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FFR$_{CT}$ and Static Computed Tomography Myocardial Perfusion Imaging for Therapeutic Decision-making and Prognosis in Patients With Coronary Artery Disease

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Purpose: The purpose of this study was to investigate the effect of integrated evaluation of resting static computed tomography perfusion (CTP) and coronary computed tomography angiography (CCTA)–derived fractional flow reserve (FFR$_{CT}$) on therapeutic decision-making and predicting major adverse cardiovascular events (MACEs) in patients with suspected coronary artery disease.

Materials and Methods: In this post hoc analysis of a prospective trial of CCTA in patients assigned to either CCTA or CCTA plus FFR$_{CT}$ arms, 500 patients in the CCTA plus FFR$_{CT}$ arm were analyzed. Both resting static CTP and FFR$_{CT}$ were evaluated by using the conventional CCTA. Perfusion defects in the myocardial segments with ≥ 50% degree of stenosis in the supplying vessels were defined as resting static CTP positive, and any vessel with an FFR$_{CT}$ value of ≤ 0.80 was considered positive. Patients were divided into 3 groups: (1) negative CTP-FFR$_{CT}$ match group (resting static CTP-negative and FFR$_{CT}$-negative group); (2) mismatch CTP-FFR$_{CT}$ group (resting static CTP-positive and FFR$_{CT}$-negative or resting static CTP-negative and FFR$_{CT}$-positive group); and (3) positive CTP-FFR$_{CT}$ match group (resting static CTP-positive and FFR$_{CT}$-positive group). We compared the revascularization-to-invasive coronary angiography ratio and the MACE rate among 3 subgroups at 1- and 3-year follow-ups. The adjusted Cox hazard proportional model was used to assess the prognostic value of FFR$_{CT}$ and resting static CTP to determine patients at risk of MACE.

Results: Patients in the positive CTP-FFR$_{CT}$ match group were more likely to undergo revascularization at the time of invasive coronary angiography compared with those in the mismatch CTP-FFR$_{CT}$ group (81.4% vs 57.7%, $P = 0.033$) and the negative CTP-FFR$_{CT}$ match group (81.4% vs 33.3%, $P = 0.001$). At 1- and 3-year follow-ups, patients in the positive CTP-FFR$_{CT}$ match group were more likely to have MACE than those in the mismatch CTP-FFR$_{CT}$ group (10.5% vs 4.2%, $P = 0.046$; 35.6% vs 9.4%, $P < 0.001$) and the negative CTP-FFR$_{CT}$ match group (10.5% vs 0.9%, $P < 0.001$; 35.6% vs 5.4%, $P < 0.001$). A positive CTP-FFR$_{CT}$ match was strongly related to MACE at 1-year (hazard ratio = 8.06, $P = 0.003$) and 3-year (hazard ratio = 6.23, $P < 0.001$) follow-ups.

Conclusion: In patients with suspected coronary artery disease, the combination of FFR$_{CT}$ with resting static CTP could guide therapeutic decisions and have a better prognosis with fewer MACE in a real-world scenario.

Key Words: myocardial ischemia, fractional flow reserve, perfusion, coronary artery disease, computed tomography angiography

Coronary artery disease (CAD) is a primary cause of death around the world.[1] Invasively physiology-guided coronary revascularization (REV) remains a mainstay of treatment for CAD. Evaluation of the functional significance of a coronary lesion rather than the anatomic severity of coronary stenosis is an important step in guiding decisions of REV and determining prognosis. Invasive fractional flow reserve (FFR) is the accepted gold standard for the assessment of the hemodynamic severity of CAD and has been shown to improve clinical outcomes during REV.[2] However, due to its invasiveness and high cost, its clinical application is limited to patients with suspected CAD. Importantly, primary results of the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA trial) found no statistical evidence of a benefit of the invasive strategy on ischemic cardiovascular events or death among patients with stable CAD.[3] Thus, guidelines recommend that noninvasive functional imaging tests will be more valuable in evaluating the hemodynamic significance of coronary stenoses to reduce the number of patients without obstructive CAD, who undergo invasive coronary angiography (ICA).[2,4,5]

With advances in computed tomography (CT) systems and postprocessing techniques, CT-based noninvasive functional imaging methods, such as coronary computed tomography angiography (CCTA)–derived FFR (FFR$_{CT}$)

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and CT myocardial perfusion imaging, have emerged as recently developed methods for the functional assessment of CAD.[6] As shown in our previous studies, many patients with $FFR_{CT} \leq 0.80$ had no poor clinical outcomes during 1- and 2-year follow-ups.[7,8] The combination of FFR_{CT} and stress dynamic computed tomography perfusion (CTP) has shown promise for further improving the accuracy of CCTA in the evaluation of stable chest pain and is associated with clinical outcomes.[9,10] However, stress dynamic CTP requires stress-inducing pharmacology with some potential contra-indications, increased scanner hardware requirements, and higher radiation exposure. Compared with stress dynamic CTP, resting static CTP has the potential to become the most widely used imaging modality for the evaluation of myocardial perfusion in the routine clinical setting because every CCTA can be used for mining resting static CTP data without the aforementioned shortcomings of dynamic stress CTP.[11,12] However, to date, the clinical impact of the combination of resting static CTP and FFR_{CT} remains unknown.

Therefore, we hypothesize that combined FFR_{CT} and resting static CTP can provide incremental value in patients with CAD by allowing a 1-stop-shop anatomical and functional evaluation.[11] The purpose of this study was to evaluate the effect of integrated FFR_{CT} and resting static CTP on guiding therapeutic management and predicting adverse outcomes in patients with CAD in a real-world scenario.

MATERIALS AND METHODS

Subjects

This trial was a single-center prospective 2-arm con-trolled study of CCTA in patients with suspected CAD referred for CCTA as the first-line diagnostic test. The pri-mary results have been reported previously.[7] In brief, 1184 patients with 25% to 80% coronary stenosis on CCTA were assigned to anatomical CCTA alone (CCTA alone arm, n = 593) or anatomical CCTA plus FFR_{CT} group (FFR_{CT} arm, n = 591). This secondary post hoc study analyzed the data in the FFR_{CT} arm. Of the 1184 enrolled patients, 591 patients were assigned to the FFR_{CT} group, and 566 were successfully sent for FFR_{CT} analysis.

CCTA Examination and Image Analysis

CCTA was performed using a dual-source CT scanner (Somatom Definition Flash; Siemens Healthineers) in all 566 patients according to the societal guideline.[13] CCTA was performed using prospective electrocardiographic trig-gering at 30% to 80% of the R-R interval. The scan parameters are given as follows: tube voltage: 100 to 120 kVp; effective tube current: 370 mAs; detector colli-mation: $64 \times 2 \times 0.6$ mm; and temporal resolution: 75 ms; 60 mL of iopromide (Ultravist 370 mg I/mL; Bayer Schering Pharma) was injected into an antecubital vein with a flow rate of 4 to 5 mL/s. Then, 40 mL saline was injected with the same flow rate.

All CCTA images were transferred to a dedicated workstation (Syngo.Via; Siemens) for image postprocessing. CCTA studies were interpreted independently by 2 observ-ers (Long Jiang Zhang and Hong Yan Qiao, with 22 and 10 y of experience in CCTA, respectively) with a half-day interval, blinded to all participants' clinical data and all other modalities. The readers were able to access various image postprocessing and display tools. Maximal degree of

stenosis (DS) was recorded as follows: mild (25% to 49%), moderate (50% to 69%), and severe ($\geq$ 70%). A $\geq$ 50% DS was considered as obstructive CAD recommended by the Society of Cardiovascular Computed Tomography on a per-participant basis.[14]

FFR_{CT} Measurement

FFR_{CT} calculations were blindly and independently conducted on CCTA datasets using a software prototype (cFFR, version 3.0.1; Siemens Healthcare). The software is based on the machine learning platform for the noninvasive computation of FFR values using existing CCTA data, and the detailed algorithm has been reported in previous studies.[7,15,16] An observer (Hong Yan Qiao with 5 y of experience in FFR_{CT} analysis), who was blinded to all participants' baseline clinical data, measured lesion-specific FFR_{CT} values at 2 to 4 cm distal to coronary stenosis in real time. Any vessel with an FFR_{CT} value of ≤ 0.80 was con-sidered positive.[17] Additional FFR_{CT}-positive cutoff values of ≤ 0.75 and ≤ 0.70 were also used for this subgroup analysis, respectively. A gray zone was defined for the range of $FFR_{CT} > 0.70 \leq 0.80$.[18] Interobserver agreement was evaluated by selecting 100 consecutive subjects analyzed by the same observers (Long Jiang Zhang and Hong Yan Qiao).[7] Excellent interobserver agreement of the FFR_{CT} analysis was reported (intraclass correlation coefficients [ICCs] = 0.82, 95% CI: 0.78-0.86, and $P < 0.001$) in our previous study.[7]

Resting Static CTP Studies

All resting static CTP were reconstructed using routine CCTA datasets and analyzed using a resting static CTP software prototype (CT Cardiac Function, Syngo.Via Frontier; Siemens). The scientific basis of this resting static CTP evaluation has been described previously.[19] This software allows fully automatic segmentation of the left ventricle for noninvasive evaluation of myocardial perfusion using 2 series of CCTA data (both diastole and systole phases). Polar maps were automatically generated. Resting static CTP images were evaluated according to a standard 17-segment model by visual analysis according to the American Heart Association (AHA) myocardial segment model.[20] One reader (Su Yu Li with 2 y of experience in CCTA) independently evaluated the resting static CTP for evaluation of perfusion defects, blinded to the clinical and FFR_{CT} findings. Perfusion defects were defined as resting static CTP positive when a red overlay in the myocardium polar map had $\geq 50\%$ DS in the corresponding supplying vessels.[12,19] We evaluated interobserver agreement by selecting 60 consecutive subjects analyzed by 2 observers (Su Yu Li and Rui Zuo, with 2 and 1 y of experience in CCTA, respectively). The analysis was repeated after 6 months to calculate intraobserver variability by the same observer (Su Yu Li) blinded to the identities of the patients and the timing of the studies.

Evaluation of CCTA Combined With FFR_{CT} and Resting Static CTP

All patients were classified into 3 subgroups according to resting static CTP and FFR_{CT} results: (1) negative CTP-FFR_{CT} match group, that is, resting static CTP-negative and FFR_{CT}-negative group; (2) mismatch CTP-FFR_{CT} group, that is, resting static CTP-positive and FFR_{CT}-negative or resting static CTP-negative and FFR_{CT}-positive group; and (3) positive CTP-FFR_{CT} match group, that is,

resting static CTP-positive and FFR$_{CT}$-positive group. For the FFR$_{CT}$ analysis, we adjusted FFR$_{CT}$ thresholds of ≤ 0.80, ≤ 0.75, and ≤ 0.70 to observe the interaction of myocardial perfusion and hemodynamic significance of coronary stenosis, respectively.

Clinical Endpoints

Clinical follow-ups were conducted at 90 days, 1, and 3 years after enrollment. The primary endpoint was the REV-to-ICA ratio at 90 days. The secondary endpoint was the occurrence of major adverse cardiovascular events (MACEs), including all-cause mortality, nonfatal myocardial infarction, and acute coronary syndrome (ACS) leading to unplanned REV and stroke at 1- and 3-year follow-ups.[5,7]

Statistical Analysis

IBM SPSS, version 21.0 (SPSS) and MedCalc 3.0 (MedCalc Software) were used for the statistical analyses. Continuous data were presented as mean ± SD or median (interquartile range), as appropriate. Categorical data were presented as numbers or proportions. We calculated the power of this study using Power Analysis and Sample Size (PASS) 2008 Statistical Software (version 15.0). Based on this, a sample size of 488 patients can provide 100% power at a 1-year follow-up, and 402 patients can provide 100% power at a 3-year follow-up (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JTI/A259). Interobserver and intraobserver agreements of resting static CTP were analyzed with ICC analysis. The non-obstructive CAD rate and the REV-to-ICA ratio were compared among groups with the χ^2 or Fisher exact test. The incidence of MACE was compared using the Chi-square or Fisher exact test. The ICA rates and incidence of MACE were analyzed when the participants were divided into 3 subgroups according to FFR$_{CT}$ values (≤ 0.70, $> 0.70 \leq 0.80$, and > 0.80). Cumulative probabilities of MACE were compared among the negative CTP-FFR$_{CT}$ match group, the mismatch CTP-FFR$_{CT}$ group, and the positive CTP-FFR$_{CT}$ match groups by using the Kaplan-Meier analysis and the log-rank test. The effect size of 3 groups on MACE was analyzed with a Cox proportional hazard survival model, adjusting for age, sex, hypertension, diabetes mellitus, hyperlipidemia, present smoking, and presenting chest pain symptoms at baseline with a *P*-value < 0.10 in univariate comparisons. Relative risks were expressed as a hazard ratio (HR) with 95% CIs. A 2-sided level of *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline Patient Characteristics

A total of 66 (11.7%, 66/566) patients were excluded due to failure to conduct resting static CTP calculations (n = 41) and incomplete CCTA datasets (n = 25), and 500 patients were included in this substudy (Fig. 1). The patients' demographics are provided in Table 1. Patients had a mean age of 62.4 ± 10.6 years and 67.8% were male. Of the 500 patients, with FFR$_{CT} \leq 0.80$ as the cutoff value, 47.4% (n = 237) were in the negative CTP-FFR$_{CT}$ match group, 29.4% (n = 147) in the mismatch CTP-FFR$_{CT}$ group, and 23.2% (n = 116) in the positive CTP-FFR$_{CT}$ match group. With FFR$_{CT} \leq 0.80$ as the cutoff value, patients in the positive CTP-FFR$_{CT}$ match group were more likely to

present with $\geq 50\%$ DS and $\geq 70\%$ DS compared with those in the mismatch CTP-FFR$_{CT}$ group (98.3% vs 70.7%, *P* < 0.001; 70.7% vs 7.0%, *P* < 0.001, respectively) and those in the negative CTP-FFR$_{CT}$ match group (47.4% vs 9.5%, *P* < 0.001; 9.5% vs 0%, *P* < 0.001, respectively) compared with those in the positive CTP-FFR$_{CT}$ match group. One-year follow-up was successfully obtained in 488 patients (97.6%) and 3-year follow-up in 402 (80.4%) patients (Fig. 1). Excellent interobserver and intraobserver reproducibilities for resting static CTP were shown with ICCs (95% CI) of 0.967 (0.865-0.992) and 0.980 (0.901-0.995), respectively.

Impact of FFR$_{CT}$ and Resting Static CTP on Downstream Clinical Management

During the 90-day follow-up period, 20.4% (102/500) of the patients were referred for ICA. Of those referred patients, 79.4% (81/102) actually underwent ICA with 64.2% (52/81) undergoing subsequent coronary REV (percutaneous coronary intervention, n = 46; coronary artery bypass grafting, n = 6). With FFR$_{CT} \leq 0.80$ as the cutoff value, patients in the positive CTP-FFR$_{CT}$ match group were more likely to be referred to ICA (44.8% vs 20.4%, *P* < 0.001), actually receive ICA (37.1% vs 17.7%, *P* < 0.001), and undergo REV at the time of ICA (81.4% vs 57.7%, *P* = 0.033) compared with those in the mismatch CTP-FFR$_{CT}$ group (Table 2, Fig. 2A). Patients in the negative CTP-FFR$_{CT}$ match group were less likely to be referred to ICA (7.6% vs 44.8%, *P* < 0.001), actually receive ICA (5.1% vs 37.1%, *P* < 0.001), and undergo REV at the time of ICA (33.3% vs 81.4%, *P* = 0.001) compared with those in the positive CTP-FFR$_{CT}$ match group. The non-obstructive CAD rate in ICA was the lowest in the positive CTP-FFR$_{CT}$ match group compared with those in the mismatch CTP-FFR$_{CT}$ group (0 vs 11.5%, *P* = 0.050) and the negative CTP-FFR$_{CT}$ match group (0% vs 41.7%, *P* < 0.001). No significant differences in the REV-to-ICA ratio (81.4% vs 57.7%, *P* = 0.163) and the nonobstructive CAD rate in ICA (11.5% vs 41.7%, *P* = 0.081) were found between the mismatch CTP-FFR$_{CT}$ group and the negative CTP-FFR$_{CT}$ match group (Table 2, Fig. 2A). Similar results were found when FFR$_{CT}$-positive cutoff values were adjusted to ≤ 0.75 and ≤ 0.70 (Table 2, Figs. 2B, C).

When the patients were divided into 3 subgroups according to FFR$_{CT}$ values (≤ 0.70, the gray zone, and > 0.80), the referred and actual rates for ICA and the REV-to-ICA ratios were higher in patients with positive resting static CTP compared with those with negative resting static CTP (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/JTI/A260). The nonobstructive CAD rate in ICA was slightly lower among those in the positive resting static CTP group than in those in the negative resting static CTP group among all 3 subgroups (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/JTI/A260); however, these differences were not significant (all *P* > 0.05) (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/JTI/A260).

MACEs

MACE occurred in 20 patients (4.1%) at a 1-year follow-up and 57 patients (14.2%) at a 3-year follow-up. We analyzed all clinical factors and imaging parameters with potential association with MACEs. In univariable analysis, we found that DS $\geq 50\%$ (HR = 3.40; 95% CI: 1.88-6.14;
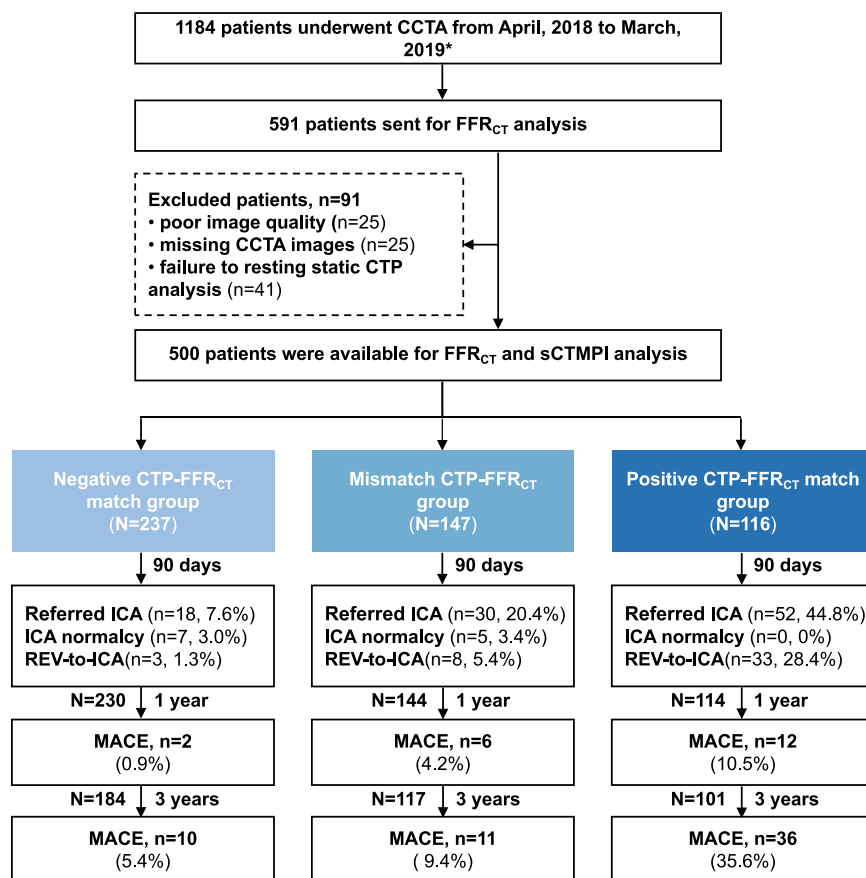
FIGURE 1. Study flowchart. *The prospective cohort screening 2677 patients undergoing CCTA with 1493 patients excluded due to coronary stenosis <25% or >80% (n = 1242), declined to participate (n = 53), prior coronary stents (n = 101), and poor image quality (n = 97), and 1184 patients were recruited finally. [full color online]

and $P < 0.001$), FFR_{CT} (HR = 5.03; 95% CI: 2.74-9.23; and $P < 0.001$), and resting static CTP (HR = 3.30; 95% CI: 1.86-5.84; $P < 0.001$) were all significant predictors for MACE at 3-year follow-up, which were subsequently included in multivariable logistic regression analysis. According to multivariable logistic regression analysis, only FFR_{CT} (HR = 3.77; 95% CI: 1.93-7.35; and $P < 0.001$) was identified as an independent risk factor for 3-year MACE. Similar

TABLE 1. Baseline Characteristics of Participants

Variables	All	Negative CTP-FFR$_{CT}$ match group (n = 237)	Mismatch CTP-FFR$_{CT}$ group (n = 147)	Positive CTP-FFR$_{CT}$ match group (n = 116)	P
Baseline characteristics					
Age (mean ± SD) (y)	62.4 ± 10.6	61.5 ± 10.5	63.0 ± 11.4	63.3 ± 10.6	0.236
Sex (men)	339 (67.8)	150 (63.3)	100 (68.0)	89 (76.7)	0.040
Diabetes	117 (23.4)	52 (21.9)	36 (24.5)	29 (25.0)	0.762
Hypertension	317 (63.4)	149 (62.9)	95 (64.6)	73 (62.9)	0.935
Smokers	124 (24.8)	62 (26.2)	31 (26.7)	31 (26.7)	0.460
Hypercholesterolemia	217 (43.4)	109 (46.0)	61 (41.5)	47 (40.5)	0.533
Chest pain	449 (89.8)	205 (86.5)	139 (94.6)	105 (90.5)	0.106
Typical angina	91 (18.2)	41 (17.3)	26 (17.7)	24 (20.7)	0.727
Atypical angina	215 (43.0)	92 (38.8)	67 (45.6)	56 (48.3)	0.182
Nonanginal chest pain	50 (10.0)	22 (9.3)	18 (12.2)	10 (8.6)	0.548
Dyspnea/palpitation	91 (18.2)	50 (21.1)	26 (17.7)	15 (12.9)	0.036
≥ 50% DS	234 (46.8)	16 (7.0)	104 (70.7)	114 (98.3)	< 0.001
≥ 70% DS	69 (13.8)	0	14 (9.5)	55 (47.4)	< 0.001

Values are mean ± SD and n (%).

(1) Negative CTP-FFR$_{CT}$ match group (resting static CTP-negative and FFR$_{CT}$-negative group); (2) mismatch CTP-FFR$_{CT}$ group (resting static CTP-positive and FFR$_{CT}$-negative or resting static CTP-negative and FFR$_{CT}$-positive group); and (3) positive CTP-FFR$_{CT}$ match group (resting static CTP-positive and FFR$_{CT}$-positive group).

TABLE 2. Impact of FFR$_{CT}$ and Resting Static CTP on Therapeutic Decision-making

Variables	Negative CTP-FFR$_{CT}$ match group	Mismatch CTP-FFR$_{CT}$ group	Positive CTP-FFR$_{CT}$ match group	P
	n (%)			
Cutoff of FFR$_{CT}$ = 0.80				
N	237	147	116	
Referred ICA rate	18 (7.6)	30 (20.4)	52 (44.8)	< 0.001
Actual ICA rate	12 (5.1)	26 (17.7)	43 (37.1)	< 0.001
ICA normalcy rate*	5 (41.7)	3 (11.5)	0	< 0.001
REV-to-ICA ratio*	4 (33.3)	15 (57.7)	35 (81.4)	< 0.001
Cutoff of FFR$_{CT}$ = 0.75				
N	259	162	79	
Referred ICA rate	24 (9.3)	37 (22.8)	39 (49.4)	< 0.001
Actual ICA rate	17 (6.6)	30 (18.5)	34 (43.0)	< 0.001
ICA Normalcy rate*	5 (29.4)	3 (10.0)	0	< 0.001
REV-to-ICA ratio*	7 (41.2)	16 (53.3)	29 (85.3)	< 0.001
Cutoff of FFR$_{CT}$ = 0.70				
N	274	167	59	
Referred ICA rate	26 (9.5)	42 (25.1)	32 (54.2)	< 0.001
Actual ICA rate	19 (6.9)	33 (19.8)	29 (49.2)	< 0.001
ICA normalcy rate*	6 (31.6)	2 (6.1)	0	< 0.001
REV-to-ICA ratio*	8 (42.1)	19 (57.6)	25 (86.2)	< 0.001

(1) Negative CTP-FFR$_{CT}$ match group (resting static CTP-negative and FFR$_{CT}$-negative group); (2) mismatch CTP-FFR$_{CT}$ group (resting static CTP-positive and FFR$_{CT}$-negative or resting static CTP-negative and FFR$_{CT}$-positive group); (3) positive CTP-FFR$_{CT}$ match group (resting static CTP-positive and FFR$_{CT}$-positive group).
*The denominator is the number of patients in whom ICA was actually performed.

results were found at 1-year follow-up. The details of logistic regression analysis are presented in Supplemental Table 3 (Supplemental Digital Content 3, http://links.lww.com/JTI/A261). Resting static CTP, DS ≥ 50%, and FFR$_{CT}$ achieved a c-index of 0.65, 0.70, and 0.74 to predict MACE, respectively. Compared with FFR$_{CT}$, adding resting static CTP to FFR$_{CT}$ resulted in a numerically higher c-index for predicting all causes of MACE, but there was no statistical difference (c-index: 0.75 and $P = 0.331$) (Supplemental Table 4, Supplemental Digital Content 4, http://links.lww.com/JTI/A262).

MACE rates were higher in patients in the positive CTP-FFR$_{CT}$ match group compared with those in the mismatch CTP-FFR$_{CT}$ group at 1-year (10.5% vs 4.2%, $P = 0.046$) and 3-year follow-ups (35.6% vs 9.4%, $P < 0.001$) (Table 3, Fig. 3). Patients in the positive CTP-FFR$_{CT}$ match

group were more likely to have MACE than those in the negative CTP-FFR$_{CT}$ match group at 1-year (10.5% vs 0.9%, $P < 0.001$) and 3-year follow-ups (35.6% vs 5.4%, $P < 0.001$) (Table 3, Fig. 3). Similar results were found when FFR$_{CT}$ thresholds were adjusted to 0.75 and 0.70 (all $P < 0.05$) (Table 3, Fig. 3).

When FFR$_{CT}$ thresholds were adjusted to 0.75 and 0.70, the differences were more significant between the mismatch CTP-FFR$_{CT}$ group and the negative CTP-FFR$_{CT}$ match group at 3-year follow-up (all $P < 0.05$). The rates of ACS leading to unplanned REV in the positive CTP-FFR$_{CT}$ match group were the highest among all causes of MACE when FFR$_{CT}$-positive cutoff values were adjusted to 0.80, 0.75, and 0.70 (Table 3).

In multivariate Cox regression models adjusting for age, sex, hypertension, diabetes mellitus, hyperlipidemia,

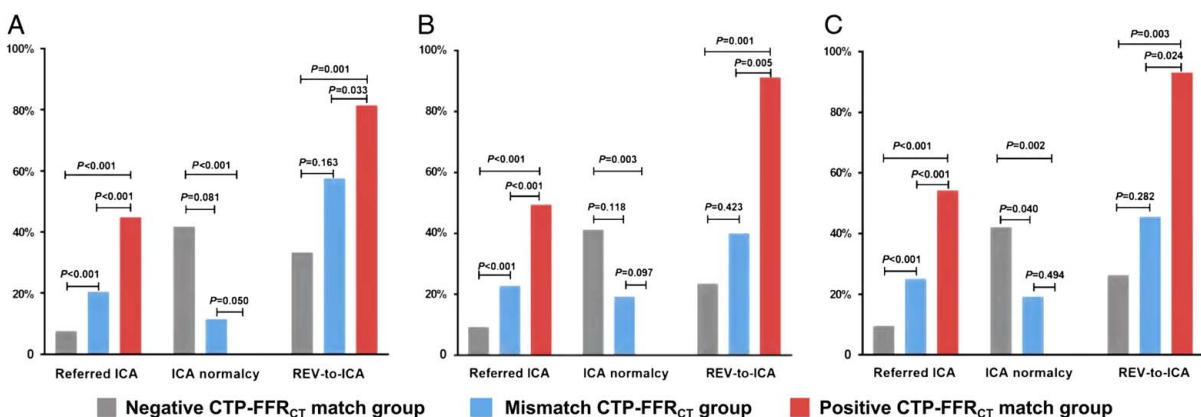**FIGURE 2.** Ninety-day outcomes of different CTP-FFR$_{CT}$ groups. A, FFR$_{CT}$-positive cutoff value was ≤ 0.80. B, FFR$_{CT}$-positive cutoff value was adjusted to ≤ 0.75. C, FFR$_{CT}$-positive cutoff value was adjusted to ≤ 0.70. [full color online]

TABLE 3. Impact of FFR$_{CT}$ and Resting Static CTP on MACE at 1- and 3-Year Follow-ups

	1-y follow-up, n (%)			3-y follow-up, n (%)		
Variables	Negative CTP-FFR$_{CT}$ match group	Mismatch CTP-FFR$_{CT}$ group	Positive CTP-FFR$_{CT}$ match group	Negative CTP-FFR$_{CT}$ match group	Mismatch CTP-FFR$_{CT}$ group	Positive CTP-FFR$_{CT}$ match group
Cutoff of FFR$_{CT}$ = 0.80						
N	230	144	114	184	117	101
MACE*	2 (0.9)	6 (4.2)	12 (10.5)	10 (5.4)	11 (9.4)	36 (35.6)
All-Cause Death	1 (0.4)	0	0	4 (2.2)	4 (3.4)	6 (5.9)
Nonfatal MI	0	1 (0.7)	3 (2.6)	4 (2.2)	1 (0.9)	6 (5.9)
Unplanned REV	1 (0.4)	5 (3.5)	9 (7.9)	2 (1.1)	5 (4.3)	17 (16.8)
Stroke	0	0	0	0	1 (0.9)	7 (6.9)
Cutoff of FFR$_{CT}$ = 0.75						
N	252	148	78	205	129	68
MACE*	3 (1.2)	7 (4.7)	10 (12.8)	12 (5.9)	18 (14.0)	27 (39.7)
All-Cause Death	1 (0.4)	0 (0.0)	0 (0.0)	4 (2.0)	4 (3.1)	6 (8.8)
Nonfatal MI	0	1 (0.7)	3 (3.8)	4 (2.0)	2 (1.5)	5 (7.4)
Unplanned REV	2 (0.8)	6 (4.1)	7 (9.0)	3 (1.5)	8 (6.2)	13 (19.1)
Stroke	0	0	0	1 (0.5)	4 (3.1)	3 (4.4)
Cutoff of FFR$_{CT}$ = 0.70						
N*	267	162	59	218	132	52
MACE	4 (1.5)	7 (4.3)	9 (15.3)	14 (6.4)	19 (14.4)	24 (46.2)
All-cause death	1 (0.4)	0	0	5 (2.3)	4 (3.0)	5 (9.6)
Nonfatal MI	1 (0.4)	0	3 (5.1)	5 (2.3)	2 (1.5)	4 (7.7)
Unplanned REV	2 (0.7)	7 (4.3)	6 (10.2)	3 (1.4)	9 (6.8)	12 (23.1)
Stroke	0	0	0	1 (0.5)	4 (3.0)	3 (5.8)

*Twelve patients were excluded due to follow-up loss during a 1-year follow-up, and 98 patients were excluded due to follow-up loss during a 3-year follow-up. Thus, 488 and 402 patients were finally included in the final 1- and 3-year follow-up cohorts, respectively.

MI indicates myocardial infarction.

present smoking, and presenting chest pain symptoms, patients in the positive CTP-FFR$_{CT}$ match group were strongly predisposed to MACE compared with patients in the negative CTP-FFR$_{CT}$ match group during 1-year (HR = 8.06; 95% CI: 2.22-29.27; and P = 0.003) and 3-year (HR = 6.23; 95% CI: 3.04-12.79; and P < 0.001) follow-ups

(Table 4, Fig. 4). Similar results were found when the FFR$_{CT}$-positive cutoff values were adjusted to FFR$_{CT}$ thresholds of 0.75 and 0.70 (Table 4, Fig. 4). Representative cases are illustrated in Figure 5.

According to different FFR$_{CT}$ cutoff values ($\leq$ 0.70, the gray zone, and > 0.80), patients with positive resting static CTP
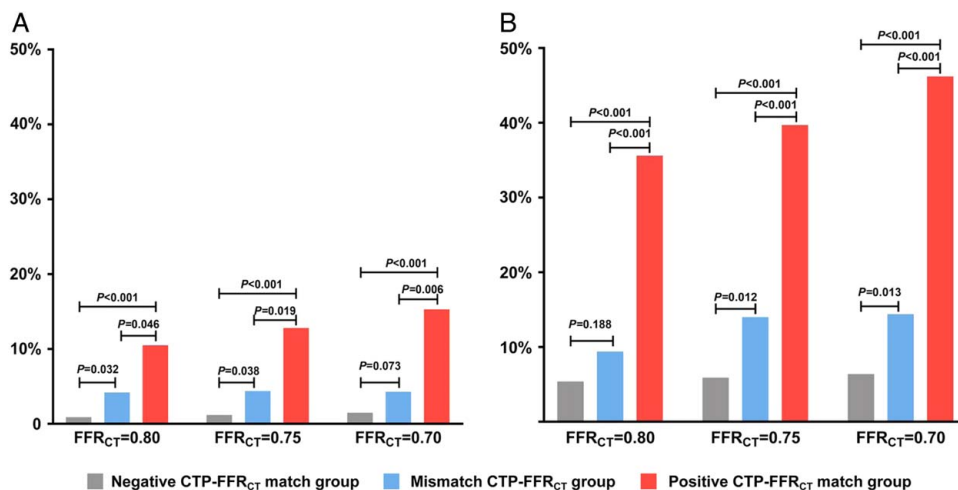

FIGURE 3. MACE rate at 1- and 3-year follow-ups in FFR$_{CT}$ subgroups. A, Comparison of MACE rate in 3 subgroups at 1-year follow-up. B, Comparison of MACE rate in 3 subgroups at 3-year follow-up.

TABLE 4. Multivariate Cox Regression Analyses for the Association Between Hemodynamic Metrics of Coronary Stenoses and 1- and 3-Year Outcomes

Variables	1-y MACE (N = 488)*		3-y MACE (N = 402)*	
	HR (95% CI)	P	HR (95% CI)	P
Cutoff of FFR$_{CT}$ = 0.80				
Negative CTP-FFR$_{CT}$ match group	Reference		Reference	
Mismatch CTP-FFR$_{CT}$ group	2.35 (0.56-9.92)	0.081	1.52 (0.64-3.63)	0.342
Positive CTP-FFR$_{CT}$ match group	8.06 (2.22-29.27)	0.003	6.23 (3.04-12.79)	< 0.001
Cutoff of FFR$_{CT}$ = 0.75				
Negative CTP-FFR$_{CT}$ match group	Reference		Reference	
Mismatch CTP-FFR$_{CT}$ group	2.98 (0.75-11.75)	0.119	1.74 (0.82-3.69)	0.148
Positive CTP-FFR$_{CT}$ match group	8.76 (2.31-33.19)	0.001	8.37 (4.15-16.89)	< 0.001
Cutoff of FFR$_{CT}$ = 0.70				
Negative CTP-FFR$_{CT}$ match group	Reference		Reference	
Mismatch CTP-FFR$_{CT}$ group	2.29 (0.66-7.93)	0.193	1.70 (0.84-3.44)	0.143
Positive CTP-FFR$_{CT}$ match group	8.45 (2.40-29.74)	0.001	9.35 (4.67-18.72)	< 0.001

*Adjusted for age, sex, diabetes, hypertension, smoking, hypercholesterolemia, typical angina, atypical angina, nonanginal chest pain, and dyspnea.

had a higher MACE rate than those with negative resting static CTP among all subgroups at one- and 3-year follow-ups (Supplemental Table 5, Supplemental Digital Content 5, http://links.lww.com/JTI/A263), respectively. At 3-year follow-up, the rate of MACE in patients with FFR$_{CT}$ ≤ 0.70 and positive resting static CTP was significantly higher than in those with FFR$_{CT}$ ≤ 0.70 and negative resting static CTP (46.2% vs 17.6%, P = 0.047) (Supplemental Table 5, Supplemental Digital Content 5, http://links.lww.com/JTI/A263). No difference was found between positive resting static CTP and negative resting static CTP subgroups at one- and 3-year follow-ups in patients with the FFR$_{CT}$ values in the range of the gray zone (both P > 0.05)

(Supplemental Table 5, Supplemental Digital Content 5, http://links.lww.com/JTI/A263).

DISCUSSION

In this post hoc analysis of a prospective study of CCTA among patients with suspected CAD, we demonstrated the incremental value of the integration of FFR$_{CT}$ and resting static CTP, which allows functional perfusion evaluation for determining the downstream hemodynamic significance of lesions for guiding treatment decisions and evaluating the validity of stenosis-specific interventions in a real-world scenario. Our data suggest that combining resting static CTP with
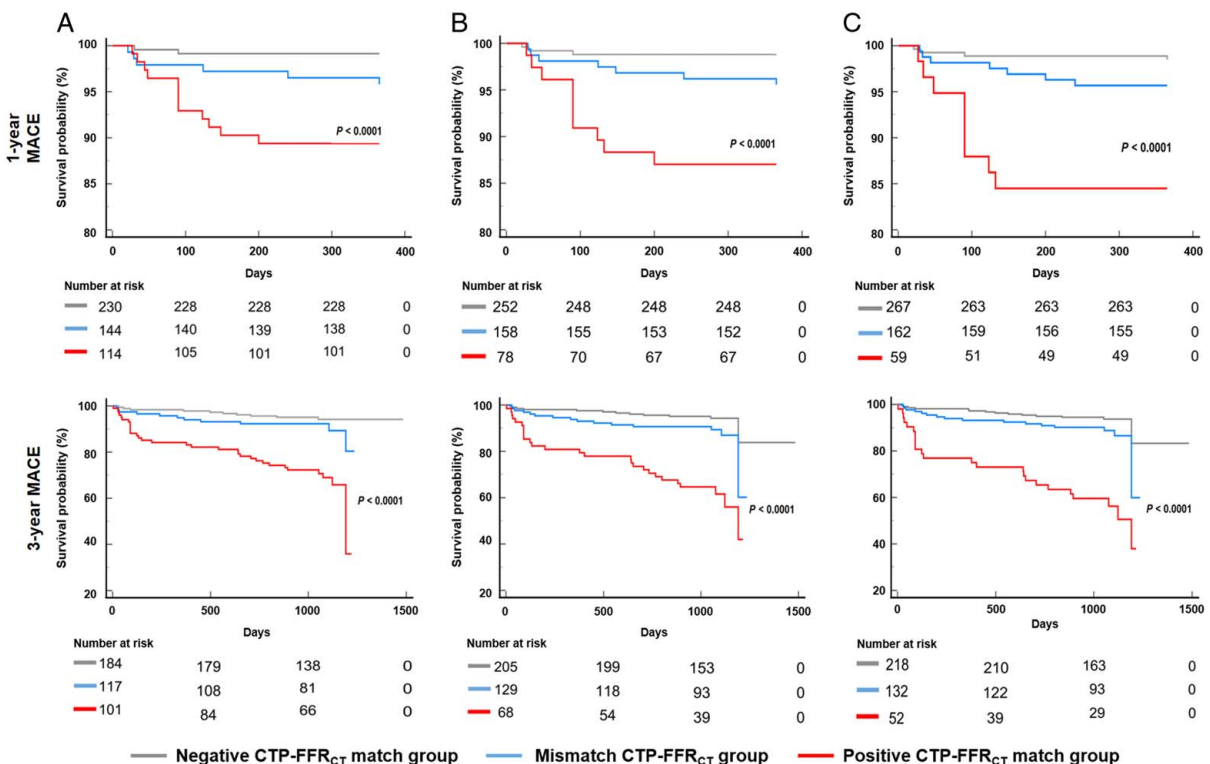

FIGURE 4. Kaplan-Meier survival curves showing MACEs at 1 and 3 years. A, FFR$_{CT}$ thresholds of 0.80. B, FFR$_{CT}$ thresholds of 0.75. C, FFR$_{CT}$ thresholds of 0.70. MACE: all-cause mortality, myocardial infarction, ACS leading to unplanned REV, and stroke. full color online
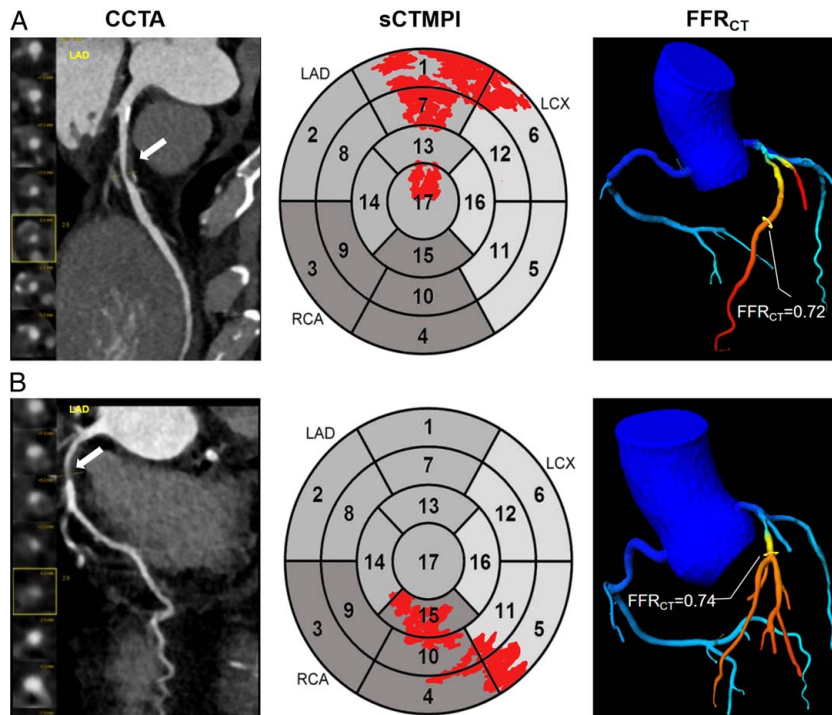
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FIGURE 5. Representative cases with CCTA, FFR$_{CT}$, and resting static CTP resting static CTP. A, A 62-year-old man experienced a nonfatal myocardial infarction at a 1-year follow-up. CCTA with multiplanar reformation shows severe stenosis in the proximal segment of the LAD (arrow) with perfusion defects in segments 1 and 7 in resting static CTP resting static CTP and positive FFR$_{CT}$ (0.72). B, A 58-year-old woman had no MACE during a 3-year follow-up. CCTA with multiplanar reformation shows stenosis degree > 50% in the proximal LAD (arrow) without perfusion defect in the corresponding myocardial segments in the polar map and positive FFR$_{CT}$ (0.74). LAD indicates left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; sCTMPI, static computed tomography myocardial perfusion imaging.

FFR$_{CT}$ may improve the efficiency of referral to ICA by increasing the rate of subsequent REVs. Importantly, we demonstrated that the integration of positive FFR$_{CT}$ and resting static CTP had a better predictive value for MACE than a mismatched FFR$_{CT}$ and resting static CTP or a negative FFR$_{CT}$ and resting static CTP.

Current guidelines recommend that CCTA is an excellent "gatekeeper" for ICA referral, especially by enhancing its value through methods such as FFR$_{CT}$ and CTP, which further improves the accuracy of CCTA by identifying candidates who might receive unnecessary ICA.[4,21–24] Some studies highlighted the potential for FFR$_{CT}$ to increase the efficiency of subsequent coronary REV.[8,25] In the CRESCENT II trial, adding CTP when CCTA revealed a > 50% stenosis resulted in fewer ICA without a class I indication for REV. However, the integration of FFR$_{CT}$ and CTP was not included in previous studies.[8,25–28] Although we did not find that resting static CTP alone had an independent prognosis value compared with FFR$_{CT}$, this study did demonstrate that patients with FFR$_{CT}$ ≤ 0.80 and positive resting static CTP were substantially more likely to undergo REV compared with those in the resting static CTP-positive and FFR$_{CT}$-negative or resting static CTP-negative and FFR$_{CT}$-positive groups. Our findings further demonstrated that the hemodynamic significance of CAD evaluation was more important for mechanical REV by combining myocardial perfusion with the functional significance of coronary stenosis by FFR$_{CT}$. Importantly, we directly analyzed the data from the conventional diagnostic CCTA datasets without concomitant increased contrast material use or radiation dose. However, in our study, 4 patients in the negative CTP-FFR$_{CT}$ match group underwent REV due to coronary stenosis of ≥ 80% in ICA and a chest pain symptom, which is rational for clinical management according to comprehensive phenotype. In a post hoc analysis of the PROMISE trial, adding information on FFR$_{CT}$ to CCTA improved the efficiency of referral to ICA by lowering the number of ICA and decreasing the nonobstructive CAD rate in ICA[29] In our study, the integration of resting static CTP and FFR$_{CT}$ caused a modest net increase in referral for and actual use of ICA. This is notable because the resting static CTP results were not available to physicians during the trial, while the FFR$_{CT}$ results guided clinical management. Meanwhile, a higher REV efficiency was reported in the positive CTP-FFR$_{CT}$ match group. Thus, robust evidence-based recommendations await well-conducted prospective studies in this arena.

The prognostic value of the integration of both FFR$_{CT}$ and resting static CTP was demonstrated in our prospective cohort. Many previous studies have reported a definitive link between FFR$_{CT}$ and patient prognosis.[24,30,31] Building on the 90-day experience,[32] the 1-year clinical outcomes of the ADVANCE registry highlighted the favorable prognosis associated with a negative FFR$_{CT}$ (> 0.80) with significantly lower cardiovascular death and myocardial infarction rate among those participants compared with those with a positive FFR$_{CT}$ (0.80% vs 0.20%; *P* = 0.01).[24] However, FFR$_{CT}$

only evaluates the hemodynamic significance of coronary stenosis rather than myocardial functional status. Thus, the combination of the hemodynamic significance of coronary stenosis and myocardial perfusion evaluation can provide incremental value in this clinical setting. We observed that the patients with matched positive resting static CTP and FFR_{CT} results were more likely to suffer from MACE compared with those in the negative CTP-FFR_{CT} match group at 1- and 3-year follow-ups (HR = 8.06 and 6.23, and both $P < 0.05$). Our observed MACE rates were higher than the ones in the ADVANCE registry (1.2%)[24] and the CONSERVE study (4.6%).[30] It can be explained that the patients who were both resting static CTP-positive and FFR_{CT}-positive in our study represented cases with relatively severe myocardial ischemia. Meanwhile, invasive FFR was not utilized in our study, and no additional non-invasive functional tests were utilized subsequent to CCTA to help guide treatment decisions. Therefore, the benefits seen in the positive resting static CTP and FFR_{CT} match group might be attributable to the ability to discriminate lesion-specific ischemia, allowing for optimal management, thus reducing the incidence of ACS leading to unplanned REV.

The additional value of resting static CTP over FFR_{CT} might increase especially in patients in the "gray zone" of FFR_{CT}, in which empirical watchful waiting for ICA is often chosen, due to the low prevalence of invasive FFR ≤ 0.80.[18] Previous studies reported that the conventional cutoff value of $FFR_{CT} \leq 0.80$ and the range of gray zone were associated with low specificity and a high false-positive rate with invasive FFR ≤ 0.80 as the reference standard for hemodynamically significant ischemia.[9,18,33,34] Our study found that a positive resting static CTP can slightly reduce the rate of ICA yielding nonobstructive CAD and increase the REV-to-ICA ratio in patients within the gray zone of FFR_{CT} and $FFR_{CT} \leq 0.70$ but without statistical significance. The main reason may be that these patients with suspected CAD did not have relevant myocardial ischemia.

Our study has some limitations. First, this was a retrospective post hoc analysis of a single-center prospective 2-arm study, and the results of resting static CTP were not available to caregivers and did not affect clinical decision-making. Second, this prospective study enrolled patients with 25% to 80% coronary stenosis on CCTA; thus, our study results cannot be generalized to all CAD patients. Third, the rate of 3-year follow-up loss was relatively high; however, our study sample size was adequately powered. Finally, this study did not use stress CTP to evaluate myocardial ischemia because of the potentially severe complications of stress CTP. The use of resting static CTP is convenient and safe, especially in a real-world scenario.

In conclusion, this study shows that, in patients with CAD, the addition of resting static CTP to CCTA plus FFR_{CT} resulted in an increased rate of subsequent coronary REV and a better prognosis with fewer MACE than FFR_{CT} or resting static CTP alone. Multicenter prospective, randomized, controlled trials with long-term follow-up are needed to further validate our study results.

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