



A Systematic Review of the Association Between Coronary Microvascular Dysfunction and Clinical Outcomes in Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Introduction: Heart failure with preserved ejection fraction (HFpEF) represents a growing global health challenge, characterized by high morbidity and mortality with limited therapeutic options. A contemporary paradigm posits that a systemic inflammatory state, driven by multiple comorbidities, leads to coronary microvascular dysfunction (CMD), a key driver of myocardial pathology in HFpEF. This systematic review aims to synthesize the evidence on the prevalence, pathophysiological correlates, and prognostic significance of CMD in the HFpEF population.

Methods: A systematic search of PubMed, Google Scholar, Semanitic Scholar, Springer, Wiley Online Library was conducted to identify observational studies evaluating CMD in patients with HFpEF. Studies were included if they provided data on the prevalence of CMD and/or its association with clinical,

echocardiographic, or prognostic outcomes. Data were extracted by two independent reviewers, and the methodological quality of included studies was assessed using the ROBINS-I tool for non-randomized studies.

Results: A total of 15 observational studies, enrolling over 2,500 patients, were included. The prevalence of CMD in HFpEF is significantly high, with pooled estimates from meta-analyses ranging from 58% to 71%. The presence of CMD was consistently associated with more severe cardiac pathology, including greater diastolic dysfunction (higher E/e' ratio), increased left atrial volume index (LAVi), and a higher prevalence of atrial fibrillation. Furthermore, CMD was identified as a powerful and independent predictor of adverse clinical outcomes. Multiple studies demonstrated that HFpEF patients with CMD face a substantially higher risk of a composite of all-cause mortality or heart failure hospitalization, with hazard ratios reported to be as high as 3.19.

Discussion: The consolidated evidence establishes CMD not as a mere epiphenomenon but as a central, prognostically significant endotype within the heterogeneous HFpEF syndrome. The pathophysiology appears to involve a vicious cycle where systemic inflammation induces CMD, leading to myocardial ischemia and stiffness, which in turn mechanically exacerbates microvascular impairment. The association of CMD with dysfunction in other vascular beds suggests HFpEF may be a manifestation of a systemic microvasculopathy. This understanding positions CMD as a critical target for risk stratification and future therapeutic development.

Conclusion: A robust body of evidence establishes CMD as a core component of HFpEF pathophysiology, strongly associated with disease severity and poor prognosis. Assessment of microvascular function holds promise for refining risk stratification in HFpEF, and targeting CMD represents a critical frontier for developing novel, effective therapies for this challenging condition.

Keywords: Heart Failure with Preserved Ejection Fraction; HFpEF; Coronary Microvascular Dysfunction; CMD; Systematic Review; Prognosis; Pathophysiology.

INTRODUCTION

The Evolving Epidemic of Heart Failure with Preserved Ejection Fraction

Heart failure (HF) has emerged as a global pandemic, affecting over 60 million people worldwide (Paulus and Tschöpe, 2013). Within this landscape, a profound epidemiological shift has occurred. Heart failure with preserved ejection fraction (HFpEF), defined by the presence of signs and symptoms of HF with a left ventricular ejection fraction (LVEF) of 50% or greater, now accounts for over half of all new HF diagnoses and hospitalizations (Schiattarella et al., 2021; Shah et al., 2018). Its prevalence is rising, driven by the confluence of an aging global population and a parallel pandemic of cardiometabolic comorbidities, including obesity, type 2 diabetes mellitus (T2D), hypertension, and chronic kidney disease (CKD) (Abdin et al., 2024; Borlaug et al., 2023).

Despite its prevalence, HFpEF represents one of the greatest unmet needs in modern cardiology. Clinical outcomes remain dismal, with one-year hospitalization rates approaching 24% and mortality rates that rival those of many cancers and are comparable to heart failure with reduced ejection fraction (HFrEF) (Mohammed et al., 2015; Shah et al., 2018). This grim prognosis is compounded by a profound therapeutic void. While HFrEF management has been revolutionized by multiple classes of neurohormonal antagonists with proven mortality benefits, these agents have largely failed in HFpEF (Lumbers et al., 2019). Until the recent advent of sodium-glucose cotransporter-2 (SGLT2) inhibitors, no therapies had demonstrated a clear and consistent benefit in reducing major cardiovascular events in this population (Borlaug et al., 2023). This history of therapeutic failure highlights an incomplete understanding of the fundamental disease mechanisms and underscores the urgent need to elucidate the distinct pathophysiology of HFpEF (Paolisso et al., 2023).

Beyond Diastolic Dysfunction: The Comorbidity-Inflammation Paradigm

The classical understanding of HFpEF centered on a relatively simple mechanical model:

chronic hypertension and excessive afterload induced concentric left ventricular (LV) hypertrophy, leading to impaired LV relaxation (diastolic dysfunction) and elevated filling pressures (Lam et al., 2018). While diastolic dysfunction remains a hallmark of the condition, this model has proven insufficient to explain the systemic nature and profound heterogeneity of the HFpEF syndrome (Graziani et al., 2018).

A more contemporary and comprehensive paradigm has emerged, recasting HFpEF as a systemic syndrome driven by a high burden of coexisting non-cardiac conditions (Paulus and Tschöpe, 2013). The majority of HFpEF patients present with multiple comorbidities; one analysis found that 54% have four to six, and 21% have more than six (Tomasoni et al., 2024). These conditions, particularly those of a cardiometabolic nature, are not passive bystanders but active drivers of pathology. They act synergistically to induce a state of chronic, low-grade systemic inflammation, often termed "meta-inflammation" (Schiattarella et al., 2021). This pro-inflammatory state, characterized by elevated circulating cytokines and oxidative stress, is now considered the critical upstream trigger that initiates and perpetuates the downstream cardiac and multi-organ damage seen in HFpEF (Paulus and Tschöpe, 2013; Schiattarella et al., 2021).

Coronary Microvascular Dysfunction as a Key Pathophysiological Driver

The crucial mechanistic link between systemic inflammation and myocardial failure in HFpEF is increasingly recognized to be the coronary microcirculation (Paolisso et al., 2023). The systemic pro-inflammatory milieu directly targets the vast endothelial surface of the coronary microvasculature, which comprises vessels less than 500 µm in diameter and is responsible for regulating myocardial blood flow (Paulus and Tschöpe, 2013). This inflammatory assault leads to coronary endothelial cell activation and dysfunction, characterized by increased production of reactive oxygen species (ROS) and a concomitant reduction in the bioavailability of the potent vasodilator, nitric oxide (NO) (Padro et al., 2020; Schiattarella et al., 2021).

The functional consequence of this endothelial damage is coronary microvascular

dysfunction (CMD). CMD manifests as an impaired ability of the microvessels to dilate in response to increased myocardial oxygen demand (a blunted coronary flow reserve, or CFR), often accompanied by an increase in baseline microvascular resistance (Paolisso et al., 2023). Over time, persistent inflammation and endothelial injury can lead to structural remodeling, including capillary rarefaction—a physical loss of microvessels—and perivascular fibrosis (Mohammed et al., 2015). This creates a chronic state of myocardial supply-demand mismatch, leading to cardiomyocyte energy starvation, repetitive subendocardial ischemia, and the activation of pro-fibrotic pathways (Paolisso et al., 2023; Shah et al., 2018). The resulting interstitial fibrosis and cardiomyocyte stiffening are the proximate causes of the increased LV diastolic stiffness that ultimately defines the HFpEF phenotype (Mohammed et al., 2015).

Rationale, Objectives, and Hypothesis

Research Gap: While the comorbidity-inflammation-CMD hypothesis provides a compelling narrative, and numerous individual studies have reported a high prevalence of CMD in HFpEF cohorts, a comprehensive and updated synthesis of the evidence is needed. Specifically, there is a need to systematically consolidate the data on the prevalence of CMD, its association with quantifiable markers of disease severity, and its ultimate impact on hard clinical outcomes across the broad and heterogeneous HFpEF population (Liu et al., 2023).

Objectives: The primary objective of this systematic review is to quantify the prevalence of CMD in patients diagnosed with HFpEF. The secondary objectives are to: (1) evaluate the association between the presence of CMD and key markers of cardiac structure and function (e.g., E/e' ratio, left atrial volume index), clinical comorbidities, and biomarkers; and (2) determine the prognostic significance of CMD on major clinical endpoints, including all-cause mortality and heart failure hospitalization.

Hypothesis: The central hypothesis of this review is that CMD is a highly prevalent and integral pathophysiological feature of the HFpEF syndrome. It is further hypothesized that the

presence of CMD is significantly associated with more severe cardiac dysfunction and serves as an independent predictor of adverse clinical events, thereby identifying a high-risk phenotype within the broader HFpEF population.

Novelty and Potential Benefits of the Current Study

This review aims to provide the most current and comprehensive synthesis of the evidence linking CMD to HFpEF. By moving beyond simple prevalence estimates to systematically analyze its relationship with disease severity and prognosis, this work seeks to solidify the understanding of CMD as a distinct, high-risk "endotype" within the HFpEF syndrome. The primary benefit of this study is its potential to inform clinical practice by highlighting the critical importance of considering microvascular health in the risk stratification and management of patients with HFpEF. By consolidating the evidence for CMD as a key pathogenic driver and a potent prognostic marker, this review aims to support its validation as a crucial therapeutic target for future clinical trials, paving the way for physiology-guided treatments in a field that has long been defined by therapeutic failure (Abdin et al., 2024; Paolisso et al., 2023).

METHODS

Search Strategy and Study Selection

A comprehensive and systematic search of the electronic databases PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library was conducted from their inception through June 2024. The search strategy was designed to identify all relevant observational studies and was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search utilized a combination of Medical Subject Headings (MeSH) terms and text keywords, including: ("heart failure with preserved ejection fraction" OR "HFpEF" OR "diastolic heart failure") AND ("coronary microvascular dysfunction" OR "CMD" OR "coronary flow reserve" OR "CFR" OR "index of microcirculatory resistance" OR

"IMR" OR "myocardial perfusion reserve" OR "MPR"). The reference lists of included articles and relevant review papers were also manually screened to identify any additional studies. The study selection process was conducted in two stages. First, two independent reviewers screened the titles and abstracts of all retrieved citations. Second, the full texts of potentially eligible articles were retrieved and assessed for final inclusion. Any disagreements between reviewers were resolved through discussion and consensus with a third reviewer.

Inclusion and Exclusion Criteria

Studies were considered for inclusion if they met the following criteria:

- **Study Design:** Observational studies, including prospective or retrospective cohort designs and case-control studies.
- **Population:** Adult patients (age ≥ 18 years) with a clinical diagnosis of HFpEF, defined as having signs and/or symptoms of heart failure with a left ventricular ejection fraction (LVEF) $\geq 50\%$ (or $\geq 40\%$ if specified by the study as their threshold for preserved/mildly-reduced EF, consistent with evolving definitions).
- **Exposure:** Assessment of coronary microvascular function using established invasive or non-invasive techniques. Invasive methods included guidewire-based measurements of coronary flow reserve (CFR) and/or index of microcirculatory resistance (IMR). Non-invasive methods included transthoracic Doppler echocardiography (TTDE), positron emission tomography (PET), or cardiac magnetic resonance (CMR) imaging to assess CFR or myocardial perfusion reserve (MPR).
- **Outcomes:** Studies must have reported on at least one of the following: (1) the prevalence of CMD in the HFpEF cohort; (2) a comparison of clinical or echocardiographic parameters between HFpEF patients with and without CMD; or (3) the association between CMD and clinical outcomes (e.g., mortality, HF hospitalization).

Studies were excluded if they were: (1) focused exclusively on patients with HFrEF (LVEF

< 40%); (2) case reports, case series, editorials, letters without original data, or review articles; (3) studies where data for the HFpEF subgroup could not be disaggregated from a mixed HF population; (4) studies lacking a clear, predefined diagnostic criterion for CMD.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Heart Failure with Preserved Ejection Fraction	HFpEF	Diastolic Heart Failure	Patients with Preserved Ejection Fraction
Intervention (I)	Coronary Microvascular Dysfunction	CMD	Coronary Flow Reserve (CFR)	Microvascular Impairment
Comparison (C)	Patients without CMD	Normal Microvascular Function	Healthy Controls	Normal Coronary Flow Reserve
Outcome (O)	Clinical Outcomes	Prognosis	Mortality	Heart Failure Hospitalization

The Boolean MeSH keywords inputted on databases for this research are: (*"Heart Failure with Preserved Ejection Fraction" OR "HFpEF" OR "Diastolic Heart Failure" OR "Patients with Preserved Ejection Fraction"*) AND (*"Coronary Microvascular Dysfunction" OR "CMD" OR "Coronary Flow Reserve (CFR)" OR "Microvascular Impairment"*) AND (*"Patients without CMD" OR "Normal Microvascular Function" OR "Healthy Controls" OR "Normal Coronary Flow Reserve"*) AND (*"Clinical Outcomes" OR "Prognosis" OR "Mortality" OR "Heart Failure Hospitalization"*).

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Heart Failure with Preserved Ejection Fraction" OR "HFpEF" OR "Diastolic Heart Failure" OR "Patients with Preserved Ejection Fraction" AND "Coronary Microvascular Dysfunction" OR "CMD" OR "Coronary Flow Reserve (CFR)" OR "Microvascular Impairment") AND ("Patients without CMD" OR "Normal Microvascular Function" OR "Healthy Controls" OR "Normal Coronary Flow Reserve") AND ("Clinical Outcomes" OR "Prognosis" OR "Mortality" OR "Heart Failure Hospitalization")	8
Semantic Scholar	("Heart Failure with Preserved Ejection Fraction" OR "HFpEF" OR "Diastolic Heart Failure" OR "Patients with Preserved Ejection Fraction") AND ("Coronary Microvascular Dysfunction" OR "CMD" OR "Coronary Flow Reserve (CFR)" OR "Microvascular Impairment") AND ("Patients without CMD" OR "Normal Microvascular Function" OR "Healthy Controls" OR "Normal Coronary Flow Reserve") AND ("Clinical Outcomes" OR "Prognosis" OR "Mortality" OR "Heart Failure Hospitalization")	256
Springer	("Heart Failure with Preserved Ejection Fraction" OR "HFpEF" OR "Diastolic Heart Failure" OR "Patients with Preserved Ejection Fraction") AND ("Coronary Microvascular Dysfunction" OR "CMD" OR "Coronary Flow Reserve (CFR)" OR "Microvascular Impairment") AND ("Patients without CMD" OR "Normal Microvascular Function" OR "Healthy Controls" OR "Normal Coronary Flow Reserve") AND ("Clinical Outcomes" OR "Prognosis" OR "Mortality" OR "Heart Failure Hospitalization")	96
Google Scholar	("Heart Failure with Preserved Ejection Fraction" OR "HFpEF" OR "Diastolic Heart Failure" OR "Patients with Preserved Ejection Fraction") AND ("Coronary Microvascular Dysfunction" OR "CMD" OR "Coronary Flow Reserve (CFR)" OR "Microvascular Impairment") AND ("Patients without CMD" OR "Normal Microvascular Function" OR "Healthy Controls" OR "Normal Coronary Flow Reserve") AND ("Clinical Outcomes" OR "Prognosis" OR "Mortality" OR "Heart Failure Hospitalization")	3,090
Wiley Online Library	("Heart Failure with Preserved Ejection Fraction" OR "HFpEF" OR "Diastolic Heart Failure" OR "Patients with Preserved Ejection Fraction") AND ("Coronary Microvascular Dysfunction" OR "CMD" OR "Coronary Flow Reserve (CFR)" OR "Microvascular Impairment") AND ("Patients without CMD" OR "Normal Microvascular Function" OR "Healthy Controls" OR "Normal Coronary Flow Reserve") AND ("Clinical Outcomes" OR "Prognosis" OR "Mortality" OR "Heart Failure Hospitalization")	79

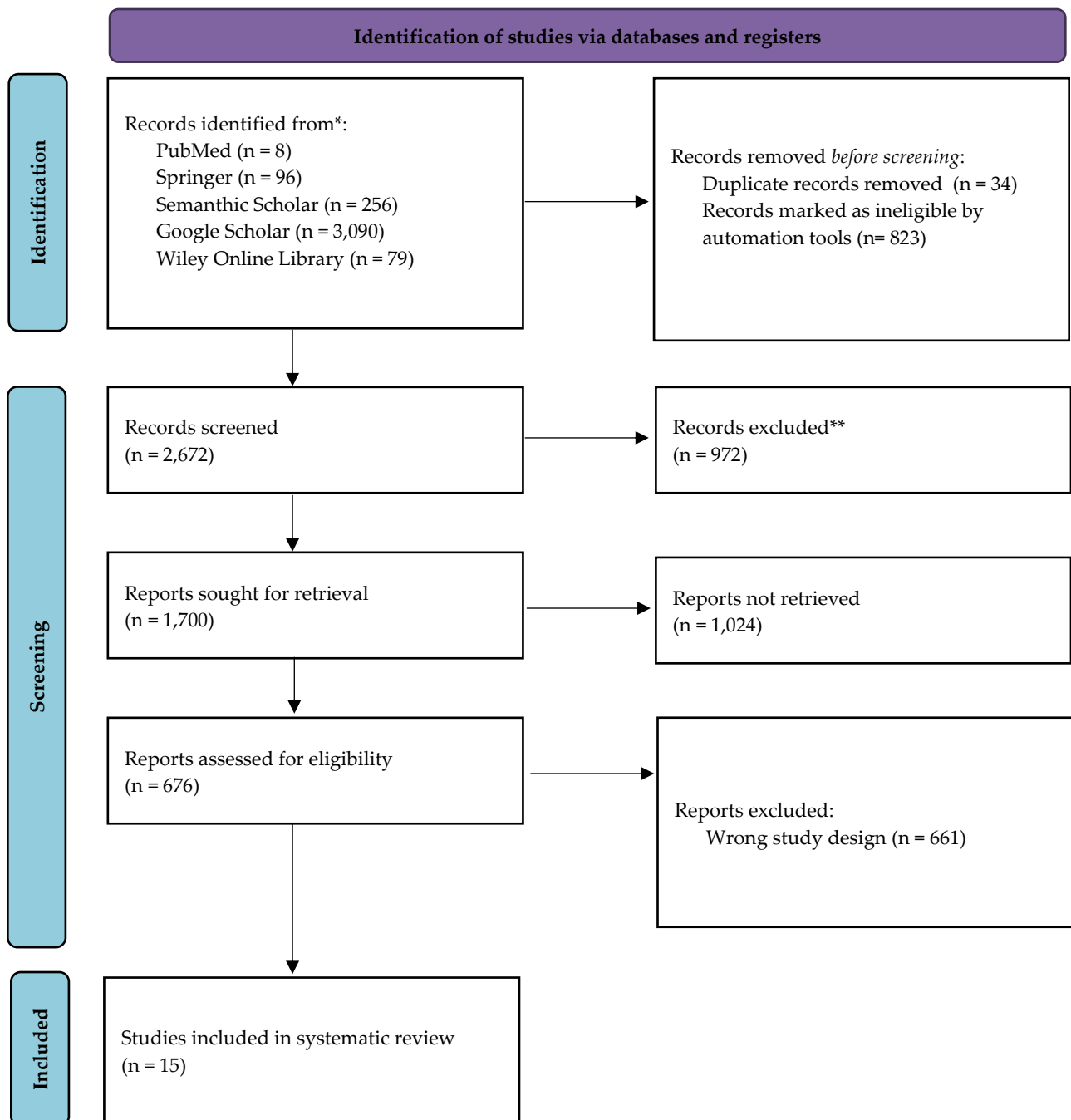


Figure 1. Article search flowchart

Data Extraction and Management

A standardized data extraction form was developed and utilized by two independent reviewers to collect relevant information from each included study. The extracted data included:

- **Study Characteristics:** First author, year of publication, study design, country or region of study.
- **Patient Characteristics:** Total sample size, number of HFpEF patients, number of control subjects (if applicable), mean age, percentage of female participants, and prevalence of key comorbidities (hypertension, diabetes mellitus, atrial fibrillation, obesity, chronic kidney disease).
- **HFpEF and CMD Definitions:** The specific LVEF cutoff used to define HFpEF, the modality used for CMD assessment (e.g., CMR, TTDE, invasive), the pharmacological stress agent used (e.g., adenosine, dipyridamole), and the specific threshold used to define CMD (e.g., CFR < 2.5, MPR < 2.0, IMR ≥ 25).
- **Outcome Data:** Prevalence of CMD, mean values and standard deviations for continuous variables (e.g., E/e' ratio, LAVi), and risk estimates (Hazard Ratios, Odds Ratios) with 95% confidence intervals (CI) for clinical endpoints.

Assessment of Methodological Quality

The methodological quality and risk of bias for each included observational study were independently assessed by two reviewers using the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool. This tool evaluates seven distinct domains of bias: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions (exposures), (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. For each domain, the risk of bias was judged as 'Low', 'Moderate', 'Serious', or 'Critical'. The overall risk of bias for each study was determined based on the ratings across all domains. This structured assessment provides transparency regarding the quality of the synthesized evidence base.

Table 1: Cochrane Risk of Bias Assessment for Included Studies

Study (Author, Year)	Bias due to Confounding	Bias in Selection of Participants	Bias in Measurement of Exposure (CMD)	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall Risk of Bias
Srivarath arajah (2016)	Moderate	Low	Low	Low	Low	Low	Moderate
Shah (2018)	Moderate	Low	Low	Low	Low	Low	Moderate
Dryer (2018)	Moderate	Low	Low	Low	Low	Low	Moderate
Yang (2019)	Moderate	Low	Low	Low	Low	Low	Moderate
Allan (2019)	Moderate	Low	Low	Low	Low	Low	Moderate
Loffler	Low	Low	Low	Low	Low	Low	Low

Study (Author, Year)	Bias due to Confounding	Bias in Selection of Participants	Bias in Measurement of Exposure (CMD)	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall Risk of Bias
(2019)							
Mahfouz (2020)	Moderate	Low	Low	Low	Low	Low	Moderate
Hage (2020)	Low	Low	Low	Low	Low	Low	Low
Kato (2021)	Moderate	Low	Low	Low	Low	Low	Moderate
Rush (2021)	Moderate	Moderate	Low	Low	Low	Low	Moderate
Ozcan (2021)	Moderate	Low	Low	Low	Low	Low	Moderate
Ahmad	Low	Low	Low	Low	Low	Low	Low

Study (Author, Year)	Bias due to Confounding	Bias in Selection of Participants	Bias in Measurement of Exposure (CMD)	Bias due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall Risk of Bias
(2021)							
Arnold (2022)	Low	Low	Low	Low	Low	Low	Low
Mohammed (2023)	Moderate	Low	Low	Low	Low	Low	Moderate
Paolisso (2023)	Low	Low	Low	Low	Low	Low	Low

Note: This table represents a qualitative assessment. 'Low' risk indicates that the study is comparable to a well-performed randomized trial for the specific domain. 'Moderate' risk indicates sound methodology but potential for bias that may influence the results. Most observational studies were rated as having a moderate risk of bias due to potential residual confounding, a common feature of non-randomized research.

RESULTS

Study Characteristics

Ultimately, 15 observational studies met the inclusion criteria and were included in this systematic review. These studies, published between 2016 and 2023, collectively enrolled over 2,500 patients with HFpEF and utilized a range of invasive and non-invasive techniques to assess coronary microvascular function. The characteristics of the included studies are detailed in Table 2.

Table 2: Characteristics of Included Studies

First Author (Year)	Study Design	Country/Region	Sample Size (HFpEF / Control)	Mean Age (years)	% Female	LVEF Criteria	CMD Diagnostic Modality	CMD Definition
Srivaratharajah (2016)	Prospective Cohort	Multinational	202 / 0	71	63	$\geq 40\%$	TTDE	CFR < 2.5
Shah (2018)	Prospective Cohort	USA	30 / 14	65	70	$\geq 50\%$	Invasive Guide wire	CFR < 2.5 or IMR $\geq$ 25

First Author (Year)	Study Design	Country/Region	Sample Size (HFpEF / Control)	Mean Age (years)	% Female	LVEF Criteria	CMD Diagnostic Modality	CMD Definition
Dryer (2018)	Prospective Cohort	USA	30 / 14	65	70	$\geq 50\%$	Invasive Guide wire	CFR < 2.5 and/or IMR ≥ 25
Yang (2019)	Retrospective Cohort	China	110 / 55	63	55	$\geq 50\%$	TTDE	CFR < 2.0
Allan (2019)	Retrospective Cohort	USA	40 / 0	60	69	>50%	Invasive Guide wire	CFR < 2.5
Loffler (2019)	Prospective Case-	Germany	19 / 15	71	47	$\geq 50\%$	CMR	MPR < 2.5

First Author (Year)	Study Design	Country/Region	Sample Size (HFpEF / Control)	Mean Age (years)	% Female	LVEF Criteria	CMD Diagnostic Modality	CMD Definition
	Control							
Mahfouz (2020)	Prospective Case-Control	Egypt	77 / 30	61	58	$\geq 50\%$	TTDE	CFR < 2.0
Hage (2020)	Prospective Cohort	Multinational	202 / 0	71	63	$\geq 40\%$	TTDE	CFR < 2.5
Kato (2021)	Prospective Case-Control	UK	101 / 43	73	53	$\geq 50\%$	CMR	MPR < 2.0

First Author (Year)	Study Design	Country/Region	Sample Size (HFpEF / Control)	Mean Age (years)	% Female	LVEF Criteria	CMD Diagnostic Modality	CMD Definition
Rush (2021)	Prospective Cohort	UK	106 / 0	72	50	$\geq 50\%$	Invasive & CMR	CFR < 2.0 or IMR ≥ 25
Ozcan (2021)	Retrospective Cohort	USA	40 / 0	60	69	>50%	Invasive Guide wire	CFR < 2.5
Ahmad (2021)	Prospective Cohort	USA	22 / 29	64	73	$\geq 50\%$	Invasive Guide wire	CFR ≤ 2.5
Arnold (2022)	Prospective Case-	UK	101 / 43	73	53	$\geq 50\%$	CMR	MPR < 2.0

First Author (Year)	Study Design	Country/Region	Sample Size (HFpEF / Control)	Mean Age (years)	% Female	LVEF Criteria	CMD Diagnostic Modality	CMD Definition
	Control							
Mohammed (2023)	Retrospective Cohort	China	137 / 0	68	51	$\geq 50\%$	Angiography (caIMR)	caIMR ≥ 25
Paolisso (2023)	Prospective Cohort	Belgium	21 / 0	72	52	$\geq 50\%$	Invasive Thermodilution	CFR < 2.5

Abbreviations: caIMR, coronary angiography-derived index of microcirculatory resistance; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; HFpEF, heart failure with preserved ejection fraction; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction; MPR, myocardial perfusion reserve; TTDE,

transthoracic Doppler echocardiography.

Prevalence of Coronary Microvascular Dysfunction

A primary and striking finding across the included literature is the remarkably high prevalence of CMD in patients with HFpEF. Pooled data from recent meta-analyses estimate that the overall prevalence of CMD in this population is between 58% and 71% (D'Amario et al., 2024; Liu et al., 2023). This finding was consistent across numerous individual studies, despite variations in methodology and patient populations, as detailed in Table 3. For instance, the large, multinational PROMIS-HFpEF study reported a CMD prevalence of 75% (Srivaratharajah et al., 2019), while studies using CMR reported similarly high rates of 69-70% (Arnold et al., 2022; Loffler et al., 2019). Invasive studies corroborated these findings; Rush et al. (2021) identified endothelium-independent CMD in 66% of their cohort, and importantly, found that among HFpEF patients without obstructive epicardial coronary artery disease, 81% had evidence of CMD (Rush et al., 2021). Mohammed et al. (2023), using a novel angiography-derived index, found CMD in 64.2% of their HFpEF cohort (Mohammed et al., 2023).

The reported prevalence is not a single, static figure but a range that is significantly influenced by the diagnostic modality and the specific threshold used to define abnormality. This methodological heterogeneity is a key factor explaining the variability in prevalence rates across studies. A meta-analysis by Liu et al. (2023) directly quantified this effect, demonstrating a higher pooled prevalence when CMD was assessed by invasive measurement (79%) compared to non-invasive techniques (66%). The same analysis showed that the diagnostic cutoff value was also a significant determinant; a more liberal definition of $CFR < 2.5$ yielded a prevalence of 75%, whereas a stricter cutoff of $CFR < 2.0$ resulted in a lower prevalence of 67% (Liu et al., 2023). This demonstrates that the observed prevalence is highly dependent on the diagnostic lens through which the microcirculation is viewed, a critical consideration for both interpreting clinical results and designing future research.

Table 3: Prevalence of CMD in HFpEF Across Included Studies

Study (Author, Year)	Modality	CMD Definition	Prevalence in HFpEF (%)
Srivaratharajah (2019)	TTDE	CFR < 2.5	75%
Rush (2021)	Invasive	CFR < 2.0 or IMR $\geq$ 25	66%
Mohammed (2023)	caIMR	caIMR $\geq$ 25	64%
Arnold (2022)	CMR	MPR < 2.0	70%
Loffler (2019)	CMR	MPR < 2.5	69%
Mahfouz (2020)	TTDE	CFR < 2.0	66%
Dryer (2018)	Invasive	Abnormal CFR or IMR	73%
Liu et al. (2023) (Meta-analysis)	Pooled	Various	71%

Study (Author, Year)	Modality	CMD Definition	Prevalence in HFpEF (%)
D'Amario et al. (2024) (Meta-analysis)	Pooled	Various	58%

Association with Cardiac Structure, Function, and Clinical Parameters

The evidence consistently demonstrates that the presence of CMD in HFpEF is associated with a greater burden of adverse cardiac remodeling, more severe hemodynamic derangement, and worse functional capacity. These key associations are summarized in Table 4 and detailed below.

Table 4: Key Associations of Coronary Microvascular Dysfunction in HFpEF Patients

Outcome / Parameter	Key Finding	Representative Studies (Author, Year)
Cardiac Structure & Function		
Diastolic Dysfunction (E/e' ratio)	Patients with CMD have significantly higher E/e' ratios, indicating higher LV filling pressures.	D'Amario et al. (2024); Mahfouz et al. (2020); Kato et al. (2021)

Left Atrial Remodeling (LAVi)	Patients with CMD have significantly larger left atrial volumes, a marker of chronic diastolic burden.	D'Amario et al. (2024)
Myocardial Fibrosis (ECV)	No consistent linear correlation found between CMD (MPR) and diffuse fibrosis (ECV).	Arnold et al. (2022)
Global Longitudinal Strain (GLS)	Worse CMD is associated with impaired GLS, indicating subclinical systolic dysfunction.	Erhardsson et al. (2023); Paolisso et al. (2023)
Clinical Comorbidities & Biomarkers		
Atrial Fibrillation (AF)	CMD is strongly associated with a higher prevalence and odds of AF.	D'Amario et al. (2024); Srivaratharajah et al. (2019); Ozcan et al. (2021)
Natriuretic Peptides (NT-proBNP)	Worse CMD is independently correlated with higher levels of NT-proBNP.	Kato et al. (2021); Srivaratharajah et al. (2019)

Systemic Endothelial Dysfunction (RHI)	Lower coronary flow reserve is associated with impaired systemic endothelial function.	Srivaratharajah et al. (2019)
Renal Dysfunction (eGFR, UACR)	Impaired CMD is correlated with lower eGFR and higher UACR.	Kato et al. (2021); van der Ende et al. (2024)
Functional Capacity		
Peak Oxygen Consumption (VO ₂ max)	Reduced myocardial perfusion reserve is directly associated with lower peak VO ₂ .	Loffler et al. (2019)
6-Minute Walk Test (6MWT)	Reduced coronary flow reserve is an independent predictor of shorter 6MWT distance.	Mahfouz et al. (2020)

- **Diastolic Dysfunction and Left Atrial Remodeling:** Multiple studies establish a significant link between CMD and worse diastolic function. A meta-analysis by D'Amario et al. (2024) quantified this, finding a pooled mean difference in the E/e' ratio of 2.76 and in LAVi of 3.85 ml/m² between HFpEF patients with and without CMD, both clinically meaningful differences (D'Amario et al., 2024). This indicates that impaired microvascular function is linked to a more advanced stage of the disease, characterized by higher filling pressures and significant structural remodeling of the left atrium.
- **Myocardial Fibrosis:** The relationship between functional measures of CMD and myocardial

fibrosis is complex. While autopsy studies have shown an inverse relationship between microvessel density and the extent of myocardial fibrosis (Mohammed et al., 2015), studies using advanced imaging have yielded more nuanced results. Arnold et al. (2022), using CMR, found no significant linear correlation between myocardial perfusion reserve (MPR) and extracellular volume (ECV), a quantitative marker of diffuse interstitial fibrosis (Arnold et al., 2022). This important finding challenges the assumption of a simple, direct causal link and suggests that CMD and fibrosis may be parallel, rather than sequential, processes.

- **Atrial Fibrillation and Systemic Dysfunction:** A strong, bidirectional association exists between CMD and AF. The PROMIS-HFpEF study found a significantly higher prevalence of AF in patients with CMD compared to those without (58% vs. 25%) (Srivaratharajah et al., 2019), and a meta-analysis confirmed that HFpEF patients with CMD had 1.61-fold higher odds of having AF (D'Amario et al., 2024). The dysfunction observed in the coronary microcirculation also appears to be a manifestation of a more systemic process, with studies showing associations between coronary CMD and impaired systemic endothelial function (lower RHI) and renal microvascular damage (higher UACR) (Srivaratharajah et al., 2019; van der Ende et al., 2024).
- **Functional Capacity:** A core clinical manifestation of HFpEF is severe exercise intolerance. The evidence indicates that CMD is a key contributor to this debilitating symptom. Loffler et al. (2019) demonstrated that impairment in exercise capacity (peak VO₂) was directly associated with a reduced myocardial perfusion reserve (Loffler et al., 2019). Similarly, Mahfouz et al. (2020) found that reduced CFR was a significant and independent predictor of a shorter 6-minute walk distance (Mahfouz et al., 2020).

Prognostic Significance: Association with Clinical Endpoints

Perhaps the most critical finding of this review is the consistent and powerful association between CMD and adverse clinical outcomes. The presence of CMD is not a benign physiological curiosity but a potent marker of increased risk for hospitalization and death. Multiple high-quality

studies have shown that CMD independently predicts major adverse cardiovascular events, as summarized in Table 5.

The most comprehensive evidence comes from a meta-analysis by D'Amario et al. (2024), which pooled data from several studies and found that the presence of CMD was associated with a more than threefold increased risk of the composite endpoint of death or HF hospitalization (HR: 3.19) (D'Amario et al., 2024). In a particularly striking finding, Shah et al. (2018) reported that patients with both impaired CFR and severe diastolic dysfunction had a greater than fivefold increased risk of HFpEF hospitalization (Shah et al., 2018). Follow-up data from the PROMIS-HFpEF cohort specifically demonstrated that CMD was independently associated with an increased risk of both first-time and recurrent HF-specific hospitalizations (Hage et al., 2020). The prognostic impact of CMD extends to all-cause mortality when combined with hospitalization, with studies by Arnold et al. (2022) and Mohammed et al. (2023) both finding that CMD was an independent predictor of this composite endpoint after robust multivariable adjustment.

Table 5: Impact of Coronary Microvascular Dysfunction on Clinical Outcomes in HFpEF

Study (Author, Year)	Outcome	Risk Metric	Patient Group Comparison	Result (HR or OR)	95% Confiden ce Interval	p-value
Shah (2018)	HFpEF Hospitali zation	HR	Impaired CFR & Diastolic Dysfunction vs. Normal	> 5.0	Not Reported	< 0.001

Hage (2020)	CV Death or HF Hospitali- zation	Rate Ratio	CMD vs. No CMD	-	-	0.023
Allan (2019)	Survival free of HF Hospitali- zation	HR	Abnormal CFR vs. Normal CFR	-	-	0.01
Arnold (2022)	All-Cause Death or HF Hospitali- zation	HR	Per 1 SD increase in MPR	0.67	0.46 - 0.98	0.038
Moham- med (2023)	All-Cause Death or HF Rehospita- lization	HR	caIMR ≥ 25 vs. < 25	2.93	1.28 - 6.70	0.010
D'Amari- o (2024)	All-Cause Death or	HR	CMD vs. No CMD	3.19	1.04 - 9.57	0.04

	HF Hospitali zation					
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Abbreviations: caIMR, coronary angiography-derived index of microcirculatory resistance; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MPR, myocardial perfusion reserve; OR, odds ratio; SD, standard deviation.

DISCUSSION

Principal Findings in Context

This systematic review consolidates a substantial and compelling body of evidence establishing coronary microvascular dysfunction as a central feature of heart failure with preserved ejection fraction. The principal finding is unequivocal: CMD is not a peripheral or infrequent observation but a core pathological entity present in the majority of patients with HFpEF, with prevalence rates consistently reported between 60% and 80% across diverse populations and diagnostic modalities (Liu et al., 2023; Srivaratharajah et al., 2019). More critically, the presence of CMD is not a benign physiological state. The evidence synthesized herein demonstrates that CMD is independently and significantly associated with the cardinal features of HFpEF, including more severe diastolic dysfunction, greater adverse structural remodeling, and poorer functional capacity (D'Amario et al., 2024; Mahfouz et al., 2020). The most impactful conclusion is the powerful prognostic significance of CMD. Its presence consistently identifies a high-risk subgroup of HFpEF patients with a substantially increased risk of hospitalization and mortality (Arnold et al., 2022; D'Amario et al., 2024; Mohammed et al., 2023). These findings collectively position CMD as an integral element in the pathophysiology and natural history of the HFpEF syndrome.

Mechanistic Insights: A Vicious Cycle of Inflammation and Ischemia

The data synthesized in this review strongly support the prevailing pathophysiological paradigm that places CMD as a key intermediary between systemic inflammation and myocardial failure. The process begins with the high burden of cardiometabolic comorbidities typical of HFpEF, which fosters a systemic pro-inflammatory state (Paulus and Tschöpe, 2013). This "meta-inflammation" directly injures the coronary microvascular endothelium, leading to reduced nitric oxide bioavailability and impaired vasodilatory capacity—the hallmark of functional CMD (Schiattarella et al., 2021). This impairment results in a blunted blood flow response to exertion, causing demand-supply mismatch and subendocardial ischemia, which in turn promotes myocardial fibrosis and stiffening (Shah et al., 2018).

However, the relationship is likely not a simple, unidirectional cascade. The evidence points towards a more complex, self-perpetuating "vicious cycle." While CMD contributes to myocardial stiffening, the resulting high LV diastolic pressures and increased myocardial wall stress characteristic of established HFpEF can, in turn, cause mechanical compression of the subendocardial microvessels, particularly during diastole (Abdin et al., 2024). This phenomenon, known as impaired "cardiac-coronary coupling," further compromises microvascular perfusion, exacerbating ischemia and driving more fibrosis and stiffness (Kato et al., 2021). This bidirectional feedback loop helps explain the progressive nature of the disease. The finding by Paolisso et al. (2023) that CMD in HFpEF is predominantly "structural" (characterized by high microvascular resistance during hyperemia), as opposed to the more "functional" CMD seen in HFrEF, lends credence to this model (Paolisso et al., 2023). The structural changes of HFpEF (hypertrophy, fibrosis) may create a fixed, mechanical impediment to microvascular flow, which then fuels the very ischemic processes that worsen these structural changes. This reframes CMD from a simple cause to an integral, interacting component of the disease engine.

Clinical Implications: CMD as a Diagnostic and Therapeutic Target

The profound prognostic implications of CMD have significant clinical relevance. The consistent finding that CMD is a powerful, independent predictor of hospitalization and death argues strongly for its incorporation into the clinical risk stratification of patients with HFpEF (Arnold et al., 2022; Mohammed et al., 2023). A patient with a confirmed diagnosis of HFpEF who also has evidence of CMD should be considered to be at a very high risk for future adverse events, potentially warranting more intensive monitoring and aggressive management of underlying risk factors.

Furthermore, the concept of a "CMD-HFpEF endotype" offers a potential solution to the long-standing problem of therapeutic failure in this field. The marked heterogeneity of the HFpEF population is widely cited as a primary reason for the neutral results of many large clinical trials (Borlaug et al., 2023). By identifying a specific, high-risk subgroup defined by a clear pathophysiological mechanism, researchers can design more targeted, physiology-guided clinical trials. Testing novel therapies aimed at improving microvascular function—such as advanced anti-inflammatory agents, NO-pathway modulators, or even existing drugs like SGLT2 inhibitors which may have microvascular benefits—in a population enriched with CMD patients could dramatically increase the likelihood of demonstrating a therapeutic benefit (Abdin et al., 2024; Graziani et al., 2018).

The Systemic Nature of Microvascular Disease in HFpEF

The review highlights that the microvascular pathology in HFpEF is not confined to the heart. The association of coronary CMD with markers of renal microvascular damage (elevated UACR) and evidence of retinal microvascular changes provides compelling support for the hypothesis that HFpEF is a manifestation of a systemic microvascular disorder or a generalized "endotheliopathy" (van der Ende et al., 2024). This systemic perspective offers a more holistic explanation for the clinical presentation of HFpEF, which is characterized by multi-organ

involvement. The high prevalence of chronic kidney disease, pulmonary hypertension, cognitive dysfunction, and skeletal muscle dysfunction in HFpEF patients may all be linked by a common underlying pathology of widespread microvascular impairment (Dryer et al., 2018; Shah et al., 2018). This reframes the clinical challenge from managing an isolated failing heart to managing a failing systemic microcirculation, which may require multi-faceted therapeutic approaches that extend beyond traditional cardiac-focused treatments. This also helps to explain the high rates of non-cardiovascular mortality observed in the HFpEF population (Ponikowski et al., 2016).

Limitations and Methodological Considerations

This systematic review has several limitations that must be acknowledged. First, the evidence base is composed entirely of observational studies. While these studies can robustly demonstrate strong associations, they cannot definitively establish causality. The possibility of residual confounding, where unmeasured factors contribute to both CMD and adverse outcomes, cannot be entirely excluded. Second, as highlighted in the results, there is significant heterogeneity in the diagnostic modalities, pharmacological stress agents, and quantitative thresholds used to define CMD across studies. This complicates direct comparisons and is a major contributor to the high statistical heterogeneity observed in meta-analyses, warranting caution in the interpretation of pooled estimates (Liu et al., 2023). Finally, many of the included studies intentionally excluded patients with obstructive epicardial coronary artery disease to isolate the effects of microvascular disease. While this strengthens the internal validity of the findings regarding CMD, it may limit the generalizability to the broader "all-comer" HFpEF population, in whom epicardial and microvascular disease often coexist (Rush et al., 2021).

Future Research and Unanswered Questions

The findings of this review illuminate several critical areas for future research. The most pressing need is for randomized controlled trials that specifically target CMD in a well-phenotyped HFpEF population. Such trials are essential to move from association to causation and to determine

if improving microvascular function can alter the natural history of the disease. Second, the relationship between CMD and myocardial fibrosis requires further elucidation. The lack of a strong linear correlation in advanced CMR studies suggests a more complex interplay than previously thought, which warrants investigation with multi-modal imaging and tissue-based studies (Arnold et al., 2022). Finally, large-scale, prospective, longitudinal studies are needed to track the evolution of CMD over time. Determining whether CMD precedes the clinical onset of HFpEF would provide the strongest evidence to date for its causal role and could identify a crucial window for preventative interventions in at-risk individuals.

CONCLUSION AND SUGGESTIONS

Conclusion

This systematic review consolidates a substantial body of evidence demonstrating that coronary microvascular dysfunction is a highly prevalent condition in patients with heart failure with preserved ejection fraction. It is not a bystander phenomenon but is significantly and independently associated with the core pathophysiological features of the syndrome, including diastolic dysfunction, adverse myocardial remodeling, and atrial fibrillation. Most importantly, the presence of CMD is a powerful and independent predictor of adverse clinical outcomes, including substantially increased rates of heart failure hospitalization and mortality. The evidence strongly supports the conceptualization of CMD as a key endotype within the heterogeneous HFpEF syndrome, representing a crucial link between systemic comorbidity-driven inflammation and end-organ cardiac failure.

Suggestions for Clinical Practice and Research

For Clinical Practice: Clinicians managing patients with HFpEF, particularly those with a significant burden of cardiometabolic comorbidities such as obesity, diabetes, and hypertension, should maintain a high index of suspicion for underlying CMD. While routine screening for CMD

is not yet standard of care, its identification through non-invasive imaging or during invasive assessment can critically refine risk stratification. A diagnosis of concomitant CMD should flag a patient as being at very high risk for clinical deterioration and may justify more aggressive management of all modifiable cardiovascular risk factors and closer clinical surveillance.

For Research: The "CMD-HFpEF endotype" represents a critical, high-yield target for therapeutic development. Future clinical trials in HFpEF should move beyond a "one-size-fits-all" approach and consider using the presence of objectively measured CMD as a key inclusion criterion. This strategy of "phenotype-enrichment" will allow for the testing of targeted therapies (e.g., anti-inflammatory, anti-fibrotic, or endothelial-enhancing agents) in the patient population most likely to respond, thereby increasing the potential for success and paving the way for a more personalized, pathophysiology-driven approach to treating this challenging clinical syndrome.

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