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Authors: Jiani Tang, M.D; Yan Lai, M.D; Shengxian Tu, PhD; Fei Chen, M.D; Yian Yao, M.D; Zi Ye, M.D; Jianyun Gu, M.D; Yanhua Gao, M.D; Chunyu Guan, M.D; Jiapeng Chu, M.D; Cheng Yang, M.D; Xuebo Liu, M.D

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Quantitative Flow Ratio guided Residual Functional SYNTAX Score for Risk Assessment in Patients with ST-Segment Elevation Myocardial Infarction undergoing Percutaneous Coronary Intervention

Jiani Tang, MD[1*]; Yan Lai, MD[1*]; Shengxian Tu, PhD[3]; Fei Chen, MD[1]; Yian Yao, MD[1]; Zi Ye, MD[1]; Jianyun Gu, MD[1]; Yanhua Gao, MD[1]; Chunyu Guan, MD[1]; Jiapeng Chu, MD[1]; Cheng Yang, MD[2]; Xuebo Liu, MD[1]

1. Department of Cardiology, Tongji Hospital, Tongji University, Shanghai, China

2. Department of Cardiac Surgery, Zhongshan hospital, Fudan University, Shanghai, China

3. Biomedical Instrument Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

*Drs. Tang and Lai contributed equally to this work.

Short running title: *QFR guided Residual Functional SS Predicts Events*

Address for Correspondence:
Xuebo Liu, MD
Director of cardiology Department
Tongji Hospital
Tongji University
No.389, Xincun Rd, Putuo District
Shanghai 200065, China
E-mail: liuxuebo70@126.com

Conflict of interest statement

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Abstract

Aims: This study was aimed at investigating the prognostic ability of quantitative flow ratio (QFR) guided residual functional SYNTAX score (Q-rFSS) and functional incomplete revascularization (IR) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).

Methods and results: A total of consecutive 354 STEMI patients was included. Q-rFSS was defined as residual SYNTAX score (rSS) measured in vessels with QFR ≤0.8. At 2-year follow-up, functional IR (Q-rFSS⩾1) showed significantly higher risk for major adverse cardiac events (MACE) than functional complete revascularization (CR) (Q-rFSS=0) (functional IR vs. CR, 22.0% vs. 7.4%; hazard ratio: 3.21; 95% confidence interval (Cl): 1.74 to 5.91; p<0.001). The area under curve (AUC) of Q-rFSS (0.738, 95% CI: 0.659 to 0.817) was significantly greater than that of rSS (0.648, 95% CI: 0.547 to 0.749). C-statistic for MACE increased from 0.656 (0.582 to 0.729) to 0.767 (0.705 to 0.829) after the addition of Q-rFSS to the clinical risk factors. Q-rFSS significantly improved risk classification compared with rSS (net reclassification improvement 0.439, 95% CI: 0.201 to 0.548; p<0.001).

Conclusions: Functional IR is associated with higher risk of MACE during long-term follow-up in STEMI patients undergoing PCI. Q-rFSS has a better prognostic ability for the risk of MACE.

KEY WORDS: STEMI, Multiple vessel disease, Other techniques

Abbreviations

ACS = acute coronary syndrome

AUC = area under the curve

CI = confidence interval

CR = complete revascularization

FFR = fractional flow reserve

IDI = integrated discrimination improvement

IR = incomplete revascularization

MACE = major adverse cardiac events

NRI = net reclassification improvement

STEMI = ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

Q-rFSS = quantitative flow ratio guided residual functional SYNTAX score

QFR = quantitative flow ratio

ROC = receiver-operating characteristic

rSS = residual SYNTAX score

SPECT = single-photon emission computed tomography

CONDENSED ABSTRACT

Angiographically incomplete revascularization have been reported to have worse clinical outcomes. Quantitative flow ratio (QFR), an approach for calculation of functional parameters, could detect hemodynamically significant lesions. The aim of this study was to determine whether QFR-guided residual functional SYNTAX score (Q-rFSS) incorporating anatomic and functional significance of lesions is a better predictor of 2-year clinical outcome in STEMI patients. In our study, functional IR is associated with higher risk of MACE during follow-up and Q-rFSS has a better prognostic ability for the risk of MACE in STEMI patients undergoing PCI.

Introduction

In patients presenting with ST-segment elevation myocardial infarction (STEMI), about 50% patients have multivessel disease[1]. Patients with angiographically incomplete revascularization (IR) have been reported to associated with worse clinical outcomes than those with complete revascularization (CR)[2,3]. However, CR is often limited when treating complex lesions with a potentially higher risk for occurrence of complications and is not always achievable in STEMI patients. The strategy of performing percutaneous coronary intervention (PCI) in non-infarct-related coronary artery lesions remains controversial.

It is important to know whether reasonable IR would attribute to poor prognosis and confirm the acceptable degree of IR in the real-world clinical practice. In previous trials, the decision to perform PCI for these non-infarct-related lesions was mainly based on angiographic characteristics, regardless of whether the lesions were causing ischemia[3,4]. The residual SYNTAX score (rSS) was introduced to quantify the degree of residual stenosis by recalculating the SYNTAX score (SS)[5,6]. However, it is well established that the discrepancy between anatomic lesion severity and coronary physiology by means of fractional flow reserve (FFR)[7,8]. Thus, the concept of the functional SS recalculating the SS after counting only ischemia-producing lesions with FFR ≤0.8 was developed. Functional SS was proved to have a better prognostic implication compared with classic SS[9].

To further expand the use of physiological lesions evaluation, quantitative flow ratio (QFR), a reliable and fast approach for calculation of functional parameters to detect hemodynamically significant lesions based on 3-dimensional quantitative coronary angiography, could be an attractive solution for clinical daily practice. Previous studies have reported the QFR has good agreement with FFR measurements[10-12].

The aim of this study was to determine whether QFR-guided residual functional SYNTAX score (Q-rFSS), defined as a recalculated SS counting only ischemia-related lesions assessed by QFR ≤0.8, is a better predictor of 2-year clinical outcomes in STEMI patients undergoing PCI.

Methods

STUDY POPULATION AND STUDY DESIGN

This was a retrospective analysis of consecutive STEMI patients prospectively enrolled who had undergone PCI at Tongji Hospital, Tongji University, Shanghai in the period from 2014 to 2016. STEMI was diagnosed if a patient had a chest pain for >30 min and <24 h, and persistent ST-segment elevation >2 mm in at least 2 contiguous precordial electrocardiography leads or >1 mm in at least 2 contiguous limb electrocardiography leads or a newly developed left bundle branch block. Exclusion criteria included significant left main disease, previous coronary artery bypass graft (CABG) surgery, cardiogenic shock and those who underwent planned CABG. All patients were managed according to usual practice. Angiography views were preceded by administration of intracoronary nitrate.

After successful treatment of the culprit lesion in the infarct-related artery (defined as a thrombolysis in myocardial infarction [TIMI] flow of 3 and residual stenosis <30%) with drug-eluting stents, the decision for PCI to lesions located in the non-infarct-related arteries was at the discretion of the operators. Images from staged procedures were used for QFR computation if second procedures were performed. The study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board or ethics committee approved the study protocol, and all patients provided written informed consent before enrollment.

OFF-LINE QFR ASSESSMENT

Details of the off-line QFR assessment are described in **Supplementary Appendix 1**[10-12].

CALCULATION OF THE Q-RFSS AND RSS

The Q-rFSS and rSS were calculated from post-procedural angiograms by 2 interventional cardiologists who were masked to other information, including patient characteristics, therapies, and clinical outcomes. Each coronary lesion producing 50% diameter stenosis in vessels >1.5 mm by visual estimation was scored separately using the SS score algorithm from its website, and individual scores were added to provide the overall rSS. The classic SS takes into account the presence of lesions in very small vessels (>1.5 mm), which are almost always functionally insignificant and in which the benefit of revascularization is uncertain. Thus, when we calculated Q-rFSS value, we simplified this score and only took into account the lesions in vessels > 2.0 mm. The Q-rFSS was defined as modified rSS (diameter stenosis >50% in vessels >2.0 mm) measured only in lesions with QFR ≤0.8.

DATA COLLECTION AND FOLLOW-UP

All data was prospectively collected and entered a central database. Clinical data was obtained at outpatient clinic visits or by telephone contact. An independent clinical event committee whose members were unaware of clinical, angiographic, and physiologic data adjudicated all events. Clinical follow-up information about the endpoints was obtained after 24 months (interquartile range, 19 to 26). Follow-up was completed in all patients. The primary endpoint was major adverse cardiac events (MACE), defined as a composite of all-cause mortality, myocardial infarction, or ischemia-driven revascularization. Elective revascularizations performed within 45 days after the primary intervention were not counted as events. All clinical outcomes were defined according to the Academic Research Consortium. Ischemia-driven revascularization was defined as a

revascularization procedure with at least one of the following: (i) recurrence of angina, (ii) positive non-invasive test, and (iii) positive invasive physiologic test.

STATISTICAL ANALYSIS

Details of the statistical analysis are described in **Supplementary Appendix 2**[13-16].

Results

PATIENTS CHARACTERISTICS

The flow of this study was showed in **Figure 1**. Three hundred and fifty-four consecutive STEMI patients (median age 63 years) undergoing PCI were enrolled in our study between 2014 and 2016. According to the Q-rFSS value, 204 patients (57.6%) were classified into the functional CR group (Q-rFSS=0) and 150 patients (42.4%) were classified into the functional IR group (Q-rFSS≥1). The baseline characteristics of study population were summarized in **Supplementary Table 1**. Patients with functional IR were older; had a higher rate of Killip class > 1, higher prevalence of 3-vessel disease and non-infarct-related artery > 70%, lower prevalence of 2-vessel disease, lower total implanted stents and eGFR value compared with functional CR.

Planned staged procedures were performed in 35 patients during index admission or after discharge within one month. We calculated QFR values of 52 non-culprit lesions available index and staged angiography. The correlation between QFR values at index and staged procedures was r=0.98 **(Supplementary Figure 1)**. Bland-Altman plot showed a mean difference of -0.003 (-0.045 to 0.040) **(Supplementary Figure 2).**

Three hundred and fifty-four patients were divided into tertiles of risk based on the rSS namely low-risk (<7), intermediate-risk (7 to 11) and high-risk (>11) group (34.8%, n=123; 32.5%, n=115; and 32.7%, n=116, respectively). After calculation of Q-rFSS, 35.5% of patients were reclassified from the high- or intermediate-risk group into the low-risk group **(Figure 2)**.

CLINICAL OUTCOMES

During a median follow-up of 24 months, 48 patients (13.6%) reached the combined endpoints of MACE. Compared with the functional CR group, the functional IR group showed a higher incidence of MACE (22% vs. 7.4%; HR: 3.21; 95% CI: 1.74 to 5.91; p<0.001), non-infarct related ischemia-driven revascularization (18% vs. 3.9%; HR: 4.97; 95% CI: 2.26 to 9.7; p<0.001) and ischemia-driven revascularization (19.3% vs. 4.4%; HR: 4.74; 95% CI: 2.24 to 9.9; p<0.001) **(Supplementary Table 2)**. The log-rank test based on the Kaplan-Meier curves showed a significant association between functional IR and MACE (p <0.001) **(Figure 3)**.

Survival analysis using the Cox regression model showed that after adjusted variables, Q-rFSS was an independent predictor of 2-year MACE (HR: 1.092, 95% CI: 1.054 to 1.113; p<0.001) **(Table 1)**. Compared with the model consisted of conventional risk factors, the C-statistic for MACE increased from 0.656 (0.582 to 0.729) to 0.767 (0.626 to 0.778) after the addition of Q-rFSS value **(Supplementary Table 3)**. Category-free reclassification analysis was used as described by Pencina et al[16]. Q-rFSS significantly improved risk classification compared with rSS (NRI: 0.439; 95% CI: 0.201 to 0.548; p<0.001). The extended model with further inclusion of Q-rFSS value could significantly improve NRI. After inclusion of Q-rFSS to the reference model, IDI for MACE (IDI: 0.102; 95% CI: 0.038 to 0.169; p<0.001) also significantly improved **(Supplementary Table 3)**.

ROC curves were plotted for the Q-rFSS and rSS. The AUC of Q-rFSS was significantly greater than that of anatomical rSS (AUC: 0.738, 95% CI: 0.659 to 0.817 vs. AUC: 0.648, 95% CI: 0.547 to 0.749, p<0.001) **(Figure 4)**. The AUC of Q-rFSS added to clinical factors (AUC: 0.798, 95% CI: 0.732 to 0.864) was also significantly higher than AUC of rSS added to clinical factors (AUC:

0.720, 95% CI: 0.636 to 0.805) and clinical factors alone (AUC: 0.671, 95% CI: 0.591 to 0.750) **(Supplementary Figure 3)**.

SUBGROUP AND SENSITIVITY ANALYSIS

During the follow-up period, higher Q-rFSS levels were consistently associated with higher risks of MACE in various subpopulations. There was no significant interaction in the risk of MACE among pre-specified subgroups (all p values for interaction>0.05; **Supplementary Figure 4**).

Discussion

This present study is the first to evaluate the prognostic role of QFR-guided residual functional SYNTAX score in patients with STEMI after successful PCI. The principal findings of the present study are as follows: 1) the MACE rate was significantly higher in patients with functional IR than in those with functional CR; 2) A progressively Q-rFSS was shown to be a surrogate marker of increasing clinical outcomes in a multivariate-adjusted model; and 3) When Q-rFSS and rSS were added to clinical factors, the model with Q-rFSS showed higher discrimination ability for MACE.

Previous predominant studies demonstrated that IR was associated with higher risk of adverse clinical outcomes and confirmed the prognostic clinical impact of IR[17,18]. They mainly used anatomical features as diagnostic criteria of CR and the definitions were various in those studies. The SS is the most accepted objective computational tool to grade the anatomic complexity of coronary artery disease and improve clinical outcome by establish evidence-based guidelines for determining the most appropriate revascularization strategy[19,20]. Although the rSS, which is a marker of the residual ischemia burden, was introduced to predict the outcomes, rSS also just concerned the anatomic severity. Large randomized studies have proved that FFR is superior to angiographic assessment for the detection of hemodynamically important coronary obstruction and

that coronary revascularization improves clinical outcomes by guidance of FFR[21]. Performing PCI to a functionally nonsignificant coronary lesion has been proved to be of no benefit to the patients, neither from a prognostic nor from a symptomatic point of view[22]. For this reason, this study focused on the prognostic role of functional IR. In our study, functional IR determined by QFR was associated with higher risk of MACE compared with functional CR up to 2 years and could provide important prognostic information for STEMI patients after PCI in line with previous studies.

FFR-guided PCI in multivessel disease was associated with improved long-term clinical outcomes compared with PCI guided by angiography in the FAME study[23]. Nam et al.[9] first presented the concept of functional SYNTAX score to estimate the functional severity of lesions incorporating both anatomic and functional significance of lesions in pre-PCI evaluation. Kobayashi et al.[24] have demonstrated that residual angiographic disease is not associated with subsequent ischemic events in patients with acute coronary syndrome (ACS) based on the rSS after CR of functionally significant stenosis determined by FFR. Furthermore, the improved discriminant ability of the residual functional SS guided by FFR for clinical outcomes was identified compared with anatomic assessment alone[25]. These observations are in line with earlier noninvasive studies by single-photon emission computed tomography (SPECT) in large numbers of patients which indicated that the most important prognostic factor in patients with coronary artery disease is the presence and extent of inducible ischemia[26]. PCI with the guidance of functional examination such as FFR seems to be more reasonable than with the anatomic characteristics.

Two large randomized trials demonstrated the superiority of FFR-guided revascularization of non-culprit lesions performed in early phase of STEMI when compared with culprit lesion PCI

alone[27,28]. However, the clinical utility of FFR is still infrequent in real-world setting, especially in STEMI patients. There are many reasons for this, including equipment and drug costs, physician preferences, and the risk of related complications. Progress in angiography-derived FFR such as QFR can reduce these limitations by calculation of functional parameters in a simpler and rapid way. Recently, a study including 110 STEMI patients has demonstrated the QFR computation of non-culprit lesions is feasible in the STEMI setting and found that functional IR identified by QFR was associated with adverse clinical outcomes in the long-term follow-up[29]. However, the prognostic ability was not further studied in this study. A post-hoc substudy of the SYNTAX II trial has also demonstrated the feasibility in measuring and calculating a QFR based functional SS in predicting the clinical outcomes of CAD patients[30]. Our study expanded on identified clinical potentials and findings of the application of this scoring system and investigated the prognostic ability of residual SS combined with functional assessment guided by QFR in STEMI patients.

Another potential limitation of classic SYTAX score is that it takes into account the presence of lesions in very small vessels (1.5 mm), which are almost always functionally insignificant and in which the benefit of revascularization is uncertain. Therefore, it is inappropriate to adopt the scoring system with limited applicability in acute setting as performing PCI to STEMI patients. To make the scoring system more feasible for the real-world clinical practice, we modified the score by accounting the presence of lesions in vessels whose diameters were >2 mm. We found the improved discriminant capability of the Q-rFSS for clinical outcome in comparison with anatomic rSS. Our results demonstrate that Q-rFSS guided by a safer and quicker method combining both anatomic and functional information on the residual disease burden can better predict risk of STEMI patients after PCI than anatomic assessments alone. The favorable outcomes

of STEMI patients who had untreated non-culprit lesions in the functional CR group support the idea that deferral treatment of non-ischemia producing lesions is safe.

Limitations

This study had several limitations. First, the study population was relatively small. Our study was not powered to detect differences in low-frequency events, such as death, reinfarction and other adverse clinical events. Second, the study was not a randomized study, and the decision for non-infarcted artery revascularization at index procedure was left to the operator's discretion. Therefore, the optimal treatment strategy for patients with functional IR could not be evaluated. Third, patients were not randomized to IR and CR. Therefore, we had to risk-adjust the data to take into account the fact that IR patients tended to be older and more severe than CR patients. Fourth, since patients with left main disease and patients scheduled for CABG were excluded from the present analysis, our findings cannot be extrapolated to these patients.

Conclusions

Functional IR is associated with a higher risk of MACE during long-term follow-up in STEMI patients undergoing PCI. Q-rFSS has a better prognostic ability for the risk of adverse clinical outcomes in STEMI patients after PCI.

Impact on daily practice

This present study is the first to evaluate the prognostic role of QFR-guided residual functional SYNTAX score and IR in patients with STEMI after successful PCI. Functional IR and rFSS guided by QFR could be fast and feasible risk stratification systems for clinical daily practice

treating non-infarct-related coronary artery lesions in STEMI patients. It is warranted to validate this concept and find the optimal revascularization strategy for STEMI patients with multivessel disease using QFR.

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Conflict of interest statement

Dr. Tu has received research support from Medis Medical Imaging and Pulse Medical Imaging. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Figure legends

Figure 1. Flow Chart of Inclusion in this study. CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; SCAD: spontaneous coronary artery dissection; STEMI: ST-segment elevation myocardial infarction.

Figure 2. Reclassification by QFR-guided residual Functional SYNTAX Score. QFR: quantitative flow ratio; rFSS: residual functional SYNTAX score.

Figure 3. Kaplan-Meier curves of major adverse cardiac events (MACE) at 2-year follow-up according to quantitative flow ratio guided residual functional SYNTAX score (Q-rFSS) value.

Figure 4. Receiver operator curves for discrimination of MACE. The blue line is Q-rFSS (AUC: 0.738, 95% CI: 0.659 to 0.817); the red line is rSS (AUC: 0.648, 95% CI: 0.547 to 0.749). AUC: area under curve; CI: confidence interval; MACE: major adverse cardiac events. Q-rFSS: quantitative flow ratio guided residual functional SYNTAX score; rSS: residual SYNTAX score.

Table 1. Multivariable Cox regression analyses for MACE（n=48）

	Multivariable Analysis	
	HR (95% CI)	***p*-value**
Age	1.011(0.985-1.038)	0.40
Previous MI	2.742(1.138-5.780)	0.03
Anterior MI	1.935(1.074-3.567)	0.03
Peak TnI	1.009 (0.999-1.020)	0.07
3-vessel disease	1.681(0.892-3.331)	0.11
Q-rFSS	1.092 (1.054-1.113)	<0.001

Models after LASSO variable selection procedure.

CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiac event; MI: myocardial infarction; Q-rFSS: quantitative flow ratio guided residual functional SYNTAX score; SYNTAX: Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TnI: troponin I.

Figure 1

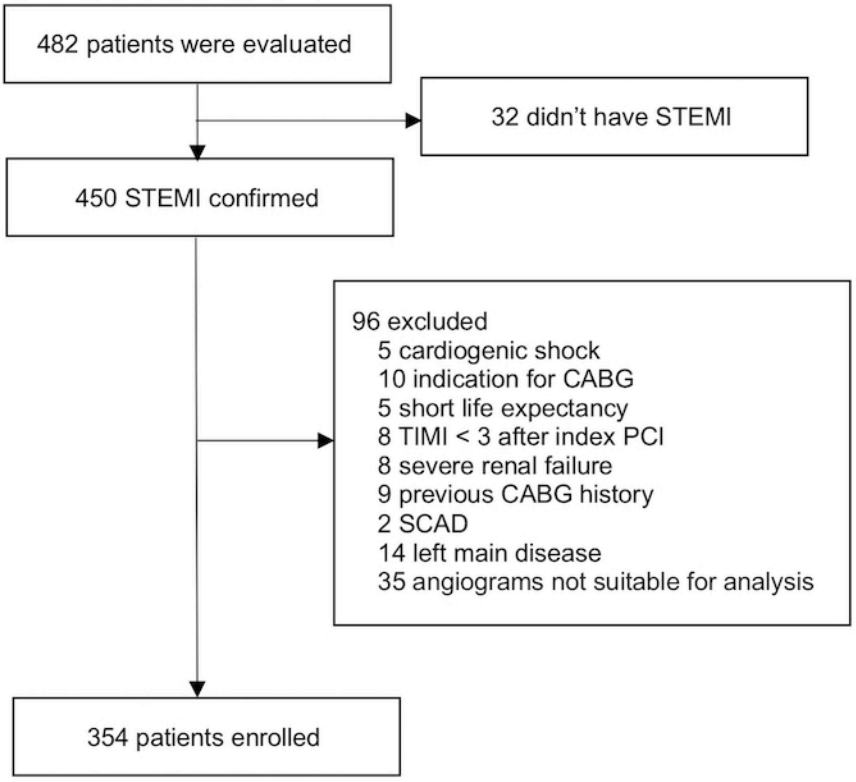


Figure 2

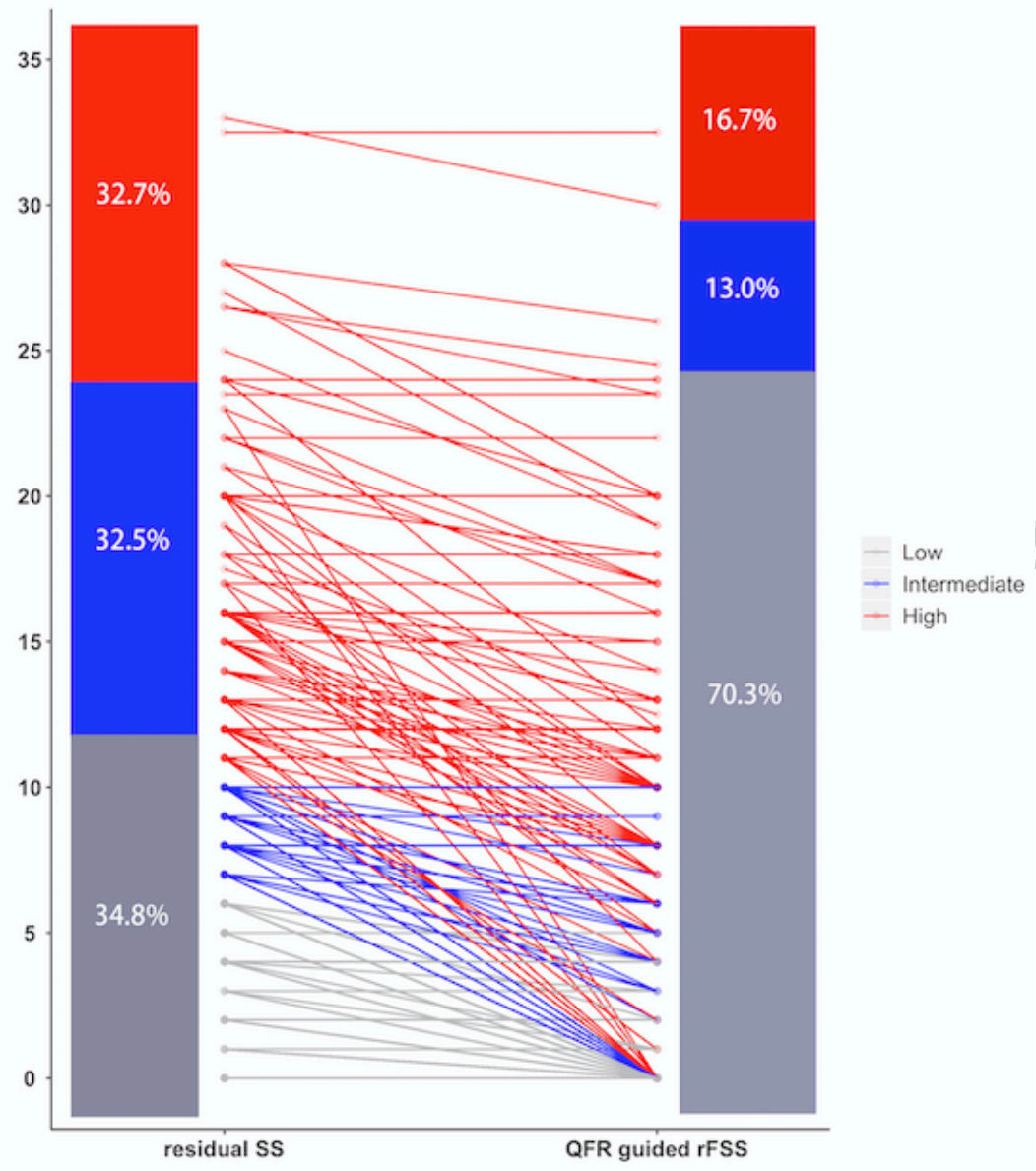


Figure 3

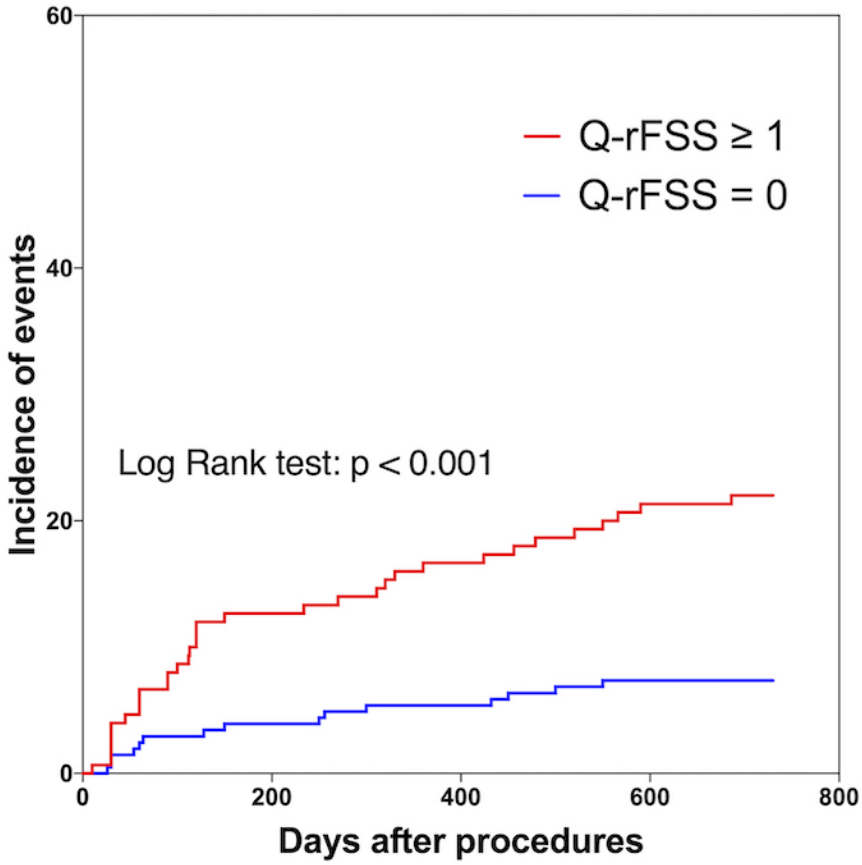
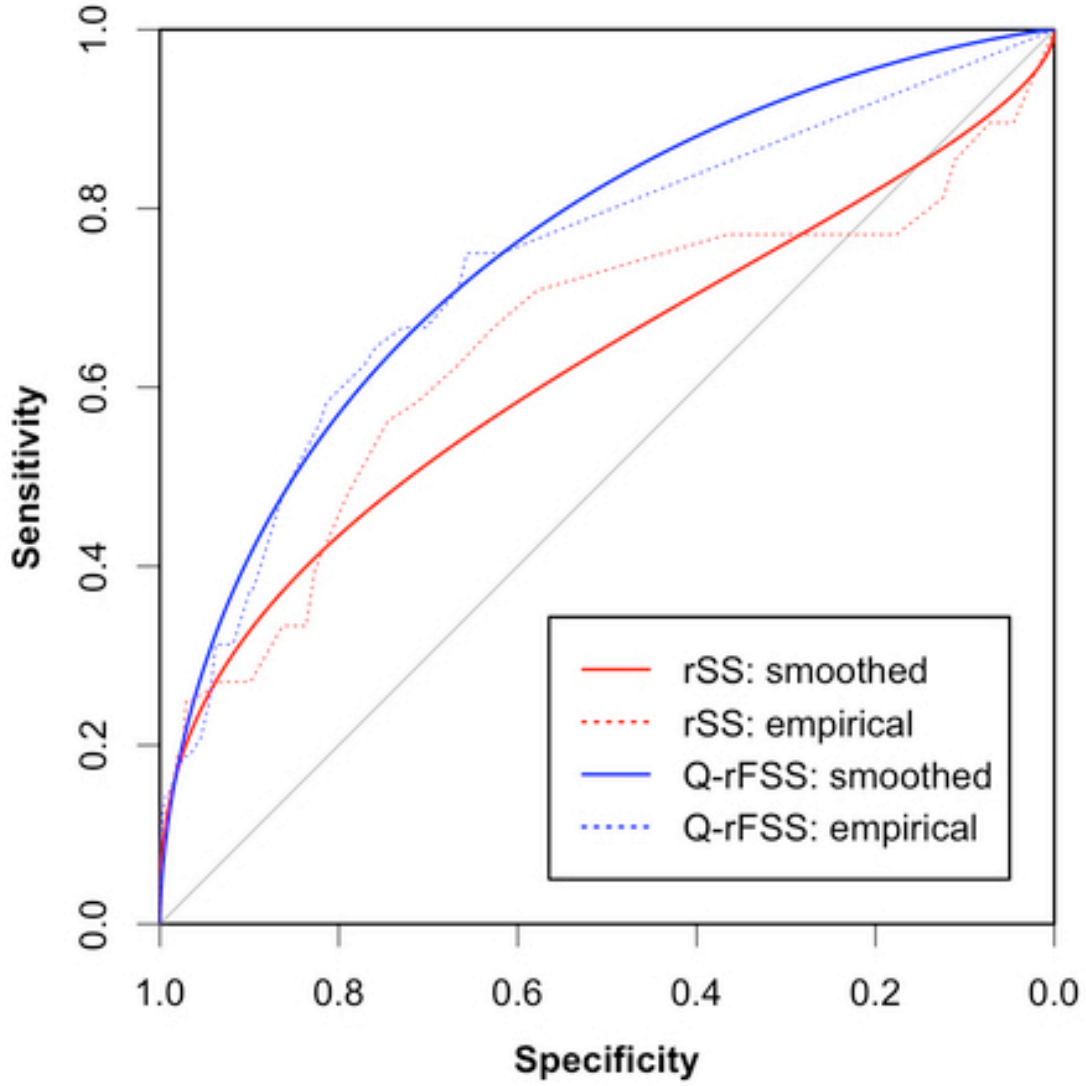


Figure 4



Supplementary data

Supplementary Appendix 1. OFF-LINE QFR ASSESSMENT

Off-line QFR analysis was performed by experienced analysts certified for use of the software with QFR system (AngioPlus, Pulse Medical Imaging Technology, Shanghai Co., Ltd., Shanghai, China). In the first step, 2 angiographic projections, at least 25° apart, were transferred to the QFR system, and 3-dimensional reconstruction of the interrogated vessel without its side branches was performed as previously described[10-12]. Three-dimensional quantitative coronary analysis data were readily available. Then, QFR was computed.

Supplementary Appendix 2. STATISTICAL ANALYSIS

Baseline characteristics were summarized using proportions or medians with interquartile range (IQR) (Q1 - Q3) and compared using chi-square statistics for categorical variables and Wilcoxon rank sum tests for continuous variables. Correlation and agreement between QFR values calculated at index and staged procedures were determined by Pearson correlation coefficient and Bland and Altman plot. We selected the variables by means of the LASSO (Least Absolute Shrinkage and Selection Operator) method[13]. The final model obtained after penalization included the following variables: age, anterior MI, history of MI, peak troponin I (TnI), 3-vessel disease and Q-rFSS. For the concern of the small sample size, we used Firth's penalized maximum likelihood bias reduction method

for Cox regression[14]. Firth's correction is an approach to reduce the bias of maximum likelihood estimates in the setting of cox regression models when a dataset has small events. The increased discriminative value of Q-rFSS in the prediction of clinical outcomes were assessed using the C-statistic[15]. The Kaplan-Meier method was used to demonstrate the timing of events during long-term follow-up in relation to the Q-rFSS value, and the log-rank test was applied to compare survival curves between groups. The prognostic ability of Q-rFSS and rSS was quantified using the receiver-operating characteristic (ROC) curve and the area under curve (AUC) by using the DeLong method. The prognostic values of Q-rFSS, and rSS, in addition to clinical risk factors, were also assessed using ROC curve and AUC. Baseline clinical risk model included age, gender, symptom-to-balloon, anterior MI, killip class, hypertension, hyperlipidemia, diabetes, current smoker, history of MI. Logistic regression was used to develop the model. The net reclassification improvements (NRI) and integrated discrimination improvements (IDI) were also used to assess the improvement of goodness of fit and predictive performance after the addition of Q-rFSS to the reference model[16]. A significant level was defined when $p<0.05$. We performed sensitivity analysis for the subgroup of participants. All analyses were performed using R software, version 3.2.3. (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 20.0 (IBM, Armonk, New York).

Supplementary data

Supplementary Appendix 1. METHODS. OFF-LINE QFR ASSESSMENT.

Supplementary Appendix 2. METHODS. STATISTICAL ANALYSIS.

Supplementary Table 1. Demographics and Baseline Clinical Characteristics between the Q-rFSS Subgroups.

Supplementary Table 2. Clinical Outcomes

Supplementary Table 3. Discrimination and Reclassification Performance of the Addition of rSS and Q-rFSS in Predicting MACE Based on C-Statistics, NRI, and IDI.

Supplementary Figure 1. Correlation between QFR values at index and staged procedures.

Supplemental Figure 2. Bland-Altman plot of QFR values at index and staged procedures.

Supplementary Figure 3. Comparison of Predictive Models With rSS, and Q-rFSS in Addition to Clinical Model.

Supplementary Figure 4. Hazard ratio and 95% confidence interval of Q-rFSS value for major adverse cardiac events in subgroup analyses.

Supplementary Table 1. Demographics and Baseline Clinical Characteristics between the Q-rFSS Subgroups

	Overall (n=354)	Q-rFSS = 0 (n=204)	Q-rFSS ≥ 1 (n=150)	*p*-value
Clinical characteristics				
Age (yrs)	63 (56-70)	61(54-68)	65 (59-73)	<0.001
Male	289(81.6)	168(82.3)	121(80.7)	0.68
Hypertension	242(68.4)	136(66.7)	106(70.7)	0.49
Diabetes	99(28.0)	49(24.0)	50(33.3)	0.60
Hyperlipidemia	98(27.7)	57(27.9)	41(27.3)	0.98
Current smoker	229(64.7)	132(64.7)	97(64.7)	0.99
Previous MI	22(6.2)	10(4.9)	12(8.0)	0.27
Previous PCI	30(8.5)	13(6.4)	17(11.3)	0.12
Killip class > 1	72(20.3)	33(16.2)	39(26.0)	0.03
eGFR (ml/min)	79(65-93)	82(69-97)	74(60-88)	<0.001
LDL-c (mmol/l)	3.22(2.68-3.75)	3.22(2.72-3.82)	3.17(2.60-3.66)	0.20
HbA1c (%)	6.2(5.9-7.2)	6.1(5.9-6.9)	6.3(5.9-7.4)	0.29
Anterior MI	179(50.6)	109(53.4)	70(46.7)	0.24
Peak TnI (ug/l)	68(19-78)	70(23-76)	66(15-78)	0.84
Symptom-to-balloon (min)	240(180-380)	240(180-420)	240(180-360)	0.68
Angiographic and procedural characteristics				
N-IRA stenoses >70%	202(57.1)	74(36.3)	128(85.3)	<0.001
3-vessel disease	169(47.7)	61(29.9)	108(72.0)	<0.001
2-Vessel disease	124(35.0)	89(43.6)	35(23.3)	<0.001
Balloon pump	10(2.8)	7(3.4)	3(2.0)	0.42
Femoral approach	45(12.7)	25(12.3)	20(13.3)	0.87
Thrombectomy	232(65.5)	138(67.6)	94(62.7)	0.37
Total implanted stents per patient	1(1-2)	1(1-2)	1(1-1)	0.002
Residual SYNTAX score	7(6-12)	6(4-7)	13(9-17)	<0.001
Q-rFSS	0(0-8)	0	10(5-15)	<0.001
Medical treatments				
Statins	340(96.0)	195(95.6)	145(96.7)	0.78

Beta-blockers	287(81.1)	164(80.4)	123(82.0)	0.78
ACEI or ARB	246(69.5)	141(69.1)	105(70.0)	0.91
Dual antiplatelet therapy	328(92.7)	190(93.1)	138(92.0)	0.69
Glycoprotein IIb/IIIa inhibitor	232(65.5)	130(63.7)	102(68.0)	0.43

Values are median (interquartile range) or n (%).

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor antagonists; eGFR: estimated glomerular filtration rate; HbA_{1c}: glycosylated hemoglobin; LDL-c: low-density lipoprotein cholesterol; MI: myocardial infarction; N-IRA: non-infarct related artery; PCI: percutaneous Coronary Intervention; Q-rFSS: quantitative flow ratio guided residual functional SYNTAX score; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TnI: troponin I.

Supplementary Table 2. Clinical Outcomes

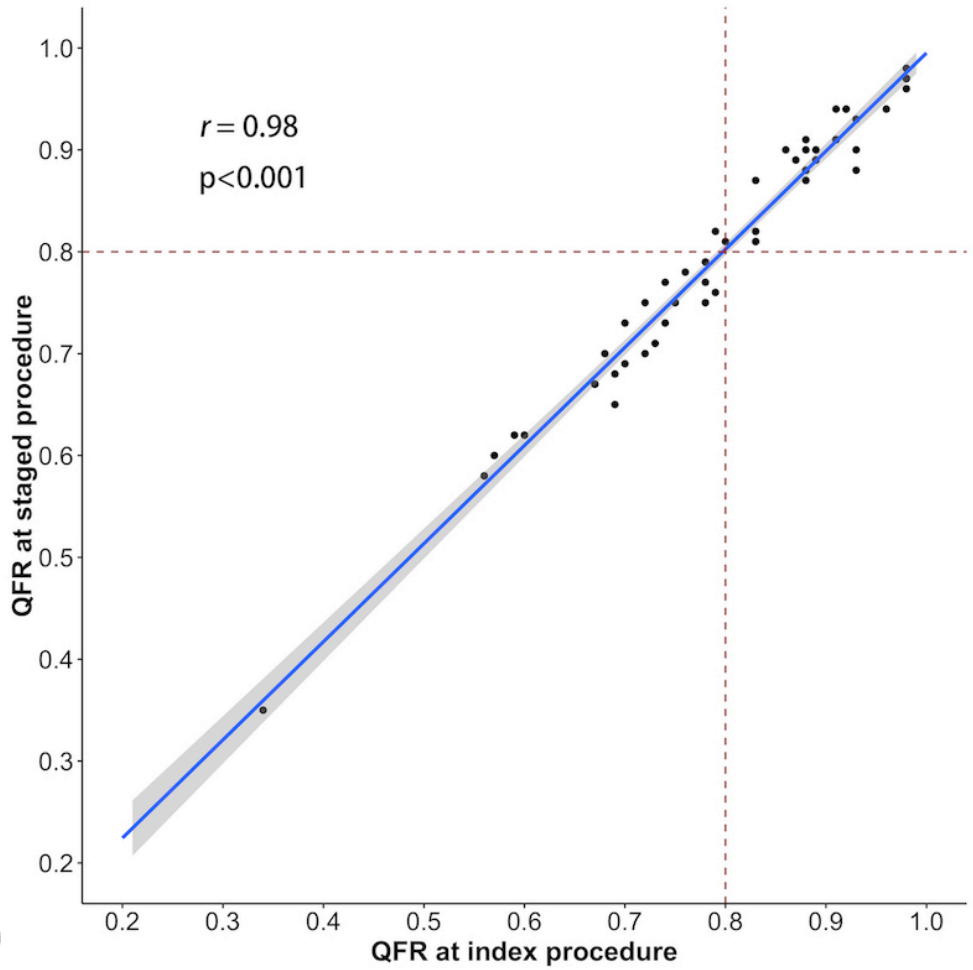
24-Month Follow-Up	Functional IR (n=150)	Functional CR (n=204)	HR (95% CI)	*p*-value
MACE	33(22.0))	15(7.4)	3.21(1.74-5.91)	<0.001
Death	3(2.0)	2(1.0)	1.38(0.28-6.85)	0.69
Recurrent MI	9(6.0)	7(3.4)	1.75(0.65-4.7)	0.27
Non-infarct artery IDR	27(18.0)	8(3.9)	4.97(2.26-9.7)	<0.001
IDR	29(19.3)	9(4.4)	4.74(2.24-9.9)	<0.001

Major adverse cardiac event was defined as a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization. CI: confidence interval; CR: complete revascularization; HR: hazard ratio; IDR: ischemia-driven revascularization; IR: incomplete revascularization; MACE: major adverse cardiac event; MI: myocardial infarction.

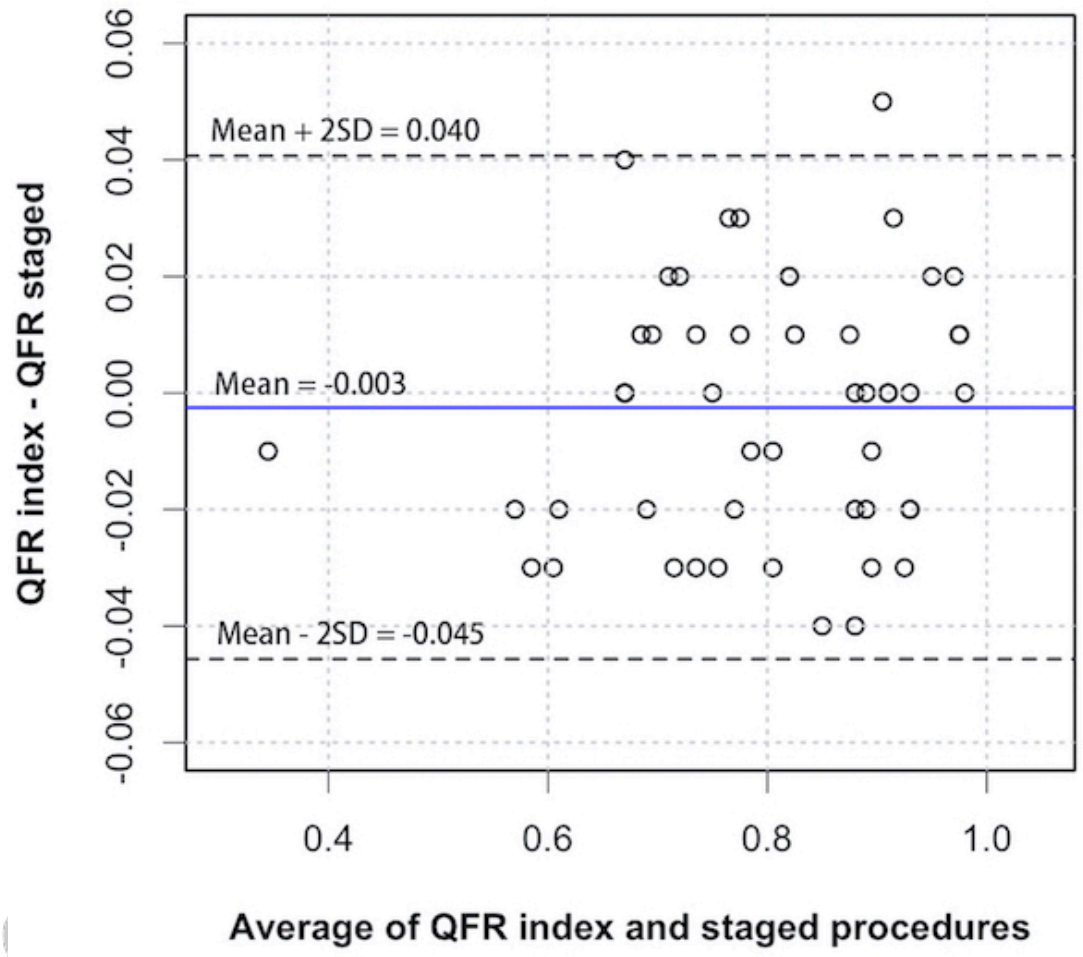
Supplementary Table 3. Discrimination and Reclassification Performance of the Addition of rSS and Q-rFSS in Predicting MACE Based on C-Statistics, NRI, and IDI

Model	Addition variables	C-Statistics (95% CI)	Category Free NRI (95% CI)	*p*-value	IDI (95% CI)	*p*-value
Baseline clinical model		0.656 (0.582 - 0.729)	Reference	-	Reference	-
	rSS	0.702 (0.626 - 0.778)	0.315 (0.094 - 0.433)	0.01	0.056 (0.015 - 0.117)	<0.001
	Q-rFSS	0.767 (0.705 - 0.829)	0.402 (0.194 - 0.516)	<0.001	0.102 (0.038 - 0.169)	<0.001

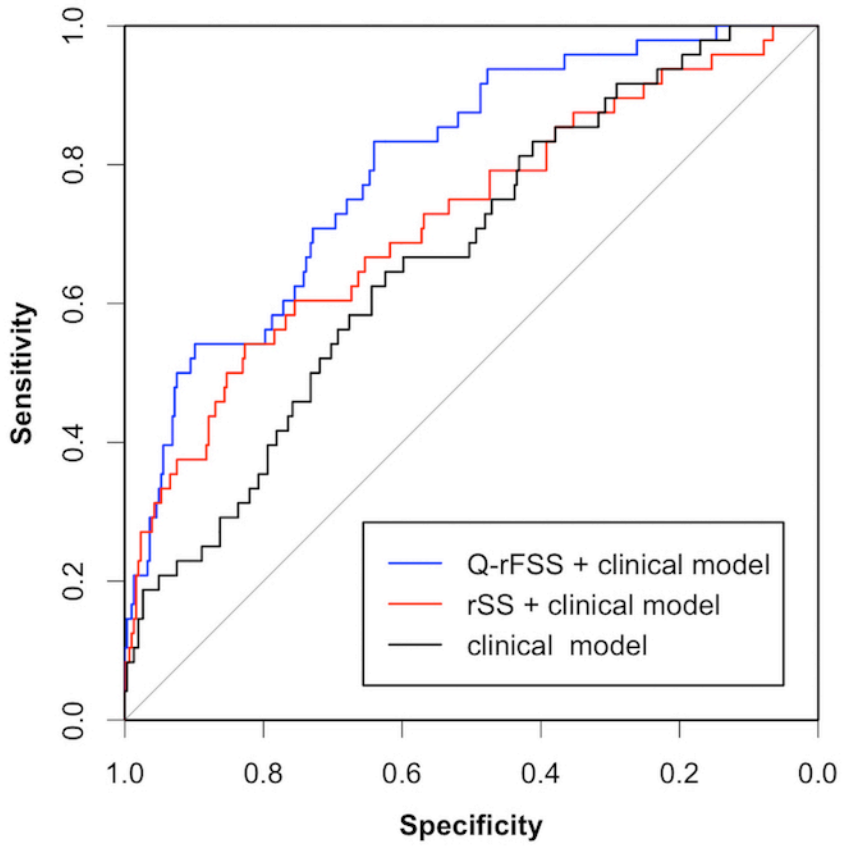
Baseline clinical model included age, gender, symptom-to-ballon, anterior MI, killip class, hypertension, hyperlipidemia, diabetes, current smoker, history of MI, eGFR. CI: confidence interval; eGFR: estimated glomerular filtration rate; IDI: integrated discrimination index; MI: myocardial infarction; NRI: net reclassification improvement; Q-rFSS: quantitative flow ratio guided residual functional SYNTAX score; rSS: residual SYNTAX score; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.



Supplementary Figure 1. *Correlation between QFR values at index and staged procedures. QFR: quantitative flow ratio.*

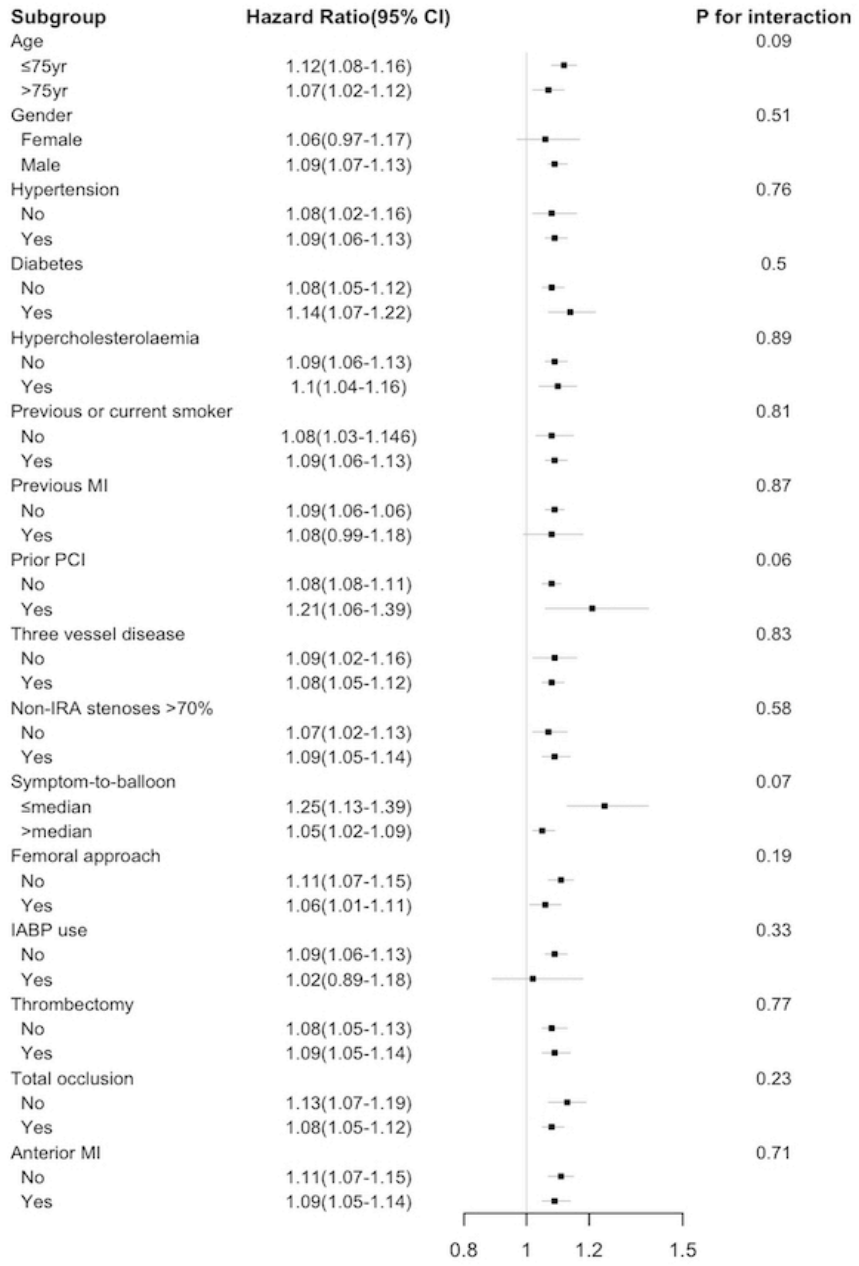


Supplementary Figure 2. *Bland-Altman plot of QFR values at index and staged procedures. QFR: quantitative flow ratio.*



Model	AUC	95% CI	*P* Value
Baseline clinical model	0.671	0.591 - 0.750	reference
rSS + clinical model	0.720	0.636 - 0.805	0.115
Q-rFSS + clinical model	0.798	0.732 - 0.864	<0.001

Supplementary Figure 3. *Comparison of Predictive Models With rSS, and Q-rFSS in Addition to Clinical Model. Baseline clinical model included age, gender, symptom-to-ballon, anterior MI, killip class, hypertension, hyperlipidemia, diabetes, current smoker, history of MI, eGFR. AUC: area under curve; CI: confidence interval; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; Q-rFSS: quantitative flow ratio guided residual functional SYNTAX score; rSS: residual SYNTAX score; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.*



Supplementary Figure 4. Hazard ratio and 95% confidence interval of Q-rFSS value for major adverse cardiac events in subgroup analyses. CI: confidence interval; IABP: intra-aortic balloon pump; MI: myocardial infarction; N-IRA: non-infarct related artery; PCI: percutaneous coronary intervention; Q-rFSS: quantitative flow ratio guided residual

functional SYNTAX score; SYNTAX: Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery