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Long-term prognostic value of ^{82}Rubidium PET/CT-determined myocardial perfusion and flow reserve in cancer patients

Josef J. Fox[1], Audrey Mauguen[2], Kimiteru Ito[1], Dipti Gupta[3], Alice Yu[1], Thomas H. Schindler[4], H. William Strauss[1], Heiko Schöder[1]

[1]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY

[2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

[3]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[4]Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University, St. Louis, MO

Corresponding Author:
Heiko Schöder, MD
Molecular Imaging and Therapy Service
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065
Phone: 212-639-7373
Email: schoderh@mskcc.org
ORCID ID: 0000-0002-5170-4185

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ABSTRACT

Myocardial flow reserve, derived from quantitative measurements of myocardial blood flow during positron emission tomography (PET) imaging, provides prognostic information in patients with coronary artery disease but it is not known if this also applies to cancer patients with competing risk for mortality. **Methods:** To determine the prognostic value of myocardial flow reserve (MFR) in patients with cancer, we designed a retrospective cohort study comprising 221 patients with known or suspected coronary artery disease (median age: 71 years, range: 41–92 years), enrolled between 6/2009 and 1/2011. The majority of patients were referred for perioperative risk assessment. Patients underwent measurement of myocardial blood flow at rest and during pharmacologic stress, using quantitative ^{82}Rb PET imaging. Patients were divided into early-stage vs. advanced-stage cancer groups based on cancer histopathology and clinical state and were further stratified by myocardial perfusion summed stress score, summed difference score, and calculated MFR. Overall survival was assessed using the Kaplan-Meier estimator and Cox proportional hazard regression helped identify independent predictors for overall survival. **Results**: During a follow-up period of 85.6 months, 120 deaths occurred. MFR, summed difference score, and cancer stage were significantly associated with overall survival. In the age-adjusted Cox hazard multivariable analysis, MFR and cancer stage remained independent prognostic factors. MFR combined with cancer stage provided enhanced overall survival discrimination. The groups had significantly different outcomes ($p<0.001$), with five-year overall survival of 88% (MFR≥1.97 and early-stage), 53% (MFR<1.97 and early-stage), 33% (MFR≥1.97 and advanced-stage), and 13% (MFR <1.97 and advanced-stage), respectively. **Conclusion:** Independent of cancer stage, MFR derived from quantitative PET was found to be prognostic of overall survival in our cohort of cancer patients with known or suspected coronary artery disease. Combining these two parameters provided enhanced discrimination of overall

survival, suggesting that myocardial flow reserve improves risk stratification and may serve as a treatment target to increase survival in cancer patients.

Key words: Rubidium-PET, quantitative myocardial perfusion imaging, myocardial flow reserve, cancer, survival

INTRODUCTION

An increasing number of adult patients with cancer are also afflicted with coronary artery disease (CAD) (1). Therefore, it is important to monitor the cardiovascular health of cancer patients with risk factors for CAD or documented cardiovascular events. Cancer itself creates an immunocompromised and hypercoagulable milieu, which, in combination with potentially cardiotoxic cancer therapies, renders patients increasingly vulnerable to cardiac morbidity and mortality (2, 3). Cardiotoxic culprits include mediastinal irradiation, fluoropyrimidines, alkylating agents, androgen deprivation therapy, and targeted therapies such as tyrosine kinase inhibitors.

Whereas single-photon emission computed tomography (SPECT) and SPECT/CT myocardial perfusion imaging (MPI) is widely available and well-established for evaluating cardiac risk in the general population (4), positron emission tomography/computed tomography (PET/CT) MPI offers two major advantages (5-7): (a) superior diagnostic accuracy; and (b) the ability to quantify myocardial blood flow at rest and during vasodilator stress, and hence derive myocardial flow reserve. Although PET/CT MPI has prognostic value beyond routine clinical predictors for all-cause mortality and major adverse cardiovascular events (8, 9), its prognostic value in patients with cancer (a major competing risk for death) is unclear. Therefore, we set out to evaluate the prognostic value of myocardial blood flow and flow reserve in patients with cancer and a suspected or known CAD co-morbidity.

MATERIALS AND METHODS

Study Population

This is a retrospective investigation of consecutive patients with cancer who underwent rest-stress ^{82}Rb-chloride PET/CT MPI over a 20-month period between June 2009-January 2011. During this time, 1,233 patients were referred for MPI, including 236 patients who underwent ^{82}Rb-chloride PET MPI (19%) and 997 patients (81%) who underwent SPECT/CT MPI. MPI modality (PET vs. SPECT) was generally determined by logistical factors (e.g., availability of ^{82}Rb-chloride generator) rather than clinical criteria. Exclusion criteria for pharmacologic cardiac stress testing included acute myocardial infarction, unstable angina, overt heart failure, history of severe asthma or contraindications to vasodilation with adenosine, dipyridamole, or regadenoson (10). Fifteen patients were excluded because dynamic PET/CT datasets were not available for analysis. The final study population comprised 221 patients, the majority of which were referred for perioperative risk assessment (**Figure 1**). A detailed history was obtained from the patient, the referring clinician, and the center's electronic medical record (EMR) prior to MPI PET/CT to define cardiac risk factor profile. Lipid profiles were not available in all patients, as this is not part of routine diagnostic evaluation. Clinical risk factors were scored and summed according to the Morise risk assessment for predicting cardiac events (11). The EMR was reviewed to identify the incidence of cardiac catheterization, percutaneous revascularization, coronary artery bypass graft (CABG), or cardiac death within 90 days after ^{82}Rb-chloride PET/CT. Patient survival was accurately determined by scrupulous review of the EMR. The institutional review board approved this retrospective, HIPAA-compliant, single-institution study (IRB #11-150) and waived the requirement for informed consent. Data collection was

finalized in December 2021. Details of the ^{82}Rb-chloride PET/CT rest/stress protocol, as well as details on image analysis, are shown in the Supplemental Data.

Cancer Status

Patients had a variety of primary cancers and disease stages (**Supplemental Table 1**). We divided the population into two groups, advanced-stage vs. early-stage cancer, using estimated cancer life expectancy based on historical five-year survival rates at the time of ^{82}Rb PET-CT imaging. The advanced-stage cancer group was defined as patients with expected five-year survival rate < 50%, unknown primary cancer, or confirmed local recurrence and/or distant metastases within three months after the ^{82}Rb PET/CT scan. The remaining patients were assigned to the early-stage cancer group. If patients had multiple primary cancers, staging was determined by the cancer with the lowest expected five-year survival rate. Expected five-year survival rates were based on the American Cancer Society and the American Joint Committee on Cancer, Cancer Staging Manual, 7th edition (12). Lymphomas were staged according to Ann Arbor classification.

Statistical Analysis

Data are expressed as mean ± SD, median (range), or frequency (%). Student's *t*-test was used for comparison of normally distributed continuous variables between groups, while the Wilcoxon rank sum test was used for non-normal variables. The chi-squared or Fisher's exact tests were used to compare categorical variables.

Kaplan-Meier estimator was used to determine whether there was an association between clinical parameters or PET MPI, and overall survival (OS), which was defined as time from ^{82}Rb PET/CT until death from any cause. Patients who remained alive were censored at last follow-up. Median follow-up time was calculated using the reverse Kaplan-

Meier method (13). Date of death and last follow-up were obtained from the EMR. A log-rank test was performed to test for differences between survival curves. Hazard ratios and 95% confidence interval (CI) were calculated using univariable and multivariable Cox proportional hazard regression models. To assess potential confounding effects on survival due to the retrospective nature of the study, multivariable analyses were performed as stepwise backward regression, with an entry probability for each variable set at 0.05. The final model is defined as the model after variable selection, i.e., after exclusion of variables that were not significant after adjustment. A sensitivity analysis was conducted by repeating the analysis on patients with both normal SSS (<4) and normal SDS (<3) only. Only a few missing values were observed, and a complete case analysis was conducted. Reported P values were two-tailed; a p value of 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS (Version 25, Chicago, IL) and Rv6.3.0.

RESULTS

Patient Characteristics and Qualitative Assessment of Regional Perfusion

A flow diagram summarizing patient selection is shown in **Figure 1**. Patient characteristics are detailed in **Table 1**. A total of 221 patients were included in the study. The overwhelming majority of patients had at least an intermediate pretest probability for CAD (96.4%); 178 patients were referred for risk assessment prior to cancer surgery, 9 patients for risk assessment before undergoing chemotherapy or bone marrow transplantation, and 34 patients for evaluation of symptoms/signs attributable to coronary disease.

Myocardial Perfusion and Function

Abnormal stress perfusion (SSS ≥ 4) was observed in 52 of 221 patients (23.5%). Regional ischemia (SDS ≥ 3) was found in 46 patients (20.8%). In patients referred for

symptoms, 14 of 34 (41.2%) showed evidence for ischemia with SDS ≥ 3. Within 90 days after ^{82}Rb PET/CT, seven patients underwent percutaneous coronary intervention, one underwent CABG, and one suffered from cardiac death after myocardial infarction; all nine patients had ischemia (SDS ≥ 3) on PET MPI.

An LVEF < 50% was observed at rest in 26 (11.8%) and at stress in 22 (10.0%) patients. An abnormal LVEF reserve was observed in 24 patients.

Myocardial Blood Flow and Flow Reserve

Mean rest MBF was 1.01 ml/min/g (SD=0.42); mean rest MBF after adjusting for RPP was 0.88 ml/min/g (SD=0.32), and mean stress MBF was 1.93 ml/min/g (SD=0.74). Mean MFR was 2.04 (SD=0.74) and mean-adjusted MFR was 2.31 (SD=0.85). Factors correlating with a low MFR value (defined as MFR lower than the median of 1.97) were a lower stress MBF (p<0.001), a higher rest MBF or adjusted rest MBF (p<0.001), a higher rest heart rate (p=0.006), a lower stress ejection fraction (p=0.002), and a higher SSS (p=0.003) and SDS (p=0.021, **Table 2**). In addition, a lower hemoglobin level (p<0.001), a history of CAD (p<0.001), an Agatston score classified as severe (score >400, p<0.001), and older age (p<0.001) were all associated with lower MFR (**Table 2**). However, stress heart rate, rest ejection fraction, body mass index, or type of vasodilator were not significantly associated with a low MFR.

Survival Outcome

The median follow-up time was 7.1 years (95% CI: 6.6-7.5 years;). Median OS was 5.1 years (range: 14 days–8.8 years). During follow-up, 120 patients died. OS was significantly worse in patients with advanced-stage cancer than in those with early-stage cancer (adjusted HR = 4.06, p < 0.001; **Supplemental Table 2**). A higher stress MBF and

lower rest MBF were both significantly associated with better OS in univariable analysis (p=0.007 and 0.012, respectively). However, they were not entered in the multivariable model due to collinearity with adjusted MFR. A lower adjusted MFR was significantly associated with higher risk of death (increased by 3% for every 0.1-unit decrease in MFR); this translates to an increase in the risk of death of 17% when MFR decreases by 0.5 (p=0.026). When stratifying MFR by quartiles, the five-year survival rate for patients with MFR<1.45 was 22%, while for those with MFR>2.45 it was 73% (**Supplemental Figure 1**). Other independent predictors of OS were age, history of CAD, hemoglobin, and obesity (**Supplemental Table 2**). Therefore, MFR provided additional prognostic value to known clinical risk factors. Four risk categories were defined by stratifying the patients on MFR and cancer stage. These groups had significantly different outcomes, with five-year OS of 88%, 53%, 33%, and 13%, respectively (**Figure 2**). Additional analyses classified by cancer staging and MFR are shown in **Supplemental Table 3**. When analysis was restricted to 163 patients without regional perfusion abnormalities (SSS < 4 and SDS < 3), MFR still provided additional prognostic value for overall survival **(Supplemental Figure 2**), with five-year OS of 88%, 55%, 36%, and 15%, respectively. Factors associated with OS in this restricted analysis of patients without regional perfusion abnormalities are listed in **Supplemental Table 4**.

DISCUSSION

This study demonstrates that MFR is an independent predictor of OS in a population of patients with active cancer, even after stratifying for cancer stage, and regardless of presence or absence of visual perfusion defects. *suggesting that cardiovascular risk assessment and appropriate care remain paramount even in a population with significant competing morbidity*.

PET-derived MFR is an established prognostic biomarker for the risk of major adverse cardiovascular events in the general population (5). In our cohort, we chose to focus on overall outcome rather than limiting our investigation to these adverse events and cardiac-specific death. Given the complex nature of cancer care and follow-up, cardiac symptoms and events may be underestimated and erroneously ascribed to the underlying oncologic disease or therapy. On the other hand, OS is a robust and reliable outcome measure (14), and may indicate a holistic significance of impaired MFR beyond its association with cardiac health.

In a large study of over 4,000 patients (15) MFR <2.0 was an independent prognostic factor of all-cause mortality (hazard ratio [HR] 1.72), with an average mortality of 4.4% per year during a median follow-up of 5.6 years (total mortality 24.9%). In comparison, our patients had a higher all-cause mortality of 7.6% per year during a median follow-up of 7.1 years (total mortality 54.3%). Although patient populations differ, MFR as an independent prognostic factor and the median values for MFR (1.97 vs. 2.0, respectively) were quite similar. In a study of 87 patients with breast cancer, those with MFR in the lowest tertile had a higher cumulative incidence of MACE when compared to patients with MFR in the highest MFR tertile (16). In another study (17), abnormal MFR remained predictive of cardiovascular death in patients with chronic kidney disease. Similarly, in a retrospective study of 198 patients with systemic inflammatory disorders, those with the lowest tertile of MFR (defined as <1.65) experienced higher all-cause mortality than those in the highest tertile (HR: 2.4), regardless of other variables (18). In aggregate, these data suggest that reduced MFR is a useful prognostic indicator *even in the presence of significant non-cardiac comorbidities*. Accordingly, cardiac risk stratification should be performed in cancer patients with known or suspected CAD and primary and secondary prevention strategies

implemented to improve outcomes, similar to current practice in non-selected populations (19-22).

Previous epidemiological studies have demonstrated that cardiovascular disease has a major impact on the long-term survival of cancer patients (23). Our study suggests that impaired MFR during periods of stress may be a significant contributing factor. There are several potential ways in which cancer, by itself or by virtue of cancer therapy, could affect the cardiovascular system and control of vasomotion.

First, a recognized hallmark of cancer is the systemic inflammatory state (24, 25), which may contribute to coronary microvascular dysfunction (26, 27), akin to traditional cardiac risk factors (28). Inflammation-induced microvascular dysfunction is proposed to result from a reduction in microvascular nitric oxide bioavailability. The principal mechanism for the effect of nitric oxide on vasomotion is its binding to and activation of guanylate cyclase, increasing the production of cGMP, which through second messengers promotes arterial smooth muscle relaxation. Interestingly, phosphodiesterase 5 (PDE5) inhibition, preventing the breakdown of cGMP, has recently gained interest as a potential anticancer therapy (29) beyond its established role as a systemic arterial vasodilator.

Another prevalent finding in cancer is autonomic dysfunction (30-33), another recognized contributor to abnormal myocardial flow reserve (34) (35). The sympathetic nervous system can regulate the tumor microenvironment in multiple ways (36, 37), and its chronic activation can promote cancer progression. Beta-adrenergic signaling, for instance, stimulates the transcription of pro-inflammatory cytokines and inhibits the transcription of interferons, thereby contributing to tumor progression and metastasis (36). Conversely, experimental inhibition of the sympathetic nervous system (38-40) has been shown to decrease tumor growth and improve outcomes.

Thus, impaired MFR, as seen in our study, may signify cancer-related coronary endothelial dysfunction or autonomic dysfunction. On the contrary, cancer and CAD may simply co-exist. Regardless of a causal link, our data suggest that cardiovascular risk assessment and appropriate care are important targets in the management of cancer patients.

Study limitations. This was a retrospective study with potential deficiencies in the documentation of cardiovascular risk factors. The study only included patients who were referred for MPI PET by their oncologist or cardiologist, which may introduce a selection bias. The study population was heterogeneous regarding age, cancer type, and treatment applied. Also, 11.8% had a resting LVEF<50%, and 31.5% had a coronary calcium score above 400. Nevertheless, none of these factors proved significant in the statistical analysis.

CONCLUSION

PET MFR was a strong independent prognostic marker of OS, irrespective of cancer stage. Therefore, MFR assessment may contribute to improved risk stratification and may serve as a treatment target to improve survival of cancer patients. Prospective clinical studies are warranted to validate the utility of MFR and impact of optimized cardiovascular care in this population.

FINANCIAL DISCLOSURE

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KEY POINTS

QUESTION: Are cancer patients with abnormal myocardial blood flow and flow reserve, as derived from quantitative PET imaging, at higher risk for mortality, independent of their underlying disease?

PERTINENT FINDINGS: In a retrospective cohort study of 221 patients, we found that abnormal myocardial flow reserve provides independent prognostic information; patients with abnormal flow reserve had shorter survival, regardless of cancer type and stage.

IMPLICATIONS FOR PATIENT CARE: Myocardial flow reserve improves risk stratification in cancer patients and may serve as a treatment target to increase their survival, suggesting a need for dedicated cardiac care in cancer patients, regardless of competing risk from their underlying disease.

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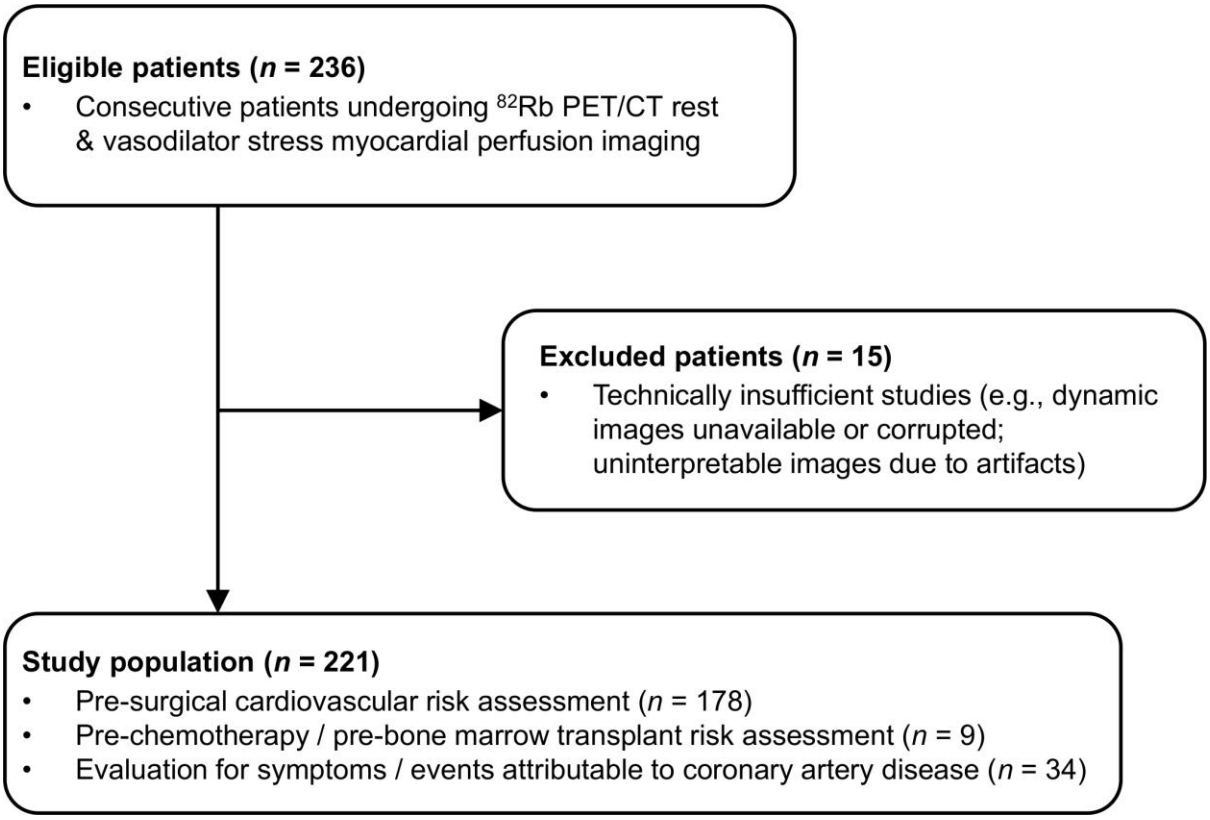
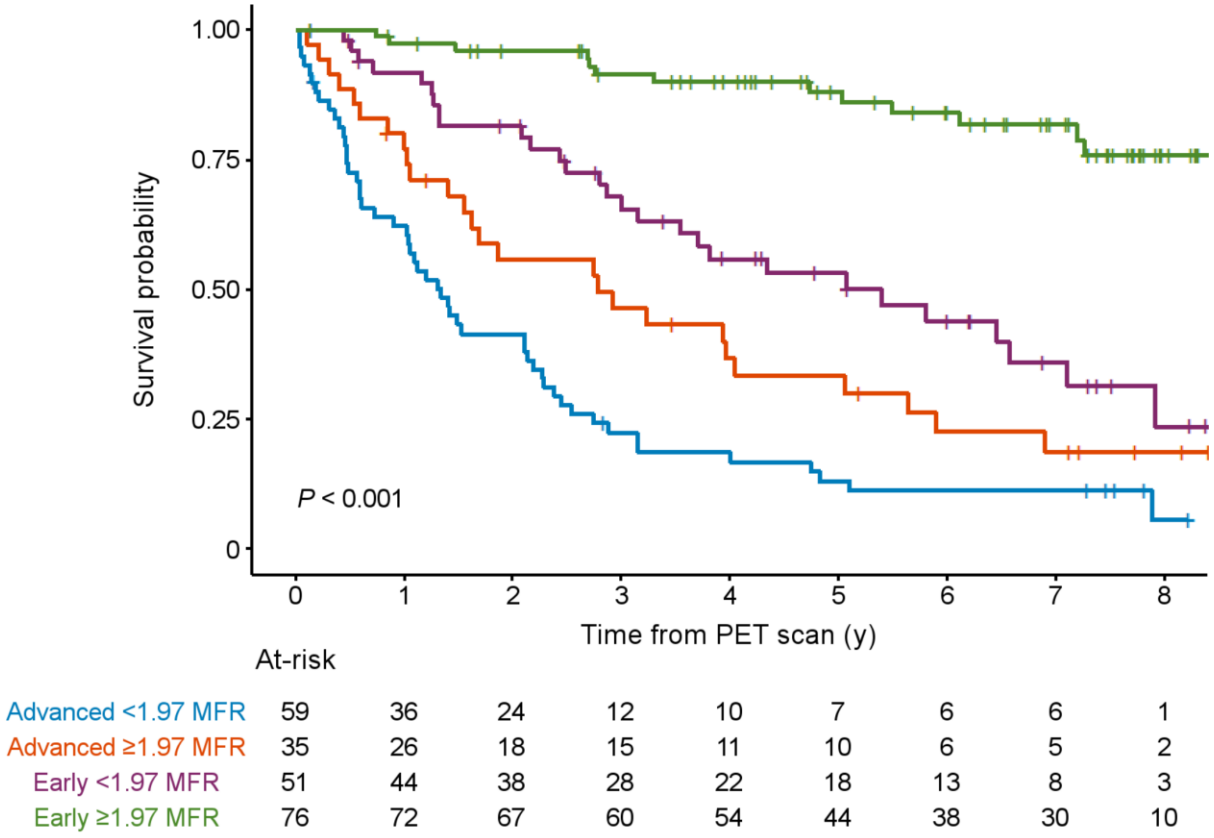


Figure 1. Flow diagram of study patients.



Characteristic	At 2 years	At 5 years
Strata		
Advanced <1.97 MFR	41% (31%, 56%)	13% (6.6%, 26%)
Advanced ≥1.97 MFR	56% (41%, 75%)	33% (20%, 54%)
Early <1.97 MFR	81% (71%, 93%)	53% (40%, 70%)
Early ≥1.97 MFR	96% (92%, 100%)	88% (80%, 96%)

Figure 2. Kaplan-Meier curve stratified by MFR and stage in overall cohort (n=221).

Table 1. Demographics and characteristics of study cohorts

Characteristic	N = 221*	Characteristic	N = 221*
Age (years)	71 [41 – 92]	**History of Coronary Artery Disease**	82 (37.1%)
Age (years), binary		**VASODILATOR**	
<65	73 (33.0%)	Dipyridamole	93 (42.1%)
>=65	148 (67.0%)	Regadenoson	128 (57.9%)
Gender			
Female	97 (43.9%)	**Heart rate (rest)**	70.05 ± 13.15
Male	124 (56.1%)	**Heart rate (stress)**	87.44 ± 16.56
Height	168 [132 – 193]	Unknown	2
Weight	79 [36 – 161]	**REST Systolic Blood Pressure**	140.60 ± 20.55
Body Mass Index	27.82 [16.00 – 68.78]	**STRESS Systolic Blood Pressure**	131.53 ± 22.53
		Unknown	3
Obesity		**Transient ischemic dilatation RATIO**	1.06 ± 0.15
BMI <30	136 (61.5%)		
BMI >=30	85 (38.5%)	Unknown	1
Stress %LVEF	71 [18 – 90]	**Stress MBF (mg/mL/min)**	1.93 ± 0.74
Unknown	1	**Rest MBF (mg/mL/min)**	1.01 ± 0.42
Stress %LVEF <50		**Adjusted Rest MBF (mg/mL/min)**	0.88 ± 0.32
≥50	198 (90.0%)	**MFR**	2.04 ± 0.74
<50	22 (10.0%)	**Adjusted MFR**	2.31 ± 0.85
Unknown	1		
Rest %LVEF	66 [21 – 90]	**Morise**	
Unknown	1	Low (0-8)	8 (3.6%)
Rest %LVEF <50		Intermediate (9-15)	93 (42.1%)
≥50	194 (88.2%)	High (>15)	120 (54.3%)
<50	26 (11.8%)	**Summed Stress Score**	
Unknown	1	Normal (0-3)	169 (76.5%)
LVEF reserve	5 [-22 – 21]	Mild (4-7)	26 (11.8%)
Unknown	1	Moderate (8-11)	8 (3.6%)
Abnormal LVEF reserve		Severe (≥12)	18 (8.1%)
Normal	196 (89.1%)	**Ischemia (SDS ≥3)**	
Abnormal	24 (10.9%)	Abnormal	46 (20.8%)
Unknown	1	Normal	175 (79.2%)
Hemoglobin	12.40 [7.60 – 16.70]	**Coronary Calcium (Agatston Score)**	
Unknown	4	None/Minimal (0-10)	47 (21.8%)
Hemoglobin		Mild (11-100)	37 (17.1%)
>=10 g/dL	189 (87.1%)	Moderate (101-400)	46 (21.3%)
<10 g/dL	28 (12.9%)	Severe (>400)	68 (31.5%)
Unknown	4	Stent	9 (4.2%)
Diabetes		CABG	9 (4.2%)
0	143 (64.7%)	Unknown	5
2	78 (35.3%)	**eGFR**	64 [22 – 109]
Dyslipidemia	157 (71.0%)	**eGFR, binary**	
Hypertension	172 (77.8%)	≥60	96 (43.4%)
Smoker/Ex-smoker	159 (71.9%)	>60	125 (56.6%)

*n (%); Median [Range]; Mean +- SD

BMI: body mass index; LVEF: left ventricular ejection fraction; MBF: myocardial blood flow; MFR: myocardial flow reserve; eGFR: estimated glomerular filtration rate

Table 2. Factors contributing to low MFR (all patients)

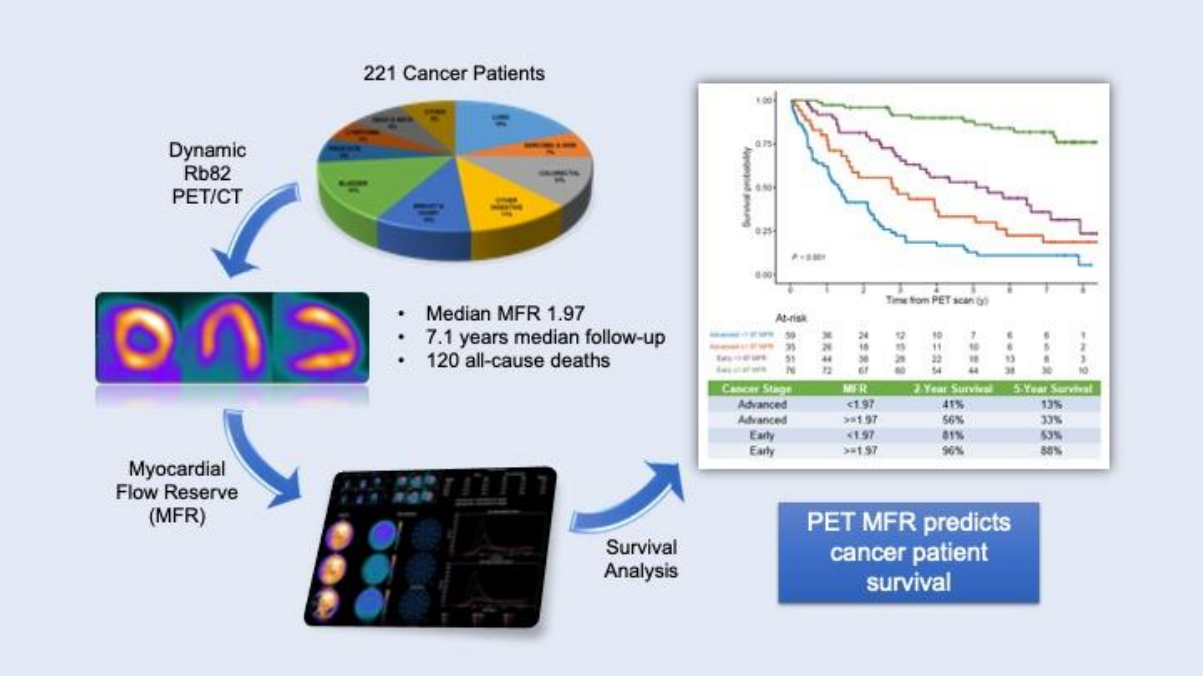
Characteristic	MFR ≥1.97, N = 111[*]	MFR <1.97, N = 110[a]	p-value[†]
Stress MBF (mg/mL/min)	2.14 [0.85 – 4.64]	1.57 [0.39 – 3.64]	<0.001
Rest MBF (mg/mL/min)	0.81 [0.40 – 2.25]	1.01 [0.48 – 2.61]	<0.001
Adjusted Rest MBF (mg/mL/min)	0.77 [0.31 – 1.40]	0.88 [0.39 – 2.60]	<0.001
Heart rate (stress)	87 [52 – 126]	84 [51 – 141]	0.33
Unknown	2	0	
Heart rate (rest)	66 [44 – 102]	71 [42 – 112]	0.006
Ejection fraction (stress, %)	73 [40 – 90]	67 [18 – 90]	0.002
Unknown	0	1	
Ejection fraction (rest, %)	67 [27 – 90]	64 [21 – 86]	0.084
Unknown	0	1	
Summed stress score	0.0 [0.0 – 21.0]	1.0 [0.0 – 40.0]	0.003
Summed difference score	0.0 [0.0 – 9.0]	0.0 [0.0 – 26.0]	0.021
Hemoglobin (g/dL)	12.85 [7.60 – 16.70]	11.80 [7.60 – 15.60]	<0.001
Unknown	1	3	
Body Mass index	28 [19 – 51]	27 [16 – 69]	0.26
Vasodilator			0.64
Dipyridamole	45 (41%)	48 (44%)	
Regadenoson	66 (59%)	62 (56%)	
History of Coronary Artery Disease	29 (26%)	53 (48%)	<0.001
Coronary Calcium (Agatston Score)			<0.001
None/Minimal (0-10)	32 (29%)	15 (14%)	
Mild (11-100)	25 (23%)	12 (11%)	
Moderate (101-400)	25 (23%)	21 (20%)	
Severe (>400)	25 (23%)	43 (40%)	
Stent	1 (1%)	8 (7%)	
CABG	1 (1%)	8 (7%)	
Unknown	2	3	
Age (years)	67 [44 – 92]	75 [41 – 90]	<0.001

[*]Median [Range]; n (%)

[†]Welch two-sample t-test; Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

MBF: myocardial blood flow; MFR: myocardial flow reserve

GRAPHICAL ABSTRACT



Supplemental Table 1. Type of tumor and stages (n = 221).

Primary site, no. of patients	Early-stage	Advanced-stage
Bladder	8	14
Brain	1	0
Breast	11	5
Cervix/uterus	5	0
Colon/rectum	18	9
Esophagus	2	2
Head and neck	10	7
Hematologic	2	2
Kidney	6	1
Liver/biliary tract	1	1
Lung/pleura	24	19
Lymphoma	4	3
Ovary	0	6
Pancreas	2	6
Prostate	7	5
Skin	5	2
Soft tissue	2	5
Stomach	8	2
Unknown primary	0	2
Multiple primary cancers	1	3
Benign tumors or dysplasia[a]	6	0
Inflammation[b]	3	0
No evidence of disease[c]	1	0
Total	127	94

[a] 2 cervical dysplasia, 1 meningioma, 1 vestibular schwannoma, 1 serous cystadenoma in ovary, 1 adenoma in duodenum, 1 leiomyoma in esophagus
[b] 2 granuloma in lung, 1 fibrous pleuritis
[c] Chief complaint of hemoptysis

Supplemental Table 2. Factors associated with OS (Cox proportional hazard model)

	Univariable			Multivariable		
Characteristic	**HR***	**95% CI***	**p-value**	**HR***	**95% CI***	**p-value**
Smoker/Ex-smoker	0.95	0.64, 1.40	0.79			
Hypertension	1.23	0.79, 1.92	0.36			
Diabetes	0.98	0.81, 1.18	0.81			
Dyslipidemia	0.84	0.57, 1.24	0.39			
Prior history of CAD	1.70	1.19, 2.44	0.004	**1.52**	**1.02, 2.28**	**0.043**
Vasodilator			0.67			
Dipyridamole	—	—				
Regadenoson	1.08	0.75, 1.55				
TID RATIO	1.51	0.49, 4.60	0.48			
Age (for 1-year)	1.05	1.03, 1.07	<0.001	**1.03**	**1.01, 1.05**	**0.009**
Gender			0.43			
Female	—	—				
Male	1.16	0.80, 1.67				
Obesity			<0.001			**0.002**
BMI <30	—	—		**—**	**—**	
BMI ≥30	0.42	0.28, 0.64		**0.52**	**0.33, 0.80**	
Hemoglobin			0.002			**0.019**
≥10 g/dL	—	—		**—**	**—**	
<10 g/dL	2.29	1.42, 3.67		**1.85**	**1.14, 2.99**	
Rest %LVEF			0.020			*0.91*
≥50	—	—		—	—	
<50	1.87	1.15, 3.07		*0.97*	*0.57, 1.66*	
Abnormal LVEF reserve			0.14			
Normal	—	—				
Abnormal	1.52	0.89, 2.57				
Morise			0.034			*0.82*
Low (0-8)	—	—		—	—	
Intermediate (9-15)	2.24	0.54, 9.26		*0.61*	*0.13, 2.76*	
High (>15)	3.24	0.79, 13.2		*0.64*	*0.13, 3.18*	
Summed Stress Score	1.02	1.00, 1.05	0.082			

	Univariable			Multivariable		
Characteristic	**HR***	**95% CI***	**p-value**	**HR***	**95% CI***	**p-value**
Summed Difference Score	1.05	1.01, 1.09	0.031	*0.99*	*0.95, 1.04*	*0.75*
Coronary Calcium (Agatston Score)			0.038			*0.63*
None/Minimal (0-10)	—	—		—	—	
Mild (11-100)	1.09	0.55, 2.15		*0.59*	*0.28, 1.21*	
Moderate (101-400)	1.30	0.70, 2.39		*0.66*	*0.35, 1.24*	
Severe (>400)	1.84	1.07, 3.14		*0.82*	*0.45, 1.49*	
Stent	1.90	0.76, 4.75		*0.55*	*0.20, 1.51*	
CABG	3.44	1.49, 7.93		*0.68*	*0.25, 1.84*	
Stress MBF (for a one-unit decrease)	1.45	1.10, 1.91	0.007	*0.93*	*0.67, 1.30*	*0.67*
Rest MBF (for a one-unit decrease)	0.59	0.40, 0.87	0.012	*0.72*	*0.46, 1.10*	*0.14*
MFR			<0.001			
for a 0.1 decrease	1.09	1.06, 1.13				
for a 0.5 decrease	1.56	1.34, 1.82				
Adjusted MFR			<0.001			
for a 0.1 decrease	1.07	1.04, 1.09		**1.03**	**1.00, 1.06**	**0.026**
for a 0.5 decrease	1.39	1.23, 1.57		**1.17**	**1.02, 1.34**	
Stage			<0.001			**<0.001**
Early-stage	—	—		**—**	**—**	
Advanced-stage	4.72	3.21, 6.92		**4.06**	**2.72, 6.06**	
eGFR			0.033			*0.95*
≤60	—	—		—	—	
>60	0.68	0.47, 0.97		*0.99*	*0.67, 1.45*	

*HR = hazard ratio, CI = confidence interval

Multivariable model: in bold are the variables in the final model; in italic are the results of the variables introduced in the model but not kept in the final model, adjusted on the final model.

CAD: coronary artery disease; TID: transient ischemic dilatation; BMI: body mass index; LVEF: left ventricular ejection fraction; MBF: myocardial blood flow; MFR: myocardial flow reserve; eGFR: estimated glomerular filtration rate

Supplemental Table 3. Parameters in groups classified by cancer staging and MFR.

	Early Cancer Staging					Advanced Cancer Staging				
Character-istic	**≥1.97, N = 76[a]**	**95% CI[b]**	**<1.97, N = 51[a]**	**95% CI[b]**	**p-value**	**≥1.97, N = 35[a]**	**95% CI[b]**	**<1.97, N = 59[a]**	**95% CI[b]**	**p-value**
Stress MBF (mg/mL/min)	2.14	2.0, 2.3	1.56	1.4, 1.8	<0.001[c]	2.30	2.0, 2.6	1.78	1.6, 2.0	0.003[c]
Rest MBF (mg/mL/min)	0.83	0.77, 0.90	1.04	0.93, 1.2	0.002[c]	0.94	0.81, 1.1	1.25	1.1, 1.4	<0.001[c]
Adjusted Rest MBF (mg/mL/min)	0.77	0.72, 0.82	0.89	0.79, 1.0	0.031[c]	0.84	0.76, 0.93	1.04	0.94, 1.1	0.003[c]
MFR	2.67	2.5, 2.8	1.49	1.4, 1.6		2.49	2.3, 2.7	1.45	1.4, 1.5	
Adjusted MFR	2.87	2.7, 3.0	1.80	1.6, 2.0		2.71	2.5, 2.9	1.79	1.6, 1.9	
Heart rate (stress)	89	86, 92	85	80, 89	0.14[c]	87	82, 93	88	83, 93	0.90[c]
Unknown						*1*		*0*		
Heart rate (rest)	67	65, 70	71	67, 74	0.14[c]	69	65, 73	74	70, 78	0.053[c]
Ejection fraction (stress, %)	72	69, 74	65	61, 68	0.003[d]	72	68, 76	65	61, 70	0.14[d]
Unknown						*0*		*1*		
Ejection fraction (rest, %)	66	63, 68	60	57, 64	0.031[d]	67	63, 71	63	59, 67	0.54[d]
Unknown						*0*		*1*		
Summed stress score	1.3	0.68, 1.9	4.9	2.7, 7.1	0.011[d]	1.9	1.0, 2.8	4.9	2.7, 7.0	0.22[d]
Summed difference score	0.89	0.51, 1.3	2.98	1.4, 4.5	0.077[d]	1.1	0.40, 1.8	3.1	1.6, 4.5	0.16[d]
Hemoglobin (g/dL)	13.03	13, 13	11.95	11, 12	<0.001[c]	12.07	11, 13	11.60	11, 12	0.31[c]
Unknown						*0*		*1*		
Body Mass index	30	29, 32	31	29, 34	0.64[c]	28.2	26, 31	26.5	25, 28	0.21[c]

[a]Mean

[b]CI = Confidence Interval

[c]Welch's Two Sample t-test

[d]Wilcoxon rank sum test

Supplemental Table 4. Factors associated with OS (Cox proportional hazard model) in 163 patients without regional perfusion abnormalities (SSS < 4 and SDS < 3).

	Univariable			Multivariable		
Characteristic	**HR[a]**	**95% CI[a]**	**p-value**	**HR[a]**	**95% CI[a]**	**p-value**
Smoker/Ex-smoker	0.91	0.57, 1.46	0.69			
Hypertension	0.99	0.58, 1.70	0.98			
Diabetes	0.96	0.77, 1.21	0.75			
Dyslipidemia	0.85	0.52, 1.37	0.50			
Prior history of CAD	1.44	0.91, 2.29	0.13			
Vasodilator			0.67			
Dipyridamole	—	—				
Regadenoson	1.10	0.71, 1.71				
TID RATIO	1.64	0.32, 8.25	0.56			
Age (for 1-year)	1.06	1.03, 1.08	<0.001	**1.05**	**1.02, 1.07**	**<0.001**
Gender			0.96			
Female	—	—				
Male	1.01	0.65, 1.57				
Obesity			<0.001			**0.016**
BMI <30	—	—		**—**	**—**	
BMI ≥30	0.38	0.23, 0.63		**0.53**	**0.31, 0.91**	
Hemoglobin			0.010			*0.16*
≥10 g/dL	—	—		—	—	
<10 g/dL	2.47	1.33, 4.57		*1.63*	*0.85, 3.12*	
Rest %LVEF			0.086			
≥50	—	—				
<50	1.94	0.97, 3.89				
Abnormal LVEF reserve			0.97			
Normal	—	—				
Abnormal	0.98	0.40, 2.43				
Morise			0.054			
Low (0-8)	—	—				
Intermediate (9-15)	4.04	0.55, 29.6				
High (>15)	5.42	0.75, 39.4				
Coronary Calcium (Agatston Score)			0.17			
None/Minimal (0-10)	—	—				
Mild (11-100)	1.33	0.60, 2.97				
Moderate (101-400)	1.86	0.90, 3.81				
severe (>400)	2.17	1.10, 4.27				
Stent	2.76	0.97, 7.87				
CABG	2.51	0.56, 11.3				

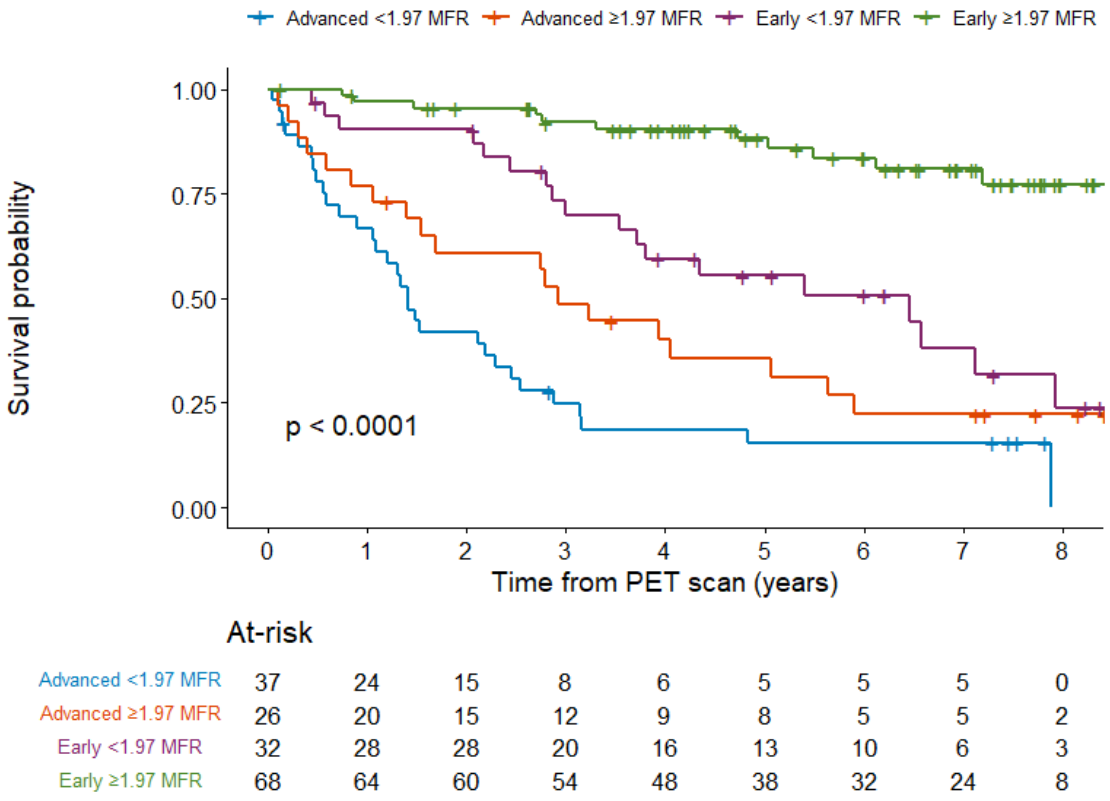
	Univariable			Multivariable		
Characteristic	**HR[a]**	**95% CI[a]**	**p-value**	**HR[a]**	**95% CI[a]**	**p-value**
Stress MBF (for a one-unit decrease)	1.29	0.93, 1.80	0.12			
Rest MBF (for a one-unit decrease)	0.54	0.35, 0.84	0.010	*1.10*	*0.62, 1.96*	*0.75*
MFR (for a one-unit decrease)	2.46	1.70, 3.57	<0.001	**1.86**	**1.24, 2.78**	**0.002**
Stage			<0.001			**<0.001**
Early-stage	—	—		**—**	**—**	
Advanced-stage	4.93	3.10, 7.83		**4.15**	**2.57, 6.69**	
eGFR, binary			0.037			*0.75*
≤60	—	—		—	—	
>60	0.63	0.40, 0.97		*0.93*	*0.59, 1.47*	

[a]HR = Hazard Ratio, CI = Confidence Interval

Multivariable model: in bold are the variables in the final model; in italic are the results of the variables introduced in the model but not kept in the final model, adjusted on the final model.

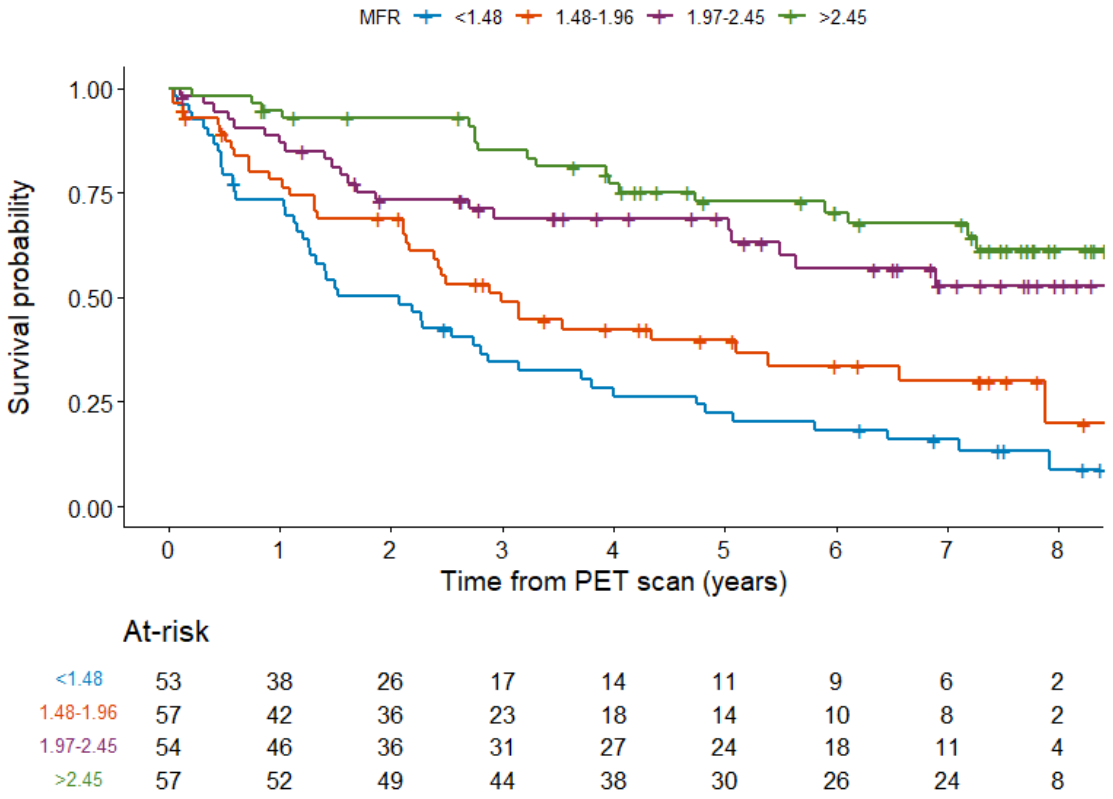
CAD: Coronary Artery Disease; TID: Transient ischemic dilatation; BMI: Body Mass Index; LVEF: Left ventricular ejection fraction; MBF: myocardial blood flow; MFR: myocardial flow reserve; eGFR: Estimated glomerular filtration rate

Supplemental Figure 1. Kaplan-Meier curve stratified by MFR and stage in patients with normal scans (n=163).



Characteristic	At 2 years	At 5 years
Strata		
Advanced <1.97 MFR	42% (28%, 61%)	15% (7.0%, 34%)
Advanced >=1.97 MFR	61% (45%, 83%)	36% (21%, 61%)
Early <1.97 MFR	90% (81%, 100%)	55% (40%, 77%)
Early >=1.97 MFR	95% (91%, 100%)	88% (80%, 97%)

Supplemental Figure 2. Kaplan-Meier curve for MFR in the whole cohort (by quartiles).



Characteristic	At 2 years	At 5 years
MFR		
<1.48	50% (38%, 66%)	22% (13%, 37%)
1.48-1.96	69% (58%, 82%)	40% (28%, 56%)
1.97-2.45	73% (62%, 86%)	69% (57%, 83%)
>2.45	93% (86%, 100%)	73% (62%, 86%)

SUPPLEMENTAL METHODS

^{82}Rb-chloride PET/CT Protocol

Patients abstained from caffeine products for at least 12 hours and fasted for 4–6 hours prior to PET/CT MPI. Written informed consent was obtained from each patient for pharmacologic stress testing. Patients were imaged on a General Electric (GE) DSTE PET/CT scanner (GE Healthcare, Chicago, IL) in 2D mode. Following low-dose CT (120 kV and 10 mA) for positioning and attenuation correction, perfusion images were acquired at rest and stress. REST: About 5 seconds prior to the start of ^{82}Rb infusion (1110-1850 MBq), list mode acquisition was started. Data on blood clearance and myocardial uptake of the tracer and the digitized ECG were acquired for 7 min. Following a review of the rest data, stress imaging was performed. STRESS: Pharmacologic stress was performed with an intravenous infusion of either 0.140 mg/kg/min dipyridamole over 4 min (n=93) or intravenous injection of regadenoson 0.4 mg/5 ml saline over 20 sec (n=128). Within 2 min of the conclusion of vasodilator administration, 1110-1850 MBq ^{82}Rb was administered and ECG-gated list mode data were acquired for a total of 7 min. All subjects were monitored during MPI with 12-lead ECG, pulse oximetry, and serial blood pressure measurements.

The PET/CT images were checked for spatial alignment of the attenuation correction CT and the emission scan; the alignment was corrected manually when necessary. The attenuation corrected PET emission data were rotated into the standard cardiac orientation for interpretation. List mode data was binned into 27 dynamic frames (14 × 5 sec, 6 × 10 sec, 3 × 20 sec, 3 × 30 sec, and 1 × 140 sec) and reconstructed using standard clinical 3D OSEM reconstruction with 2 iterations, 21 subsets, and a 5 mm Gaussian smoothing filter onto a 168 × 168 matrix (2.7 × 2.7 mm, 2.0 mm slice thickness).

A dedicated CT was routinely performed for coronary artery calcium scoring and consisted of 50–70 slices of 2.5 mm slice thickness recorded with prospective ECG-gating. The CT was acquired with 120 kV, ~250 mA, 0.6 mm collimation, 1.4 sec per cycle, ~10 sec total acquisition time, and 1–2 mSv radiation dose.

Image Analysis

Qualitative Perfusion: Summed images were displayed using Corridor 4DM software (Invia, Ann Arbor, MI). Images were reoriented to create short-axis and long-axis slices for visual analysis of regional perfusion. The extent and

severity of perfusion abnormalities were catalogued using the 17-segment model (*1*). Each of the 17 myocardial segments was scored on a scale of 0–4 (normal, mildly, moderately, or severely decreased or absent perfusion) by three-reader consensus. Summed rest score (SRS), summed stress score (SSS), and summed difference score (SDS: SSS−SRS) were calculated and categorized into SSS ≥ 4 or SSS < 4 and SDS ≥ 3 or SDS < 3, as in previous studies (*2,3*).

Left ventricular ejection fraction (LVEF) values were derived from rest and stress gated datasets. Transient ischemic dilatation ratio was obtained from non-gated images using Corridor 4DM software (INVIA, Ann Arbor, MI) using a cutoff value of 1.13 (*4*).

Quantification of MBF and MFR: Global and regional myocardial blood flow (ml/min/g) were calculated using the one-compartment analysis model in the Corridor 4DM software (INVIA, Ann Arbor, MI) (14). MBF was determined in each vascular territory and in the total LV myocardium at rest and stress. Additionally, rest MBF was adjusted (aR-MBF) for rate pressure product (RPP), where aR-MBF = (rest MBF × 8500) / RPP. Adjusted MFR (aMFR) was also recorded, where aMFR = stress MBF / aR-MBF (*5*). Each dataset was analyzed by an experienced nuclear medicine physician who was blinded to patient history and results of the outcome.

Coronary artery calcium score: Foci of coronary calcium were identified and scored with semi-automatic commercial software (Smart Score, GE Medical Systems, Chicago, IL) according to the Agatston method (*6*).

Supplemental References

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