Research Square

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Prognostic Value of CT-FFR-derived Functional SYNTAX Score in Patients with Three-Vessel Disease Without Early Revascularization

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Abstract

Background

The anatomical SYNTAX score (ASS) may overestimate risk in patients with three-vessel disease (TVD) because it does not distinguish hemodynamically significant from non-significant stenoses. Although CT-FFR-derived functional SYNTAX score (FSS) has shown prognostic value in patients undergoing revascularization, its utility in patients who do not undergo early revascularization remains uncertain. This study compared ASS and FSS for risk stratification and prediction of major adverse cardiovascular and cerebrovascular events (MACCE) in this population.

Methods

We retrospectively enrolled 262 patients with TVD who underwent CCTA between 2018 and 2020 and without revascularization within 90 days. ASS was calculated from CCTA, and FSS from CT-FFR. Risk stratification and prognostic performance for MACCE were compared. Three predictive models were constructed: Model 1 (clinical factors), Model 2 (Model 1 + ASS), and Model 3 (Model 1 + FSS).

Results

Using a cutoff of 22, FSS reclassified 61 patients (23.3%) from the ASS intermediate-to-high-risk group to the low-risk group. During a median follow-up of 55 months (range 4–86), MACCE occurred in 126 patients (48.1%). Kaplan-Meier analysis showed both ASS ($P = 0.0052$) and FSS ($P = 0.0011$) discriminated risk groups, with better separation by FSS. In the ASS intermediate-to-high-risk subgroup (n = 205), patients reclassified as FSS low-risk (n = 61) had significantly better event-free survival than those remaining FSS intermediate-to-high-risk ($P = 0.0011$). Multivariate Cox analysis identified FSS as an independent MACCE predictor (HR = 1.022, 95% CI: 1.007–1.037, $P = 0.003$), whereas ASS was not ($P = 0.167$). Time-dependent Cox regression showed a consistent association between FSS and MACCE across follow-up, whereas ASS was not significant at years 1–2. The model incorporating FSS had higher time-dependent AUC (0.664–0.701), better calibration (Brier score, 0.216), and greater clinical net benefit (35%–60% threshold probability) than the clinical model and the model incorporating ASS. NRI and IDI analyses confirmed significant incremental predictive value of FSS over ASS at years 2–5 ($P < 0.05$).

Conclusion

In TVD patients without early revascularization, CT-FFR-derived FSS refined non-invasive risk stratification beyond ASS and was independently associated with MACCE. Combining FSS with clinical factors may improve prognostic assessment and help identify patients who warrant closer follow-up.

1. Introduction

The SYNTAX score (SS) is a scoring system that quantifies coronary anatomical complexity based on invasive coronary angiography (ICA). It guides revascularization strategy decisions in patients with multivessel coronary artery disease and has been established as an independent predictor of prognosis in patients with complex coronary artery disease[1, 2].

With significant improvements in spatial resolution, coronary computed tomography angiography (CCTA) has become an important non-invasive modality for screening and assessing coronary artery disease[3]. However, CCTA is an anatomical test and cannot determine whether a stenosis causes functional ischemia, which may lead to overestimation of lesion severity[4]. Fractional flow reserve derived from CCTA (CT-FFR) combines image processing, anatomical modeling, and hemodynamic analysis to assess the functional significance of coronary lesions. CT-FFR has shown good diagnostic performance and agreement with invasive FFR [5, 6]. Its non-invasive nature and reproducibility make it a useful adjunct to CCTA for treatment planning and risk assessment in coronary artery disease.

The anatomical SYNTAX score (ASS) and functional SYNTAX score (FSS) are mainly used in patients with TVD considered for revascularization. Although FSS has demonstrated prognostic value in this setting [7], its value in TVD patients without early revascularization remains unclear. In practice, some TVD patients do not undergo early revascularization because of advanced age, comorbidities, anatomical complexity, or patient preference. These patients have heterogeneous clinical profiles and outcomes, but evidence for non-invasive risk stratification in this group remains limited. Because ASS reflects anatomical complexity without identifying ischemia-causing stenoses, it may overestimate risk in patients whose anatomically complex lesions are not functionally significant [8]. Incorporating CT-FFR into SYNTAX scoring may therefore provide a more precise estimate of ischemic burden and prognosis.

This study aimed to compare CCTA-derived ASS and CT-FFR-derived FSS for risk stratification and prediction of MACCE in patients with TVD who did not undergo early revascularization.

2. Methods

2.1 Study population

This retrospective study was approved by the Ethics Committee of the Affiliated Hospital of Dalian Medical University (No. PJ-KS-KY-2025-430), with a waiver of written informed consent. Data are available upon reasonable request. Baseline demographics, cardiovascular risk factors, and clinical data were retrieved from electronic medical records.

Patients who underwent CCTA between January 2018 and December 2020 were retrospectively and consecutively enrolled. Inclusion criteria: first diagnosis of TVD by CCTA (defined as at least one lesion with diameter stenosis > 50% in the left anterior descending, left circumflex, and right coronary arteries, with or without left main stenosis > 50%); age 35–80 years; and no early revascularization (within 90 days) after CCTA.

Exclusion criteria: prior myocardial infarction or ventricular aneurysm, atrial thrombus, valvular disease with aortic valve replacement, malignancy, or other major systemic diseases. Patients with poor image quality (score 1–2), severe diffuse calcification precluding SYNTAX score assessment, CT-FFR measurement failure, or renal insufficiency affecting evaluation were also excluded.

2.2 CCTA acquisition

All CCTA examinations were performed on second- or third-generation dual-source CT scanners (Somatom Flash/Force, Siemens Healthineers, Forchheim, Germany). Acquisition was performed with retrospective ECG-gated or prospective ECG-triggered protocols. The scan range extended from 1 cm below the carina to 2 cm below the cardiac diaphragmatic surface. Scan parameters were as follows: tube voltage, 100–120 kV; automatic tube current modulation (CARE Dose 4D); detector collimation, 2 × 64 × 0.6 mm or 2 × 192 × 0.6 mm; reconstruction slice thickness, 0.6 mm; field of view: 25 cm. All patients received 0.5 mg sublingual nitroglycerin 3–5 minutes prior to image acquisition.

2.3 CCTA image analysis and ASS

All CCTA images were retrieved from the picture archiving and communication system (PACS) and transferred to a dedicated workstation (Syngo.Via, Siemens) for post-processing and analysis. The ASS was independently assessed by two cardiovascular imaging specialists each with > 10 years of experience, and discrepancies were resolved by consensus. Multiple post-processing software tools were used. All lesions in vessels ≥ 2 mm in diameter with > 50% stenosis were scored according to the SYNTAX criteria, with the online SYNTAX Score Calculator used as needed. Evaluated parameters included lesion location, degree of stenosis, bifurcation involvement (bifurcation and trifurcation), vessel tortuosity, ostial involvement, lesion length, severe calcification, and diffuse disease[9, 10]. According to the 2023 ESC Guidelines for Management of Acute Coronary Syndrome and the 2024 ESC Guidelines for Management of Chronic Coronary Syndrome, patients were classified into low-risk (ASS ≤ 22) and intermediate-to-high-risk (ASS > 22) groups using a cutoff of 22[11, 12].

2.4 CT-FFR calculation and FSS

Based on CCTA data, CT-FFR was computed using dedicated software (CT-FFR, version 3.5, Siemens Healthineers, Germany). Two experienced cardiovascular imaging physicians independently measured all stenotic lesions (vessel diameter ≥ 2 mm with > 50%

luminal stenosis) in a double-blind manner. Inter-observer agreement was excellent (ICC = 0.987, 95% CI: 0.986–0.988) (Supplementary Fig. 1). The CT-FFR value was measured at 1–2 cm distal to the lesion, and the Δ CT-FFR was calculated as the difference between the proximal and distal CT-FFR values (Δ CT-FFR = $CT\text{-}FFR_{proximal}$ - $CT\text{-}FFR_{distal}$). A hemodynamically significant ischemic lesion was defined by either distal CT-FFR ≤ 0.80 or ΔCT-FFR > 0.15; occluded lesions were assigned a CT-FFR of 0.5[13, 14]. FSS was then calculated based on these functionally significant lesions. Patients were reclassified into low-risk (FSS ≤ 22) and intermediate-to-high-risk (FSS > 22) groups using the same cutoff.

All CT-FFR analyses were performed retrospectively, with clinicians remaining completely blinded to CT-FFR and FSS results; CT-FFR data were not incorporated into the original clinical workflow.

2.5 Endpoints and follow-up

Follow-up was conducted via medical record review, clinic visits, and telephone interviews, and was completed for all patients within a 15-day period by June 30, 2025. The primary endpoint was MACCE [11, 12], including (1) all-cause death; (2) late unplanned revascularization (> 90 days after CCTA); (3) non-fatal acute myocardial infarction (MI) not followed by late revascularization; (4) stroke; (5) acute heart failure.

2.6 Statistical analysis

Statistical analysis was performed using SPSS 26.0 and R software (version 4.3.2). Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range [M (Q1, Q3)] according to distribution. Categorical variables were expressed as counts and percentages [n (%)]. Normality and homogeneity of variance were assessed before group comparisons. The independent samples t-test was used for normally distributed variables with equal variance, whereas the Mann-Whitney U test was used for non-normal distributions or unequal variances. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. Interobserver agreement was evaluated using the intraclass correlation coefficient (ICC). Survival analysis was conducted using Kaplan–Meier curves and the log-rank test.

Univariate and multivariate Cox regression analyses were conducted to identify risk factors for MACCE. Variables with P ≤ 0.05 in univariate analysis were entered into multivariate Cox regression. Collinearity was assessed before multivariate modeling, with variance inflation factor (VIF) > 5 indicating multicollinearity. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). A clinical risk model (Model 1) was constructed, with ASS (Model 2) and FSS (Model 3) added separately as extended models. Time-dependent receiver operating characteristic (ROC) curves were used to evaluate discriminative ability for MACCE at 1–5 years, and the area under the curve (AUC) was calculated at each time point. Five-year calibration curves and Brier scores were used to assess agreement between predicted and observed risks. Decision curve analysis (DCA) evaluated clinical net benefit across threshold probabilities. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices quantified incremental predictive value at 1–5 years. All tests were two-sided, with P ≤ 0.05 considered statistically significant.

3. Results

A total of 1,427 consecutive patients with three-vessel coronary artery disease (TVD) who underwent CCTA between January 2018 and December 2020 were screened. Of these, 1,078 were excluded due to early revascularization. An additional 87 patients were excluded for the following reasons: 55 due to inadequate image quality (11 CT-FFR calculation failures, 20 cases of severe diffuse calcification, and 24 cases of motion artifacts), and 32 due to incomplete clinical or follow-up data. Ultimately, 262 patients were included in the final analysis. The study flowchart is presented in Fig. 1.

3.1 Baseline characteristics and SYNTAX score

The mean age of the 262 patients was 64.6 ± 9.0 years (range: 35—80), and 74.8% (196/262) were male. Diabetes mellitus was present in 45.8% (120/262), among whom 38.3%(46/120) were insulin-dependent. Clinical presentations were stable angina in 38.2% (100/262), silent ischemia in 40.8% (107/262), and unstable angina in 21.0% (55/262). The mean LVEF was 57.8 ± 1.9% (range: 51–64%). Baseline characteristics are summarized in Table 1.

Table 1
Patient baseline characteristics

Characteristics (n, %)	**n=262**
Age (years), mean ± SD	64.6 ± 9.0(35–80)
Male	74.8%(196)
BMI(kg/m²),mean ± SD	25.3 ± 2.8(17–36)
COPD	6(2.3%)
DM	120(45.8%)
-Insulin use	46(38.3%)
Hypertension	205(78.2%)
Dyslipidemia	140(53.4%)
Current smoking	108(41.2%)
Family history of CAD	24(9.2%)
Previous stroke	49(18.7%)
PVD,n(%)	26(10.0%)
Creatinine clearance (mL/min), mean ± SD	86.5 ± 18.0
LVEF(%),mean ± SD	57.8 ± 1.9(51–64)
Clinical presentation	
Silent ischaemia, n (%)	107(40.8%)
Stable angina, n (%)	100(38.2%)
Unstable angina, n (%)	55(21.0%)
Note: BMI=body mass index; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus; CAD=coronary artery disease; PVD=peripheral vascular disease; LVEF=left ventricular ejection fraction.	

The mean ASS and FSS were 31.4 ± 10.7 and 25.1 ± 12.6, respectively. Based on ASS, 57 patients were classified as low-risk and 205 as intermediate-to-high-risk; based on FSS, 118 classified as low-risk and 144 as intermediate-to-high-risk. Age and score values were higher in the intermediate-to-high-risk groups than in the low-risk groups for both ASS and FSS (Table 2). Notably, 61 patients (23.3%) were reclassified from the ASS intermediate-to-high-risk group to the FSS low-risk group.

3.2 Lesion characteristics according to ASS and FSS

Among the 262 patients, 23 (9.6%) had left-dominant and 239 (90.4%) right-dominant coronary circulation. A total of 3,555 coronary segments were evaluated, with 1,758 segments showing stenosis (≥ 50%), corresponding to 1,445 lesions. After CT-FFR optimization, 1,215 lesions remained, with 230 lesions (15.9%) reclassified as non-hemodynamically significant. These optimized lesions were more complex, including bifurcation lesions, aortic ostial lesions, severe tortuosity, and other types (Table 3). Additionally, the intermediate-to-high-risk group outnumbered the low-risk group based on FSS (Table 4). A representative case is illustrated in Fig. 2.

3.3 Follow-up outcomes

During a median follow-up of 55 months (range 4–86), MACCE occurred in 126 patients (48.1%). Among these events, late unplanned revascularization was the most common (77 events, 61.1%), followed by all-cause death (31, 24.6%), stroke (10, 7.9%), non-fatal acute MI not followed by late revascularization (3, 2.4%), and acute heart failure (5, 4.0%).

Stratified by ASS, the MACCE rate was significantly lower in the low-risk group than in the intermediate-to-high-risk group (31.6% vs. 52.7%, P = 0.005); no significant differences were observed in other endpoints. Stratified by FSS, the low-risk group had significantly

Table 2
Patient baseline characteristics according to ASS and FSS

Characteristics (n, %)	SS ≤ 22	SS>22	P value
ASS grouping	ASS ≤ 22 (n=57, 21.8%)	ASS>22 (n=205, 78.2%)	
Age (years), mean ± SD	61.9 ± 10.9	65.3 ± 8.2	0.010
BMI (kg/m²),mean ± SD	25.9 ± 2.8	25.1 ± 2.9	0.067
Sex(male)	40(70.2%)	157(76.6%)	0.332
DM	20(35.1%)	100(48.8%)	0.066
-insulin use	6(10.5%)	40(19.5%)	0.115
Hypertension	33(57.9%)	107(52.2%)	0.445
Dyslipidemia	43(75.4%)	162(79%)	0.667
Current smoking	19(33.3%)	89(43.4%)	0.170
Family history of CAD	7(12.3%))	17(8.3%)	0.356
COPD	0(0%)	6(2.9%)	0.345
PVD	2(3.5%)	24(11.7%)	0.067
Previous stroke	10(17.5%)	39(19%)	0.800
Creatinine clearance (mL/min)	89.6 ± 17.5	85.7 ± 18.1	0.156
LVEF(%),mean ± SD	58.1 ± 1.3	57.69 ± 2.0	0.249
Clinical presentation			
Stable angina	18(6.9%)	82(31.3%)	0.158
Unstable angina	12(4.6%)	43(16.4%)	0.745
Silent ischaemia	27(10.3%)	80(30.5%)	0.427
SYNTAX Score	18.0 ± 3.9	35.1 ± 8.9	<0.001
FSS grouping	FSS ≤ 22 (n=118, 45.0%)	FSS>22 (n=144, 55.0%)	
Age (years), mean ± SD	62.9 ± 9.4	65.9 ± 8.4	0.008
BMI (kg/m²),mean ± SD	25.5 ± 2.8	25.1 ± 2.9	0.260
Sex(male)	87(73.7%)	110(76.4%)	0.620
DM	49(41.5%)	71(49.3%)	0.209
-insulin use	16(13.6%)	30(20.8%)	0.124
Hypertension	68(57.6%)	72(50%)	0.218
Dyslipidemia	90(76.3%)	115(79.9%)	0.483
Current smoking	47(39.8%)	61(42.4%)	0.679
Family history of CAD	13(11%)	11(7.6%)	0.346
COPD	1(0.8%)	5(3.5%)	0.227
PVD	8(6.8%)	18(12.5%)	0.123

Note: BMI=body mass index; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus; CAD=coronary artery disease; PVD=perpheral vascular disease; LVEF=left ventricular ejection fraction; ASS=anatomical SYNTAX score; FSS=functional SYNTAX score.

Characteristics (n, %)	SS ≤ 22	SS>22	P value
Previous stroke	20(16.9%)	29(20.1%)	0.510
Creatinine clearance (mL/min)	88.8 ± 17.7	84.6 ± 18.2	0.063
LVEF(%),mean ± SD	57.9 ± 1.6	57.6 ± 2.1	0.079
Clinical presentation			
Stable angina	41(15.6%)	59(22.5%)	0.265
Unstable angina	26(9.9%)	29(11.1%)	0.857
Silent ischaemia	51(19.5%)	56(21.4%)	0.738
SYNTAX Score	13.9 ± 6.2	34.3 ± 8.2	<0.001

Note: BMI=body mass index; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus; CAD=coronary artery disease; PVD=perpheral vascular disease; LVEF=left ventricular ejection fraction; ASS=anatomical SYNTAX score; FSS=functional SYNTAX score.

Table 3
Comparison of the ASS and FSS

Characteristics(n = 262)	ASS	FSS	P value
SYNTAX score	31.4 ± 0.7	25.1 ± 12.6	<0.001
LMCAD	27	12	<0.001
Total occlusion	55	55	-
Trifurcation	25	21	0.103
Bifurcation(Medina)	388	319	<0.001
Medina 1,0,0	32	23	-
Medina 0,1,0	29	29	-
Medina 1,1,0	88	79	-
Medina 1,1,1	107	92	-
Medina 0,0,1	54	41	-
Medina 1,0,1	28	25	-
Medina 0,1,1	50	38	-
Aorto-ostial lesion[1]	19	5	<0.001
Severe tortuosity[2]	37	30	0.008
Long lesion (length > 20mm)[3]	302	272	<0.001
Heavy calcification[4]	547	460	<0.001
Diffuse disease[5]	45	41	0.054

Note: ASS= anatomical SYNTAX score; FSS= functional SYNTAX score. [1] A lesion was classified as aorto-ostial when located immediately at the origin of the coronary vessels stemming from the aorta (≤ 4 mm). [2] Severe tortuosity was defined as ≥ 1 bends of ≥ 90°, or ≥ 3 bends of 45°—90° proximal of the diseased segment. [3] Long lesion was defined as stenosis length > 20 mm. [4] Heavy calcification was defined as maximum encircling peripheral calcification of 180◦ or > 50% cross-sectional area. [5] Diffuse disease was defined as > 75% segment length with ≥ 50% stenosis or lumen < 2 mm; plaque area ≥ 1 mm².

Table 4
Comparison of FSS-based risk groups

Characteristics	FSS ≤ 22 (n = 118)	FSS>22 (n = 144)	P value
FSS	14.1 ± 6.2	34.7 ± 8.6	<0.001
LMCAD	0	12	<0.001
Total occlusion	8	47	-
Trifurcation	5	16	0.103
Bifurcation	75	244	<0.001
Aorto-ostial lesion	0	5	<0.001
Severe tortuosity	10	20	0.008
Long lesion (length > 20mm)	55	217	<0.001
Heavy calcification	95	365	<0.001
Diffuse disease	4	37	0.045
Note: ASS= antomical SYNTAX score; FSS= functional SYNTAX score			

lower rates of MACCE (33.9% vs. 59.7%, P < 0.001) and unplanned revascularization (21.2% vs. 36.1%, P = 0.008) than the intermediate-to-high-risk group; no significant differences were observed in other endpoints. Details are shown in Table 5.

3.4 Survival analysis

Kaplan-Meier survival analysis stratified by ASS and FSS showed that the cumulative event-free survival rates were significantly higher in the low-risk groups than in the intermediate-to-high-risk groups for both scoring systems (ASS: P = 0.0052; FSS: P = 0.0011) (Fig. 3, Fig. 4).

Table 5
MACCE according to ASS and FSS risk groups

MACCE n(%)	Total (n = 262)	ASS ≤ 22 (n=57)	ASS>22 (n=205)	P value	FSS ≤ 22 (n=118)	FSS>22 (n=144)	P value
	126(48.1%)	**18(31.6%)**	**108(52.7%)**	**0.005**	**40(33.9%)**	**86(59.7%)**	**P<0.001**
All-cause death	31(11.8%)	5(8.8%)	26(12.7%)	0.419	10(8.5%)	21(14.6%)	0.128
Unplanned revascularization	77(29.4%)	13(22.8%)	64(31.2%)	0.217	25(21.2%)	52(36.1%)	0.008
Stroke	10(3.8%)	0(0.0%)	10(4.9%)	0.089	3(2.5%)	7(4.9%)	0.330
non-fatal acute MI	3(1.1%)	0(0.0%)	3(1.5%)	1.000*	0(0.0%)	3(2.1%)	0.255*
Acute heart failure	5(1.9%)	0(0.0%)	5(2.4%)	0.589	2(1.7%)	3(2.1%)	1.000*
Note: * Fisher's exact test; ASS= antomical SYNTAX score; FSS= functional SYNTAX score							

Subgroup analysis was performed in the 205 patients classified as intermediate-to-high-risk by ASS, who were reclassified into FSS low-risk (n = 61, 29.8%) and FSS intermediate-to-high-risk (n = 144) groups. Kaplan-Meier analysis demonstrated a significant difference between these two groups (P = 0.0011) (Fig. 5).

Time-dependent Cox regression models were used to evaluate the predictive performance of ASS and FSS for MACCE at different follow-up time points (Fig. 6). ASS did not achieve statistical significance at years 1 and 2, whereas FSS showed statistically

significant predictive performance annually throughout the follow-up period. The HR of FSS was consistently higher than that of ASS after year 2.

3.5 Univariate and multivariate analyses

Univariate Cox regression analysis showed that age, COPD, creatinine clearance, lipoprotein(a), ASS, and FSS were significantly associated with MACCE (all $P < 0.05$). Collinearity diagnostics indicated no significant multicollinearity among all variables (VIF < 2).

Three multivariate Cox regression models were constructed (Table 6). In Model □ (clinical risk model), only lipoprotein(a) was an independent predictor of MACCE after adjustment for age, COPD, creatinine clearance, and lipoprotein(a) (HR = 1.001, 95% CI: 1.000–1.002, P = 0.006). In Model □ (Model □ + ASS), ASS was not an independent predictor (HR = 1.012, 95% CI: 0.995–1.029, P = 0.167), whereas lipoprotein(a) remained significant (HR = 1.001, 95% CI: 1.000–1.002, P = 0.008). In Model □ (Model □ + FSS), FSS was an independent predictor (HR = 1.022, 95% CI: 1.007–1.037, P = 0.003), as were lipoprotein(a) (HR = 1.001, 95% CI: 1.000–1.002, P = 0.008) and creatinine clearance (HR = 0.989, 95% CI: 0.978–1.000, P = 0.041).

3.6 Risk model development and predictive performance comparison

Based on independent predictors identified in multivariate Cox analysis results (Table 6), three predictive models were developed to evaluate the incremental predictive value of ASS and FSS: Model 1 included lipoprotein(a) and creatinine clearance; Model 2 added ASS to Model 1; and Model 3 added FSS to Model 1.

3.6.1 Time-dependent AUC analysis

Time-dependent AUC analysis was used to assess annual predictive performance for MACCE (Fig. 7). Model 3 yielded higher AUC values than Model 2 and Model 1 across years 1–5 (AUC: 0.664–0.701 vs. 0.630–0.655 vs. 0.587–0.624, respectively). Its highest discrimination was observed at years 2, 4, and 5 (AUC: 0.697, 0.701, and 0.689, respectively).

3.6.2 Calibration analysis

The 5-year calibration curves showed good agreement between predicted and observed risks across all three models, with most calibration points closely approximating the ideal reference line (Fig. 8).

3.6.3 Decision curve analysis

The 5-year DCA curve (Fig. 9) demonstrated that Model 3 provided greater clinical net benefit than Model 1, Model 2, and the reference line across threshold probabilities of 35%–60%.

Time-dependent NRI and IDI were used to evaluate incremental predictive value between models. Model 1 vs Model 2: NRI and IDI showed no statistical significance at years 1–5 (all $P > 0.05$). Model 1 vs Model 3: No statistical significance at year 1; NRI and IDI were significant at years 2–5 (all $P < 0.05$). Model 2 vs Model 3: No overall significant difference; IDI was significant at years 2 and 3, NRI at year 4, and both NRI and IDI at year 5 (Table 7 and Fig. 10 for details).

Table 6
Predictors of MACCE by univariate and multivariate Cox regression analysis

	Univariate analysis			Multivariate analysis(Model □)			Multivariate analysis(Model □)			Multivariate analysis(Model □)		
	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
age	1.024	1.003–1.045	0.027	1.020	0.996–1.044	0.107	1.018	0.994–1.042	0.148	1.016	0.992–1.040	0.205
Sex(male)	0.985	0.657–1.478	0.942									
BMI	1.008	0.948–1.071	0.798									
DM	0.976	0.688–1.383	0.890									
Hypertension	1.158	0.747–1.794	0.511									
Current smoking	1.080	0.755–1.546	0.673									
Dyslipidemia	0.856	0.603–1.215	0.385									
Family history of CAD	1.022	0.519–2.014	0.950									
COPD	2.534	1.032–6.222	0.042	2.418	0.760–7.701	0.135	2.469	0.775–7.870	0.126	2.363	0.742–7.531	0.146
PVD	1.131	0.637–2.008	0.675									
Previous stroke	1.341	0.876–2.053	0.177									
Creatinine clearance	0.988	0.979–0.997	0.010	0.990	0.979–1.000	0.060	0.990	0.977–0.998	0.066	0.989	0.978–1.000	0.041
Lp(a)	1.001	1.000–1.002	0.002	1.001	1.000–1.002	0.006	1.001	1.000–1.002	0.008	1.001	1.000–1.002	0.008
ASS	2.001	1.214–3.298	0.007				1.012	0.995–1.029	0.167			
FSS	2.268	1.559–3.298	< 0.001							1.022	1.007–1.037	0.003

Note: Model □ =:clinical risk model (age, COPD, creatinine clearance, and lipoprotein(a));Model □ = Model □+ASS□Model □ = Model □+FSS. HR□Hazard Ratio

4. Discussion

This study compared the prognostic value of CCTA-derived ASS and CT-FFR-derived FSS in patients with TVD who did not undergo early revascularization. The findings indicate that CT-FFR-derived functional assessment adds prognostic information beyond anatomical

Table 7
Predictive performance of different risk models for MACCE at various time points

Model Comparison	Time	NRI	NRI(95% CI)	NRI P value	IDI	IDI (95% CI)	IDI P value
Model 1 vs Model 2	Year 1	0.2696	−0.1829–0.4794	0.198	0.0073	−0.002–0.0240	0.176
	Year 2	0.2395	−0.1276–0.4417	0.136	0.0101	−0.001–0.0317	0.102
	Year 3	0.2423	−0.0531–0.4296	0.110	0.0125	−0.0007–0.0410	0.094
	Year 4	0.1902	−0.0768–0.4030	0.140	0.0121	−0.0006–0.0459	0.106
	Year 5	0.2675	−0.0384–0.5171	0.068	0.0190	−0.0000–0.0645	0.052
Model 1 vs Model 3	Year 1	0.3772	−0.0411–0.7070	0.074	0.0203	−0.0018–0.0499	0.076
	Year 2	0.4975	0.1872–0.7841	0.002	0.0362	0.0077–0.0781	0.012
	Year 3	0.4795	0.1784–0.7329	< 0.001	0.0434	0.0089–0.0920	0.006
	Year 4	0.5074	0.2435–0.7623	0.002	0.0488	0.0109–0.1057	0.004
	Year 5	0.6106	0.3470–0.8733	< 0.001	0.0666	0.0185–0.1379	< 0.001
Model 2 vs Model 3	Year 1	0.3168	−0.3081–0.6616	0.462	0.0129	−0.0088–0.0398	0.252
	Year 2	0.447	−0.0333–0.7202	0.084	0.0262	0.0002–0.0623	0.048
	Year 3	0.3355	−0.0005–0.6948	0.052	0.0309	0.0005–0.0747	0.042
	Year 4	0.3596	0.0291–0.6978	0.024	0.0367	−0.0003–0.0827	0.056
	Year 5	0.4124	0.0548–0.8360	0.018	0.0475	0.0020–0.1026	0.042
Note: Model 1 = clinical model; Model 2 = clinical model + ASS; Model 3 = clinical model + FSS							

stenosis complexity in this conservatively managed TVD cohort. Nearly one quarter of patients assigned to the ASS intermediate-to-high-risk group were reclassified as low risk by FSS, and this subgroup had more favorable event-free survival. After adjustment for clinical factors, prognostic information was retained by the functional score but not by ASS. The clinical model incorporating FSS also showed better discrimination, calibration, and net benefit than the clinical model alone or the model incorporating ASS.

CCTA is a major non-invasive modality for coronary artery disease assessment, and its agreement with invasive coronary angiography for anatomical evaluation has been widely investigated [15, 16]. In the present cohort, the assessment was based on CCTA rather than invasive angiography, reflecting the clinical context of patients who did not undergo early revascularization. A limitation of anatomical CCTA assessment is that calcified plaques and blooming artifacts can compromise luminal stenosis evaluation [17, 18]. CT-FFR adds functional information to anatomical imaging and has shown correlation with invasive FFR in prior studies. This combination provides the technical basis for calculating a functional SYNTAX score from non-invasive imaging [19, 20].

The SYNTAX score is commonly used to guide PCI or CABG strategy selection in TVD patients undergoing revascularization [21–23]. Qiao et al.[24] reported the prognostic value of CT-FFR-derived FSS in patients with de novo TVD, but their population predominantly included patients undergoing revascularization. The present study extends this question to TVD patients without early revascularization, a clinically relevant but less frequently studied group. Functional rescoring moved 23.3% of patients from the ASS intermediate-to-high-risk group to the low-risk category, supporting the concept that anatomically complex disease may not always correspond to functionally significant ischemic burden. Both ASS (31.6% vs. 52.7%, P = 0.005) and FSS (33.9% vs. 59.7%, P < 0.001) discriminated prognosis, with a larger absolute MACCE separation under the functional classification. This pattern is consistent with anatomical risk overestimation when lesion-specific ischemia is not considered.

Kaplan-Meier analysis showed significantly higher event-free survival in the lowrisk groups than in the intermediate-to-high-risk groups for both ASS and FSS (ASS: P = 0.0052; FSS: P < 0.0001). In the ASS intermediate-to-high-risk group (n = 205), 29.8% of

patients (61/205) were reclassified as low-risk by FSS, and this subgroup had significantly better event-free survival than the subgroup remaining FSS intermediateto-high-risk (P = 0.0011). This result indicates that a proportion of patients classified as anatomically higher risk may have a lower functional risk profile.

Time-dependent Cox regression analysis strengthened this interpretation. The association between FSS and MACCE was evident across years 1–5, whereas ASS did not reach statistical significance during years 1–2. The HR of FSS exceeded that of ASS from years 2 to 5. This difference may reflect the ability of functional scoring to distinguish ischemia-related lesions from non-ischemic anatomical stenoses, particularly when anatomical complexity alone does not capture short-term risk.

In multivariate Cox regression, FSS was associated with MACCE after clinical adjustment (HR = 1.022, 95% CI: 1.007–1.037, P = 0.003), whereas ASS was not (HR = 1.012, P = 0.167). This contrast supports the hypothesis that functional ischemic burden may better capture prognostic risk than anatomical complexity alone in TVD patients without early revascularization. Lipoprotein(a) and creatinine clearance were also associated with MACCE. Elevated lipoprotein(a) is linked to residual cardiovascular risk [25, 26], and renal dysfunction can increase adverse cardiovascular risk through atherosclerotic, inflammatory, and metabolic pathways [27, 28]. In contrast, diabetes, hypertension, and smoking were not significant in univariate analysis. This may reflect the advanced coronary disease burden and standardized medical therapy in this cohort, which could attenuate the discriminatory value of conventional risk factors [29, 30].

The predictive models showed a similar gradient. Compared with the clinical model and the clinical model plus ASS, the model incorporating FSS yielded higher timedependent AUC values (0.664–0.701), better calibration (Brier score, 0.2160), and greater clinical net benefit across threshold probabilities of 35%–60%. NRI and IDI analyses also indicated incremental predictive value beyond the clinical model at years 2–5 (P < 0.05), whereas ASS did not add comparable information. The calibration curves suggested acceptable agreement between predicted and observed risks, and DCA indicated improved net benefit after adding functional information.

This study has several limitations. First, it was a single-center retrospective study with a relatively limited sample size and potential selection bias, which may affect the representativeness and generalizability of the findings. Second, the median follow-up of 55 months remains insufficient for long-term prognostic assessment of coronary artery disease, requiring longer follow-up to validate the long-term predictive value of FSS. Third, this study only included TVD patients without early revascularization, lacking a contemporaneous revascularized control group. This design was based on the study objective rather than comparing the superiority of different treatment strategies; therefore, the conclusions cannot be extrapolated to revascularization decision-making itself. Fourth, some clinical data in this retrospective study (e.g., medication adherence, intensity of lifestyle interventions) were incompletely recorded, which may affect the accuracy of the results. Future multicenter, prospective studies are needed to further validate the prognostic value of FSS in this population and explore its potential to guide dynamic adjustment of treatment strategies.

5. Conclusion

In patients with TVD managed without early revascularization, CT-FFR-derived FSS added prognostic information beyond anatomical SYNTAX scoring. Its integration with clinical factors, including lipoprotein(a) and renal function, may support more individualized non-invasive risk assessment and follow-up planning, although external validation is needed before broader clinical use.

Abbreviations

CCTA, coronary computed tomography angiography; CAD, coronary artery disease; MACCE, major adverse **cardiovascular** and cerebrovascular events; ASS, anatomical SYNTAX score; FSS, functional SYNTAX score; SS, SYNTAX score; CT-FFR, fractional flow reserve derived from computed tomography; TVD, three-vessel disease; ICA, invasive coronary angiography; PACS, picture archiving and communication system; LMCAD, left main coronary artery disease;RCA, right coronary artery; LAD, left anterior descending artery; D1, first diagonal branch; D2, second diagonal branch; LCX, left circumflex artery; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CAD, coronary artery disease; PVD, peripheral vascular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; HR, hazard Ratio; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the curve.

Declarations

Acknowledgements Not applicable. Authors' contributions X.L. and Z.W. conceived and designed the study. X.L., H.M., J.Y., J.L., M.Z., and X.S. contributed to data collection, image analysis, statistical analysis, or interpretation of the results. X.L. drafted the manuscript. Z.W. and F.L. are the corresponding authors, they supervised the study and critically revised the manuscript. All authors read and approved the final manuscript. Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Availability of data and materials Data are available upon reasonable request. Ethics approval and consent to participate.This retrospective study was approved by the Ethics Committee of the Affiliated Hospital of Dalian Medical University (No. PJ-KS-KY-2025-430).The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study, in accordance with relevant national regulations. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki. Consent for publication. Not applicable. Competing interests. The authors declare that they have no competing interests.

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Figures

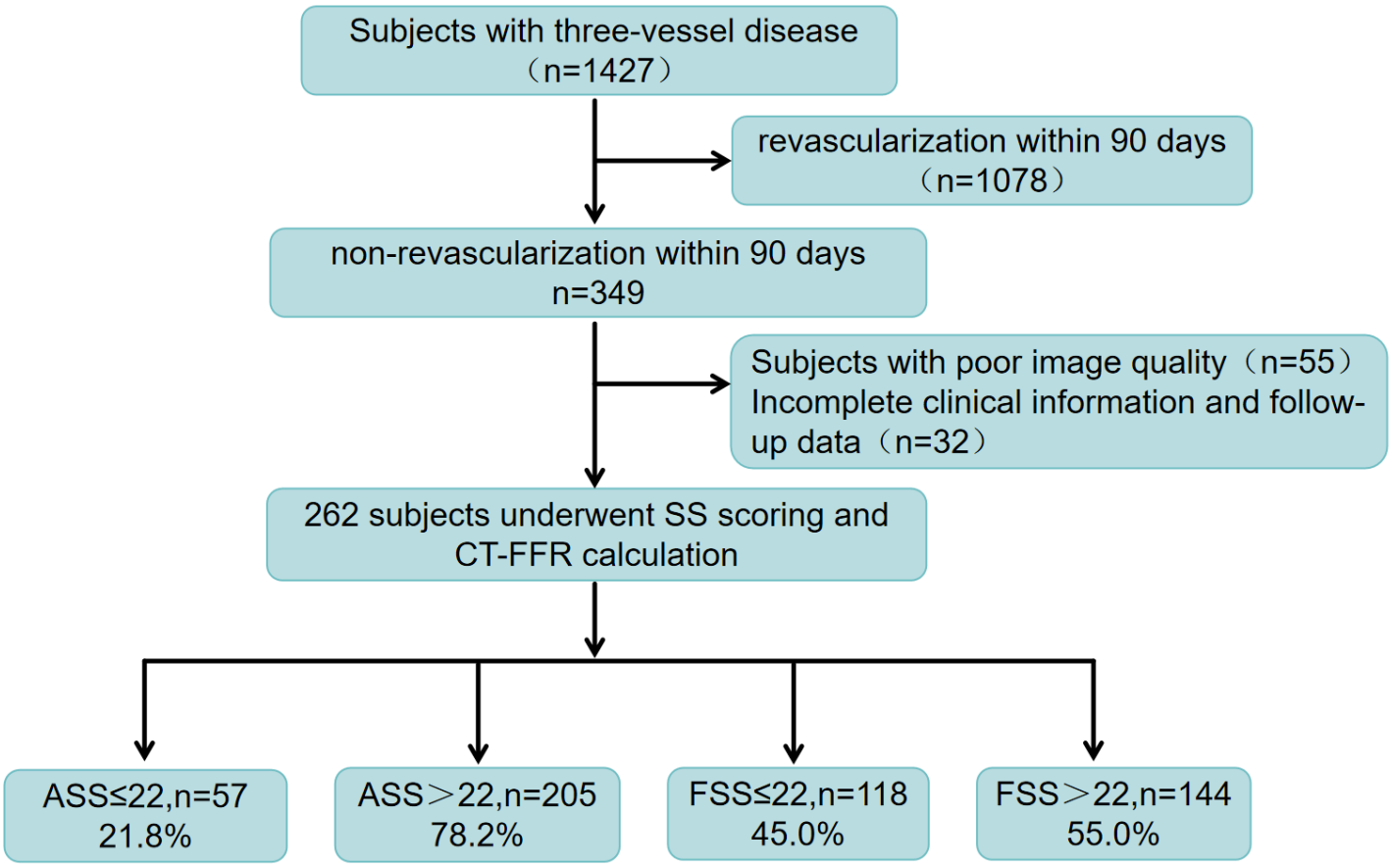


Figure 1

Study flowchart. ASS=anatomical SYNTAX score; FSS=functional SYNTAX score; SS=SYNTAX score; CT-FFR=fractional flow reserve derived from computed tomography

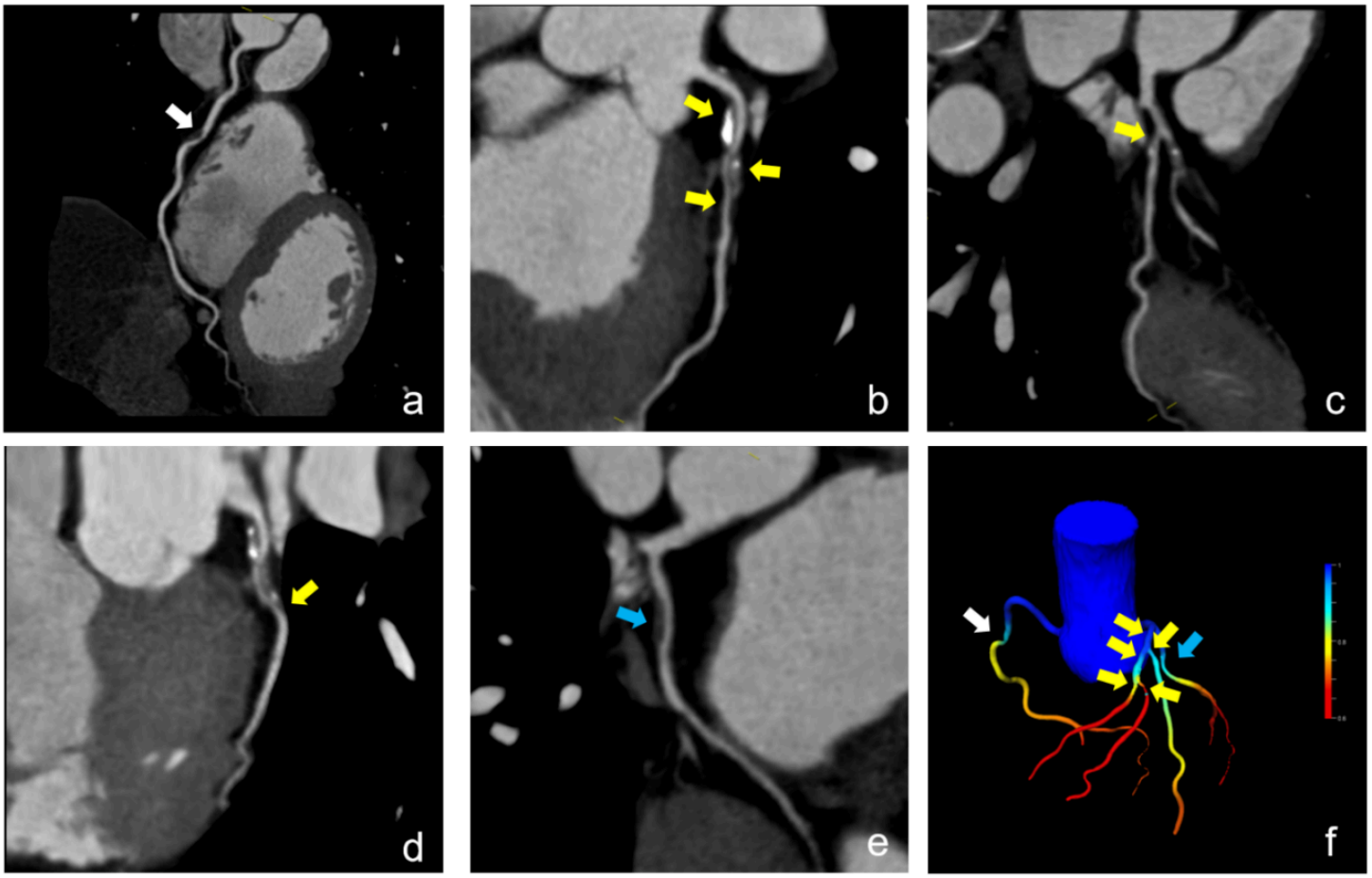


Figure 2

Representative case of the calculation of ASS and FSS in a patient with TVD. (a–e) CCTA images show significant stenosis in the RCA (segment #2, white arrows), LAD (segments #6–8, yellow arrows), D1 (segment #9, yellow arrows), D2 (segment #10, yellow arrows), and LCX (segment #11,blue arrows). The ASS was 28, classifying the patient into the intermediate-to-high-risk group. (f), Machine learning-derived CT-FFR showed no functional ischemia in RCA #2, LAD #6, D1 #9, or LCX #11. The FSS was 12, reclassifying the patient into the low-risk group.CCTA=coronary computed tomography angiography; CT-FFR,=fractional flow reserve derived from computed tomography; FSS=functional SYNTAX score; ASS=anatomical SYNTAX score; RCA=right coronary artery; LAD=left anterior descending artery; D1=first diagonal branch; D2=second diagonal branch; LCX=left circumflex artery.

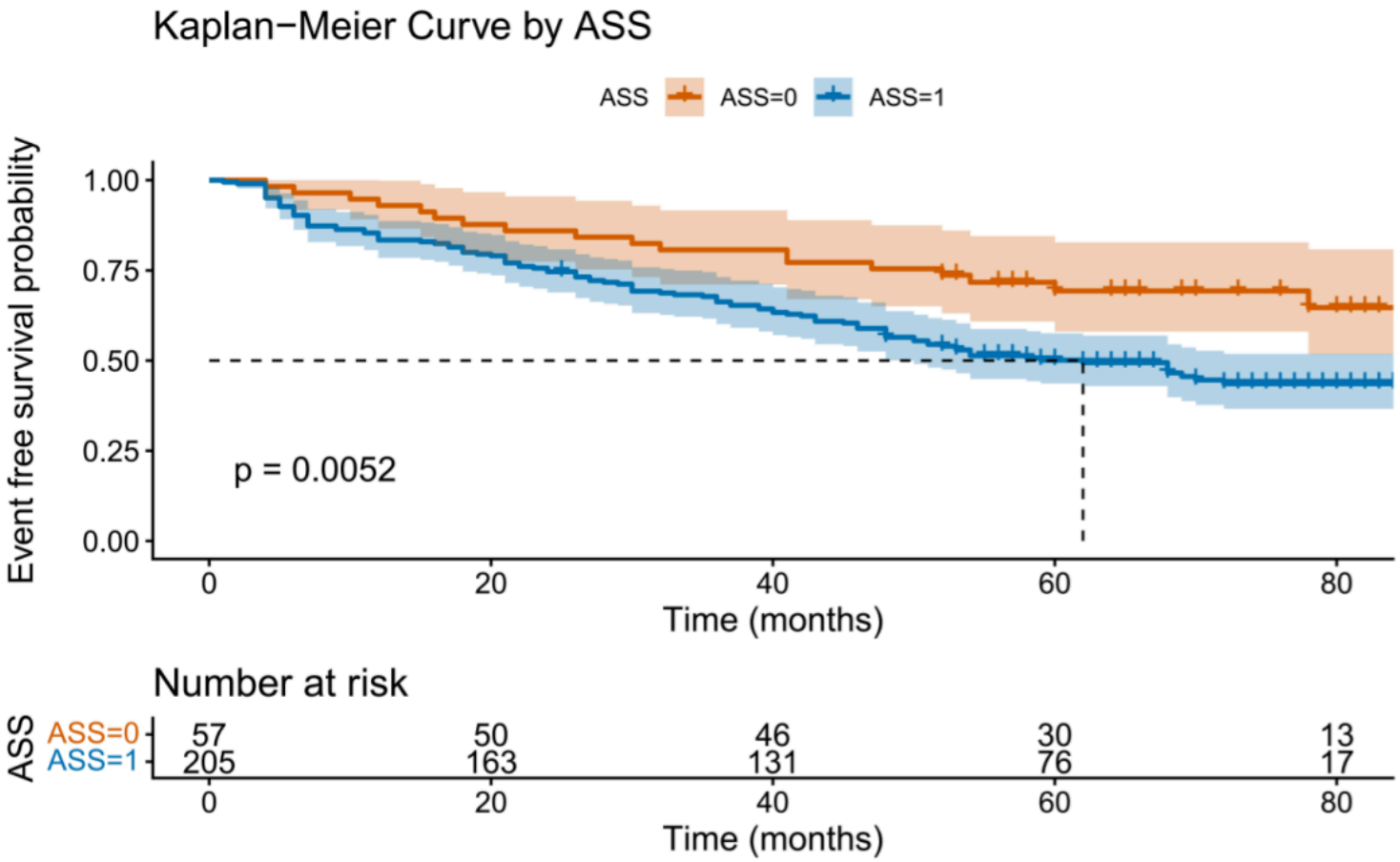


Figure 3

Kaplan-Meier curve for event-free survival stratified by ASS. The cumulative event-free survival rate was significantly higher in the ASS low-risk group than in the ASS intermediate-to-high-risk group (log-rank P = 0.0052).

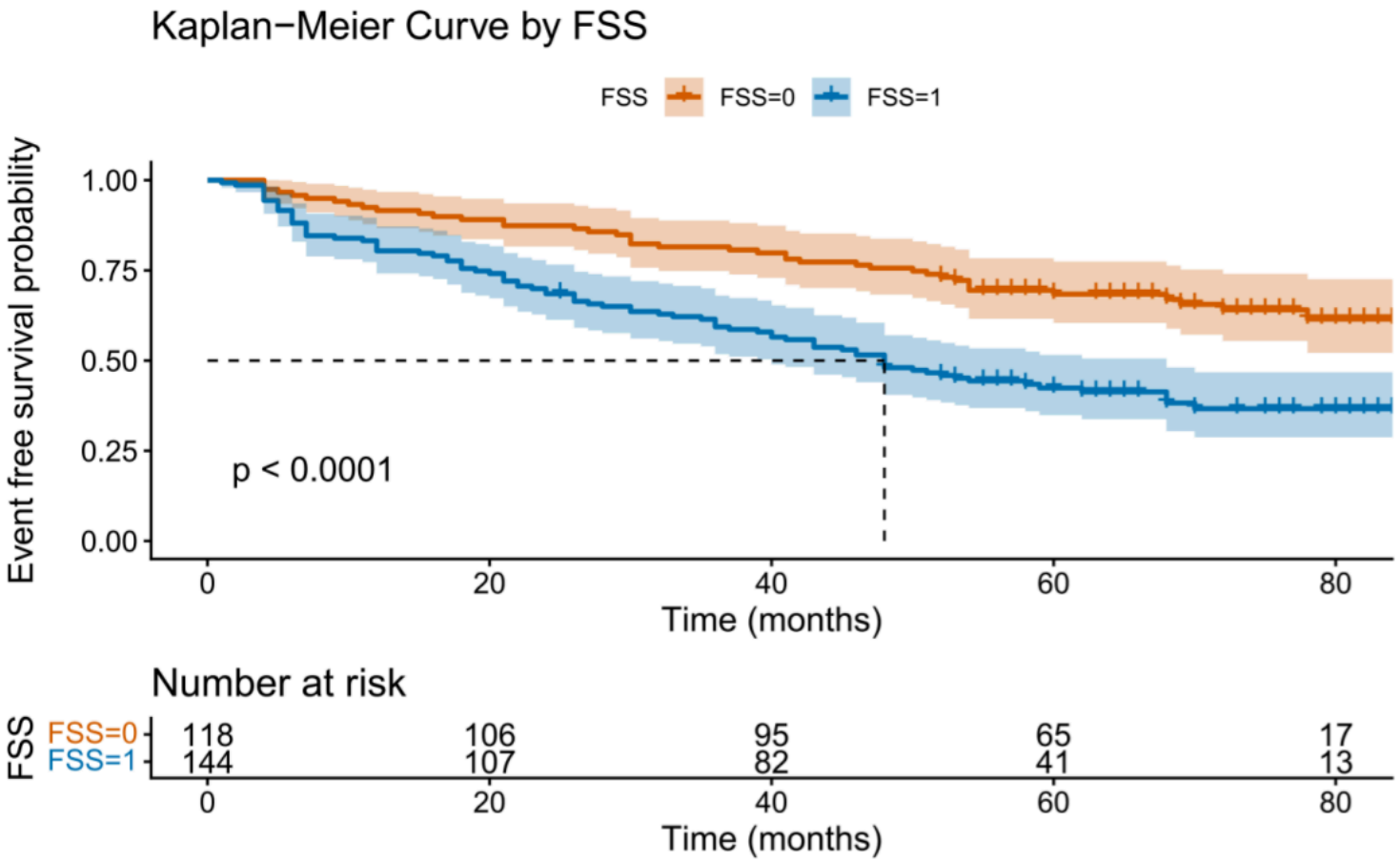


Figure 4

Kaplan-Meier curve for event-free survival stratified by FSS. The cumulative event-free survival rate was significantly higher in the FSS low-risk group than in the FSS intermediate-to-high-risk group (log-rank P < 0.0001).

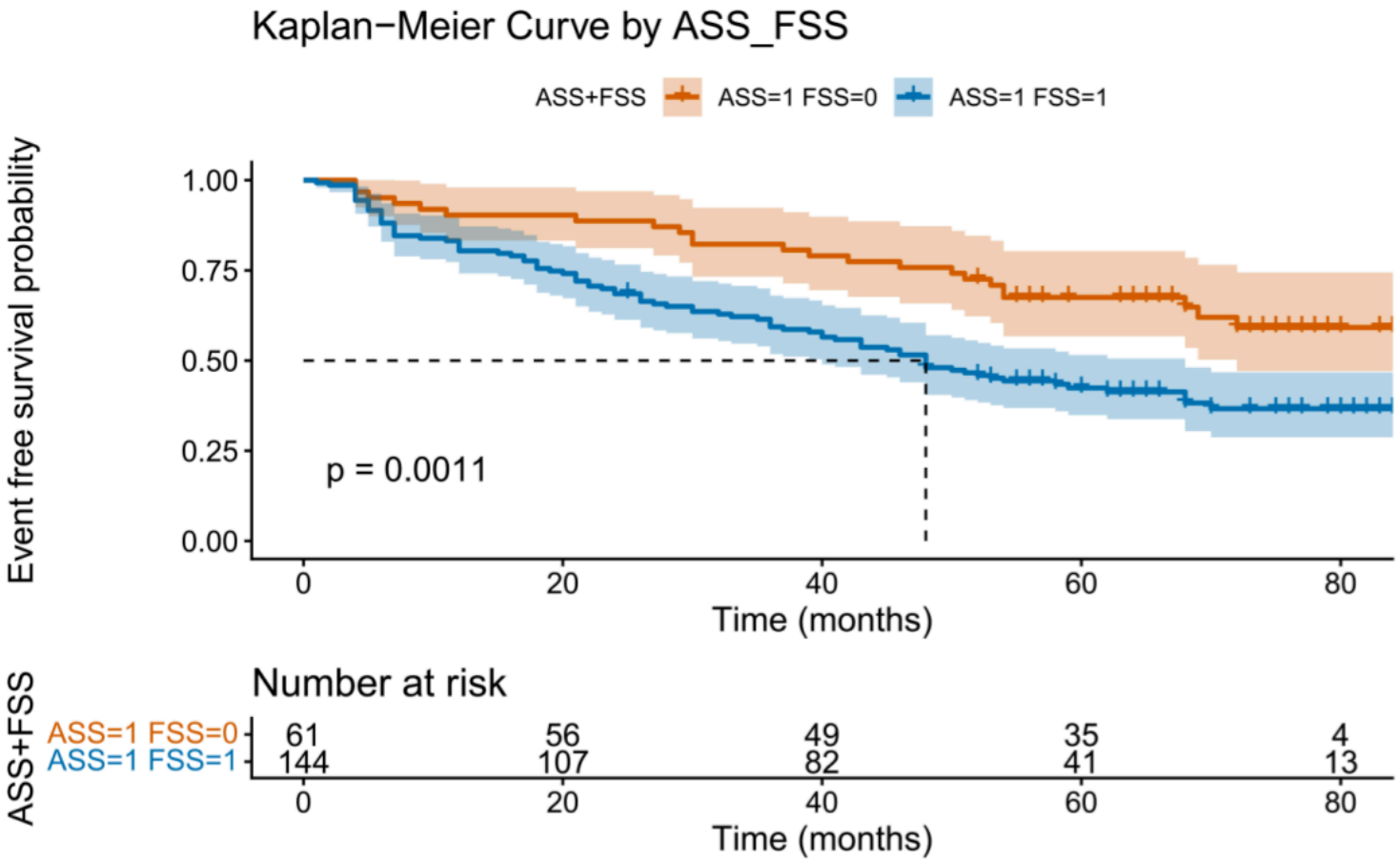


Figure 5

Kaplan-Meier curve stratified by FSS within the ASS intermediate-to-high-risk group. Among the 205 patients in the ASS intermediate-to-high-risk group, the cumulative event-free survival rate was significantly higher in the FSS low-risk subgroup (n = 61) than in the FSS intermediate-to-high-risk subgroup (n = 144) (log-rank P = 0.0011).

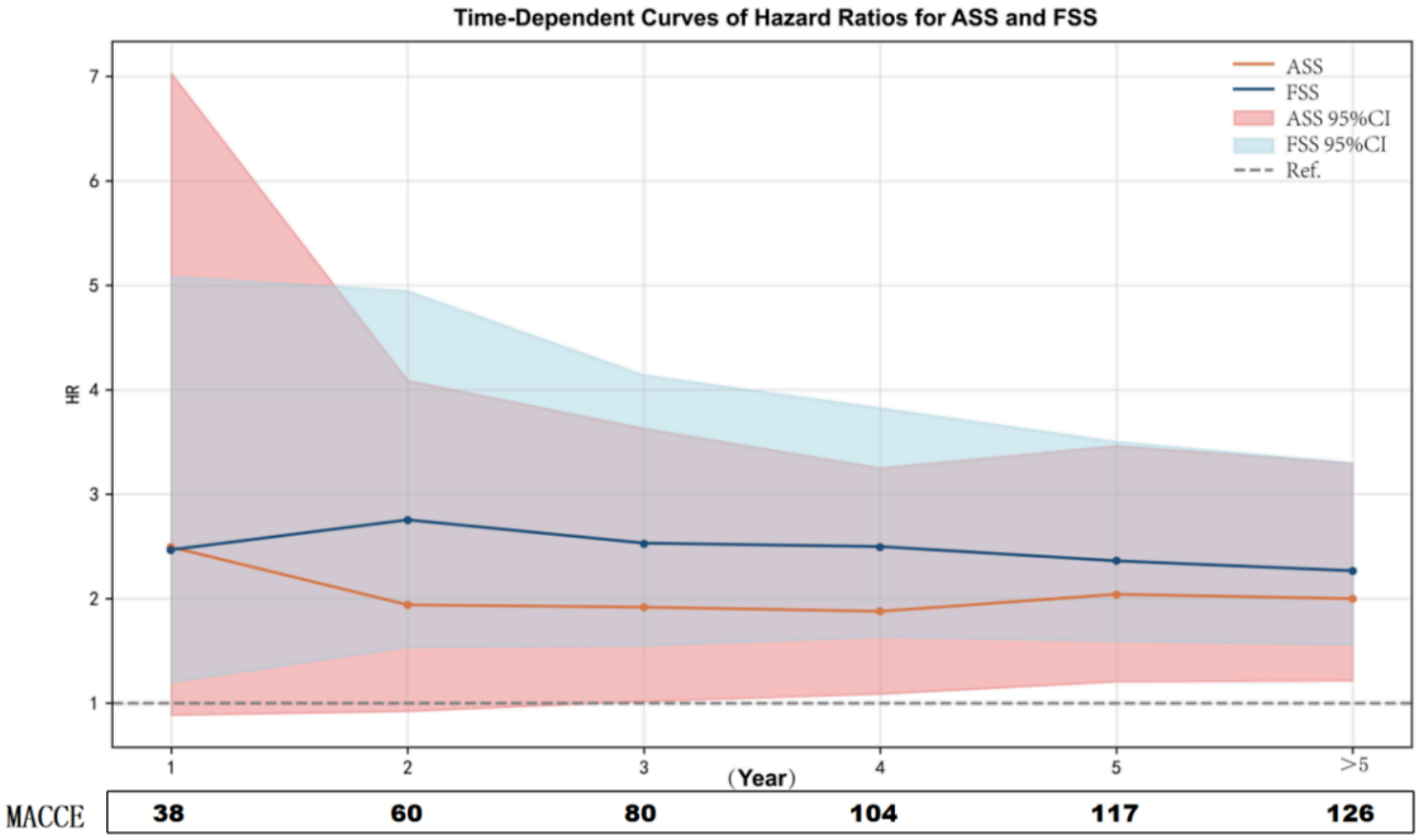


Figure 6

Time-dependent HR curves for MACCE prediction. HRs with 95% CIs are showed for ASS (orange) and FSS (blue). ASS was not significant at years 1–2, whereas FSS was significant throughout follow-up. MACCE event numbers are indicated below the x-axis. HR=Hazard Ratio.

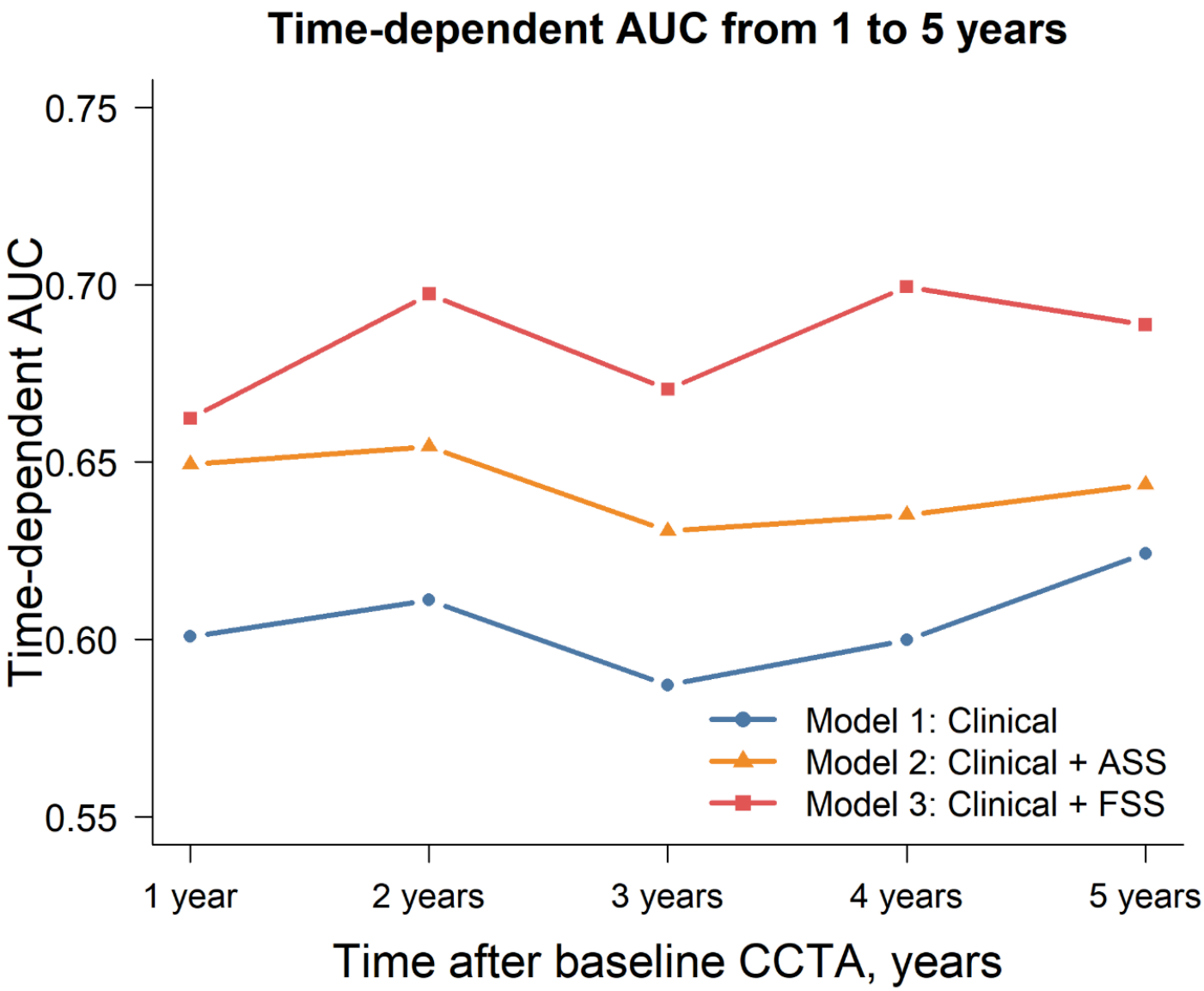


Figure 7

Time-dependent AUC for MACCE prediction at years 1–5. Annual AUC values were 0.601, 0.611, 0.587, 0.600, and 0.624 for Model 1; 0.649, 0.655, 0.630, 0.635, and 0.644 for Model 2; and 0.664, 0.701, 0.675, 0.697, and 0.690 for Model 3

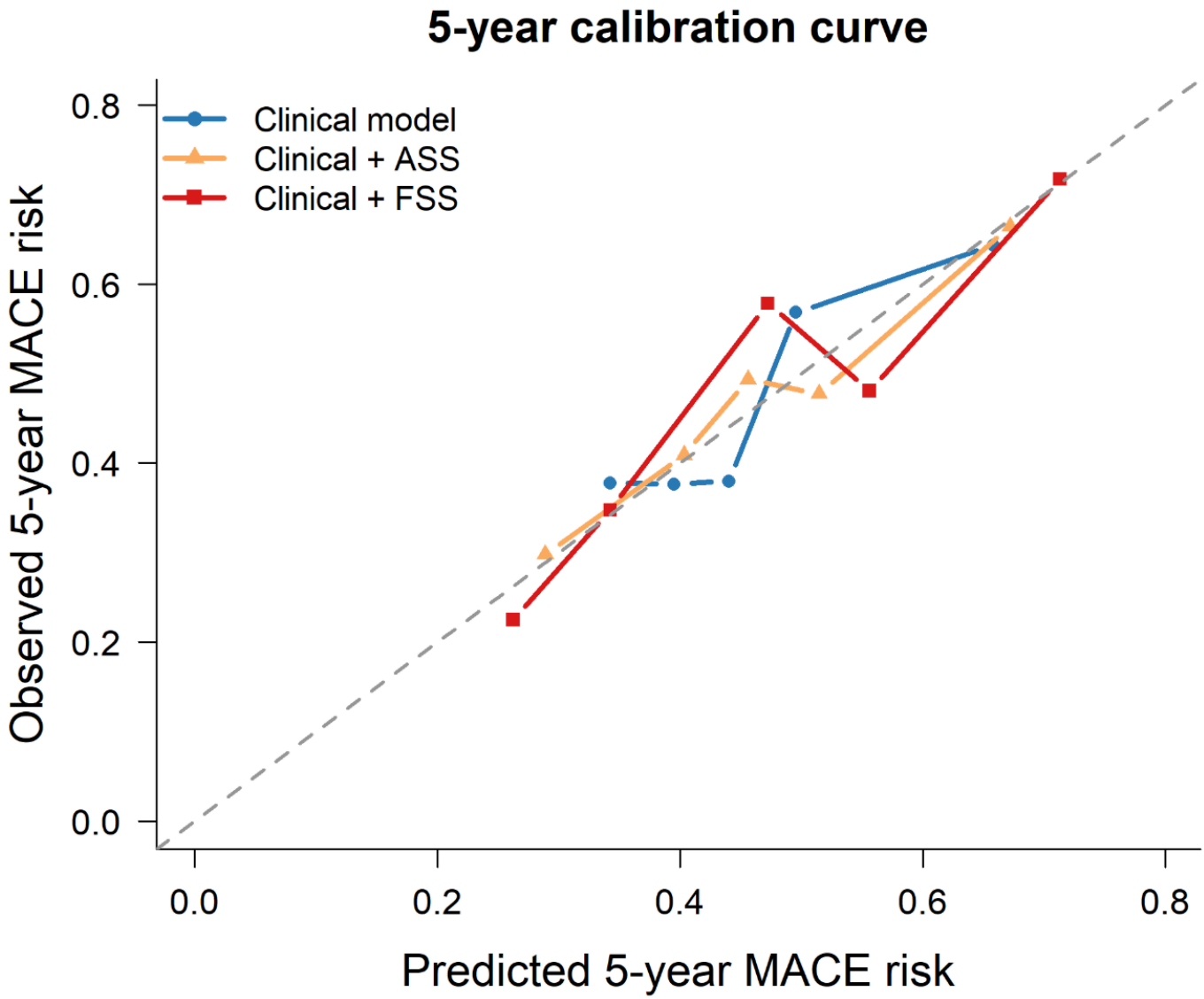


Figure 8

Five-year calibration curve. Calibration points for all three models closely approximated the ideal reference line. Brier scores were 0.2356 for Model 1 , 0.2322 for Model 2 , and 0.2160 for Model 3.

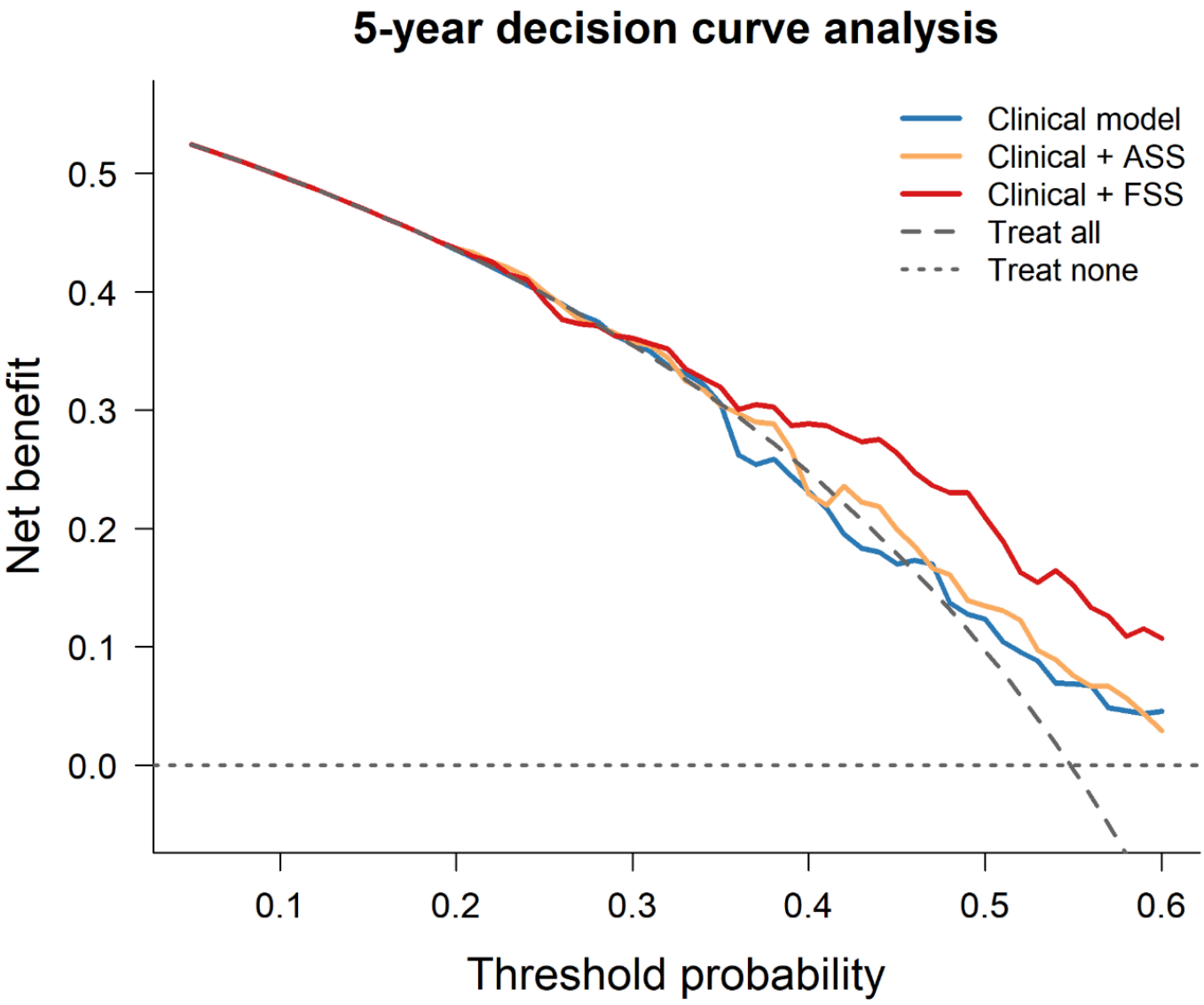


Figure 9

Five-year decision curve analysis. DCA showed clinical net benefit across threshold probabilities. Model 3 demonstrated higher net benefit than Model 1 and Model 2 within the 35%–60% threshold probability range.

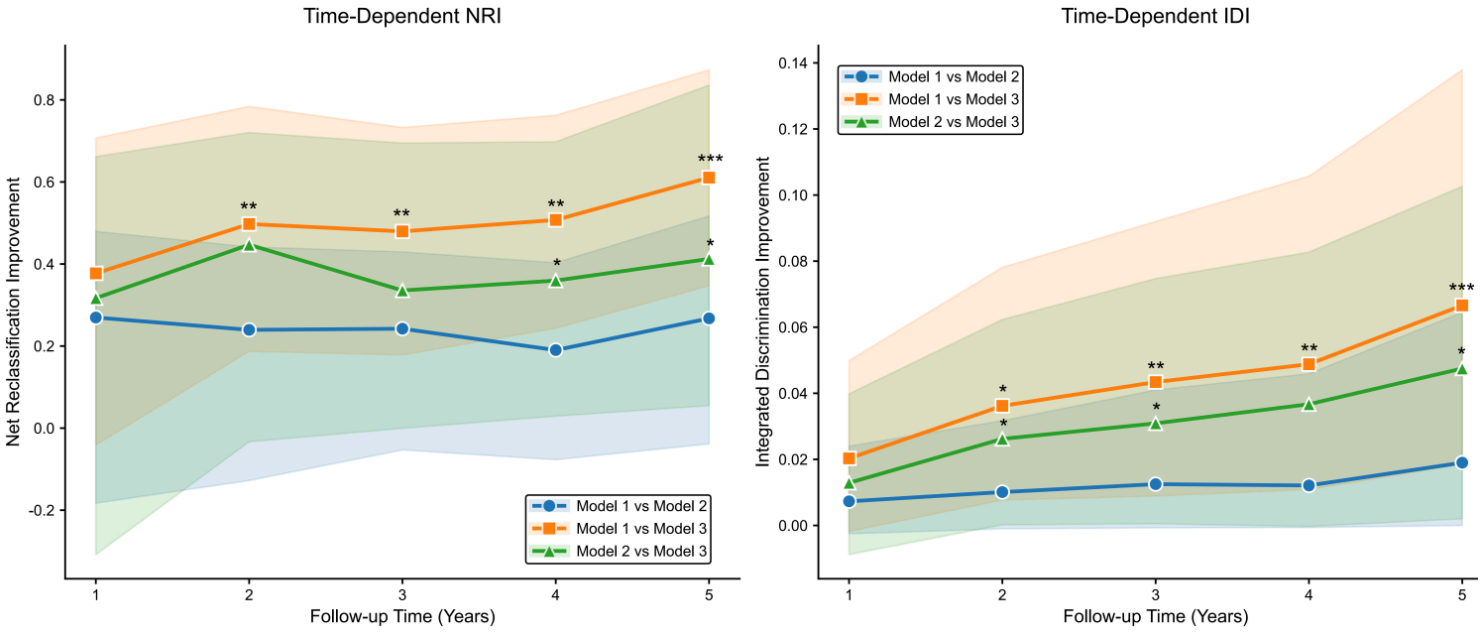


Figure 10

Time-dependent NRI and IDI curves (*P < 0.05, **P < 0.01, ***P < 0.001.) Blue indicates Model 1 vs Model 2; orange indicates Model 1 vs Model 3; green indicates Model 2 vs Model 3. Model 1 = clinical model; Model 2 = clinical model + ASS; Model 3 = clinical model + FSS

Supplementary Files

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- SupplementaryFig.1.docx