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ORIGINAL RESEARCH

Risk Stratification of Patients With NonObstructive Coronary Artery Disease Using Resistive Reserve Ratio

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BACKGROUND: Resistive reserve ratio (RRR), or the ratio of baseline to hyperemic microvascular resistance, has prognostic implications in predicting clinical outcomes in patients with obstructive coronary artery disease. However, its value in patients with angina or ischemia with nonobstructive coronary artery disease is unknown.

METHODS AND RESULTS: We included 1692 patients with nonobstructive coronary artery disease who underwent invasive coronary vasoreactivity testing. Abnormal coronary flow reserve (CFR, the ratio of hyperemic and baseline resting flow velocities) and RRR were defined as <2.5 and <2.62, respectively. The mortality rate was marginally higher in patients with abnormal CFR (428 patients [25%]) than those with normal CFR (38 [9%] versus 81 [6%]; *P*=0.08), and was significantly higher in patients with abnormal RRR (716 patients [42%]) than those with normal RRR (70 [10%] versus 49 [5%], *P*=0.0002) over the median follow-up of 11.3 years. Patients with abnormal CFR had marginally lower survival than those with normal CFR (log-rank *P*=0.08). In contrast, patients with abnormal RRR had significantly lower survival than those with normal RRR (log-rank *P*=0.001). Abnormal RRR was associated with shorter time to death even after adjustment for other covariates (adjusted hazard ratio, 1.63; 95% CI, 1.11–2.38; *P*=0.01).

CONCLUSIONS: In patients with no obstructive coronary artery disease, RRR was superior to CFR in predicting long-term survival. An RRR <2.62 was associated with 1.6 times increased risk of death in patients with nonobstructive coronary artery disease. Indices of coronary microcirculatory resistive reserve comprising flow- and pressure-derived values may reflect underlying microvascular pathology more faithfully than flow-alone indices like CFR.

Key Words: coronary flow reserve ■ coronary microvascular resistance ■ nonobstructive coronary artery disease ■ resistive reserve ratio

In the absence of significant epicardial coronary artery disease, abnormal coronary flow reserve (CFR) is an established physiologic index of coronary microvascular dysfunction and linked to an increased risk of mortality and major adverse cardiovascular events (MACEs).[1,2]

One of the reasons for its diagnostic yield is that CFR reflects a key aspect of functional microvasculature: its ability to modify coronary blood flow in response to varying myocardial oxygen demands, thus ensuring that blood supply matches metabolic myocardial requirements.[3] Ultimately, the changes of coronary blood flow are driven by changes in arteriolar resistance. Resistive reserve ratio (RRR), the ratio of baseline microvascular resistance (BMR) to hyperemic microvascular resistance (HMR), hypothetically reflects the vasodilatory microvascular capacitance in response to physiologically or pharmacologically induced increase in perfusion demand.[4] A distinct theoretical advantage of RRR over CFR in assessing

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CLINICAL PERSPECTIVE

What Is New?

- Resistive reserve ratio, the ratio of baseline to hyperemic microvascular resistance, was superior to coronary flow reserve in predicting long-term survival.
- Resistive reserve ratio <2.62 was associated with 1.6 times increased risk of death in patients with angina or ischemia with nonobstructive coronary artery disease.

What Are the Clinical Implications?

- Resistive reserve ratio comprising the flow- and pressure-derived index may reflect the ability to increase myocardial perfusion more directly than flow-alone indices like coronary flow reserve.

Nonstandard Abbreviations and Acronyms

APV	average peak velocity
BMR	baseline microvascular resistance
CFR	coronary flow reserve
HMR	hyperemic microvascular resistance
MACE	major adverse cardiovascular event
NOCAD	nonobstructive coronary artery disease
RRR	resistive reserve ratio

the vasodilatory response of the microcirculation is that RRR is not affected by modification in aortic pressure occurring as a result of administration of vasodilators used to induce maximal hyperemia. This may explain why RRR has been successfully used to identify patients at high risk of events in several conditions involving the coronary microcirculation, like myocardial infarction and coronary revascularization.[5,6] However, the prognostic impact of RRR in patients with angina or ischemia and nonobstructive coronary artery disease (NOCAD) remains unknown. Recent studies suggested that endotypes of coronary microvascular dysfunction such as functional and structural could be differentiated using CFR and HMR.[7,8] Furthermore, HMR could provide an additional prognostic value over CFR in predicting MACEs.[9] There is currently lack of evidence whether stratification of patients with NOCAD using RRR and HMR could better stratify the risk of clinical outcomes than using CFR and HMR.

We hypothesized that RRR could reflect coronary microvascular function more directly and thus better stratify the risk of mortality than CFR in patients with abnormal coronary microvascular physiology. This study aimed to compare the prognostic values of CFR and RRR on predicting all-cause mortality in patients with NOCAD. Also, we further investigated the prognostic values of CFR and RRR in combination with HMR and BMR.

METHODS

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Population

In this retrospective observational cohort study, we enrolled 1975 patients who visited the Mayo Clinic between 1992 and 2019 and underwent comprehensive invasive coronary vasoreactivity testing using Doppler flow wire to evaluate coronary microvascular function. NOCAD was defined as cardiac ischemia (assessed by stress electrocardiogram/echocardiogram, positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose/single photon emission computed tomography with thallium-201 thallous chloride, or stress perfusion cardiac magnetic resonance) or angina without obstructive coronary artery disease.[10] Patients with following exclusion criteria were not considered to be eligible for coronary vasoreactivity testing: (1) acute coronary syndrome presentation; (2) a history of myocardial infarction or cerebrovascular events within the past 6 months; (3) use of radiographic contrast agents within 12 hours before catheterization; (4) significant valvular heart disease; (5) advanced chronic kidney disease; (6) reduced left ventricular ejection fraction (<50%); (7) active malignancy; (8) local or systemic infectious disease within the past 4 weeks; (9) inflammatory diseases; (10) pregnant patients and those who were unable to provide written informed consent; and (11) patients with significant epicardial coronary artery stenosis (>50% in major vessels by diagnostic coronary angiography). This study was conducted in accordance with the guideline of the Declaration of Helsinki, and the Mayo Clinic Institutional Review Board approved the study protocol. All patients provided written informed consent for participation in the current study.

Coronary Vasoreactivity Testing

Coronary vasoreactivity testing was performed to evaluate coronary microvascular function, as previously described.[11–14] In brief, patients without significant epicardial coronary artery stenosis further proceeded with coronary reactivity testing. Doppler guidewire (Flowire, Philips/Volcano Therapeutics Inc., Rancho Cordova, CA) was advanced within a

coronary-infusion catheter and positioned in the mid-left anterior descending artery. Incremental doses (18–72 μg) of adenosine were administered until maximal hyperemia was achieved (mean adenosine dose, 46±16 μg). Hemodynamic parameters were recorded at baseline resting and hyperemic conditions. CFR was calculated as the ratio of hyperemic and baseline resting flow velocities. Abnormal CFR was defined as CFR <2.5.[8,15] BMR and HMR were calculated as the ratio of the mean aortic pressure (MAP) and the average peak velocity (APV) at baseline and hyperemia, respectively. Abnormal HMR was defined as HMR ≥2.0.[16,17] Median BMR value was used to define higher and lower BMR, since no predefined cutoff values were available and the logistic model to define the best cutoff value of BMR from receiver operating characteristic analysis was not valid (P=0.38). RRR, the ratio of BMR and HMR, was calculated using the following equation; BMR/HMR=(Baseline MAP/Baseline APV)×(Hyperemic APV/Hyperemic MAP)=(Baseline MAP/Hyperemic MAP)×CFR.[4–6,18] Definition of abnormal RRR was achieved experimentally. According to the protocol, all patients were instructed to fast at least 8 hours and stop all medications that could affect coronary vasoreactivity for at least 48 hours before the procedure (calcium-channel blockers, β blockers, and long-acting nitrates).

Clinical Assessment and Follow-Up

Clinical history, laboratory data, and current medications were collected from a detailed chart review by an investigator blinded to the results of coronary vasoreactivity testing. Patients were followed up for all-cause mortality. Mortality data were ascertained by a combination of public and institutional databases, death certificates, mail surveys, and telephone calls and were independently adjudicated by 2 investigators (A.A. and F.S.).

Statistical Analysis

Continuous variables distributed normally were expressed as the mean±SD, and those with a skewed distribution were expressed as the median (interquartile range). Categorical variables were expressed as frequency (percentage). For between-group comparisons, an unpaired t test was used for normally distributed variables, the Mann-Whitney U test for variables with skewed distribution, and χ^2 test (or Fisher's exact test) for categorical variables. Correlation between 2 variables was assessed using Pearson's correlation test. Receiver operating characteristic analysis was performed to assess the discriminative power of RRR for the prediction of all-cause mortality. The optimal cutoff of RRR was defined as the value for which the sum of sensitivity and specificity was the greatest. Kaplan-Meier methods were used to estimate survival rates. The difference between groups was analyzed using the log-rank test. Linear regression analyses were performed to estimate the effect of the baseline/hyperemic MAP ratio on CFR and RRR. Univariate and multivariate (adjusted for age and sex) Cox proportional hazard ratio analyses were performed to estimate the predictive values of CFR and RRR on the risk of all-cause mortality. CFR and RRR were included in the models either as continuous or dichotomized variables. For all tests, a 2-tailed P value <0.05 was considered statistically significant. All statistical analyses were performed using JMP Pro Software 14.3.0 (SAS Institute, Inc., Cary, NC) and Prism version 8.3.0 (GraphPad Software, La Jolla, CA).

RESULTS

Baseline Characteristics

Of 1975 patients who underwent coronary vasoreactivity testing, we excluded 283 patients because of the lack of CFR, HMR, or BMR measurements, leaving a total of 1692 patients in the analyses (Figure 1). Baseline characteristics of patients included and excluded were similar except that excluded patients were less likely to have diabetes mellitus (Table S1). Baseline characteristics are summarized in Table 1. The mean age was 51.4±12.5 years, and 573 patients (34%) were men. Mean CFR and RRR were 3.0±0.8 and 2.88±0.88, respectively. Four-hundred twenty-eight patients (25%) had abnormal CFR <2.5. Patients with abnormal CFR were older, more likely to be women, and tended to have conventional cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, and reduced renal function) more than those with normal CFR. RRR was significantly lower in patients with abnormal CFR than in those with normal CFR (2.15±0.55 versus 3.13±0.83; P<0.0001).

All-Cause Mortality

The median (interquartile range) follow-up duration was 11.3 (6.4–16.9) years. Of 1692 patients, 119 patients (7%) were deceased during follow-up. The likely cause of death is summarized in Table S1. The cause of death was unknown in 48 patients (40%), but cardiovascular and malignancy-related deaths were reported in 26 patients (22%) and 22 patients (18%), respectively. All-cause mortality tended to be higher in patients with abnormal than those with normal CFR (38 [9%] versus 81 [6%]; P=0.08); however, the cause of death was not different between the patients with normal versus abnormal CFR (P=0.95).

The Cutoff Value of RRR

Receiver operating characteristic analysis was performed to define the optimal cutoff value of RRR to

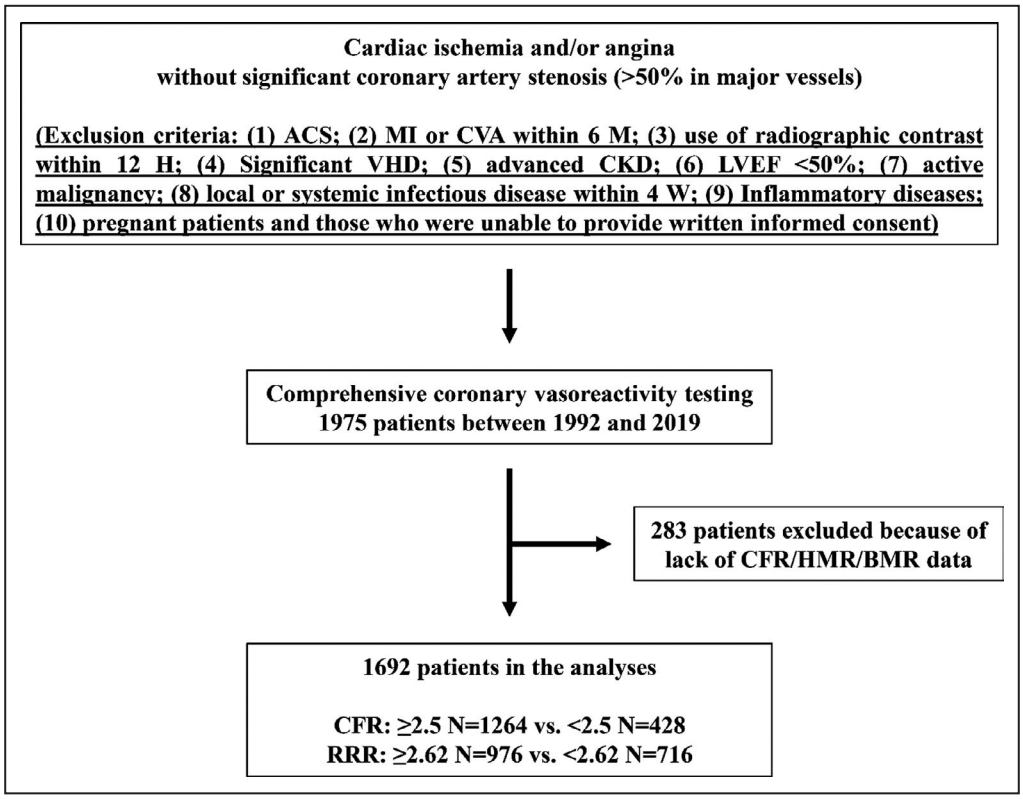

Figure 1. Study flow chart.
ACS indicates acute coronary syndrome; BMR, baseline microvascular resistance; CFR, coronary flow reserve; CKD, chronic kidney disease; CVA, cerebrovascular accident; HMR, hyperemic microvascular resistance; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RRR, resistive reserve ratio; and VHD, valvular heart disease.

predict all-cause mortality. The area under the curve was 0.60 (95% CI, 0.54–0.65; *P*=0.001), and the optimal cutoff of RRR was 2.62 (sensitivity, 0.59; 95% CI, 0.50–0.67; specificity, 0.59; 95% CI, 0.56–0.61). Then patients were divided into 2 groups using an RRR of 2.62 as a cutoff. Of 1692 patients, 716 (42%) had abnormal RRR <2.62. Patients with abnormal RRR <2.62 were older and more likely to be women and have diabetes mellitus, previous history of myocardial infarction, and impaired renal function than those with normal RRR (Table 1). All-cause mortality was 2-fold higher in patients with abnormal than those with normal RRR (70 [10%] versus 49 [5%]; *P*=0.0002); however, cause of death was not significantly different between patients with normal versus abnormal RRR (*P*=0.28) (Table S2).

Reclassification of the Risk of All-Cause Mortality Using RRR

There was a strong positive correlation between CFR and RRR (*r*=0.70; *P*<0.0001) (Figure 2). However, of 1264 patients with normal CFR, 918 patients (73%) had normal RRR, whereas 346 patients (27%) were reclassified as having abnormal RRR (Figure 2, Figure S1). Patients with abnormal RRR were older, more likely to be women, and had higher low-density lipoprotein cholesterol levels and higher MAP at baseline and during hyperemia, and had lower CFR (lower hyperemic APV and higher baseline APV), lower baseline/hyperemic MAP ratio, and lower renal function than those with normal RRR in the normal CFR group (Table 2). Of 428 patients with abnormal CFR, 370 patients (86%) had abnormal RRR, whereas 58 patients (14%) were reclassified as having normal RRR (Figure 2, Figure S1). Age, sex proportion, and MAP at baseline and during hyperemia were similar between patients with normal and abnormal RRR in abnormal CFR group. Patients with abnormal RRR had lower CFR (lower hyperemic APV and higher baseline APV) and lower baseline/hyperemic MAP ratio than those with normal RRR in abnormal CFR group (Table 2).

To estimate the effect of baseline/hyperemic MAP ratio on CFR and RRR, univariate and multivariate linear regression analyses were performed. In multivariate linear regression analysis, both CFR and baseline/hyperemic MAP ratio were independently associated with RRR (CFR: standardized beta coefficient, 0.70; *P*<0.0001; baseline/hyperemic MAP

Table 1. Baseline Characteristics Comparing Patients With Normal Versus Abnormal CFR or RRR

	Total	CFR			RRR		
		≥2.5	<2.5		≥2.62	<2.62	
	N=1692	N=1264	N=428	*P* Value	N=976	N=716	*P* Value
Age, y	51.4±12.5	50.0±12.3	55.6±12.4	<0.0001	49.6±12.1	53.9±12.7	<0.0001
Male sex, n (%)	573 (34)	484 (38)	89 (21)	<0.0001	399 (41)	174 (24)	<0.0001
White race, n (%)	1495 (88)	1121 (89)	374 (87)	0.47	870 (89)	625 (87)	0.24
Smoking status, n (%)							
Never smoked	900 (53)	663 (52)	237 (55)	0.32	529 (54)	371 (52)	0.17
Former smoker	578 (34)	431 (34)	147 (34)		314 (32)	264 (37)	
Current smoker	212 (13)	168 (13)	44 (10)		132 (14)	80 (11)	
Diabetes mellitus, n (%)	194 (11)	130 (10)	64 (15)	0.01	95 (10)	99 (14)	0.01
Hypertension, n (%)	726 (43)	526 (42)	200 (47)	0.06	418 (43)	308 (43)	0.94
Dyslipidemia, n (%)	936 (55)	682 (54)	254 (59)	0.05	527 (54)	409 (57)	0.20
Previous MI, n (%)	260 (15)	193 (15)	67 (16)	0.70	161 (17)	99 (14)	0.02
Body mass index, kg/m^2	28.1 (24.5–32.7)	28.4 (24.8–32.8)	27.3 (24.1–31.8)	0.003	28.4 (24.9–33.0)	27.7 (23.9–32.1)	0.003
HbA_{1c}, %	5.4 (5.1–5.7)	5.3 (5.1–5.6)	5.4 (5.1–5.8)	0.001	5.3 (5.1–5.6)	5.4 (5.1–5.8)	0.0004
Total cholesterol, mg/dL	185±43	185±43	184±45	0.75	184±42	186±45	0.31
LDL cholesterol, mg/dL	104±37	105±37	102±39	0.18	104±36	105±39	0.39
HDL cholesterol, mg/dL	54±18	54±18	57±18	0.001	53±18	56±17	0.02
Triglyceride, mg/dL	109 (76, 165)	109 (77, 165)	109 (74, 165)	0.48	108 (78, 166)	110 (75, 165)	0.77
eGFR, mL/min/1.73 m^2	78.8±17.8	79.7±17.2	76.1±19.1	0.001	80.2±17.1	76.9±18.5	0.0002
CFR	3.0±0.8	3.3±0.6	2.1±0.3		3.3±0.7	2.5±0.5	<0.0001
Hyperemic APV, cm/s	70.7±21.6	72.1±21.3	66.5±22.0	<0.0001	74.5±21.6	65.5±20.4	<0.0001
Baseline APV, cm/s	26.2±9.6	24.2±8.3	31.9±10.8	<0.0001	22.5±7.2	31.1±10.3	<0.0001
RRR (HMR/BMR)	2.88±0.88	3.13±0.83	2.15±0.55	<0.0001	3.43±0.73	2.13±0.37	
HMR, mm Hg/cm/s	1.41 (1.17–1.77)	1.37 (1.15–1.70)	1.56 (1.24–1.98)	<0.0001	1.34 (1.12–1.63)	1.56 (1.26–1.96)	<0.0001
BMR, mm Hg/cm/s	4.04 (3.18–5.00)	4.25 (3.43–5.33)	3.38 (2.56–4.16)	<0.0001	4.46 (3.69–5.57)	3.38 (2.66–4.18)	<0.0001
Baseline MAP, mm Hg	99±14	98±14	100±15	0.02	98±13	100±15	0.01
Hyperemic MAP, mm Hg	98±14	98±14	100±15	0.01	97±13	100±15	0.0003
Baseline/hyperemic MAP	1.00±0.04	1.00±0.03	1.00±0.05	0.60	1.01±0.04	1.00±0.03	<0.0001

APV indicates average peak velocity; BMR, baseline microvascular resistance; CFR, coronary flow reserve; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HMR, hyperemic resistance reserve; LDL, low-density lipoprotein; MAP, mean arterial pressure; MI, myocardial infarction; and RRR, resistive reserve ratio.

ratio: standardized beta coefficient, 0.13; *P*<0.0001). Baseline/hyperemic MAP ratio was not associated with CFR (standardized beta coefficient, 0.0002; *P*=0.99), whereas individual components of MAP ratio was significantly associated with CFR in univariate analyses (baseline MAP: standardized beta coefficient, −0.13; *P*<0.0001; hyperemic MAP: standardized beta coefficient, −0.13; *P*<0.0001).

CFR, RRR, and All-Cause Mortality

To assess the predictive values of abnormal CFR and abnormal RRR for all-cause mortality, Kaplan-Meier curves were compared between patients with normal versus abnormal CFR or RRR. Patients with abnormal CFR tended to have lower survival than those with normal CFR (log-rank *P*=0.08) (Figure 3A). In contrast, patients with abnormal RRR had significantly lower survival than those with normal RRR (log-rank *P*=0.0001) (Figure 3B). Cox proportional hazards regression analysis showed that abnormal RRR was significantly associated with an increased risk of all-cause mortality with a hazard ratio (HR) of 1.85 (95% CI, 1.29–2.67; *P*=0.001) in univariate analysis and 1.63 (95% CI, 1.11–2.38; *P*=0.01) in multivariate analysis (adjusted for age and sex) (Figure 4). Abnormal CFR had a borderline significant association with an increased risk of all-cause mortality in univariate analysis but not after adjustment for age and sex (HR, 1.40; 95% CI, 0.96–2.07; *P*=0.08; adjusted HR, 1.23; 95% CI, 0.82–1.84; *P*=0.31) (Figure 4). RRR as a continuous variable showed a significant negative association with a risk of all-cause mortality in

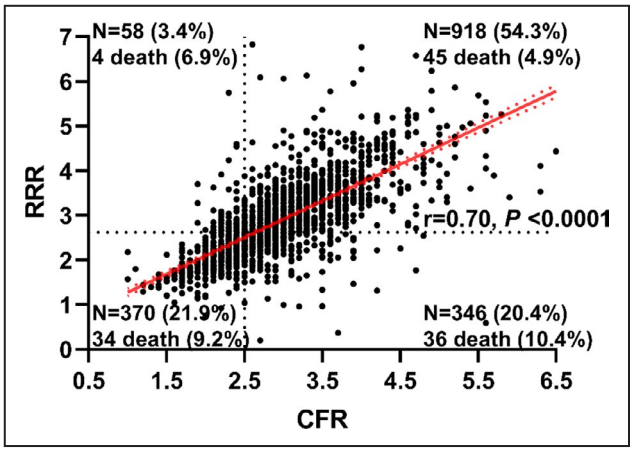

Figure 2. Relationship between CFR and RRR.
RRR is strongly correlated with CFR (r=0.70; P<0.0001). Of 1264 patients with normal CFR (≥2.5), 918 patients (73%) had normal RRR (≥2.62) and 346 (27%) patients were reclassified as having abnormal RRR (<2.62). Of 428 patients with abnormal CFR (<2.5), 370 (86%) patients had abnormal RRR and 58 (14%) patients were reclassified as having normal RRR. CFR indicates coronary flow reserve; and RRR resistive reserve ratio.

univariate and multivariate analysis (HR, 0.69; 95% CI, 0.54–0.86; P=0.002; adjusted HR, 0.76; 95% CI, 0.59–0.96; P=0.03), whereas CFR as a continuous variable showed a significant negative association with a risk of all-cause mortality only in univariate analysis (HR, 0.69; 95% CI, 0.54–0.86; P=0.01; adjusted HR, 0.79; 95% CI, 0.59–1.04; P=0.10) (Figure 4).

Patients with abnormal RRR had significantly lower survival than those with normal RRR in the normal CFR group (log-rank P=0.002) (Figure 3C). However, RRR did not provide further stratification in the abnormal CFR group (log-rank P=0.69) (Figure 3D).

Finally, we compared the prognostic values of RRR and CFR in combination with BMR and HMR. Lower BMR (less than median) and abnormal HMR were not significantly associated with an increased risk of all-cause mortality individually (Figure S2 and S3). Higher HMR provided additional risk stratification in combination with RRR in predicting the risk of all-cause mortality (log-rank P=0.01), whereas higher HMR did not provide additional risk stratification in combination with CFR (log-rank P=0.10) (Figure 3E and 3F). RRR in combination with BMR could also stratify the risk of all-cause mortality (log-rank P=0.01) (Figure 3G). Abnormal HMR and lower BMR (less than median) was associated with lower survival in patients with abnormal RRR (Figure 3F and 3G).

DISCUSSION

This study demonstrated that RRR, either as a dichotomized or continuous variable, contributes to stratifying the patients with NOCAD at a higher risk of mortality. Patients with RRR <2.62 had significantly lower survival than those with RRR ≥2.62, with 1.6 times increased risk of all-cause death after adjustment for age and sex, whereas patients with CFR <2.5 had marginally lower survival than those with CFR. Abnormal RRR was associated with lower survival than those with normal RRR in the normal CFR group, while abnormal RRR did not provide further prognostic stratification in the abnormal CFR group, suggesting that RRR could be the better marker for systemic microvascular alteration, especially in patients with normal CFR. RRR in combination with HMR could better stratify the risk of all-cause mortality than the combination of CFR and HMR. These observations imply that low RRR may be valuable for risk stratification beyond CFR.

The Rationale of CFR and RRR

RRR is calculated as the ratio of BMR to HMR, and can be transformed into CFR × (baseline MAP / hyperemic MAP) in the absence of epicardial artery disease, which explains the strong correlation between RRR and CFR observed in this study. The prognostic value of this index has been investigated in patients with acute coronary syndromes. Though subpopulation analysis of the T-TIME (Trial of Low-Dose Adjunctive Alteplase During Primary Percutaneous Coronary Intervention) trial including patients with ST-segment elevation myocardial infarction showed a stronger correlation between RRR and CFR (r=0.94; P<0.0001) than this study (r=0.70; P<0.0001), lower RRR showed a significant association with increased microvascular obstruction, infarct size, and adverse clinical outcomes, whereas CFR did not.[5] Our previous observation showing that microvascular obstruction detected in non–infarct-related myocardium is associated with increased myocardial injury and risk of MACE following myocardial infarction supports the concept that preexisting coronary microvascular dysfunction increases the risk of acute coronary syndrome and increased myocardial injury after revascularization.[19,20] In this context, RRR, comprising flow and pressure components, may reflect coronary microvascular function more closely than CFR (flow-only index) and can correct CFR for changes in arterial pressure.

Furthermore, the prognostic value of RRR has been investigated in patients with obstructive coronary artery disease, in conjunction with epicardial stenosis indices like fractional flow reserve. A previous study reported consistent findings showing that lower RRR could stratify the patients at higher risk of MACEs in deferred patients with either normal fractional flow reserve or

Table 2. Baseline Characteristics Comparing Patients With Normal Versus Abnormal RRR With Further Stratification by CFR

	Normal CFR			Abnormal CFR		
	RRR ≥2.62	RRR <2.62		RRR ≥2.62	RRR <2.62	
	N=918	N=346	*P* Value	N=58	N=370	*P* Value
Age, y	49.2±12.0	52.1±12.7	0.0003	55.8±11.3	55.5±12.6	0.88
Male sex, n (%)	389 (42)	95 (27)	<0.0001	10 (17)	79 (21)	0.47
White race, n (%)	817 (89)	304 (88)	0.57	53 (91)	321 (87)	0.32
Smoking status, n (%)						
Never smoked	496 (54)	167 (48)	0.09	33 (57)	204 (55)	0.96
Former smoker	295 (32)	136 (39)		19 (33)	128 (35)	
Current smoker	126 (14)	42 (12)		6 (10)	38 (10)	
Diabetes mellitus, n (%)	88 (10)	42 (12)	0.18	7 (12)	57 (15)	0.51
Hypertension, n (%)	390 (42)	136 (39)	0.31	28 (48)	172 (46)	0.80
Dyslipidemia, n (%)	492 (54)	190 (55)	0.68	35 (60)	219 (59)	0.87
Previous MI, n (%)	151 (16)	42 (12)	0.06	10 (17)	57 (15)	0.72
Body mass index, kg/m^2	28.7 (24.9–33.1)	28.2 (23.9–32.3)	0.08	27.4 (24.6–30.5)	27.3 (23.8–31.9)	0.80
HbA_{1c}, %	5.3 (5.1–5.6)	5.4 (5.1–5.7)	0.53	5.5 (5.2–5.8)	5.4 (5.1–5.8)	0.79
Total cholesterol, mg/dL	183±42	190±45	0.01	197±48	182±44	0.04
LDL-C, mg/dL	103±36	109±39	0.02	107±39	101±39	0.37
HDL-C, mg/dL	53±18	55±17	0.13	61±20	56±18	0.16
Triglyceride, mg/dL	108 (76–165)	113 (78–166)	0.62	110 (86–193)	108 (73–165)	0.26
eGFR, mL/min/1.73 m^2	80.4±16.8	77.9±18.0	0.02	76.6±21.0	76.0±18.9	0.82
CFR	3.4±0.7	2.9±0.4	<0.0001	2.3±0.3	2.1±0.3	<0.0001
Hyperemic APV, cm/s	74.2±21.1	66.6±20.9	<0.0001	79.7±28.8	64.4±20.0	0.0002
Baseline APV, cm/s	22.2±6.9	29.5±9.5	<0.0001	26.7±9.6	32.7±10.8	<0.0001
RRR (HMR/BMR)	3.45±0.73	2.27±0.35		3.11±0.64	2.00±0.34	
HMR, mm Hg/cm/s	1.34 (1.12–1.64)	1.50 (1.24–1.90)	<0.0001	1.29 (1.06–1.53)	1.61 (1.28–2.00)	<0.0001
BMR, mm Hg/cm/s	4.48 (3.73–5.59)	3.48 (2.84–4.30)	<0.0001	3.94 (3.19–5.01)	3.28 (2.52–4.08)	<0.0001
Baseline MAP, mm Hg	98±13	100±15	0.04	101±13	100±16	0.63
Hyperemic MAP, mm Hg	97±13	100±15	0.01	99±13	100±15	0.48
Baseline/hyperemic MAP	1.01±0.04	1.00±0.02	0.0002	1.02±0.08	1.00±0.04	0.02

APV indicates average peak velocity; BMR, baseline microvascular resistance; CFR, coronary flow reserve; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HMR, hyperemic resistance reserve; LDL, low-density lipoprotein; MAP, mean arterial pressure; MI, myocardial infarction; and RRR, resistive reserve ratio.

CFR values, suggesting that merging pressure and flow data in RRR results in superior information on the physiological status of the coronary circulation than pressure- or flow-only indices (fractional flow reserve and CFR, respectively).[6]

CFR, RRR, and MACEs in Patients With NOCAD

Our study is the first one investigating the prognostic value of RRR in predicting long-term survival in patients with NOCAD. A recent study highlighting the prognostic implication of RRR demonstrated that decreased RRR (<1.7) was associated with increased myocardial injury and worse clinical outcomes in patients with revascularized ST-segment elevation myocardial infarction.[5] Another study looking at 5-year composite outcomes including all-cause death, myocardial infarction, and revascularization in patients with epicardial coronary artery disease showed that decreased RRR (<3.5) was significantly associated with a higher rate of adverse outcomes.[6] Both studies chose the median values of RRR as their cutoffs and showed the incremental prognostic value of RRR to CFR in predicting MACEs in patients with epicardial coronary artery disease. We demonstrated that RRR of 2.62 was the optimal cutoff to predict long-term survival in a large data set including 1692 patients with NOCAD with a median follow-up of 11.3 years, whereas binary CFR could barely stratify the risk of death in this cohort. It

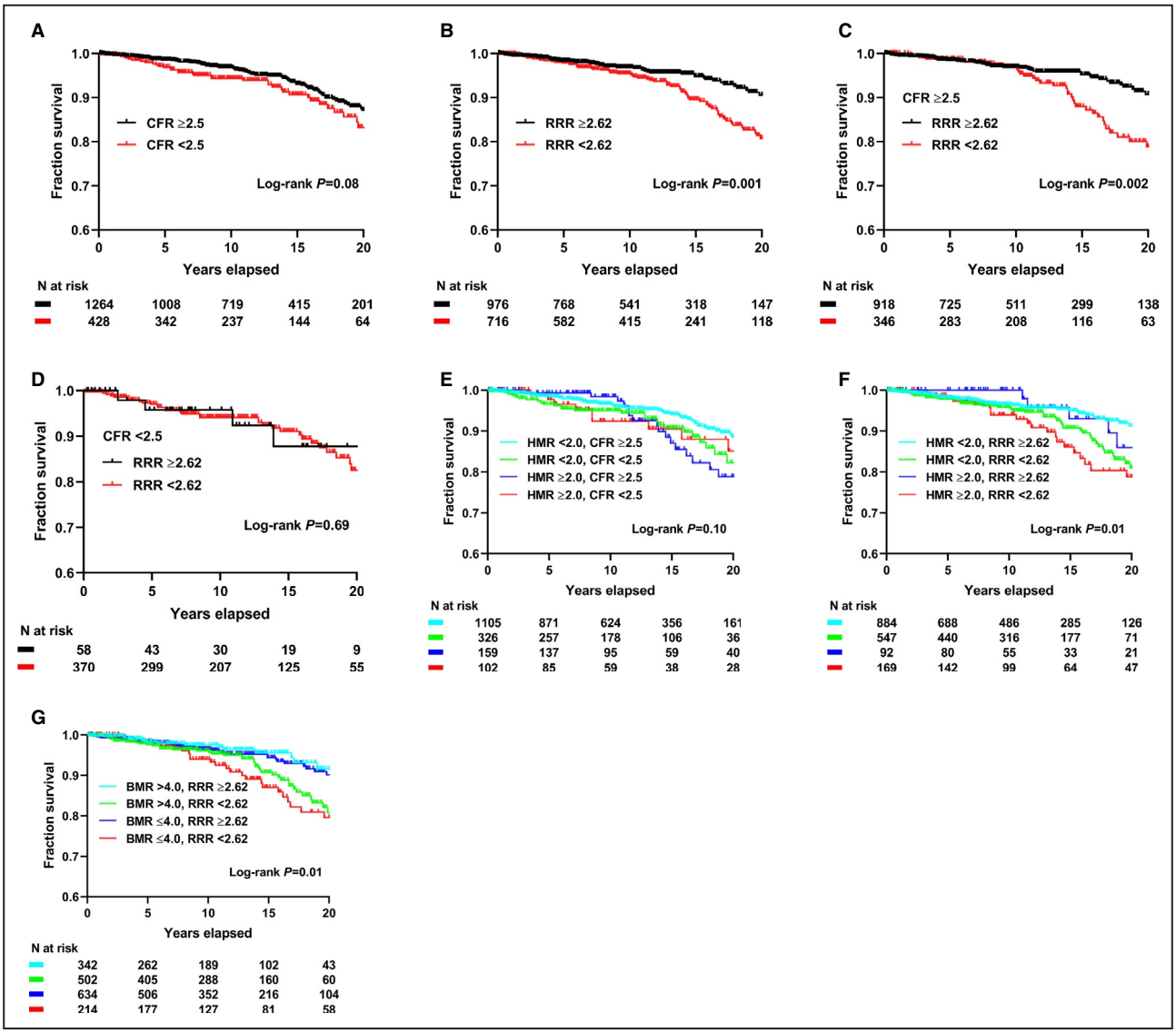

Figure 3. Comparison of Kaplan-Meier curves.

A, Comparison of Kaplan-Meier curves between patients with CFR ≥2.5 vs <2.5. Patients with CFR <2.5 tended to have lower survival compared with those with CFR ≥2.5 (log-rank *P*=0.08). **B**, Comparison of Kaplan-Meier curves between patients with RRR ≥2.62 vs <2.62. Patients with RRR <2.62 had significantly lower survival compared with those with RRR ≥2.62 (log-rank *P*=0.001). **C**, Comparison of Kaplan-Meier curves between patients with RRR ≥2.62 vs <2.62 in patients with normal CFR. Patients with RRR <2.62 had significantly lower survival compared with those with RRR ≥2.62 in patients with normal CFR (log-rank *P*=0.002). **D**, Comparison of Kaplan-Meier curves between patients with RRR ≥2.62 vs <2.62 in patients with abnormal CFR. RRR did not further stratified patients' risk for all-cause mortality in patients with abnormal CFR (log-rank *P*=0.69). **E**, Comparison of Kaplan-Meier curves using normal vs abnormal CFR and HMR. Risk of all-cause mortality was not well stratified using CFR and HMR (log-rank *P*=0.10). **F**, Comparison of Kaplan-Meier curves using normal vs abnormal RRR and HMR. Risk of all-cause mortality was well stratified using normal vs abnormal RRR and HMR (log-rank *P*=0.01).**G**, Comparison of Kaplan-Meier curves using normal vs abnormal RRR and HMR. Risk of all-cause mortality was well stratified using normal vs abnormal RRR and HMR (log-rank *P*=0.01). BMR indicates baseline microvascular resistance; CFR, coronary flow reserve; HMR, hyperemic microvascular resistance; and RRR, resistive reserve ratio.

is of great interest to detect the divergence in survival curves between patients with normal and abnormal RRR after 10 years from the coronary vasoreactivity testing, whereas the previous study observed divergence in incidence of composite adverse outcomes (described above) after 1 year.[6] Given that the cause of death was not different between patients with normal and abnormal RRR, abnormal RRR might be one of the manifestations of the systemic microvascular disease.[21] Our previous observations showing the association between peripheral microvascular dysfunction assessed by reactive hyperemia peripheral

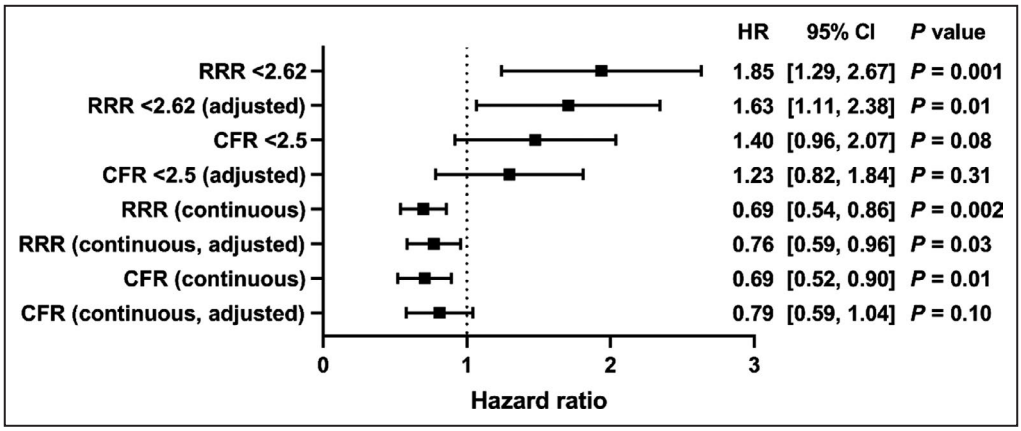

Figure 4. Cox proportional hazard analysis for all-cause mortality.
Univariate and multivariate (adjusted for age and sex) COX proportional hazard ratio analysis. Forest plot showing the hazard ratio and 95% CI. CFR indicates coronary flow reserve; HR, hazard ratio; and RRR, resistive reserve ratio.

arterial tonometry using a fingertip device and future risk of ischemic stroke, especially for cerebral small-vessel disease, support the notion of systemic microvascular disease.[22] We also reported that peripheral microvascular dysfunction was associated with an increased risk of solid-tumor cancer, indicating that peripheral microvascular dysfunction can be the marker of systemic diseases.[23] In the same context, another study reported that coronary microvascular disease was independently associated with an increased risk of cardiovascular, cancer, and noncardiovascular and noncancer mortality over 8 years.[24] Therefore, it could be hypothesized that the abnormal RRR might lead to cardiac events in the short term, but it might take a longer period of time that systemic microvascular disease links to cause of death, requiring future studies to investigate the association between abnormal RRR and composite outcomes in patients with NOCAD.

Van der Hoeven et al[18] reported that blunted hyperemic response to adenosine led to increased microvascular resistance, which was associated with increased infarct size, with a resultant decrease in RRR in patients with ST-segment elevation myocardial infarction. A recent study showed that HMR provides additional prognostic value to stratify patients' risk to CFR by reflecting structural microvascular alteration such as capillary rarefaction, arteriolar obliteration, and perivascular fibrosis in addition to functional alteration.[7,8] Since RRR accounts for the pressure change while CFR does not, RRR in combination with HMR could better stratify the risk of all-cause mortality than the combination of CFR and HMR in this study. Interestingly, both abnormal HMR and lower BMR were associated with lower survival in patients with abnormal RRR, providing additional prognostic values to RRR. Lower BMR could reflect higher resting coronary blood flow, which could be a marker of increased sympathetic activation leading to worse clinical outcomes.[25] Our data showed that patients with abnormal RRR had higher HMR and lower BMR, indicating that abnormal RRR could reflect both structural and functional alteration. Therefore, risk stratification using RRR could be further categorized by HMR and BMR into structural or functional endotypes, which potentially requires different treatment strategies, requiring future studies.

Limitations

This study has some limitations. First, because of its retrospective observational cohort design, it is challenging to derive causal associations from the current study. All the patients included in the present study were clinically referred for diagnostic coronary angiography, and coronary microvascular function testing was performed in patients without obstructive coronary artery disease. Also, a substantial number of patients (N=283) were excluded from the analyses because of the missing data in CFR/BMR/HMR; however, baseline characteristics were similar between patients included in and excluded from the analyses. Selection bias cannot be avoided, thus potentially affecting the generalizability of current observation. We defined a cutoff value of RRR based on the receiver operating characteristic analysis using the same cohort, whereas we used the predefined and validated cutoff value of CFR, requiring future studies to validate the findings of this study in different cohorts. Second, missing data regarding specific causes of death in 40% of deceased patients limits our ability to assess the association between coronary microvascular dysfunction and the specific cause of death meaningfully, requiring future studies. Third, we used aortic pressure during hyperemia

for the approximation of coronary pressure to calculate HMR. Given that only patients with NOCAD were included in the study, the difference between aortic pressure and coronary pressure is negligible, and calculation of HMR using mean aortic pressure is valid. The difference of baseline/hyperemic MAP ratio was subtle between patients with normal versus abnormal RRR (Table 1 and Table 2). However, baseline/hyperemic MAP ratio was an important determinant of RRR and provided additional prognostic value to CFR, which could be difficult to be explained by the error in MAP measurement. The strong point of this study is that we showed the association between RRR, a newer and less studied indicator of coronary microvascular function, and mortality in the largest data set from a single institution where the standardized technique was used to assess coronary microvascular physiology.

CONCLUSIONS

Lower RRR is associated with a higher risk of all-cause mortality both as continuous and dichotomized variables in patients with NOCAD. RRR correlated well with CFR; however, RRR <2.62 could stratify patients with a higher risk of all-cause mortality better than CFR <2.5 in this population. These findings generate the hypothesis that assessment of coronary microcirculatory resistive reserve comprising of flow- and pressure-derived indices may reflect the ability to increase myocardial perfusion more directly than that of flow augmentation, requiring future mechanistic studies.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Tables S1–S2
Figures S1–S3

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Supplemental Material

Table S1. Comparison of baseline characteristics between patients included and excluded from the analyses.

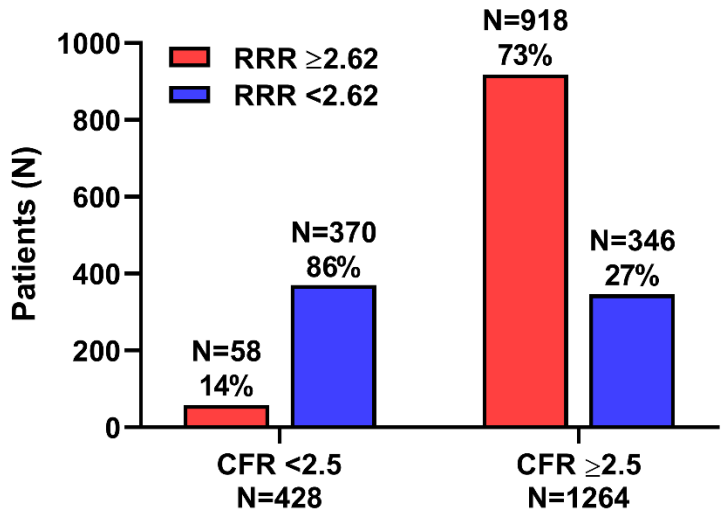
	Included patients N=1692	Excluded patients N=283	*P* value
Age, years	51.4±12.5	50.4±11.7	0.17
Male sex, N (%)	573 (34)	95 (34)	0.92
White race, N (%)	1495 (88)	240 (85)	0.09
Smoking status, N (%)			
Never smoked	900 (53)	164 (58)	0.19
Former smoker	578 (34)	95 (34)	
Current smoker	212 (13)	24 (8)	
Diabetes, N (%)	194 (11)	21 (7)	0.04
Hypertension, N (%)	726 (43)	115 (41)	0.47
Dyslipidemia, N (%)	936 (55)	158 (56)	0.87
Previous MI, N (%)	260 (15)		
Body mass index, kg/m^2	28.1 (24.5, 32.7)	28.3 (24.2, 32.3)	0.92

Table S2. Cause of death.

	Total	CFR			RRR		
	N=1692	≥2.5 N=1264	<2.5 N=428	*P* value	≥2.62 N=976	<2.62 N=716	*P* value
Total death, N (%)	119 (7)	81 (6)	38 (9)	0.08	49 (5)	70 (10)	0.0002
Cause of death, N (%)							
Cardiovascular	26 (22)	17 (21)	9 (24)	0.95	11 (22)	15 (21)	0.28
Malignancy	22 (18)	15 (19)	7 (18)		12 (24)	10 (14)	
Others	23 (19)	15 (19)	8 (21)		6 (12)	17 (24)	
Unknown	48 (40)	34 (42)	14 (37)		20 (41)	28 (40)	

CFR, coronary flow reserve; RRR, resistive reserve ratio

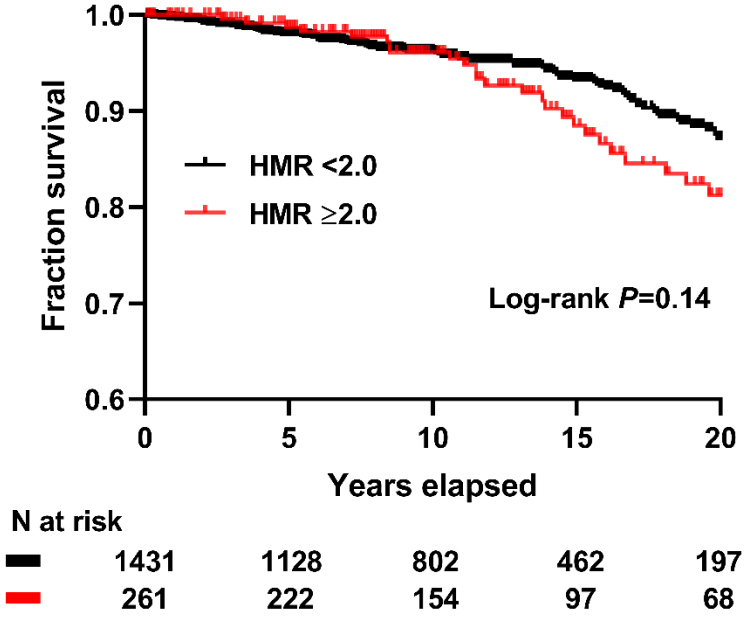
Figure S1. Association between CFR and RRR.



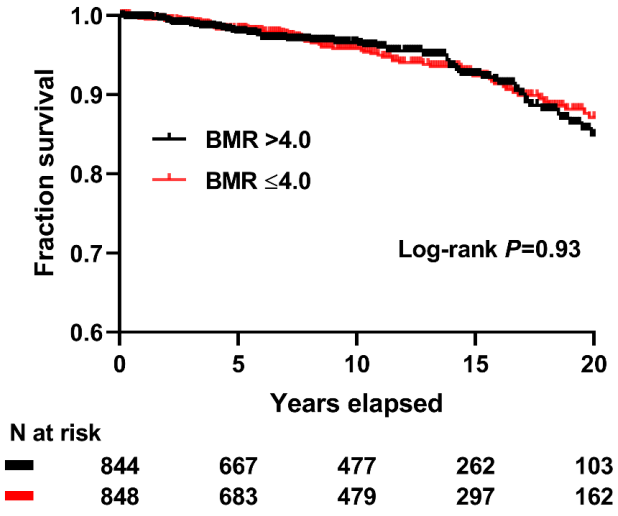
Of 1264 patients with normal CFR (≥2.5), 918 patients (73%) had normal RRR (≥2.62) and 346 (27%) patients were reclassified as having abnormal RRR (<2.62). Of 428 patients with abnormal CFR (<2.5), 370 (86%) patients had abnormal RRR and 58 (14%) patients were reclassified as having normal RRR. CFR, coronary flow reserve; RRR resistive reserve ratio.

Figure S2. Comparison of Kaplan-Meier curves.

A. Kaplan-Meier curves comparing patients with HMR <2.0 vs ≥2.0



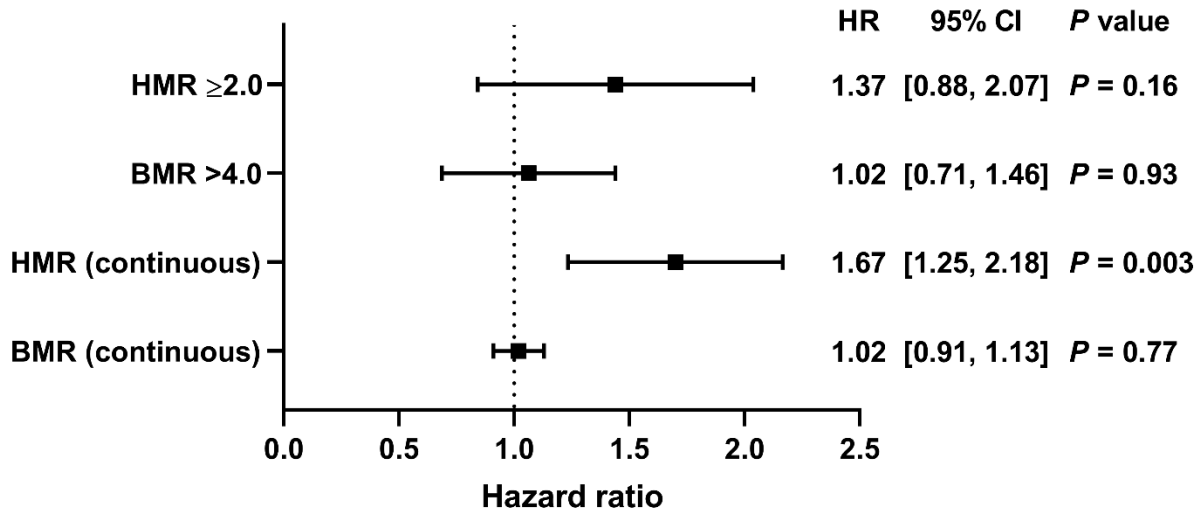
B. Kaplan-Meier curves comparing patients with BMR ≤4.0 vs >4.0



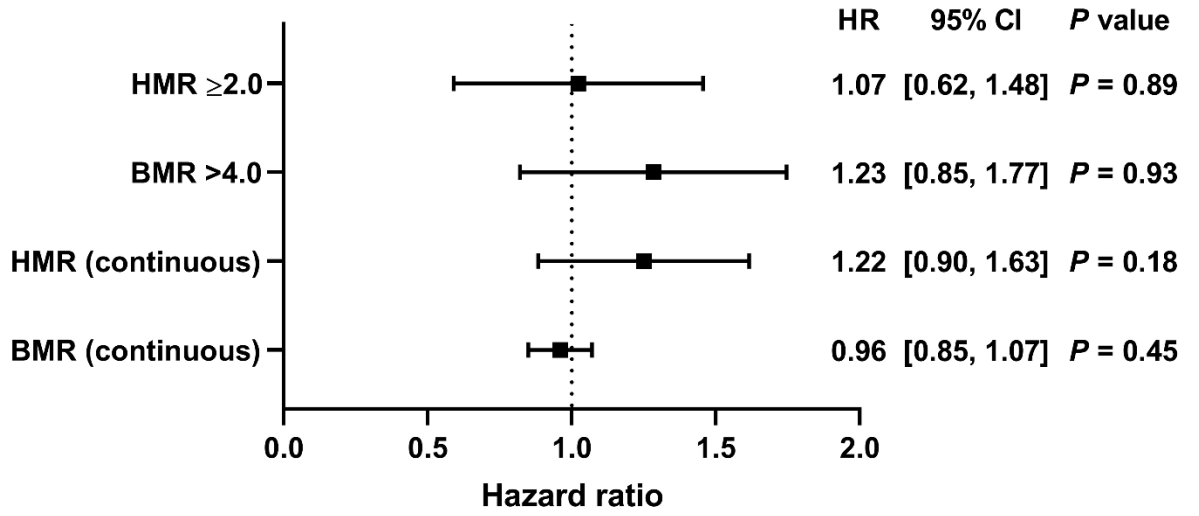
(A) Comparison of Kaplan-Meier curves between patients with HMR ≥2.0 vs. <2.0. (B) Comparison of Kaplan-Meier curves between patients with BMR >4.0 (median) vs. ≤4.0 (median). BMR, baseline microvascular resistance; HMR, hyperemic microvascular resistance.

Figure S3. Cox proportional hazard analysis for all-cause mortality.

A. Univariate



B. Multivariate (adjusted for age and sex)



(A) Univariate and (B) multivariate (adjusted for age and sex) COX proportional hazard ratio analysis. Forest plot showing the hazard ratio and 95% CI. BMR, baseline microvascular resistance; HMR, hyperemic microvascular resistance.