ORIGINAL ARTICLE

Coronary Microvascular Dysfunction in Asymptomatic Patients with Severe Psoriasis

JID Open

Stefano Piaserico[1], Evangelia Papadavid[2], Annagrazia Cecere[3], Gloria Orlando[1], Konstantrinos Theodoropoulos[2], Pelagia Katsimbri[2], George Makavos[4], Penelope Rafouli-Stergiou[4], Sabino Iliceto[3], Mauro Alaibac[1], Francesco Tona[3] and Ignatios Ikonomidis[4]

Severe psoriasis is associated with an increased cardiovascular risk, which may be independent of the traditional risk factors. Coronary microvascular dysfunction (CMD) has been shown to predict a poor cardiovascular prognosis in the general population and in patients with psoriasis. In this study, we assessed the prevalence and predictors of CMD in a large cohort of patients with psoriasis without clinical cardiovascular disease. A total of 503 patients with psoriasis were enrolled and underwent transthoracic Doppler echocardiography to evaluate coronary microcirculation. Of these, 55 patients were excluded from the analyses because of missing data. Of the 448 patients in this study, 31.5% showed CMD. Higher PASI, longer disease duration, the presence of psoriatic arthritis, and hypertension were independently associated with CMD. An increase of 1 point of PASI and 1 year of psoriasis duration were associated with a 5.8% and 4.6% increased risk of CMD, respectively. In our study, CMD was associated with the severity and duration of psoriasis. This supports the role of systemic inflammation in CMD and suggests that the coronary microcirculation may represent an extracutaneous site involved in the immune-mediated injury of psoriasis. We should diagnose and actively search for CMD in patients with severe psoriasis.

Journal of Investigative Dermatology (2023) **143,** 1929–1936; doi:10.1016/j.jid.2023.02.037

INTRODUCTION

Psoriasis is a chronic systemic immune-mediated inflammatory disease with a prevalence of 1–3% worldwide. Patients affected by severe psoriasis suffer from increased cardiovascular (CV) morbidity and mortality owing to accelerated atherosclerosis and premature coronary artery disease (CAD) (Gelfand et al., 2006; Mehta et al., 2010). This excess risk has been attributed to psoriasis-induced inflammation, which might affect atherosclerotic plaque formation and coronary microvascular function, thus leading to an increased risk of atherothrombotic and ischemic complications (Garshick et al., 2021). Coronary microvascular dysfunction (CMD) indicates an abnormal regulation of the coronary microcirculation resulting in an impaired myocardial perfusion in the absence of epicardial CAD. Coronary flow reserve (CFR) provides a robust and reproducible clinical measure of the integrated hemodynamic effects of both CAD and CMD on myocardial tissue perfusion (Levy et al., 2019). Therefore, CFR has proved to be a powerful quantitative prognostic imaging marker of clinical CV risk (Camici and Crea, 2007; Safdar et al., 2018), and a reduced CFR consistently identifies patients at increased risk of myocardial infarction and death (Gupta et al., 2017; Schroder et al., 2021).

CFR expresses the capacity of the coronary circulation to dilate and increase flow following an increased myocardial metabolic demand. In healthy subjects, CFR ranges from 3 to 6, meaning their coronary circulation can at least triple the baseline flow when needed (Camici and Crea, 2007). A CFR $\leq$ 2.5 may reflect either a coronary artery stenosis >70%, a CMD in the absence of significant stenosis of the coronary arteries, or both (Levy et al., 2019). Notably, a reduced CFR in the presence of normal epicardial vessels identifies a dysfunction of the coronary microcirculation. Coronary microcirculation in the myocardium cannot be assessed on routine coronary angiography. The recognized gold standard methodologies for non-invasive assessment of CMD are cardiac PET-CT and cardiac magnetic resonance, which provide accurate and reproducible quantification of CFR estimating global and regional myocardial perfusion (Levy et al., 2019). However, they are not always easy to perform, they are expensive, and they have limited availability. Conversely, despite some technical limitations and operator variability, transthoracic Doppler echocardiography is a highly feasible and potentially widely applicable method used to assess CFR (Safdar et al., 2018).

We previously showed in a small cohort of patients that CFR is reduced in patients with moderate-to-severe psoriasis compared with the general population (Osto et al., 2012). This was confirmed by other sparse studies (Gullu et al., 2013; Ikonomidis et al., 2015; Weber et al., 2022).

[1]*Dermatology Unit, Department of Medicine, University of Padova, Padova, Italy;* [2]*Department of Dermatology and Venereology, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece;* [3]*Division of Cardiology, Department of Cardiologic, Thoracic and Vascular Sciences, University of Padova, Padova, Italy; and* [4]*2nd Cardiology Department, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece*

Correspondence: Stefano Piaserico, Unit of Dermatology, Department of Dermatolog, University of Padua, via V. Gallucci 4, 35121 Padua, Italy. E-mail: stefano.piaserico@unipd.it

Abbreviations: CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CV, cardiovascular; MSCT, multislice computed tomography

Received 23 October 2022; revised 31 January 2023; accepted 22 February 2023

Table 1. Description of the demographic data of 448 patients included in the study

Demographics	All patients (n = 448)[1]
Male gender	346 (68.8)
Age (years), mean ± SD	45.75 ± 13.33
PASI, mean ± SD	12.00 ± 8.71
CFR, mean ± SD	2.95 ± 0.90
Duration psoriasis (years), mean ± SD	15.17 ± 12.33
Current treatment with a systemic drug for psoriasis (including biologics)	116 (25.9)
Current treatment with biologics	79 (17.6)
Psoriatic arthritis	141 (31.5)
Hypertension	109 (24.3)
Smoking status	
Current	155 (34.5)
Previous	104 (23.2)
Never	189 (42.2)
BMI (kg/m^2), mean ± SD	29.27 ± 6.44
Hyperlipidemia	165 (36.8)
Total cholesterol (mg/dl), mean ± SD	195.38 ± 44.03
TG (mg/dl), mean ± SD	120.96 ± 69.20
CRP (mg/l), mean ± SD	2.32 ± 3.18
Current treatment with statins	108 (24.1)
Current treatment with beta blocker	30 (6.7)
Current treatment with diuretics	20 (4.4)
Current treatment with ace-inhibitors	93 (20.8)

Abbreviations: BMI, body mass index; CFR, coronary flow reserve; CRP, C-reactive protein ; TG, triglycerides
[1]Values are reported as n (%) unless noted otherwise

However, the low number of patients in these studies might have hampered the analysis. These observations prompted us to carry out a more extensive, prospective, multi-center study on a larger population of patients with severe psoriasis.

In this study, we assessed the prevalence of reduced CFR assessed by transthoracic echocardiography in a broad cohort of severe psoriasis patients without clinical cardiovascular disease (CVD) and its association with psoriasis and patients' characteristics.

RESULTS

Of the 503 patients with psoriasis who were enrolled, 55 (10.9%) were excluded from the analyses as a result of technical difficulties in assessing CFR (n = 38), contraindications to adenosine (n = 11), being unable to perform multislice computed tomography (MSCT) coronary angiography (n = 1), or the presence of significant coronary artery stenosis (n = 5). Therefore, the psoriatic study population consisted of 448 patients with complete data on CFR and disease characteristics (Supplementary Figure S1).

Characteristics of the study group

The baseline characteristics of the participants are summarized in Table 1. The cohort had a mean age of 45 years (±13) and was predominantly composed of male patients (69%). The mean body mass index was 29 ± 6.4 kg/m^2. The prevalence of traditional CV risk factors was: 24%, hypertension; 37%, hyperlipidemia; 11%, diabetes mellitus; and 57.8%, current or previous smokers.

Table 2. Univariate analysis of variables in patients with normal (n = 307) or reduced CFR (≤2.5) (n = 141)

Variables[1]	CFR ≤2.5 (n = 141)	CFR >2.5 (n = 307)	*P*
Male gender	95 (67.4)	217 (70.7)	0.508
Age (years), mean ±SD	50.4 ± 12.78	42.73 ± 12.85	<0.001[2]
PASI, mean ±SD	13.45 ± 10.32	10.82 ± 7.61	0.004[2]
Duration psoriasis (years), mean ±SD	18.91 ± 13.53	12.38 ± 10.86	<0.001[2]
Under treatment with a systemic drug for psoriasis	35 (24.8)	79 (25.7)	0.791
Under treatment with biologics	26 (18.4)	53 (17.3)	0.761
Psoriatic arthritis	61 (43.3)	82 (26.7)	0.001[2]
Hypertension	48 (34)	60 (19.5)	0.001[2]
Smoking status			0.040[2]
Current	39 (27.6)	111 (36.2)	
Previous	28 (19.9)	74 (24.1)	
Never	74 (52.5)	122 (39.7)	
BMI (kg/m^2), mean ± SD	29.89 ± 6.70	28.52 ± 5.85	0.034[2]
Hyperlipidemia	54 (38.3)	111 (36.1)	0.511
Total cholesterol (mg/dl), mean ± SD	188.17 ± 43.97	197.68 ± 43.61	0.079
TG (mg/dl), mean ± SD	120.24 ± 77.13	118.89 ± 63.02	0.877
CRP (mg/l), mean ± SD	1.78 ± 2.15	2.47 ± 3.41	0.267
Current treatment with statins	45 (31.9)	63 (20.5)	0.009[2]
Current treatment with beta blocker	11 (7.8)	19 (6.2)	0.526
Current treatment with diuretics	6 (4.3)	15 (4.9)	0.769
Current treatment with ace-inhibitors	42 (29.9)	50 (16.3)	0.001[2]

Abbreviations: BMI, body mass index; CFR, coronary flow reserve; CRP, C-reactive protein ; TG, triglycerides
[1]Values are reported as n (%) unless noted otherwise.
[2]Statistically significant ($P < 0.05$) results.

The median duration of psoriasis was 15.2 ± 12.3 years, with a mean PASI of 12 ± 8.7. The vast majority of patients (332 out of 448; 74.1%) underwent a CFR assessment before starting a treatment. The remaining patients were treated with TNFα inhibitors (34; 29.3%), ustekinumab (25; 21.5%), secukinumab (20; 17.2%), methotrexate (12; 10.3%), apremilast (9; 7.7%), acitretin (8; 6.9%), and cyclosporine (8; 6.9%).

Prevalence and predictors of reduced CFR

A total of 141 patients (31.5%) showed CMD (CFR ≤ 2.5). None of these patients had coronary stenoses at the MSCT scan. Moreover, 12.9% showed a CFR ≤ 2.0, and 5.1% had a severely reduced CFR (cut-off of ≤1.5). Table 2 displays baseline characteristics according to the presence or absence of CMD (CFR ≤ 2.5). Patients with CMD compared with those without CMD were older, had a slightly higher body mass index, and were more often affected by hypertension and psoriatic arthritis. Moreover, psoriasis activity was greater in those patients. Lower CFRs were correlated with higher PASI values at the moment of CFR measurement ($P = 0.0002$) and with a longer time from diagnosis ($P = 0.01$) (Figures 1 and 2). Median CFR values were 3.02 (IQR: 2.46–3.58),

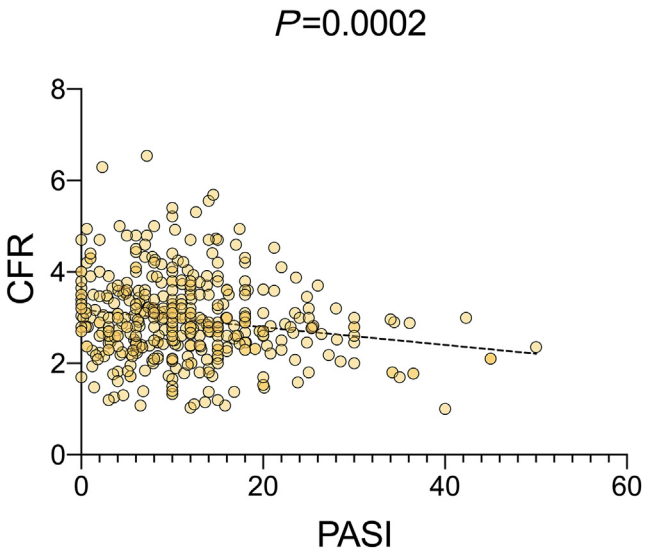


Figure 1. Correlation between CFR and PASI values (Pearson's *r* correlation coefficient = -0.18, *P* = 0.0002). CFR, coronary flow reserve.

2.85 (IQR: 2.41−3.29), and 2.51 (IQR: 2.03−2.98) for patients with PASI < 10, PASI 10−20, and PASI >20, respectively ($P = 0.0001$) (Supplementary Figure S2), and 3 (IQR: 2.50−3.50), 2.75 (IQR: 2.27−3.23), and 2.73 (IQR: 2.10−3.36) for patients with <5, 5−10, and >10 years from diagnosis, respectively ($P = 0.0003$) (Supplementary Figure S3).

Multivariable linear regression was used to model the associations of the characteristics of patients with psoriasis with CMD. As shown in Table 3, higher PASI, longer duration of psoriasis, the presence of psoriatic arthritis, and hypertension were significantly associated with lower CFR. In particular, an increase of 1 point of PASI and 1 year of psoriasis duration are associated with a 5.8% and 4.6% increased risk of CMD,

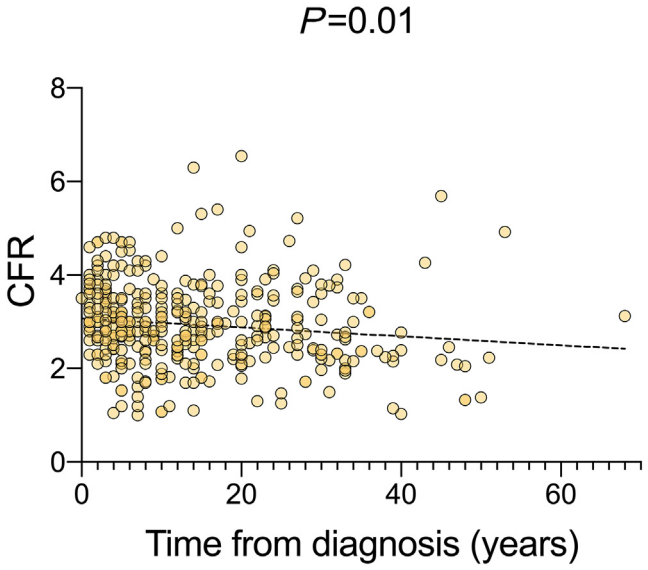


Figure 2. Correlation between CFR values and duration of psoriasis (years) (Pearson's *r* correlation coefficient = -0.13, *P* = 0.01). CFR, coronary flow reserve.

Table 3. Multivariate logistic regression analysis of variables associated with a CFR impairment (≤2.5)

Variables[1]	OR (95% IC)	*P*
PASI (per unit)	1.058 (1.025 - 1.091)	<0.001
Duration psoriasis (per year)	1.046 (1.022 - 1.069)	<0.001
Presence of psoriatic arthritis	1.938 (1.138 - 3.300)	0.015
Presence of hypertension	2.169 (1.203 - 3.911)	0.010

[1]Model included age, PASI, duration of psoriasis, BMI, hyperlipidemia, smoking status, presence of psoriatic arthritis and hypertension, and use of ace-inhibitors and statins.

respectively. The C statistic for the multivariable model was 0.703 (95% confidence interval, 0.646−0.760) without PASI and 0.894 (95% confidence interval, 0.793−0.901) with PASI.

Besides hypertension, other conventional CV risk factors were not independently associated with CFR in adjusted models. A sensitivity analysis only including patients without treatment showed similar results (data not shown). An additional sensitivity analysis forcing the inclusion of variables with *P*-values <0.20 confirmed the above statistically significant associations with only nominal differences in *P*-values (data not shown).

The receiver operating characteristic curves for a model including traditional CV risk factors (age, sex, body mass index, hyperlipidemia, diabetes mellitus, smoke, and hypertension) and model with the traditional CV risk factors + severe psoriasis duration time, PASI and psoriatic arthritis are shown in Figure 3. The model including variables related to psoriasis performed slightly but significantly better than the model without (area under curve: 0.735 vs. 0.691, $P = 0.03$).

DISCUSSION

In this cross-sectional study on a large cohort of patients with severe psoriasis, we found that CMD as defined by CFR ≤ 2.5 was prevalent in more than 30% of patients. The current study is the largest study to date of coronary flow in patients with psoriasis, which allowed a detailed assessment of clinical determinants of the impairment of CFR. Severity and duration of psoriasis and the presence of psoriatic arthritis were independent predictors of CFR ≤ 2.5. This is of particular importance, because a reduced CFR has been shown to predict a poor CV prognosis in the general population, and also in selected groups of patients, such as asymptomatic patients with diabetes (Cortigiani et al., 2014; Nakanishi et al., 2012) and systemic sclerosis (Vacca et al., 2013). Furthermore, a CFR ≤ 2.5 was associated with a lower major adverse cardiovascular event−free survival rate in a cohort of patients with psoriasis, with 21% of patients with psoriasis with an impaired CFR developing a CV event over time (Piaserico et al., 2019).

CMD and inflammation

Because a reduction in CFR can occur with both obstructive CAD and an impairment in coronary microvascular function, it is important to ascertain whether these patients have a true obstructive CAD (who could benefit from revascularization) or a predominantly microvascular disease. In our study, patients with CFR ≤ 2.5 underwent angio-CT to exclude a

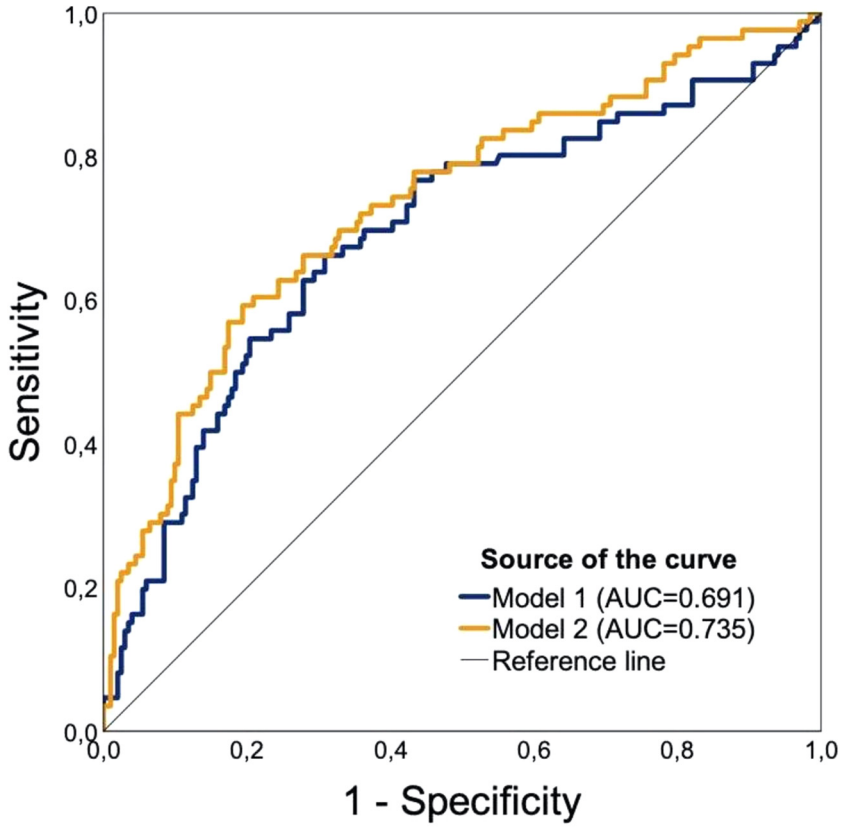


Figure 3. ROC for the prediction of CMD The models include model 1 (traditional CV risk factors: age, sex, BMI, hyperlipidemia, diabetes mellitus, smoking, and hypertension) (green) and model 2 (model 1 + severe psoriasis duration time, PASI, and psoriatic arthritis) (red). The Model 2 performs slightly but significantly better than model 1 (area under curve: 0.735 vs. 0.691, $P = 0.03$). BMI, body mass index; CMD, coronary microvascular dysfunction; CV, cardiovascular; ROC, receiver operating characteristic.

stenosis of the coronary arteries and no patients showed CAD. Therefore, all patients with an impaired CFR in our cohort were affected by CMD.

There is growing evidence that patients with chronic inflammatory diseases, including psoriasis, psoriatic arthritis, rheumatoid arthritis, and inflammatory bowel disease, have a higher prevalence of endothelial and microvascular dysfunction in the absence of clinically apparent CVD (Erre et al., 2018; Faccini et al., 2016; Godo et al., 2021). This is likely to contribute significantly to the increased risk of adverse CV outcomes in patients with psoriasis and other chronic inflammatory diseases, independently of traditional CV risk factors. Accordingly, myocardial ischemia in the absence of obstructive epicardial disease is more common in patients with psoriasis and rheumatoid arthritis than in the general population, suggesting a prominent role for CMD in these chronic diseases (Tinggaard et al., 2021). However, studies assessing microvascular dysfunction at the myocardial level in patients with psoriasis are scarce and limited to a small number of patients (Gullu et al., 2013; Ikonomidis et al., 2015; Osto et al., 2012; Weber et al., 2022).

In our study, we showed that CMD is associated with psoriasis activity, assessed at the moment of CFR evaluation with the PASI score, and the duration of the disease. This finding is in agreement with studies on rheumatoid arthritis (Ciftci et al., 2008; Recio-Mayoral et al., 2009), systemic lupus erythematosus (Recio-Mayoral et al., 2009), and systemic sclerosis (Faccini et al., 2015). This evidence supports the role of systemic inflammation in the development of CMD.

Endothelial dysfunction has a pivotal role in atherosclerotic lesion initiation and progression and is characterized by reduced vasodilator function, increased vascular adhesion of circulating inflammatory cells and platelets, and heightened procoagulant activity (Gimbrone and García-Cardeña, 2016; Gutiérrez et al., 2013).

The systemic inflammation induced by psoriasis with the consequent increase in circulating cytokines seems to be at the basis of reduced nitric oxide (NO) bioavailability, considered a common and critical step leading to endothelial dysfunction (Konst et al., 2020). In particular, TNF-α blocks the activation of endothelial NOS, degrades endothelial NOS mRNA, alters vasomotor function by acting on vascular smooth muscle cells, reduces the degradation of asymmetric dimethylarginine —an endogenous inhibitor of NOS— and induces oxidative stress by increasing the production of ROS, which contribute to modulating the availability of NO (Konst et al., 2020; Vancheri et al., 2020). IL-17 has also been shown to have a role in the regulation of NO production. In a preclinical model, it has been demonstrated that the constitutive overexpression of IL-17A in T cells can lead to altered endothelium-dependent relaxation of aortic rings (Nguyen et al., 2013; Schüler et al., 2019). A possible explanation could be the significant increase in phosphorylation of the endothelial NOS Thr495 induced by IL-17, leading to a decrease in NO production and vasodilation (Konst et al., 2020; Nguyen et al., 2013).

Interestingly, multivariate analysis in our study showed no association of CFR with conventional CV risk factors such as tobacco use, hyperlipidemia, or diabetes mellitus, which

have been shown to be associated with CMD in the general population (Camici and Crea, 2007). Only hypertension was independently associated with a lower CFR. These findings suggest the possibility that microvascular dysfunction in the psoriatic population may be driven, at least in part, by determinants other than conventional CV risk factors. In particular, these findings suggest that inflammation may be a major factor for CMD in psoriasis and are consistent with some preliminary interventional studies reporting improvement of CFR with anti-psoriasis therapy (Ikonomidis et al., 2017; Piaserico et al., 2016).

Coronary microvascular dysfunction vs macrovascular endothelial dysfunction

Endothelial function can be investigated in any artery of the body because the atherosclerotic process appears to be generalized. Macrovascular endothelial dysfunction in clinical research is commonly quantified with the flow-mediated dilation of the brachial artery (Corretti et al., 2002). More recently, reactive hyperemia peripheral arterial tonometry has been developed, which measures the reactive hyperemic response to transient arterial occlusion of the digital blood flow (Bordy et al., 2018). However, a weak correlation has been shown between microvascular and macrovascular endothelial dysfunction in the general population (Anderson et al., 2011; Bøttcher et al., 2001; Hamburg et al., 2011), suggesting that microvascular and macrovascular endothelial dysfunction may play different roles in the pathogenesis of vascular disease. Although endothelial cells are present in every vascular bed, there are differences in the function, structure, and phenotypes of these cells between vascular beds from the macrovasculature and those from the microvasculature, as well as between microvascular beds from different organs.

Furthermore, vascular structural changes (e.g., increased stiffness or thickening of the arterial wall, as indicated by the augmentation index or carotid intima-media thickness measurements, respectively) should not be mistaken for endothelial dysfunction as these processes are linked with distinctive aspects of the vascular disease.

The great deal of evidence showing a link between endothelial dysfunction and CV risk in the general population and in patients with traditional CVD suggests that macrovascular endothelial dysfunction may reflect established atherosclerosis, whereas microvascular function appears to be associated with future CV events in subjects with no established vascular disease, identifying patients at high CV risk before the development of macrovascular disease (Flammer et al., 2012; Hellmann et al., 2015). From a pathophysiological perspective, functional alterations in various microcirculatory beds most likely precede and forecast the onset of vascular dysfunction and structural abnormalities in conduit arteries (Bordy et al., 2018). Moreover, flow-mediated dilation and reactive hyperemia peripheral arterial tonometry do not appear to be very sensitive to changes during psoriasis treatment (Cohen-Barak et al., 2015; Nakao et al., 2019; Ortolan et al., 2021; von Stebut et al., 2020).

CFR for CV risk stratification

Compelling evidence supports the fact that psoriasis is associated with increased CV morbidity and mortality (Garshick et al., 2021; Gelfand et al., 2006; Mehta et al., 2010; Zhou et al., 2020). However, fundamental questions regarding psoriasis and CVD remain, including the need for validated biomarkers and/or clinical risk models to accurately predict CV events in patients with psoriasis. Arguably, an optimal CV risk prediction strategy in psoriasis should include both an emphasis on traditional CV risk factors and imaging or biomarker correlates of subclinical CVD burden. Machine learning methods might be helpful to provide a more personalized risk assessment of a patient's subclinical disease and future CV event risk, given the patient's clinical characteristics (e.g., psoriasis) (Munger et al., 2020).

Against this backdrop, CFR could represent a reliable, noninvasive, and easily reproducible tool allowing the identification of early CV dysfunction. Because of the severity of psoriasis, the presence of arthritis, and the duration of disease are independently associated with a lower CFR in our study population, we might hypothesize that an early and effective treatment of psoriasis would restore a CMD and eventually prevent the future risk of myocardial infarction and heart failure associated with it. In keeping with this, some preliminary studies showed that CFR markedly increased after 4–6 months of treatment with TNFα inhibitors (Piaserico et al., 2016), ustekinumab (Ikonomidis et al., 2017), or secukinumab (Makavos et al., 2020).

Nonetheless, prospective studies are needed to confirm the clinical significance of CFR improvement following treatment in patients with psoriasis. Indeed, whether these findings translate into reductions in CV events need to be ascertained, and this highlights the need for larger clinical trials with clinically meaningful endpoints to investigate targeting inflammation to reduce CV risk in psoriasis.

Strength and limitations

The strengths of our study are the large sample size, the use of a standardized method for assessing CFR, and the screening of patients with blunted CFR with angio-CT to exclude flow-limiting coronary artery disease, the risk of which is however increased in patients with psoriasis. Another strength is the inclusion of patients with and without CV risk factors as well as patients with early and late psoriasis, a representative sample of the psoriasis population managed in clinical practice.

There are some limitations to our study. A small portion of the study's patients were under treatment for psoriasis. However, a sensitivity analysis only including patients without treatment showed similar results. Moreover, some patients were treated for CV risk factors at the time of CFR. This was a small number of patients and it likely did not impact the main analysis. However, despite statistical adjustments, we cannot exclude some residual bias related to drugs and unmeasured variables. Lastly, we based our assessment of CMD on transthoracic Doppler echocardiography and did not use other techniques, such as PET-CT and CMR. Nonetheless, these are not always easy to perform, are expensive, and have limited availability, whereas transthoracic Doppler echocardiography represents a highly feasible and potentially widely applicable method.

CONCLUSION

Our findings extend the observations of earlier small studies by showing a high prevalence of coronary microvascular dysfunction in asymptomatic patients with severe psoriasis and by showing that the excess microvascular dysfunction is independently associated with the severity and duration of psoriasis. These findings are consistent with the view of systemic inflammation as a key contributor to atherosclerosis and suggest that the coronary microcirculation may represent an extra-cutaneous site directly involved in the immune-mediated injury characteristic of psoriasis. Accordingly, we should diagnose and actively search for microvascular dysfunction in patients with psoriasis, as this population is at particularly high risk. This assessment might have particular value in the diagnosis, stratification, and treatment of CV risk in psoriasis. Because the dysfunction is correlated to the activity and length of psoriasis and is largely independent of traditional CV risk factors, studies on CFR may also be useful for monitoring vascular function during therapy of psoriasis, which may, hopefully, be a surrogate for decreasing the risk of subsequent CV events.

MATERIAL AND METHODS

Study participants

This observational study consisted of 503 consecutive participants with psoriasis who were aged 18 years or older and were recruited from April 1, 2009, through August 1, 2020, in the University Hospital of Padova, Italy, and Attikon Hospital, National and Kapodistrian University of Athens, Greece. Psoriasis and psoriatic arthritis were diagnosed by a certified dermatologist or rheumatologist. Exclusion criteria were an estimated glomerular filtration rate < 30 mL/min/1.73 m^2, known current CVD, chronic obstructive pulmonary disease or asthma, and conditions that increase systemic inflammation such as internal solid or liquid malignancy within the past 5 years, HIV infection, any active infection 72 hours before, major surgery within the previous 3 months, current pregnancy, or lactation.

Standard Doppler echocardiography and CFR assessment

Transthoracic Doppler echocardiography was performed with a commercially available ultrasound system (Vivid 7, GE Medical System, Inc., Hortem, Norway). Coronary images were obtained in the distal part of the left anterior descending artery with a 7-MHz transducer. Coronary blood flow was obtained by Color Doppler flow-mapping guidance, and sample volume was positioned within the color signal in the left anterior descending artery by pulse wave Doppler. After baseline recordings of coronary diastolic flow velocity, adenosine was intravenously infused (140 μg/kg−1/min) for 3 minutes, obtaining hyperemic Doppler flow profiles. CFR was estimated as the ratio of hyperemia to baseline peak diastolic flow velocity. Echocardiographic methods are detailed in the Supplementary Material (Supplementary Materials and Methods). A CFR ≤ 2.5 was considered abnormal and a marker of CMD, and the population was dichotomized according to this cut-off (Cortigiani et al., 2014; Nakanishi et al., 2012).

MSCT coronary angiography protocol and interpretation

Patients with abnormal CFR (CFR ≤ 2.5) underwent MSCT coronary angiography to exclude epicardial significant CAD. Coronary MSCT was performed using a 64-slice dual-source scanner (Definition, Siemens Medical System, Forchheim, Germany). For the MSCT protocol, see Supplementary Material online.

Statistical analysis

Continuous variables are presented as a mean ± SD. Discrete variables were summarized as frequencies and percentages. Continuous data were compared with the 2-tailed unpaired *t* test. Categorical variables were compared by the χ^2 test or the Fisher exact test, as appropriate. Pearson's correlation coefficient (*r*, from −1 to +1) was used to evaluate correlations between the continuous variables. Comparisons between CFR values in groups with PASI < 10, 10−20, or >20 at the time of CFR measurement and with psoriasis duration < 5, 5−10, or >10 years were performed using ANOVA. Post-hoc comparisons were performed with Bonferroni correction. Stepwise logistic regression analysis was used to model normal versus abnormal CFR as a function of PASI and other coronary risk factors or clinical conditions. Baseline characteristics were chosen for entry into multivariable models on the basis of their discrimination between low and high CFR and their unadjusted association with CFR ≤ 2.5 of $P \leq 0.1$. A combination of forward and backward selection procedures was used to aid in determining the best model of factors independently associated with CFR. This was followed by forcing potential confounders into the models and determining their effect on the relationship of interest. Nonsignificant risk factors were removed if they did not significantly add to the model. Summary statistics for the regression models included the C statistic (a measure of the association between predicted probabilities and the observed prevalence of a binary outcome). The receiver operating characteristic curves were constructed to calculate the area under curve, and the DeLong test was performed to compare the area under curves of different models.

All tests were two-sided, and statistical significance was accepted if the null hypothesis could be rejected at $P < 0.05$. Data were analyzed with SPSS software version 26.0 (SPSS, Chicago, IL). The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree with the manuscript as written. The study protocol was reviewed and approved by the National and Kapodistrian University of Athens Medical School, Attikon Hospital, Athens, Greece, and the University Hospital of Padova ethical committees. All participants gave their written informed consent to participate in the study.

Data availability statement

All the data from this study are included in this article. Data are kept on file and are not publicly available owing to privacy legislation. Requests can be directed to the corresponding author.

ORCiDs

Stefano Piaserico: http://orcid.org/0000-0002-1091-4733
Evangelia Papadavid: http://orcid.org/0000-0002-8634-102X
Annagrazia Cecere: http://orcid.org/0000-0001-5587-1215
Gloria Orlando: http://orcid.org/0000-0002-5739-9708
Kostantinos Theodoropoulos: http://orcid.org/0000-0001-6272-4459
Pelagia Katsimbri: http://orcid.org/0000-0002-7634-6863
George Makavos: http://orcid.org/0000-0002-1123-8060
Sabino Iliceto: http://orcid.org/0000-0002-3676-8746
Mauro Alaibac: http://orcid.org/0000-0001-6524-4848
Francesco Tona: http://orcid.org/0000-0003-4828-7875
Ignatios Ikonomidis: http://orcid.org/0000-0001-8241-7886

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: SP, EP, SI, FT, II; Formal Analysis: SP, FT; Investigation: AC, KT, PK, GM, PRS, SI, II; Methodology: SP, EP, SI, MA, FT, II; Supervision: SI, FT, II; Writing — original draft: SP, EP, GO, FT, II; Writing — review & editing: AC, KT, PK, GM, PRS, SI

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2023.02.037

REFERENCES

Anderson TJ, Charbonneau F, Title LM, Buithieu J, Rose MS, Conradson H, et al. Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study. Circulation 2011;123:163–9.

Bordy R, Totoson P, Prati C, Marie C, Wendling D, Demougeot C. Microvascular endothelial dysfunction in rheumatoid arthritis. Nat Rev Rheumatol 2018;14:404–20.

Bøttcher M, Madsen MM, Refsgaard J, Buus NH, Dørup I, Nielsen TT, et al. Peripheral flow response to transient arterial forearm occlusion does not reflect myocardial perfusion reserve. Circulation 2001;103:1109–14.

Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.

Ciftci O, Yilmaz S, Topcu S, Calskan M, Gullu H, Erdogan D, et al. Impaired coronary microvascular function and increased intima-media thickness in rheumatoid arthritis. Atherosclerosis 2008;198:332–7.

Cohen-Barak E, Sah M, Kerner M, Rozenman D, Ziv M. Impact of anti-psoriatic therapy on endothelial function. Br J Dermatol 2015;173:1440–6.

Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257–65.

Cortigiani L, Rigo F, Gherardi S, Galderisi M, Bovenzi F, Sicari R. Prognostic meaning of coronary microvascular disease in type 2 diabetes mellitus: A transthoracic Doppler echocardiographic study. J Am Soc Echocardiogr 2014;27:742–8.

Erre GL, Buscetta G, Paliogiannis P, Mangoni AA, Carru C, Passiu G, et al. Coronary flow reserve in systemic rheumatic diseases: a systematic review and meta-analysis. Rheumatol Int 2018;38:1179–90.

Faccini A, Agricola E, Oppizzi M, Margonato A, Galderisi M, Sabbadini MG, et al. Coronary microvascular dysfunction in asymptomatic patients affected by systemic sclerosis — limited vs. diffuse form. Circulation Journal 2015;79:825–9.

Faccini A, Kaski JC, Camici PG. Coronary microvascular dysfunction in chronic inflammatory rheumatoid diseases. Eur Heart J 2016;37:1799–806.

Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, et al. The assessment of endothelial function: from research into clinical practice. Circulation 2012;126:753–67.

Garshick MS, Ward NL, Krueger JG, Berger JS. Cardiovascular risk in patients with psoriasis: JACC review topic of the week. J Am Coll Cardiol 2021;77:1670–80.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735–41.

Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016;118:620–36.

Godo S, Suda A, Takahashi J, Yasuda S, Shimokawa H. Coronary microvascular dysfunction. Arterioscler Thromb Vasc Biol 2021;41:1625–37.

Gullu H, Caliskan M, Dursun R, Ciftci O, Guven A, Muderrisoglu H. Impaired coronary microvascular function and its association with disease duration and inflammation in patients with psoriasis. Echocardiography 2013;30:912–8.

Gupta A, Taqueti VR, van de Hoef TP, Bajaj NS, Bravo PE, Murthy VL, et al. Integrated noninvasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. Circulation 2017;136:2325–36.

Gutiérrez E, Flammer AJ, Lerman LO, Elízaga J, Lerman A, Fernández-Avilés F. Endothelial dysfunction over the course of coronary artery disease. Eur Heart J 2013;34:3175–81.

Hamburg NM, Palmisano J, Larson MG, Sullivan LM, Lehman BT, Vasan RS, et al. Relation of brachial and digital measures of vascular function in the community: the Framingham heart study. Hypertension 2011;57:390–6.

Hellmann M, Roustit M, Cracowski JL. Skin microvascular endothelial function as a biomarker in cardiovascular diseases? Pharmacol Rep 2015;67:803–10.

Ikonomidis I, Makavos G, Papadavid E, Varoudi M, Andreadou I, Gravanis K, et al. Similarities in coronary function and myocardial deformation between psoriasis and coronary artery disease: the role of oxidative stress and inflammation. Can J Cardiol 2015;31:287–95.

Ikonomidis I, Papadavid E, Makavos G, Andreadou I, Varoudi M, Gravanis K, et al. Lowering interleukin-12 activity improves myocardial and vascular function compared with tumor necrosis factor-a antagonism or cyclosporine in psoriasis. Circ Cardiovasc Imaging 2017:10.

Konst RE, Guzik TJ, Kaski JC, Maas AHEM, Elias-Smale SE. The pathogenic role of coronary microvascular dysfunction in the setting of other cardiac or systemic conditions. Cardiovasc Res 2020;116:817–28.

Levy BI, Heusch G, Camici PG. The many faces of myocardial ischaemia and angina. Cardiovasc Res 2019;115:1460–70.

Makavos G, Ikonomidis I, Andreadou I, Varoudi M, Kapniari I, Loukeri E, et al. Effects of interleukin 17A inhibition on myocardial deformation and vascular function in psoriasis. Can J Cardiol 2020;36:100–11.

Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 2010;31:1000–6.

Munger E, Choi H, Dey AK, Elnabawi YA, Groenendyk JW, Rodante J, et al. Application of machine learning to determine top predictors of non-calcified coronary burden in psoriasis: an observational cohort study. J Am Acad Dermatol 2020;83:1647–53.

Nakanishi K, Fukuda S, Shimada K, Miyazaki C, Otsuka K, Maeda K, et al. Impaired coronary flow reserve as a marker of microvascular dysfunction to predict long-term cardiovascular outcomes, acute coronary syndrome and the development of heart failure. Circ J 2012;76:1958–64.

Nakao M, Nakamura K, Fukasawa T, Shida R, Ito A, Ichimura Y, et al. Assessment of endothelial function during the loading phase of infliximab in psoriasis: a potential predictor of its drug survival. Int J Dermatol 2019;58:54–9.

Nguyen H, Chiasson VL, Chatterjee P, Kopriva SE, Young KJ, Mitchell BM. Interleukin-17 causes Rho-kinase-mediated endothelial dysfunction and hypertension. Cardiovasc Res 2013;97:696–704.

Ortolan A, Ramonda R, Lorenzin M, Pesavento R, Spinazzè A, Felicetti M, et al. Subclinical atherosclerosis evolution during 5 years of anti-TNF-alpha treatment in psoriatic arthritis patients. Clin Exp Rheumatol 2021;39:158–61.

Osto E, Piaserico S, Maddalozzo A, Forchetti G, Montisci R, Famoso G, et al. Impaired coronary flow reserve in young patients affected by severe psoriasis. Atherosclerosis 2012;221:113–7.

Piaserico S, Osto E, Famoso G, Montisci R, de Michieli L, Zanetti I, et al. Long-term prognostic value of coronary flow reserve in psoriasis patients. Atherosclerosis 2019;289:57–63.

Piaserico S, Osto E, Famoso G, Zanetti I, Gregori D, Poretto A, et al. Treatment with tumor necrosis factor inhibitors restores coronary microvascular function in young patients with severe psoriasis. Atherosclerosis 2016;251:25–30.

Recio-Mayoral A, Mason JC, Kaski JC, Rubens MB, Harari OA, Camici PG. Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. Eur Heart J 2009;30:1837–43.

Safdar B, Ong P, Camici PG. Identifying myocardial ischemia due to coronary microvascular dysfunction in the emergency department: introducing a new paradigm in acute chest pain evaluation. Clin Ther 2018;40:1920–30.

Schroder J, Michelsen MM, Mygind ND, Suhrs HE, Bove KB, Bechsgaard DF, et al. Coronary flow velocity reserve predicts adverse prognosis in women

with angina and no obstructive coronary artery disease: results from the iPOWER study. Eur Heart J 2021;42:228–39.

Schüler R, Efentakis P, Wild J, Lagrange J, Garlapati V, Molitor M, et al. T cell-derived IL-17A induces vascular dysfunction via perivascular fibrosis formation and dysregulation of NO/cGMP Signaling ˙. Oxid Med Cell Longev 2019;2019:1–15.

Tinggaard AB, Hjuler KF, Andersen IT, Winther S, Iversen L, Bøttcher M. Prevalence and severity of coronary artery disease linked to prognosis in psoriasis and psoriatic arthritis patients: a multi-centre cohort study. J Intern Med 2021;290:693–703.

Vacca A, Montisci R, Garau P, Siotto P, Piga M, Cauli A, et al. Prognostic impact of coronary microcirculation abnormalities in systemic sclerosis: a prospective study to evaluate the role of non-invasive tests. Arthritis Res Ther 2013;15:R8.

Vancheri F, Longo G, Vancheri S, Henein M. Coronary microvascular dysfunction. J Clin Med 2020;9:2880.

von Stebut E, Boehncke WH, Ghoreschi K, Gori T, Kaya Z, Thaci D, et al. IL-17A in psoriasis and beyond: cardiovascular and metabolic implications. Front Immunol 2020;10:3096.

Weber B, Perez-Chada LM, Divakaran S, Brown JM, Taqueti V, Dorbala S, et al. Coronary microvascular dysfunction in patients with psoriasis. J Nucl Cardiol 2022;29:37–42.

Zhou W, Abdelrahman KM, Dey AK, Reddy A, Uceda DE, Lateef SS, et al. Association among noncalcified coronary burden, fractional flow reserve, and myocardial injury in psoriasis. J Am Heart Assoc 2020;9:e017417.

SUPPLEMENTARY MATERIALS AND METHODS

Standard Doppler echocardiography and coronary flow reserve assessment

Transthoracic Doppler echocardiography was performed with a commercially available ultrasound system (Vivid 7, GE Medical System, Horten, Norway). From two-dimensional guided M-mode echocardiograms, left ventricular dimensions were measured by the American Society of Echocardiography convention; left ventricular mass was calculated by the adjusted American Society of Echocardiography method (Ikonomidis et al., 2015) and indexed for body surface area or height. In each subject, ejection fraction was measured, and diastolic dysfunction was defined according to the American Society of Echocardiography criteria (Weber et al., 2022). These criteria integrate Doppler measurements of the mitral inflow and Doppler tissue imaging of the mitral annulus. Coronary images were obtained in the distal part of the left anterior descending artery with a 7-MHz transducer. After baseline recordings of coronary flow velocity, adenosine was intravenously infused (140 μg/kg/min) for 3 minutes, obtaining Doppler flow profiles. Coronary flow reserve was estimated as the ratio of hyperemic to baseline average diastolic coronary flow velocities. A coronary flow reserve value $\leq$ 2.5 was considered abnormal and a marker of CMD, and the population was dichotomized according to this cut-off (Cortigiani et al., 2014; Nakanishi et al., 2012). All subjects did not take calcium antagonists and abstained from caffeine-containing drinks for at least 24 hours before testing. Coronary flow reserve measurements were stored digitally for future offline analysis by two investigators (GF and FT in Padova, GM and II NKUA in Athens) blinded for all clinical variables. The intraobserver and interobserver variability of coronary flow reserve measurements were 4.3% and 5.8%, respectively. The following parameters were evaluated: heart rate at rest and during adenosine infusion; systolic and diastolic arterial pressure at rest (SAPr and DAPr, mmHg); systolic and diastolic arterial pressure during hyperemia (adenosine infusion) (SAPh and DAPh, mmHg); diastolic coronary flow velocity at rest (DFVr, cm/sec); hyperemic diastolic coronary flow velocity (DFVh, cm/sec); and coronary flow reserve.

Multi-slice computed tomography coronary angiography protocol and interpretation

Patients with coronary flow reserve value $\leq$ 2.5 underwent multi-slice computed tomography coronary angiography to exclude significant epicardial coronary artery disease. Coronary multi-slice computed tomography was performed using a 64-slice dual-source scanner (Definition, Siemens Medical System, Forchheim, Germany). To optimize imaging, participants received β-blockade with oral and/or intravenous metoprolol to slow the heart rate to 60–70 beats/minute. An optimized dose modulation approach using helical acquisition and reduced voltage was used to decrease radiation exposure. Coronary multi-slice computed tomography was read by consensus among two cardiologists and radiologists. Coronary multi-slice computed tomography data sets were evaluated for the presence of significant coronary artery stenosis within the left main coronary artery; proximal, mid, and distal segments of the left anterior descending coronary artery; first and second diagonal branches; proximal, mid, and distal segments of the left circumflex coronary artery; first and second marginal branches; proximal, mid, and distal segments of the right coronary artery; and the posterior descending artery according to the 15-segment American Heart Association classification.

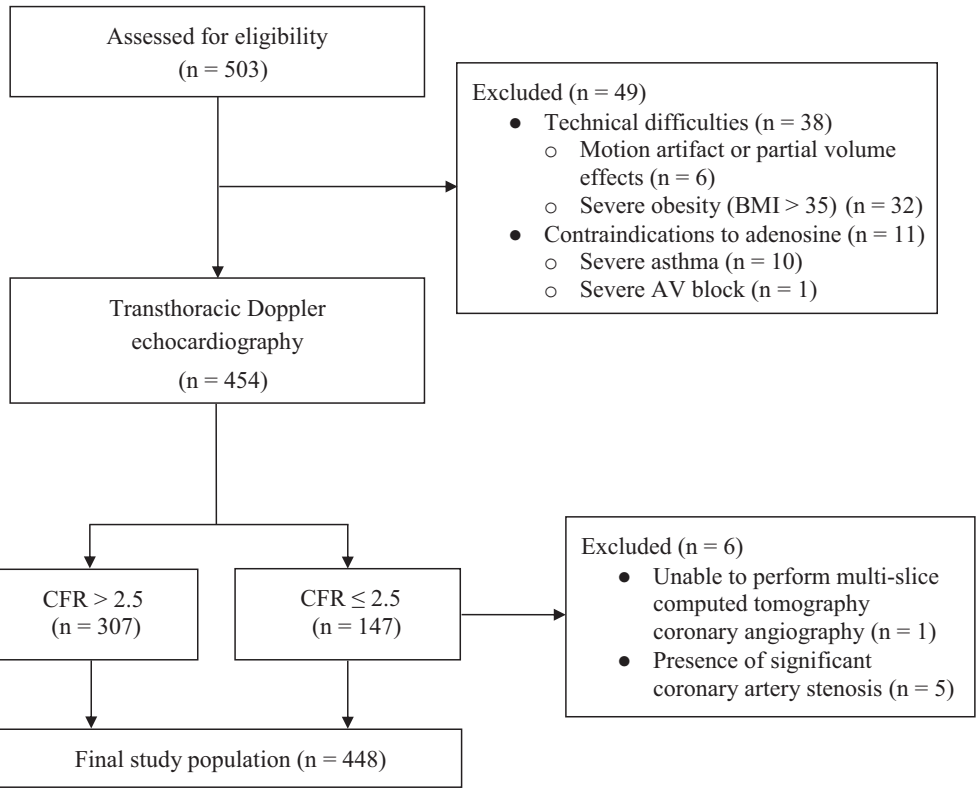
SUPPLEMENTARY REFERENCES

Cortigiani L, Rigo F, Gherardi S, Galderisi M, Bovenzi F, Sicari R. Prognostic meaning of coronary microvascular disease in type 2 diabetes mellitus: A transthoracic Doppler echocardiographic study. J Am Soc Echocardiogr 2014;27:742–8.

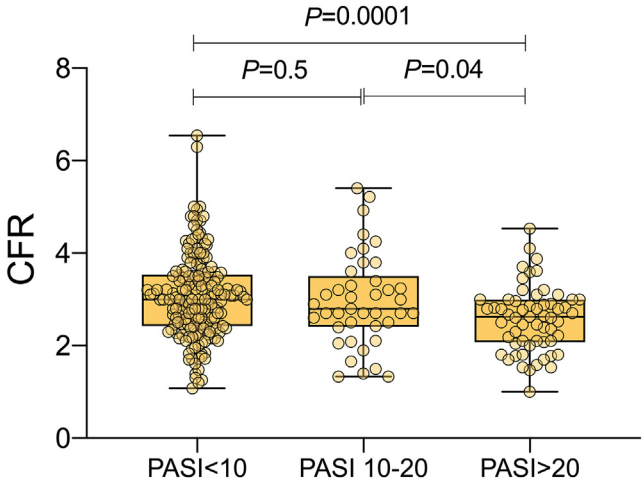
Ikonomidis I, Makavos G, Papadavid E, Varoudi M, Andreadou I, Gravanis K, et al. Similarities in coronary function and myocardial deformation between psoriasis and coronary artery disease: the role of oxidative stress and inflammation. Can J Cardiol 2015;31:287–95.

Nakanishi K, Fukuda S, Shimada K, Miyazaki C, Otsuka K, Maeda K, et al. Impaired coronary flow reserve as a marker of microvascular dysfunction to predict long-term cardiovascular outcomes, acute coronary syndrome and the development of heart failure. Circ J 2012;76:1958–64.

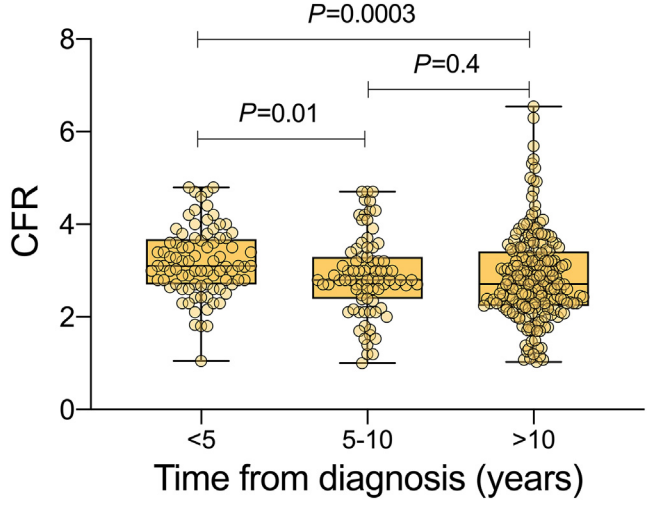
Weber B, Perez-Chada LM, Divakaran S, Brown JM, Taqueti V, Dorbala S, et al. Coronary microvascular dysfunction in patients with psoriasis. J Nucl Cardiol 2022;29:37–42.



Supplementary Figure 1. Flow chart of patient enrollment and exclusion. AV, atrioventricular; BMI, body mass index; CFR, coronary flow reserve.



Supplementary Figure 2. Boxplot illustrating CFR values according to severity of psoriasis: PASI < 10 (moderate), PASI 10–20 (severe), PASI > 20 (very severe). Boxplots describe median values, interquartile ranges, and minimum-maximum values. P-values are shown. Median CFR values were 3.02, 2.85, and 2.51 for patients with PASI < 10, PASI 10–20, and PASI > 20, respectively. Median CFR in patients with PASI > 20 was significantly lower than those in patients with PASI < 10 ($P = 0.0001$) and PASI 10–20 ($P = 0.04$). CFR, coronary flow reserve.



Supplementary Figure 3. Boxplot illustrating CFR values according to duration of psoriasis: <10 years, 10–20 years, >20 years. Boxplots describe median values, interquartile ranges, and minimum-maximum values. *P*-values are shown. Median CFR values were 3, 2.75, and 2.73 for patients with <5, 5–10, and >10 years from diagnosis, respectively. Median CFR in patients with a duration of psoriasis <5 years was significantly lower than those in patients with a duration of psoriasis of 5–10 ($P = 0.01$) and >10 years ($P = 0.0003$). CFR, coronary flow reserve.