Interaction of impaired myocardial flow reserve and extent of myocardial ischemia assessed using ^{13}N-ammonia positron emission tomography imaging on adverse cardiovascular outcomes

Shiro Miura, MD, MSc,[a] Atsutaka Okizaki, MD, PhD,[b] Hiraku Kumamaru, MD, PhD,[c] Osamu Manabe, MD, PhD,[d] Masanao Naya, MD, PhD,[e] Chihoko Miyazaki, MD, PhD,[f] and Takehiro Yamashita, MD, PhD[a]

[a] Department of Cardiology, Hokkaido Ohno Memorial Hospital, Sapporo , Japan
[b] Department of Radiology, Asahikawa Medical University, Asahikawa, Hokkaido, Japan
[c] Department of Healthcare Quality Assessment, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[d] Department of Radiology, Saitama Medical Center, Jichi Medical University, Saitama-Shi, Japan
[e] Department of Cardiovascular Medicine, Hokkaido, University Graduate School of Medicine, Sapporo, Japan
[f] Department of Diagnostic Radiology, Hokkaido Ohno Memorial Hospital, Sapporo, Japan

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Background. **Myocardial flow reserve (MFR) and the extent of myocardial ischemia identify patients at high risk of major adverse cardiovascular events (MACEs). Associations between positron emission tomography (PET)-assessed extent of ischemia, MFR, and MACEs is unclear.**

Method. **Overall, 640 consecutive patients with suspected or known coronary artery disease undergoing ^{13}N-ammonia myocardial perfusion PET were followed-up for MACEs. Patients were categorized into three groups based on myocardial ischemia severity: Group I (n = 335), minimal (myocardial ischemia < 5%); Group II (n = 150), mild (5–10%); and Group III (n = 155), moderate-to-severe (> 10%).**

Results. **Cardiovascular death and MACEs occurred in 17 (3%) and 93 (15%) patients, respectively. Following statistical adjustment for confounding factors, impaired MFR (global MFR < 2.0) was revealed as an independent predictor of MACEs in Groups I (hazard ratio [HR], 2.89; 95% confidence interval [CI], 1.48–5.64; $P = 0.002$) and II (HR, 3.40; 95% CI 1.37–8.41; $P = 0.008$) but was not significant in Group III (HR, 1.15; 95% CI 0.59–2.26; $P = 0.67$), with a significant interaction ($P < 0.0001$) between the extent of myocardial ischemia and MFR.**

Conclusion. **Impaired MFR was significantly associated with increased risk of MACEs in patients with ≤ 10% myocardial ischemia but not with those having > 10% ischemia, allowing a clinically effective risk stratification. (J Nucl Cardiol 2023)**

Key Words: Myocardial flow reserve • Myocardial ischemia • Coronary artery disease

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Reprint requests: Shiro Miura, MD, MSc, Department of Cardiology, Hokkaido Ohno Memorial Hospital, 2-1-16-1 Miyanosawa, Nishi-Ku, Sapporo 063-0052, Japan; *shirotan1027m@yahoo.co.jp*

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Abbreviations	
CAD	Coronary artery disease
HF	Heart failure
MACE	Major adverse cardiac event
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
MPI	Myocardial perfusion imaging
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
SDS	Summed difference score

INTRODUCTION

The diagnostic and prognostic benefits of myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are important. The magnitude of ischemia on SPECT-MPI scans could be a gatekeeper to identify ideal revascularization candidates with improved long-term major adverse cardiac event (MACE) outcomes.[1] Patients with 10–12.5% myocardial ischemia may have a survival benefit with early revascularization.[1,2] The diagnostic accuracy of MPI using ^{82}Rb- or ^{13}N-ammonia PET appears to be superior to that of SPECT-MPI, although its disadvantages include lower patient access, higher costs, and technical/logistical difficulties related to radiotracer use.[3] Reportedly, patients with higher PET-MPI-measured ischemia levels had a greater survival benefit from early revascularization with a potential ischemia threshold of 5%, lower than that for SPECT-MPI.[4] Thus, PET-MPI allows accurate obstructive coronary artery disease (CAD) detection, myocardial ischemia assessment, and discrimination between low- and high-risk patients for MACEs, helping to identify ideal revascularization candidates with improved long-term cardiovascular outcomes.[5]

PET can provide quantitative myocardial perfusion measurement, offering information on macro- and microcirculation, leading to more accurate detection of early and advanced CAD. Quantitative myocardial flow reserve (MFR), calculated as the ratio of hyperemic to resting myocardial blood flow (MBF), integrates the hemodynamic effects of epicardial coronary stenosis, diffuse atherosclerosis, and microvascular dysfunction, contributing to risk estimation for future MACEs.[6,7] Moreover, the combined MFR and myocardial ischemia measurements could identify at-risk patients.[8] However, the relationships among PET-assessed extent of myocardial ischemia, MFR, and MACEs are unknown. MFR is associated with MACEs independently of angiographic score and modifies the effect of revascularization with an interaction between myocardial ischemia and early revascularization.[4,9] Therefore, we investigated the clinical impact of impaired MFR in predicting future MACEs when combined with the extent of myocardial ischemia, assessed using ^{13}N-ammonia PET-MPI, considering the effect of early revascularization. We examined the annualized MACE rates for each ischemia level and the prognostic value of MFR over the semi-quantitative assessment of myocardial ischemia.

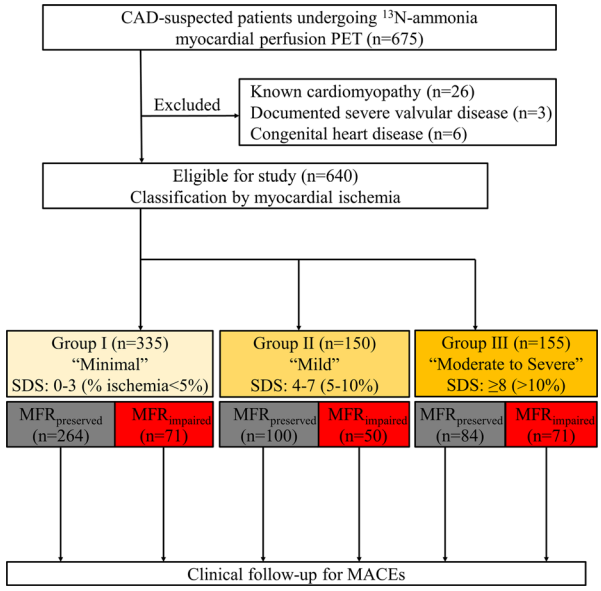

Figure 1. Schematic showing the selection of the study population. *CAD*, coronary artery disease; *PET*, positron emission tomography; *SDS*, summed difference score; *MFR*, myocardial flow reserve; *MACEs*, major adverse cardiovascular events.

METHODS

Study population

Myocardial perfusion and MFR were assessed in 675 consecutively admitted patients with suspected or known CAD from January 2017 to April 2021 at our institution (Figure 1). Patients with cardiomyopathy (n = 26), severe valvular disease (n = 3), and congenital heart disease (n = 6) were excluded. The remaining 640 patients were categorized into three groups based on the extent of total myocardial ischemia indicated by the summed difference score (SDS) assigned segmentally by software: Group I (n = 335), minimal (SDS = 0–3, < 5% myocardium ischemia); Group II (n = 150), mild (SDS = 4–7, 5–10%); and Group III (n = 155), moderate-to-severe (SDS ≥ 8, > 10%).[8,10] MFR ≥ 2.0 was defined as MFR$_{preserved}$, and MFR < 2.0 was defined as MFR$_{impaired}$.[6,11,12] Early revascularizations

with PCI or coronary artery bypass grafting (CABG) were defined as those occurring within 90 days of PET imaging results.[8,9,12] Pretest CAD probability scores integrating age, gender, chest pain type, diabetes mellitus, hyperlipidemia, and smoking status were calculated.[13] Prognostic scores (five-year death risk) were also calculated using the CALIBER model (www.caliberresearch.org/model), and this included the following baseline predictors as validated previously[14]: age, gender, CAD diagnosis, deprivation, smoking, hypertension, diabetes, lipids, heart failure (HF), peripheral arterial disease, atrial fibrillation, stroke, chronic kidney disease, chronic pulmonary disease, liver disease, cancer, depression, anxiety, heart rate, creatinine, white cell count, and hemoglobin level. Demographic and risk factors and medication use data were obtained from medical records. This study complied with the Declaration of Helsinki and ethical principles in the Belmont Report and was approved by the Institutional Review Board of Hokkaido Ohno Memorial Hospital (approval number: 20197). The requirement for informed consent was waived because the study was retrospective.

PET acquisition protocol and imaging analysis

Patients underwent single-day stress (pharmacological)/rest ^{13}N-ammonia PET with a PET/CT scanner (Biograph mCT Flow 64-4R PET/CT system; Siemens Healthcare, Germany) in the 3D list mode. PET images were reconstructed using the vendor-recommended blob-based ordered-subset expectation maximization time of flight algorithm with the default setting of 2 iterations and 21 subsets and a 256 × 256 matrix, acquiring a field of view (FOV) of 407 mm.[13] CT was used for attenuation correction, and the acquisition was obtained in a helical mode, using 120 kV, 20 mAs, and a 512 × 512 matrix size, acquiring a FOV of 500 mm. Patients fasted for > 6 h; caffeinated beverages and foods were avoided for at least 12 h prior. The pharmacological stress scan was performed during adenosine triphosphate (ATP)-induced hyperemia for 5 min, at a rate of 160 μg·kg − 1·min − 1; ^{13}N-ammonia dose of 3 MBq/kg was injected for 30 s, 3 min after ATP infusion commencement. The rest scan was performed with 3 MBq/kg of ^{13}N-ammonia for 30 s, 1 h after the stress scan. Heart rate, blood pressure, and electrocardiograms were recorded every minute during ATP infusion and image acquisition. PET images were quantitatively analyzed using a dedicated software package (Syngo MBF, Siemens Healthcare, Germany). Segmental perfusion scores based on a 17-segment, multi-point scale with corresponding summed scores were automatically calculated as summed rest score (SRS), summed stress score (SSS), and SDS (SSS-SRS) with the QPET software from Cedars-Sinai.[15] These indices (SSS, SDS, and SRS) were converted to the percentage of the myocardium having stress, ischemia (% ischemia), or fixed defects by normalizing to the maximum potential score (4 × 17). Absolute MBF was quantified at rest and peak hyperemia with automated factor analysis and a validated 2-compartment kinetic model.[16]

Outcome assessment

Follow-up data were obtained via phone questionnaires from patients and/or general practitioners or attending cardiologists and from medical charts. The overall follow-up period was 2.0 years (interquartile range [IQR]: 1.2–3.0), with a 99% follow-up rate (Online Resource 1). The primary endpoint was MACEs, including cardiovascular death, non-fatal myocardial infarction (MI), hospitalization for HF, and late coronary revascularization (> 90 days post-PET) with PCI/CABG. The secondary outcome was defined as hard events (all-cause death, non-fatal MI, admission for HF, or unstable angina). Cardiovascular deaths resulted from MI, sudden cardiac arrest, HF, stroke, cardiovascular hemorrhage, or other cardiovascular causes.

Statistical analysis

Baseline characteristics are expressed as number (percentage) for categorical variables and median (IQR) for continuous variables. We used the Fisher exact and Wilcoxon rank-sum tests to compare categorical and continuous baseline characteristics. Enrollment year, follow-up period, and detailed outcomes for patients with and without MACEs stratified by group (I-III) and MFR status were compared. Box plots demonstrated the distribution of pretest CAD probability scores and prognostic scores comparing patients with $MFR_{preserved}$ and $MFR_{impaired}$ according to the ischemia level. Cox proportional-hazards models were used to examine the association between $MFR_{impaired}$ and MACEs in Groups I-III, adjusting for pretest CAD probability scores plus early revascularization. Interaction between % ischemia and MFR (value) was also tested. At each level, the

models were examined for the validity of the proportional-hazard assumption. Adjusted survival curves for MACEs were plotted from the Cox model, including early revascularization and pretest CAD probability scores, stratified by MFR status in Groups I-III. Similarly, adjusted survival curves for cardiovascular death and MACEs were plotted by replacing pretest CAD probability scores with prognostic scores. We performed additional analysis to examine the association between $MFR_{impaired}$ and hard events in Cox regression models with first revascularization as a time-dependent variable, testing the two-way interaction of % ischemia and MFR.[17] The codes for the adjusted survival curves are shown in Online Resource 2. Starting with the pretest score (Model 1), % ischemia (Model 2) and MFR (Model 3) were sequentially added as continuous variables. The models' discriminatory power was assessed using the Harrell C-index with 95% confidence intervals (CI), and the Akaike information criterion and computed models were compared by the likelihood ratio test. We estimated the annualized event rates of MACEs in Groups I-III by fitting Poisson regression models in patients with $MFR_{preserved}$ and $MFR_{impaired}$. Sensitivity analyses assessed the prognostic value of $MFR_{impaired}$ by re-defining early revascularization ($\leq$ 60 days post-PET) in the Cox model for future MACEs, including late revascularization (> 60 days post-PET), after adjustment for pretest CAD probability scores plus early revascularization.[6,18] The correlation between global MFR and % ischemia was calculated using Spearman's rank correlation coefficient in patients with and without early revascularization. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata 14.0 (StataCorp, College Station, TX, USA) and R software, version 4.1.1 (R Project for Statistical Computing).

RESULTS

Patient and imaging characteristics

Baseline and PET imaging characteristics for Groups I-III are presented in Tables 1 and 2. Overall, the patients were predominantly male (n = 451, 71%), with a median age of 72 years; 17% had a history of MI, and early revascularization was performed in 33%. The incidence of early revascularization was 18%, 35%, and 63% in Groups I-III, respectively ($P < 0.001$). There was a higher proportion of males ($P = 0.002$), pretest CAD probability scores ($P < 0.001$), and incidence of previous MI ($P < 0.001$), with a greater extent of myocardial ischemia from Groups I-III. Pretest CAD probability and prognostic scores significantly differed between patients with $MFR_{preserved}$ and $MFR_{impaired}$ regardless of the ischemia level (Group I-III) except for the pretest CAD probability score in Group II ($P = 0.08$) (Online Resource 3). Regarding PET findings, rest MBF was 0.88 (IQR 0.74–1.04) mL/g/min; stress MBF, 2.10 (1.60–2.56) mL/g/min; and global MFR, 2.41 (1.87–2.86). Global MFR and % ischemia were inversely correlated ($r = -0.27$; $P < 0.0001$) (Figure 2). An MFR scatterplot illustrated a wide range of values, even within Group I, and early revascularization was often deferred even in Group III patients with $MFR_{impaired}$.

Outcome events

The annualized rate of cardiovascular death and MACEs in Group I-III patients with $MFR_{preserved}$ and $MFR_{impaired}$ is shown in Figure 3. Annualized cardiovascular death rates were 1.3% (95% CI 0.8–2.0) overall, 1.2% (0.6–2.3) in Group I, 0.9% (0.3–2.8) in Group II, and 1.8% (0.8–4.0) in Group III, while those for MACEs were 10.8% (9.2–12.7), 7.9% (6.0–10.3), 9.4% (6.7–13.4), and 18.1% (14.1–23.3), respectively. The annualized MACEs rate significantly differed between patients with $MFR_{preserved}$ and $MFR_{impaired}$ in Group I ($P < 0.0001$) and II ($P < 0.001$), but not in Group III ($P = 0.05$). Table 3 summarizes clinical outcomes in Groups I-III by MFR status. The percentage of MACEs ($P = 0.001$), non-fatal MI ($P = 0.03$), and late revascularization ($P = 0.001$) significantly differed among Group I-III patients.

Survival analysis

Figure 4 displays survival curves for MACEs for Groups I-III patients according to MFR status, adjusted for pretest CAD probability scores and early revascularization. A significant difference in MACEs between patients with $MFR_{preserved}$ and $MFR_{impaired}$ was observed overall (risk-adjusted $P < 0.001$), in Groups I (risk-adjusted $P = 0.002$) and II (risk-adjusted $P = 0.008$), but not in Group III (risk-adjusted $P = 0.67$). These associations remained evident even after adjusting for prognostic scores and early revascularization, as demonstrated in the risk-adjusted survival curves and Cox proportional-hazards analysis (Online Resource 4 and 5, respectively), but a significantly higher rate of cardiovascular death was observed only in Group I (risk-adjusted $P = 0.02$).

Table 1. Baseline characteristics of study participants

Characteristic	Overall (n = 640)	I (n = 335)	II (n = 150)	III (n = 155)	*P* Value
Demographic characteristics					
Age, years	72 [65, 77]	72 [64, 77]	73 [66, 77]	71 [64, 77]	0.35
Male gender, n (%)	451 (71)	218 (65)	108 (72)	125 (81)	0.002
Body mass index, kg/m^2	24 [22, 27]	24 [22, 26]	24 [22, 27]	25 [23, 27]	0.06
PET indication					
Chest pain	394 (62)	211 (63)	90 (60)	93 (60)	0.48
Dyspnea	55 (9)	27 (8)	18 (12)	10 (7)	
Preoperative	31 (5)	18 (5)	7 (5)	6 (4)	
Others	160 (25)	79 (24)	35 (23)	46 (30)	
Pretest CAD probability score, %	48 [29, 68]	43 [25, 62]	48 [30, 69]	56 [39, 76]	< 0.001
Prognostic score, %	12 [7, 20]	12 [7, 20]	13 [7, 23]	12 [7, 19]	0.39
Medical history, n (%)					
Hypertension	420 (66)	205 (61)	105 (70)	110 (71)	0.04
Dyslipidemia	391 (61)	196 (59)	93 (62)	102 (66)	0.29
Diabetes mellitus	239 (37)	103 (31)	64 (43)	72 (47)	0.001
Prior PCI	224 (35)	100 (30)	56 (37)	68 (44)	0.008
Prior CABG	53 (8)	14 (4)	12 (8)	27 (17)	< 0.001
Prior myocardial infarction	108 (17)	37 (11)	33 (22)	38 (25)	< 0.001
Prior heart failure	76 (12)	34 (10)	21 (14)	21 (14)	0.36
Atrial fibrillation	83 (13)	41 (12)	22 (15)	20 (13)	0.76
Hemodialysis	17 (3)	7 (2)	4 (3)	6 (4)	0.52
Current smoker	129 (20)	68 (20)	29 (20)	32 (21)	0.95
Chronic lung disease	44 (7)	28 (8)	10 (7)	6 (4)	0.18
Malignancy	47 (7)	30 (9)	11 (7)	6 (4)	0.13
Medications, n (%)					
Antiplatelet therapy	355 (56)	151 (45)	85 (57)	119 (77)	< 0.001
Calcium channel blockers	257 (40)	147 (44)	56 (37)	54 (35)	0.11
β-blockers	224 (35)	96 (29)	64 (43)	64 (41)	0.002
Cholesterol-lowering agents	367 (57)	182 (54)	86 (57)	99 (64)	0.13
ACEIs or ARBs	280 (44)	130 (39)	74 (49)	76 (49)	0.03
Nitrates	42 (7)	17 (5)	12 (8)	13 (8)	0.27
Diuretics	70 (11)	35 (10)	20 (13)	15 (10)	0.54
Oral hypoglycemic agents	170 (27)	77 (23)	41 (27)	52 (34)	0.04
Insulin	32 (5)	12 (4)	9 (6)	11 (7)	0.20
Early revascularization, n (%)	210 (33)	60 (18)	52 (35)	98 (63)	< 0.001
PCI	168 (26)	55 (16)	43 (29)	70 (45)	< 0.001
CABG	43 (7)	6 (2)	8 (5)	29 (19)	< 0.001

Data are presented as medians [interquartile range] or n (%) of patients. *PET*, positron emission tomography; *CAD*, coronary artery disease; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *ACEI*, angiotensin converting enzyme inhibitors; *ARB*, angiotensin II receptor blockers

Following adjustments for pretest CAD probability scores and early revascularization, $MFR_{impaired}$ was a significant predictor of MACEs in Groups I (hazard ratio [HR], 2.89; 95% CI 1.48–5.64; $P = 0.002$) and II (HR, 3.40; 95% CI 1.37–8.41; $P = 0.008$) but not in III (HR, 1.15; 95% CI 0.59–2.26; $P = 0.67$) (Table 4). A significant interaction was found between MFR and % ischemia ($P < 0.0001$) in the adjusted model. We found similar results with hard events, and the Cox proportional-hazards model using first revascularization as a

Table 2. PET findings

Parameter	Overall (n = 640)	I (n = 335)	II (n = 150)	III (n = 155)	*P* value
Rest EDV, mL	91 [75, 115]	88 [73, 110]	89 [73, 117]	100 [83, 128]	< 0.001
Rest LVEF, %	67 [57, 74]	69 [61, 76]	68 [54, 75]	62 [53, 68]	< 0.001
Stress LVEF, %	65 [55, 72]	67 [61, 73]	66 [53, 73]	58 [49, 65]	< 0.001
Myocardium fixed, %	3 [1, 9]	3 [0, 6]	4 [1, 10]	7 [3, 15]	< 0.001
Myocardium stress, %	10 [4, 19]	4 [1, 9]	12 [9, 18]	25 [18, 35]	< 0.001
Myocardium ischemia, %	4 [1, 10]	1 [0, 3]	7 [6, 9]	16 [13, 19]	< 0.001
Rest MBF, mL/g/min	0.88 [0.74, 1.04]	0.91 [0.77, 1.08]	0.89 [0.73, 1.08]	0.81 [0.68, 0.97]	< 0.001
Stress MBF, mL/g/min	2.10 [1.60, 2.56]	2.33 [1.90, 2.73]	1.99 [1.56, 2.48]	1.63 [1.33, 2.07]	< 0.001
MFR	2.41 [1.87, 2.86]	2.59 [2.11, 3.09]	2.33 [1.78, 2.76]	2.07 [1.70, 2.51]	< 0.001
$MFR_{impaired}$, n (%)	192 (30)	71 (21)	50 (33)	71 (46)	< 0.001

Data are presented as medians [interquartile range] or n (%) of patients. *PET*, positron emission tomography; *EDV*, end-diastolic volume; *LVEF*, left ventricular ejection fraction; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve

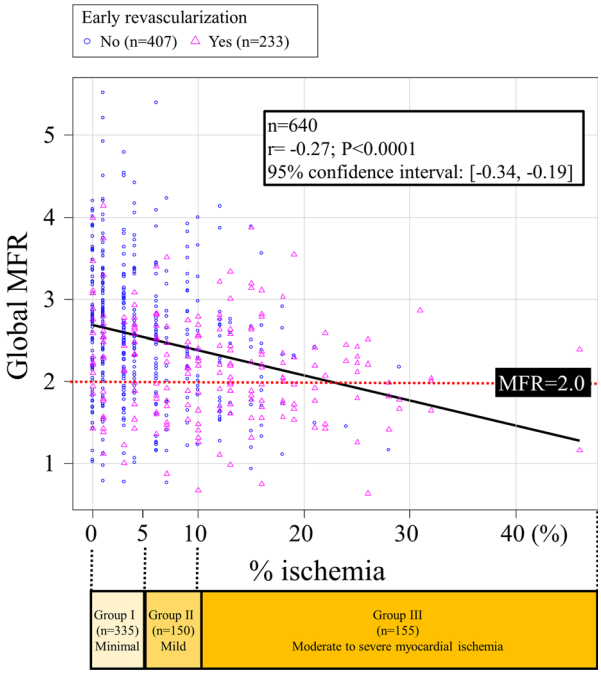

Figure 2. Association between MFR and % myocardial ischemia with and without early revascularization (≤ 90 days post-PET). Abbreviations as in Figure 1.

time-dependent variable revealed that $MFR_{impaired}$ was a significant predictor of MACEs in Groups I (HR, 5.09; 95% CI 2.17–11.9; $P < 0.0001$) and II (HR, 4.16; 95% CI 1.49–11.6; $P = 0.006$), but not in III (HR, 1.20; 95% CI 0.48–3.01; $P = 0.68$), with a significant interaction between them ($P < 0.0001$). Additionally, sensitivity

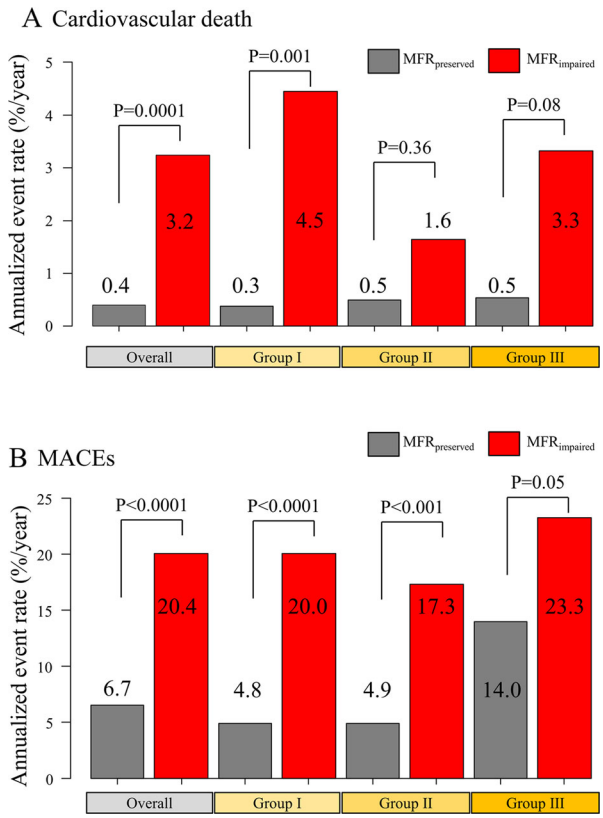

Figure 3. Annualized event rate of cardiovascular death and MACEs by MFR in Groups I-III. Abbreviations as in Figure 1.

Table 3. Detailed clinical outcomes in patients with $MFR_{preserved}$ and $MFR_{impaired}$ in Groups I-III

Outcomes	Overall (n = 640)	I (n = 335)	II (n = 150)	III (n = 155)	*P* value
$MFR_{preserved}$, n	448	264	100	84	
$MFR_{impaired}$, n	192	71	50	71	
All-cause death, n (%)	25 (4)	12 (4)	6 (4)	7 (5)	0.88
$MFR_{preserved}$	10 (2)	4 (2)	4 (4)	2 (2)	0.35
$MFR_{impaired}$	15 (8)	8 (11)	2 (4)	5 (7)	0.32
Cardiovascular death, n (%)	17 (3)	8 (2)	3 (2)	6 (4)	0.54
$MFR_{preserved}$	4 (1)	2 (1)	1 (1)	1 (1)	0.92
$MFR_{impaired}$	13 (7)	6 (9)	2 (4)	5 (7)	0.62
MACEs, n (%)	93 (15)	36 (11)	21 (14)	36 (23)	0.001
$MFR_{preserved}$	46 (10)	20 (8)	8 (8)	18 (21)	0.001
$MFR_{impaired}$	47 (25)	16 (23)	13 (26)	18 (25)	0.88
Non-fatal myocardial infarction, n (%)	13 (2)	3 (1)	3 (2)	7 (5)	0.03
$MFR_{preserved}$	7 (2)	2 (1)	1 (1)	4 (5)	0.03
$MFR_{impaired}$	6 (3)	1 (1)	2 (4)	3 (4)	0.57
Late revascularization, n (%)	53 (8)	20 (6)	9 (6)	24 (16)	0.001
$MFR_{preserved}$	34 (8)	15 (6)	5 (5)	14 (17)	0.002
$MFR_{impaired}$	19 (10)	5 (7)	4 (8)	10 (14)	0.32
Heart failure admission, n (%)	41 (6)	15 (5)	11 (7)	15 (10)	0.08
$MFR_{preserved}$	13 (3)	4 (2)	2 (2)	7 (8)	0.004
$MFR_{impaired}$	28 (15)	11 (16)	9 (18)	8 (11)	0.56

MFR, myocardial flow reserve; *MACEs*, major adverse cardiovascular events

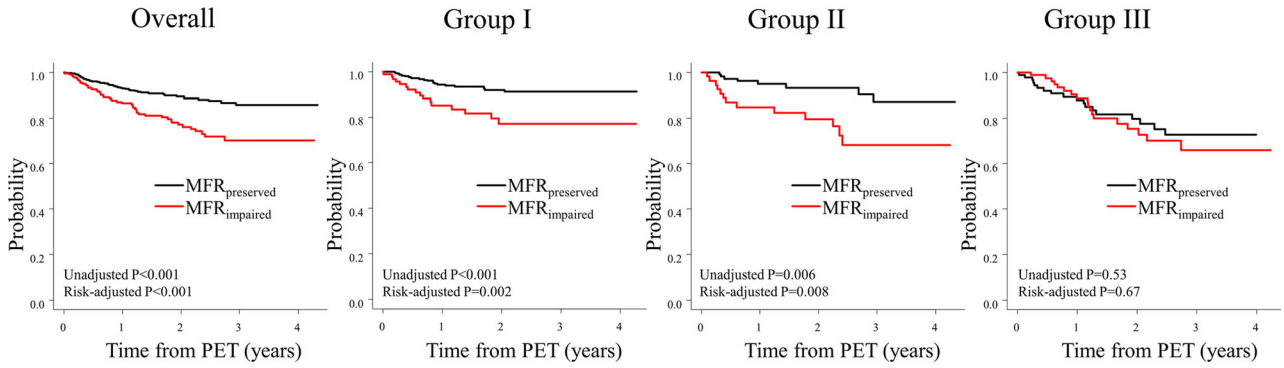

Figure 4. MACE-free survival adjusted for pretest CAD probability scores and early revascularization (≤ 90 days post-PET) in each group. Abbreviations as in Figure 1.

analysis with early revascularization re-defined to ≤ 60 days post-PET revealed that $MFR_{impaired}$ was a significant prognostic indicator in Groups I and II, but not in III, with significant interaction found between % ischemia and MFR ($P < 0.0001$) (Online Resource 6). A series of multivariable models were constructed to assess the incremental value of MFR (Figure 5). The addition of MFR to Model 2 resulted in a significant improvement in the model fit ($P < 0.0001$), and the addition of % ischemia to Model 1 also improved risk discrimination ($P = 0.009$).

DISCUSSION

This study is the first to demonstrate the added and independent prognostic value of $MFR_{impaired}$ and the differential effect of $MFR_{impaired}$ based on the myocardial ischemia level assessed by PET-MPI. In Groups I

Table 4. Association of MFR with MACEs and hard events in Cox proportional-hazards analysis

Outcome	Group	Variable	Beta coefficient	HR (95% CI)	*P* value
MACEs	Overall	Pretest CAD probability score	0.01	1.01 (1.00–1.02)	0.001
		Early revascularization	− 0.17	0.84 (0.54–1.31)	0.44
		$MFR_{impaired}$	0.82	2.27 (1.49–3.47)	< 0.001
	Group I	Pretest CAD probability score	0.02	1.01 (1.00–1.03)	0.01
		Early revascularization	0.27	1.30 (0.62–2.75)	0.47
		$MFR_{impaired}$	1.06	2.89 (1.48–5.64)	0.002
	Group II	Pretest CAD probability score	0.01	1.01 (0.99–1.03)	0.27
		Early revascularization	− 0.60	0.54 (0.21–1.45)	0.22
		$MFR_{impaired}$	1.22	3.40 (1.38–8.41)	0.008
	Group III	Pretest CAD probability score	0.01	1.01 (0.99–1.03)	0.22
		Early revascularization	− 0.60	0.54 (0.28–1.06)	0.07
		$MFR_{impaired}$	0.15	1.15 (0.59–2.26)	0.67
	Overall (Interaction)*	Pretest CAD probability score	0.01	1.01 (1.00–1.02)	0.002
		Early revascularization	− 0.44	0.64 (0.40–1.03)	0.07
		MFR	− 1.40	0.24 (0.15–0.39)	< 0.0001
		% ischemia	− 0.15	0.85 (0.77–0.94)	0.001
		MFR x %ischemia*	0.09	1.09 (1.04–1.14)	< 0.0001
Hard events†	Overall	Pretest CAD probability score	0.01	1.01 (1.00–1.03)	0.01
		$MFR_{impaired}$	1.15	3.17 (1.86–5.41)	< 0.0001
	Group I	Pretest CAD probability score	0.03	1.03 (1.02–1.06)	< 0.001
		$MFR_{impaired}$	1.63	5.09 (2.17–11.9)	< 0.0001
	Group II	Pretest CAD probability score	0.01	1.00 (0.98–1.03)	0.54
		$MFR_{impaired}$	1.43	4.16 (1.49–11.6)	0.006
	Group III	Pretest CAD probability score	− 0.01	0.99 (0.97–1.01)	0.53
		$MFR_{impaired}$	0.19	1.20 (0.48–3.01)	0.68
	Overall (Interaction)*	Pretest CAD probability score	0.02	1.01 (1.00–1.02)	0.01
		MFR	− 2.01	0.13 (0.07–0.24)	< 0.0001
		% ischemia	− 0.21	0.80 (0.71–0.91)	< 0.001
		MFR x %ischemia*	0.12	1.12 (1.06–1.19)	< 0.0001

MFR, myocardial flow reserve; *MACEs*, major adverse cardiovascular events; *HR*, hazard ratio; *CI*, confidence interval; and *CAD*, coronary artery disease
*Statistics for the interaction were obtained from different models including the main effects and the interaction term
†Cox regression models for hard events were used with first revascularization as time-dependent variable

and II, $MFR_{impaired}$ allowed for further risk stratification (high and low) for MACEs. Conversely, $MFR_{impaired}$ was not associated with reduced event-free survival for MACEs in Group III. These results remained unchanged when adjusted for prognostic scores instead of pretest CAD probability scores or when early revascularization

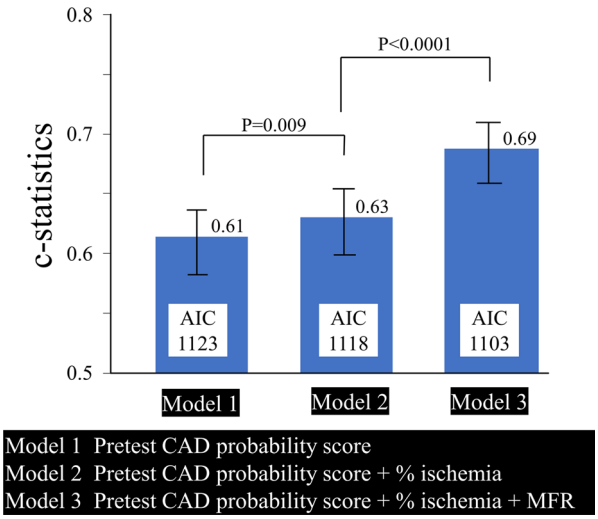

Figure 5. Comparative analysis of C-statistics and Akaike's information criterion (AIC) with 95% confidence interval to predict future MACEs. Abbreviations as in Figure 1.

was re-defined from 90 days post-PET to 60 days post-PET. We also obtained similar results for hard events with the first revascularization as a time-dependent variable. Additionally, patients with $MFR_{preserved}$ had consistently low cardiovascular death rates ($\leq 0.5\%$) regardless of the ischemia level. An interaction term between the severity of myocardial ischemia and MFR was significant for both MACEs and hard events.

In patients with minimal-to-mild ischemia, $MFR_{impaired}$ was significantly associated with reduced event-free survival from MACEs. These patients (18% in Group I; 35% in Group II) underwent early revascularization, with potentially little impact on MACEs as previously discussed.[4,17] The annualized MACE rate was less than 5% in Group I-$MFR_{preserved}$ and Group II-$MFR_{preserved}$ compared with 20% and 17% in Group I-$MFR_{impaired}$ and Group II-$MFR_{impaired}$, respectively, allowing for effective risk stratification. These findings suggest that we should carefully manage patients with $MFR_{impaired}$, including those with low levels of myocardial ischemia. In line with prior studies,[9,19] we speculated that microvascular dysfunction might be associated with increased cardiovascular risk via multifactorial mechanisms; however, these discussions are beyond the scope of this study. Significant variability in the relationship between global MFR and myocardial ischemia level was found, particularly in Group I, where 21% had microvascular dysfunction reflected by $MFR_{impaired}$. The annualized cardiovascular death rate in patients with $MFR_{impaired}$ differed between Group I (4.5%) and II (1.6%); however, Table 3 shows no statistical difference between patients with $MFR_{impaired}$ among Groups I-III for both cardiovascular and all-cause deaths. No meaningful difference was observed in the cardiovascular death rates between Groups I and II. However, we have not analyzed these points further because of the relatively low event rate and sample size in both groups.

In patients with moderate-to-severe ischemia (Group III), $MFR_{impaired}$ did not stratify cardiovascular risk, although patients with $MFR_{impiared}$ tended to have higher annualized cardiovascular death ($P = 0.08$) and MACE rates ($P = 0.05$) than those with $MFR_{preserved}$, suggesting that patients with $MFR_{preserved}$ could be at relatively high risk for MACEs and low risk for cardiovascular death. Our findings are consistent with those of a large-scale study[8] in which the 3-year survival rate for patients with normal MFR (> 1.8) was much higher ($> 90\%$) than that of those with lower MFR (≤ 1.8) regardless of the ischemia level (0%, 1–10%, and $> 10\%$). The annualized MACEs rate was much higher in Group III than in other groups. Survival analysis showed no statistical difference in MACE-free survival between Group III patients with $MFR_{preserved}$ and $MFR_{impaired}$ after adjusting for pretest CAD probability scores and early revascularization. These unique findings require careful interpretation because survival benefits can alter with early revascularization based on the extent of ischemia and MFR status, as previously mentioned.[4,8] Furthermore, ischemia reduction may not have been fully achieved through early revascularization in patients with greater ischemia. In recent studies, early revascularization in CAD patients with moderate-to-severe ischemia resulted in no clear survival or MACEs outcome benefits, though early revascularization more effectively reduced ischemia[10] and anginal symptoms than optimal medical therapy alone.[20]

We performed additional analyses to ensure the robustness and generalizability of our results. Instead of pretest CAD probability scores, prognostic scores were used to conduct risk-adjusted survival analysis, though these prognostic models may require further external validation.[21] Pretest CAD probability scores increased in patients with both $MFR_{preserved}$ and $MFR_{impaired}$ with increased ischemia levels; in contrast, prognostic scores were comparable in patients with $MFR_{preserved}$ and $MFR_{impaired}$. These findings imply that $MFR_{imapired}$ might have greater prognostic impact than the extent of myocardial ischemia. We obtained similar results with prognostic scores: $MFR_{impaired}$ was significantly associated with a higher MACE risk in Group I and II patients but not in Group III patients, confirming the prognostic impact of

$MFR_{impaired}$ in the lower level of ischemia with different approaches. We also revealed the interaction between MFR and % ischemia for two outcomes: MACEs and hard events. Analyzing the effect of early revascularization was challenging because PET-triggered revascularization showed survival benefits in patients with greater ischemia.[8] Thus, early revascularization was excluded from MACEs as a frequently used method,[4,6,18,21] though there were limited data for comparison of defining early revascularization between $\leq$ 90 days,[4,6,21] and $\leq$ 60 days.[1,18] Nevertheless, the associations between $MFR_{impaired}$ and MACEs were similar for both definitions at each ischemia level. An alternative approach was implemented to examine the relationship between $MFR_{impaired}$ and clinical outcomes by considering first revascularization after PET as a time-dependent variable with hard events as the main outcome to prevent misclassification.[8] We found similar results with hard events; thus, these findings should reinforce our conclusions.

Study limitations and strengths

First, the retrospective nature, limited subgroup sample size, and overfitting models for events may be considered limitations of this study. The evidence was insufficient for analyzing differential effects of $MFR_{impaired}$ based on the myocardial ischemia level assessed by PET-MPI. Therefore, larger prospective studies are required to validate the prognostic value of quantitative PET imaging. Second, this was a single-center observational study; there may be a selection bias in patients referred for PET-MPI. For instance, relatively high-risk patients may have been included, such as those with significant coronary calcium or plaque burden or undiagnosed silent subendocardial MI, because myocardial perfusion PET is often applied in Japan when other methods are inconclusive. This may have resulted in relatively high event rates. Third, we conducted all myocardial perfusion PET examinations with pharmacological stress testing, not exercise stress testing that can be a more physiological procedure with the added prognostic value of heart rate reserve.[22] Nevertheless, myocardial perfusion PET with exercise stress testing is not commercially available in Japan. Fourth, we adopted the CALIBER model in the survival analysis as a well-validated prognostic indicator, although the model might be difficult to implement in a retrospective study.[14,23] However, we were able to calculate the scores by integrating our comprehensive electronic medical record systems. Finally, we emphasize the accuracy and effectiveness of ^{13}N-ammonia PET for qualitative and quantitative analyses. ^{82}Rb and ^{13}N-ammonia are the only FDA-approved radiotracers to assess myocardial perfusion as positron radiopharmaceuticals, and ^{82}Rb, not commercially available in Japan, has somewhat worse spatial resolution and reduced first-pass extraction, resulting in a potential underestimation of flow at maximal hyperemia compared to ^{13}N-ammonia.[3]

NEW KNOWLEDGE GAINED

Our study clarified an interaction between myocardial ischemia severity and PET-measured MFR to predict future MACEs in patients with suspected or known CAD. A similar interaction was observed for hard events, highlighting the robustness of the association. Quantitation with MFR had significant prognostic power in addition to semi-quantitative findings and pretest CAD probability scores. Accordingly, our study provided evidence to support the combination of myocardial ischemia and global MFR utilizing perfusion ^{13}N-ammonia PET as a novel risk stratification method in these patients.

CONCLUSIONS

$MFR_{impaired}$ was independently associated with a higher MACE risk in patients with $\leq$ 10% myocardial ischemia but not in those with $>$ 10% myocardial ischemia. The robustness of this result was supported by the similar association observed after statistically adjusting for prognostic scores instead of pretest CAD probability scores or after replacing MACEs with hard events with first revascularization after PET as a time-dependent variable. Our findings depict the significance of risk stratification using PET-measured MFR and the extent of ischemic burden, especially in patients with lower ischemic burden, providing additional evidence to support physiologically based revascularization strategies. Quantitative PET assessments could help understand potential mechanisms of impaired MFR despite the level of myocardial ischemia. Prospective evidence from a PET-based revascularization strategy is required to confirm our results.

DISCLOSURES

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