

Risk Stratification in Coronary Artery Disease using NH3-PET Myocardial Flow Reserve and CAD-RADS on Coronary CT Angiography

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Abstract

Purpose

Myocardial flow reserve (MFR) derived from ^{13}N -ammonia positron emission tomography (NH_3 -PET) can predict the prognosis of patients with various heart diseases. Coronary computed tomography angiography (CCTA) is a non-invasive investigation for ischemic heart disease. The coronary artery disease reporting and data system (CAD-RADS) was established to standardize and facilitate the reporting of CCTA data regarding CAD. This study aimed to investigate the prognostic value of CAD-RADS and MFR.

Methods

A total of 133 patients who underwent NH_3 -PET and CCTA within 3 months were enrolled. Patients were divided into groups with CAD-RADS 0-2 and ≥ 3 and into groups with MFR ≥ 2.0 and < 2.0 . The endpoint was major adverse cardiac events (MACE) comprising all-cause death, acute coronary syndrome, hospitalization due to heart failure, and cerebrovascular disease. The ability of CAD-RADS and MFR to predict MACE was analyzed using Kaplan-Meier analysis.

Results

There was no significant difference in MFR between patients with CAD-RADS 0-2 and ≥ 3 (2.3 ± 0.9 vs. 2.2 ± 0.7 , $p=0.50$). The MACE rate for patients with CAD-RADS 0-2 and ≥ 3 was equivalent (log-rank test, $p=0.64$). Patients with MFR < 2.0 had a significantly higher MACE rate than those with MFR ≥ 2.0 ($p=0.017$). In patients with CAD-RADS ≥ 3 , patients with MFR < 2.0 had a significantly higher MACE rate than those with MFR ≥ 2.0 ($p=0.034$).

Conclusion

CAD-RADS did not contribute to MACE prediction. Conversely, MFR was useful in predicting MACE, allowing for further risk stratification in addition to CAD-RADS.

Introduction:

^{13}N -ammonia positron emission tomography (NH_3 -PET) has high temporal and spatial resolutions [1]; it can evaluate myocardial blood flow (MBF) at rest, hyperemia-induced adenosine, myocardial flow reserve (MFR), and the ratio of MBF at stress to that at rest. The combination of MFR and myocardial perfusion imaging (MPI) is useful in diagnosing ischemic heart disease (IHD) [2,3]. Additionally, MFR can predict the prognosis of patients with various heart diseases because low MFR (< 2.0) indicates a poor prognosis in both IHD and non-IHD patients [2-4].

Coronary computed tomography angiography (CCTA) is also a non-invasive tool for investigating IHD. It has high sensitivity and negative predictive value for significant coronary artery disease (CAD) and is

useful in characterizing atherosclerotic plaques [5]. High-risk plaques (HRP) have been described as strong predictors of adverse events, and low-attenuation plaques are related to reduced MFR [6-12].

The CAD reporting and data system (CAD-RADS) was established to standardize and facilitate the reporting of CCTA data regarding CAD [13,14]. The prognostic value of CAD-RADS for predicting major adverse cardiac events (MACE) in stable CAD patients remains controversial compared with traditional classifications [14,15]. Moreover, it is unknown whether the combination of CAD-RADS and MFR is helpful in predicting MACE. Therefore, we aimed to investigate the utility of CAD-RADS and MFR for risk stratification in stable CAD patients.

Materials And Methods:

Study population

Between April 2015 and January 2020, 172 consecutive patients with suspected or known stable CAD who underwent NH₃-PET and CCTA within 3 months at a single center were enrolled. Patients with a history of coronary artery bypass graft surgery, congenital heart disease, or adenosine ineffectiveness were excluded. Finally, 133 patients were enrolled in this study and prospectively analyzed. The study was performed in compliance with the Declaration of Helsinki, and the protocol was approved by ethics committee of our hospital (authorization number: 5260). Informed consent was obtained from all patients.

NH₃-PET image acquisition

Patients refrained from caffeine for ≥ 12 hours before NH₃-PET study and did not take any antianginal medications on the morning of the test. Imaging was performed using a 3-dimensional PET system (Biograph, mCT, Siemens Healthcare). A sequential CT scan (120 kV, 20 mAs, and 3 mm slice collimation) was acquired for attenuation correction. Immediately after administering 185 MBq ¹³N-ammonia intravenously, electrocardiographic-gated acquisition was performed for 10 min with 16 frames per cardiac cycle using parallel list-mode acquisition. We visualized MBF images in the initial 2 min and MPI in the next 8 min. After the PET MPI at rest, an adenosine stress test was performed (0.12 mg/kg/min x 6 min). Approximately 555 MBq of ¹³N-ammonia was infused 3 min after the administration of the vasodilator, and the stress and rest MPIs were evaluated.

Calculation of MBF and MFR

Images were reconstructed using Fourier rebinning and filtered back-projection with a 12 mm 3-dimensional Hann window of the ramp filter. Automatic reorientation of the images, automatic extraction of the mean myocardial and cavity time-activity curves (TACs), and generation of polar maps of the

absolute MBF and MFR were performed using a dedicated software (Syngo MI cardiology, Siemens Healthcare). MBF was estimated using the TAC of the left ventricle input and myocardial uptake using a 3-compartment model and dataset of list-mode images obtained in the first 2 min. MFR was determined as the ratio of hyperemic MBF to resting MBF. Global MFR <2.0 was considered abnormal [2,4].

Myocardial perfusion assessment using static imaging

The observers had access to polar maps and 16 slices each on the short axis, vertical long axis, and horizontal long axis. The images were interpreted using a 17-segment model and semi-quantitative scoring system (0=normal, 1=mildly abnormal, 2=moderately abnormal, 3=severely abnormal, and 4=complete defect) to detect the severity [16]. Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS = SSS – SRS) were calculated. SSS \geq 4 in each region of the three major territories was considered abnormal.

CCTA image acquisition

A 320-row CT scanner (Aquilion One Vision Genesis, Canon) with a section collimation of 320 \times 0.5 mm and a gantry rotation time of 275 ms was used for CCTA imaging. Metoprolol (20 mg or 40 mg, oral) was administered for a target heart rate of <65 bpm 1 hour before CCTA was performed. If necessary, landiolol (0.125 mg/kg, intravenous) was additionally administered. Sublingual nitroglycerine was administered to all patients immediately before the scan. To determine the optimal scan timing for CCTA, a test-bolus injection of small contrast media was scanned in the ascending aorta at the slice level of the pulmonary trunk. CCTA with a tube current of 700 mA and 100 kV, and prospective electrocardiogram gating were performed at 75% of the R-R interval. A bolus of contrast media (Oypalomin 370, Fuji Pharma) was injected at a flow rate of 4-5 mL/s, followed by a saline flush.

Assessment of coronary artery stenosis and plaque

Coronary arteries with a diameter \geq 2 mm were evaluated according to a 17-segment coronary artery model using axial, multi-planar reformation, maximum intensity projection, and cross-sectional images [17]. CAD-RADS 0, 1, 2, 3, 4A, 4B, and 5 were defined as 0% (absence of CAD) stenosis; 1-24% stenosis; 25-49% stenosis; 50-69% stenosis; 70-99% stenosis in one or two vessels; 70-99% stenosis in three vessels or left main coronary artery stenosis \geq 50%; and 100% stenosis (total coronary occlusion), respectively (Figure 1) [13-15]. The most severe stenosis was considered if a single vessel had multiple lesions. The V (vulnerable plaque), S (stent), or G (graft) category modifiers were not used for grouping.

Coronary lesions were also analyzed in terms of the four HRP characteristics as previously defined [18-20]. The stenosis severity and plaque characteristics on CCTA were analyzed using a dedicated workstation (Ziostation 2, Ziosoft Inc.). The CCTA assessment was determined by the consensus of two

radiologists and two cardiologists with more than 10 years of experience in nuclear cardiology and cardiac CT.

Assessment of clinical outcomes

The endpoint was defined as the occurrence of MACE consisting of all-cause death, acute coronary syndrome, hospitalization due to heart failure, and cerebrovascular disease. The event data were retrospectively gathered from the patients' records, including in- and out-of-hospital reports. Coronary events within 90 days were not included. Based on the results of CCTA and NH_3 -PET, it was left to the attending physician to decide whether coronary revascularization was required.

Statistical Analysis

Patients were divided into two groups based on the thresholds of CAD-RADS 3 and MFR 2.0, and the prognosis was compared. Continuous variables are expressed as mean \pm SD, while categorical variables are presented as absolute counts and percentages. Comparisons were made using the Mann–Whitney U test for continuous variables, the chi-square test or Fischer exact test for categorical variables, and the Wilcoxon rank-sum test for ordinal variables. The Cox proportional hazards regression model was used to calculate hazard ratios with 95% confidence intervals (CI). The ability of CAD-RADS and MFR to predict MACE was assessed using the C-statistic. Survival curves of the patient subgroups were created using the Kaplan-Meier method to clarify the time-dependent cumulative MACE-free rates and were compared using the log-rank test. A p-value <0.05 was considered to indicate a statistically significant difference. All analyses were performed using JMP Pro version 14 (SAS Institute Inc., Cary, NC).

Results:

Patient's characteristics

The age was 67 ± 11 years, and 93 patients (70%) were men (Table 1). Over a follow-up period of 40 ± 18 months, MACE occurred in 14 patients (11%).

Table 1**Patient's Characteristics**

Number of patients	133
Age (years)	67±11
Male	93 (70%)
Coronary Risk Factor	
BMI (kg/m ²)	24±3.6
Hypertension	103 (79%)
Diabetes Mellitus	65 (50%)
Dyslipidemia	88 (67%)
Current or Past Smoker	44 (33%)
Family History of CAD	29 (22%)
Heart Failure	10 (8%)
Old Myocardial Infarction	11 (8%)
Therapy	
β blocker	52 (40%)
ACEI/ARB	67 (51%)
Statin	80 (61%)
Aspirin	75 (57%)
P2Y inhibitor	27 (21%)
DOAC	10 (8%)
Continuous variables are expressed as mean ± SD, and categorical variables are presented as absolute counts and percentages.	
BMI = body mass index, CAD = coronary artery disease, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, DOAC = direct oral anticoagulant	

The interval between NH₃-PET and CCTA was 45±20 days. The overall stress and rest MBF were 2.0±0.6 and 1.0±0.2 ml/g/min, respectively, and MFR was 2.2±0.7. There were 58 patients (44%) with MFR <2.0 (Table 2).

Table 2
NH₃-PET parameter

Stress MBF (ml/g/min)	2.0±0.6
Rest MBF (ml/g/min)	1.0±0.2
MFR	2.2±0.7
MFR <2.0	58 (44%)
End-diastolic Volume (ml)	90±28
End-systolic Volume (ml)	29±21
Ejection Fraction (%)	70±12
Summed Stress Score	5.6±6.9
Summed Rest Score	1.2±2.5
Summed Difference Score	4.5±5.9
Summed Stress Score >4	62 (47%)
Continuous variables are expressed as mean ± SD, and categorical variables are presented as absolute counts and percentages.	
NH ₃ -PET = ¹³ N-ammonia Positron Emission Tomography, MBF = myocardial blood flow, MFR = myocardial flow reserve	

There were 121 patients (91%) with CAD-RADS ≥3 (Table 3). The heart rate for all patients was 55±10 bpm at CCTA. CTDI and DLP for all CCTA were 30±12 mGy and 365±135 mGy·cm, respectively.

Table 3
CCTA parameter

CAD-RADS	
0	3 (2%)
1	4 (3%)
2	5 (4%)
3	23 (17%)
4A	68 (51%)
4B	10 (8%)
5	20 (15%)
CAD-RADS ≥ 3	121 (91%)
Agatston score	786 \pm 1128
High-risk plaque	
Low attenuation plaque	42 (32%)
Napkin-ring sign	24 (18%)
Spotty calcification	25 (19%)
Positive remodeling	18 (14%)
Continuous variables are expressed as mean \pm SD, and categorical variables are presented as absolute counts and percentages.	
CCTA = coronary computed tomography angiography, CAD-RADS = Coronary Artery Disease Reporting and Data System	

Relationship between CAD-RADS and NH3-PET measurements

MFR for patients with CAD-RADS 0-2 was equivalent to that with CAD-RADS ≥ 3 (2.3 \pm 0.9 vs. 2.2 \pm 0.7, p=0.50). The frequency of MFR <2.0 did not significantly differ between the CAD-RADS 0-2 and ≥ 3 groups (33% vs. 45%, p=0.45) (Figure 2). There was no significant difference in the frequency of SSS ≥ 4 between the CAD-RADS 0-2 and ≥ 3 groups (25% vs. 49%, p=0.12) (Figure 3).

Prognostic value of CAD-RADS, MFR, and SSS

In 14 patients with MACE, all except one patient were in the CAD-RADS ≥ 3 group. CAD-RADS did not contribute to predicting MACE (hazard ratio [HR]:1.3, 95% CI: 0.16–11.1). The C-statistic, sensitivity, and specificity of CAD-RADS for MACE were 0.69, 71%, and 60%, respectively. The MACE rate was equivalent between the CAD-RADS 0-2 and ≥ 3 groups (log-rank test, $p=0.64$) (Figure 4a).

Eleven patients with MACE were in the MFR <2.0 group. The MFR <2.0 group was significantly associated with MACE compared with the MFR ≥ 2.0 group (HR 5.6, 95% CI: 1.49–21.2). The C-statistic, sensitivity, and specificity of MFR for MACE were 0.70, 79%, and 61%, respectively. Patients with MFR <2.0 had a significantly higher MACE rate than those with MFR ≥ 2.0 ($p=0.017$). Eleven patients with MACE had SSS ≥ 4 (one had MFR ≥ 2.0). The SSS ≥ 4 group had a significantly higher MACE rate than the SSS 0-3 group ($p=0.019$) (Figure 4b).

Incremental value of NH₃-PET beyond CAD-RADS to predict MACE

The MACE rate was equivalent between the CAD-RADS 0-2 with any MFR group and the CAD-RADS ≥ 3 with MFR ≥ 2.0 group ($p=0.77$). The MACE rate was significantly higher in the CAD-RADS ≥ 3 with MFR <2.0 group than in the CAD-RADS ≥ 3 with MFR ≥ 2.0 group ($p=0.034$). The MACE rate for the CAD-RADS ≥ 3 with MFR <2.0 group tended to be higher than that for the CAD-RADS 0-2 with any MFR group, although the difference was not significant ($p=0.33$). Likewise, the MACE rate was significantly higher in the CAD-RADS ≥ 3 with SSS ≥ 4 group than in the CAD-RADS ≥ 3 with SSS 0-3 group ($p=0.011$) (Figure 5).

Discussion:

One of the major findings in our study was that the addition of MFR and SSS to CAD-RADS contributed to further risk stratification in patients with CAD-RADS ≥ 3 . The combination of NH₃-PET and CAD-RADS is more effective than CAD-RADS alone in predicting MACE. This result suggests that it is useful to perform a functional assessment in patients with CAD-RADS ≥ 3 .

J-ACCESS study, which evaluated CAD prognosis in the Japanese population using myocardial perfusion scintigraphy, showed that SSS predicted cardiac events and is consistent with the results of this study [21]. MFR derived from NH₃-PET is also useful in predicting MACE. A previous study reported that NH₃-PET was more predictive of MACE than invasive fractional flow reserve [22]. This study showed a higher event rate in the MFR < 2.0 group than in the MFR ≥ 2.0 group (19% vs. 4%, $p = 0.005$). Moreover, the MACE rate was significantly lower if MFR ≥ 2.0 , even if CAD-RAD ≥ 3 . Conversely, the event rate of patients with CAD-RADS ≥ 3 and MFR < 2.0 further increased. Therefore, comprehensive cardiac treatment, including revascularization, atherosclerosis prevention, and heart failure management, should be enhanced in patients with CAD-RADS ≥ 3 and MFR < 2.0 .

Although the ISCHEMIA trial showed that invasive treatment did not significantly improve prognosis in patients with moderate or severe ischemia, the results of this study suggest that the addition of MFR to moderate or severe stenosis could help select a group of patients who would truly benefit from revascularization [23].

PROMISE trial showed that CAD-RADS was a prognostic factor for cardiac events [14], but it did not contribute to the prediction of MACE in this study. We believe that this difference is caused by the fact that only 12 patients with CAD-RADS 0–2 (9%) were included in the present study.

Limitations:

This study has several limitations. First, this is a single-center study that included a small number of patients. There are only a few cyclotrons in our country, which are required for ^{13}N -ammonia production. Second, this study focused on patients with high risk of CAD, and those with lower risk were not examined. Finally, it included patients who underwent revascularization for stable CAD during follow-up. The implementation of revascularization is left to the attending physician, with reference to the imaging findings, which is more reflective of actual clinical practice.

Conclusions

Although CAD-RADS did not contribute to the prediction of MACE, MFR was useful in predicting prognosis, allowing for further risk stratification in addition to CAD-RADS. This suggests that it may be useful to perform a functional assessment in patients with CAD-RADS ≥ 3 .

Declarations

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Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Availability of data and material

Not applicable

Code availability

Not applicable

Author contributions:

Atsushi Yamamoto: Conceptualization, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Visualization Preparation

Michinobu Nagao: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing, Project administration

Kiyoe Ando: Investigation, Resources

Risako Nakao: Investigation, Resources

Akiko Sakai: Resources

Eri Watanabe: Resources

Mitsuru Momose: Conceptualization, Methodology

Kayoko Sato: Resources

Kenji Fukushima: Investigation

Shuji Sakai: Project administration

Nobuhisa Hagiwara: Project administration

Ethics approval

The study was performed in compliance with the Declaration of Helsinki, and the protocol was approved by ethics committee of our hospital (authorization number: 5260).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Patients signed informed consent regarding publishing their data and photographs.

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Figures

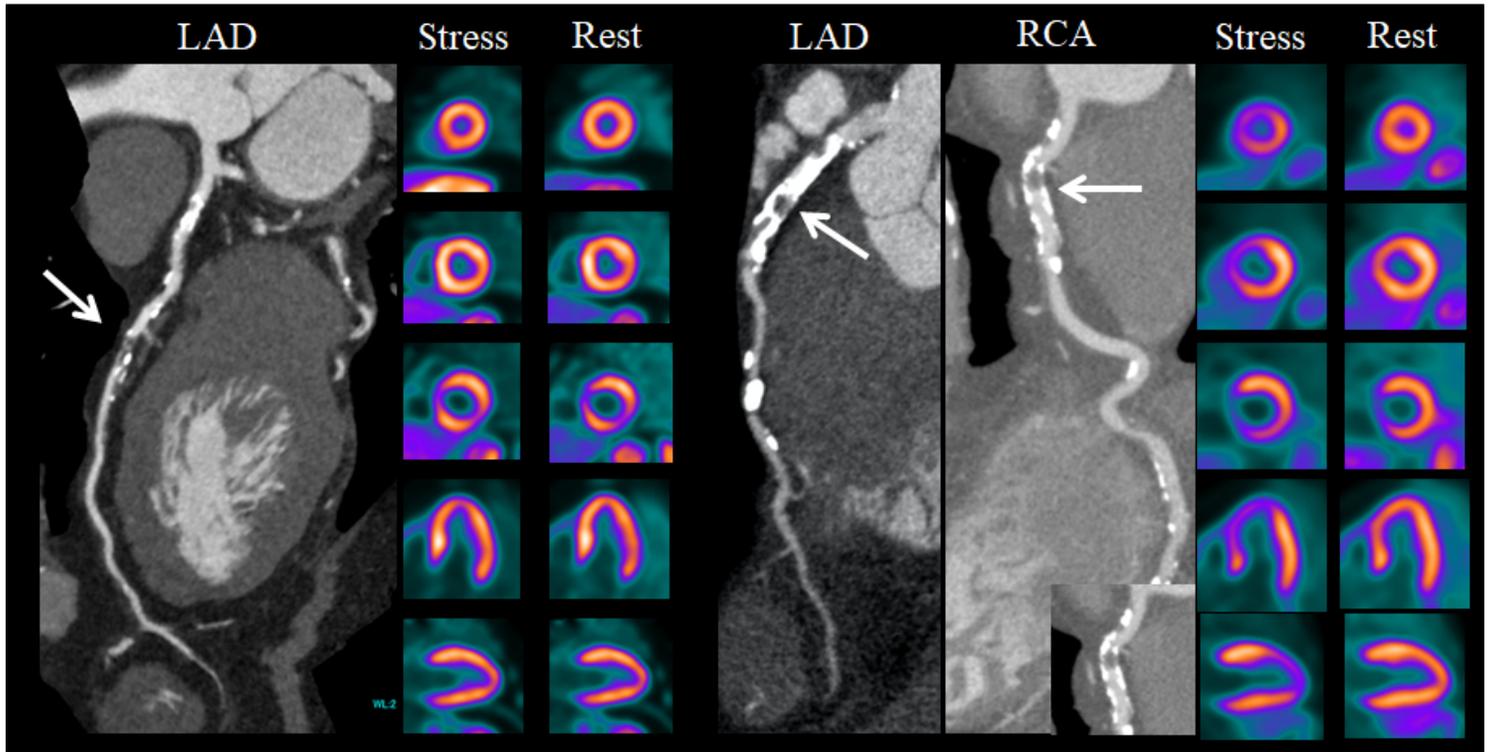


Figure 1

Representative cases with and without MACE Left: A 59-year-old man with hypertension, dyslipidemia, and diabetes mellitus. He was classified as CAD-RADS 4a with 90% stenosis in the LAD (arrow) and 50% stenosis in the LCX and RCA on a curved multi-planar reconstructed CCTA image. NH₃-PET perfusion images at stress and rest showed no obvious areas of hypoperfusion. Global MFR was maintained at 2.28. Revascularization was not performed, and no cardiovascular events were observed during 3 years of follow-up with medical treatment only. Right: A 59-year-old man with hypertension and a history of smoking. He had 90-99% stenoses in both the LAD and RCA (arrow) on CCTA and was classified as CAD-RADS 4a. NH₃-PET perfusion images showed hypoperfusion in the anteroseptal and inferior wall under stress and normal perfusion at rest. This was thought to be ischemia in the LAD and RCA territories. Global MFR decreased to 1.73. Immediately after CCTA and NH₃-PET, he underwent percutaneous coronary intervention but was admitted to the hospital 1 year later with heart failure. CAD-RADS=coronary artery disease reporting and data system, CCTA=coronary computed tomography angiography, LAD=left anterior descending coronary artery, LCX=left circumflex coronary artery, MACE=major adverse cardiac events, MFR=myocardial flow reserve, NH₃-PET=¹³N-ammonia positron emission tomography, RCA=right coronary artery.

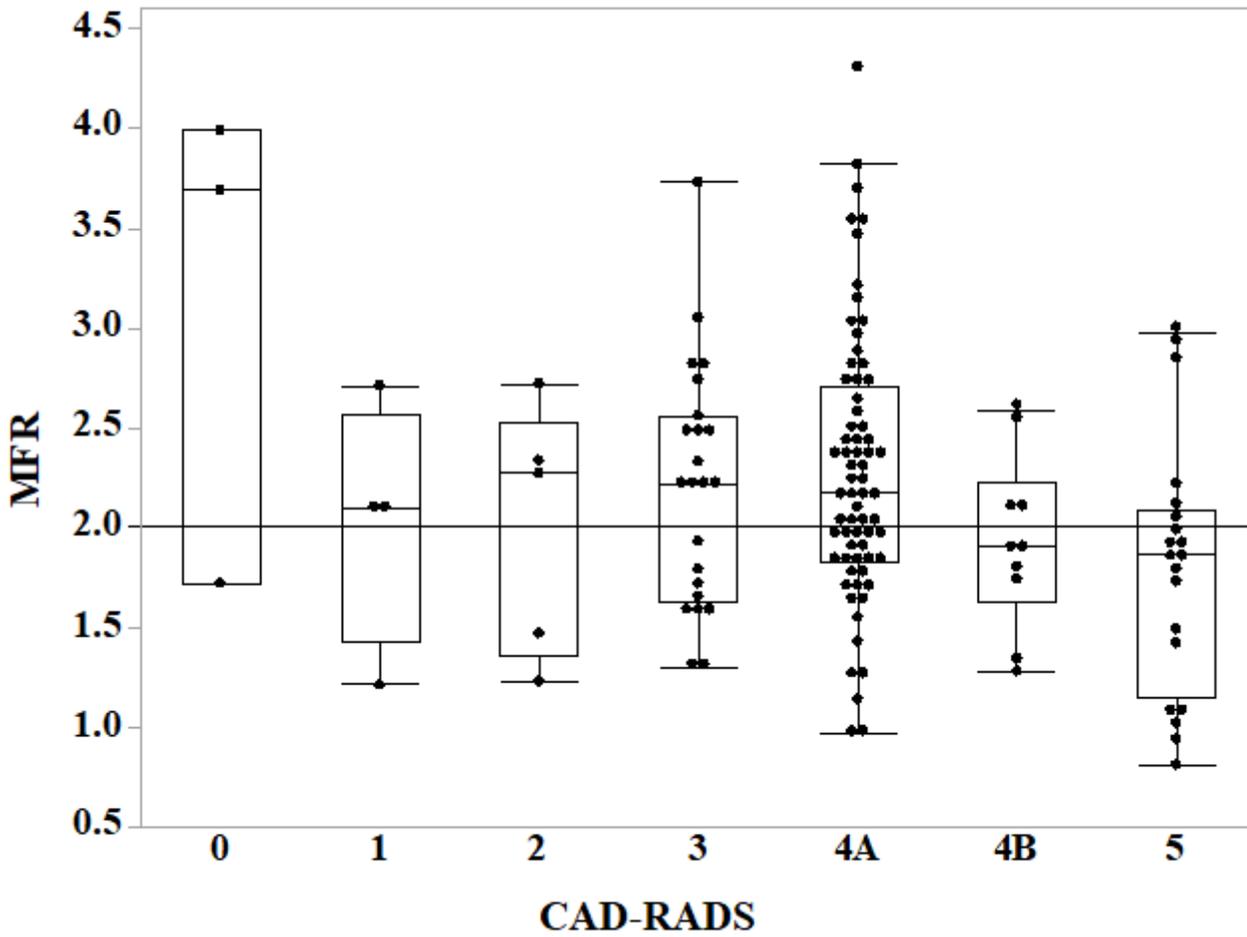


Figure 2

Box and whisker plots of MFR for patients in each CAD-RADS category. The horizontal lines indicate the maximum and minimum, and the ends of the box (whiskers) indicate the upper and lower tertiles. All categories included patients with MFR < 2.0. CAD-RADS=coronary artery disease reporting and data system, MFR=myocardial flow reserve

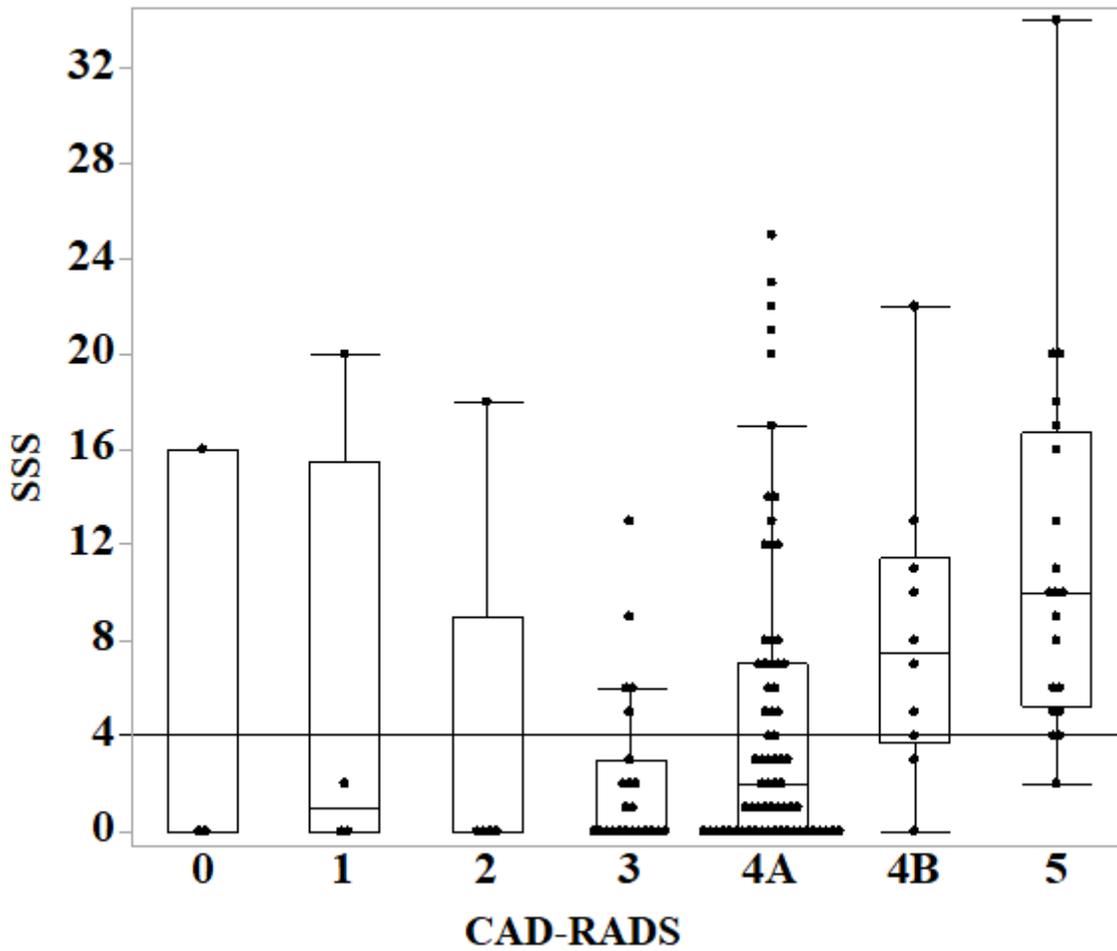


Figure 3

Box and whisker plots of SSS for patients in each CAD-RADS category All categories included patients with $SSS \geq 4$. CAD-RADS=coronary artery disease reporting and data system, SDS=summed difference score

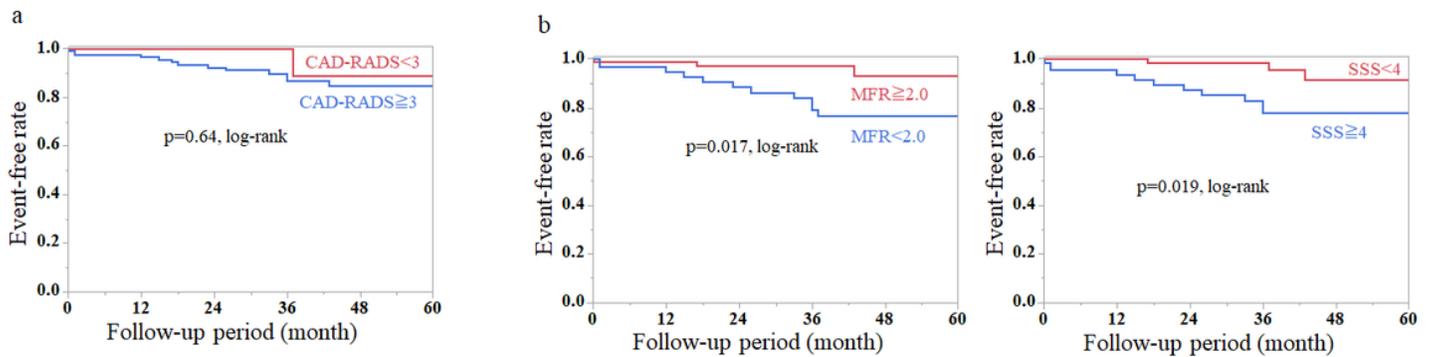


Figure 4

Kaplan-Meier curve for MACE by CAD-RADS, MFR, and SSS a: Patients were divided into two groups by CAD-RADS 3, which was the threshold for functional assessment recommendation. The blue curve represents patients with CAD-RADS ≥ 3 , while those with CAD-RADS 0-2 are represented in red. The MACE rate for patients with CAD-RADS 0-2 was equivalent to that for patients with CAD-RADS ≥ 3 . b: Left: Patients were divided into two groups by MFR 2, which was the threshold for poor prognosis. The blue curve represents patients with MFR < 2.0 , while those with MFR ≥ 2.0 are presented in red. Patients with MFR < 2.0 had a significantly higher MACE rate than those with MFR ≥ 2.0 . Right: Patients were divided into two groups by SSS 4, which was defined as abnormal. The blue curve represents patients with SSS ≥ 4 , while those with SSS 0-3 are represented in red. Patients with SSS ≥ 4 had a significantly higher MACE rate than those with SSS 0-3. CAD-RADS=coronary artery disease-reporting and data system; MACE=major adverse cardiac events; MFR=myocardial flow reserve; SSS=summed stress score

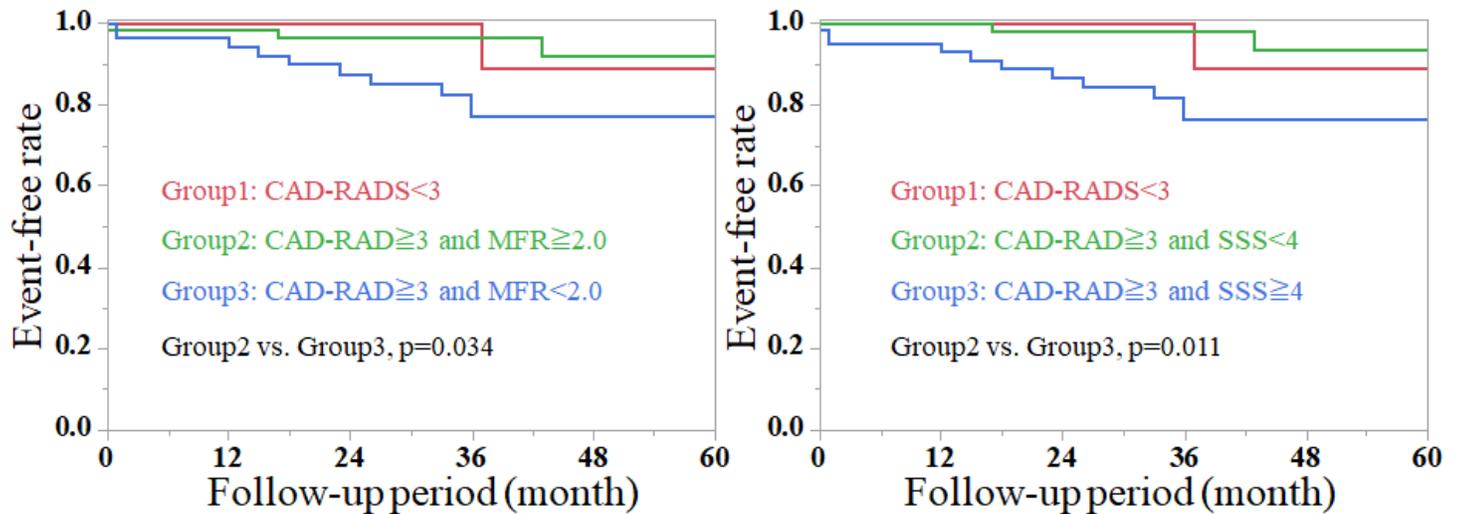


Figure 5

Kaplan-Meier curve for MACE by the combination of CAD-RADS with MFR or SSS Left: Patients were divided into three groups by CAD-RADS and MFR. The red curve represents patients in the CAD-RADS 0-2 with any MFR group, those in the CAD-RADS ≥ 3 with MFR ≥ 2.0 group are shown in green, and those in the CAD-RADS ≥ 3 with MFR < 2.0 group are represented in blue. The MACE rate was equivalent between the CAD-RADS 0-2 with any MFR and CAD-RADS ≥ 3 with MFR ≥ 2.0 groups. The MACE rate was significantly higher in the CAD-RADS ≥ 3 with MFR < 2.0 group than in the CAD-RADS ≥ 3 with MFR ≥ 2.0 group. Right: Patients were divided into three groups by CAD-RADS and SSS. The red curve represents patients in the CAD-RADS 0-2 group, those in the CAD-RADS ≥ 3 with SSS 0-3 group are shown in green, and those in the CAD-RADS ≥ 3 with SSS ≥ 4 group are represented in blue. The MACE rate was equivalent between the CAD-RADS 0-2 with any MFR group and the CAD-RADS ≥ 3 with SSS 0-3 group. The MACE rate was significantly higher in the CAD-RADS ≥ 3 with SSS ≥ 4 group than in the CAD-RADS ≥ 3 with SSS 0-3 group. CAD-RADS=coronary artery disease-reporting and data system; MACE=major adverse cardiac events; MFR=myocardial flow reserve; SSS=summed stress score