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ORIGINAL RESEARCH

Long-Term Prognosis of Patients With Coronary Microvascular Disease Using Stress Perfusion Cardiac Magnetic Resonance

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ABSTRACT

OBJECTIVES This study investigated the prognosis of coronary microvascular disease (CMD) as determined by stress perfusion cardiac magnetic resonance (CMR) in patients with ischemic symptoms but without significant coronary artery disease (CAD).

BACKGROUND Patients with CMD have poorer prognosis with various cardiac diseases. The myocardial perfusion reserve index (MPRI) derived from noninvasive stress perfusion CMR has been established to diagnose microvascular angina with a threshold MPRI <1.4. The prognosis of CMD as determined by MPRI is unknown.

METHODS Chest pain patients without epicardial CAD or myocardial disease from January 2009 to December 2017 were retrospectively included from 3 imaging centers in Hong Kong (HK). Stress perfusion CMR examinations were performed using either adenosine or adenosine triphosphate. Adequate stress was assessed by achieving splenic switch-off sign. Measurement of MPRI was performed in all stress perfusion CMR scans. Patients were followed for major adverse cardiovascular events defined as all-cause death, acute coronary syndrome (ACS), epicardial CAD development, heart failure hospitalization and non-fatal stroke.

RESULTS A total of 218 patients were studied (mean age 59 ± 12 years; 49.5% male) and the average MPRI of that cohort was 1.56 ± 0.33. Females and a history of hyperlipidemia were predictors of lower MPRI. Major adverse cardiovascular events (MACE) occurred in 15.6% of patients during a median follow-up of 5.5 years (interquartile range: 4.6 to 6.8 years). The optimal cutoff value of MPRI in predicting MACE was found with a threshold MPRI ≤1.47. Patients with MPRI ≤1.47 had three-fold increased risk of MACE compared with those with MPRI >1.47 (hazard ratio [HR]: 3.14; 95% confidence interval [CI]: 1.58 to 6.25; $p = 0.001$). Multivariate Cox regression after adjusting for age and hypertension demonstrated that MPRI was an independent predictor of MACE (HR: 0.10; 95% CI: 0.03 to 0.34; $p < 0.001$).

CONCLUSIONS Stress perfusion CMR-derived MPRI is an independent imaging marker that predicts MACE in patients with ischemic symptom and no overt CAD over the medium term. (J Am Coll Cardiol Img 2021;14:602–11)
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Coronary microvascular disease (CMD) is receiving increasing clinical attention as 20% to 80% of patients with stable chest pain have normal or nonobstructive coronary arteries on invasive coronary angiography (ICA) and coronary computed tomography angiography (CCTA) (1,2). CMD is characterized as an impaired flow reserve of coronary arterioles (<500 μm in diameter) (3) or stress-inducible microvascular spasm (4). As a result, the coronary microvasculature fails to dilate for maintaining normal myocardial perfusion (5,6). Thus, CMD is an important pathology resulting in chest pain and myocardial ischemia in the absence of significant coronary artery disease (CAD) (7,8).

Furthermore, patients with impaired coronary microvascular function have been reported to carry poor prognosis, especially in the postmenopausal female study group (9–16). There are various methods to detect coronary microvascular dysfunction. The index of microcirculatory resistance is one method that can be used but this method requires an invasive pressure measurement and thus carries increased risk to patients compared to noninvasive imaging (14). Coronary flow reserve evaluated by transthoracic Doppler echocardiography (15) and myocardial perfusion reserve assessed by positron emission tomography (PET) (16) have been used. However, coronary flow reserve by stress echocardiography can only be performed in the left anterior descending artery and is thus not necessarily reflective of the whole myocardium (17). Also PET exposes patients to ionizing radiation, which is not ideal for regular follow-up measurements.

Stress perfusion cardiac magnetic resonance (CMR) is a promising imaging tool to quantify myocardial perfusion beyond qualitatively significant CAD diagnosis (18–20). CMR-derived myocardial perfusion reserve index (MPRI) is a robust semiquantitative imaging marker representing the vasodilating capacity of small vessels, defined as the ratio of stress/rest upslope normalized to the upslope of left ventricular (LV) blood pool (21,22). A recent study has established the MPRI cutoff threshold <1.4 of diagnosing microvascular angina with an accuracy of 92% (23). However, the prognostic value of microvascular disease determined by stress perfusion CMR and MPRI has not been well explored. This study investigated the prognostic role of MPRI in chest pain patients without obstructive CAD.

METHODS

STUDY POPULATION AND DATABASE. Consecutive patients who were referred to undergo clinical CMR examinations since 2009 were retrospectively included into this study (n = 2,106). These CMR studies were performed at 3 different imaging centers in Hong Kong (HK), including 147 CMR cases from Department of Diagnostic Radiology of the University of Hong Kong (HKU); 511 CMR cases from Department of Radiology of Pamela Youde Nethersole Eastern Hospital (PYNEH); and 1,448 CMR cases from Department of Radiology and Imaging of Queen Elizabeth Hospital (QEH). For the stress examinations, HKU used adenosine triphosphate, and PYNEH and QEH used adenosine for pharmacological stress. Digital Imaging and Communications in Medicine (DICOM; Arlington, Virginia) images of all CMR examinations were anonymized at 3 imaging centers. Clinical outcomes were determined through the HK electronic patient resource (EPR) system which holds data for the whole city. The study was approved by the local Institutional Review Board of the Hospital Authority Hong Kong West Cluster (ref.: UW 18-470).

STUDY DESIGN. Inclusion criteria were patients with CMR examinations performed at HKU, PYNEH, and QEH imaging centers. Stress CMR examinations in those 3 centers were performed in patients referred with ischemic symptoms and abnormal cardiac tests, such as ST changes on electrocardiography or positive treadmill results suggestive of myocardial ischemia. Exclusion criteria were developed to retain patients referred for stress CMR with ischemic symptoms while removing patients with epicardial coronary artery disease that could cause low MPRI values and confounders which could result in no perfusion defects on stress CMR. Exclusion criteria were: 1) nonstress perfusion CMR scans; 2) asymptomatic or non-ischemic-related symptoms (8); 3) significant CAD with prior or after (within 1 year) coronary imaging (i.e., invasive coronary angiography and CCTA) showing any main coronary artery

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

CMD = coronary microvascular disease

CMR = cardiac magnetic resonance

ICA = invasive coronary angiography

MACE = major adverse cardiovascular event(s)

MPRI = myocardial perfusion reserve index

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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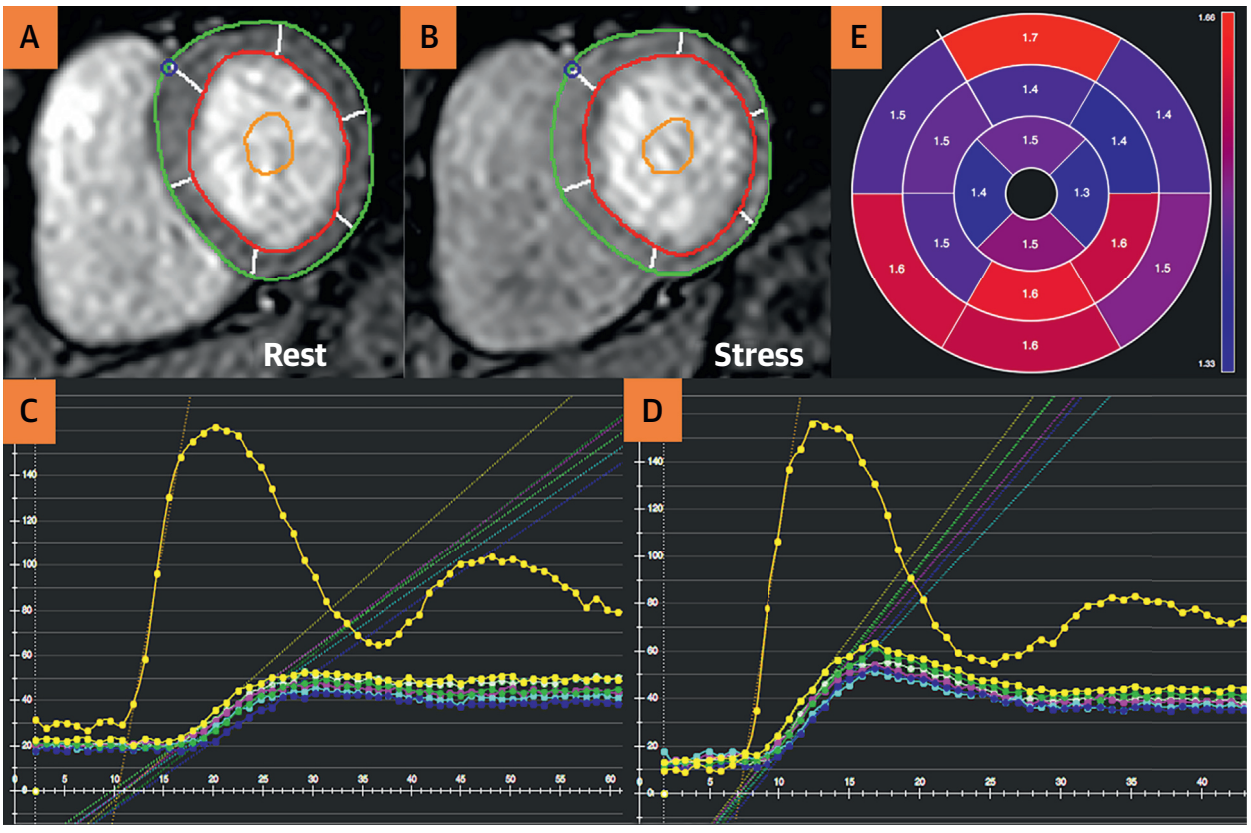
FIGURE 1 How MPRI Is Derived



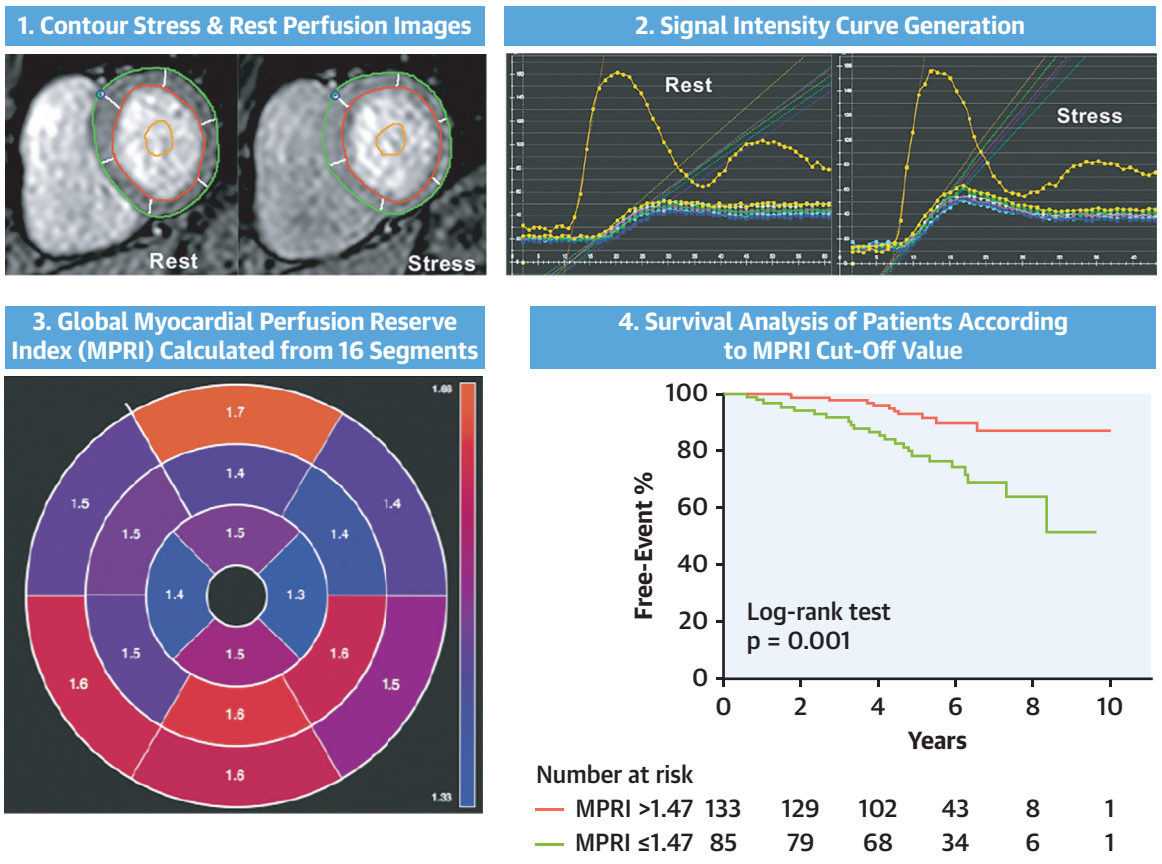
(A) Rest imaging contouring. **(B)** Stress imaging contouring. **(C)** Rest SI curve. **(D)** Stress SI curve. **(E)** Polar map demonstrates MPRI values in each segment. MPRI = myocardial perfusion reserve index; SI = signal intensity.

narrowing >50% (24) or fractional flow reserve <0.8 (25). If patients did not have available anatomic coronary imaging but had perfusion defects on CMR, these were considered to have suspected obstructive CAD and were excluded; 4) myocardial diseases including primary and secondary cardiomyopathies, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (26); 5) congenital cardiac abnormalities including anomalous coronary arteries; 6) images which could not be analyzed including failed study, poor image quality, and inadequate stress test (defined as the absence of the splenic switch-off sign as determined by an independent reviewer) (27,28); 7) follow-up time of <1 year; and 8) patients who had consumed caffeine within 24 h of the stress perfusion CMR scan.

CMR IMAGING ANALYSIS. CMR-derived parameters of cardiac function such as ejection fraction and end-diastolic volume were obtained from CMR reports. CMR42 (Circle Inc., Calgary, Alberta, Canada) was used to evaluate MPRI. Manual contouring was drawn along the epicardium and endocardium on every cardiac phase of basal, middle, and apical slices of both stress and rest perfusion images. A segment of LV blood pool in each slice was contoured centrally, avoiding ventricular papillary muscles. The superior insertion point was then labeled on the junction of left and right anterior walls to identify 16 American Heart Association myocardial segments (Figure 1).

Signal intensity curves of segmental myocardium and LV blood pool were automatically generated by the perfusion module of this software (Figure 1). Segments 1, 2, 7, 8, 13, and 14 were assigned to the left anterior descending artery; segments 5, 6, 11, 12, and 16 were assigned to the left circumflex artery; and segments 3, 4, 9, 10, and 15 were assigned to the right coronary artery (29). Global MPRI was calculated as the average value of all 16 segments

CENTRAL ILLUSTRATION **Analysis of MPRI by Stress Perfusion CMR and its Impact on Outcomes in Patients With Coronary Microvascular Disease**



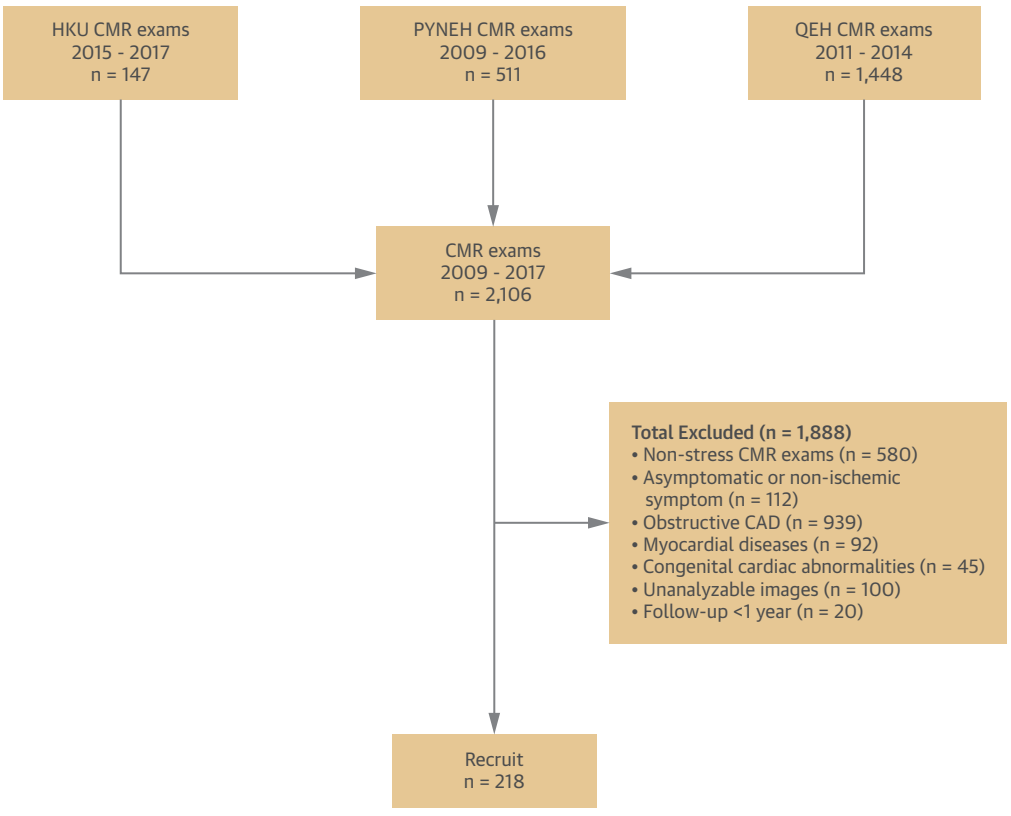
Zhou, W. et al. J Am Coll Cardiol Img. 2021;14(3):602-11.

Top row shows the contoured rest and stress perfusion cardiac magnetic resonance images. These images help to generate signal intensity curves for the blood pool (arterial input function) and the myocardial segments. The software uses the curves to calculate the stress and rest myocardial signal intensity upslopes relative to the arterial input function upslopes at stress and rest, respectively. The ratio of the relative stress and rest upslopes determines the MPRI. In the bottom row, the bull's eye plot demonstrates the MPRI for the 16 myocardial segments. When these segments are combined, they derive the global MPRI. A global MPRI cutoff value of ≤1.47 was shown to be significant in predicting patient outcomes. Abbreviations as in Figures 1 and 2.

(Central Illustration). MPRI ≥2.0 was defined as the normal value (23,30,31).

PATIENT FOLLOW-UP. All patients were followed subsequently from the scan date by reviewing the EPR system for patient information. Primary endpoint was a composite of major adverse cardiovascular events (MACE). The events comprising MACE were all-cause death, acute coronary syndrome (ACS), progressive development of epicardial CAD, nonfatal stroke, and hospitalization for heart failure. All endpoint events were determined by clinicians blinded to the MPRI result, and the related clinical profiles were derived from record notes on the EPR system. Of these endpoints, ACS, which includes ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (32) was based on the evidence of clinical presentation at presentation to hospital, electrocardiography, troponin I and catheter coronary angiography, and nuclear or computed tomography (CT) imaging results. Diagnosis of ACS was confirmed by a blinded cardiologist. Development of epicardial CAD was confirmed with positive imaging showing coronary arteries narrowing >50% stenosis or fractional flow reserve <0.8 (24,25).

FIGURE 2 Consort Diagram of Patients Included in This Study



Patients who underwent CMR examination from the University of Hong Kong (HKU), Pamela Youde Nethersole Eastern Hospital (PYNEH), and Queen Elizabeth Hospital (QEH) were identified. After exclusion criteria were applied, 218 patients remained in the final cohort.
CAD = coronary artery disease; CMR = cardiac magnetic resonance.

STATISTICAL ANALYSIS. The interobserver and intraobserver variability assessment of MPRI was calculated by intraclass correlation coefficient (ICC) based on 20 cases which were randomly selected. The associations of conventional cardiovascular (CV) risk factors and MPRI were assessed by general linear regression model. The difference of MPRI among multiple subgroups was analyzed by 1-way ANOVA. A 1-sample Student's *t*-test was used to compare this cohort's MPRI with previously established normal values. For prognostic analysis, the optimal cutoff value of MPRI in outcome prediction was determined by using the point closest-to-corner method on the receiver-operating characteristic curve. A Kaplan-Meier curve was then applied to compare the prognosis between the 2 subgroups based on this predictive threshold. The prognostic value of MPRI, as a continuous variable, was assessed by univariate and multivariate Cox proportional hazards model. Variables with univariate significance were selected for multivariate analysis. A p value <0.05 was regarded as statistically significant for all statistical tests. All statistical analyses were performed using SPSS version 23 software (IBM, Armonk, New York), and Kaplan-Meier curves were drawn by Prism version 8.3.0 software (GraphPad, San Diego, California).

RESULTS

PATIENT COHORT. A total of 2,106 CMR examinations since 2009 were collected from HKU (2015 to 2017), PYNEH (2009 to 2016), and QEH (2011 to 2014). After applying the exclusion criteria, 218 symptomatic patients without obstructive CAD were eventually included. The consort diagram (Figure 2) shows further details.

Ninety-two patients (42.2%) underwent CCTA (n = 33) or ICA (n = 59), confirming nonobstructive coronary arteries at the time of inclusion. The remaining 126 patients had normal myocardial perfusion but without CCTA or ICA.

PATIENT CHARACTERISTICS. Patients' clinical characteristics and medications are summarized in Table 1. The mean age of this cohort was 59 ± 12 years old, and 49.5% were males. In terms of conventional CV risk factors, 18.8% had type 2 diabetes, 60.0% had hypertension, 50.0% had hyperlipemia, 9.2% were current smokers, and 12.8% were ex-smokers. Compared with the normal value of MPRI of 2.0 (23,30,31), the mean MPRI of the cohort in this study was significantly reduced (1.56 vs. 2.00, respectively; $p < 0.001$). This indicated an impairment of myocardial perfusion reserve in this cohort, based on previously established normal values (30,31). A total of 91.3% of patients had impaired MPRI or MPRI <2.0.

CMR-DERIVED PARAMETERS AND MYOCARDIAL PERFUSION. CMR determined LV volumes, ejection fraction, and MPRI evaluated by stress CMR are listed in Table 1. Overall, all patients had preserved LV ejection fraction (mean: 68.0 ± 7.1%) and LV size (65.2 ± 13.2 ml/m^2). In terms of myocardial perfusion, 87.6% of patients had no visual inducible perfusion defects, whereas 12.4% had visual inducible perfusion defects but <50% coronary arterial narrowing on subsequent angiography. There were no significant differences in MPRI between patients with coronary imaging and without coronary imaging (Supplemental Table 1 and Supplemental Figure 1 for comparison of patient characteristics between patients with and without coronary imaging).

Interobserver and intraobserver variability of MPRI measurement showed strong agreement with ICC of 0.95 (95% confidence interval [CI]: 0.91 to 0.98; $p < 0.001$) and ICC of 0.97 (95% CI: 0.83 to 1.00; $p < 0.001$), respectively. Each coronary artery territory had a similar MPRI (left anterior descending artery vs. the left circumflex artery vs. the right coronary artery = 1.57 vs. 1.55 vs. 1.56, respectively; $p = 0.71$).

ASSOCIATIONS OF CONVENTIONAL CV RISK FACTORS AND MPRI. The associations of MPRI with conventional CV risk factors such as age, female sex, and lifestyle-related factors are displayed in Supplemental Table 2. Patients at older ages ($\beta = -0.006$; $p = 0.001$); females ($\beta = -0.15$; $p < 0.001$), hypertension ($\beta = -0.12$; $p = 0.006$), hyperlipidemia ($\beta = -0.11$; $p = 0.01$), and current smoking had lower MPRI than their counterparts. After variables with

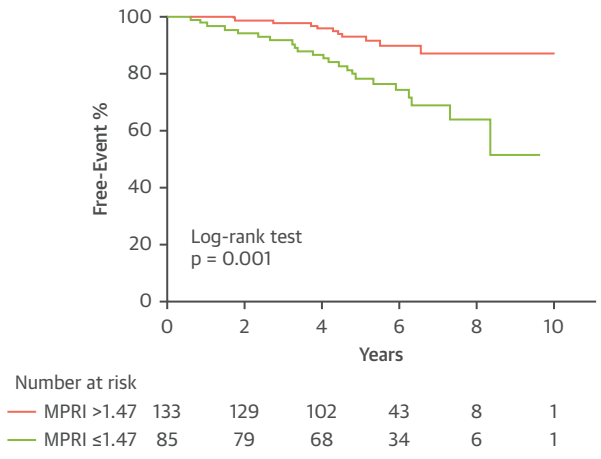
TABLE 1 Patient Clinical and CMR Characteristics (N = 218)

Patient demographics	
Age, yrs	59 ± 12
BMI, kg/m^2	23.8 ± 6.0
Males	108 (49.5)
CV risk factors	
Diabetes	41 (18.8)
Hypertension	122 (60.0)
Hyperlipidemia	109 (50.0)
Smoker	20 (9.2)
Ex-smoker	28 (12.8)
Diabetic medications	
Alpha glucosidase	2 (0.9)
Sulfonylureas	17 (7.8)
Biguanide	26 (11.9)
DDP-4 inhibitor	3 (1.4)
Insulin	4 (1.8)
Thiazolidinediones	1 (0.5)
Hypertension-controlled medications	
Beta-blocker	65 (29.8)
Alpha-blocker	4 (1.8)
ACE inhibitors/ARBs	48 (22.0)
Calcium channel blocker	60 (27.5)
Diuretics	12 (5.5)
Hyperlipidemia-controlled medications	
Statin	93 (42.7)
Fibrates	2 (0.9)
Antiplatelet medications	
Clopidogrel	15 (6.9)
Aspirin	102 (46.8)
Cardiac function and size	
LV EDVi, ml/m^2	65.2 ± 13.2
LV ESVi, ml/m^2	21.1 ± 7.5
LV SVi, ml/m^2	44.1 ± 8.5
LV EF, %	68.0 ± 7.1
LVEF <50%	0 (0)
CMR scan hemodynamics	
Resting heart rate, beats/min	71 ± 13
Stress heart rate, beats/min	94 ± 15
Rest SBP, mm Hg	136 ± 21
Stress SBP, mm Hg	130 ± 20
Splenic switch-off sign	218 (100.0)
Stress inducible perfusion defect	27 (12.4)
MPRI	
Global	1.56 ± 0.33
<2.0	199 (91.3)
≤1.47	85 (39.0)
Basal slice	1.54 ± 0.34
Middle slice	1.57 ± 0.35
Apical slice	1.57 ± 0.42
LAD territory	1.57 ± 0.35
LCX territory	1.55 ± 0.33
RCA territory	1.56 ± 0.34

Value are mean ± SD or n (%).

ACE = angiotensin-converting-enzyme; ARBs = angiotensin-receptor blockers; BMI = body mass index; CMR = cardiac magnetic resonance; CV = cardiovascular; DDP4-inhibitor = inhibitors of dipeptidyl peptidase 4; EDVi = end-diastolic volume index; EF = ejection fraction; ESVi = end-systolic volume index; LAD = left anterior descending artery; LCX = left circumflex artery; LV = left ventricular; MPRI = myocardial perfusion reserve index; SVi = stroke volume index; SBP = systolic blood pressure; RCA = right coronary artery.

FIGURE 3 Kaplan-Meier Curve of Patients With MPRI ≤1.47 and >1.47



An MPRI cutoff value of 1.47 was identified as the highest predictive threshold for patient outcome. At that value, the Kaplan-Meier curve demonstrates an increased event rate (p = 0.001; unadjusted hazard ratio = 3.14). Abbreviations as in Figures 1 and 2.

p values < 0.05 were placed in the multivariate regression model, females (β = −0.18; p < 0.001) and hyperlipidemia (β = −0.10; p = 0.03) were independent predictors of coronary microvascular dysfunction.

CLINICAL OUTCOMES. Thirty-four endpoint events occurred in 218 subjects (15.6%) during a median follow-up of 5.5 years (interquartile range: 4.6 to 6.8 years). Of these events, there were 7 (3.2%) all-cause deaths; 17 (7.8%) admissions for acute coronary syndrome (1 STEMI case, 6 NSTEMIs, and 10 subjects in whom unstable angina was diagnosed (Supplemental Table 3); 5 subjects (2.3%) who developed obstructive epicardial CAD; and 4 subjects (1.8%) who were hospitalized with heart failure; and 1 patient (0.5%) received a diagnosis with nonfatal stroke.

The optimal predictive threshold of MPRI was found to be 1.47 (Supplemental Figure 2). Patients with MPRI ≤1.47 had three-fold increased risk of having MACE (hazard ratio [HR]: 3.14; 95% CI: 1.58 to 6.25; p = 0.001) compared to subjects with MPRI >1.47 (Figure 3). For the univariate survival analysis, age (HR: 1.09; 95% CI: 1.05 to 1.12; p < 0.001), hypertension (HR: 4.32; 95% CI: 1.78 to 10.44; p = 0.001), and MPRI (HR: 0.06; 95% CI: 0.02 to 0.19; p < 0.001) were significant predictors of poor prognosis. In the multivariate analysis, age (HR: 1.07; 95% CI: 1.03 to 1.11; p < 0.001) and MPRI (HR: 0.10; 95% CI: 0.03 to 0.34; p < 0.001) remained independent predictors after adjusting for hypertension. The results are summarized in Table 2.

DISCUSSION

To the best of the authors' knowledge, this is the first study to investigate the prognostic significance of noninvasive CMR-derived MPRI in patients with ischemic signs but without obstructive CAD, with a median follow-up of 5.5 years. Overall, MACE occurred in 15.6% of patients. Patients with MPRI ≤1.47 were found to have MACE that were significantly increased compared to those with MPRI >1.47 (HR: 3.14) (Central Illustration). MPRI was an independent predictor, with a 90% decrease in risk for every 1 U increase (HR: 0.10; 95% CI: 0.03 to 0.34). Therefore, the study calls for more clinical attention to CMD and the potential role of MPRI for assessment of patients.

CMD: A NEGLECTED SUBCLINICAL CARDIAC ABNORMALITY. Stress perfusion CMR is an excellent tool to rule out obstructive CAD based on visual analysis (18,33). However, the absence of visually detectable perfusion defects does not equate with normal myocardial perfusion status (23). In this study, only 12.4% of patients had visual myocardial perfusion deficits on stress, and all subjects had preserved cardiac function and normal myocardial structure assessed by CMR. As such, the absence of significant findings, especially the absence of reversible perfusion abnormalities, resulted in patients not undergoing further investigations.

However, when semiquantitative analysis was performed, the average global MPRI (1.56 vs. 2.00, respectively; p < 0.001) of the cohort in this study was significantly reduced. Of importance, >90% of subjects had MPRI values lower than the normal reference, which indicated that most had impaired coronary microvascular function despite having "normal" myocardial perfusion qualitatively. Although angina-like symptoms suggest myocardial ischemia, these results revealed hidden myocardial ischemia due to CMD (34,35), which is otherwise missed by qualitative stress CMR and regional assessment.

Based on the manifestations of CMD, it should be considered a subclinical cardiac condition characterized by no clinical symptoms or unrecognizable clinical findings using conventional medical examinations (36). Increased awareness of this subclinical cardiac abnormality is suggested for establishing appropriate clinical management in ischemic heart disease and thus reducing CV risk in the early stage.

TABLE 2 Univariate and Multivariate Prognosis Analyses of Symptomatic Patients Without Epicardial CAD

	Univariate Cox Regression			Multivariate Cox Regression		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.09	1.05–1.12	<0.001	1.07	1.03–1.11	<0.001
Sex						
Males	1.00					
Females	0.66	0.33–1.30	0.23			
DM						
No	1.00					
Yes	0.78	0.30–2.02	0.61			
HT						
No	1.00			1.00		
Yes	4.32	1.78–10.44	0.001	1.89	0.75–4.78	0.18
HL						
No	1.00					
Yes	1.72	0.87–3.41	0.12			
Smoking						
Nonsmoker	1.00					
Ex-smoker	1.16	0.35–3.87	0.81			
Smoker	2.07	0.92–4.63	0.78			
MPRI	0.06	0.02–0.19	<0.001	0.10	0.03–0.34	<0.001

MPRI in this Cox regression model is a continuous variable.

CI = confidence interval; DM = diabetes mellitus; EF = ejection fraction; HL = hyperlipidemia; HT = hypertension; HR = hazard ratio; MPRI = myocardial perfusion reserve index.

MPRI: A NOVEL PROGNOSTIC INDICATOR IN PATIENTS WITHOUT OBSTRUCTIVE CAD. Few studies have investigated the prognosis of CMD by perfusion CMR. A CMR study by Erbel et al. (37) studied patients who were undergoing second heart transplantations and showed that patients with microvasculopathy (based on an MPRI <1.75) had poorer prognoses than those without microvasculopathy. A recent PET-CT study showed the prognostic value of MPRI in patients with aortic stenosis and no overt CAD (16). That study found that impaired myocardial perfusion can induce adverse LV remodeling and increase clinical risk. Both studies concluded that MPRI could be a reliable predictor regarding CMD prognosis. More recently, a study by Knott et al. (38) demonstrated the prognostic value of artificial intelligence to determine myocardial blood flow and MPRI in known or suspected cases of coronary artery disease. The present study differs in that only patients with ischemic symptoms were included but without evidence of obstructive CAD, whereas the study by Knott et al. (38) included patients with and without obstructive CAD.

Overall, MPRI shows significant promise as a marker with which to identify impaired myocardial perfusion beyond obstructive coronary artery disease and provides a more global understanding of impaired myocardial perfusion in patients. One of the clinical limitations of MPRI is the post-processing time, but recent software and CMR improvement means that we are now in an era of fully automated quantification (39), thus overcoming this limitation of post-processing. Therefore, MPRI holds significant promise in being clinically translatable.

STUDY LIMITATIONS. First, this was a retrospective cohort study in 3 centers in a single city. Prospective studies investigating CMD prognosis by stress CMR in other centers are needed in future to confirm the present findings. Second, because the images were collected from 3 different imaging centers in Hong Kong, scanned from 2009 to 2017, there may be slight differences in the scanning protocols at different centers, and different time periods may bias the cohort study. For example, 2 different pharmacological stress agents were used among 3 centers, but the pathway for inducing stress physiology with adenosine and adenosine triphosphate is similar (40). Furthermore, the normal range of MPRI of each center was absent in the present study. Nonetheless, this is reflective of real life, where scanning procedures and patients are not homogenous, and therefore our findings should be more generalizable. Third, not all patients underwent coronary imaging, so false negative stress CMR cases

with obstructive CAD might have been included. However, the study was designed to minimize unwanted inclusion of patients with obstructive CAD. Furthermore, the study showed that there were no significant differences in MPRI between patients with and without coronary imaging. Finally, fully quantitative myocardial perfusion reserve measurements may have advantages over the present semiquantitative approach, but this would require further trials to determine.

CONCLUSIONS

Stress CMR-derived MPRI is an independent imaging biomarker used to predict adverse clinical outcomes in patients with ischemic symptoms and no obstructive CAD in the long term.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CMD is increasingly recognized and carries a worse prognosis in patients experiencing ischemic symptoms and without obstructive CAD. A previous CMR study showed that the semiquantitative perfusion parameter MPRI, which is extrapolated from stress and rest perfusion images can diagnose CMD. This study extended this capacity by showing that an MPRI threshold of 1.47 is predictive of increased major adverse cardiovascular events in patients with ischemic symptoms and without obstructive CAD. Furthermore, for every unit of increase in MPRI, indicating better myocardial perfusion, there is a 90% decrease in likelihood of having a major adverse cardiovascular event.

TRANSLATIONAL OUTLOOK: CMR MPRI shows promise in patients with ischemic symptoms and nonobstructive coronary artery disease to identify CMD and determine prognosis. Prospective studies are required and reproducibility in other centers and settings would be of interest. Furthermore, as effective treatments are lacking for CMD, this study helps establish a role for CMR in future studies for assessing the impact of treatment on myocardial perfusion. CMR's lack of radiation exposure makes CMR follow-up assessment highly appealing.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.