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# Prognostic Value of Integrated Assessment of Cardiac Magnetic Resonance-Derived Global Coronary Flow Reserve and Cardiopulmonary Exercise Testing-Derived Peak Oxygen Consumption in Patients With Acute Myocardial Infarction

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***Background:*** This study investigated the prognostic value of cardiovascular magnetic resonance (CMR)-derived global coronary flow reserve (G-CFR) in addition to cardiopulmonary exercise testing (CPET) variables in patients with acute myocardial infarction (AMI).

***Methods and Results:*** We investigated 127 patients with AMI who underwent primary or urgent percutaneous coronary intervention (PCI) and post-intervention CMR and CPET. The incidence of major cardiac and cerebrovascular events (MACCE), defined as all-cause death, recurrent non-fatal myocardial infarction, re-hospitalization due to congestive heart failure, and stroke, was evaluated (median follow-up, 2.8 years). Patients with MACCE (n=14) had lower ejection fraction (EF) (50 [43–59] vs. 58 [51–63]%; P=0.014), lower G-CFR (1.74 [1.19–2.20] vs. 2.40 [1.61–3.66]; P=0.008), and lower peak oxygen consumption ($\dot{V}O_2$) (15.16±2.64 vs. 17.19±3.70 mL/kg/min; P=0.049) than patients without MACCE. G-CFR<2.33 and peak $\dot{V}O_2$<15.65 mL/kg/min (cut-off values derived from receiver operating characteristic curve analyses) were significantly associated with the incidence of MACCE (log-rank test, P=0.01). The combination of low G-CFR and low peak $\dot{V}O_2$ improved risk discrimination for MACCE when added to the reference clinical model including age, male sex, post-PCI peak creatine kinase, EF, and left anterior descending artery culprit lesion.

***Conclusions:*** G-CFR and peak $\dot{V}O_2$ showed incremental prognostic information compared with the reference model using historically important clinical risk factors, indicating that this approach may help identify high-risk patients who suffer subsequent adverse events.

**Key Words:** Acute myocardial infarction; Cardiac magnetic resonance imaging; Cardiopulmonary exercise testing; Coronary flow reserve; Peak oxygen consumption

The increased utilization of primary percutaneous coronary intervention (PCI) has reduced the mortality rate after acute myocardial infarction (AMI); however, the development of heart failure (HF) after AMI still contributes to the increased risk of mortality.[1] Therefore, prognostication and risk stratification for adverse outcomes after PCI is of utmost interest in patients with AMI.

Cardiopulmonary exercise testing (CPET) is a non-invasive method widely used to estimate exercise capacity and predict outcomes.[2,3] In contrast, recent studies reported the predictive significance of global coronary flow reserve (G-CFR) assessed using non-invasive imaging modalities including positron emission tomography (PET)[4,5] and cardiovascular magnetic resonance (CMR).[6,7] However, the prognostication of combined application of CMR and

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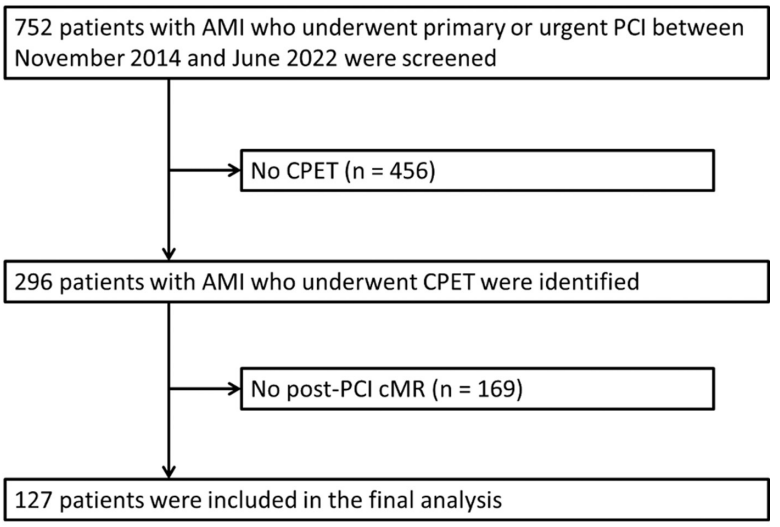


**Figure 1.** Study flow diagram. AMI, acute myocardial infarction; CMR, cardiovascular magnetic resonance; CPET, cardiopulmonary exercise testing; PCI, percutaneous coronary intervention.

CPET findings remains to be determined in patients with AMI.

In the present study, we aimed to investigate the prognostic value of CMR-derived G-CFR in addition to CPET variables in patients with AMI.

## Methods

### Study Population

This retrospective analysis included patients from the institutional AMI registry database enrolled between November 2014 and June 2022 at Tsuchiura Kyodo General Hospital. In this registry, 752 patients with AMI who underwent primary or urgent PCI were screened. Of the total 752 patients screened, 127 patients with AMI who underwent post-intervention CMR and CPET were identified and studied (**Figure 1**). Diagnosis of AMI included ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), according to the previously reported definition.[8] The Global Registry of Acute Coronary Events (GRACE) score was calculated on admission for each patient.[9] Laboratory data were obtained on admission. In patients with multivessel disease, when significant non-infarct-related artery stenoses were considered as candidates for revascularization by physiological assessment, an ad-hoc procedure at the time of the index primary/urgent PCI or a planned staged procedure during the index hospitalization was performed. Post-intervention CMR and CPET were performed after non-infarct-related lesion revascularization in patients with multivessel disease. Patient characteristics, angiography findings of the culprit lesions, post-PCI peak creatine kinase (CK) values, CMR findings, CPET findings, and the incidence of major cardiac and cerebrovascular events (MACCE) during the follow-up period were evaluated. All patients were managed with optimal medical therapy according to the latest guidelines.[10,11] Representative images of a case presenting with AMI are shown in **Figure 2**.

### Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee on human research of Tsuchiura Kyodo General Hospital (approval number: 2022FY68). All patients provided written informed consent for enrollment in the institutional AMI registry database for potential future investigations. All patient data and procedural details were obtained from their medical records and the institutional AMI registry database.

### Coronary Catheterization and PCI Procedure

Each patient underwent selective coronary angiography and primary or urgent PCI via the radial artery with a 6-Fr system. PCI was performed according to the standard technique. The PCI strategy was determined by the interventionist and the use of intravascular imaging was left to the operator's discretion. All patients were treated with coronary drug-eluting stent implantation and the stent type was selected at the operator's discretion. Quantitative coronary angiography and intravascular imaging findings were used to help determine the appropriate stent size and obtain optimal stent expansion. The culprit lesion was identified based on angiography findings, electrocardiogram (ECG) changes, and/or left ventricular (LV) wall motion abnormalities. In patients with multiple stenoses, the culprit lesion was identified as the lesion having the most severe stenosis or with evidence of recent plaque disruption such as filling defect suggestive of thrombus on angiogram.

### CMR Image Acquisition and Analysis

CMR image acquisition was performed using a 1.5-Tesla scanner (Achieva, Philips Medical Systems, Best, The Netherlands) with 32-channel cardiac coils within 30 days after PCI, as previously described.[7] Late gadolinium enhancement (LGE) images were acquired 15 min after the injection of gadolinium contrast (0.10 mmol/kg). All CMR images were analyzed using a dedicated workstation (Virtual Place, AZE Ltd, Tokyo, Japan) by two independent investigators who were blinded to clinical and angiography data. Microvascular obstruction (MVO) was defined as the hypo-enhanced region within and included in the infarcted

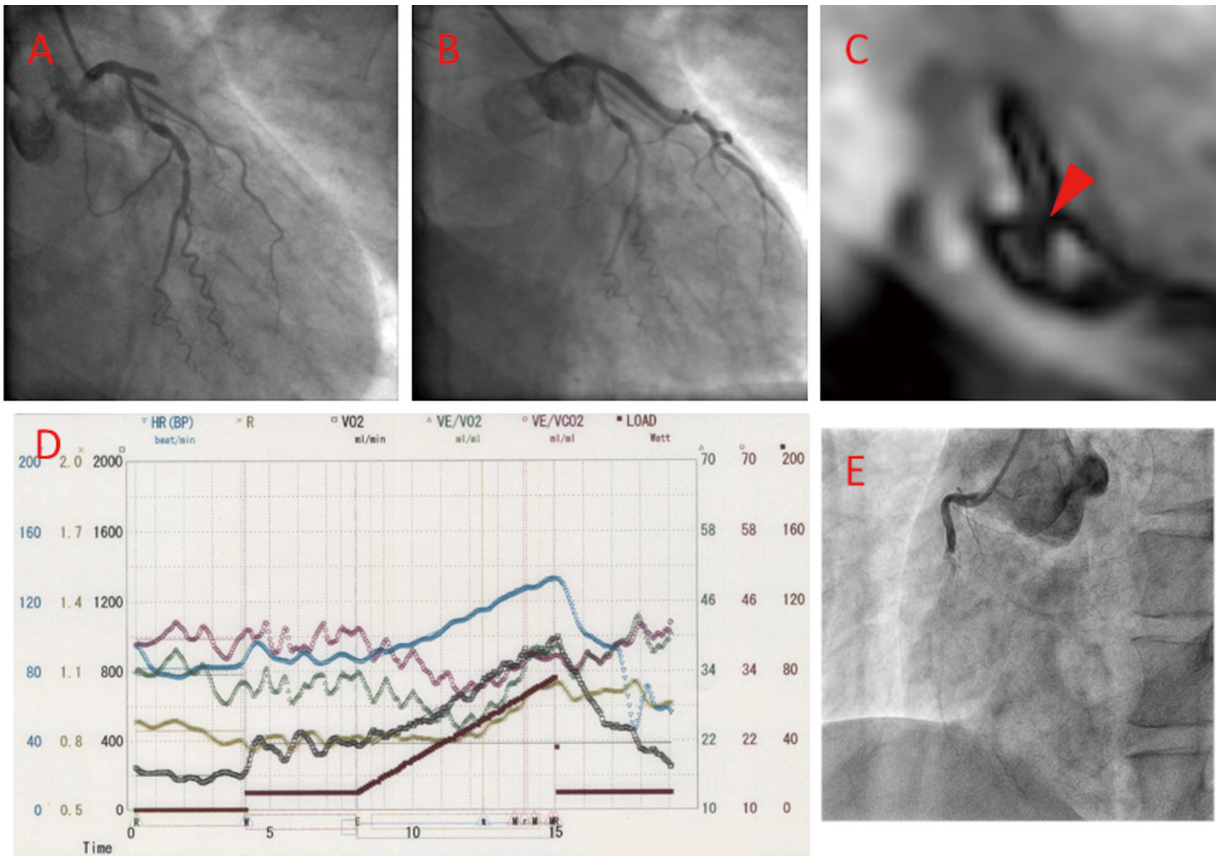


**Figure 2.** Representative images of a 56-year-old man who presented with ST-elevation myocardial infarction (STEMI) of the anterior wall. (**A**) Pre-percutaneous coronary intervention (PCI) angiogram revealed total occlusion in the proximal left anterior descending artery. (**B**) PCI was successfully performed and Thrombolysis in Myocardial Infarction flow grade 3 was obtained. (**C**) The proximal coronary sinus was detected in the cross-section on the magnitude and phase-contrast cine-magnetic resonance image (red arrow indicates coronary sinus). The global coronary flow reserve of this patient was 2.31. (**D**) Cardiopulmonary exercise testing revealed that peak oxygen consumption ($\dot{V}O_2$) was 15.6 mL/kg/min. (**E**) This patient suffered from STEMI of the inferior wall 16 months later.

myocardium. Quantitative analyses of coronary sinus flow (CSF) by phase contrast (PC) cine-CMR were performed using a dedicated workstation (ViewForum, Philips Medical Systems, Best, The Netherlands) by two independent investigators who were blinded to clinical and angiography data. PC-CMR of the coronary sinus (CS) measurements was performed during maximal hyperemia and at rest. Maximal stable hyperemia was induced by using intravenous adenosine triphosphate (160 $\mu$g/kg/min through a central vein). The duration between the end of hyperemia and the resting image acquisition was 10 min. The CS contour was traced on the magnitude images throughout the cardiac cycle. CSF was quantified by integrating the flow rates from each cardiac cycle and multiplying them by the mean heart rate during the acquisition period. The resting CSF values were corrected using rate pressure products as follows: rate pressure product (RPP) = systolic blood pressure (mmHg) × heart rate (beats/min); corrected CSF (mL/min) = (CSF / RPP) × 10,000; and corrected CSF (mL/min/g) = corrected CSF / LV mass (g).[7,12] G-CFR was evaluated by using the corrected CSF reserve, which was calculated as CSF during maximal hyperemia divided by corrected CSF at rest.[7]

## CPET

CPET was performed on an upright cycle ergometer (StrengthErgo 8, BK-ERG-121; Mitsubishi Electric Engineering, Tokyo, Japan) with an ECG machine (Stress Test System, ML-9000; Fukuda Denshi, Co., Ltd, Tokyo, Japan) within 30 days after PCI. All patients underwent cardiac rehabilitation after AMI, prior to CPET. Anaerobic threshold (AT) and peak oxygen consumption ($\dot{V}O_2$) were assessed using symptom-limited exercise testing. The ramp CPET protocol included a 4-min rest and a 4-min warm-up period at 0 watt (W), followed by a continuous increase in the work rate by 1 W every 6 s until exhaustion. The increments in work rate level were selected based on the patients' ability to perform the exercises within 8–12 min. $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$) were measured on a breath-by-breath basis using a gas analyzer (Aeromonitor, AE-310S; Minato Medical Science Co., Ltd, Osaka, Japan). AT was measured using the V-slope method.[13] $\dot{V}E/\dot{V}CO_2$ slope was calculated using linear regression of $\dot{V}E$ and $\dot{V}CO_2$

**Table 1. Baseline Patient Characteristics**

| | All (n=127) | No MACCE (n=113) | MACCE (n=14) | P value |
|---|---|---|---|---|
| Age (years) | 58.0±11.2 | 57.4±11.5 | 62.5±7.0 | 0.108 |
| **Sex** | | | | |
| Male | 115 (90.6) | 103 (91.2) | 12 (85.7) | 0.621 |
| Female | 12 (9.4) | 10 (8.8) | 2 (14.3) | |
| STEMI | 96 (75.6) | 84 (74.3) | 12 (85.7) | 0.515 |
| Height (cm) | 166.7±7.2 | 166.9±7.0 | 165.4±8.5 | 0.469 |
| Weight (kg) | 71.1±14.2 | 71.6±14.2 | 67.2±14.4 | 0.272 |
| BMI (kg/m$^2$) | 25.5±4.4 | 25.6±4.4 | 24.4±3.9 | 0.317 |
| Hypertension | 59 (46.5) | 53 (46.9) | 6 (42.9) | 1.000 |
| Dyslipidemia | 67 (52.8) | 60 (53.1) | 7 (50.0) | 1.000 |
| Diabetes | 44 (34.6) | 39 (34.5) | 5 (35.7) | 1.000 |
| Current smoking | 57 (44.9) | 50 (44.2) | 7 (50.0) | 0.779 |
| Prior MI | 11 (8.7) | 8 (7.1) | 3 (21.4) | 0.104 |
| Prior PCI | 10 (7.9) | 7 (6.2) | 3 (21.4) | 0.081 |
| Prior CABG | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.000 |
| GRACE score | 101 [73, 119] | 94 [71, 113] | 114 [108, 125] | 0.009 |
| eGFR (mL/min/1.73 m$^2$) | 74.9 [61.0, 87.9] | 75.4 [61.1, 88.6] | 68.5 [60.3, 77.2] | 0.251 |
| LDL-cholesterol (mg/dL) | 122 [96, 157] | 121 [94, 159] | 127 [113, 148] | 0.636 |
| HDL-cholesterol (mg/dL) | 45 [35, 50] | 45 [36, 50] | 40 [34, 46] | 0.157 |
| Triglyceride (mg/dL) | 108 [70, 155] | 108 [70, 155] | 139 [69, 157] | 0.481 |
| Hemoglobin A1C (%) | 6.9 [5.6, 6.7] | 5.9 [5.6, 6.6] | 6.2 [6.0, 7.3] | 0.089 |
| CRP (mg/dL) | 0.21 [0.08, 0.52] | 0.19 [0.07, 0.51] | 0.32 [0.15, 0.65] | 0.167 |
| NT-proBNP (pg/mL) | 234 [88, 608] | 229 [87, 603] | 321 [141, 813] | 0.324 |
| Post-PCI peak CK (U/L) | 1,917 [846, 4,031] | 1,743 [830, 3,905] | 3,388 [1,276, 6,004] | 0.131 |
| LVEF (%) | 57 [50, 63] | 58 [51, 63] | 50 [43, 59] | 0.014 |
| TAPSE (mm) | 19 [17, 23] | 19 [17, 22] | 21 [16, 25] | 0.913 |
| RV S' (cm/s) | 12.4 [11.0, 14.0] | 12.4 [11.0, 14.0] | 12.6 [11.7, 13.6] | 0.851 |
| ePAP (mmHg) | 20 [16, 25] | 20 [16, 25] | 21 [17, 25] | 0.617 |
| **Culprit vessel** | | | | 0.672 |
| RCA | 48 (37.8) | 41 (36.3) | 7 (50.0) | |
| LAD | 62 (48.8) | 56 (49.6) | 6 (42.9) | |
| LCX | 17 (13.4) | 16 (14.2) | 1 (7.1) | |
| Initial TIMI flow 0–1 | 78 (61.4) | 70 (61.9) | 8 (57.1) | 0.775 |

Data are presented as number (%), mean±SD, or median [interquartile range]. BMI, body mass index; CABG, coronary artery bypass graft; CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ePAP, estimated pulmonary arterial pressure; GRACE, Global Registry of Acute Coronary Events; HDL, high-density lipoprotein; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MACCE, major cardiac and cerebrovascular events; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; RCA, right coronary artery; RV, right ventricular; STEMI, ST-elevation myocardial infarction; TAPSE, tricuspid annular plane systolic excursion; TIMI, Thrombolysis in Myocardial Infarction.

obtained from the start of incremental exercise to the respiratory compensation point. Peak $\dot{V}O_2$ was determined as $\dot{V}O_2$ at the highest work rate. Peak oxygen ($O_2$) pulse was defined as peak $\dot{V}O_2$ divided by peak heart rate. The predicted values of peak $\dot{V}O_2$ and peak $O_2$ pulse were determined based on the data from a healthy Japanese population.[14]

## Clinical Follow-up

All patients were followed up for the primary outcome of MACCE defined as the composite of all-cause death, recurrent non-fatal myocardial infarction (MI), re-hospitalization due to congestive HF, and stroke. Clinical endpoints were determined by the assessment of hospital records or via telephone interviews. Time to event was calculated as the period between the PCI procedure and the first occurrence of MACCE. Patients without MACCE were censored at the time of last follow-up.

## Statistical Analysis

All analyses were performed using R for Windows 4.1.1 (The R Foundation, Vienna, Austria). Categorical data were expressed as absolute frequencies and percentages, and compared using the chi-square test or Fisher's exact test, as appropriate. Normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation for normally distributed variables and as median (interquartile range [IQR]) for non-normally distributed variables, and compared using the Student's t-test, one-way analysis of variance, or Mann-Whitney test, as appropriate. Correlation was evaluated using the Pearson correlation coefficient. A

**Table 2. Cardiac Magnetic Resonance Imaging Findings**

| | All (n=127) | No MACCE (n=113) | MACCE (n=14) | P value |
|---|---|---|---|---|
| CSF at rest (mL/min) | 102.27 [67.41, 137.83] | 99.31 [65.86, 137.41] | 129.78 [108.73, 139.29] | 0.064 |
| Corrected CSF at rest (mL/min) | 122.54 [85.57, 172.92] | 119.55 [84.68, 172.32] | 158.30 [122.07, 182.45] | 0.120 |
| Corrected CSF at rest (mL/min/g) | 0.89 [0.60, 1.19] | 0.88 [0.58, 1.19] | 1.01 [0.87, 1.24] | 0.161 |
| CSF at hyperemia (mL/min) | 293.36 [206.37, 362.60] | 299.93 [215.60, 376.37] | 276.20 [146.31, 306.47] | 0.124 |
| CSF at hyperemia (mL/min/g) | 1.99 [1.40, 2.61] | 2.06 [1.45, 2.61] | 1.51 [1.08, 2.44] | 0.129 |
| G-CFR | 2.31 [1.50, 3.47] | 2.40 [1.61, 3.66] | 1.74 [1.19, 2.20] | 0.008 |
| LGE volume (mL) | 12.15 [4.40, 19.70] | 11.55 [4.38, 18.27] | 16.70 [7.85, 23.38] | 0.227 |
| LGE % | 14.90 [5.97, 24.40] | 14.35 [5.72, 24.15] | 20.90 [10.25, 28.22] | 0.314 |
| MVO volume (mL) | 0.00 [0.00, 0.30] | 0.00 [0.00, 0.30] | 0.15 [0.00, 1.35] | 0.067 |
| MVO % | 0.00 [0.00, 0.30] | 0.00 [0.00, 0.20] | 0.15 [0.00, 1.05] | 0.095 |

Data are presented as median [interquartile range]. CSF, coronary sinus flow; G-CFR, global coronary flow reserve; LGE, late gadolinium enhancement; MACCE, major cardiac and cerebrovascular events; MVO, microvascular obstruction.

**Table 3. Cardiopulmonary Exercise Testing Findings**

| | All (n=127) | No MACCE (n=113) | MACCE (n=14) | P value |
|---|---|---|---|---|
| $\dot{V}E/\dot{V}CO_2$ slope | 37.82±6.33 | 37.38±5.90 | 41.44±8.53 | 0.023 |
| AT load (W) | 57.56±18.95 | 58.91±19.19 | 46.64±12.79 | 0.022 |
| AT $\dot{V}O_2$/W (mL/kg/min) | 12.62±3.22 | 12.75±3.34 | 11.64±1.95 | 0.226 |
| Peak load (W) | 87.91±23.51 | 89.97±23.24 | 71.29±19.17 | 0.005 |
| Peak $\dot{V}O_2$ (mL/kg/min) | 16.97±3.65 | 17.19±3.70 | 15.16±2.64 | 0.049 |
| % predicted peak $\dot{V}O_2$ | 67.45±13.97 | 68.14±14.24 | 61.86±10.41 | 0.113 |
| Peak $O_2$ pulse (mL/beat) | 10.18±2.35 | 10.36±2.32 | 8.73±2.18 | 0.014 |
| % predicted peak $O_2$ pulse | 74.22±14.72 | 75.22±14.50 | 66.14±14.50 | 0.029 |
| Minimum $\dot{V}E/\dot{V}CO_2$ (mL/min) | 34.50±5.64 | 34.03±5.27 | 38.30±7.14 | 0.007 |
| % minimum $\dot{V}E/\dot{V}CO_2$ | 123.21±20.12 | 121.55±18.84 | 136.64±25.45 | 0.008 |

Data are presented as mean±SD. AT, anaerobic threshold; MACCE, major cardiac and cerebrovascular events; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption.

P value <0.05 was considered statistically significant. The area under the curve (AUC) by receiver operating characteristic (ROC) analysis was used to assess the diagnostic accuracy of G-CFR, peak $\dot{V}O_2$, and peak $O_2$ pulse for predicting MACCE. Survival curves using the Kaplan-Meier methods were produced for predicting MACCE based on the cut-off values of G-CFR, peak $\dot{V}O_2$, and peak $O_2$ pulse derived from the ROC curve analyses, and they were compared using the log-rank test. Four prediction models were used to determine the incremental discriminatory and reclassification performance for identifying the predictors of MACCE. Clinical model 1 as the reference model included established or historically reported significant factors associated with MACCE (age, male sex, post-PCI peak CK value, LV ejection fraction [LVEF], left anterior descending [LAD] culprit). Clinical model 2 included a combination of Clinical model 1 and G-CFR. Clinical model 3 included a combination of Clinical model 2 and peak $\dot{V}O_2$. Clinical model 4 included a combination of Clinical model 2 and peak $O_2$ pulse. The discriminatory abilities of Clinical models 2–4 were assessed by the reclassification performance of each model using the relative integrated discrimination improvement (IDI) and category-free net reclassification improvement (NRI) values.

## Results

### Patient Characteristics

Of the total 127 patients, the median age was 58 years, and 115 (90.6%) patients were male. Ninety-six (75.6%) patients presented with STEMI. MACCE occurred in 14 (11.0%) patients during the follow-up period (median [IQR], 2.8 [2.0, 4.5] years). Patients' baseline clinical characteristics and laboratory findings of the study population are described in **Table 1**. Patients with MACCE had lower LVEF (50 [43, 59] vs. 58 [51, 63] %; P=0.014) than patients without MACCE. There was no significant difference in the angiography findings between patients with and without MACCE (**Table 1**).

### CMR Findings

CMR findings are summarized in **Table 2**. Median time between PCI and CMR was 10 [8, 14] days. Patients with MACCE had lower G-CFR (1.74 [1.19, 2.20] vs. 2.40 [1.61, 3.66]; P=0.008) than those without MACCE. Patients with MACCE had a trend towards greater CSF at rest (129.78 [108.73, 139.29] vs. 99.31 [65.86, 137.41]; P=0.064) compared with those without MACCE.

### CPET Findings

CPET findings are summarized in **Table 3**. Median time

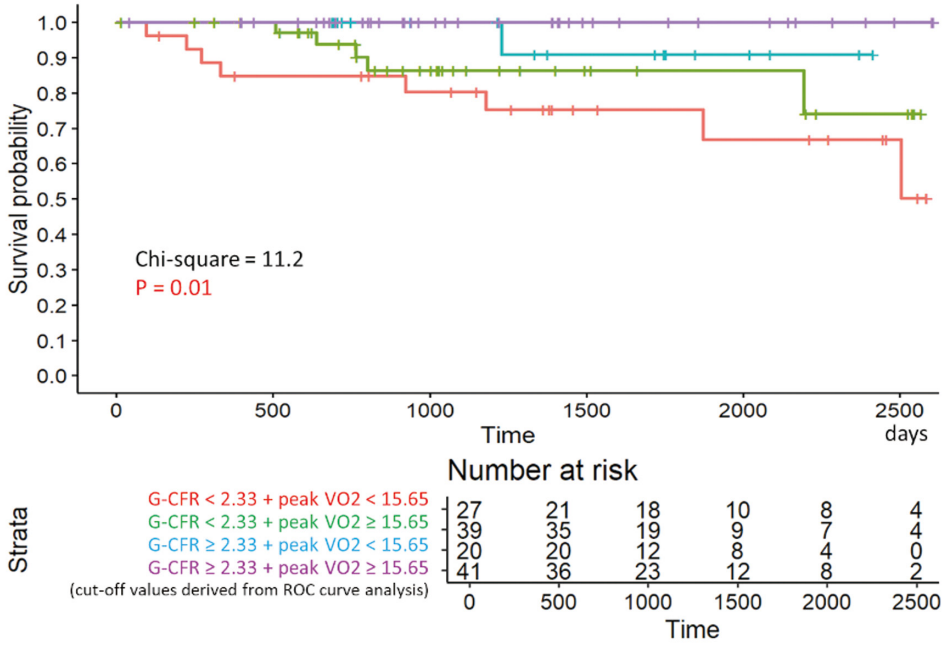


**Figure 3.** Survival curves for predicting major cardiac and cerebrovascular events based on the cut-off values of global coronary flow reserve (G-CFR) and peak oxygen consumption ($\dot{V}O_2$). ROC, receiver operating characteristic.

**Table 4. Prediction Models for the Incidence of MACCE**

| | C statistics | 95% CI | Relative IDI | | Continuous NRI | |
|---|---|---|---|---|---|---|
| | | | Value | P value | Value | P value |
| Model 1 (Age, male sex, post-PCI peak CK, LVEF, LAD culprit) | 0.777 | 0.660, 0.893 | Reference | | Reference | |
| Model 2 (Model 1+G-CFR<2.33) | 0.834 | 0.752, 0.917 | 0.054 | 0.035 | 0.937 | <0.001 |
| Model 3 (Model 2+peak $\dot{V}O_2$<15.65 mL/kg/min) | 0.858 | 0.775, 0.941 | 0.026 | 0.244 | 0.613 | 0.024 |

CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement. Other abbreviations as listed in Tables 1–3.

between PCI and CPET was 11 [8, 14] days. Patients with MACCE had greater $\dot{V}E/\dot{V}CO_2$ slope (41.44±8.53 vs. 37.38±5.90; P=0.023) and lower workload (46.64±12.79 vs. 58.91±19.19 W; P=0.022) at AT than those without MACCE. Patients with MACCE had lower peak $\dot{V}O_2$ (15.16±2.64 vs. 17.19±3.70 mL/kg/min; P=0.049), lower peak $O_2$ pulse (8.73±2.18 vs. 10.36±2.32 mL/beat; P=0.014), and greater minimum $\dot{V}E/\dot{V}CO_2$ (38.30±7.14 vs. 34.03±5.27 mL/min; P=0.007) than those without MACCE.

## Clinical Outcomes

During the follow-up period (median [IQR], 2.8 [2.0, 4.5] years), the incidence of MACCE was 11.0%; 3 (2.4%) patients died, 7 (5.5%) patients experienced recurrent non-fatal MI, 3 (2.4%) patients experienced re-hospitalization due to congestive HF, and 3 (2.4%) patients experienced stroke.

## Predictors of MACCE

ROC curve analysis showed that the best cut-off values of G-CFR, peak $\dot{V}O_2$, and peak $O_2$ pulse for predicting MACCE were 2.33 (AUC=0.717; sensitivity, 0.929; specificity, 0.531; accuracy, 0.575), 15.65 mL/kg/min (AUC=0.660; sensitivity, 0.643; specificity, 0.664; accuracy, 0.661), and 9.25 mL/beat (AUC=0.693; sensitivity, 0.714; specificity, 0.673; accuracy, 0.677), respectively. There was no correlation of G-CFR with peak $\dot{V}O_2$ (r=−0.0008; P=0.993) and peak $O_2$ pulse (r=−0.060; P=0.506). Survival curves demonstrated that low G-CFR and low peak $\dot{V}O_2$ were significantly associated with the incidence of MACCE (chi-square=11.2; P=0.01; **Figure 3**). Low G-CFR and low peak $O_2$ pulse were also significantly associated with the incidence of MACCE (chi-square=15.8; P=0.001; **Supplementary Figure**). The combination of low G-CFR and low peak $\dot{V}O_2$ improved risk discrimination for MACCE when added to the reference clinical model including age, male sex, post-PCI peak CK values, LVEF, and LAD culprit (continuous NRI=0.613; P=0.024; relative IDI=0.026; P=0.244; **Table 4**). The combination of low G-CFR and low peak $O_2$ pulse

also improved risk discrimination for MACCE when added to the reference clinical model (continuous NRI=0.756; P=0.003; relative IDI=0.056; P=0.039; **Supplementary Table**).

## Discussion

The principal findings of the present study are as follows: (1) patients with MACCE had greater GRACE score, lower LVEF, lower G-CFR, lower peak $\dot{V}O_2$, and lower peak $O_2$ pulse than patients without MACCE; (2) low G-CFR was significantly and independently associated with the incidence of MACCE; (3) the combination of low G-CFR and low peak $\dot{V}O_2$ showed significant incremental reclassification ability for predicting the incidence of MACCE when added to the reference clinical model including age, male sex, post-PCI peak CK values, LVEF, and LAD culprit.

### G-CFR as a Predictor of MACCE

The clinical significance of residual microvascular dysfunction after optimal angiography epicardial revascularization is widely recognized in patients with AMI treated with primary/urgent PCI.[15] The mechanisms of residual microvascular dysfunction are likely to be multifactorial. The CFR is affected by epicardial stenosis, diffuse narrowing, and microvascular function.[16] The efficacy of vessel/regional CFR as an indicator of worse prognosis has been shown using various modalities such as Doppler flow velocity-derived coronary flow velocity reserve,[17,18] thermodilution-derived CFR,[19,20] and echocardiography[21,22] in the AMI population. The predictive value of G-CFR assessed using PET[4,5,23–25] and CMR[6,26] has been explored in patients with suspected or known coronary artery disease. Recent studies have shown the prognostic value of CMR-derived G-CFR in patients with AMI.[7,27] Our results demonstrating the association between low G-CFR (<2.33; cut-off value derived from ROC curve analysis) and the incidence of MACCE in the AMI population are in line with these studies using the cut-off values around 2.0, ranging from 1.5[18,24] to 2.88.[25] Our results indicate that the low G-CFR is suggestive of residual microvascular dysfunction after PCI, which may lead to the higher incidence of MACCE.

### Peak $\dot{V}O_2$ and Peak $O_2$ Pulse as Predictors of MACCE

Various studies have shown the feasibility of CPET to estimate exercise capacity and predict outcomes. Several CPET variables such as peak $\dot{V}O_2$,[3,28,29] % predicted peak $\dot{V}O_2$,[30] peak $O_2$ pulse,[31,32] and $\dot{V}E/\dot{V}CO_2$ slope[33] have been utilized as predictors of worse prognosis. CPET variables are affected by several factors, including cardiovascular systems, such as myocardial ischemia, diastolic and/or systolic ventricular dysfunction, and mitral/tricuspid valve regurgitation; and pulmonary, muscular, and cellular oxidative systems.[34] Peak $\dot{V}O_2$ is the gold standard measure of cardiorespiratory fitness and exercise capacity.[35] Peak $O_2$ pulse represents peak $\dot{V}O_2$ corrected for heart rate and is a non-invasive indicator of stroke volume and arteriovenous oxygen difference at the highest work rate.[31] Therefore, we focused on peak $\dot{V}O_2$ and peak $O_2$ pulse in the present study. Our results indicated that low peak $\dot{V}O_2$ and peak $O_2$ pulse were associated with the incidence of MACCE, which were in concordance with previous studies.[3,28,29,31,32]

### Clinical Implication of the Present Study

Our results explored the clinical significance of non-invasive assessment using CMR and CPET in patients with AMI. Our findings indicated that the combination of CMR-derived G-CFR and CPET-derived peak $\dot{V}O_2$ can provide better risk stratification in patients with AMI and residual microvascular dysfunction after PCI.

### Study Limitations

First, this is a retrospective observational study from a single center with a small sample size and therefore has an intrinsic risk of selection bias. Furthermore, since our study population included relatively younger patients who were able to perform cycle ergometer CPET, the present study was merely a hypothesis-generating study with a sample size and number of events too small to draw definitive conclusions. However, our results suggest that the non-invasive assessment using the combination of CPET and CMR may provide significant incremental reclassification ability for predicting MACCE when added to the clinically significant factors. Second, although all patients underwent CPET and were managed with guideline-directed medical therapy after discharge, not all participants were followed up with outpatient cardiac rehabilitation program. Therefore, the association between the improvement of CPET variables during follow-up and prognosis was not evaluated.

## Conclusions

CMR-derived G-CFR and CPET-derived peak $\dot{V}O_2$ showed incremental prognostic information compared with the reference model using historically important clinical risk factors, indicating that this approach may help identify high-risk patients who suffer subsequent adverse events, and thereby need an intensive therapeutic strategy and watchful observation.

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None.

### Disclosures

The authors declare no conflicts of interest.

### IRB Information

The study protocol was approved by the institutional ethics committee on human research of Tsuchiura Kyodo General Hospital (approval number: 2022FY68).

### Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

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## Supplementary Files

Please find supplementary file(s);
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