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ORIGINAL RESEARCH

Prognostic Impact of Cardiac Diastolic Function and Coronary Microvascular Function on Cardiovascular Death

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BACKGROUND: Coronary microvascular dysfunction (CMD) has been considered as a possible cause of cardiac diastolic dysfunction. The current study evaluated the association between cardiac diastolic dysfunction and CMD, and their prognostic implications in patients without significant left ventricular systolic dysfunction and epicardial coronary stenosis.

METHODS AND RESULTS: A total of 330 patients without left ventricular systolic dysfunction (ejection fraction ≥50%) and significant epicardial coronary stenosis (fractional flow reserve >0.80) were analyzed. Cardiac diastolic dysfunction was defined by echocardiographic parameters (early diastolic transmitral flow velocity/early diastolic mitral annular velocity, e' velocity, tricuspid regurgitation velocity, and left atrial volume index). Overt CMD was defined as coronary flow reserve <2.0 and index of microcirculatory resistance ≥25 U. The primary end point was cardiovascular death or admission for heart failure during 5 years of follow-up. In patients without left ventricular systolic dysfunction and significant epicardial coronary stenosis, prevalence of cardiac diastolic dysfunction and overt CMD was 25.5% and 11.2%, respectively. Overt CMD was independently associated with cardiac diastolic dysfunction (adjusted odds ratio, 3.440 [95% CI, 1.599–7.401]; *P*=0.002). Patients with cardiac diastolic dysfunction showed significantly higher risk of the primary outcome than those without (adjusted hazard ratio [HR], 2.996 [95% CI, 1.888–4.755]; *P*<0.001). Patients with overt CMD also showed significantly higher risk of the primary outcome than those without (adjusted HR, 2.939 [95% CI, 1.642–5.261]; *P*<0.001). Presence of overt CMD was associated with significantly increased risk of cardiovascular death among the patients with cardiac diastolic dysfunction (43.8% versus 14.5%; *P*=0.006) but not in patients without cardiac diastolic dysfunction (interaction *P*<0.001). Inclusion of overt CMD into the model with cardiac diastolic dysfunction significantly improved predictive ability for cardiovascular death or heart failure admission (concordance index, 0.719 versus 0.737; *P* for comparison=0.034).

CONCLUSIONS: There was significant association between the presence of cardiac diastolic dysfunction and overt CMD. Both cardiac diastolic dysfunction and overt CMD were associated with increased risk of cardiovascular death or admission for heart failure. Integration of overt CMD into cardiac diastolic dysfunction showed improvement of the risk stratification in patients without significant left ventricular systolic dysfunction and epicardial coronary stenosis.

REGISTRATION: DIAST-CMD (Prognostic Impact of Cardiac Diastolic Function and Coronary Microvascular Function) registry; Unique identifier: NCT05058833.

Key Words: cardiac diastolic dysfunction ■ coronary flow reserve ■ coronary microvascular dysfunction ■ index of microcirculatory resistance ■ prognosis

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CLINICAL PERSPECTIVE

What Is New?

- The current study investigated the prognostic implications of cardiac diastolic dysfunction and invasive physiologic index-defined coronary microvascular dysfunction (CMD) in patients without significant left ventricular systolic dysfunction and epicardial coronary stenosis.
- None of the previous studies used the standardized definition of CMD using invasive physiologic indexes and exclusively evaluated patients with functionally insignificant epicardial coronary stenosis (fractional flow reserve >0.80).
- There was significant association between cardiac diastolic dysfunction and CMD, and the presence of CMD was an independent predictor of cardiac diastolic dysfunction; both cardiac diastolic dysfunction and CMD were significantly associated with a higher risk of cardiovascular death and admission for heart failure.

What Are the Clinical Implications?

- Integration of both cardiac diastolic dysfunction and CMD into clinical risk factors showed incremental discrimination abilities to predict cardiovascular death or admission for heart failure.
- These results imply that integration of well-established invasive and noninvasive indexes for cardiac diastolic dysfunction and CMD in patients without significant left ventricular systolic dysfunction and epicardial coronary stenosis will provide incremental prognostic implications.

Nonstandard Abbreviations and Acronyms

CFR	coronary flow reserve
CMD	coronary microvascular dysfunction
FFR	fractional flow reserve
HFpEF	heart failure with preserved ejection fraction
IMR	index of microcirculatory resistance
Pa	aortic pressure
Pd	distal pressure
Tmn	mean transit time
TR V_{max}	peak tricuspid regurgitation velocity

Cardiac diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole and is an independent predictor of mortality, even in patients with preserved left ventricular (LV) systolic function.[1] Cardiac diastolic dysfunction is related to various clinical risk factors, myocardial ischemia, or myocardial infiltrative disease.[2] Clinical manifestations of cardiac diastolic dysfunction are also variable, from asymptomatic subclinical heart failure (HF) to HF with preserved ejection fraction (HFpEF), angina or exercise intolerance without significant epicardial coronary artery disease, or end-stage HF.[2] Although its pathophysiology remains incompletely understood, it has been suggested that systemic endothelial dysfunction, oxidative stress, and coronary microvascular dysfunction (CMD) could play an important role.[2,3]

In this regard, recent studies evaluated the association of CMD with cardiac diastolic dysfunction using noninvasively measured global coronary flow reserve (CFR) as a marker of CMD.[4–6] However, it is unclear that the cause of depressed global CFR was a result of CMD or epicardial coronary stenosis in previous studies. Conversely, invasive physiologic assessment using fractional flow reserve (FFR), CFR, and index of microcirculatory resistance (IMR) can discriminate the domain of abnormal coronary circulation.[7–9] Furthermore, a previous study demonstrated the prognostic impact of overt CMD, defined by both depressed CFR (<2.0) and elevated IMR (≥25 U), in patients without functionally significant epicardial coronary stenosis (FFR >0.80).[9] Nevertheless, limited studies have evaluated cardiac diastolic dysfunction and CMD using invasive physiologic indexes and their prognostic implications, especially in patients without LV systolic dysfunction and significant coronary artery stenosis.

Therefore, we sought to evaluate 3 important questions as to whether: (1) cardiac diastolic dysfunction is associated with CMD; (2) both cardiac diastolic dysfunction and CMD are significantly associated with cardiovascular death or admission for HF; and (3) integration of both conditions would allow incremental prognostic stratification in patients without LV systolic dysfunction and significant coronary artery stenosis.

METHODS

Study Population

The study population was derived from DIAST-CMD (Prognostic Impact of Cardiac Diastolic Function and Coronary Microvascular Function) registry (NCT05058833). Patients were prospectively enrolled from Samsung Medical Center in Korea from April 2016 to December 2020. All patients underwent clinically indicated invasive coronary angiography and comprehensive physiologic assessments, including FFR, CFR, and IMR measurements for at least 1 vessel for the evaluation of epicardial coronary stenosis and coronary microvasculature. Patients with hemodynamic instability, severe LV dysfunction, a culprit vessel of acute coronary syndrome, or severe valvular stenosis or regurgitation were excluded. Among the

registered population, patients with unavailable echocardiography data, LV ejection fraction (LVEF) <50%, or functionally significant epicardial coronary artery stenosis (FFR ≤0.80) were excluded from the current analysis, leaving 330 patients without functionally significant epicardial coronary artery stenosis (FFR >0.80) (Figure S1). The study protocol was approved by the institutional review board and conducted according to the principals of the Declaration of Helsinki. All patients provided written informed consent before enrollment in the registry (clinicaltrials.gov identifier, NCT05058833).

Coronary Angiography and Physiological Measurement

Diagnostic coronary angiography was performed using standard techniques. All angiograms were analyzed at a core laboratory (Samsung Medical Center) in a blinded manner using validated software (Centricity CA 1000; GE, Waukesha, WI). Significant coronary stenosis in coronary angiography was defined by ≥50% diameter stenosis in visual assessment. The atherosclerotic burden in epicardial coronary arteries was assessed by the SYNTAX (Synergy Between PCI [Percutaneous Coronary Intervention] With Taxus and Cardiac Surgery) score.

All coronary physiologic measurements were performed after diagnostic angiography, as previously described.[9] Standardized measurement protocols for resting coronary distal pressure (Pd) to aortic pressure (Pa), FFR, CFR, and IMR were adopted before the beginning of the study. In brief, the pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100–200 μg) was administered before each physiologic measurement. Three injections of 4 mL room temperature saline were performed to obtain resting mean transit time (Tmn) by using a thermodilution curve. Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg per min) or intracoronary bolus injection of nicorandil (2 mg). Hyperemic Pa, Pd, and hyperemic Tmn were measured during sustained hyperemia after the pressure curve reached a nadir point. The hyperemic period was recognized by a decreased Pd/Pa pattern and a left shift in the Tmn. After measurements were complete, the guide wire was pulled back to the guide catheter, and the presence of a pressure drift was checked. With a drift larger than >0.03 FFR unit, re-equalizations and repeated measurements were recommended. Resting Pd/Pa was calculated as the ratio of mean Pd/mean Pa. CFR was calculated as resting Tmn/hyperemic Tmn. FFR was calculated as the lowest average of 3 consecutive beats during hyperemia. IMR was calculated by Pd×Tmn during hyperemia and expressed as U. All coronary physiologic data were collected and validated at a core laboratory (Samsung Medical Center) in a blinded manner.

Echocardiography

All patients underwent comprehensive 2-dimensional echocardiography within median 1.0 days (interquartile range, 0–16.3 days) before or after coronary angiography using commercially available ultrasound systems (Vivid 7, GE Medical Systems, Milwaukee, WI; Acuson 512, Siemens Medical Solution, Mountain View, CA; or Sonos 5500, Philips Medical System, Andover, MA). LVEF was assessed by the biplane Simpson technique, M-mode, or visual estimation. Left atrial volume was measured by the biplane method using dedicated apical 4- and 2-chamber views at the end-systolic frame to avoid foreshortening. The left atrial volume index was calculated as left atrial volume/body surface area (mL/m^2). Transmitral inflow velocities (E and A) and deceleration time were obtained by pulsed-wave Doppler analysis performed in the apical-4 chamber plane. Tissue Doppler imaging was used to get early (e') and late (a') atrial diastolic annular velocities in the apical 4-chamber view at the lateral and septal mitral annulus and averaged.[10] Right ventricular systolic pressure measurement was performed using peak tricuspid regurgitation velocity (TR V_{max}) recorded using continuous Doppler.

Definitions of Cardiac Diastolic Dysfunction and Overt CMD

Cardiac diastolic dysfunction was defined according to the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations.[10] Briefly, the 4 recommended variables and their abnormal cutoff values were used (annular e' velocity [septal e' <7 cm/s, lateral e' <10 cm/s], average E/e' ratio >14, left atrial volume index >34 mL/m^2, and TR V_{max} >2.8 m/s) and cardiac diastolic dysfunction was defined if more than half of the available parameters meet these cutoff values.

On the basis of the European Society of Cardiology guideline of Chronic Coronary Syndrome and recent Expert Consensus Documents, which proposed a universal definition of CMD based on (1) functionally nonobstructive coronary artery disease defined by an FFR >0.80 and (2) impaired coronary microvascular function determined by abnormal CFR or microvascular resistance,[7,8] and a previous study, which presented prognostic implication of CMD among patients with functionally insignificant epicardial coronary stenosis (FFR >0.80),[9] overt CMD was defined as having both depressed CFR (<2.0) and elevated IMR (≥25 U).

Outcome Measurement and Follow-Up

Clinical data were obtained by outpatient clinic visits or telephone contact. An independent clinical event committee, whose members were unaware of clinical,

echocardiographic, and physiologic data, adjudicated all events. For patients who were lost to follow-up, mortality data with cause of death were confirmed by National Death Records. The primary end point was cardiovascular death or admission for HF. Secondary outcomes were all-cause death, cardiovascular death, admission for HF, myocardial infarction (MI), any revascularization, and ischemic or hemorrhagic cerebrovascular accidents. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI. All deaths were considered cardiovascular unless a definitive noncardiovascular cause was identified. MI was defined as an elevation of creatine kinase–myocardial band or troponin level greater than the upper limit of normal with concomitant ischemic symptoms or electrocardiography findings indicative of ischemia. Admission for HF was defined as first hospitalization for HF. Hospitalization for HF should include all of the following criteria: (1) hospitalization with primary diagnosis of HF, (2) duration of hospitalization of at least 12 hours, (3) new or worsening symptoms of HF, (4) objective evidence of new or worsening HF on physical examination or laboratory findings, and (5) initiation or intensification of HF treatment.

Statistical Analysis

Data were analyzed on a per-patient basis. Among patients with multivessel physiologic interrogation, vessels with the highest IMR value were selected as representative vessels. Categorical variables are presented as numbers and relative frequencies (percentages), and continuous variables are presented as mean±SD. Student *t*-test and χ^2 test were used to compare continuous and categorical variables, respectively. Correlations were tested using Pearson or Spearman correlation coefficient, according to their distributions. Multivariable logistic regression analysis was fitted to evaluate the independent predictors associated with cardiac diastolic dysfunction. The multivariable model was constructed using all variables with a $P<0.10$ from the univariable analyses. Odds ratio (OR) and 95% CI were calculated. The cumulative incidence of clinical events was evaluated by Kaplan-Meier analyses, and the log-rank test was used to compare survival curves between groups. In comparisons of clinical outcomes according to cardiac diastolic dysfunction or overt CMD, the adjusted hazard ratio (HR) and 95% CI were calculated by a multivariable Cox proportional hazards model. The assumption of proportionality was assessed by the Schoenfeld residuals and graphically by the log-log plot. Adjusted covariates included age, sex, diabetes, and LVEF. For sensitivity analysis, competing risk analysis was performed, where noncardiovascular death was considered as a competing event for clinical outcomes including cardiovascular death and all-cause death was considered as a competing event for the other outcomes.[11] The incremental prognostic values of cardiac diastolic dysfunction and overt CMD, in addition to clinical risk factors, were assessed using the comparison of the Harrell C-index. All probability values were 2 sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics, According to Cardiac Diastolic Dysfunction or Overt CMD

Among the total population, mean age was 59.7±13.6 years, and one-third were women. Patients showed a mean LVEF of 63.2±6.3% and minimal epicardial coronary artery stenosis (mean percentage diameter stenosis, 37.0±21.9%; and mean FFR, 0.89±0.05). Distributions of echocardiographic parameters and invasive physiologic indexes are shown in Figures S2 and S3.

Among the study population, prevalence of cardiac diastolic dysfunction was 25.5% (84 patients). Patients with cardiac diastolic dysfunction showed higher proportion of chronic kidney disease and history of congestive HF, and higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) level. There were significant differences in echocardiographic parameters according to presence of cardiac diastolic dysfunction. Although there were no significant differences in angiographic lesion severity and FFR between the 2 groups, patients with cardiac diastolic dysfunction showed significantly lower CFR and numerically higher IMR (Table 1). The prevalence of overt CMD was 11.2% (37 patients), and patients with overt CMD showed higher prevalence of cardiovascular risk factors and significantly worse profiles in echocardiographic parameters than those without overt CMD (Table S1).

Association Between Cardiac Diastolic Dysfunction and Overt CMD

Figures S4 and S5 show the correlations between echocardiographic parameters (E/e', e', TR V_{max}, left atrial volume index, and LVEF) and invasive physiologic indexes (CFR, IMR, and FFR). There were significant but less than modest correlations between echocardiographic parameters and invasive physiologic indexes. CFR was negatively correlated with E/e' (R=−0.242; $P<0.001$) and TR V_{max} (R=−0.209; $P=0.001$). Conversely, IMR showed positive correlations with E/e' (R=0.186; $P=0.001$) and TR V_{max} (R=0.129; $P=0.036$).

Table 1. Baseline Characteristics, According to Cardiac Diastolic Dysfunction

Variables	Total (N=330)	No diastolic dysfunction (N=246)	Diastolic dysfunction (N=84)	*P* value
Demographics				
Age, y	59.7±13.6	59.3±14.1	60.9±12.3	0.346
Women	96 (29.1)	66 (26.8)	30 (35.7)	0.159
Body mass index, kg/m^2	23.4±3.8	23.5±3.8	23.1±3.9	0.415
Cardiovascular risk factors				
Hypertension	200 (60.6)	148 (60.2)	52 (61.9)	0.879
Diabetes	152 (46.1)	112 (45.5)	40 (47.6)	0.837
Hyperlipidemia	187 (56.7)	150 (61.0)	37 (44.0)	0.010
Chronic kidney disease	49 (14.8)	27 (11.0)	22 (26.2)	0.001
Current smoking	162 (49.1)	129 (52.4)	33 (39.3)	0.051
Family history of cardiovascular disease	85 (25.8)	62 (25.2)	23 (27.4)	0.803
Previous myocardial infarction	33 (10.0)	22 (8.9)	11 (13.1)	0.376
Previous congestive heart failure	157 (47.6)	105 (42.7)	52 (61.9)	0.004
Clinical presentation				0.002
Chest pain on exertion	173 (52.4)	142 (57.7)	31 (36.9)	
Dyspnea on exertion and/or chest pain	157 (47.6)	104 (42.3)	53 (63.1)	
Presumed diagnosis before coronary angiography				0.006
Stable ischemic heart disease	194 (58.8)	157 (63.8)	37 (44.0)	
Unstable angina	12 (3.6)	8 (3.3)	4 (4.8)	
Heart failure with preserved ejection fraction	124 (37.6)	81 (32.9)	43 (51.2)	
Hemodynamic parameters				
Systolic blood pressure, mm Hg	120.8±17.2	121.4±16.9	118.9±18.1	0.276
Diastolic blood pressure, mm Hg	72.8±10.6	73.3±10.6	71.3±10.6	0.157
Heart rate, beats/min	78.5±14.9	78.0±14.2	79.8±16.9	0.402
Laboratory findings				
High-sensitivity CRP, mg/dL	0.8±6.2	0.8±7.1	0.7±2.0	0.832
Low-density lipoprotein, mg/dL	92.2±37.3	92.4±37.0	91.8±38.8	0.911
Serum creatinine, mg/dL	1.0±0.6	0.9±0.3	1.1±1.1	0.120
NT-proBNP, pg/mL	2667.8±4659.3	1613.0±2891.9	5193.7±6711.3	<0.001
Range of NT-proBNP, pg/mL				<0.001
<125	67 (26.0)	61 (33.5)	6 (7.9)	
≥125 and <900	68 (26.4)	55 (30.2)	13 (17.1)	
≥900	123 (47.7)	66 (36.3)	57 (75.0)	
Echocardiographic findings				
Ejection fraction, %	63.2±6.3	63.6±6.2	62.0±6.7	0.049
LVEDD, mm	47.4±5.0	47.9±4.9	45.9±5.1	0.002
LVESD, mm	28.7±4.2	28.9±4.1	28.3±4.2	0.321
Septal wall thickness, mm	9.9±2.1	9.6±1.8	11.0±2.3	<0.001
Posterior wall thickness, mm	9.5±1.7	9.2±1.5	10.3±2.0	<0.001
LA volume index, mL/m^2	45.0±20.8	42.1±21.4	53.3±16.6	<0.001
E velocity, cm/s	71.9±21.7	68.5±20.2	81.2±23.2	<0.001
A velocity, cm/s	60.8±27.7	60.4±24.4	62.1±35.5	0.702
e' velocity, cm/s	6.5±2.3	7.2±2.2	4.5±1.3	<0.001
a' velocity, cm/s	7.9±2.6	8.3±2.5	6.5±2.5	<0.001
E/e'	12.6±6.4	10.1±3.1	19.4±8.2	<0.001
Peak TR velocity, m/s	2.4±0.3	2.3±0.3	2.6±0.4	<0.001
RV systolic pressure, mm Hg	29.2±8.1	27.5±6.2	34.8±10.8	<0.001

(*Continued*)

Table 1. Continued

Variables	Total (N=330)	No diastolic dysfunction (N=246)	Diastolic dysfunction (N=84)	*P* value
Medications at discharge				
Antiplatelet agent	138 (41.8)	115 (46.7)	23 (27.4)	0.003
Oral anticoagulant	20 (6.1)	14 (5.7)	6 (7.1)	0.828
β-Blocker	70 (21.2)	59 (24.0)	11 (13.1)	0.051
ACE inhibitor or ARB	76 (23.0)	59 (240)	17 (20.2)	0.580
Statin	198 (60.0)	160 (65.0)	38 (45.2)	0.002
Nitrate	110 (33.4)	94 (38.4)	16 (19.0)	0.002
Calcium channel blocker	88 (26.7)	68 (27.6)	20 (23.8)	0.587
Interrogated vessels				0.038
Left anterior descending artery	256 (77.6)	183 (74.4)	73 (86.9)	
Left circumflex artery	39 (11.8)	35 (14.2)	4 (4.8)	
Right coronary artery	35 (10.6)	28 (11.4)	7 (8.3)	
Coronary angiographic parameters				
Angiographic disease extent				0.153
Insignificant stenosis	169 (51.2)	117 (47.6)	52 (61.9)	
1-Vessel disease	58 (17.6)	46 (18.7)	12 (14.3)	
2-Vessel disease	65 (19.7)	53 (21.5)	12 (14.3)	
3-Vessel disease	38 (11.5)	30 (12.2)	8 (9.5)	
Reference vessel diameter, mm	3.0±0.5	3.0±0.6	3.0±0.5	0.777
Diameter stenosis, %	37.0±21.9	38.4±21.8	32.4±21.9	0.080
Lesion length, mm	13.5±9.9	13.9±9.8	12.3±10.2	0.351
SYNTAX score	5.2±5.9	5.9±6.1	3.2±4.8	0.019
Coronary physiologic parameters				
Resting Pd/Pa	0.95±0.04	0.95±0.04	0.94±0.03	0.051
FFR	0.89±0.05	0.89±0.05	0.90±0.04	0.053
Resting mean transit time, s	0.89±0.49	0.92±0.51	0.78±0.41	0.013
Hyperemic mean transit time, s	0.32±0.22	0.30±0.19	0.36±0.30	0.082
CFR	3.2±1.6	3.4±1.6	2.8±1.5	0.002
IMR, U	22.6±14.4	21.8±12.8	25.1±18.2	0.131

Cardiac diastolic dysfunction was defined according to 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations for the evaluation of left ventricular diastolic function. Data are presented as mean±SD or number (percentage). A indicates late diastolic transmitral flow velocity; a', late diastolic mitral annular velocity; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CFR, coronary flow reserve; CRP, C-reactive protein; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LA, left atrial; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Pa, aortic pressure; Pd, distal pressure; RV, right ventricular; SYNTAX, Synergy Between PCI (Percutaneous Coronary Intervention) With Taxus and Cardiac Surgery; and TR, tricuspid regurgitation.

Neither CFR nor IMR showed significant correlation with left atrial volume index (R=−0.054; *P*=0.334 for CFR; R=−0.004; *P*=0.937 for IMR) or LVEF (R=−0.005; *P*=0.931 for CFR; R=−0.049; *P*=0.375 for IMR) (Figure S4). FFR showed no significant correlation with echocardiographic parameters (Figure S5).

When proportion of overt CMD was compared according to presence of cardiac diastolic dysfunction, patients with cardiac diastolic dysfunction showed higher proportion of overt CMD (7.3% versus 22.6%; *P*<0.001). Although 22.2% of patients without overt CMD showed cardiac diastolic dysfunction, conversely, more than half of patients with overt CMD had cardiac diastolic dysfunction (*P*<0.001) (Figure 1). In multivariable logistic regression analysis, presence of overt CMD was independently associated with cardiac diastolic dysfunction (adjusted OR, 3.440 [95% CI, 1.599–7.401]; *P*=0.002) (Table 2).

Clinical Outcomes, According to Cardiac Diastolic Dysfunction or Overt CMD

During median follow-up of 1256.5 days (quartile 1–quartile 3, 890.8–1655.5 days), patients with cardiac diastolic dysfunction showed significantly higher risk of cardiovascular death or admission for HF (43.6% versus 18.5%; adjusted HR, 2.996 [95% CI, 1.888–4.755]; *P*<0.001) than those without cardiac

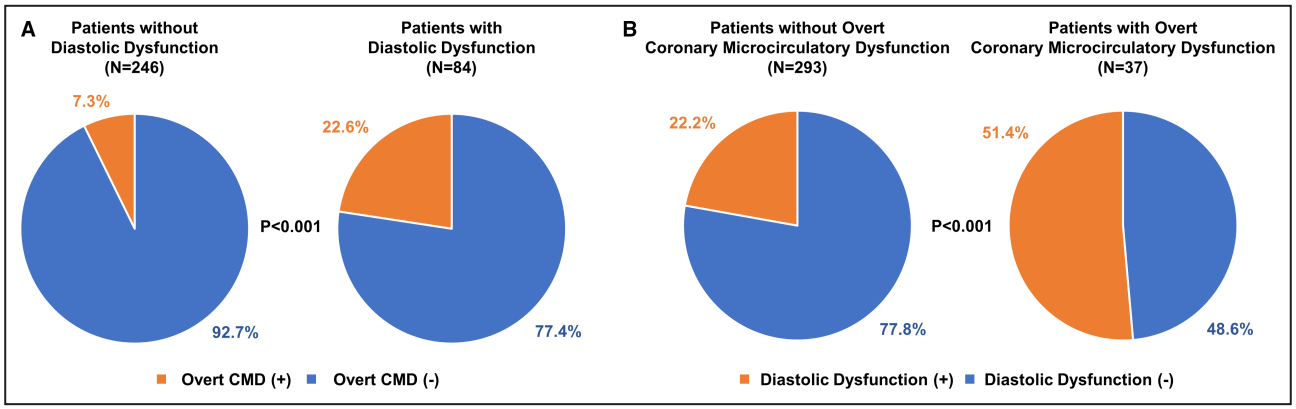


Figure 1. Proportion of overt CMD and cardiac diastolic dysfunction.
A, Proportions of overt CMD, according to the presence of cardiac diastolic dysfunction, are shown. **B**, Proportions of cardiac diastolic dysfunction, according to the presence of overt CMD, are shown. CMD indicates coronary microvascular dysfunction.

diastolic dysfunction (Table 3). Presence of cardiac diastolic dysfunction showed significantly increased risk of both cardiovascular death and admission for HF (Figure S6). However, there were no significant differences in the risk of MI, any revascularization, or cerebrovascular accident between the 2 groups (Table 3).

Similarly, patients with overt CMD had significantly higher risk of cardiovascular death or admission for HF (43.2% versus 22.7%; adjusted HR, 2.939 [95% CI, 1.642–5.261]; *P*<0.001) than those without overt CMD (Table 4). Overt CMD related with increased risk of both cardiovascular death and admission for HF (Figure S7). As with cardiac diastolic dysfunction, no significant differences were observed in the risk of MI, any revascularization, or cerebrovascular accident, according to presence of overt CMD (Table 4). Furthermore, overall results were consistent when competing risk analyses were performed (Tables S2 and S3).

Cumulative incidence of cardiovascular death or admission for HF was significantly different according to the presence of diastolic dysfunction and overt CMD (no diastolic dysfunction and overt CMD, 17.4%; overt CMD without diastolic dysfunction, 33.3%; diastolic dysfunction without overt CMD, 41.4%; both diastolic dysfunction and overt CMD, 52.6%; overall *P*<0.001) (Figure 2).

Table 2. Independent Predictors of Cardiac Diastolic Dysfunction

	Univariable analysis		Multivariable analysis*	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.009 (0.990–1.028)	0.359		
Women	1.538 (0.907–2.611)	0.110		
Body mass index	0.973 (0.911–1.039)	0.414		
Diabetes	1.080 (0.657–1.774)	0.763		
Hyperlipidemia	0.504 (0.305–0.832)	0.007	0.517 (0.300–0.890)	0.017
Chronic kidney disease	2.865 (1.526–5.377)	0.001	2.864 (1.407–5.829)	0.004
Previous myocardial infarction	1.527 (0.707–3.301)	0.281		
Previous congestive heart failure	2.182 (1.313–3.626)	0.003	1.651 (0.900–3.03)	0.105
Current smoking	0.582 (0.351–0.964)	0.035	0.591 (0.339–1.032)	0.064
Fractional flow reserve (per 0.01 increase)	1.053 (0.999–1.111)	0.056	1.020 (0.959–1.084)	0.530
Ejection fraction (per 1% increase)	0.961 (0.922–1.000)	0.053	0.969 (0.927–1.013)	0.162
SYNTAX score	0.915 (0.848–0.987)	0.021	0.957 (0.883–1.037)	0.279
Overt coronary microvascular dysfunction†	3.686 (1.828–7.432)	<0.001	3.440 (1.599–7.401)	0.002

Discriminant ability of multivariable logistic regression models was 0.732 (0.669–0.795). OR indicates odds ratio; and SYNTAX, Synergy Between PCI (Percutaneous Coronary Intervention) With Taxus and Cardiac Surgery.
*The multivariable model was constructed using all variables with a *P*<0.10 from the univariable analyses.
†Overt coronary microvascular dysfunction was defined as coronary flow reserve <2.0 and index of microcirculatory resistance ≥25 U.

Table 3. Clinical Outcomes at 5 Years, According to Cardiac Diastolic Dysfunction

Variable	No diastolic dysfunction (N=246)*	Diastolic dysfunction (N=84)*	Univariate analysis		Multivariable analysis†	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cardiovascular death or admission for heart failure	41 (18.5)	35 (43.6)	3.098 (1.970–4.870)	<0.001	2.996 (1.888–4.755)	<0.001
Cardiovascular death	10 (5.4)	14 (21.0)	4.824 (2.137–10.890)	<0.001	4.251 (1.847–9.785)	0.001
All-cause death	11 (5.8)	17 (24.1)	5.250 (2.453–11.230)	<0.001	4.834 (2.223–10.513)	<0.001
Myocardial infarction	1 (0.9)	1 (1.2)	3.736 (0.230–60.730)	0.354	2.229 (0.111–44.791)	0.600
Any revascularization	7 (4.1)	4 (6.0)	2.055 (0.598–7.067)	0.253	1.942 (0.555–6.795)	0.299
Admission for heart failure	33 (14.2)	28 (34.2)	2.975 (1.796–4.927)	<0.001	2.990 (1.782–5.016)	<0.001
Cerebrovascular accident	3 (2.2)	2 (2.6)	2.366 (0.391–14.310)	0.348	2.825 (0.446–17.909)	0.270

Cumulative incidence of events was presented as Kaplan-Meier estimates. HR indicates hazard ratio.
*Values are number (percentage).
†Adjusted variables included age, sex, diabetes, and left ventricular ejection fraction.

Prognostic Implications of Cardiac Diastolic Dysfunction and Overt CMD

Prognostic impact of overt CMD on cardiovascular death or admission for HF was different according to presence of combined cardiac diastolic dysfunction. Overt CMD was significantly associated with the increased risk of cardiovascular death among patients with cardiac diastolic dysfunction. Conversely, it was significantly associated with the increased risk of admission for HF among patients without cardiac diastolic dysfunction. Significant interaction between cardiac diastolic dysfunction and overt CMD was observed for both the risk of cardiovascular death (interaction *P*<0.001) and admission for HF (interaction *P*=0.002) (Figure 3).

Furthermore, incremental prognostic value was observed when cardiac diastolic dysfunction was added to the model with clinical risk factors only (C-index, 0.625 versus 0.719; *P*<0.001) for the occurrence of cardiovascular death or admission for HF. Integration of overt CMD into the model with clinical risk factors and cardiac diastolic dysfunction further increased the discrimination ability for cardiovascular death or admission for HF (C-index, 0.719 versus 0.737; *P*=0.034) (Figure 4).

Stratification of CMD, According to Patterns of CFR and IMR

Proportion of diastolic dysfunction and cumulative incidence of cardiovascular death or admission for HF were both significantly different according to patterns of CFR and IMR (all overall *P*<0.001). Patients with overt CMD (depressed CFR [<2.0] and elevated IMR [≥25 U]) had both the highest proportion of diastolic dysfunction and cumulative incidence of the primary end point (Figure S8).

DISCUSSION

In the current study, we investigated the association between cardiac diastolic dysfunction and overt CMD, and their prognostic implications in patients without significant LV systolic dysfunction and epicardial coronary stenosis. The main findings were as follows. First, there was substantial proportion of overlap between cardiac diastolic dysfunction and overt CMD, and the presence of overt CMD was an independent predictor of cardiac diastolic dysfunction. Second, both cardiac diastolic dysfunction and overt CMD were significantly

Table 4. Clinical Outcomes at 5 Years, According to Presence of Overt CMD

Variable	No Overt CMD (N=293)*	Overt CMD (N=37)*	Univariate analysis		Multivariable analysis†	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Cardiovascular death or admission for heart failure	60 (22.7)	16 (43.2)	2.601 (1.498–4.518)	0.001	2.939 (1.642–5.261)	<0.001
Cardiovascular death	17 (7.7)	7 (22.0)	3.563 (1.477–8.592)	0.005	3.014 (1.197–7.590)	0.019
All-cause death	19 (8.4)	9 (26.2)	4.085 (1.848–9.030)	0.001	3.541 (1.530–8.195)	0.003
Myocardial infarction	2 (1.2)	0 (0)	NA	NA	NA	NA
Any revascularization	11 (5.2)	0 (0)	NA	NA	NA	NA
Admission for heart failure	47 (16.9)	14 (38.1)	2.883 (1.586–5.238)	0.001	3.801 (2.008–7.195)	<0.001
Cerebrovascular accident	4 (2.3)	1 (2.9)	2.138 (0.468–19.140)	0.497	4.959 (0.380–64.754)	0.222

Overt CMD was defined as coronary flow reserve <2.0 and index of microcirculatory resistance ≥25 U. Cumulative incidence of events was presented as Kaplan-Meier estimates. CMD indicates coronary microvascular dysfunction; HR, hazard ratio; and NA, not applicable.
*Values are number (percentage).
†Adjusted variables included age, sex, diabetes, and left ventricular ejection fraction.

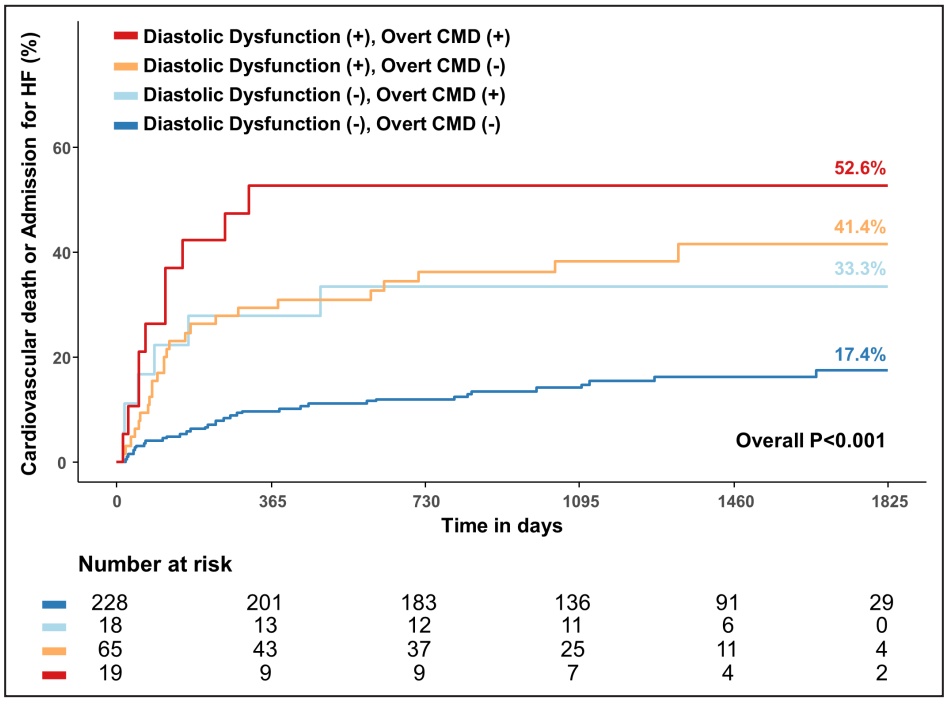


Figure 2. Cumulative incidence of cardiovascular death or admission for HF, according to diastolic dysfunction and overt coronary microvascular disease.
Cumulative incidences of cardiovascular death or admission for HF are presented, according to the presence of cardiac diastolic dysfunction and overt CMD. CMD indicates coronary microvascular dysfunction; and HF, heart failure.

associated with an increased risk of cardiovascular death and admission for HF. Prognostic impact of overt CMD was differently observed according to the presence of cardiac diastolic dysfunction, with significant interaction between 2 disease entities. Third, both cardiac diastolic dysfunction and overt CMD showed incremental discrimination abilities, in addition to clinical risk factors, to predict cardiovascular death or admission for HF.

Clinical Relevance of Cardiac Diastolic Dysfunction and CMD in Patients Without Significant LV Systolic Dysfunction or Coronary Artery Stenosis

Cardiac diastolic dysfunction could be an important cause for symptomatic patients without LV structural abnormality.[12] Cardiac diastolic dysfunction is a multifactorial process associated with impaired relaxation

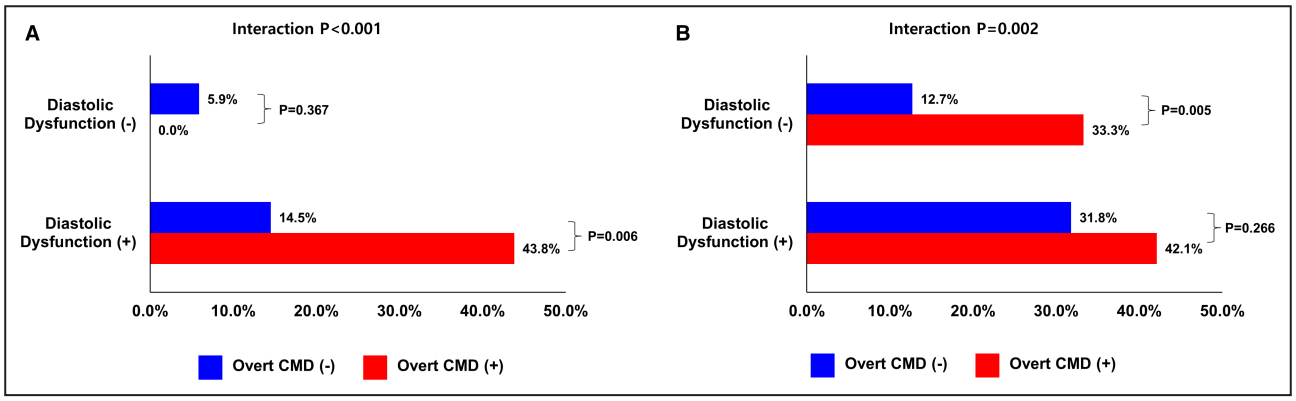
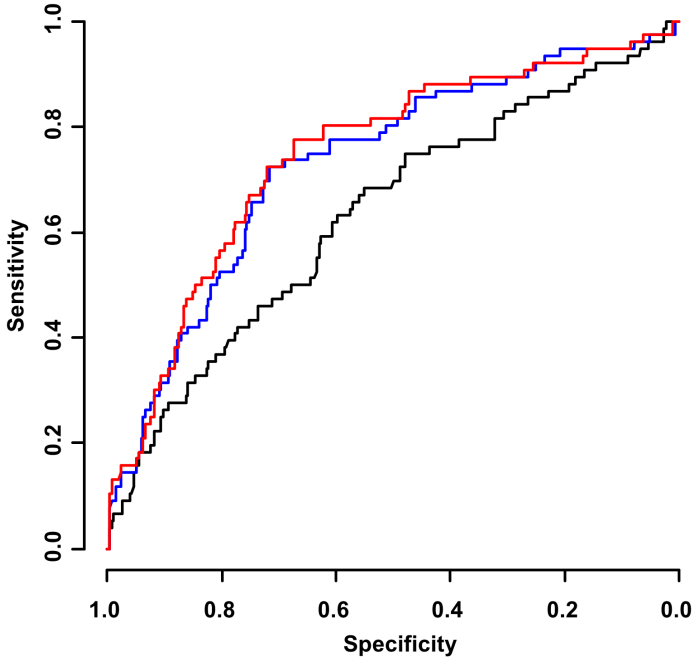


Figure 3. Risk of cardiovascular death or admission for heart failure, according to the presence of overt CMD, in patients with or without cardiac diastolic dysfunction.
Cumulative incidences of cardiovascular death (**A**) and admission for heart failure (**B**) are presented, according to the presence of cardiac diastolic dysfunction and overt CMD. Significant interaction between cardiac diastolic dysfunction and overt CMD was observed for both the risk of cardiovascular death (interaction *P*<0.001) and admission for heart failure (interaction *P*=0.002). CMD indicates coronary microvascular dysfunction.



	Models	C-index	95% CI	Vs. Model 1	Vs. Model 2
Model 1	Clinical Risk Factors	0.625	0.559-0.690		
Model 2	Model 1 + Diastolic Dysfunction	0.719	0.661-0.776	<0.001	
Model 3	Model 2 + Overt CMD	0.737	0.681-0.794	<0.001	0.034

Figure 4. Incremental prognostic impact of overt CMD and diastolic dysfunction to predict cardiovascular death or admission for heart failure.
To explore the additive prognostic impact of cardiac diastolic dysfunction and overt CMD in addition to clinical risk factors, the discrimination abilities of 3 models for the risk of cardiovascular death or admission for heart failure were compared: (1) model 1 included clinical risk factors (age, sex, diabetes, and left ventricular ejection fraction); (2) model 2 added cardiac diastolic dysfunction to model 1; and (3) model 3 added overt CMD into model 2. C-index, indicates concordance index; and CMD, coronary microvascular dysfunction.

and increased stiffness of LV, leading to elevated filling pressures, and an independent predictor of mortality, regardless of LV systolic function.[1] Although hemodynamic consequences and prognostic importance of cardiac diastolic dysfunction are well known, debate remains about its definition and underlying mechanisms.[12] Previous studies suggested that CMD might play an important role in the development and progression of cardiac diastolic dysfunction and HFpEF.[13] It was also consistently reported that CMD is associated with myocardial ischemia and a higher risk of clinical events in patients without significant epicardial coronary artery stenosis.[9,14] In this regard, increased awareness of both cardiac diastolic dysfunction and CMD and clarifying their relationship would be important to further understand the cause of patients' symptoms, to develop an effective treatment strategy, and to identify high-risk patients.

A significant number of patients with prominent symptoms did not meet the criteria for CMD or diastolic dysfunction. This is in line with previous studies that presented the proportion of CMD or diastolic dysfunction in patients with angina without significant epicardial coronary stenosis.[15,16] As supported by high incidence of clinical events in this population in the current study, they should not be considered as normal population. Especially, because of the difference of diagnostic criteria between diastolic dysfunction and HFpEF, some patients with HFpEF may have been classified into groups without diastolic dysfunction or CMD.[10,17] These results imply that although assessing CMD and diastolic dysfunction is important, they could not explain all symptoms and further systemic causative evaluation is also important.

Association Between Cardiac Diastolic Dysfunction and CMD

Preclinical studies have presented possible associations among the presence of endothelial dysfunction and CMD, increased myocardial inflammation, interstitial fibrosis, microvascular rarefaction, and progression of cardiac diastolic dysfunction through multiple biologic pathways.[13] A recent clinical study presented a significant association between elevated LV filling pressure (E/e' >15) and depressed positron emission tomography–derived global CFR (<2.0).[4] The PROMIS-HFpEF (PRevalence Of MIcrovascular dySfunction in Heart Failure with Preserved Ejection Fraction) registry also showed that CMD, defined by depressed Doppler echocardiography-derived CFR in left anterior descending artery (<2.5), was associated with systemic endothelial dysfunction and elevated NT-proBNP level.[6] Similar association was shown by Kato et al, in which CMD was defined by depressed magnetic resonance imaging–derived global CFR (<2.5).[5]

However, these studies considered depressed global CFR from noninvasive imaging studies as a specific marker of CMD, and the presence of epicardial coronary stenosis was not evaluated by angiography with FFR measurements. Global CFR cannot fully differentiate regional perfusion abnormalities because of flow-limiting epicardial stenosis from diffuse atherosclerosis or CMD.[18] Moreover, depressed CFR can be caused by increased resting coronary flow without decreased hyperemic coronary flow or increased microvascular resistance, which are key physiologic changes with CMD. Therefore, depressed CFR alone does not necessarily imply the presence of CMD, whereas invasive physiologic assessment of both CFR and IMR could be a more specific method to define overt CMD originating from depressed vascular reserve and increased microvascular resistance.[7–9] Furthermore, a previous study presented that only patients with overt CMD, defined by both depressed CFR and elevated IMR, showed significantly increased risk of clinical events at 2 years in the absence of functionally significant epicardial coronary stenosis (FFR >0.80).[9] A recent cross-sectional study by Dryer et al showed a significantly higher incidence of overt CMD in patients with HFpEF than control subjects.[19] Similarly, a recent study by Rush et al investigated the prevalence of overt CMD in patients with HFpEF; however, this study did not exclude patients with significant epicardial coronary stenosis, and 51% of patients had obstructive coronary artery stenosis.[20] In the current study, more than half of patients with overt CMD showed cardiac diastolic dysfunction, and overt CMD was an independent predictor of cardiac diastolic dysfunction. Although a causal relationship could not be clarified, the current results support the significant association of overt CMD with cardiac diastolic dysfunction in symptomatic patients without significant LV systolic dysfunction and functionally significant epicardial coronary artery stenosis. For other independent predictors of cardiac diastolic dysfunction, such as hyperlipidemia and chronic kidney disease, previous studies demonstrated the possible association of hyperlipidemia and chronic kidney disease with cardiac diastolic dysfunction.[3,21] However, a causal relationship is still uncertain, and results should be interpreted as exploratory.

Prognostic Implications of Cardiac Diastolic Dysfunction and CMD

Despite significant association between cardiac diastolic dysfunction and overt CMD, the presence of overt CMD did not necessarily indicate the presence of cardiac diastolic dysfunction, and vice versa. Indeed, only 22.6% of patients with cardiac diastolic dysfunction showed overt CMD, and 7.3% of patients without cardiac diastolic dysfunction had overt CMD. These results imply that both cardiac diastolic dysfunction and CMD have diverse underlying mechanisms, despite their close association. This hypothesis was further supported by prognostic impact of cardiac diastolic dysfunction and CMD.

In the current study, the presence of cardiac diastolic dysfunction showed 3-fold increased risk of cardiovascular death or admission for HF than those without cardiac diastolic dysfunction. Although this result was in line with a previous study by Taqueti et al, possible epicardial coronary stenosis could not be excluded in that study.[4] Therefore, the results from the study by Taqueti et al should be interpreted with caution, and the increased risk of cardiovascular death could not be solely originated from the presence of cardiac diastolic dysfunction.

Conversely, the current study exclusively evaluated patients without functionally significant epicardial stenosis, defined by FFR >0.80. Similarly with cardiac diastolic dysfunction, overt CMD was also associated with significantly higher risk of cardiovascular death or admission for HF than those without overt CMD. Interestingly, there were different patterns in adverse event profiles according to the presence of cardiac diastolic dysfunction and overt CMD. The presence of overt CMD was significantly associated with the increased risk of cardiovascular death in patients who had already developed cardiac diastolic dysfunction. In contrast, overt CMD was associated with the increased risk of hospitalization attributable to HF among patients without cardiac diastolic dysfunction. More important, the integration of overt CMD into cardiac diastolic dysfunction further raised discriminant ability for the risk of cardiovascular death or admission for HF. These results suggest that integration of well-established noninvasive and invasive indexes for cardiac diastolic dysfunction and overt CMD has the potential to better

understand the patient's presentation and provide incremental prognostic implications.

Study Limitations

This study has several limitations. First, because of the nonrandomized nature of these registry data, the inherent limitations of residual confounding factors should be considered. Consequently, the results of this study should be interpreted as exploratory and hypothesis generating. Nevertheless, current results from unrestricted prospective registry might increase the generalizability of the current results. Second, selection bias should be considered. The current study mainly evaluated patients who underwent clinically indicated invasive angiography with preserved LV systolic function and without functionally significant epicardial stenosis; therefore, the results cannot be extrapolated to patients with depressed LV systolic dysfunction or with functionally significant epicardial coronary stenosis. Also, as we mainly included patients with prominent symptoms, the results cannot be generalized to patients with mild or no symptoms. However, the population of this study might be the population for which the current results are most applicable and clinically beneficial. Third, we could not evaluate dynamic progression of disease process in cardiac diastolic dysfunction and CMD according to medical treatment. Fourth, noninvasive ischemia testing for CMD could not be systematically collected. However, the current study used well-validated invasive physiologic indexes. Fifth, we could not systematically collect data on the underlying pathology of cardiac diastolic dysfunction, such as hypertensive or infiltrative cardiomyopathy. Sixth, because IMR was measured mainly in left anterior descending coronary artery as representative vessel, this study did not reflect the difference in IMR value among target vessels.

CONCLUSIONS

There was significant association between the presence of cardiac diastolic dysfunction and overt CMD. Both cardiac diastolic dysfunction and overt CMD were associated with increased risk of cardiovascular death or admission for HF. Integration of overt CMD into cardiac diastolic dysfunction showed improvement of the risk stratification in patients without significant LV systolic dysfunction and epicardial coronary stenosis.

ARTICLE INFORMATION

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Supplemental Material

Data S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics According to Presence of Overt Coronary Microvascular Dysfunction*

Variables	No Overt CMD (N=293)	Overt CMD (N=37)	P value
Demographics			
Age, years	59.1 ± 13.6	64.8 ± 12.8	0.017
Female	83 (28.3)	13 (35.1)	0.505
Body mass index, kg/m^2	23.4 ± 3.9	23.6 ± 3.4	0.786
Cardiovascular Risk Factors			
Hypertension	182 (62.1)	18 (48.6)	0.161
Diabetes mellitus	142 (48.5)	10 (27.0)	0.022
Hyperlipidemia	172 (58.7)	15 (40.5)	0.054
Chronic kidney disease	45 (15.4)	4 (10.8)	0.626
Current smoking	152 (51.9)	10 (27.0)	0.007
Family history of cardiovascular disease	81 (27.6)	4 (10.8)	0.045
Previous myocardial infarction	33 (11.3)	0 (0)	0.063
Previous congestive heart failure	143 (48.8)	14 (37.8)	0.278
Clinical presentation			0.016
Chest pain on exertion	161 (54.9)	12 (32.4)	
Dyspnea on exertion and/or chest pain	132 (45.1)	25 (67.6)	
Presumed diagnosis before coronary angiography			0.010
Stable ischemic heart disease	179 (61.1)	15 (40.5)	
Unstable angina	12 (4.1)	0 (0)	
Heart failure with preserved ejection fraction	102 (34.8)	22 (59.5)	
Hemodynamic Parameters			
Systolic blood pressure, mmHg	121.5 ± 17.0	115.4 ± 18.6	0.056
Diastolic blood pressure, mmHg	73.2 ± 10.6	69.1 ± 10.1	0.037
Heart rate, beats/min	78.4 ± 15.3	78.7 ± 11.9	0.929
Laboratory Findings			
High sensitivity CRP, mg/dL	0.8 ± 6.6	0.5 ± 0.8	0.485

Low density lipoprotein, mg/dL	91.1 ± 35.2	105.6 ± 57.1	0.253
Serum creatinine, mg/dL	1.0 ± 0.7	0.9 ± 0.3	0.705
N-terminal pro-B-type natriuretic peptide, pg/mL	2,629.5 ± 4,870.7	2,938.3 ± 2,774.2	0.601
Range of N-terminal pro-B-type natriuretic peptide			0.013
<125 pg/mL	62 (27.4)	5 (15.6)	
≥125 pg/mL and <900 pg/mL	64 (28.3)	4 (12.5)	
≥ 900 pg/mL	100 (44.2)	23 (71.9)	
Echocardiographic Findings			
Ejection fraction, %	63.4 ± 6.3	62.0 ± 6.4	0.215
LVEDD, mm	47.4 ± 5.0	47.7 ± 5.6	0.741
LVESD, mm	28.6 ± 4.1	29.7 ± 4.4	0.140
Septal wall thickness, mm	9.8 ± 1.9	11.4 ± 2.9	0.002
Posterior wall thickness, mm	9.4 ± 1.5	10.5 ± 2.7	0.016
LA volume index, ml/m^2	44.6 ± 21.3	48.5 ± 16.9	0.283
E velocity, cm/s	70.8 ± 20.0	79.9 ± 31.3	0.113
A velocity, cm/s	60.4 ± 27.2	64.2 ± 31.7	0.478
e' velocity, cm/s	6.7 ± 2.3	5.1 ± 2.2	<0.001
a' velocity, cm/s	8.0 ± 2.5	6.8 ± 3.5	0.067
E/e'	11.8 ± 5.3	18.5 ± 10.4	0.001
Peak TR velocity, m/s	2.3 ± 0.3	2.7 ± 0.4	<0.001
RV systolic pressure, mmHg	28.1 ± 6.9	37.1 ± 11.4	<0.001
Echocardiographic diastolic dysfunction[†]			<0.001
None	155 (52.9)	7 (18.9)	
Indeterminate	73 (24.9)	11 (29.7)	
Diastolic dysfunction	65 (22.2)	19 (51.4)	
Diastolic dysfunction grade			0.762
Grade 1	11 (16.9)	3 (15.8)	
Grade 2	28 (43.1)	7 (36.8)	
Grade 3	21 (32.3)	6 (31.6)	

Cannot determine grade	5 (7.7)	3 (15.8)	
Medications at Discharge			
Antiplatelet agent	127 (43.3)	11 (29.7)	0.160
Oral anticoagulant	19 (6.5)	1 (2.7)	0.587
Beta-blocker	66 (22.5)	4 (10.8)	0.153
ACE inhibitor or ARB	72 (24.6)	4 (10.8)	0.096
Statin	182 (62.1)	16 (43.2)	0.042
Nitrate	102 (34.9)	8 (21.6)	0.152
Calcium channel blocker	81 (27.6)	7 (18.9)	0.350
Interrogated Vessels			0.198
Left anterior descending artery	223 (76.1)	33 (89.2)	
Left circumflex artery	37 (12.6)	2 (5.4)	
Right coronary artery	33 (11.3)	2 (5.4)	
Coronary Angiographic Parameters			
Angiographic disease extent			0.261
Insignificant stenosis	147 (50.2)	22 (59.5)	
1-vessel disease	50 (17.1)	8 (21.6)	
2-vessel disease	59 (20.1)	6 (16.2)	
3-vessel disease	37 (12.6)	1 (2.7)	
Reference vessel diameter, mm	3.0 ± 0.5	2.9 ± 0.5	0.525
Diameter stenosis, %	36.9 ± 22.1	37.7 ± 20.5	0.860
Lesion length, mm	13.5 ± 10.1	12.6 ± 8.4	0.746
SYNTAX score	5.4 ± 5.7	4.1 ± 7.3	0.417
Coronary Physiologic Parameters			
Resting Pd/Pa	0.95 ± 0.04	0.92 ± 0.03	<0.001
FFR	0.89 ± 0.05	0.89 ± 0.04	0.712
Resting mean transit time, s	0.89 ± 0.49	0.87 ± 0.42	0.853
Hyperemic mean transit time, s	0.27 ± 0.16	0.65 ± 0.32	<0.001
CFR	3.5 ± 1.5	1.4 ± 0.3	<0.001

IMR, Unit	20.1 ± 11.5	42.9 ± 19.0	<0.001

Data are presented as mean ± standard deviation, or n (%).

*Overt CMD was defined as CFR <2.0 and IMR ≥25U.

†Echocardiographic diastolic dysfunction was defined according to 2016 ASE/EACVI recommendations for the evaluation of left ventricular diastolic function.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CRP, C-reactive protein; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LA, left atrium; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; Pa, aortic pressure; Pd, distal pressure; RV, right ventricle; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; TR, tricuspid regurgitation.

Table S2. Competing Risk Analysis of Clinical Outcomes According to Cardiac Diastolic Dysfunction*

	No Diastolic Dysfunction (N=246)	Diastolic Dysfunction (N=84)	Univariate analysis		Multivariable analysis†	
			HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or admission for heart failure	41 (18.5)	35 (43.4)	3.081 (1.963–4.838)	<0.001	2.978 (1.890–4.691)	<0.001
Cardiovascular death	10 (5.4)	14 (20.4)	4.695 (2.105–10.475)	<0.001	4.156 (1.825–9.463)	0.001
All-cause death	-	-	-	-	-	-
Myocardial infarction	1 (0.9)	1 (1.2)	3.251 (0.234–45.238)	0.380	1.898 (0.197–18.294)	0.580
Any revascularization	7 (4.0)	4 (5.2)	1.806 (0.538–6.067)	0.340	1.737 (0.531–5.681)	0.360
Admission for heart failure	33 (14.1)	28 (33.6)	2.902 (1.753–4.801)	<0.001	2.924 (1.772–4.825)	<0.001
Cerebrovascular accident	3 (2.1)	2 (2.4)	2.128 (0.372–12.169)	0.400	NA	NA

Values are *n* (%). Cumulative incidence of events was presented as Kaplan-Meier estimates.
*For clinical outcomes including cardiovascular death, non-cardiovascular death was treated as a competing event. For other outcomes, all-cause death was treated as a competing event.
†Adjusted variables included age, sex, diabetes mellitus, and left ventricular ejection fraction.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Table S3. Competing Risk Analysis of Clinical Outcomes According to Overt Coronary Microvascular Dysfunction*

	No Overt CMD† (N=293)	Overt CMD† (N=37)	Univariate analysis		Multivariable analysis‡	
			HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death or admission for heart failure	60 (22.7)	16 (43.2)	2.603 (1.457–4.651)	0.001	2.942 (1.522–5.687)	0.001
Cardiovascular death	17 (7.7)	7 (20.8)	3.370 (1.396–8.137)	0.007	2.884 (1.030–8.077)	0.044
All-cause death	-	-	-	-	-	-
Myocardial infarction	2 (1.1)	0 (0)	NA	NA	NA	NA
Any revascularization	11 (5.0)	0 (0)	NA	NA	NA	NA
Admission for heart failure	47 (16.7)	14 (37.8)	2.860 (1.540–5.310)	0.001	3.780 (1.822–7.844)	<0.001
Cerebrovascular accident	4 (2.2)	1 (2.7)	1.917 (0.210–17.487)	0.560	NA	NA

Values are *n* (%). Cumulative incidence of events was presented as Kaplan-Meier estimates.

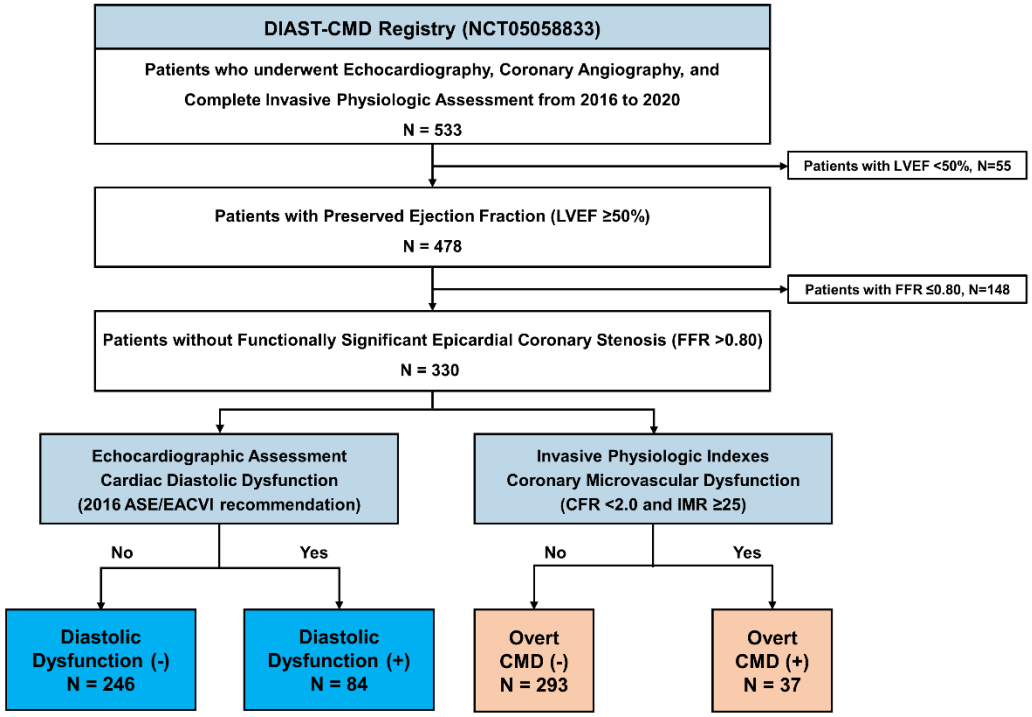
*For clinical outcomes including cardiovascular death, non-cardiovascular death was treated as a competing event. For other outcomes, all-cause death was treated as a competing event.

†Overt CMD was defined as CFR<2.0 and IMR ≥25U.

‡Adjusted variables included age, sex, diabetes mellitus, and left ventricular ejection fraction.

Abbreviations: CI, confidence interval; HR, hazard ratio.

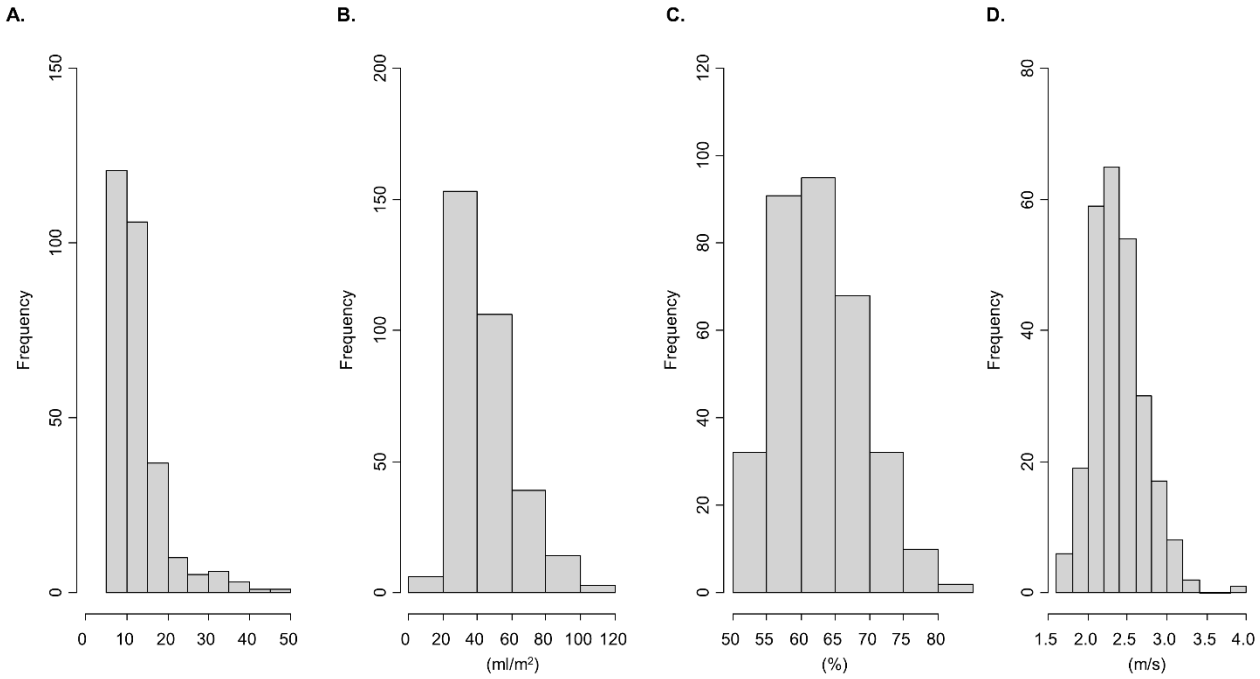
Figure S1. Study Flow



Study flow is shown. Among the registered population, patients with unavailable echocardiography data, left ventricular ejection fraction (LVEF) <50%, or functionally significant epicardial coronary artery stenosis (FFR≤0.80) were excluded from the current analysis, leaving 330 patients without left ventricular systolic dysfunction (LVEF≥50%) and functionally significant epicardial coronary artery stenosis (FFR>0.80).

Abbreviations: ASE, American Society of Echocardiography; EACVI, European Association of Cardiovascular Imaging; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; LVEF, left ventricular ejection fraction.

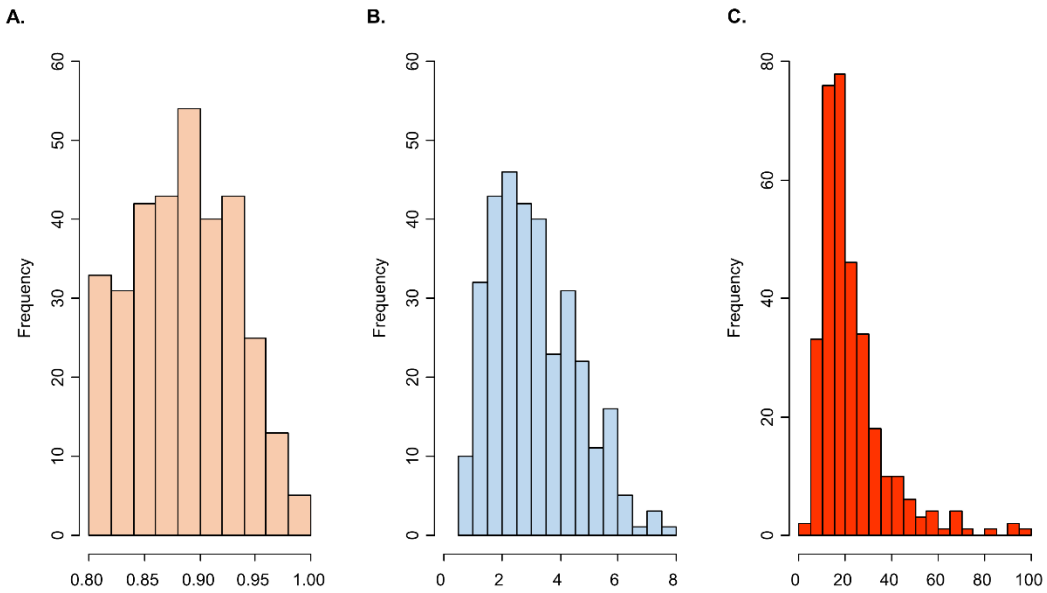
Figure S2. Distributions of Echocardiographic Parameters



Distributions of echocardiographic parameters are shown.

Abbreviations: LA, left atrium; TR, tricuspid regurgitation.

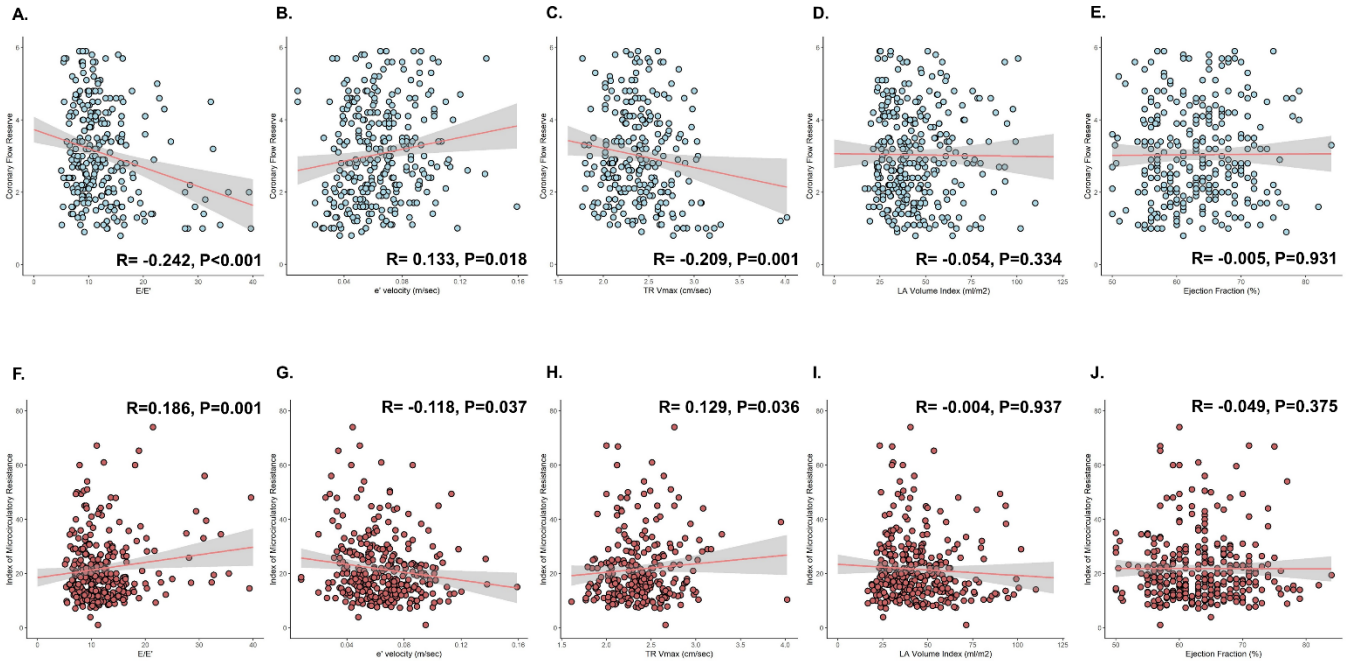
Figure S3. Distributions of Invasive Physiologic Indexes



Distributions of invasive physiologic indexes are shown.

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance.

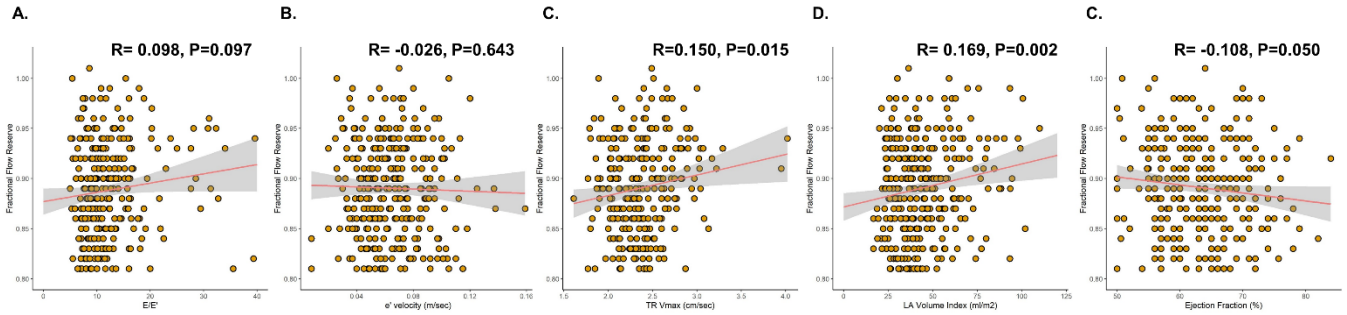
Figure S4. Correlation Between Echocardiographic Parameters and Invasive Physiologic Indexes



Correlation of CFR with (A) E/e', (B) e' velocity, (C) TR V_{max}, (D) LA volume index, and (E) LVEF are shown. Correlation of IMR with (F) E/e', (G) e' velocity, (H) TR V_{max}, (I) LA volume index, and (J) LVEF are shown.

Abbreviations: CFR, coronary flow reserve; IMR, index of microcirculatory resistance; LA, left atrium; TR, tricuspid regurgitation.

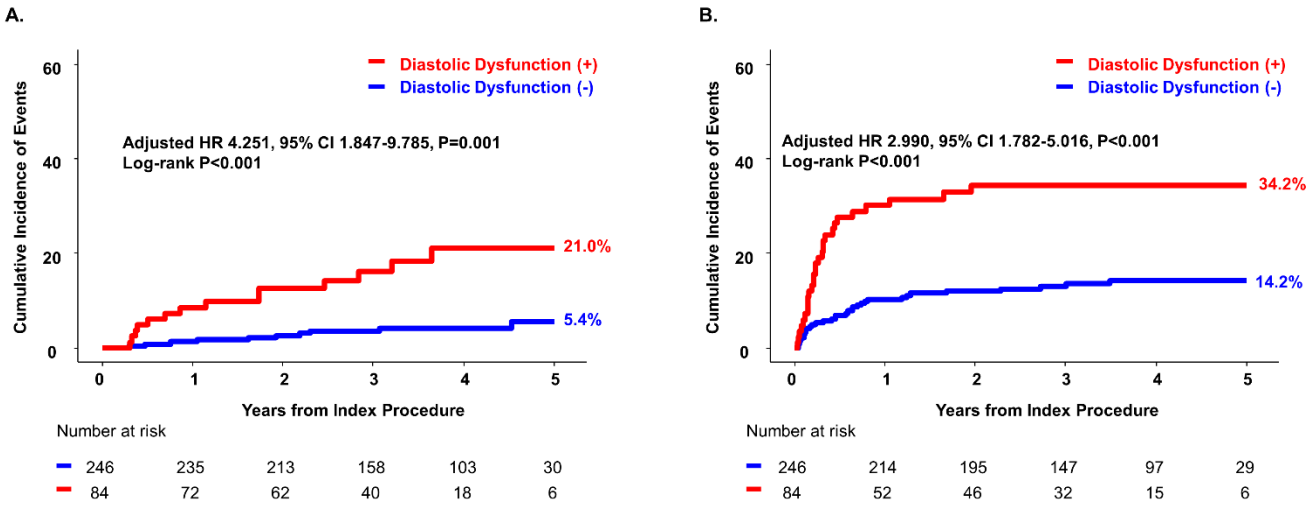
Figure S5. Correlation Between Echocardiographic Parameters and Fractional Flow Reserve



Correlation of FFR with (A) E/e', (B) e' velocity, (C) TR V_{max}, (D) LA volume index, and (E) ejection fraction are shown.

Abbreviations: FFR, fractional flow reserve; LA, left atrium; TR, tricuspid regurgitation.

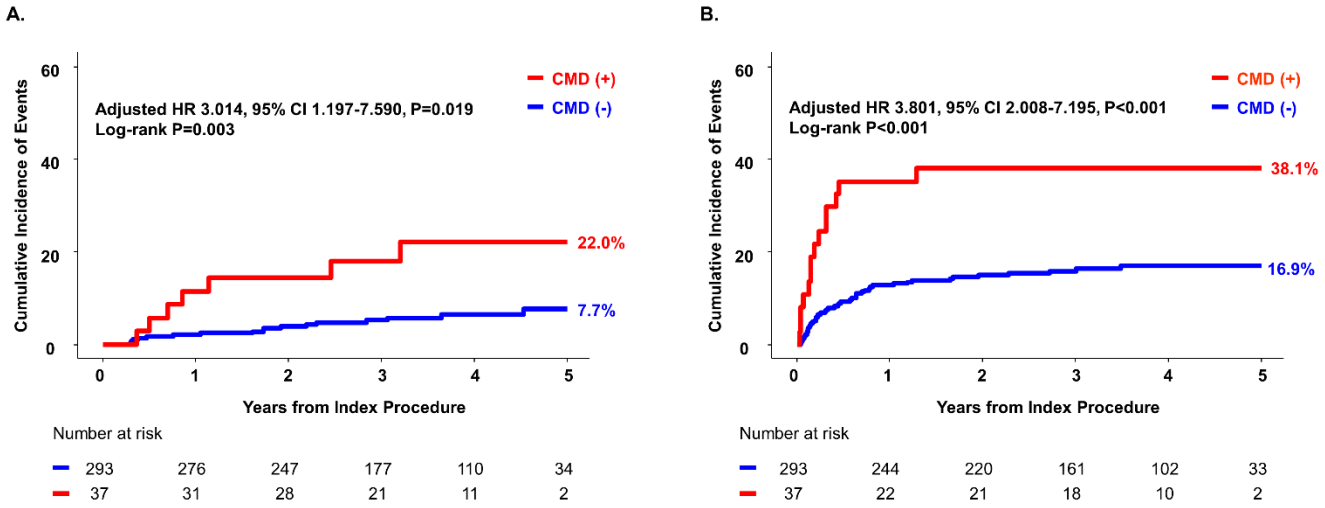
Figure S6. Prognostic Impact of Cardiac Diastolic Dysfunction



Kaplan-Meier curve is presented for cumulative incidence of (A) cardiovascular death and (B) admission for heart failure according to cardiac diastolic dysfunction. Adjusted variables in multivariable Cox regression model were age, sex, hyperlipidemia, and chronic kidney disease.

Abbreviations: CI, confidence interval; HR, hazard ratio.

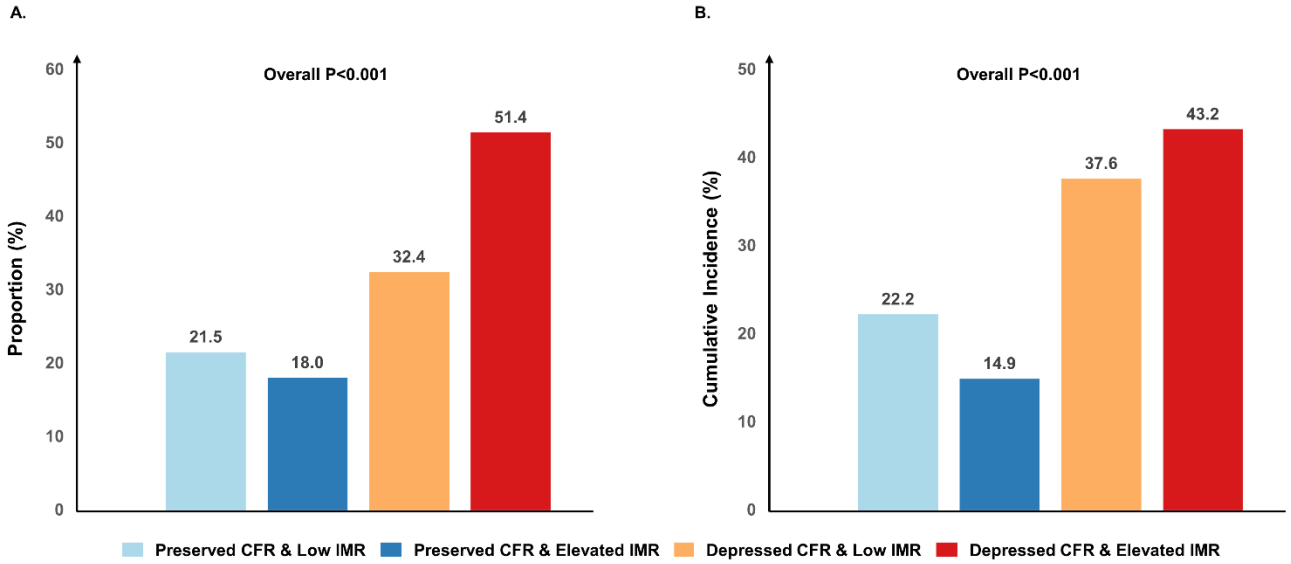
Figure S7. Prognostic Impact of Overt Coronary Microcirculatory Dysfunction



Kaplan-Meier curve is presented for cumulative incidence of (A) cardiovascular death and (B) admission for heart failure according to overt CMD. Adjusted variables in multivariable Cox regression model were age, sex, hyperlipidemia, and chronic kidney disease.

Abbreviations: CI, confidence interval; CMD, coronary microvascular dysfunction; HR, hazard ratio.

Figure S8. Incremental Value of IMR over CFR



(A) Proportion of diastolic dysfunction and (B) cumulative incidence of cardiovascular death or admission for heart failure is compared between 4 groups according to CFR (preserved [≥2.0] vs. depressed [<2.0]) and IMR (low [<25U] vs. elevated [≥25U]).

Abbreviations: CFR, coronary flow reserve; IMR, index of microcirculatory resistance.