BRITISH JOURNAL OF HOSPITAL MEDICINE

SYSTEMATIC REVIEW

Assessment of Subclinical Atherosclerosis in Patients with Psoriasis Using Echocardiographic Coronary Flow Reserve Parameters: A Systematic Review and Meta-Analysis

Hritvik Jain[1], Muhammad Daoud Tariq[2], Abdul Moiz Khan[3], Areeba Ahsan[2], Eeshal Zulfiqar[4], Syeda Shahnoor[4], Jyoti Jain[1], Raheel Ahmed[5,*], Ramez M. Odat[6], Agha Wali[7], Rozi Khan[8]

[1]Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, India
[2]Department of Internal Medicine, Foundation University Medical College, Islamabad, Pakistan
[3]Department of Internal Medicine, Ayub Medical College, Abbottabad, Pakistan
[4]Department of Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan
[5]National Heart and Lung Institute, Imperial College London, London, UK
[6]Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan
[7]Department of Cardiology, University of Arizona, Phoenix, AZ, USA
[8]Department of Internal Medicine, University of Pittsburgh Medical Center, Harrisburg, PA, USA
*Correspondence: raheel-ahmed@doctors.org.uk (Raheel Ahmed)

Abstract

Aims/Background Psoriasis is a chronic inflammatory condition associated with an elevated risk of cardiovascular diseases including coronary artery disease (CAD). This study assessed coronary microvascular dysfunction (CMD) in psoriasis patients using echocardiographic coronary flow parameters, controlling for traditional cardiovascular risk factors and atherosclerosis, to fill gaps identified in previous research.

Methods A comprehensive literature search was performed using multiple electronic databases for studies on echocardiographic coronary flow parameters in patients with psoriasis. The outcomes of interest included the coronary flow velocity reserve (CFVR), hyperemic diastolic peak flow velocity (DPFV), and baseline DPFV. Data were extracted and analyzed using RevMan 5.4 (Nordic Cochrane Center, Copenhagen, Denmark), with pooled standard mean differences (SMDs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set at $p < 0.05$.

Results Four studies involving 557 patients were included in this analysis. Pooled analysis revealed a significant reduction in CFVR in patients with psoriasis compared to controls (SMD: –0.71; 95% CI: –0.97, –0.45; $p < 0.00001$). Hyperemic DPFV was significantly reduced (SMD: –0.71; 95% CI: –1.30, –0.12; $p = 0.02$), whereas baseline DPFV showed no signficant difference (SMD: 0.20; 95% CI: –0.92, 1.32; $p = 0.73$).

Conclusion Psoriasis was associated with reduced CFVR and hyperemic DPFV, suggesting early CMD. CFVR could aid in early CMD detection in psoriasis patients, informing cardiovascular risk management and potential anti-inflammatory treatment benefits.

Systematic Review Registration PROSPERO: CRD42024574085.

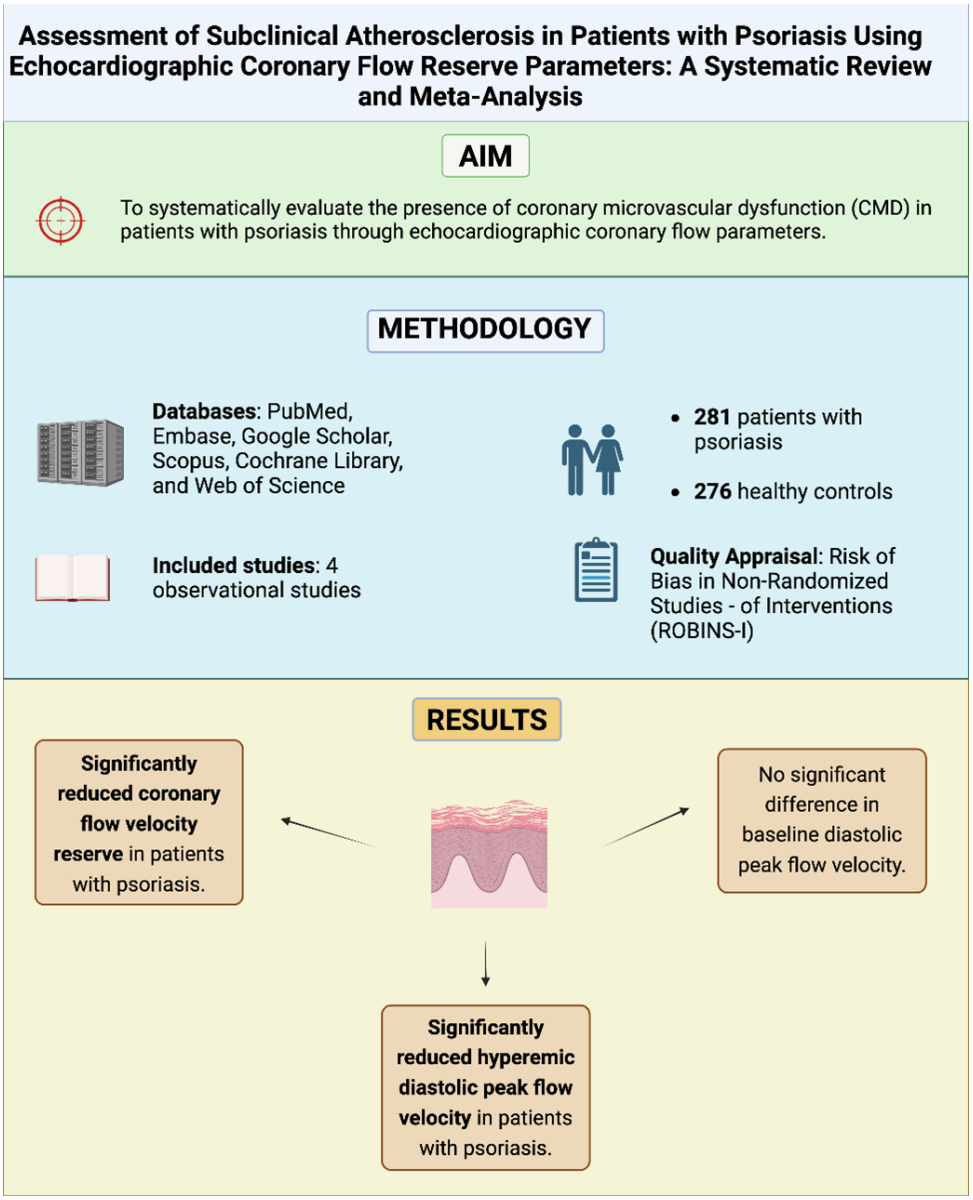
Key words: psoriasis; microcirculation; echocardiography; coronary artery disease; atherosclerosis

Submitted: 6 September 2024 Revised: 29 October 2024 Accepted: 31 October 2024

How to cite this article:
Jain H, Tariq MD, Khan AM, Ahsan A, Zulfiqar E, Shahnoor S, Jain J, Ahmed R, Odat RM, Wali A, Khan R. Assessment of Subclinical Atherosclerosis in Patients with Psoriasis Using Echocardiographic Coronary Flow Reserve Parameters: A Systematic Review and Meta-Analysis. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0618

Introduction

Psoriasis is a chronic inflammatory disease that decreases a patient's quality of life, affecting approximately 125 million or 2–3% of the total world population



Graphical Abstract.

(Armstrong and Read, 2020; Nestle et al, 2009; World Health Organization, 2016). Psoriasis involves the skin and nails, and in 30% of cases, it is associated with joint involvement (Alinaghi et al, 2019). Patients with severe psoriasis are at increased risk of coronary artery disease (CAD), heart failure, and cardiovascular (CV) mortality (Karbach et al, 2020; Khalid et al, 2014; Mehta et al, 2010). The CV risk is the highest in young individuals with severe psoriasis, with a potential 8.2% increase in the mortality rate compared to healthy controls (Gelfand et al, 2006). Although the underlying mechanisms remain unclear, inflammation is thought to play a key role in this association (Gupta et al, 2017).

Coronary flow reserve (CFR), a metric used to assess the health of the coronary arteries and microvascular function, is measured as the ratio of maximal blood flow in the coronary arteries during stress to the blood flow at rest. Impairments in CFR are considered early indicators of CAD and can signal coronary microvascular

dysfunction (CMD) (Britten et al, 2004). Transthoracic Doppler echocardiography (TTDE) and positron emission tomography (PET) are noninvasive methods commonly used to measure CFR. These techniques provide reliable and reproducible assessments, with TTDE showing a strong correlation with PET measurements (Caiati et al, 1999; Saraste et al, 2001). The myocardial flow reserve (MFR), also measured as the ratio of myocardial blood flow during peak stress to that at rest, is assessed using PET and is another important indicator of CAD, atherosclerosis, and CMD (Gupta et al, 2017). Recent studies have demonstrated that many asymptomatic patients with psoriasis have reduced CFR, particularly in the left anterior descending (LAD) artery (Joshi et al, 2018; Piaserico et al, 2019; Weber et al, 2022). However, these studies often do not control for coronary risk factors and atherosclerotic burden, limiting their ability to determine whether reduced CFR is due to CMD or diffuse atherosclerosis.

Despite evidence of the association between psoriasis and increased CV morbidity and mortality, there is a lack of comprehensive research directly comparing CMD in psoriatic patients without considering traditional CV risk factors and atherosclerotic burden. This meta-analysis aimed to address this gap by evaluating the prevalence and implications of CMD in psoriasis patients. By analyzing data from various studies, we sought to determine whether CMD is a distinctive feature of psoriasis. TTDE and PET measurements of the coronary flow reserve will be the focus of the analysis, which will provide a thorough understanding of coronary microvascular function in patients with psoriasis without significant epicardial coronary disease.

Methods

This systematic review and meta-analysis was formulated, conducted, and reported adhering to the guidelines established by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (**Supplementary Table 1**) (Page et al, 2021). The protocol of this review is registered with the PROSPERO registry under the unique identifier number (CRD42024574085), available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=574085.

Data Sources and Search Strategy

A comprehensive literature search was performed across multiple bibliographic databases, including PubMed, Google Scholar, Embase, Scopus, Web of Science, and Cochrane Library, from inception until July 2024 to retrieve studies reporting data on echocardiographic coronary flow parameters in patients with psoriasis. The search strategy employed both Medical Subject Headings (MeSH) terms and free-text keywords related to psoriasis and echocardiographic coronary flow parameters. Specific MeSH terms and free text keywords were used: "Psoriasis" or "Psoriatic disease" or "Coronary Flow Reserve" or "Coronary Flow Velocity" or "Echocardiography" or "Coronary Flow Velocity Reserve" or "Diastolic Peak Flow Velocity" or "Hyperemic Diastolic Peak Flow Velocity" or "Transthoracic Doppler Echocardiography" or "TTDE" or "Positron Emission tomography" OR "PET". Boolean operators such as "AND" and "OR" were used to create a search strategy in combination

with free text keywords. The search was supplemented by manual screening of references from the included studies and relevant review articles to identify additional studies. A detailed search strategy for each database is provided in **Supplementary Table 2**.

Eligibility Criteria and Outcomes

Studies were considered to be eligible for inclusion in our systematic review and meta-analysis if they: (i) included adult patients diagnosed with psoriasis, regardless of disease duration, severity, or treatment status; (ii) assessed echocardiographic coronary flow measurements, including coronary flow velocity reserve (CFVR), baseline diastolic peak flow velocity (DPFV), and hyperemic DPFV; (iii) compared coronary flow measurements between psoriasis patients and age- and sex-matched healthy controls without psoriasis or any known cardiovascular diseases; (iv) reported on at least one of the following outcomes: CFVR, baseline DPFV, or hyperemic DPFV; and (v) were randomized controlled trials or observational cohort studies. Reviews, case reports, expert opinions, conference presentations, and duplicate publications were also excluded. No restrictions were imposed on sample size or publication year.

Study Selection and Data Extraction

All identified studies were imported into the reference management software EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA), and duplicate records were removed. Two independent reviewers (AA and MDT) screened the titles and abstracts for eligibility based on predefined inclusion criteria. The full-text manuscripts of the potentially eligible studies were retrieved and assessed independently by the same reviewers. Any disagreements were resolved through discussion or consultation with a third reviewer (HJ).

Two authors (HJ and MDT) independently extracted the data using a pre-piloted Microsoft Excel spreadsheet. The data extracted from each eligible study included author name, year of publication, country of origin, study design, total sample size in both groups, mean age, male %, inclusion criteria, exclusion criteria, and baseline patient characteristics, such as heart rate, blood pressure, and other comorbidities.

Quality Assessment of the Included Studies

Quality assessment of the observational studies was conducted by using the Cochrane Risk of Bias in Nonrandomized Studies-of Interventions (ROBINS-I) tool (Sterne et al, 2016). The ROBINS-I tool is a unique tool since it uses seven domains to quantify the overall bias in every included non-randomized clinical trial. Studies were classified as having a low, moderate, serious, or critical risk of bias. Studies with missing information in one or more domains were classified as non-informative (NI).

Statistical Synthesis and Data Analysis

Statistical analysis was conducted using Review Manager (RevMan) Version 5.4.1 (Nordic Cochrane Center, Copenhagen, Denmark). Statistical analysis involved calculating pooled standard mean differences (SMDs) and 95% confidence

intervals (CIs) to estimate the continuous variables. The DerSimonian-Laird random-effects model was used to pool results to account for inter-study heterogeneity (DerSimonian and Laird, 1986). The results were visualized through the generation of forest plots. Heterogeneity across trials was assessed using the Higgins I^2 test (Higgins et al, 2003), interpreted as mild (25%–50%), moderate (50%–75%), or high (>75%). Statistical significance was set at $p < 0.05$. Leave-one-out sensitivity analyses were performed to investigate the origin of the potential heterogeneity by excluding one study at a time, allowing us to evaluate the contribution of each study to the overall estimate. Publication bias was not evaluated through either visual inspection of funnel plots or statistical regression tests because of the lower statistical accuracy of those tests in meta-analyses with fewer than 10 included studies (10.2.1 Publication bias, n.d.).

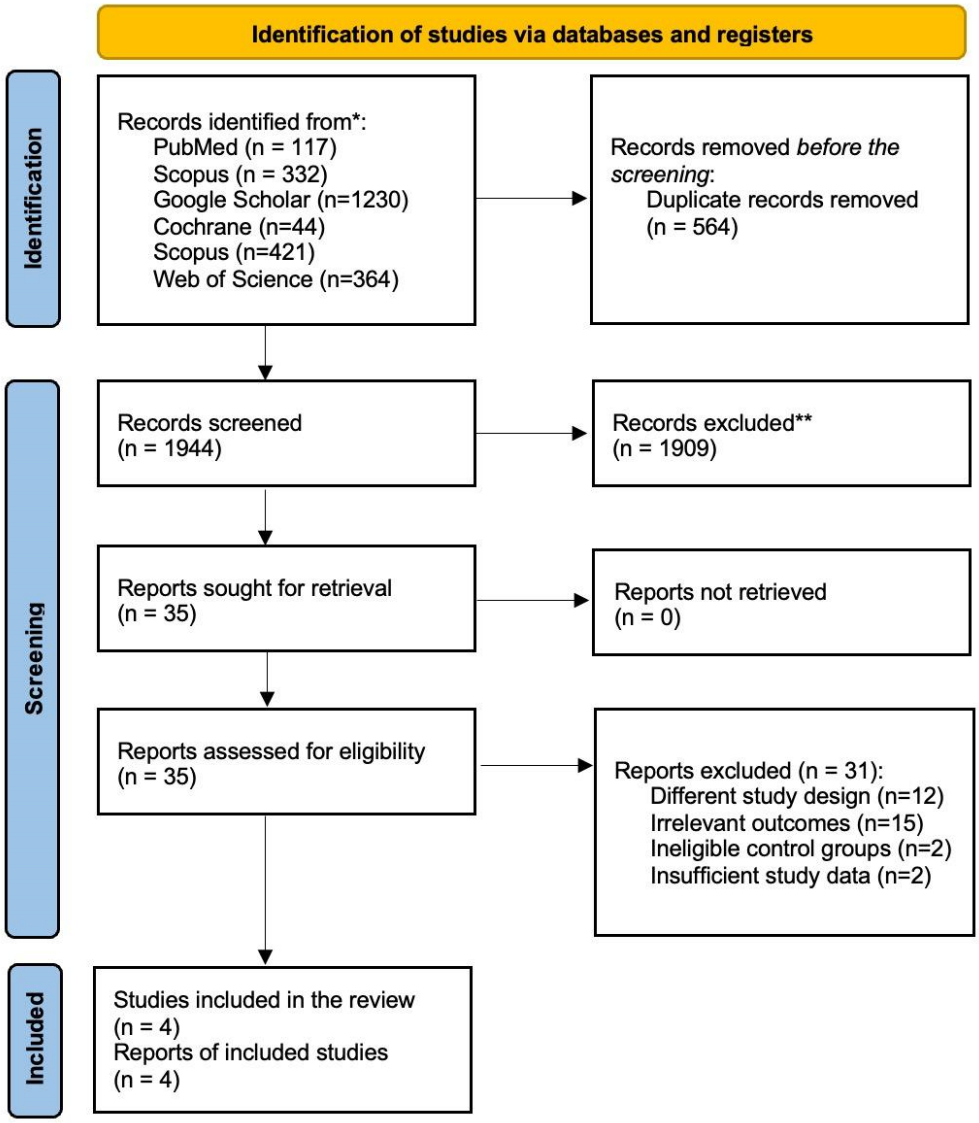


Fig. 1. The 2020 preferred reporting items for systematic reviews and meta-analyses flowchart.
* databases or registers, ** in title/abstract screening.

Results

Study Selection

After conducting an extensive search across multiple databases, we initially identified 2508 potentially relevant articles. During the removal of duplicates, we removed 564 articles. Following the initial title and abstract screening (n = 1944), 1909 articles were excluded as did not meet our inclusion criteria. Following the preliminary screening, 35 articles were subjected to an in-depth detailed assessment. Upon further screening, 12 articles were dismissed due to different study designs, 15 due to irrelevant outcomes, 2 due to ineligible control groups, and 2 due to insufficient data. Ultimately, 4 studies met our criteria and were included in the meta-analysis. The detailed steps of our literature search are illustrated in the PRISMA flowchart (Fig. 1).

Study and Patient Characteristics

After an extensive screening process, we identified 4 observational studies for this meta-analysis (Gullu et al, 2013; Osto et al, 2012b; Tona et al, 2022; Weber et al, 2022). These studies included a total of 557 patients: 281 in the psoriasis group and 276 in the control group. The mean age of participants in the psoriasis and control groups were 44.75 $\pm$ 7.73 years and 45.17 $\pm$ 5.97 years, respectively. The detailed baseline characteristics of these studies and patient demographic details are provided in Table 1. A summary of the inclusion and exclusion criteria for the studies is shown in **Supplementary Table 3**.

Endpoints

The outcome of CFVR was reported by all the included studies (Gullu et al, 2013; Osto et al, 2012b; Tona et al, 2022; Weber et al, 2022). In the pooled analysis, a statistically significant difference was observed between the two groups (SMD: –0.71; 95% CI: –0.97, –0.45; $p < 0.00001$; $I^2 = 50\%$) (Fig. 2A). Moderate heterogeneity was observed among studies. Upon performing a leave-one-out sensitivity analysis, the heterogeneity was reduced to zero after excluding Gullu et al (2013) (**Supplementary Fig. 1**).

Baseline DPFV as an outcome was reported in three studies (Gullu et al, 2013; Osto et al, 2012b; Tona et al, 2022). Based on the pooled analysis, the two groups did not reach statistical significance (SMD: 0.20; 95% CI: –0.92, 1.32; $p = 0.73$; $I^2 = 96\%$) (Fig. 2B). A high heterogeneity was observed among the studies. Heterogeneity was reduced to a moderate level ($I^2 = 68\%$) upon performing the leave-one-out sensitivity analysis, excluding Gullu et al (2013) (**Supplementary Fig. 2)**.

Three studies reported the outcomes of hyperemic DPFV (Gullu et al, 2013; Osto et al, 2012b; Tona et al, 2022). Pooled analysis showed a statistically significant difference between the two groups (SMD: –0.71; 95% CI: –1.30, –0.12; $p = 0.02$; $I^2 = 86\%$) (Fig. 2C). A high heterogeneity was observed among the studies. The leave-one-out sensitivity analysis reduced the heterogeneity to zero after excluding Tona et al (2022) from the analysis (**Supplementary Fig. 3**).

Table 1. Baseline characteristics of these studies and patients' demographic details.

Study ID	Country of origin	Study design	Participants, n		Sex (Males), n		Age (years), Mean ± SD		Body Mass Index (kg/m^2), Mean ± SD		Heart rate (beats/min), Mean ± SD		Systolic blood pressure (mmHg), Mean ± SD		Diastolic blood pressure (mmHg), Mean ± SD		E/A ratio, Mean ± SD		Ejection fraction (%), Mean ± SD		Hypertension, n (%)		Current smokers, n (%)	
			Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control	Psoriasis	Control
Osto et al (2012b)	Italy	Observational study	56	56	42	42	37 ± 3	37 ± 3	25 ± 3	25 ± 3	74 ± 13	NR	121 ± 21	NR	76 ± 10	NR	1.4 ± 0.6	NR	60 ± 2	NR	7 (12.5)	NR	18 (32)	NR
Gullu et al (2013)	Turkey	Observational study	36	56	NR	NR	36.4 ± 8.1	35.1 ± 6.6	26.9 ± 2.9	27.2 ± 2.8	72.2 ± 4.8	71.6 ± 4.3	117.3 ± 7.1	118.5 ± 12.4	75.3 ± 4.4	75.4 ± 7.5	NR	NR	NR	NR	NR	NR	NR	NR
Tona et al (2022)	Italy	Observational study	127	52	104	43	36 ± 8	40 ± 3	NR	NR	NR	NR	NR	NR	NR	NR	1.49 ± 0.32	1.51 ± 0.21	61 ± 3	62 ± 3	NR	NR	NR	NR
Weber et al (2022)	United States	Observational study	62	112	44	76	69.6 ± 11.8	68.6 ± 11.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	48 (77.4)	84 (75)	6 (9.7)	7 (6.3)

Abbreviations: NR, Not reported; SD, standard deviation.

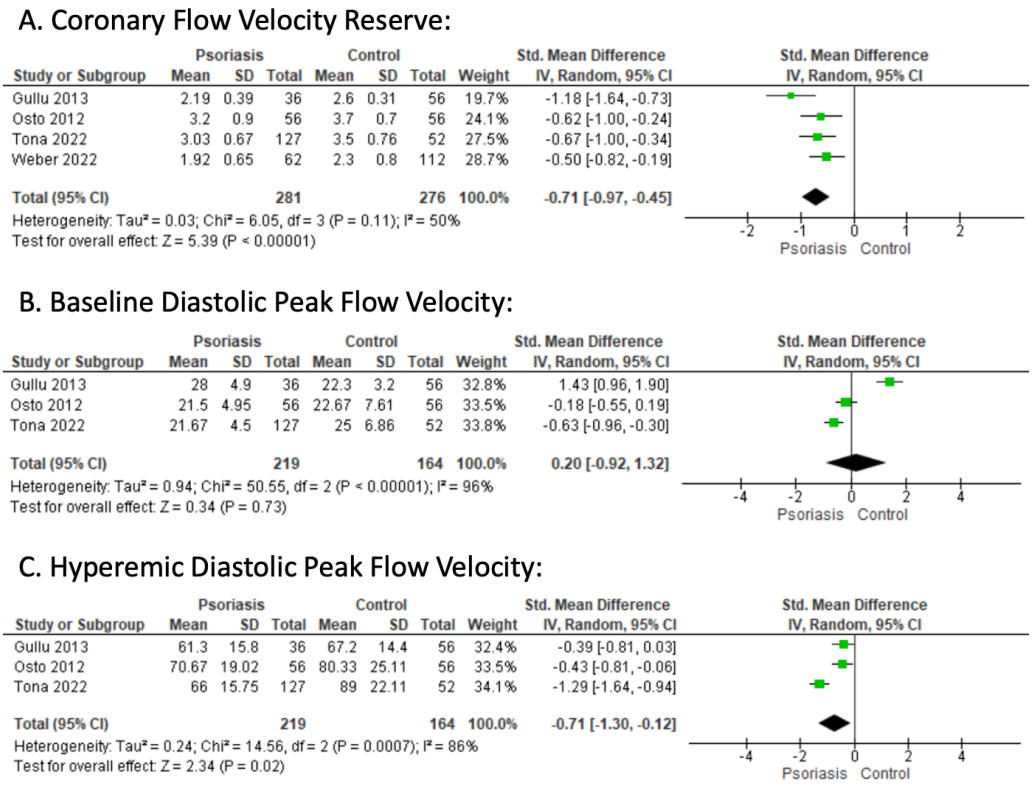


Fig. 2. Individual and pooled analyses illustrating the efficacy of echocardiographic coronary flow parameters in the assessment of subclinical atherosclerosis in psoriasis patients. The standardized mean differences (SMD) with the 95% confidence intervals (CI) are displayed using a logarithmic scale, with the box scaling in accordance with the sample size. The diamond symbolizes the combined or overall effect. (A) Coronary flow velocity reserve [SMD: –0.71; 95% CI: –0.97, –0.45; $p < 0.00001$]. (B) Baseline diastolic peak flow velocity [SMD: 0.20; 95% CI: –0.92, 1.32; $p = 0.73$]. (C) Hyperemic diastolic peak flow velocity [SMD: –0.71; 95% CI: –1.30, –0.12; $p = 0.02$].

Risk of Bias Assessment

The risk of bias for most of the included studies was determined to be "low" according to the ROBINS-I (Fig. 3). However, Osto et al (2012b) showed "some concerns".

Discussion

Psoriasis significantly reduces CFVR, a key indicator of coronary microvascular function. The CFVR measures the capacity of the coronary microcirculation to enhance blood flow during stress and is calculated as the ratio of hyperemic DPFV to baseline DPFV (Tona et al, 2022). This measure reflects the heart's ability to adapt to blood flow to meet increased metabolic demands (Gould et al, 1974). In patients with psoriasis with normal epicardial arteries (Piaserico et al, 2019; Weber et al, 2022), impaired CFVR suggests CMD, which may arise from structural or functional abnormalities. These abnormalities could result from an elevated baseline DPFV with reduced baseline coronary microvascular resistance or diminished

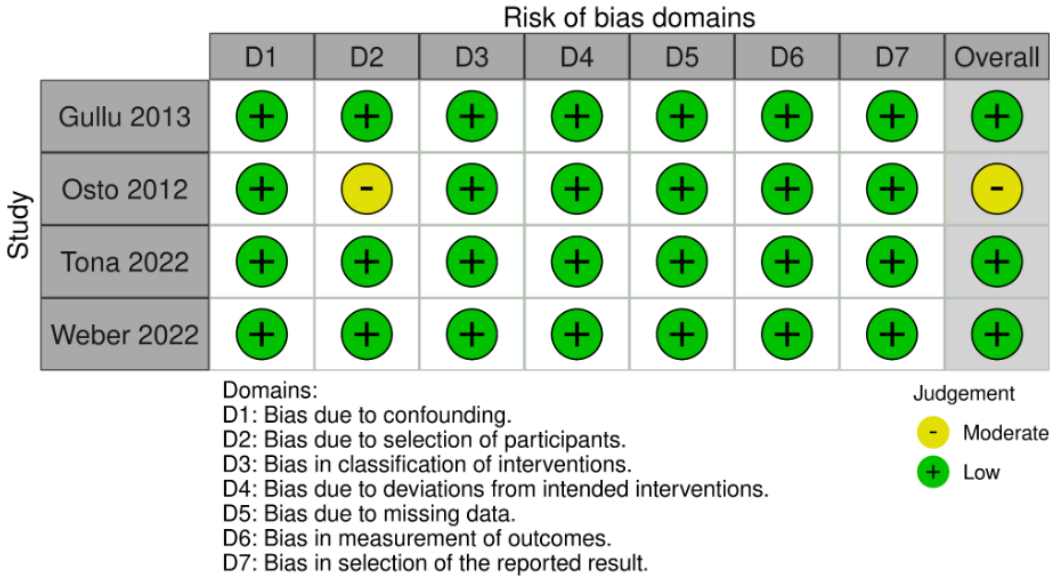


Fig. 3. Risk of bias assessment using the ROBINS-I tool.

hyperemic DPFV due to high microvascular resistance during hyperemia, indicating impaired vasodilation (Camici and Crea, 2007).

CFVR impairment in psoriasis can be detected before visible CAD and in the absence of traditional risk factors, indicating that inflammation may drive early CMD (Britten et al, 2004; Gullu et al, 2013). Echocardiographic CFVR assessment is a sensitive marker for CAD, especially when the epicardial arteries appear normal (Hozumi et al, 1998). Prolonged Mitral E-wave Deceleration Time (DT) and Isovolumic Relaxation Time (IVRT) further suggest early cardiac involvement related to reduced CFVR even without overt symptoms (Galderisi et al, 2002). Chronic inflammation in psoriasis accelerates atherosclerosis by damaging blood vessels, reducing nitric oxide availability, and causing microvascular rarefaction (Libby and Crea, 2010; Nakai et al, 2009). Elevated levels of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), impair endothelial and microvascular function. Inflammation-driven endothelial dysfunction leads to CMD, partly due to elevated endothelin-1 activity (Takahashi et al, 2010; Vaccarino et al, 2011). Thus, impaired CFVR serves as an early indicator of CAD and can predict atherosclerosis even in mild cases of psoriasis (Friedewald et al, 2008; Ishimori et al, 2011). Psoriasis affects arterial physiology, leading to micro- and macrovascular dysfunction in terms of arterial stiffening and atherosclerosis (Elnabawi et al, 2019). Oxidative stress also plays a major role in potentiating inflammation and driving progression to CMD. Increased systemic production of reactive oxygen species (ROS), including hydrogen peroxide and superoxide anions, paired with simultaneous activation of the noxious redox-sensitive pathways (Galis and Khatri, 2002; Scioli et al, 2020). All of the pathways mentioned above terminate at triggering systemic and coronary vascular dysfunction leading to CMD. Further research is needed to clarify and delineate the biochemical mechanisms involved in CMD specifically.

Reduced hyperemic DPFV in psoriasis patients indicates diminished maximal blood flow during stress. This observation may indicate impaired vasodilation or diminished capacity of the coronary microvasculature in response to increased demand. Investigators attribute the observed hemodynamic patterns to two factors: (1) structural changes in the microvasculature (Sezer et al, 2016), and (2) functional alterations, as evidenced by improvements following therapy (Ikonomidis et al, 2017). Osto et al (2012b) findings support the notion that functional factors contribute to diminished arteriolar vasodilatory capacity and CFVR. This is evidenced by the normalization of CFVR in most patients after six months of treatment with immune-inflammatory modulators, such as TNF-α inhibitors and interleukin blockers, despite the absence of additional cardiovascular risk factors (Ikonomidis et al, 2017; Osto et al, 2012a). Ikonomidis et al (2017) enrolled 150 psoriasis patients and randomized them to receive ustekinumab (n = 50), anti-TNF-α (n = 50), and cyclosporine (n = 50). By comparing baseline values to follow-up values at 4 months, they demonstrated a significant improvement (normalization) in CFR from 2.8 to 3.1—this improvement was most significant in those psoriasis patients who were treated with anti-IL-12/23 agent (ustekinumab). The normalization of physiological parameters was also observed in global longitudinal strain, left ventricular twist, and circulating levels of N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), TNF-α, and other inflammatory cytokines. Another study by Piaserico et al (2016) evaluated the effect of TNF-α inhibitors in young psoriasis patients (mean age = 37.7 years). They demonstrated a significant improvement in CFR from 2.2 at baseline to 3.02 at follow-up ($p < 0.0001$) (Piaserico et al, 2016). This reinforces the importance of timely treatment with anti-inflammatory and biologic medications to reverse microvascular dysfunction and systemic inflammation in psoriasis. Additionally, further prospective studies are required to evaluate this normalization effect of psoriatic therapies across varying severity of psoriasis and to also investigate other potential therapeutics that lead to the reversal of CMD.

Normalization and improvement of the psoriasis area and severity index (PASI) and CFVR values reflect functional improvements and functional aspects of the disease. Various methods, such as PET, cardiac magnetic resonance imaging, and cardiac catheterization, measure the coronary flow. PET is the gold standard for efficiency (Saraste et al, 2001), but it is limited in availability and challenging to perform. In our analysis, all studies except Weber et al (2022) used echocardiography for CFVR measurement. Although not the gold standard, echocardiography is practical, non-invasive, cost-effective, and typically completes a CFVR test in approximately 15 minutes (Caiati et al, 1999). The PASI, the gold standard for assessing psoriasis severity, evaluates psoriatic plaques on a scale from 0 to 4. PASI correlates with coronary microvascular dysfunction, independent of traditional cardiovascular risk factors (Coimbra et al, 2010; Paul et al, 2010; Takahashi et al, 2010). Multivariable analyses identified PASI as the sole determinant of CFVR $\leq$2.5 (Osto et al, 2012b). Targeted anti-inflammatory treatments also enhance this functional aspect of the disease (Makavos et al, 2020), supporting our observations of CFVR and PASI scores.

Likewise, our study observed a slight increase in the baseline DPFV, although this change was not statistically significant. This modest increase may suggest an initial increase in blood flow velocity in patients with psoriasis, potentially reflecting underlying adaptations or changes in the coronary vessels. However, the change in baseline DPFV remains controversial; one study in our meta-analysis reported an increase (Gullu et al, 2013), whereas two others indicated a decrease (Osto et al, 2012b; Tona et al, 2022). Baseline DPFV directly influences CFVR, which is calculated as the ratio of hyperemic DPFV to baseline DPFV (Tona et al, 2022). CFVR, a dimensionless ratio comparing maximum flow during stress to baseline flow, may not reveal significant structural changes in coronary flow if both baseline and hyperemic DPFV increase proportionally. In some patients, despite treatment, a decline in CFVR was observed (Tona et al, 2022). This decline is accompanied by low flow velocities and high microvascular resistance, suggesting potential irreversible structural changes such as reduced vascular capacity and fibrosis, which may not be fully captured by CFVR alone.

To address this limitation, Tona et al (2022) used a complementary metric, cCFVR, which offers a more detailed assessment by capturing the variations in both coronary flow velocity measured during hyperemic conditions (CFV_h) and maximal diastolic coronary flow velocity at rest (CFV_r) more effectively than the traditional CFVR ratio. cCFVR, calculated as the quadratic mean, offers physical units (cm/s) and is thus more effective in detecting structural CMD and variations in microvascular function (Diaz-Navarro and Kerkhof, 2021; Kerkhof et al, 2019a,b). Because CFVR is a dimensionless ratio, it may not fully capture these structural changes, leading to the proposal of cCFVR, which is calculated as the quadratic mean (Kerkhof et al, 2019a,b). This combined approach helps to elucidate CMD better.

CMD as a finding is seen in numerous other diseases other than psoriasis. Inflammatory bowel disease, including Crohn disease and ulcerative colitis, demonstrates significantly reduced CFVR in patients, that improves on treatment of the underlying condition (Kakuta et al, 2021). Even infectious diseases like COVID-19 have demonstrated significant alterations in CFVR, which also shows correlation with the severity of the infection—the more severe the infection, the lower the CFVR is (Çalışkan et al, 2022). Systemic disorders like systemic sclerosis have also been shown to significantly alter CFR, and its significant reduction has been proposed to be an indirect marker of cardiac involvement in the disease (Sulli et al, 2004). In patients with hypertrophic cardiomyopathy, a lower CFVR has been associated with impaired biventricular systolic function as well as functional capacity (Aguiar Rosa et al, 2022). The aforementioned various clinical diseases all demonstrate a significant reduction in CFVR that corresponds to CMD, hence, underscoring the importance of CMD in detecting cardiovascular dysfunction.

Our findings suggest that CFVR monitoring in patients with psoriasis can reveal early coronary microvascular dysfunction before visible CAD develops. Utilizing cCFVR offers a more nuanced evaluation of both structural and functional changes in coronary microcirculation compared to traditional CFVR. Furthermore,

targeted anti-inflammatory treatments can enhance CFVR and PASI scores, reflecting functional improvements in the disease.

Limitations

Our meta-analysis had several limitations. First, the small sample size of the included studies and the limited number of studies limited the strength and generalizability of our conclusions. This also affected the statistical power, particularly in detecting significant differences related to coronary flow parameters. These studies relied on echocardiography for measuring CFVR, which, although practical and non-invasive, is not the gold standard compared to intracoronary methods or PET imaging. Additionally, the lack of data on inflammatory markers prevents us from exploring the relationships between CFR and other cytokines such as TNF-α or IL-6. Furthermore, the absence of histological data or detailed assessments of myocardial fibrosis and other biomarkers restricts our ability to fully understand the pathophysiological mechanisms underlying CMD in psoriasis patients. Future studies with larger sample sizes, varied demographics, and additional biomarkers are required to provide more comprehensive insights into the relationship between psoriasis and CMD.

Conclusion

Our meta-analysis highlights a significant reduction in CFVR and hyperemic DPFV among patients with psoriasis, suggesting early CMD, even in the absence of overt CAD. CMD stems from various underlying mechanisms including inflammation, oxidative stress, etc. These findings emphasize that patients with psoriasis should undergo routine cardiovascular evaluation to detect and manage CMD effectively. Further research with larger cohorts and more comprehensive assessments is needed to deepen our understanding of CMD in psoriasis.

Key Points

- CMD can be identified using echocardiographic coronary flow parameters.
- Psoriasis leads to a significant reduction in CFVR and hyperemic DPFV compared to controls.
- No significant reduction in baseline DPFV was noted in psoriasis.
- Even in the absence of overt CAD, psoriasis patients should undergo CFVR evaluation as it can facilitate early targeted intervention.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

HJ: Conceptualization, Methodology, Formal Analysis, Writing — Original Draft, Writing — Review & Editing; MDT: Investigation, Formal Analysis, Writing — Original Draft, Writing — Review & Editing; AMK: Investigation, Writing — Original Draft, Writing — Review & Editing; AA: Investigation, Writing — Original Draft, Writing — Review & Editing; EZ: Methodology, Writing — Original Draft, Writing — Review & Editing; SS: Investigation, Writing — Original Draft, Writing — Review & Editing; JJ: Investigation, Conceptualization, Supervision, Writing — Original Draft, Writing — Review & Editing; RA: Project Administration, Validation, Writing — Original Draft, Writing — Review & Editing; RMO: Validation, Writing — Original Draft, Writing — Review & Editing; AW: Validation, Writing — Original Draft, Writing — Review & Editing; RK: Investigation, Conceptualization, Supervision, Resources, Writing — Original Draft, Writing — Review & Editing. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0618.

References

10.2.1 Publication bias. (n.d.). Available at: https://handbook-5-1.cochrane.org/chapter_10/10_2_1_publication_bias.htm (Accessed: 12 August 2024).

Aguiar Rosa S, Lopes LR, Branco L, Galrinho A, Fiarresga A, Thomas B, et al. Blunted coronary flow velocity reserve is associated with impairment in systolic function and functional capacity in hypertrophic cardiomyopathy. International Journal of Cardiology. 2022; 359: 61–68. https://doi.org/10.1016/j.ijcard.2022.04.032

Alinaghi F, Calov M, Kristensen LE, Gladman DD, Coates LC, Jullien D, et al. Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies. Journal of the American Academy of Dermatology. 2019; 80: 251–265.e19. https://doi.org/10.1016/j.jaad.2018.06.027

Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA. 2020; 323: 1945–1960. https://doi.org/10.1001/jama.2020.4006

Britten MB, Zeiher AM, Schächinger V. Microvascular dysfunction in angiographically normal or mildly diseased coronary arteries predicts adverse cardiovascular long-term outcome. Coronary Artery Disease. 2004; 15: 259–264. https://doi.org/10.1097/01.mca.0000134590.99841.81

Caiati C, Zedda N, Montaldo C, Montisci R, Iliceto S. Contrast-enhanced transthoracic second harmonic echo Doppler with adenosine: a noninvasive, rapid and effective method for coronary flow reserve assessment. Journal of the American College of Cardiology. 1999; 34: 122–130. https://doi.org/10.1016/s0735-1097(99)00164-3

Çalışkan M, Baycan ÖF, Çelik FB, Güvenç TS, Atıcı A, Çağ Y, et al. Coronary microvascular dysfunction is common in patients hospitalized with COVID-19 infection. Microcirculation. 2022; 29: e12757. https://doi.org/10.1111/micc.12757

Camici PG, Crea F. Coronary microvascular dysfunction. The New England Journal of Medicine. 2007; 356: 830–840. https://doi.org/10.1056/NEJMra061889

Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. C-reactive protein and leucocyte activation in psoriasis vulgaris according to severity and therapy. Journal of the European Academy of Dermatology and Venereology. 2010; 24: 789–796. https://doi.org/10.1111/j.1468-3083.2009.03527.x

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986; 7: 177–188. https://doi.org/10.1016/0197-2456(86)90046-2

Diaz-Navarro RA, Kerkhof PLM. Left Ventricular Global Function Index and the Impact of its Companion Metric. Frontiers in Cardiovascular Medicine. 2021; 8: 695883. https://doi.org/10.3389/fcvm.2021.695883

Elnabawi YA, Oikonomou EK, Dey AK, Mancio J, Rodante JA, Aksentijevich M, et al. Association of Biologic Therapy With Coronary Inflammation in Patients With Psoriasis as Assessed by Perivascular Fat Attenuation Index. JAMA Cardiology. 2019; 4: 885–891. https://doi.org/10.1001/jamacardio.2019.2589

Friedewald VE, Cather JC, Gelfand JM, Gordon KB, Gibbons GH, Grundy SM, et al. AJC editor's consensus: psoriasis and coronary artery disease. The American Journal of Cardiology. 2008; 102: 1631–1643. https://doi.org/10.1016/j.amjcard.2008.10.004

Galderisi M, Cicala S, Caso P, De Simone L, D'Errico A, Petrocelli A, et al. Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. The American Journal of Cardiology. 2002; 90: 860–864. https://doi.org/10.1016/s0002-9149(02)02708-x

Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circulation Research. 2002; 90: 251–262.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006; 296: 1735–1741. https://doi.org/10.1001/jama.296.14.1735

Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. The American Journal of Cardiology. 1974; 33: 87–94. https://doi.org/10.1016/0002-9149(74)90743-7

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: 912–918. https://doi.org/10.1111/echo.12156

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: 2325–2336. https://doi.org/10.1161/CIRCULATIONAHA.117.029992

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Research Ed.). 2003; 327: 557–560. https://doi.org/10.1136/bmj.327.7414.557

Hozumi T, Yoshida K, Ogata Y, Akasaka T, Asami Y, Takagi T, et al. Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. Circulation. 1998; 97: 1557–1562. https://doi.org/10.1161/01.cir.97.16.1557

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. Circulation. Cardiovascular Imaging. 2017; 10: e006283. https://doi.org/10.1161/CIRCIMAGING.117.006283

Ishimori ML, Martin R, Berman DS, Goykhman P, Shaw LJ, Shufelt C, et al. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. JACC. Cardiovascular Imaging. 2011; 4: 27–33. https://doi.org/10.1016/j.jcmg.2010.09.019

Joshi AA, Lerman JB, Dey AK, Sajja AP, Belur AD, Elnabawi YA, et al. Association Between Aortic Vascular Inflammation and Coronary Artery Plaque Characteristics in Psoriasis. JAMA Cardiology. 2018; 3: 949–956. https://doi.org/10.1001/jamacardio.2018.2769

Kakuta K, Dohi K, Yamamoto T, Fujimoto N, Shimoyama T, Umegae S, et al. Coronary Microvascular Dysfunction Restored After Surgery in Inflammatory Bowel Disease: A Prospective Observational Study. Journal of the American Heart Association. 2021; 10: e019125. https://doi.org/10.1161/JAHA.120.019125

Karbach S, Hobohm L, Wild J, Münzel T, Gori T, Wegner J, et al. Impact of Psoriasis on Mortality Rate and Outcome in Myocardial Infarction. Journal of the American Heart Association. 2020; 9: e016956. https://doi.org/10.1161/JAHA.120.016956

Kerkhof PLM, Osto E, Tona F, Heyndrickx GR, Handly N. Sex-Specific Interpretation of Coronary Flow Reserve and Fractional Flow Reserve Metrics, Including Their Companions. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference. 2019a; 2019: 7006–7009. https://doi.org/10.1109/EMBC.2019.8857589

Kerkhof PLM, Peace RA, Handly N. Ratiology and a Complementary Class of Metrics for Cardiovascular Investigations. Physiology. 2019b; 34: 250–263. https://doi.org/10.1152/physiol.00056.2018

Khalid U, Ahlehoff O, Gislason GH, Kristensen SL, Skov L, Torp-Pedersen C, et al. Psoriasis and risk of heart failure: a nationwide cohort study. European Journal of Heart Failure. 2014; 16: 743–748. https://doi.org/10.1002/ejhf.113

Libby P, Crea F. Clinical implications of inflammation for cardiovascular primary prevention. European Heart Journal. 2010; 31: 777–783. https://doi.org/10.1093/eurheartj/ehq022

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. The Canadian Journal of Cardiology. 2020; 36: 100–111. https://doi.org/10.1016/j.cjca.2019.06.021

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. European Heart Journal. 2010; 31: 1000–1006. https://doi.org/10.1093/eurheartj/ehp567

Nakai K, Yoneda K, Maeda R, Munehiro A, Fujita N, Yokoi I, et al. Urinary biomarker of oxidative stress in patients with psoriasis vulgaris and atopic dermatitis. Journal of the European Academy of Dermatology and Venereology. 2009; 23: 1405–1408. https://doi.org/10.1111/j.1468-3083.2009.03327.x

Nestle FO, Kaplan DH, Barker J. Psoriasis. The New England Journal of Medicine. 2009; 361: 496–509. https://doi.org/10.1056/NEJMra0804595

Osto E, Fallo F, Pelizzo MR, Maddalozzo A, Sorgato N, Corbetti F, et al. Coronary microvascular dysfunction induced by primary hyperparathyroidism is restored after parathyroidectomy. Circulation. 2012a; 126: 1031–1039. https://doi.org/10.1161/CIRCULATIONAHA.111.081307

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. 2012b; 221: 113–117. https://doi.org/10.1016/j.atherosclerosis.2011.12.015

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical Research Ed.). 2021; 372: n71. https://doi.org/10.1136/bmj.n71

Paul C, Gourraud PA, Bronsard V, Prey S, Puzenat E, Aractingi S, et al. Evidence-based recommendations to assess psoriasis severity: systematic literature review and expert opinion of a panel of dermatologists. Journal of the European Academy of Dermatology and Venereology. 2010; 24: 2–9. https://doi.org/10.1111/j.1468-3083.2009.03561.x

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. https://doi.org/10.1016/j.atherosclerosis.2019.08.009

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. https://doi.org/10.1016/j.atherosclerosis.2016.05.036

Saraste M, Koskenvuo J, Knuuti J, Toikka J, Laine H, Niemi P, et al. Coronary flow reserve: measurement with transthoracic Doppler echocardiography is reproducible and comparable with positron emission tomography. Clinical Physiology. 2001; 21: 114–122. https://doi.org/10.1046/j.1365-2281.2001.00296.x

Scioli MG, Storti G, D'Amico F, Rodríguez Guzmán R, Centofanti F, Doldo E, et al. Oxidative Stress and New Pathogenetic Mechanisms in Endothelial Dysfunction: Potential Diagnostic Biomarkers and Therapeutic Targets. Journal of Clinical Medicine. 2020; 9: 1995. https://doi.org/10.3390/jcm9061995

Sezer M, Kocaaga M, Aslanger E, Atici A, Demirkiran A, Bugra Z, et al. Bimodal Pattern of Coronary Microvascular Involvement in Diabetes Mellitus. Journal of the American Heart Association. 2016; 5: e003995. https://doi.org/10.1161/JAHA.116.003995

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical Research Ed.). 2016; 355: i4919. https://doi.org/10.1136/bmj.i4919

Sulli A, Ghio M, Bezante GP, Deferrari L, Craviotto C, Sebastiani V, et al. Blunted coronary flow reserve in systemic sclerosis. Rheumatology. 2004; 43: 505–509. https://doi.org/10.1093/rheumatology/keh087

Takahashi H, Tsuji H, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Serum cytokines and growth factor levels in Japanese patients with psoriasis. Clinical and Experimental Dermatology. 2010; 35: 645–649. https://doi.org/10.1111/j.1365-2230.2009.03704.x

Tona F, Osto E, Kerkhof PLM, Montisci R, Famoso G, Lorenzoni G, et al. Multiparametric analysis of coronary flow in psoriasis using a coronary flow reserve companion. European Journal of Clinical Investigation. 2022; 52: e13711. https://doi.org/10.1111/eci.13711

Vaccarino V, Khan D, Votaw J, Faber T, Veledar E, Jones DP, et al. Inflammation is related to coronary flow reserve detected by positron emission tomography in asymptomatic male twins. Journal of the American College of Cardiology. 2011; 57: 1271–1279. https://doi.org/10.1016/j.jacc.2010.09.074

Weber B, Perez-Chada LM, Divakaran S, Brown JM, Taqueti V, Dorbala S, et al. Coronary microvascular dysfunction in patients with psoriasis. Journal of Nuclear Cardiology. 2022; 29: 37–42. https://doi.org/10.1007/s12350-020-02166-5

World Health Organization. Global report on psoriasis. 2016. Available at: https://iris.who.int/handle/10665/204417 (Accessed: 18 August 2024).