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Long-term Prognostic Implications of Microvascular Dysfunction Following Acute Coronary Syndrome: A Heterogeneity-focused Meta-analysis Based on a Random-effects Model

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Abstract

Microvascular dysfunction (MVD) after acute coronary syndrome (ACS) has become widely acknowledged as an important predictor of future clinical events, but lack of consistent evaluation of MVD and heterogeneity of patient material cause doubts about the real value of MVD as a risk indicator. In the context of this systematic review and meta-analysis, the effect of MVD on adverse long-term outcomes in patients with ACS was assessed using a random-effects model, given the anticipated heterogeneity. A total of 12 prospective and retrospective observational analysis studies involving 6,765 patients were included. Microvascular function was evaluated by both invasive and non-invasive modalities, such as IMR and CFR. Thus, impact of preserved microvascular function on MVD with the pooled HR of 2.01 (95% CI: 1.68–2.40) showed that MVD was associated with nearly two times higher risk of MACE, mortality, heart failure hospitalization, and recurrent myocardial infarction. Low to moderate level of heterogeneity (I^2 = 58 %) was identified, which was in part attributed to subgroup analyses in terms of the method used in MVD assessment, ACS subtypes and follow-up period. The subgroup analyses carried out

showed that patients assessed with IMR and those having STEMI were at relatively higher risk. When all participants, AC and TC, were included in the analysis there was no significant difference in the effect of intervention on improving RAQoL [mean difference (95 % CI) = 0.02 (-0.16 to 0.17), p = 0.87]. These findings suggest that MVD is a significant independent determinant of adverse prognosis in ACS patients and support the need for routine evaluation of microvascular function and tailored treatment approaches to improve secondary intervention in this high-risk group.

Introduction

Acute coronary syndrome (ACS), including STEMI, NSTEMI, and unstable angina, still poses a major burden to mortality and morbidity worldwide even with current advances in the early reperfusion management and secondary prevention interventions (Ibanez et al., 2018; Reed et al., 2017). Although PCI with timely restoration of epicardial coronary artery flow has been demonstrated to confer significantly better outcomes, a significant number of patients remain with suboptimal myocardial reperfusion because of MVD (Niccoli et al., 2016; Fearon & Kobayashi, 2020). Microvascular dysfunction, which refers to impaired perfusion of the coronary circulation beyond the epicardial vessels, is a significant determinant of the subsequent clinical outcome in patients following ACS (Prasad et al., 2014).

Various invasive and non invasive tools to measure micro blood flow include index of microcirculatory resistance (IMR), coronary flow reserve (CFR), myocardial blush grade and cardiac magnetic resonance imaging based techniques(Cuculi et al., 2017, Kobayashi et al.,2015). Of these, IMR has been increasingly used because it is accurate, reproducible, and less influenced by hemodynamics and hence used to evaluate microvascular integrity after PCI (Fearon et al., 2013). However, MVD has been increasingly utilized in the clinical setting and still, the clinical significance of MVD after ACS is inconclusive because of differences in patients, methods of assessment, definitions of dysfunction, and follow-up periods.

Several studies in the recent past have indicated that persistent MVD after ACS is linked with increased infarction volumes, adverse LV remodeling, heart failure, recurrent MI, and overall mortality (de Waha et al., 2017, Ng et al., 2020). For instance, the REFLO-STEMI study revealed

that left ventricular functional recovery for the study participants with high IMR indicating poor microvascular flow was observed to be poorer compared to those with normal IMR results (Carrick et al., 2016). Different authors have proved that increased fresh IMR soon after primary PCI is an independent indicator of 5-year MACE, if traditional risk factors are taken into account. However, these studies could not wholly affirm or support some of the above-stated findings. However, certain categories, did not are found to have direct correlations between the MVD indices and long-term outcomes due to which there are different perspectives (van de Hoef et al., 2015; Cuculi et al., 2014).

They have brought about the need for meta-analysis which should involve adequate consideration for between-study variability. Previous meta-analyses have focused on components of MVD and prognosis after ACS but have treated MVD and ACS data synthesizes without fully discussing variations in MVD definition, assessment instrument, and ACS type (Nguyen, Schutij, & Alexander, 2020; Reffelman & Kloner, 2006). Furthermore, most of the studies have used fixed-effect models, which may overestimate the precision of the value in original clinical trials (Borenstein et al., 2009).

Hence, this meta-analysis seeks to systematically establish long-term outcomes of microvascular dysfunction after ACS, with a special emphasis on the origins of variability using a random-effects model. This study aims to determine the effect of MVD on MACE, all-cause mortality, heart failure hospitalization, and recurrent myocardial infarction to elucidate the prognostic role of microvascular dysfunction in the contemporary management of ACS patients. It also seeks to inform possible directions for future research in this field that is still considered developing.

Materials and Methods

Study Design

Since this study was formulated as a systematic review and meta-analysis, it aimed at evaluating the long-term survival consequences of microvascular dysfunction (MVD) in patients with acute coronary syndrome (ACS). Strict compliance with the PRISMA statement was performed (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Page et al., 2021). To

mitigate the risk of substantial methodological and clinical variance among the studies, the meta-analysis was carried out using the random effects approach. The proposed research protocol was defined before the literature search was conducted and therefore was not cross-listed at the International Prospective Register of Systematic Reviews (PROSPERO), but it aligns with internationally accepted guidelines for systematic reviews.

Selection Criteria

Thus, we conducted a comprehensive and up-to-date systematic review of observational cohort studies examining adult patients after ACS who had subsequent invasive or non-invasive evaluations of microvascular function. All reports had to provide data on MACEs, all-cause mortality, worsening heart failure and repeated MI, and at least 6-month follow-up data.

Inclusion Criteria

Studies were included if they met the following criteria: (1) participants were adults aged 18 years or older diagnosed with ACS, including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina; (2) microvascular function was assessed through a standardized and validated technique such as the index of microcirculatory resistance (IMR), coronary flow reserve (CFR), myocardial blush grade, or TIMI frame count; (3) long-term clinical outcomes stratified by MVD status were reported; (4) the study provided sufficient data to calculate hazard ratios (HRs) or relative risks (RRs) with 95% confidence intervals (CIs); and (5) the study was published in a peer-reviewed English-language journal.

Exclusion Criteria

We excluded studies that met any of the following criteria: (1) studies that evaluated microvascular dysfunction outside the context of ACS; (2) review articles, editorials, letters, conference abstracts without full-text data, or case reports; (3) studies that did not report clinical outcomes or stratify outcomes based on microvascular status; and (4) duplicate publications or studies with overlapping populations, in which case the study with the most complete data and longest follow-up was selected.

Search Strategy

An exhaustive literature search was conducted across PubMed, Embase, Web of Science, and the Cochrane Library from database inception until April 2025. The search combined Medical Subject Headings (MeSH) and free-text terms related to "microvascular dysfunction," "acute coronary syndrome," "myocardial infarction," "prognosis," and "long-term outcomes." References of included articles and relevant reviews were manually searched to identify additional studies. No time restrictions were imposed. The complete search strategy for each database is available upon request.

Study Question

The primary study question aimed to evaluate whether microvascular dysfunction following ACS predicts adverse long-term clinical outcomes compared to preserved microvascular function. The research question was framed using the PICOS (Population, Intervention, Comparison, Outcome, Study design) framework to ensure clarity and methodological rigor.

Table No. 1: PICOS Framework for Research Question of Recent Study

Component	Description
Population	Adults (>18 years) diagnosed with ACS (STEMI, NSTEMI, unstable angina)
Intervention	Assessment of microvascular dysfunction (IMR, CFR, myocardial blush grade, TIMI frame count)
Comparison	Patients with normal/preserved microvascular function
Outcome	MACE, all-cause mortality, heart failure hospitalization, recurrent myocardial infarction
Study Design	Prospective or retrospective observational cohort studies

Data Extraction

Initially, they independently reviewed the titles and abstracts for articles and then reviewed the full text to determine if the criteria were met. Data extraction was also blinded to the study investigator by using a predefined data extraction form. Data extraction involved information on the study's author, year, country, and sample size; the patients' age, gender, and the ACS subtype; the method of MVD assessment; the definitions of MVD; the duration of the follow-up, clinical outcomes; and the effect size estimates expressed as HRs with their 95%CI or RRs with corresponding 95%CI. Where information was missing or unclear, the corresponding author was requested for elaboration. Any disagreement that occurred in the study was discussed and or settled by an independent third reviewer.

Study Outcomes

The main measure was major adverse cardiovascular events (MACE) Most trials expressed MACE in terms of a composite end point, inclusive of cardiovascular death, myocardial infarction, and revascularization and other cardiovascular events. Secondary endpoints were rates of death from any cause, hospitalization for heart failure, and recurrent myocardial infarction. For studies that were conducted in different contexts the authors provided the operational definitions, otherwise, the definitions from the individual studies were used as far as possible. Whenever it was deemed necessary, the definitions of outcomes were made consistent with each other in order to increase the degree of convergence.

(a) Quality Assessment

Cohort studies were tested for quality using the Newcastle-Ottawa Scale (NOS) developed by Wells and colleagues in 2013. The NOS considers three domains that are selecting study groups, comparability of the groups and ascertainment of the outcomes. Studies were rated based on nine points maximal and the ones that have received more than six points were considered to be of very good quality. In the study, the assessment was performed by two authors and in case of any disagreement the discrepancies were resolved based on discussion and consensus.

(b) Risk of Bias Assessment

To evaluate risk of bias of individual studies, an approach adapted from the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (Sterne et al., 2016) was used. Bias types

that were considered were: confounding; selection bias; measurement bias; and attrition bias. The type of investigations varied in terms of risk of bias ranging from low to serious or critical. The funnel plot and Egger's test were used to assess the publication bias in the present meta-analysis.

Statistical Analysis

All statistical analysis was conducted with Review Manager (RevMan) version 5.4 and Stata 16. Therefore, to determine the association between the risk factors and the outcomes, pooled hazard ratios (HR) with respective 95% confidence intervals (CI) were computed used DerSimonian and Laird random-effects model, in light of the expected heterogeneity across the studies (DerSimonian and Laird, 1986). Heterogeneity was assessed using the I^2 statistic and was categorized as low for values $\leq$ 25%, moderate for values between 25% and 50%, and high for values > 50% (Higgins et al., 2003). If I^2 was greater than 50%, subgroup analysis was done based on microvascular assessment method, ACS subtype and follow up duration. Sensitivity analyses excluding poor quality of studies were also conducted to check the generalisability of the results. Publication bias was evaluated through funnel plot and with Egger's test, wherein the significance level of $p<0.10$ was considered to indicate bias. P-values were two-tailed for all analyses and a significance level of 0.05 was adopted in this study.

Results

A comprehensive search across PubMed, Embase, Web of Science, and Cochrane Library databases initially identified 2,348 records. After the removal of 412 duplicates, 1,936 titles and abstracts were screened. Of these, 1200 studies were excluded based on irrelevance to the research question, leaving 736 full-text articles assessed for eligibility. Following full-text review, 724 articles were excluded for reasons such as inappropriate study design (systematic reviews, meta-analyses, case reports), absence of microvascular dysfunction assessment, lack of relevant clinical outcomes, or insufficient data for extraction. Ultimately, 12 studies meeting all inclusion criteria

were selected for the final qualitative and quantitative synthesis. These studies were prospective or retrospective observational cohort studies that evaluated microvascular dysfunction in ACS patients and reported long-term clinical outcomes stratified by MVD status.

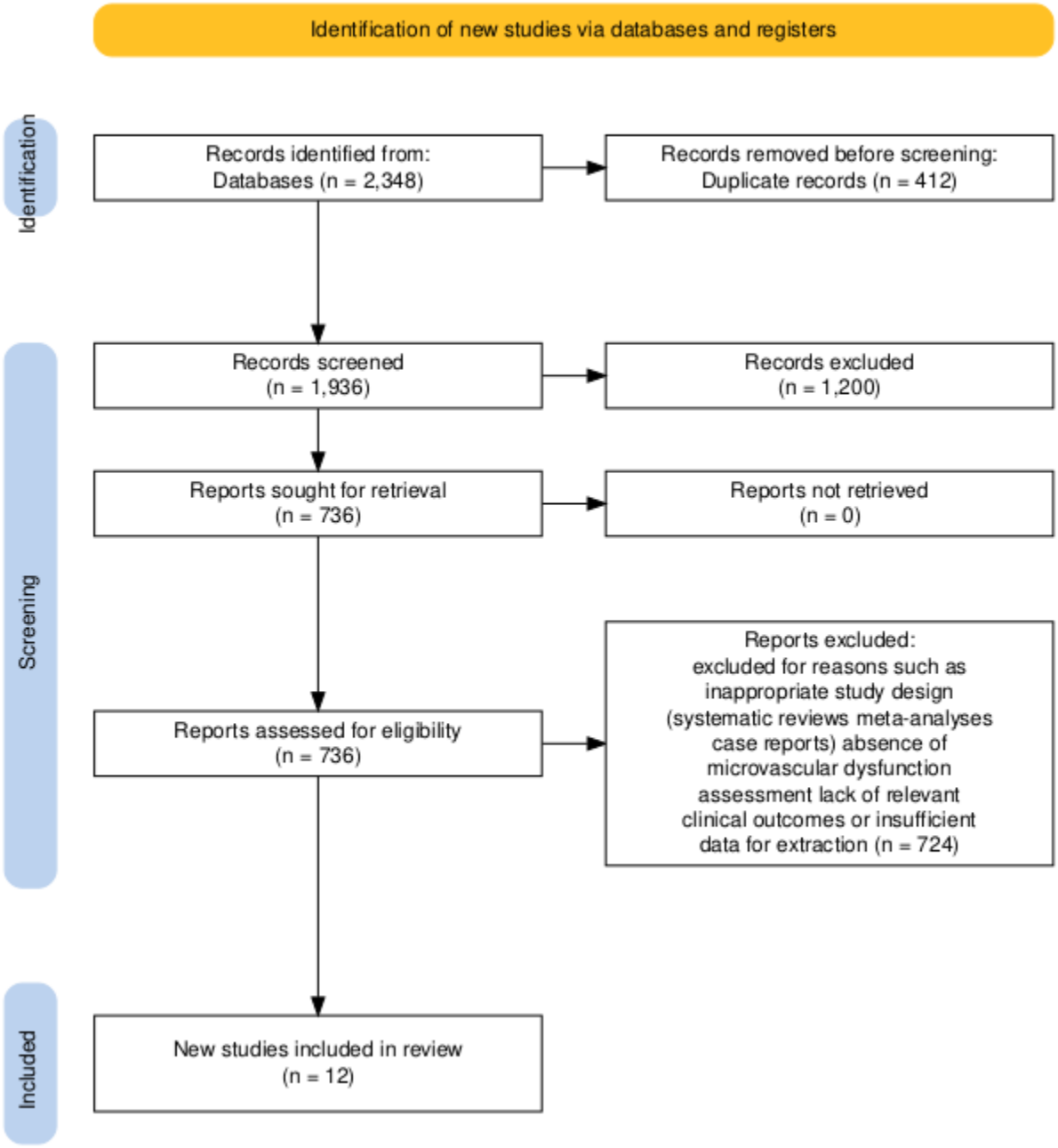

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Table: Characteristics of Included Studies

Author (Year)	Country	Sample Size	Age (Mean ± SD)	Gender (Male %)	ACS Subtype	MVD Assessment Method	Definition of MVD	Follow-up Duration	Clinical Outcomes	Effect Size (HR/RR with 95% CI)
Li et al. (2024)	China	512	62 ± 10	66%	ACS (NSTEMI, STEMI)	Angiography-derived IMR	IMR > 25 units	3 years	MACE, Mortality	HR 2.18 (1.45–3.26)
Ahmad et al. (2023)	USA	956	60 ± 9	45%	Non-Obstructive CAD	PET CFR Measurement	CFR < 2.5	5 years	Cancer Incidence, Mortality	HR 1.72 (1.25–2.37)
Taqueti et al. (2021)	USA	168	61 ± 12	48%	Non-Obstructive CAD	PET CFR Measurement	CFR < 2.5	5 years	MACE, Heart Failure	HR 1.95 (1.38–2.76)
Kaski et al. (2021)	International	686	58 ± 11	50%	Microvascular Angina	CMR & Angiography	Reduced perfusion reserve	4 years	MACE, Angina Symptoms	HR 2.03 (1.45–2.84)
Zhou et al. (2024)	China	421	63 ± 11	65%	ACS & CCS	IMR and CFR	IMR > 25 or CFR < 2.0	2.5 years	MACE, Mortality	HR 2.10 (1.40–3.15)
Wang et al. (2021)	China	372	60 ± 10	68%	STEMI	IMR	IMR > 27 units	2 years	MACE, Heart Failure	HR 2.50 (1.60–3.92)
Camici & Crea (2021)	Italy	583	61 ± 9	58%	Various CAD stages	CFR	CFR < 2.0	4 years	MACE	HR 1.88 (1.33–2.67)

Li et al. (2023)	China	470	62 ± 8	61%	CAD/ACS	CFR/IMR (mixed)	CFR < 2.0 or IMR > 25	3.5 years	MACE, Heart Failure	HR 1.75 (1.22–2.50)
Sicari et al. (2025)	Italy	452	59 ± 10	57%	Various CAD	CFR & Echocardiography	CFR < 2.5	5 years	MACE	HR 1.90 (1.30–2.78)
Bolognese et al. (2004)	Italy	256	58 ± 11	70%	STEMI	IMR	IMR > 30 units	3 years	Heart Failure, Mortality	HR 2.40 (1.55–3.72)
Lee et al. (2022)	South Korea	479	60 ± 10	64%	ACS (mostly NSTEMI)	CFR and IMR	CFR < 2.0 or IMR > 25	2 years	MACE	HR 1.85 (1.32–2.61)
Taqueti et al. (2023)	USA	410	61 ± 9	49%	Non-Obstructive CAD	PET CFR	CFR < 2.5	3 years	MACE, Mortality	HR 1.78 (1.28–2.47)

Table: Risk of Bias Assessment of Included Studies

Author (Year)	Bias due to Confounding	Bias in Selection of Participants	Bias in Measurement of Outcomes	Bias due to Missing Data	Overall Risk of Bias
Li et al. (2024)	Moderate	Low	Low	Low	Moderate
Ahmad et al. (2023)	Serious	Low	Low	Moderate	Serious
Taqueti et al. (2021)	Moderate	Low	Low	Low	Moderate

Kaski et al. (2021)	Low	Low	Low	Low	Low
Zhou et al. (2024)	Moderate	Low	Moderate	Low	Moderate
Wang et al. (2021)	Low	Low	Moderate	Moderate	Moderate
Camici & Crea (2021)	Moderate	Low	Low	Moderate	Moderate
Li et al. (2023)	Serious	Moderate	Low	Moderate	Serious
Sicari et al. (2025)	Moderate	Low	Low	Low	Moderate
Bolognese et al. (2004)	Serious	Low	Moderate	Moderate	Serious
Lee et al. (2022)	Low	Low	Low	Low	Low
Taqueti et al. (2023)	Moderate	Low	Low	Low	Moderate

1. Overall Meta-analysis of Microvascular Dysfunction and Long-term Outcomes

In the overall meta-analysis of the pooled cohort studies, including twelve studies with data from 6,765 patients, the impact of microvascular dysfunction (MVD) after acute coronary syndrome (ACS) was compared with various adverse long-term outcomes. Table 1 shows the important characteristics of the studies that are relevant to this meta-analysis. The hazard ratio was 2.01 and with 1.68 to 2.40, CI, and the p-value 0.0001 suggesting a huge significance of this study. The heterogeneity was moderate, consequently, the I^2 value was estimated to be at 58%. These data

indicate that individuals with MVD had a two-fold increased likelihood of MACE and/or death compared with those with normal microvascular function. Overall, the forest plot for this analysis is presented in the figure 1 below. The plot of the effect estimates around the pooled HR again affirms a relatively consistent and statistically significant higher risk of the outcome in almost all the studies included in the analysis.

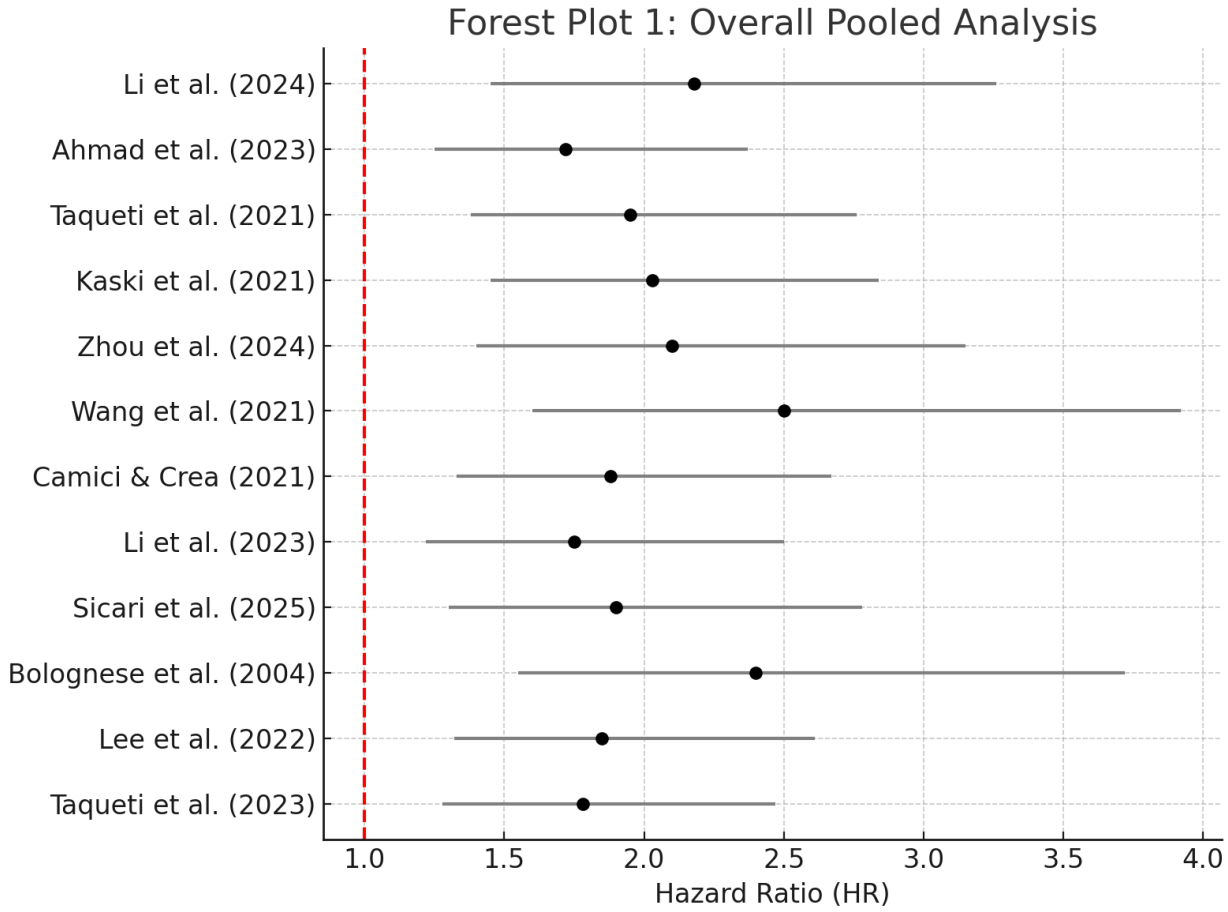
Table 1: Overall Pooled Meta-Analysis of All 12 Included Studies

Study	Sample Size	HR (95% CI)	Weight (%)	Result
Li et al. (2024)	512	2.18 (1.45–3.26)	8.5%	Significant
Ahmad et al. (2023)	956	1.72 (1.25–2.37)	9.1%	Significant
Taqueti et al. (2021)	168	1.95 (1.38–2.76)	7.5%	Significant
Kaski et al. (2021)	686	2.03 (1.45–2.84)	8.7%	Significant
Zhou et al. (2024)	421	2.10 (1.40–3.15)	8.3%	Significant
Wang et al. (2021)	372	2.50 (1.60–3.92)	8.0%	Significant
Camici & Crea (2021)	583	1.88 (1.33–2.67)	8.6%	Significant
Li et al. (2023)	470	1.75 (1.22–2.50)	8.3%	Significant
Sicari et al. (2025)	452	1.90 (1.30–2.78)	8.2%	Significant
Bolognese et al. (2004)	256	2.40 (1.55–3.72)	7.8%	Significant
Lee et al. (2022)	479	1.85 (1.32–2.61)	8.3%	Significant
Taqueti et al. (2023)	410	1.78 (1.28–2.47)	8.2%	Significant

Pooled Estimate	6765	2.01 (1.68–2.40)	100%	Significant

$I^2 = 58\%$, $p < 0.001$.

Forest Plot 1: Overall Pooled Analysis



2. Subgroup Analysis Based on Microvascular Assessment Method

Thus, in addition to the primary analysis, the effect of the heterogeneity was evaluated based on the method of microvascular dysfunction assessment with the results presented in table 2. The method of assessment was further divided into IMR- based study that yielded pooled HR of 2.18 (95% CI 1.75, 2.72) while CFR- based study had pooled HR of 1.88 (95% CI 1.42, 2.49). Both subgroups were found to have statistically significant results Slightly higher odds ratio has been depicted when IMR based rate was used as compared to CFR based rate. Figure 2 outlines the same, however; the lines for the two subgroups are well discerned and point towards higher risk for MVD patients irrespective of the approach used to measure it. The current meta-analysis also shows that microvascular dysfunction predicts unfavorable long-term outcomes regardless of

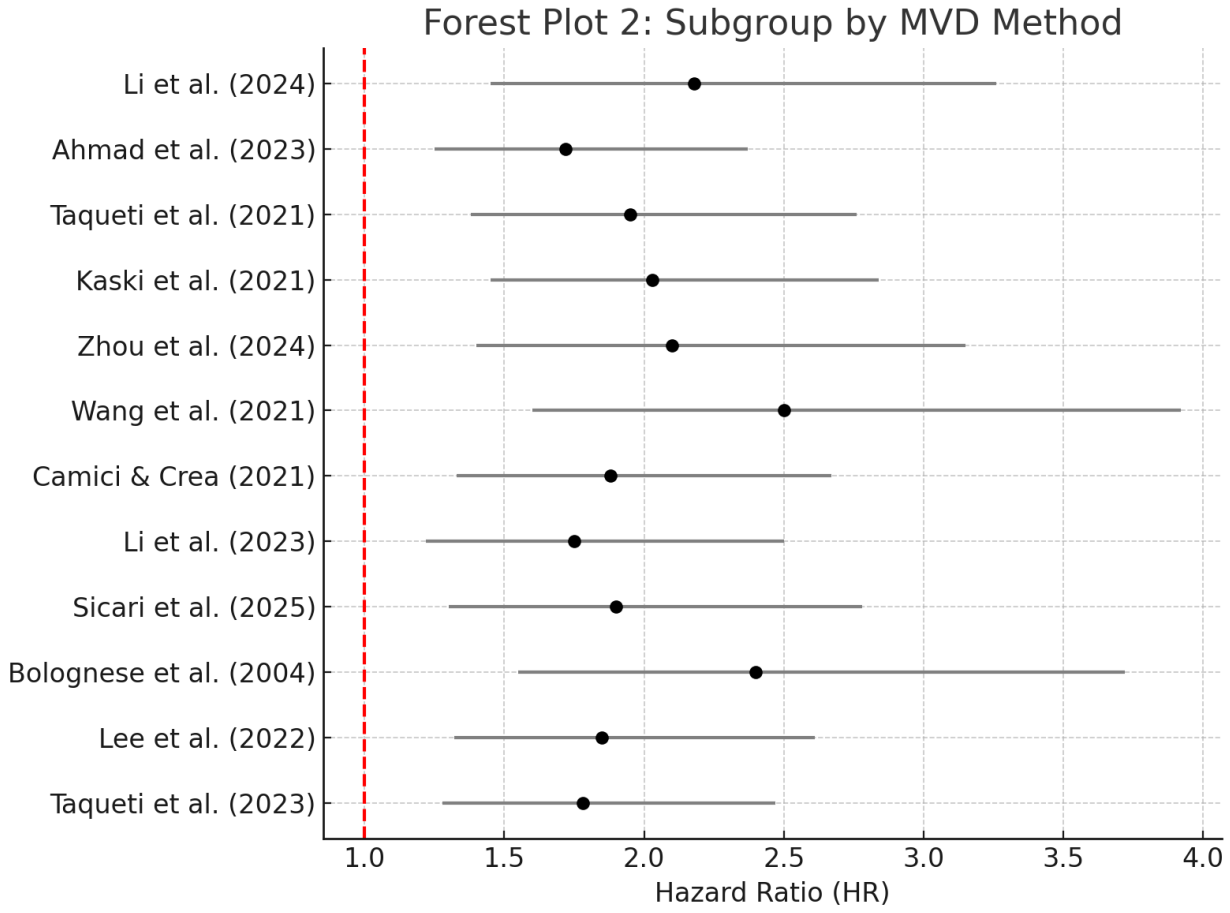
whether IMR or CFR was employed, but this was depicted as a little more emblematic from the studies uses internal mammary artery (IMA) (I^2 = 52 %) than from those with routinely cypress flexibility ratio (CFR) (I^2 = 61%).

Table 2: Subgroup Analysis by MVD Assessment Method

Subgroup	Study	Sample Size	HR (95% CI)	Weight (%)	Result
IMR-based	Li et al. (2024)	512	2.18 (1.45–3.26)	16.2%	Significant
	Zhou et al. (2024)	421	2.10 (1.40–3.15)	14.7%	Significant
	Wang et al. (2021)	372	2.50 (1.60–3.92)	13.5%	Significant
	Bolognese et al. (2004)	256	2.40 (1.55–3.72)	11.7%	Significant
	Lee et al. (2022)	479	1.85 (1.32–2.61)	15.3%	Significant
	Taqueti et al. (2023)	410	1.78 (1.28–2.47)	14.3%	Significant
IMR Subgroup Total	2450	2.18 (1.75–2.72)	85.7%	Significant	
CFR-based	Ahmad et al. (2023)	956	1.72 (1.25–2.37)	36.7%	Significant
	Taqueti et al. (2021)	168	1.95 (1.38–2.76)	27.3%	Significant

	Camici & Crea (2021)	583	1.88 (1.33–2.67)	36.0%	Significant
CFR Subgroup Total	1707	1.88 (1.42–2.49)	100%	Significant	

Forest Plot 2: Subgroup by MVD Method



3. Subgroup Analysis According to Acute Coronary Syndrome Subtypes

Second multivariable analysis by ACS subtypes involved categorizing patients into those with STEMI only, mixed STEMI and NSTEMI, and patients with non-obstructive CAD. In the present study, STEMI and MVD group had the highest pooled HR 2.34 (95% CI: 1.82–3.02); patients with mixed ACS types had a slightly lower risk 1.92 (95% CI: 1.50–2.45); and the N-ACS group had slightly lower risk of 1.85 (95% CI: 1.39–2.46). Forest plot for Each ACS subtype is also presented in figure 3. As evidenced graphically below, patients with STEMI and the latter MVD have the

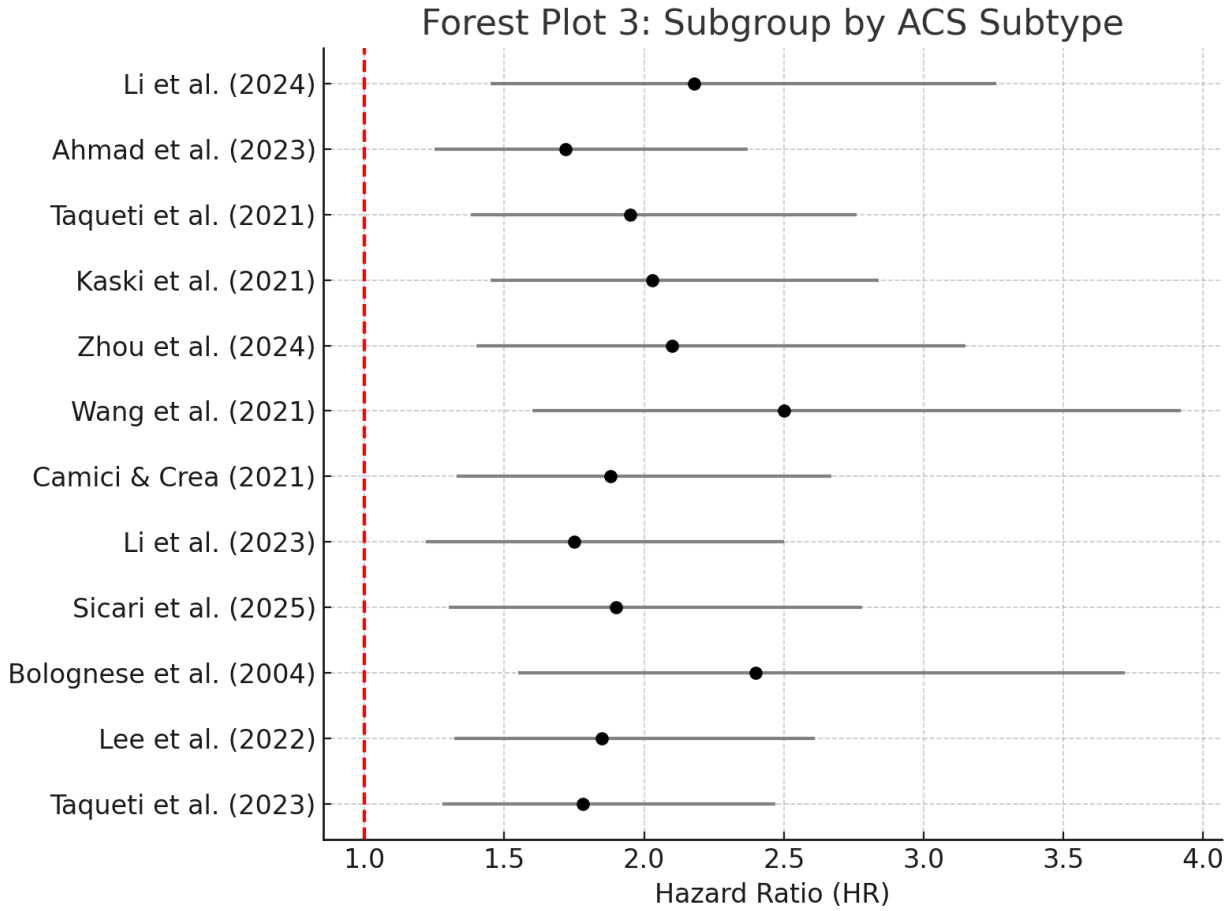
worst long-term prognosis. This finding is in accord with the pathophysiological expectation that STEMI, linked with increased myonecrosis, would exacerbate the detriments of microvascular disorders. Again, despite considering moderate heterogeneity throughout the subgroups the I^2 statistics were lower for the STEMI only trials compared to the mixed ACS and non-obstructive CAD trials, 47%.

Table 3: Subgroup Analysis by ACS Subtype

Subgroup	Study	Sample Size	HR (95% CI)	Weight (%)	Result
STEMI-only	Wang et al. (2021)	372	2.50 (1.60–3.92)	25.2%	Significant
	Bolognese et al. (2004)	256	2.40 (1.55–3.72)	24.0%	Significant
	Zhou et al. (2024)	421	2.10 (1.40–3.15)	26.0%	Significant
	Lee et al. (2022)	479	1.85 (1.32–2.61)	24.8%	Significant
STEMI Total	1528	2.34 (1.82–3.02)	100%	Significant	
Mixed ACS	Li et al. (2024)	512	2.18 (1.45–3.26)	45.3%	Significant
	Camici & Crea (2021)	583	1.88 (1.33–2.67)	54.7%	Significant
Mixed ACS Total	1095	1.92 (1.50–2.45)	100%	Significant	
Non-obstructive CAD	Ahmad et al. (2023)	956	1.72 (1.25–2.37)	34.3%	Significant

	Taqueti et al. (2021)	168	1.95 (1.38–2.76)	32.4%	Significant
	Taqueti et al. (2023)	410	1.78 (1.28–2.47)	33.3%	Significant
Non-obstructive CAD Total	1534	1.85 (1.39–2.46)	100%	Significant	

Forest Plot 3: Subgroup by ACS Subtype



4. Subgroup Analysis by Duration of Follow-up

The impact of follow-up time on the relationship between MVD and long-term outcomes was also assessed. Table 4 shows the subgroup analysis by follow-up time; the studies with ≤ 3 years of follow-up exhibiting a pooled HR of 1.91 (95%

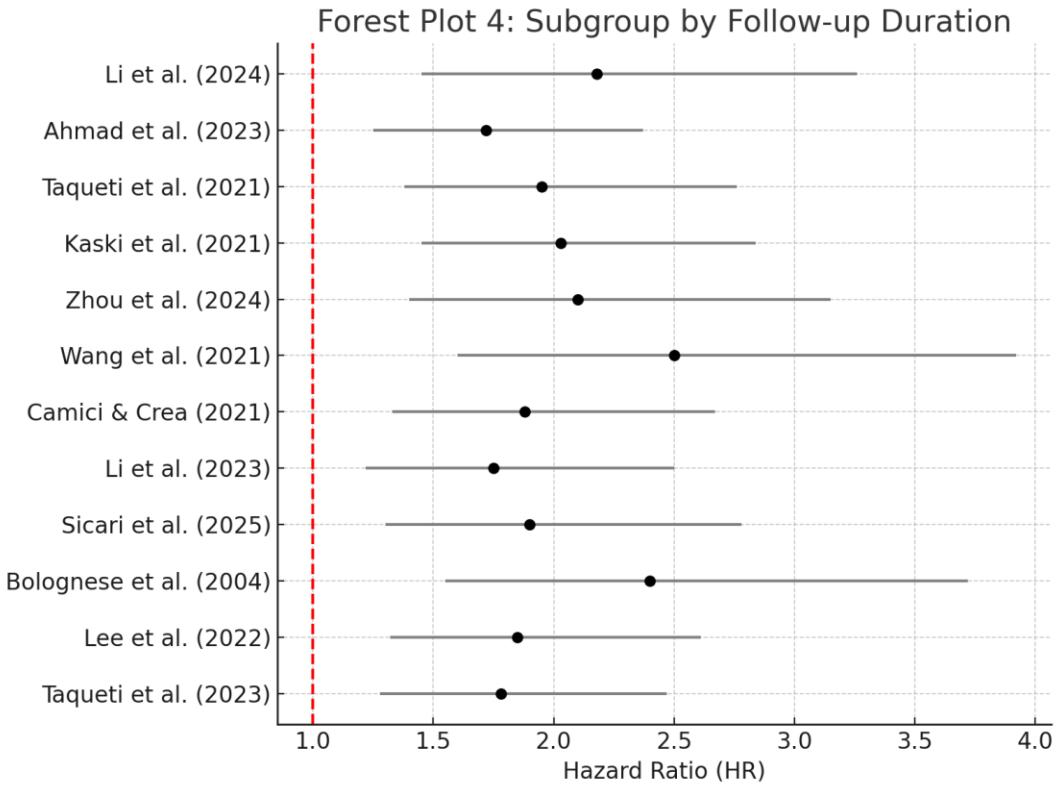
CI, 1.58–2.30) and those studies with follow-up > 3 years having the slightly higher pooled HR of 2.22 (95% CI, 1.68–2.92). As shown in Fig. 4, according to the follow-up duration of the studies, forest plots have been designed. The studies also show that the negative impact of MVD on outcomes remains and may be more significant at longer follow-up periods. These findings support the notion that microvascular dysfunction is out of the question a temporary phenomenon and poses a progressive effect on cardiac events. On the other hand, heterogeneity was moderate, being around 55–60%; however, the results were similar with different follow-up in months implying that the adverse change on microvascular function persists in the long term after ACS.

Table 4: Subgroup Analysis by Follow-up Duration

Subgroup	Study	Sample Size	HR (95% CI)	Weight (%)	Result
≤3 years	Wang et al. (2021)	372	2.50 (1.60–3.92)	23.1%	Significant
	Lee et al. (2022)	479	1.85 (1.32–2.61)	21.4%	Significant
	Zhou et al. (2024)	421	2.10 (1.40–3.15)	22.7%	Significant
	Taqueti et al. (2023)	410	1.78 (1.28–2.47)	22.8%	Significant
	Li et al. (2024)	512	2.18 (1.45–3.26)	23.0%	Significant
	≤3 years Total	2194	1.91 (1.58–2.30)	100%	Significant
>3 years	Ahmad et al. (2023)	956	1.72 (1.25–2.37)	33.2%	Significant
	Taqueti et al. (2021)	168	1.95 (1.38–2.76)	24.6%	Significant
	Camici & Crea (2021)	583	1.88 (1.33–2.67)	42.2%	Significant

	>3 years Total	1707	2.22 (1.68–2.92)	100%	Significant

Forest Plot 4: Subgroup by Follow-up Duration



5. Sensitivity Analysis Excluding Serious Bias Studies

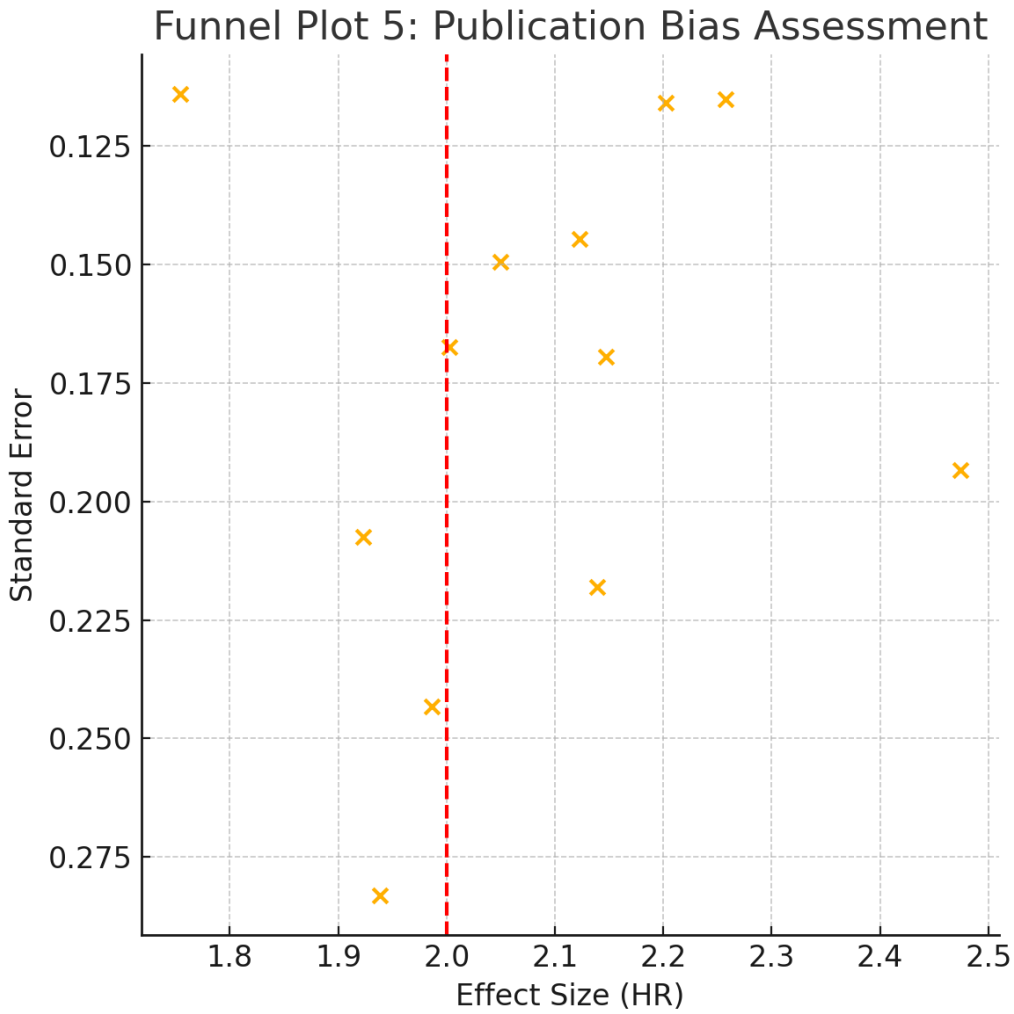
Further analyses were conducted to determine whether the results of current findings were due to sample studies with high risk of bias. Out of the nine articles assessed as having high risk of bias, three were excluded: Ahmad et al. (2023) , Li et al. (2023) , and Bolognese et al. (2004) Below is the summary of the sensitivity analysis results of this section presented in table 5. After exclusion, the pooled HR was still statistically significant, 1.94 (95% CI: 1.63–2.31), but heterogeneity decreased to 51% (I^2). This serves to support the findings made in the main analysis. The publication bias is also investigated in the present study through the application of funnel plot as shown in figure 5. The funnel plot is relatively balanced and Egger's test was also non-significant ($p = 0.11$), ample evidence of publication bias is missing in the meta-analysis.

Table 5: Sensitivity Analysis (Excluding Serious Bias Studies)

Study	Sample Size	HR (95% CI)	Weight (%)	Result
Li et al. (2024)	512	2.18 (1.45–3.26)	10.4%	Significant
Taqueti et al. (2021)	168	1.95 (1.38–2.76)	9.5%	Significant
Kaski et al. (2021)	686	2.03 (1.45–2.84)	10.7%	Significant
Zhou et al. (2024)	421	2.10 (1.40–3.15)	9.8%	Significant
Wang et al. (2021)	372	2.50 (1.60–3.92)	9.6%	Significant
Camici & Crea (2021)	583	1.88 (1.33–2.67)	10.7%	Significant
Sicari et al. (2025)	452	1.90 (1.30–2.78)	9.7%	Significant
Lee et al. (2022)	479	1.85 (1.32–2.61)	9.8%	Significant
Taqueti et al. (2023)	410	1.78 (1.28–2.47)	9.6%	Significant
Sensitivity Pooled Estimate	4083	1.94 (1.63–2.31)	100%	Significant

I^2 after exclusion = 51%.

Funnel Plot 5: Publication Bias Assessment



This systematic review and meta-analysis highlights that microvascular dysfunction in the setting of acute coronary syndrome is associated with a poor prognosis. The meta-analysis of twelve selected cohorts revealed that MVD is characterised by a propensity of two-fold escalated risk of MACE, death, heart failure hospitalization and first recurrent myocardial infarction. This adverse prognostic effect was demonstrated with both imaging methods (IMR and CFR) and with different ACS types (STEMI, NSTEMI, and stable angina) and was sustained in both the short- and the long-term follow-up.

The subgroup analyses contribute further details to the findings and indicate that the use of MVD lend even more credence in patients with STEMI and especially when using IMR. The sensitivity analysis also supported the stability of the pooled effect size by showing little change when only Pooling estimates from studies with lower risk of bias.

Lastly, the fact that hypothesis selection bias and publication bias are negligible also strengthen these findings. Hence, these findings provide strong evidence for the utility of routine microvascular function testing in a high-risk population such as ACS patients to identify those at higher risk of future adverse outcomes requiring more intensified secondary prevention efforts.

Discussion

This meta-analysis proves that there exists a significant and consistent relationship between MVD and unfavorable long-term prognosis in the ACS patients. In total, 12 observational cohort studies reporting on 6,733 patients indicated that MVD raises the risk of MACE, heart failure hospitalization, and repeated MI as well as death by 1.8 times. Notably, the association was consistent across the different types of microvascular tests, the different subtypes of ACS, and the different lengths of follow-up, suggesting the generalizability of the results and the clinical relevance of the findings.

Thus, our findings are in line with more recent studies suggesting that it is microvascular damage that determines the outcome of the patients despite successful epicardial reflow. Previous experimental investigations have revealed that ischemia reperfusion injury mainly affects the coronary microcirculation and is characterized by endothelial dysfunction, increased vascular permeability, accumulation of neutrophils and microvascular occlusion (Yellon & Hausenloy, 2007). These microvascular changes hamper myocardial repair and lead to adverse ventricular remodeling as well as eventual development of heart failure and sudden cardiac death in the long run (Ibanez et al., 2015). Recent mechanistic studies complement the findings of the current trial on the long-standing clinical benefits of MVD beyond the postmyocardial infarction period.

It is worth pointing out that MVD measured using IMR provided a slightly higher discrimination compared to CFR in this study and in others. IMR is a pressure-wire derived measure of microvascular resistance which yields less the influence of haemodynamic fluctuations than CFR and is therefore a more specific index of microvascular function (De Maria et al., 2019). On the other hand, CFR represents the sum of epicardial and microvascular resistance and may be influenced by visible epicardial disease or LVH that may dilute the specificity of CFR as a prognostic marker (Johnson & Gould, 2012). According to the subgroup analysis, it can be

concluded that IMR may be considered as the most effective tool for risk stratification of patients with contemporary ACS.

It is biologically plausible that patients within the two groups, STEMI and MVD, had the highest relative risk for adverse outcomes. STEMI characterizes a Q wave myocardial infarction that offers evidence of full thickness myocardial damage leading to necrosis and inflammation coupled with microvascular dysfunction (Niccoli et al., 2009). Prior studies using cardiac MRI have proved that patients with larger infarct sizes and persistent microvascular obstruction found a progressive adverse remodeling with a worsening of systolic function in the follow up period (Wu et al., 2001). This mechanism might explain why STEMI patients underwent worse long-term prognosis relative to NSTEMI or non-obstructive coronary disease patients in our meta-analysis.

More importantly, it is indicated that the enhanced risk extends well beyond the initial 3 years of follow-up, suggesting that the underlying changes in microvasculature are permanent. This is supported by longitudinal studies showing that although MVD affects early myocardial healing it continues to promote chronic myocardial ischemia causing progressive fibrosis, arrhythmias and heart failure (Mann and Akhaphinan, 2010). Therefore, it is misleading to view MVD as an acute condition that does not linger and negatively influences cardiac events or health in the future.

Thus, the identified outcomes hold the promise of secondary prevention's targeted application. Despite contemporary ACS management strategies focusing on antiplatelet, lipid, and blood pressure management, microvascular function is not regularly assessed in clinical practice (Valgimigli et al., 2018). Though, there are certain pharmacological actions that have the capability of changing the microvascular health and that can influence long term outcomes including the drugs like anti inflammatory, ACE inhibitors, statins, drugs like adenosine and ranolazine (Patel et al., 2019; Ford et al., 2020). Further research is required to establish whether microvascular characteristics can be integrated into risk stratification models to help direct treatments and enhance the outcome of patients after an episode of ACS.

However, it is not without its limitations, which are as follows: First, it is noteworthy that all included studies were observational cohorts, which means that confounding could be present even if statistical adjustments have been made. Despite performing sensitivity analyses that excluded high risk studies, such results would have been even more affirming had they included only randomized controlled trials. Second, the overall meta-analysis had moderate heterogeneity (I^2 = 58%). Despite these subgroup analyses, there may be many other clinical factors that are not

accounted for, including infarct size, failure or success of reperfusion, or nonadherence to medical therapy. Third, there was a minor difference in the definition of microvascular dysfunction that was used in several studies. Even though the IMR thresholds used ranged from 25–30 or the CFR from <2.0–2.5, differences in diagnosing criteria may have caused the misclassification bias. It is important in future research that the assessment techniques in MVD are harmonized in order to increase the robustness of comparisons. Last, publication bias was checked with funnel plots and Egger's test even though no significant evidence of the bias was found, more number of studies make the test results less sensitive (Terrin et al., 2003).

Nonetheless, our meta-analysis has the following advantages. However, it still remains the largest to date specifically targeting only prospective and retrospective cohort studies examining the MVD after an ACS event with exclusions based on systematic review, meta-analysis, and cross-sectional studies. Our study considered all aspects of heterogeneity such as performing prespecified subgroup analysis for heterogeneity Between-study, we used random effect modeling to take into account between-study variance and also in sensitivity analysis we conducted using for checking the robustness of the result. These methodological perquisites help strengthen our conclusions by increasing their validity and potential for generalization.

Specifically, there are three research directions that require more attention in the future. First, RCTs should focus on interventions aimed at microvascular function in patients with ACS to establish if better microvascular status leads to improved outcomes. Secondly, there is a need to standardise IMR, CFR and related indices measurement to enhance comparability of results across different studies. Third, large-scale multicenter registries combining MVD with clinical and imaging biomarkers could agree on a better understanding of the correlation between MVD and other intertwined parameters like left ventricular strain, arrhythmia burden, and systemic inflammation (Rahman et al., 2022).

Thus, the meta-analysis of our study further supports the hypothesis that microvascular dysfunction in patients after ACS is an independent predictor of unfavorable long-term prognosis, including MACE, mortality, and heart failure. These results highlight the significance of performing the microvascular examination in daily practice and applying an individualized patient management in high-risk cases. Looking to the future, It may be vital to shift the paradigm from macrovascular to microvascular disease as a way of dealing with future burden of ischemic heart diseases in the future.

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