IJC Heart & Vasculature 58 (2025) 101677

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Prognostic value of myocardial flow reserve by PET imaging in patients with suspected coronary artery disease: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
PET
Prognostic application

ABSTRACT

Purpose: We performed a systematic review and *meta*-analysis of published studies evaluating the value of myocardial flow reserve (MFR) assessed by positron emission tomography (PET) imaging in predicting adverse cardiovascular events in patients with suspected coronary artery disease (CAD).
Material and methods: Studies published until December 2024 were identified by database search. We included studies evaluating MFR by PET imaging with data on adjusted hazard ratio (HR) for the occurrence of adverse cardiovascular events.
Results: We identified 8 eligible articles including 12.087 patients with a mean follow-up of 2.98 ± 0.69 years. The pooled HR for the occurrence of events was 2.19 (95 % CI 1.80–2.68) and no heterogeneity was observed. The pooled incidence rate ratio (IRR) was 3.26 (95 % CI 2.43–4.37) and the heterogeneity was 37.7 %. At *meta*-regression analysis no significant association was found between HR for adverse events and demographic and clinical variables considered.
Conclusion: MFR assessed by PET imaging is a valuable noninvasive prognostic indicator in the evaluation of patients with suspected CAD.

1. Introduction

Accurate risk stratification has become increasingly important to optimize patient outcomes escalating medical care costs [1,2]. Non-invasive modalities such as SPECT and PET imaging have been proved useful for detecting significant coronary artery disease and determining its prognostic significance in the evaluation of CAD, in different patient risk categories [3–5]. Among the different clinical parameters obtained by MPI procedures, myocardial blood flow (MBF) and myocardial flow reserve (MFR) have been established as important predictors of prognosis in patients with cardiovascular disease [6]. Coronary microvascular dysfunction (CMD) is an important clinical disease spectrum which has gained widespread attention due to chronic anginal symptoms, and worse clinical outcomes, with or without obstructive coronary artery disease (CAD). In patients with suspected or known CAD, the diagnostic and prognostic value of PET imaging combining perfusion to functional parameters has been widely recognized [7–9]. Less data are available demonstrating the prognostic value of MBF and MFR measurements by PET in a selected patient population without evidence of CAD, to better discriminate the presence of CMD. Thus, we performed a systematic review and *meta*-analysis of published studies including patients with suspected CAD to assess the prognostic value of

Abbreviations: SPECT, Single-photon emission computed tomography; PET, Positron emission tomography; CT, Computed Tomography; MPI, Myocardial perfusion imaging; CAD, Coronary artery disease; MBF, Myocardial blood flow; MFR, Myocardial flow reserve; HR, Hazard ratio; IRR, Incidence rate ratio.

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https://doi.org/10.1016/j.ijcha.2025.101677
Received 28 February 2025; Received in revised form 27 March 2025; Accepted 31 March 2025

MFR by PET imaging.

2. 2.Materials and methods

The present *meta*-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (see the supplementary material for PRISMA Checklist) [10] and was registered as record ID642349 in the PROSPERO database (University of York, UK; http://www.crd.york.ac.uk/PROSPERO/).

2.1. Data Sources and study selection

An English literature search was performed using the PubMed and Embase databases to identify articles published until December 2024. The search strategy was designed and conducted by an experienced research methodologist. Controlled vocabulary, including Medical Subject Heading (MeSH) terms, with all subheadings, supplemented with keywords, was used to search for studies of PET. Studies search was restricted to data obtained in humans and adults, and was conducted using the following key words: prognosis, prognostic value, clinical outcome, risk stratification, adverse outcome, follow-up, hazard ratio (OR HR), myocardial perfusion imaging (OR MPI), positron emission tomography (OR PET), coronary flow reserve (OR CFR), myocardial perfusion reserve, myocardial flow reserve (OR MFR), microvascular dysfunction, myocardial blood flow (OR MBF), (not known) suspected coronary artery disease (OR CAD). The full search strategy is shown in the supplementary material. The title and abstract of potentially relevant studies were screened for appropriateness before retrieval of the full article by two reviewers (V.C. and R.G.) and disagreements were resolved by consensus. The full-published reports of the abstracts selected by the reviewers were retrieved and the same reviewers independently performed a second-step selection based on the inclusion criteria; disagreements were resolved by consensus. In addition, the bibliographies of retrieved articles were manually reviewed for additional citations. We included as supplementary material a list of full-text articles excluded and a table reporting the exclusion criteria for each article (Supplementary Material, Table S1).

2.2. Data Extraction and eligibility

Each study was initially identified considering journal, authors, and year of publication. Population data were also collected on age and on prevalence of female, traditional cardiovascular risk factors (diabetes, dyslipidemia, smoking, hypertension, family history of CAD), angina-like symptoms and history of CAD (including previous myocardial infarction and coronary revascularization). Follow-up time and occurrence of the different endpoints were recorded. To harmonize the predictors of interest, a study was included if all of the following criteria were met: 1) the study presented data of MFR in subjects with suspected CAD, referred to stress MPI by PET; the study evaluated the population with both suspected and known CAD was considered only if possible to extrapolate data only in patients without CAD; 2) the study provided unadjusted and/or adjusted hazard ratio (HR) of MFR as dichotomous variable for the occurrence of adverse cardiovascular events; or the unadjusted and/or adjusted HR could be obtained from Kaplan-Meier curves between patients with impaired vs. preserved MFR. In the case of multiple studies reported from the same research group, potential cohort duplication was avoided by including the largest study only. Reviews, editorials, abstracts, animal studies, conference presentations, or studies on diagnostic performance were excluded.

2.3. Quality assessment QUIPS

We utilized the modified Quality in Prognostic Studies (QUIPS) appraisal tool considering study participation, attrition, prognostic factor measurement, outcome measurement, confounding account, and statistical analysis [11]. First, the risk of bias was determined for each domain (as low, unclear, or high-risk). Then, the overall risk for each study was judged. Study quality was not considered restrictive for inclusion, but it was comprehensively evaluated.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical data as percentages. The HR with 95 % confidence interval (CI) of each study was abstracted [12]. Univariable HRs, as well as multivariable HRs from maximally adjusted models, were used where available. To minimize the effect of confounding, we included the most extensively adjusted HR (with associated 95 % CI derived from multivariable regression analysis) from each original study, if available. In studies that did not report univariable HRs, HRs were derived to reconstruct time-to-event data from published Kaplan–Meier curves.

All *meta*-analyses were carried out using HR estimates for major adverse cardiac events (MACE) including cardiac death, myocardial infarction, late revascularization, heart failure or acute coronary syndrome, and for hard events including cardiac death and myocardial infarction. A subgroup analysis was performed considering only studies evaluated population with normal myocardial perfusion at semi-quantitative imaging analysis. The pooled estimates of HR and 95 % CI were computed using the random effects model of DerSimonian and Laird [13]. The weight of each study was calculated with the inverse variance method [14]. Between-study heterogeneity was evaluated with Cochran's Q and I^2 statistics [15].

Meta-regression analysis was performed to assess if study-level variables were associated with HR. Publication bias was examined using the effective sample size funnel plot and associated regression test of asymmetry described by Egger et al. [16]. The funnel plot is a scatter plot, where each dot represents an individual study and is positioned according to its effect size or strength of association (x-axis) and the precision around its estimate (y-axis). The construction of the funnel is done using three lines, a vertical line that shows the summary parameter point estimate, and two diagonal lines (funnel) that show the 95 % CI. A reversed (y-axis) scale can be used to place the larger studies towards the top of the plot. For ratio measures a log scale should be used. As the standard error increases, the distance between the funnel lines increases.

The incidence rate ratio (IRR) with 95 % CI was evaluated in the selected studies when outcome data were presented separately in patients with impaired versus preserved MFR. Annualized event rates were calculated by dividing the number of events by the mean or median follow-up duration for each study. The IRR was calculated and log transformed, to obtaining a sampling distribution closer to normality, and pooled using a random effects model. The summary estimates were back transformed and presented as IRR.

All analyses were performed using Stata, version 18.0 (StataCorp, College Station, TX). Two-sided P values ≤ 0.05 were considered statistically significant.

3. Results

3.1. Search results

The complete literature search is presented in Fig. 1. The initial search identified 399 potentially eligible citations. After removing 96 duplicates, 303 records were screened based on titles and abstracts. After the titles and abstracts evaluation, 192 citations were discharged because they were editorials, reviews, case-control studies, congress abstracts, posters, and *meta*-analyses. Thus, 111 full-text articles were blinded assessed by each investigator for eligibility. After revision, 103 articles were excluded, leaving 8 articles including 12.087 patients.

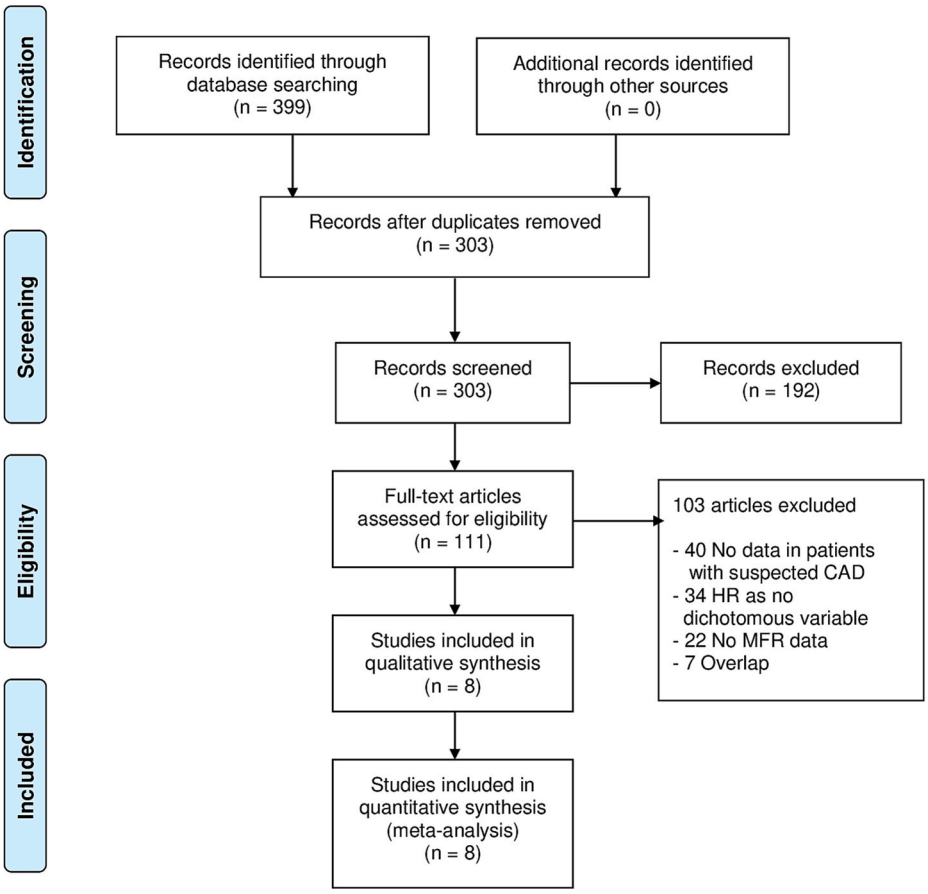

Fig. 1. Literature search and selection process of studies included in the *meta*-analysis. CAD, coronary artery disease; HR, hazard ratio; MFR, myocardial flow reserve.

3.2. Quality assessment

Fig. 2 summarizes the quality assessment of included studies using the QUIPS tool. The risk of bias was considered globally low. The domains that showed a sustained uncertain risk of bias were the 'study participation' and 'study attrition, due to the presence of analysis performed in sub-populations extrapolated from the total population and the different clinical outcome considered in the studies.

3.3. Characteristics of the studies

Demographic data and clinical characteristics of patients are detailed in Tables 1 and 2. For the eight studies included in the analysis [17–24], sample size ranged from 150 to 4008 subjects. The mean age ranged from 58 to 66 years, with the proportion of women ranging from 45 % to 66 %. Follow-up ranged from 0.96 to 6.9 years.

3.4. Prognostic value of MFR by PET

The HR for the occurrence of adverse cardiovascular events was reported in 8 studies. The HR ranged from 1.70 to 3.44. The pooled HR was 2.19 (95 % CI 1.80–2.68) and no heterogeneity was detected (Fig. 3).

3.5. Potential bias and meta-regression analysis

The funnel plots did not show a significant asymmetry ($p = 0.26$) among studies that evaluated adverse cardiovascular events (Fig. 4). At *meta*-regression analysis no significant association was found between the pooled HR for adverse cardiovascular events and demographic and clinical variables.

3.6. Incidence rate ratio

A total of 4 studies [17,19,21,24] reported data useful to calculate separately the incidence rate of adverse cardiovascular events in patients with impaired vs. preserved MFR. The pooled IRR was 3.26 (CI 95 % 2.43–4.37) and the heterogeneity was 37.7 % (Fig. 5).

3.7. Prognostic value of MFR by PET in patients with normal myocardial perfusion

A total of 4 studies [17,19,22,24] evaluated population with normal myocardial perfusion at semiquantitative imaging analysis, the pooled HR for the occurrence of adverse cardiovascular events was 2.27 (95 % CI 1.69–3.06) and the heterogeneity was 9 %. (Fig. 6).

4. Discussion

In the present study we performed a systematic review and *meta*-analysis of published studies including patients with no evidence of CAD to assess the prognostic value of MFR obtained by PET imaging in predicting adverse cardiovascular events. Analyzing 8 selected studies, we found that the assessment of MFR performed by PET showed a significant prognostic power. The summary HR of 2.19 for adverse cardiovascular events indicates that a patient with impaired MFR has about twice and half times the probability of event at the next point in time compared to patient with the same characteristic and preserved MFR.

Since there has been a growing demand for personalized, risk-based, or stratified medicine, information on the prognosis of the individual patient is crucial, leading to an increase in the number of studies investigating biomarkers, prognostic factors, and prognostic models. In this context, *meta*-analysis of prognostic studies can help to identify

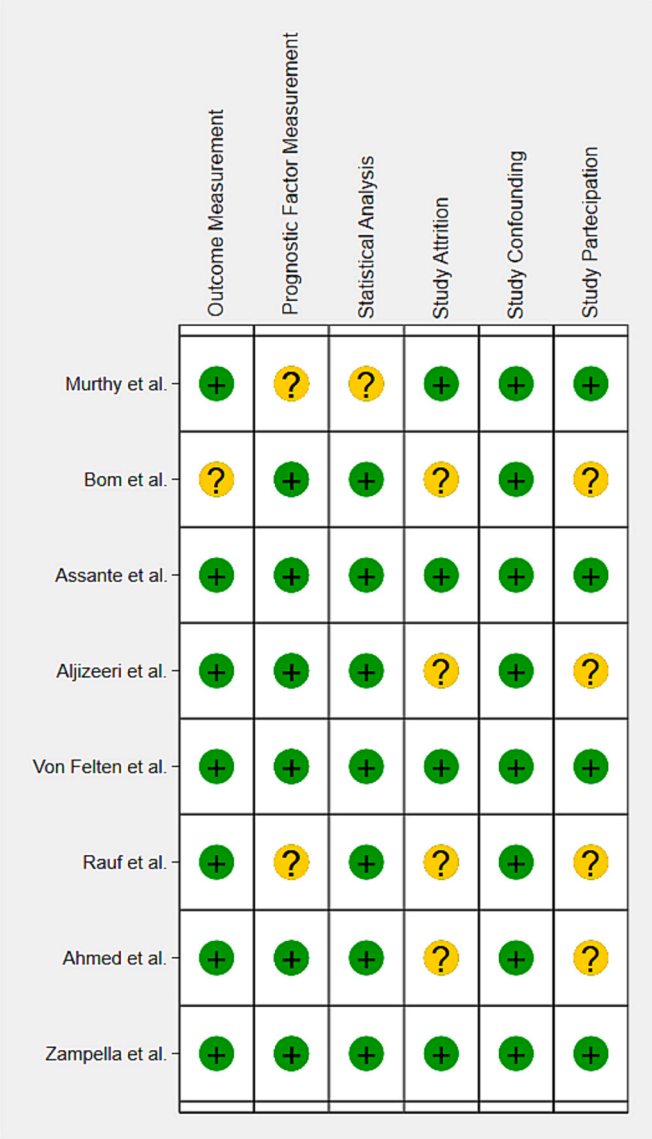

Fig. 2. Methodological quality of the included studies assessed with QUIPS tool for risk of bias and applicability concerns. The green circle represents low risk of bias, the yellow circle unclear risk of bias and the red circle high risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

characteristics that are associated with the occurrence of certain outcomes in a particular time frame for individuals with a particular health condition [25]. Accurate risk stratification has become increasingly important in patients with suspected CAD to adopt appropriate treatment strategies and to improve patient outcomes. It should be considered that CAD is a heterogeneous process that may involve myocardial vascular beds at different levels, and its dynamic nature may lead to a long latent phase in which the disease evolves without significant clinical evidence. During this time, the patients can be still asymptomatic or showing normal diagnostic tests [26,27]. Current guidelines underly the role of functional imaging in management of patients with suspected CAD [28]. Among radionuclide modalities, cardiac imaging with PET/CT can be considered the gold standard for the evaluation of both myocardial ischemia and microvascular dysfunction [4,28,29]. In addition to information on regional perfusion defects, ^{82}Rb PET provides information on MFR, an important measure integrating the effects of epicardial stenoses, diffuse atherosclerosis and microvascular disease on myocardial perfusion [9,30]. Therefore, it offers a unique overall picture of the patient's total vascular health. It should be underlined that microvascular dysfunction as defined by reduced MFR at PET could be considered related to hyperemic MBF or higher resting MBF. Non-invasive identification of structural and/or functional impairment flow-mediated epicardial vasodilation may precede coronary microvascular dysfunction in a cardiometabolic risk population [31,32]. The prognostic value of MFR has been extensively investigated, and the presence of impaired MFR is strongly associated with adverse outcomes also in the absence of other perfusion and structural abnormalities. Moreover, the inclusion of MFR in risk prediction models provides incremental risk stratification beyond clinical and perfusion variables in patients with suspected or known CAD [33–36]. Previous metanalysis have demonstrated that PET-derived MFR was significantly associated with outcomes across patients with any CAD status [37,38]. In particular, in a previous *meta*-analysis performed in patients with suspected and known CAD, Green et al. [38] demonstrated that the presence of impaired MFR by PET is associated with adverse cardiovascular events. Our results in patients without evidence of CAD showed an association between impaired MFR and the occurrence of adverse cardiovascular events, with a pooled hazard ratio of 2.19. Especially, MFR demonstrated to be a good predictor of all-cause mortality and MACE, and its decrease was a better predictor of outcome than stress MBF and other common risk factors for CAD, including hypertension, dyslipidemia, and typical angina. In patients with suspected CAD, reduced MFR may be the major discriminant in the identification of patients at higher risk, and in guiding risk reduction strategies that should go beyond targeting the epicardial coronary vessels. As observed in our analysis, patients with normal perfusion but reduced MFR had a higher event rate as compared to those with normal perfusion and normal MFR. Also, in a subgroup analysis evaluating data on MFR in patients with normal perfusion, the results on prognostic power of the data were confirmed, without significative heterogeneity, confirming that the absence of perfusion abnormalities may not exclude the presence of underlying disease, helping in the identification of microvascular involvement. Identification of impaired MFR in these patients could have important impact on

Table 1
Demographic data and clinical characteristics of patients included PET studies.

	Patients (n)	Age (years)	Women (%)	Diabetes (%)	Dyslipidemia (%)	Smoking (%)	Hypertension (%)	Angina (%)	Family historyof CAD (%)
Murthy et al. [17]	1218	61	66	29	54	9	73	15	26
Bom et al. [18]	648	59 ± 10	45	20	39	34	48	33	53
Assante et al. [19]	1842	58 ± 12	55	24	66	19	73	–	45
Aljizeeri et al. [20]	4008	59 ± 11	55	58	59	5	77	72	–
Von Felten et al. [21]	150	64 ± 11	45	16	43	33	64	35	27
Rauf et al. [22]	1587	66 ± 11	49	17	61	50	63	28	34
Ahmed et al. [23]	1704	66 ± 11	47	47	79	–	87	–	–
Zampella et al. [24]	1967	60	55	24	61	29	69	45	48

Values are mean ± standard deviation or as number or percentage of subjects.
PET, positron emission tomography; *CAD*, coronary artery disease.

Table 2
Characteristics of included PET studies reporting adverse events.

	Vasodilation agent	Tracer and dose	Endpoint	FU (years)	AbnormalMFR	Hazard ratio	Multivariableadjustment
Murthy et al. [17]	Adenosine, dipyridamole, dobutamine, regadenoson	^{82}Rb (1480–2200 MBq)	CD, MI, HF, R	1.2	<2	Univariable*	–
Bom et al. [18]	Adenosine	$^{[15O]}$ H2O (370 MBq)	All-cause death, MI	6.9	<2.88	Multivariable	Clinical variables
Assante et al. [19]	Adenosine	^{82}Rb (1110 MBq)	CD, MI, R	3.6	<2	Multivariable	–
Aljizeeri et al. [20]	Dipyridamole, adenosine	^{82}Rb (25–35 mCi)	CD, MI	1.9	<2	Multivariable	Clinical and imaging variables
Von Felten et al. [21]	Adenosine	^{13}N-ammonia (700–900 MBq)	All-cause death, MI, R	4.1	<2	Multivariable	–
Rauf et al. [22]	Adenosine	^{82}Rb (1110 MBq)	All-cause death, MI, HF, R, stroke	1.7	<2	Multivariable	–
Ahmed et al. [23]	Adenosine	^{82}Rb (10–25 mCi)	All-cause death, MI, R	0.96	<2	Multivariable	Baseline and PET variables
Zampella et al. [24]	Adenosine	^{82}Rb (1110 MBq)	CD, MI	3.4	<2	Multivariable	–

FU, follow-up; *R*, late revascularization; *CD*, cardiac death; *MI*, myocardial infarction; *HF*, heart failure; *MFR* myocardial flow reserve.
* Derived from Kaplan Meier analysis.

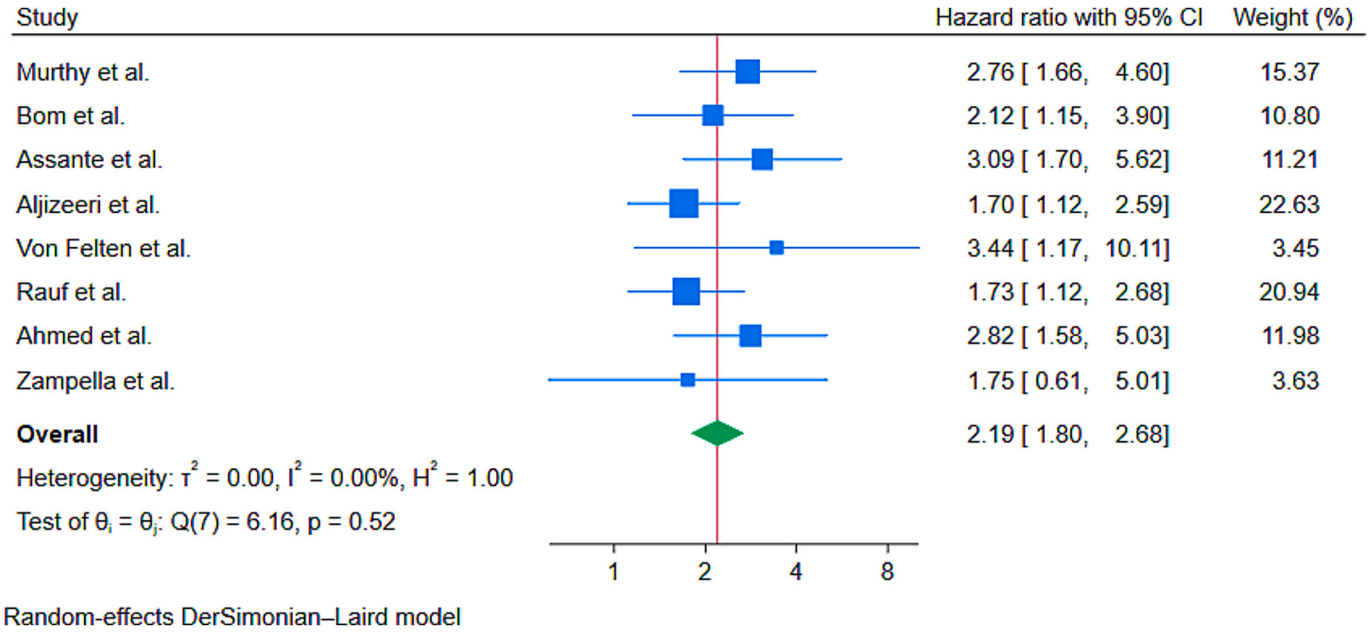

Fig. 3. Forest plot of HR for adverse events associated with impaired myocardial flow reserve. Horizontal lines represent 95 % CI of the point estimates. The diamond represents the pooled estimate (size of the diamond = 95 % CI). The solid vertical line represents the reference of no increased risk, and the dashed vertical line represents the overall point estimate. The size of the blue square indicates the weight of the study in the *meta*-analysis. CI, confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

decisions for invasive angiography and revascularization, considering that different parameters including atherosclerosis and microvascular dysfunction may contribute to the pathophysiology of cardiovascular death and heart failure and may impact the outcomes of revascularization [9,39]. In accordance with our results, previously published data have pointed up the relevant prognostic value of reduced MFR in patients with normal perfusion, as index of coronary endothelial and microcirculatory dysfunction excluding relevant epicardial coronary obstructive disease [35].

Routine integration of MFR with relative MPI could represent a valuable tool for the clinicians to better stratify patient's risk of adverse cardiac events. Impaired MFR means worse outcomes in any category of MPI perfusion, and this could affect management decisions for these patients [38].

In the present study we evaluate hazard ratio as effect size, most interpretable when the ratio of risks is relatively constant over the follow-up period, but it summarizes the overall reduction in risk for one group compared to another group even when the ratio of risks is not constant over time. Moreover, the use of hazard ratios as outcome measure can produce valid synthesis and provide results easier to interpret. The robustness of our findings was demonstrated by quality assessment, showing that risk of bias is globally low, and the uncertain risk of bias was identified in the study participation considering that in some studies, sample was extracted from the overall population and study attrition due to the systematic differences in participants lost at follow-up [11,40]. Moreover, to explore consistency of findings, a *meta*-regression analysis was performed to evaluate the potential effect modifiers. No significant association was found between clinical variables and pooled HR, underlining the robustness of the results in a specific cohort of patients with suspected CAD. However, it should be

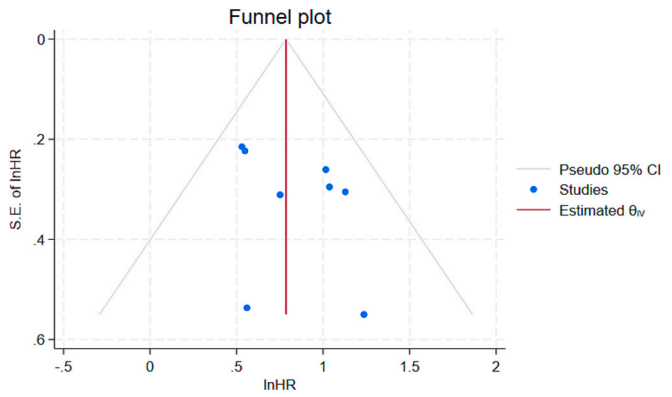

Fig. 4. Funnel plot for the risk of adverse events associated with impaired myocardial perfusion reserve. Each dot represents a study; the y-axis represents study precision (standard error of effect size) and the x-axis shows the effect size. Large studies appear toward the top of the graph and tend to cluster near the mean effect size. Small studies appear toward the bottom of the graph and are dispersed across a range of values since there is more sampling variation in effect size estimates. The vertical solid line (theta IV, inverse-variance) represents the estimated effect-size line. The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of biases and heterogeneity. lnHR, natural logarithm of hazard ratio; S.E., standard error; CI, confidence interval.

considered that other unmeasured confounders (e.g., medication use, genetic factors) could still influence results. We also evaluated the estimated IRR of adverse cardiovascular events in patients with impaired and preserved MFR. The results confirm that patients with impaired MFR had a worse outcome and underline the role of MPI as a predictor of risk in these patients.

5. Study limitations

Our study has different limitations such as variability in PET tracers, imaging protocols and differences in cut-off to define impaired MFR. The studies evaluating the prognostic value of impaired MFR in patients with suspected CAD are complex to examine, due to the large variety of endpoints considered in each study, therefore we included studies with variable designs, baseline characteristics, cardiovascular event definitions and follow-up durations. Another limitation of the present study may be the use of global but not regional MFR, because in the global value the regional findings may be diluted. However, the global MFR seems to be most appropriate to include the aspect of microcirculatory dysfunction without or in addition to epicardial coronary disease.

Finally, in the absence of coronary angiography data, the presence of balanced ischemia cannot be excluded in the setting of patient's population analyzed.

6. New Knowledge gained and clinical Implications

Absolute quantification of MFR by using PET imaging is able to predict outcome in patients with suspected CAD. This evidence supports the routine integration of quantification of MFR by using PET imaging in the risk-stratification and management of patients with suspected CAD.

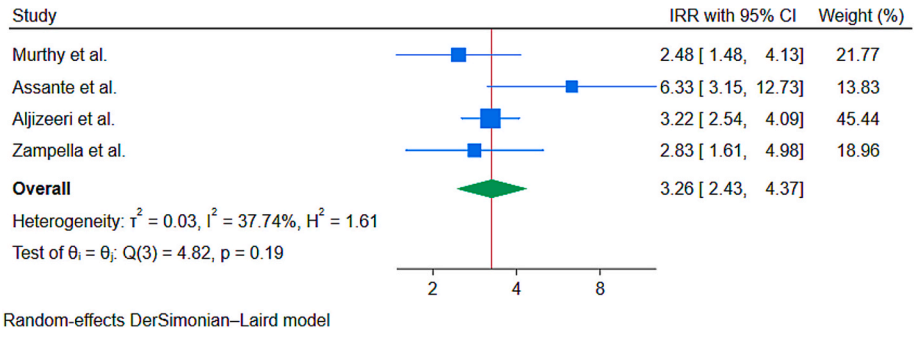

Fig. 5. Forest plot for the incidence rate ratio of adverse events in patients with impaired and normal myocardial flow reserve. Horizontal lines represent 95 % CI of the point estimates. The diamond represents the pooled estimate (size of the diamond = 95 % CI). The solid vertical line represents the reference of no increased risk, and the dashed vertical line represents the overall point estimate. The size of the blue square indicates the weight of the study in the metanalysis. The size of the blue square indicates the weight of the study in the *meta*-analysis. IRR, incidence rate ratio; CI, confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

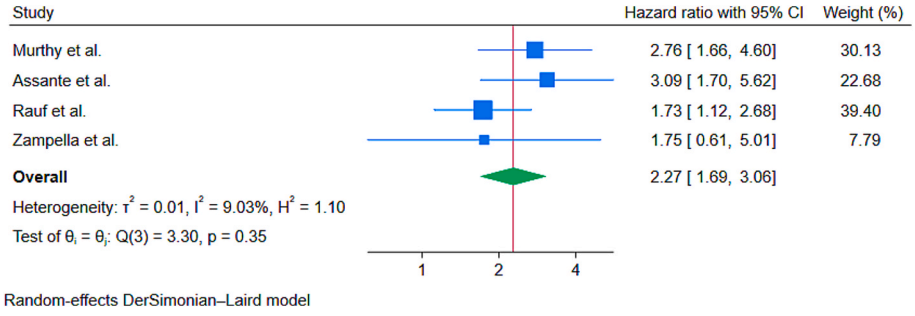

Fig. 6. Forest plot of HR for adverse events associated with impaired myocardial flow reserve in patients with normal myocardial perfusion. Horizontal lines represent 95 % CI of the point estimates. The diamond represents the pooled estimate (size of the diamond = 95 % CI). The solid vertical line represents the reference of no increased risk, and the dashed vertical line represents the overall point estimate. The size of the blue square indicates the weight of the study in the metanalysis. The size of the blue square indicates the weight of the study in the *meta*-analysis. CI, confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

7. Conclusion

The assessment of MFR evaluated by PET showed a high prognostic power in the evaluation of patients with suspected CAD. Our findings pointed out that an impaired MFR is strongly associated with an increased risk of adverse cardiovascular events and could affect management decisions for these patients.

Funding

Open access funding provided by Università degli Studi di Napoli Federico II within the CRUI-CARE Agreement.

Authors' contributions

A.D.A., A.C., and W.A. conceptualized the paper; R.A., E.Z., V.C., R. G., V.G., C.N., T.M., P.B. and M.P. evaluated and reported the imaging findings; A.D.A., R.A., A.C., and W.A. drafted the manuscript; and all the authors revised and commented on the paper and approved the final version of the manuscript.

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These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

CRediT authorship contribution statement

Adriana D'Antonio: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Roberta Assante:** Writing – review & editing, Investigation, Formal analysis. **Emilia Zampella:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Valeria Cantoni:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Roberta Green:** Writing – review & editing, Investigation, Formal analysis. **Valeria Gaudieri:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Teresa Mannarino:** Methodology, Formal analysis. **Maria Falzarano:** Methodology, Investigation. **Federica Volpicelli:** Formal analysis, Data curation. **Paolo Cutillo:** Methodology, Data curation. **Francesca Matrisciano:** Investigation, Data curation. **Pietro Buongiorno:** Methodology, Data curation. **Mariarosaria Panico:** Methodology, Investigation. **Carmela Nappi:** Methodology, Investigation. **Domenico Cozzolino:** Methodology, Investigation. **Mario Petretta:** Formal analysis. **Alberto Cuocolo:** Writing – review & editing, Conceptualization. **Wanda Acampa:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101677.

Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101677.

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