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SYSTEMATIC REVIEW

Prognostic value of normal positron emission tomography myocardial perfusion imaging in patients with known or suspected coronary artery disease: a meta-analysis

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Objective: Several studies have confirmed high diagnostic performance of positron emission tomography (PET) myocardial perfusion imaging (MPI) in patients with known or suspected coronary artery disease. However, whether the superior diagnostic accuracy could translate into improved mortality outcomes remains unknown. The aim of this study was to define the prognostic value of normal PET MPI.

Methods: PubMed and EMBASE were searched to identify related studies up to June 2016. All studies using PET MPI to evaluate subjects with known or suspected coronary artery disease and providing absolute number of patients with a negative test and primary data on clinical outcomes with a follow-up time ≥ 3 months were included for analysis.

Results: The search yielded 11 studies comprising 20,471 patients for final analysis. The negative-predictive value (NPV) for cardiac death, all-cause death and major adverse cardiovascular events (MACE) were

98.80% [95% confidence interval (CI), 97.64%–99.39%], 94.89% (95% CI: 92.99–96.30%) and 90.26% (95% CI: 78.01–96.03%), over 36.9 months of follow-up for cardiac death, over 26.8 months for all-cause death and 35.7 months for MACE. The corresponding annualized event rates were 0.39%, 2.29% and 3.27%, respectively. In subgroup analyses of different imaging analysis methods for PET MPI, studies using perfusion abnormality had a similar NPV as compared with those using coronary flow reserve (98.46% vs 98.86%, p -value = NS), with a corresponding annualized event rate after negative tests (equal to $1 - \text{NPV}$) as 0.45% and 0.42%, respectively.

Conclusion: Normal PET has a high NPV for cardiac death, MACE and all-cause mortality. Different indexes used for PET imaging analysis have a comparable prognostic value.

Advances in knowledge: A normal PET MPI conferred a very low risk of cardiac death of 0.39% per year, which is close to that of a normal aged-matched population.

INTRODUCTION

Globally, coronary artery disease (CAD) remains the top cause of mortality with an estimated 7.3 million cases in 2008.¹ The need for comprehensive risk stratification among patients with documented or suspected CAD is paramount to identify high-risk patients for major adverse cardiovascular events (MACE).^{2–4} The use of non-invasive cardiac imaging has remained the cornerstone for the diagnosis and prognosis in CAD, which has been well validated.^{5–12} A normal single-photon emission CT myocardial perfusion imaging (MPI) has a low

cardiac event rate ($<1\%$ per year),^{13–15} whereas a normal stress cardiac MR has a negative-predictive value (NPV) of 98.12% for adverse cardiac events with an event rate of 1.88%.^{16–19}

Positron emission tomography (PET) MPI has a superior spatial resolution and robust attenuation correction, and it demonstrated superior sensitivity and specificity in CAD assessment than single-photon emission CT MPI.²⁰ In addition, we had concluded our previous analysis²¹ that PET has a high sensitivity and specificity, leading to a high

diagnostic accuracy comparable to cardiac MRI in detecting functional CAD determined by fractional flow reserve; however, whether the superior diagnostic accuracy of PET MPI based on receiver operating characteristics translate into improved mortality outcomes in a larger cohort of patients is uncertain. This meta-analysis evaluates the prognostic value of a normal PET MPI in patients with known or suspected CAD.

METHODS AND MATERIALS

Search strategy

PubMed and EMBASE were searched on the 15 June 2016 to identify all trials on prognostic value of PET MPI in patients with known or suspected CAD, published up to June 2016. Keywords used were: “positron emission tomography”, “prognostic”, “outcomes”, “major adverse cardiac events”, “cardiac infarction” and “mortality”. Additionally, we limited our search to “humans” and “English”.

Selection criteria

Two authors (A'DC and HSW) identified the relevant original articles and extracted the data independently, and the third author (ND) checked the results. Any disagreement was resolved by discussion until a consensus was reached. Studies were included if they met the following criteria: (1) patients referred for suspected or known CAD without recent myocardial infarction (MI), percutaneous coronary intervention or coronary artery bypass graft surgery within 30 days prior to the study; (2) negative or normal test was defined; (3) absolute number of patients with a negative test and primary data on clinical outcomes of MACE, all-cause death, non-fatal MI, cardiac death or in any combination; and (4) a follow-up time of more than 3 months. In cases of multiple studies conducted in the same research centre during the same period, potential cohort duplication was avoided by including the largest study only.

Data extraction

Two authors extracted the study and patient characteristics, inclusion and exclusion criteria and outcomes of patients with negative PET MPI study. In cases where multiple variables were analyzed [e.g. coronary flow reserve (CFR) *vs* visual interpretation], each evaluation method was considered separately.

A quality assessment was performed on the basis of the (1) presence of complete follow-up for 90% or more of the baseline cohort; (2) outcome data obtained by investigators who were blinded to the test results; and (3) use of hospital records and death certificates to corroborate the outcomes. Studies were categorized as good quality if they fulfilled the criterion of 90% follow-up or greater, in addition to at least one of the other two criteria: fair quality if it fulfilled one of the criteria or poor quality if none of the criteria were met.

Data synthesis

The baseline characteristics of all patients were obtained as weighted averages of those reported in single studies with the weighting factor proportional to the study's total sample size. Statistical heterogeneity between studies was assessed using

the Cochrane Q statistic ($p < 0.1$ indicating significant heterogeneity) and I^2 statistic^{22,23} that measures the percentage of total variability across studies not due to sampling error. If a large heterogeneity was observed, the pooled estimates of NPV for hard and soft events and the pooled estimates of the event rate after negative tests ($ERNT = 1 - NPV$) were computed using the random effects model.²⁴ For all other analysis, the fixed effects model was used. The annualized ERNT was obtained as an average of the duration of follow-up. Publication bias was assessed visually using a funnel plot and formally using the Egger test.²⁵ The pooled analyses by both fixed effects and random effects models, and the publication bias analysis, are displayed in the [Supplementary materials](#). All analyses were performed with R statistics v. 2.15.0 and the META e METAFOR.

RESULTS

The initial search identified 1068 potentially eligible studies, and 1057 studies were excluded for reasons listed in [Figure 1](#), leaving a total of 11 studies for the final analysis.^{26–36} Patient demographics and clinical characteristics are depicted in [Table 1](#).

Predictive value of normal PET MPI for cardiac death
All studies included cardiac death as the primary or secondary outcome. The NPV was 93.70–100%; the pooled NPV was

Figure 1. Flow chart of the study of 1068 potentially relevant citations, 11 articles met our inclusion criteria and were included for final analysis. CABG, coronary artery bypass grafting; CAD, coronary artery disease; DM, diabetes mellitus; MI, myocardial infarction; PET, positron emission tomography; SPECT, single-photon emission CT.

Table 1. Demographical and clinical characteristics of patients included in the studies enrolled in meta-analysis

Study, year	Indexes for imaging analysis	Standard for negative test	Tracer	Scanner	Age (years)	Men (%)	History of CAD (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	Smoking (%)	Study quality
Murthy et al ²⁶ 2014	CFR	CFR $\geq$ 2.0	⁸² Rb	PET/CT scan (Discovery TM LS, GE Healthcare, Milwaukee, WI)	61.9	33.3	0	73.4	29.8	54.4	9.9	Good
Chow et al ³³ 2014	Percentage abnormal myocardium at rest or stress	0	⁸² Rb	PET (ECAT ART; custom tissue imaging; Siemens, Knoxville, TN; Positron HZL/R; Positron Corporation, Houston, TX) or a hybrid PET/CT scanner [Discovery Rx or STE LightSpeed [®] (GE Healthcare); Biograph 64 (Siemens)]	62.4	51.9	26.5	66.3	26.8	64.0	23.6	Fair
Farhad et al ²⁷ 2013	SDS	SDS $\leq$ 2	⁸² Rb	Discovery LS (GE Healthcare)	64.6	63.5	34.6	65.1	38.5	55.7	34.9	Good
Dorbala et al ²⁸ 2013	Percentage abnormal myocardium at stress	0	⁸² Rb	A dedicated or hybrid PET/CT scanner	63.3	52.6	NA	67.9	27.2	63.9	21.6	Good
Rischpler et al ³⁴ 2012	TID	TID $\leq$ 1.13	⁸² Rb	Discovery STRx PET/CT system (GE Healthcare)	60	44.3	36.0	66.0	37.0	49.0	35.0	Good
Murthy et al ³⁵ 2011	CFR	CFR $\geq$ 2.0	⁸² Rb	PET/CT scanner (Discovery RX or STE LightSpeed 64)	64.8	47.9	42.2	81.6	36.2	66.6	10.6	Good
Van Tosh et al ²⁹ 2010	SSS	SSS = 0	⁸² Rb	PET camera (Positron; Positron Corporation)	63	0	0	48.3	14.2	42.3	17.5	Fair
Herzog et al ³⁶ 2009	CFR/SSS	CFR $\geq$ 2.0/ SSS < 4	¹³ N-ammonia	GE Advance PET scanner or on a Discovery (LS/RX) PET/CT scanner (both GE Healthcare)	60	30.1	28.8	26.2	7.9	25.8	18.3	Good
Lertsburapa et al ³⁰ 2008	SSS	SSS < 4	⁸² Rb	Discovery LS PET/CT scanner (GE Healthcare, Waukesha, WI)	69.5	41.7	53.6	79.3	29.9	78.4	18.7	Good
Schindler et al ³¹ 2005	MBF to sympathetic stimulation	% Δ MBF $\geq$ 40	¹³ N-ammonia	PET (951 ECAT; Siemens, Erlangen, Germany)	57.6	37.5	19.4	41.7	5.6	41.7	25.0	Good
Marwick et al ³² 1997	Percentage abnormal myocardium at rest and stress	0	⁸² Rb	PET camera (Positron; Positron Corporation)	62	74.0	NA	53.0	24.0	55.0	36.0	Good

¹³N, nitrogen-13; ⁸²Rb, rubidium-32; CAD, coronary artery disease; CFR, coronary flow reserve; MBF, myocardial blood flow; NA, not available; PET, positron emission tomography; SDS, summed difference score; SSS, summed stress score; TID, transient ischaemic dilation ratio.

Figure 2. Negative-predictive value (NPV) and event rate after negative test (ERNT) for cardiac death. The pooled NPV and ERNT for cardiac death in all patients with normal positron emission tomography (PET) myocardial perfusion imaging. The analysis revealed a pooled NPV of 98.80% [95% confidence interval (CI), 97.64–99.39%], a pooled ERNT of 1.20% (95% CI, 0.61–2.36%) and a corresponding annualized ERNT of 0.39%. Nr., number.

98.80% [95% confidence interval (CI), 97.64–99.39%]; and the pooled ERNT was 1.20% (95% CI, 0.61–2.36%). During a mean follow-up of 36.9 months, the corresponding annualized ERNT was 0.39% for patients with normal PET MPI (Figure 2). A high level of heterogeneity was identified ($I^2 = 83.2\%$; $p < 0.0001$), and the randomized effects model was applied.

PET MPI interpretation using semi-quantitative and quantitative methods (Figure 3) revealed similar NPVs (98.46% vs 98.72%, respectively), with a higher annualized ERNT (0.46% vs 0.35%) in the semi-quantitative group. Fair-quality studies demonstrated a high NPV (99.21% vs 98.51%) with a lower annualized ERNT (0.29% vs 0.46%), but no statistical significance was reached (Figure 4).

Studies using PET perfusion variables had a lower NPV than those using CFR (98.46% vs 98.86%), which is computed by dividing the stress myocardial blood flow (MBF) by the

corrected rest MBF, with a corresponding annualized ERNT as 0.45% and 0.42%, respectively (Figure 5).

Predictive value of normal PET MPI for all-cause death

All-cause death was reported in seven studies, with a pooled NPV of 94.89% (95% CI: 92.99–96.30%), with the ERNT and annualized ERNT of 5.11% (95% CI: 3.70–7.01%) and 2.29%, respectively (Figure 6). Studies using semi-quantitative analysis had a similar NPV compared with quantitative analysis (94.66% vs 94.26%) but with a lower annualized ERNT (2.10% vs 2.97%) (Figure 7).

Predictive value of normal PET MPI for MACE

MACE as the outcome was available for 4 studies. Figure 8 shows the forest plot of the NPV and ERNT for each study, and the pooled estimates using the random effects model ($I^2 = 94.3\%$; $p < 0.0001$). The individual NPVs were 76.38–96.53%. The summary NPV, during a weighted mean follow-up of 35.7 months, was 90.26% (95% CI:

Figure 3. Negative-predictive value (NPV) and event rate after negative test (ERNT) for cardiac death for different positron emission tomography (PET) imaging analysis methods. Subgroup analysis according to semi-quantitative and quantitative PET myocardial perfusion imaging (MPI) interpretation methods applied in included studies for the pooled NPV and ERNT for cardiac death in patients with normal PET MPI. The analysis revealed that in the semi-quantitative analysis subgroup, the pooled NPV is 98.46% [95% confidence interval (CI), 96.43–99.34%], the pooled ERNT is 1.54% (95% CI, 0.66–3.57%) with a corresponding annualized ERNT of 0.46%; in the quantitative analysis subgroup, the pooled NPV is 98.72% (95% CI, 93.77–99.75%), the pooled ERNT is 1.29% (95% CI, 0.25–6.32%) with a corresponding annualized ERNT of 0.35%. Nr., number.

Figure 4. Negative-predictive value (NPV) and event rate after negative test (ERNT) for cardiac death for quality of studies. Subgroup analysis according to quality of included studies for the pooled NPV and ERNT for cardiac death in patients with normal positron emission tomography (PET) myocardial perfusion imaging. The analysis revealed that in the studies with fair study quality, the pooled NPV is 99.21% [95% confidence interval (CI), 98.82–99.48%] and the pooled ERNT is 0.79% (95% CI, 0.52–1.18%) with a corresponding annualized ERNT of 0.29%; in the studies with good study quality, the pooled NPV is 98.51% (95% CI, 96.15–99.44%) and the pooled ERNT is 1.49% (95% CI, 0.57–3.85%) with a corresponding annualized ERNT of 0.46%. Nr., number.

78.01–96.03%), with a pooled ERNT of 9.74% (95% CI: 3.97–21.99%).

DISCUSSION

To our knowledge, this is the first comprehensive meta-analysis evaluating the prognostic value of normal PET MPI in patients with known or suspected CAD. A normal PET MPI conferred a very low risk of cardiac death, all-cause death and MACE. A cardiac death rate of 0.39% per year is close to that of a normal age-matched population.³⁷

The clinical use of PET MPI has experienced marked growth with advancement in hardware and software, and the ease of on-site production of specific cardiac PET radiotracers. Besides the superior diagnostic accuracy of PET MPI in CAD assessment,⁵ the absolute quantification of MBF and CFR provides incremental prognostic information. Evidence from a multi-centre PET MPI registry totalling 7061 patients demonstrated a NPV of 99.2% for cardiac death with an annualized ERNT of 0.37%. Our meta-analysis with a sample size of 20,471 patients demonstrated a NPV of 98.80% with an annualized ERNT of

Figure 5. Negative-predictive value (NPV) and event rate after negative test (ERNT) for cardiac death for different positron emission tomography (PET) imaging analysis indexes. Subgroup analysis according to different PET myocardial perfusion imaging (MPI) interpretation indexes [perfusion defect (PD) vs coronary flow reserve (CFR)] applied in included studies for the pooled NPV and ERNT for cardiac death in patients with normal PET MPI. The analysis revealed that in the studies using PD as the analysis index, the pooled NPV is 98.46% [95% confidence interval (CI), 96.43–99.34%] and the pooled ERNT is 1.54% (95% CI, 0.66–3.57%) with a corresponding annualized ERNT of 0.45%; in the studies using CFR as the analysis index, the pooled NPV is 98.86% (95% CI, 92.95–99.83%) and the pooled ERNT is 1.14% (95% CI, 0.17–7.06%) with a corresponding annualized ERNT of 0.42%. Nr., number.

Figure 6. Negative-predictive value (NPV) and event rate after negative test (ERNT) for all-cause death. The pooled NPV and ERNT for all-cause death in all patients with normal positron emission tomography (PET) myocardial perfusion imaging. The analysis revealed a pooled NPV of 94.89% [95% confidence interval (CI), 92.99–96.30%], a pooled ERNT of 5.11% (95% CI, 3.70–7.01%) and a corresponding annualized ERNT of 2.29%. Nr., number.

0.39%. During study interpretation, various PET MPI variables can be used to risk stratify patients beyond standard perfusion variables (e.g. summed stress score and left ventricular ejection fraction) and have shown to provide incremental prognostic information such as CFR, and calcium score.³⁸ In this meta-analysis, perfusion defect size and severity, left ventricular ejection fraction, MBF, CFR and transient ischaemic dilatation were used.

In our analysis, PET perfusion variables had a lower NPV than CFR, though not statistically significant. Patients with a normal perfusion but abnormal CFR during nitrogen-13 ammonia PET MPI had a higher annual event rate for MACE (1.4% vs 6.3%, $p < 0.05$) and cardiac death (0.5% vs 3.1%, $p < 0.05$) over 3 years than those with normal perfusion and CFR.³⁶ Our study provided a new knowledge that inclusion of additional PET variables during study interpretation might affect the predictive accuracy of PET MPI for cardiac death. Future research into this aspect is required to provide better understanding.

Similar to any meta-analysis, study heterogeneity and publication bias cannot be entirely excluded. Our study did not demonstrate significant publication bias. We were unable to verify the source images of the normal studies. This has potential implications of what “true” normal is and the standard reference used for comparison such as invasive coronary angiography. This analysis was limited to evaluating normal PET MPI studies; a normal MPI has different implications in patients with known and suspected CAD, and we could not identify studies that included suspected CAD or known CAD alone, which would bias the results, and how our findings would translate among patients with abnormal PET MPI, which will require further research.

CONCLUSION

A normal PET MPI conferred a high NPV and low event rates for cardiac events in patients with suspected or known CAD. Inclusion of additional imaging variables may influence its prognostic performance and warrants further study.

Figure 7. Negative-predictive value (NPV) and event rate after negative test (ERNT) for all-cause death for different positron emission tomography (PET) imaging analysis methods. Subgroup analysis according to different PET imaging analysis methods for the pooled NPV and ERNT for all-cause death in patients with normal PET myocardial perfusion imaging. The analysis revealed that in the semi-quantitative analysis sub-group, the pooled NPV is 94.66% [95% confidence interval (CI), 93.27–95.78%], the pooled ERNT is 5.34% (95% CI, 4.22–6.73%) with a corresponding annualized ERNT of 2.10%; in the quantitative analysis sub-group, the pooled NPV is 94.26% (95% CI, 88.46–97.23%), the pooled ERNT is 5.74% (95% CI, 2.77–11.54%) with a corresponding annualized ERNT of 2.97%. Nr., number.

Figure 8. Negative-predictive value (NPV) and event rate after negative test (ERNT) for major adverse cardiac events. The pooled NPV and ERNT for major adverse cardiac events in all patients with normal positron emission tomography (PET) myocardial perfusion imaging. The analysis revealed a pooled NPV of 90.26% [95% confidence interval (CI), 78.01–96.03%], a pooled ERNT of 9.74% (95% CI, 3.97–21.99%) and a corresponding annualized ERNT of 3.27%. Nr., number.

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