA), no sufficient data exist on precise methodologies for accurately measuring this risk.

Carotid-femoral pulse wave velocity (cfPWV) has consistently predicted CV risk in the general population; nonetheless, its application as a surrogate marker in PsA remains limited, with scarce publications addressing this topic.

What was learned from the study

In the largest cfPWV/PsA cohort to date, increased aortic stiffness was independently predicted by disease duration, indicating an association between chronic complications and CV risk in PsA.

Essential predictors of increased aortic stiffness among patient-associated characteristics and traditional CV risk factors were identified and a significant association of cfPWV with a marker of major CV events (MACE) was established.

cfPWV offers a non-invasive method to assess CV risk, aiding in early identification of end-organ disease and prompting timely intervention to improve overall outcomes.

INTRODUCTION

Psoriatic arthritis (PsA) is a complex chronic autoimmune disease with heterogeneous clinical manifestations, characterized by inflammatory arthritis and comorbid skin and/or nail psoriasis [1, 2]. It belongs to the disease group of spondyloarthropathies and affects 0.1–1% of the general population [1, 2]. PsA is associated with painful, swollen joints, functional impairment, and in cases of inadequate treatment, progressive structural damage of the affected joints [3]. Beyond skin and joint involvement, PsA is characterized by a high prevalence of extra-articular manifestations and comorbidities, such as infections, cardiovascular disease (CVD), malignancies, and further autoimmune conditions [4].

Since PsA lacks specific autoantibodies and in some cases laboratory signs of systemic inflammatory activity, diagnosis is often made clinically and with the assistance of the Classification Criteria for Psoriatic Arthritis (CASPAR), which are mainly applied by rheumatologists [5]. These facts combined with the known problem of insufficient resources in several clinical settings can lead to a diagnostic delay of PsA from months to several years [6]. Delay of diagnosis can, however, be associated with major complications, such as physical functional impairment and worse overall long-term disease outcomes [7].

PsA is associated with a high risk for cardiometabolic disorders, such as hypertension, dyslipidemia, diabetes, obesity, and CVD [8]. Particularly, a meta-analysis of 11 studies found a 43% increased risk of CVD in patients with PsA compared with the general population [9], and CV events have been described as one of the leading causes of death in patients with PsA [8]. In order to estimate the CV risk in the general population, several CV prediction scores such as Systemic Coronary Risk Evaluation (SCORE)

[10], Framingham score [11], or PROCAM score [12] have been proposed. However, these scores do not factor in the effects of systemic inflammation and can thus lead to an underestimation of CV risk in patients with autoimmune rheumatic diseases [13]. For this reason, the European Alliance of Associations for Rheumatology (EULAR) guidelines for CV risk management recommend the adaptation of such CV risk prediction models by a 1.5 multiplication factor in the case of rheumatoid arthritis (RA) and other inflammatory arthritides [14]. Nevertheless, no conclusive evidence regarding precise means of CV risk calculation is available in PsA and the task force spoke against the use of 1.5 × SCORE in these patients [2]. For these reasons, new diagnostic markers of CV risk are greatly needed in the field of PsA.

One of the most important causes of CV disease is atherosclerosis [15]. Arterial stiffness is a well-established CV surrogate marker strongly associated with atherosclerosis. Interestingly, stiffness of the aorta can predict CVD in the general population independently of traditional CV risk factors [16]. In clinical practice, carotid-femoral pulse wave velocity (cfPWV) is considered the gold standard for aortic stiffness evaluation and has emerged as a useful method for the diagnosis and risk stratification of CVD [16–19]. cfPWV can be assessed in a non-invasive manner, without known complications, and is easily replicable. Thus, assessing cfPWV was recommended in the 2013 and 2018 ESC guidelines for the management of arterial hypertension [20, 21]. Arterial stiffness is a reflection of arterial compliance and thus of the elastic properties of the examined arteries. Vlachopoulos et al. highlighted, that in contrast to parameters such as blood pressure, lipids, or glucose, which match the instantaneous intensity of traditional CV risk factors (and can therefore vary highly), cfPWV reflects the long-term effects of established and unknown risk factors together with the individual genetic predisposition of each patient [22].

To date, studies examining established markers of CV risk in PsA, such as arterial stiffness, are scarce. In particular, stiffness of the aortic vasculature has been examined only in a few and small PsA case–control studies [23, 24] despite its known high predictive value in the general population [19, 25] and in patients with other rheumatic diseases, such as rheumatoid arthritis or connective tissue diseases [26–32].

Thus, the objective of the present study was to compare the aortic stiffness of patients with PsA with healthy controls in a large cohort from Germany and to identify predictors of cfPWV among clinical PsA-associated parameters, various patient characteristics, and traditional CV risk factors.

METHODS

Study Participants

The prospective PSOriatic Arthritis CARDiovascular Disease (PSOCARD) cohort consists of patients with PsA being treated at the acute Rheumatology Center Rhineland-Palatinate and the University Medical Center, Mainz, Germany and is part of the multicenter CARD cohort examining CV markers of different rheumatologic diseases. Patients of the PSOCARD cohort have been consecutively enrolled for CV risk classification after being diagnosed with PsA by the CASPAR criteria [33]. Moreover, hospital employees and their circle of acquaintances, without underlying systemic inflammatory diseases, who freely responded to an open call for study participation, served as control subjects. Aortic stiffness was assessed in both groups using cfPWV. Exclusion criteria in both groups were malignancy, pregnancy, age < 18 years, kidney failure, body mass index (BMI) > 45 kg/m^2, and active infection. The study has been reviewed and approved by the local standing committee for ethical conduct (Medical Board Rhineland-Palatinate, approval number 13762_2), and adhered to the Declaration of Helsinki. Written informed consent was obtained from all study subjects prior to enrollment.

Data Collection

Epidemiological data (age, gender), current medication, and traditional CV risk factors (diabetes mellitus, hypertension, dyslipidemia, nicotine

use) were documented in all subjects. BMI was calculated by dividing the weight by the square of the height of a patient and BMI values ≥ 30 kg/m^2 were defined as obesity. Mean arterial pressure (MAP) was calculated in relation to systolic (SAP) and diastolic arterial pressure (DAP) by the formula MAP = DAP + 1/3(SAP − DAP). Arterial hypertension was defined as SAP > 140 mmHg. Moreover, the use of non-biologic disease-modifying antirheumatic drugs (DMARDs), glucocorticoids (GC), non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensive drugs, and statins was documented. Joint swelling and tenderness were evaluated clinically by a trained examiner and disease activity was calculated by the Disease Activity in PSoriatic Arthritis (DAPSA) score and the Disease Activity Score 28 (DAS28).

Laboratory assessments of the patient group included inflammation markers [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and red cell distribution width], high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), differential blood counts, and glomerular filtration rate (GFR).

cfPWV

cfPWV measurements were conducted by one trained blinded medical assistant, using a validated non-invasive oscillometric device (Vicorder®, SMT medical, Wuerzburg, Germany). The cfPWV examination protocol was carried out in accordance with the manufacturer's instructions and the expert consensus document on arterial stiffness [16]. All measurements were performed in a quiet room after 10 min of rest.

cfPWV was measured as the velocity value calculated as 0.8 × the distance between the right common carotid artery and the right femoral artery in meters (m), divided by the time that one pulse wave needed to cover this distance in seconds ($\Delta s/\Delta t$) (m/s) ("foot-to-foot" velocity method) [16]. The average value of three measurements was calculated. A threshold value of cfPWV > 10 m/s was considered as an indicator of increased CV risk [20, 34]. This cutoff value for aortic stiffness was also applied in the current study.

SCORE Calculation

SCORE provides a predictive assessment of the total 10-year risk for a fatal CV event, taking into consideration specific patient characteristics and traditional CV risk factors, such as gender, age, cholesterol, smoking habits, and blood pressure values. In our study, SCORE was assessed in all eligible patients (40–70 years old) and based on the European guidelines for CV disease prevention [35]. As there is no conclusive evidence in PsA regarding the multiplication factor during CV risk assessment, the task force suggested not including the multiplication factor (×1.5) for SCORE results in the PSA disease [2]. For this reason, we did not apply the multiplication factor for the assessed SCORE values. As proposed by the guidelines, patients with SCORE values > 5% denoted high CV risk [36].

Statistical Analysis

The assumption of normality of distribution was evaluated by the Shapiro–Wilk numerical test and quantile–quantile plots. Continuous variables are presented as the mean (SD) if they were normally distributed or the median (25th/75th percentiles) if they were skewed. Categorical variables were summarized as absolute (n) and relative (%) frequencies. A comparison of categorical variables was performed through a chi-squared test.

The differences in cfPWV and SCORE between patients with PsA and controls were evaluated by t test when the variables were normally distributed and by Mann–Whitney U test when they were skewed. To assess the correlation between CV surrogates and continuous characteristics, Spearman's (rho) or Pearson's (r) correlation coefficients were used. A p value less than 0.05 was considered significant.

Linear regression was used to assess the difference in cfPWV between PsA and control groups, after adjusting for confounding factors including age, gender, diabetes, nicotine, cholesterol, heart rate, and GFR. Statistical analysis

was performed using the SPSS software version using IBM SPSSVR 23.0 software (USA).

RESULTS

Study Populations

Within the framework of this study, cfPWV measurements, clinical, and laboratory assessments were performed in 150 consecutive patients with PsA [61.3% female, age 55 years (47.0–63.0)], as well as in 88 healthy control subjects [85.2% female, age 51 years (36.5–58.0)].

All descriptive characteristics of patients with PsA and healthy controls included in the study are reported in Table 1.

Associations Between Group Status (Psoriatic Arthritis Group vs. Control Group): cfPWV and SCORE

cfPWV median was significantly higher in the patient group compared with the control group [7.80 (6.87–9.32) m/s vs. 6.76 (6.03–7.68) m/s, $p < 0.001$] (Fig. 1). A linear regression model showed that cfPWV remained significantly higher in the patient group compared to the control group, even after adjusting for the effect of traditional CV risk factors such as age, gender, diabetes, nicotine, cholesterol, heart rate, and GFR (0.457, 95% CI 0.035–0.879, $p_{adj} = 0.034$) (Table 2) and thus pointing to a higher aortic stiffness in patients with PsA independently from cfPWV-influencing factors.

Furthermore, an additional multivariate analysis including the variables age, gender, diabetes, nicotine, MAP, obesity, and arterial hypertension was performed showing also a statistically significant difference of cfPWV between the patients and the control group (0.646, 95% CI 0.230–1.062, $p_{adj} = 0.002$) (S1, supplementary material).

cfPWV and SCORE Values of Patients with Estimated High CV Risk

A total of 150 patients with PsA underwent cfPWV measurement, out of whom 24 (16%) had cfPWV values > 10 m/s, indicating end-organ disease and exaggerated CV risk. Of these 150 patients, 103 were eligible for the calculation of SCORE. Interestingly, out of these only 9 (8.73%) showed SCORE values > 5%, indicative of high CV risk. Cohen's kappa between SCORE and cfPWV was 0.20 showing a poor agreement between those two parameters ($p = 0.34$).

Associations of cfPWV in Patients with PsA and Controls

Among patients with PsA, cfPWV correlated strongly with age (rho = 0.688, $p < 0.001$) and moderately with systolic blood pressure (rho = 0.351, $p < 0.001$) and disease duration (r = 0.304, $p = 0.001$) (Fig. 2, Table 3). Moreover, we conducted a regression model to ensure that the correlation between cfPWV and disease duration was not due to confounding factors such as older age. Even after the adjustment, the correlation remained significant (0.028, 95% CI 0.011–0.045, $p_{adj} = 0.020$], pointing to an independent relationship between these two variables.

Furthermore, cfPWV is associated with mean arterial pressure (rho = 0.253, $p = 0.002$) and red cell distribution width (r = 0.190, $p = 0.020$), as well as inversely with GFR (rho = – 0.264, $p = 0.001$) (Table 3). No statistically significant associations were found within the patient group between cfPWV and VAS, CRP, or further disease activity parameters (number of swollen joints, DAS28, DAPSA) (all $p > 0.05$).

However, patients with diabetes had higher cfPWV values compared with those without [9.40 (8.40–10.85) m/s vs. 7.60 (6.80–8.72) m/s, $p < 0.001$] and subjects with known hypertension also exhibited higher cfPWV values compared with their hypertension-free counterparts [8.40 (6.90–9.70) m/s vs. 7.50(6.70–8.40) m/s, $p = 0.003$] (Table 3).

Among controls, cfPWV correlated strongly with age (rho = 0.656, $p < 0.001$), and moderately with BMI (rho = 0.395, $p = 0.001$), SCORE (rho = 0.412, $p < 0.001$), and MAP ($r = 0.429$, $p < 0.001$), respectively (Table 4).

Table 1 Descriptive characteristics by group

	Controls ($n = 88$)	Patients ($n = 150$)	Significance (p)
Age[a] (years)	51.00 (36.50–58.00)	55.00 (47.00–63.00)	0.003**
Gender (female)	75.00 (85.20%)	92.00 (61.30%)	< 0.001***
Nicotine (smokers)	14.00 (15.90%)	42.00 (28.00%)	0.034*
Hyperlipidemia (yes)	19.00 (21.60%)	45.00 (30%)	0.159
Hypertension (yes)	18.00 (20.50%)	73.00 (48.70%)	< 0.001***
Antihypertensive drugs (yes)	18.00 (20.50%)	62.00 (41.30%)	0.002**
BMI[a] (kg/m^2)	23.91 (21.71–27.09)	27.63 (24.29–33.68)	< 0.001***
MAP[a] (mmHg)	92.83 (84.25–101.161)	97.00 (90.00–102.00)	0.014*
Heart rate[b] (/min)	66.00 (± 10.54)	76.00 (± 11.46)	< 0.001***
HDL[a] (mg/dl)	52.00 (41.00–66.00)	66.00 (55.00–77.00)	< 0.001***
LDL[a] (mg/dl)	123.00 (99.00–153.00)	126.00 (102.00–151.50)	0.979
Cholesterol[b] (mg/dl)	210.53 (± 44.73)	201.08 (± 40.60)	0.174
Statins (yes)	4.00 (4.50%)	15.00 (10.00%)	0.135
Diabetes (yes)	1.00 (1.13%)	20.00 (13.30%)	0.001**
GFR[a] ($ml/min/1.73\ m^2$)	93.00 (83.00–103.00)	88.23 (75.18–97.23)	0.035*
cfPWV[a] (m/s)	6.76 (6.03–7.68)	7.80 (6.87–9.32)	0.034*,‡
ESC SCORE[a]	1.00 (0.00–2.00)	1.00 (0.00–3.00)	0.044*
ESR[a] (mm/h)	–	22.00 (12.00–39.00)	–
CRP[a] (mg/l)	–	3.85 (1.33–10.65)	–
DAS28[a]	–	3.69 (3.06–4.46)	–
DAPSA[a]	–	16.00 (12.00–22.00)	–
Disease duration[a] (years)	–	7.00 (2.00–16.00)	–
csDMARD (yes)	–	32.00 (21.30%)	–
NSAID (yes)	–	51.00 (34.00%)	–
Glucocorticoids (yes)	–	34.00 (22.70%)	–
bDMARD (yes)	–	36.00 (24.00%)	–

BMI body mass index,*MAP* mean arterial pressure, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *GFR* glomerular filtration rate, *cfPWV* carotid-femoral pulse wave velocity, *ESC SCORE* European Society of Cardiology-Systematic COronary Risk Evaluation, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* Disease Activity Score 28, *DAPSA* Disease Activity in Psoriatic Arthritis, *csDMARD* conventional-synthetic disease-modifying anti-rheumatic drugs, *NSAID* non-steroidal anti-inflammatory drug, *bDMARD* biologic disease-modifying anti-rheumatic drugs

[a]Non-normal distribution: presentation as median (interquartile range)

[b]Normal distribution: presentation as mean (standard deviation)

‡ p value adjusted for age, gender, diabetes, nicotine, cholesterol, heart rate, and GFR

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

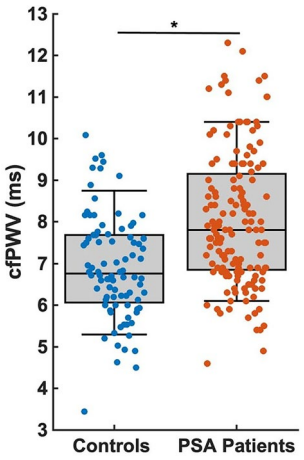

Fig. 1 Distribution of cfPWV values in control subjects and patients with PsA [$p < 0.001^{***}$ and p_{adj} (age, gender, diabetes, nicotine, cholesterol, heart rate, and GFR) = 0.034*]. *cfPWV* carotid-femoral pulse wave velocity, *PsA* psoriatic arthritis, *GFR* glomerular filtration rate

Effects of Immunosuppressive Medication on cfPWV

We conducted a subgroup analysis to compare the median cfPWV results of patients with PsA who received biologic disease-modifying anti-rheumatic drugs (bDMARDs) or conventional-synthetic disease-modifying anti-rheumatic drugs (csDMARDs) against those who did not, respectively. In both cases, no statistically significant cfPWV differences were found between patients with PsA treated with bDMARDs [7.80 (6.90–9.05) m/s vs. 7.80 (6.04–9.40) m/s; $p = 0.236$)] or csDMARDs [7.65 (6.90–8.90) m/s vs. 7.90 (6.80–9.40) m/s, ($p = 0.635$)], and their counterparts, respectively.

DISCUSSION

In the present study, patients with PsA had higher cfPWV values than controls, even after adjustment for confounding factors. Moreover, we were able to show that cfPWV was predicted

Table 2 Results of multiple linear regression model of cfPWV values as the dependent variable: associations with CV risk factors

Parameter	*B*	Beta	*T*	*p* value	95% confidence interval (*B*)	
Constant	2.675		2.786	0.006	0.783	4.567
PsA	0.457	0.116	2.134	0.034*	0.035	0.879
Age	0.740	0.520	9.095	< 0.001*	0.058	0.090
Gender	0.277	0.67	1.326	0.186	− 0.135	0.689
Diabetes	1.798	0.273	5.414	< 0.001*	1.143	2.452
Nicotine	− 0.362	− 0.820	− 1.640	0.102	− 0.798	0.073
Cholesterol	− 0.002	− 0.048	− 0.950	0.343	− 0.007	0.002
Heart rate	0.022	0.137	2.644	0.009*	0.006	0.038
GFR	− 0.005	− 0.056	− 1.044	0.297	− 0.015	0.005

We present the name of the parameter, the regression coefficient (*B*), standardized regression coefficient (Beta), *T* statistics (*T*), *p* value, and the 95% confidence interval of *B*. *B* indicates how cfPWV values change with a one-unit increase in the listed parameters (independent variables)

cfPWV carotid-femoral pulse wave velocity, *CV* cardiovascular, *PsA* psoriatic arthritis, *GFR* glomerular filtration rate

*Significant as $p < 0.05$

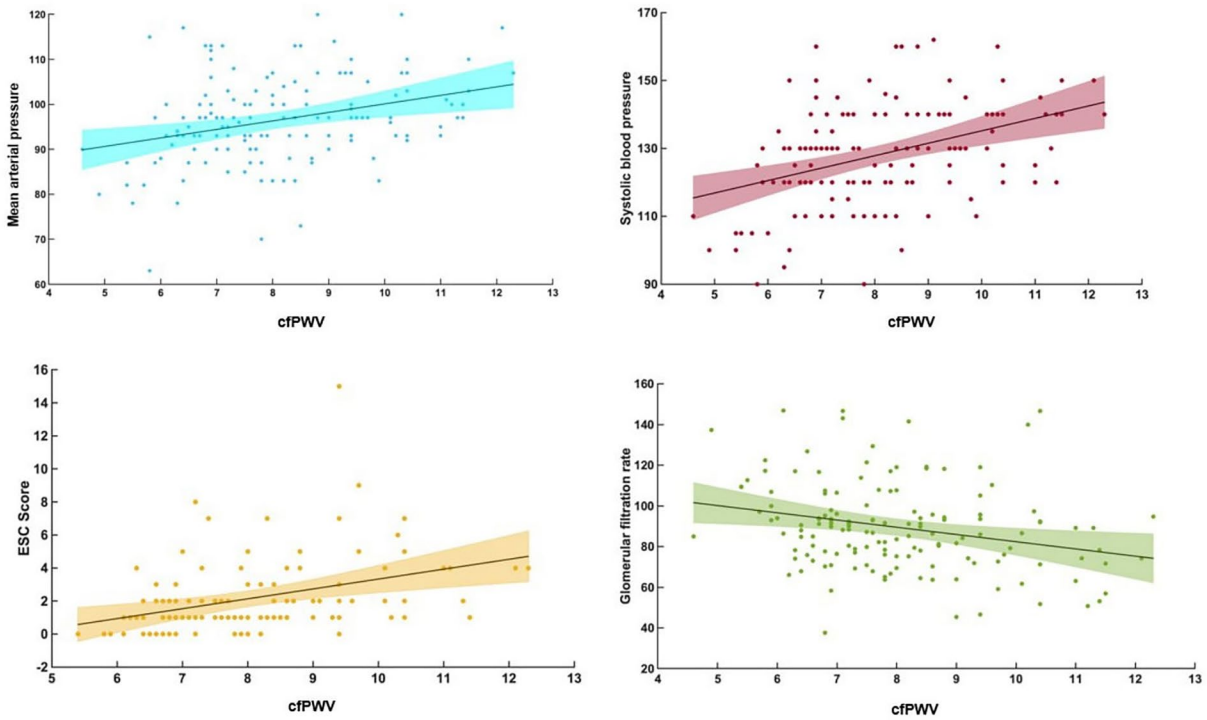

Fig. 2 Associations between cfPWV and traditional CV factors (including ESC SCORE); (all $p < 0.05$*). *cfPWV* carotid-femoral pulse wave velocity, *CV* cardiovascular, *ESC SCORE* European Society of Cardiology Systematic Coronary Risk Evaluation

not only by traditional CV risk factors such as systolic blood pressure but also by disease-related factors, such as disease duration. To the best of our knowledge, this study is the largest to date to examine the gold standard assessment method of aortic stiffness in patients with PsA.

Overall, data concerning markers of CV risk in PsA are scarce. We were able to identify only two previous studies that examined cfPWV in patients with PsA [23, 24]. However, these studies included a low number of patients ($n = 9$ and $n = 20$, respectively) making the extraction of concrete statistical results difficult: Soy et al. reported increased cfPWV in nine patients with PsA in comparison with 39 controls [23], and Costa et al. found higher cfPWV values in 20 patients with PsA in a case–control study [24]. Another PsA study of arterial stiffness focused on a marker known as brachial-ankle pulse wave velocity (baPWV), which is less established than cfPWV, and can thus not be directly compared with our exploration, or the results of the two aforementioned works [37]. The high number of included patients in our exploration gave us the possibility to reveal a hitherto undescribed significant association with a disease chronicity parameter like disease duration.

The age-independent association between disease duration and cfPWV indicates that cumulative inflammatory burden, medication effects, and ultimately chronic damage during the course of the disease might affect developing aortic stiffness and thus high CV risk. Even though this relationship has not been described in PsA until today, Vazquez-Del Mercado et al. came across a similar result examining the arterial status of patients with rheumatoid arthritis [38]. Here, the most pronounced arterial stiffness was found in patients with a disease duration of 10 years or longer [38].

Interestingly, in our study, cfPWV is also associated with red cell distribution width which has been suggested to be a marker for major cardiovascular events (MACE) and a novel psoriasis

Table 3 Associations between cfPWV values and patients' characteristics

	Rho/*r*	**Significance (*p*)**
Age[a](years)	0.688	< 0.001***
MAP[a] (mmHg)	0.253	0.002**
SAP[a] (mmHg)	0.351	< 0.001***
Heart rate[b] (/min)	0.167	0.041*
Cholesterol[b] (mg/dl)	0.110	0.181
LDL[a] (mg/dl)	0.036	0.663
HDL[a] (mg/dl)	0.008	0.928
SCORE[a] (%)	0.429	< 0.001***
GFR[a] (ml/min/1.73 m^2)	− 0.264	0.001**
CRP[a] (mg/l)	− 0.078	0.342
ESR[a] (mm/h)	0.019	0.814
Red cell distribution width[b]	0.190	0.020*
Disease duration[b] (years)	0.304	0.001**
DAS28-(ESR)[a]	− 0.036	0.660
DAS28-(CRP)[a]	− 0.100	0.227
DAPSA[a]	− 0.149	0.070
	Median (IQR)	**Significance (*p*)**
Gender[a]		
Female	7.90 (6.82–9.40)	0.457
Male	7.75 (6.87–9.02)	
Nicotine[a]		
Non-smokers	8.00 (6.90–9.40)	0.031*
Smokers	7.45 (6.67–8.42)	
Antihypertensive drugs[a]		
No	7.65 (6.72–8.60)	0.038*
Yes	8.20 (6.90–9.72)	
Hyperlipidemia[a]		
No	7.60 (6.85–9.25)	0.327
Yes	8.20 (6.90–9.40)	
Obesity[a]		
No	7.85 (6.97–9.12)	0.921
Yes	7.75 (6.80–9.40)	

Table 3 continued

	Median (IQR)	Significance (*p*)
Diabetes[a]		
No	7.60 (6.80–8.72)	< 0.001***
Yes	9.40 (8.40–10.85)	
Hypertension[a]		
No	7.50 (6.70–8.40)	0.003**
Yes	8.40 (6.90–9.70)	
Statins[a]		
No	7.80 (6.80–9.30)	0.107
Yes	8.50 (7.60–9.70)	
Glucocorticoids[a]		
No	7.80 (6.90–9.35)	0.484
Yes	7.95 (6.80–9.35)	

Quantitative characteristics: Spearman's (a) (non-normal distribution, rho) and Pearson's (b) (normal distribution, *r*). Qualitative characteristics: (a) non-normal distribution: presentation as median (interquartile range); (b) normal distribution: presentation as mean (standard deviation)

cfPWV carotid-femoral pulse wave velocity, *MAP* mean arterial pressure, *SAP* systolic arterial pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ESC SCORE* European Society of Cardiology-Systematic COronary Risk Evaluation, *GFR* glomerular filtration rate, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* Disease Activity Score 28, *DAPSA* Disease Activity in PSoriatic Arthritis

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

(PsO)/ PsA disease activity marker [39, 40]. Even though no correlations of cfPWV with other markers of acute inflammation (CRP, ESR) were found in our cohort, an association between aortic stiffness and acute inflammation in the context of autoimmune diseases has been extensively discussed and multiple potential mechanisms concerning the interplay between inflammation and arterial stiffening have been suggested. Increased levels of known inflammatory markers, e.g., interleukin-6 (IL-6), CRP, and interferons, can directly alter the endothelial nitric oxide bioavailability [41] by impairing the vasodilatory effects of NO [42]. Moreover, these mediators trigger the increased production of matrix metalloproteinases with subsequent degeneration of elastin fibers, leading to decreased arterial compliance [43]. Accelerated atherosclerosis due to systemic inflammation-mediated effects may also lead to an increase in arterial stiffness, even though their pathophysiological associations have not been clearly established, mainly due to their complex interplay [44].

Shen et al. evaluated several established CV risk assessment tools, including the Framingham risk score (FRS), SCORE, and the 10-year atherosclerotic cardiovascular disease risk algorithm (ASCVD) in patients with PsA [13]. The study revealed only a moderate discriminative ability of these risk calculators compared to ultrasound-assessed carotid subclinical atherosclerosis (SCA), depicting a possible underestimation of the atheromatosis burden by those CV risk scores. However, since SCA does not directly assess CV risk, more studies on this topic with follow-up examinations are needed. In general, cfPWV has been proven to predict future CV events and it is plausible to assume that it can assess the effects of chronic inflammation in PsA

Table 4 Associations between cfPWV and control subjects' characteristics

	Rho/*r*	Significance (*p*)
Age[a] (years)	0.656	< 0.001***
MAP[b](mmHg)	0.429	< 0.001***
Heart rate[a] (/min)	0.183	0.090
BMI[a] (kg/m^2)	0.395	0.001**
Cholesterol[b] (mg/dl)	0.169	0.126
LDL[b](mg/dl)	0.242	0.027*
HDL[a] (mg/dl)	− 0.092	0.429
ESC SCORE[a] (%)	0.412	< 0.001***
GFR[a] (ml/min/1.73 m^2)	0.183	0.090
	Median (IQR)	**Significance (*p*)**
Gender[a]		
Female	6.70 (6.65–8.09)	0.100
Male	7.47 (6.65–8.09)	
Nicotine[a]		
Non-smokers	6.71 (6.03–7.66)	0.680
Smokers	6.76 (5.76–8.93)	
Antihypertensive drugs[a]		
No	7.68 (6.60–8.56)	0.009**
Yes	6.67 (5.96–7.52)	
Hyperlipidemia[a]		
No	6.72 (6.00–7.60)	0.277
Yes	7.44 (6.20–7.97)	
Statins[a]		
No	6.71 (6.00–7.63)	0.043*
Yes	7.92 (7.44–8.46)	

Quantitative characteristics: Spearman's (a) (non-normal distribution; rho) and Pearson's (b) (normal distribution; *r*). Qualitative characteristics: (a) non-normal distribution: presented as median (interquartile range); (b) normal distribution: presented as mean (standard deviation)

cfPWV carotid-femoral pulse wave velocity, *MAP* mean arterial pressure, *BMI* body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ESC SCORE* European Society of Cardiology-Systematic COronary Risk Evaluation, *GFR* glomerular filtration rate

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

in a more accurate manner than traditional CV tools since the latter do not take inflammatory burden or other disease-specific markers into account [45].

Age was associated with cfPWV not only in our PsA cohort but also in the control group. This statistical association between age and cfPWV is not surprising, since age is a known risk factor for CV disease [46]. The influence of age on aortic stiffness results from structural changes in the media layer of the vessel wall during a person's lifetime. The mechanical properties of the arterial wall change with increasing age, especially as a result of the loss of elastic fibers and accumulation of collagen [28].

Moreover, cfPWV correlated with diabetes in both groups, signaling the influence of metabolic factors on aortic stiffness and hence the overall CV risk. Poznyak et al. postulated that chronic inflammation may be regarded as one of the possible links between atherosclerosis and diabetes mellitus and supports the hypothesis that systemic inflammation promotes insulin resistance [47]. Furthermore, in our patient group, cfPWV was associated with MAP. Cecelja et al. described MAP as the main factor impacting cfPWV even in the general population [48]. As a result of the elasticity of the aorta, the vessel wall gets stretched if a force is applied to it. The higher the blood pressure is, the higher the stretching of the vessel wall; and by stretching, the vessel wall gets stiffer [28].

Our study has some limitations. First, there were no longitudinal associations of cfPWV with future morbidity or mortality data. Nonetheless, a plethora of studies have assessed the predictive value of cfPWV and this marker has been suggested as a valid CV risk stratification tool by the European Society of Cardiology Working Group on peripheral circulation and the ARTERY Association (level of evidence A, Recommendation IIa) [22]. Second, differences in age, gender, and some traditional CV risk factors were statistically observed between the patient and the control group. To avoid confounding, we have performed linear regression models adjusting the findings for the effects of multiple possible cfPWV-influencing factors, like traditional CV parameters and of course age/gender. These statistical models revealed higher cfPWV values in the PsA group, even after statistical corrections and thus a statistical bias seems unlikely. However, results should be controlled in future studies. A third possible limitation is that cfPWV of patients with PsA was compared with the respective values of controls without rheumatologic diseases and not with a diseased group. However, the aim of our study was to examine comparisons between patients with PsA and controls without rheumatic diseases, given the scarcity of data regarding this research question.

CONCLUSION

This is one of the largest surrogate CV marker studies in PsA and the first report of an independent association between aortic stiffness and PsA duration pointing to a possible link with disease-related cumulative damage or comorbidities. Since aortic stiffness can reflect the long-term effects of both traditional CV risk factors and inflammation-associated vascular damage in a non-invasive and radiation-free manner, cfPWV could prove to be a useful tool for the identification of patients with PsA with end-organ disease and thus high CV risk. Further research and follow-up data from longitudinal studies are warranted.

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Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. All authors, Konstantinos Triantafyllias, Stefanie Liverakos, Muthuraman Muthuraman, Lorenzo Cavagna, Ioannis Parodis and Andreas Schwarting, declare that they have no competing interests.
Andreas Schwarting is an Editorial Board member of *Rheumatology and Therapy*. Andreas Schwarting was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. The study has been reviewed and approved by the local standing committee for ethical conduct (Medical Board Rhineland-Palatinate, approval number 13762_2), and adhered to the Declaration of Helsinki. Written informed consent was obtained from all study subjects prior to enrollment.

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