Clinical outcomes guided by quantitative flow ratio in multivessel disease and ST-elevation myocardial infarction patients with diabetes mellitus

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Research Article

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Abstract

Background
Quantitative flow ratio (QFR) had good feasibility and accuracy in assessing the hemodynamic compared with fraction flow reservation (FFR) as the reference. Diabetes mellitus (DM) worsens the prognosis of multivessel disease and ST-elevation myocardial infarction (MVD-STEMI) patients. However, the role of QFR in MVD-STEMI patients with DM is unknown. The purpose of this study is to investigate the clinical outcomes of patients with MVD-STEMI under different diabetes status and revascularization assignment guided by quantitative flow ratio (QFR).

Methods
A total 724 patients were enrolled in our study and allocated into nondiabetes mellitus (nonDM) cohort and DM cohort. Under the guidance of QFR, cohorts are divided into functional complete revascularization (FCR) layering and functional incomplete revascularization (FIR) layering. The primary outcome was a composite of major adverse cardiovascular events (MACE) including cardiac death, ischemia-driven revascularization (target vessel revascularization and nontarget vessel revascularization), rehospitalization due to unstable angina pectoris, and nonfatal myocardial infarction at 3-year follow up.

Results
DM cohort (22.9% vs 13.6%, $P = 0.002$) and FIR layering (24.0% vs 12.6%, $P < 0.001$) were more prone to MACE. The incidence of MACE in four groups were as follows: 27.9% DM + FIR > 18.5% nonDM + FIR > 16.1% DM + FCR > 9.8% nonDM + FCR. Besides, DM and FIR had been proven to be important predictors of MACE after adjustment for baseline clinical differences (HR = 1.60, 95%CI = 1.03–2.49, $P = 0.036$; HR = 1.71, 95%CI = 1.13–2.57, $P = 0.011$). By incorporating QFR-guided residual SYNTAX score (rSS$_{QFR}$) into model of clinical risk factors, the predictive ability of the model for MACE was significantly improved, especially in the DM (+IR) population (AUC = 0.812, 95%CI = 0.750–0.874) vs AUC = 0.666, 95%CI = 0.581–0.751, $P < 0.001$).

Conclusions
Diabetes status and functional incomplete revascularization strategy increased 3-year rates of MACE in patients with MVD-STEMI. The use of QFR by DM population is more valuable than that of nonDM population.

Introduction
Diabetes mellitus (DM) is an independent risk factor for coronary artery disease (CAD) [1]. Patients with DM have more complex coronary anatomy (more frequently multivessel and diffuse epicardial CAD with calcification and negative remodeling, often with microvascular disease), more high risk lipidic “vulnerable” plaques, more frequent comorbidities (including hypertension, renal dysfunction, and heart failure), and a higher risk of stent-related complications, including thrombosis and restenosis, compared with patients without diabetes [2−4]. Multivessel disease and ST-elevation myocardial infarction (MVD-STEMI) patients had worst prognosis in different types of CAD [5]. The addition of diabetes increased the incidence of clinical outcomes in MVD-STEMI patients [6]. Thus, more attention and precise evaluated method for this high-risk cohort should be paid.

Recently, the angiography-based quantitative flow ratio (QFR) has been validated as a method to accurately derive fraction flow reservation (FFR) across a wide spectrum of patients and lesion characteristics without the need for invasive pressure wire use or hyperemia induction [7, 8]. It is shown that the beneficial outcomes of QFR guidance for lesion selection during percutaneous coronary intervention (PCI) is similar in different diabetes status [9, 10]. A QFR-guided lesion selection strategy improves PCI outcomes compared with standard angiography guidance in patients whether combined with diabetes or not [9]. In our study, clinical prognosis efficiency of QFR is higher in diabetes cohort compared to non-diabetes cohort. QFR may be a powerful tool to PCI strategy and prognostic prediction in patients with diabetes.

Methods

Study population and study design

Between January 2017 and December 2018, a total of 724 patients with MVD-STEMI who underwent emergency PCI based on standard angiography guidance were consecutively selected at the 2nd Affiliated Hospital of Harbin Medical University. Multivessel disease was defined at least 1 non-infarct-related lesion with $\geq 50\%$ lumen diameter stenosis. Single-vessel disease was not considered because it was definitely complete revascularization (CR) without randomization. The main exclusion criteria were left main disease (n = 43), and data missing (n = 31). Angiography images with ostial lesions (n = 8), severe overlap (n = 6), and lack of 2 appropriate projections (n = 13) were not included because of the potential difficulty in performing QFR in such situations. Final study population consisted of 623 patients were divided into two cohorts: the nondiabetes cohort and the diabetes cohort. Cohorts were further divided into functional complete revascularization (FCR) and functional incomplete revascularization (FIR) group according to QFR-guided residual SYNTAX score (rSS$_{QFR}$): nonDM + FCR group (n = 164, rSS$_{QFR}$=0), nonDM + FIR (n = 131, rSS$_{QFR}>0$), DM + FCR group (n = 138, rSS$_{QFR}=0$), and DM + FIR (n = 190, rSS$_{QFR}>0$), as shown in the study flowchart (Fig. 1).

Off-line QFR assessment
QFR was assessed offline by two independent certified operators using the AngioPlus system (Pulse Medical Imaging Technology, Shanghai, China). The principle of QFR is three-dimensional coronary reconstruction and frame counting technique based on angiography. Analyses were performed according to a previously suggested standard operating procedure. Measure was started from the ostium of the index vessel to a distal anatomic landmark visible on both projections at a vessel diameter of \( \geq 1.5 \text{ mm} \) [11]. All of three vessels including major side branches (obtuse marginal, intermediate branch, diagonal branch) require QFR analysis pre-PCI and post-PCI. Vessels with a conventional cutoff \( \leq 0.80 \) will be calculated for next SYNTAX score.

**Calculation of SYNTAX score**

The extent of CAD can be measured by the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score (SS). The SS is an angiographic grading tool that quantifies CAD based on lesion number, location, and complexity [12]. Each coronary lesion producing 50% diameter stenosis in vessels > 1.5 mm by visual estimation was scored separately using the SS algorithm from its website. Physiological ischemic vessels (QFR \( \leq 0.80 \)) would be further calculated functional SYNTAX score [13]. An overall SYNTAX score was achieved by summing individual scores. Finally, Angiography-guided anatomical SS (pre-PCI) and residual SYNTAX score (rSS) (post-PCI), QFR-guided functional SYNTAX score (SS\(_{QFR}\)) (pre-PCI) and rSS\(_{QFR}\) (post-PCI) were obtained.

SS\(_{QFR}\) and rSS\(_{QFR}\) are defined as modified SS and rSS measured only in lesions with QFR \( \leq 0.80 \), respectively [14, 15]. Functional CR was defined as an rSS\(_{QFR}\)=0. Functional IR was defined as an rSS\(_{QFR}\)>0 [14, 15]. Scores were calculated by two interventional cardiologists who were blinded to other information, including patient characteristics, therapies, and clinical outcomes.

**Clinical outcomes**

All enrolled patients were followed at 6, 12, 18, 24, 30 and 36 months by phone call or hospital visit after discharge. Major adverse cardiovascular events (MACE) were defined as a composite of cardiac death, ischemia-driven revascularization including target vessel revascularization (TVR) and nontarget vessel revascularization (non-TVR),rehospitalization due to unstable angina pectoris (UAP), and non-fatal myocardial infarction (MI) [16]. All endpoint events were adjudicated by an independent committee blinded to randomization assignment.

**Statistical analysis**

Statistical analyses were performed by SPSS, version 27.0, and Graphpad Prism, version 8.0. Categorical data are presented as counts (proportions) and compared by using the Pearson chi-square test or Fisher exact test depending on category cell size. Kolmogorov-Smirnov test was used to assess the normality of continuous data. Normally distributed variables are described as mean \( \pm \) SD and compared by using the Student’s t-test, whereas non-normally distributed variables are described as median (interquartile range [IQR]) and compared by using the Mann-Whitney U test. Logistic regression analysis was used to identify the independent predictors of FIR. Variables with \( P<0.1 \) in the univariate analysis were taken into
multivariate analysis. Time-to-event data are presented as Kaplan-Meier estimates and compared by the log-rank test. A multivariable Cox regression model was used to identify independent predictors of MACE and estimated between-group risks by hazard ratio (HR) with 95% confidence interval (CI). Receiver-operating characteristic curve (ROC) analysis was used to compare the recognition ability of MACE between rSS and rSSQFR. A 2-tailed \( P < 0.05 \) was considered to indicate statistical significance.

Results

Patients and clinical characteristics

Overall, 47.4% patients (n = 295) were DM, 52.6% patients (n = 328) were nonDM according to diaetebes status, and 48.5% patients (n = 302) were FCR (rSSQFR=0), 51.5% patients (n = 321) were FIR (rSSQFR>0) according to rSSQFR value (Fig. 1). The distribution of rSS and rSSQFR were shown in the violin plot (Supplemental Fig. 1). Functional CR in the rSSQFR distribution was not shown because it had the rSSQFR value of 0.

Clinical characteristics of patients are presented in Table 1. Results suggested that patients with nonDM + FIR had more hypertension (\( P = 0.011 \)), aspirin use (\( P = 0.044 \)) and P2Y12 inhibitors use (\( P = 0.044 \)) than nonDM + FCR in nondiaetebes cohort. In diaetebes cohort, patients with DM + FIR had lower estimated glomerular filtration rate (eGFR) (\( P = 0.001 \)) and more insulin use (\( P = 0.021 \)) than DM + FCR. Besides, in the FCR layering, patients with DM + FCR had more previous MI (\( P = 0.032 \)), higher low-density lipoprotein cholesterol (LDL-C) (\( P = 0.008 \)), higher high-density lipoprotein cholesterol (HDL-C) (\( P = 0.003 \)), higher hemoglobin A1c (HbA1c) (\( P < 0.001 \)) and higher fasting blood glucose (FBG) (\( P < 0.001 \)) than nonDM + FCR. In the FIR layering, patients with DM + FIR had more smoking history (\( P = 0.023 \)), higher cardiac troponin I (cTNI) (\( P = 0.009 \)), lower eGFR (\( P = 0.013 \)), higher HbA1c (\( P < 0.001 \)), higher FBG (\( P < 0.001 \)) than nonDM + FIR.

There are some differences between diaetebes cohort and nondiaetebes cohort such as age (\( P = 0.017 \)), current smoking (\( P = 0.001 \)), TG (\( P = 0.003 \)), LDL-C (\( P < 0.001 \)), HDL-C (\( P = 0.002 \)), cTNI (\( P = 0.003 \)), HbA1c (\( P < 0.001 \)), and FBG (\( P < 0.001 \)). Other baseline clinical characteristics were not comparable (\( P > 0.05 \)).

Procedural characteristics

Procedural characteristics of patients are presented in Table 2. Patients with nonDM + FIR had more 3-vessel disease (\( P = 0.004 \)), higher SS (\( P < 0.001 \)), higher rSS (\( P < 0.001 \)), higher SSQFR (\( P < 0.001 \)), higher rSSQFR (\( P < 0.001 \)), more non-infarcted vessel number (\( P < 0.004 \)), higher non-infarcted vessel with initial thrombolysis in myocardial infarction (TIMI) flow grade \( \leq 1 \) (\( P < 0.001 \)), higher non-infarcted vessel with diameter stenosis (DS) \( \geq 90 \) (\( P < 0.001 \)), higher non-infarcted vessel location at left circumflex artery (LCX) (\( P < 0.048 \)), higher non-infarcted vessel with QFR \( \leq 0.8 \) (\( P < 0.001 \)), higher non-infarcted vessel with QF \( \leq 0.8 \) location at left anterior descending artery (LAD) (\( P < 0.001 \)), higher non-infarcted vessel with QFR \( \leq 0.8 \) location at LCX (\( P < 0.001 \)), and higher non-infarcted vessel with QFR \( \leq 0.8 \) location at right
coronary artery (RCA) \((P < 0.001)\) than nonDM + FCR when compared nondiabetes cohort. Situation of diabetes cohorts is similar to that of nondiabetes cohorts, except for DM + FIR had smaller stent diameter \((P = 0.020)\) and longer stent length \((P = 0.040)\) than DM + FCR.

When compare FCR layering, results showed DM + FCR had more non-infarcted vessel with QFR \(\leq 0.8\) location at LCX \((P = 0.008)\), and more number of stents \((P = 0.024)\) than nonDM + FCR. Patients with DM + FIR had higher SS\(_{QFR}\) \((P < 0.001)\), higher rSS\(_{QFR}\) \((P < 0.001)\), higher non-infarcted vessel with QFR \(\leq 0.8\) \((P < 0.001)\), and higher non-infarcted vessel with QFR \(\leq 0.8\) location at RCA \((P = 0.008)\) than nonDM + FIR. Other baseline procedural characteristics were not comparable \((P > 0.05)\). (Table 2).

In addition, the clinical and procedural characteristics were taken into univariate and multivariate logistic regression analyses to identify the independent predictors of FIR. Results showed hypertension \((P = 0.003)\), SS \((P < 0.001)\), rSS \((P < 0.001)\), SS\(_{QFR}\) \((P < 0.001)\), non-infarcted vessels of DS \(\geq 90\) \((P = 0.036)\), and non-infarcted vessels at LCX \((P = 0.002)\) were associated with FIR in nondiabetes cohort, while eGFR \((P = 0.041)\), SS \((P < 0.001)\), rSS \((P < 0.001)\), SS\(_{QFR}\) \((P < 0.001)\), non-infarcted vessels at LCX \((P < 0.001)\) were associated with FIR in diabetes cohort (Supplemental Fig. 2). The reason for the correlation between LCX and FIR may be that the volume of LCX is smaller than the other two blood vessels, leading to a decrease in QFR [17].

**Clinical outcomes**

99.0% (617/623) patients were not lost during the clinical follow-up with a median follow-up period of 36 months. Overall, incidence of MACE in diabetes cohort was higher than that of nondiabetes cohort (22.9% vs 13.6%, HR = 1.79, 95%CI = 1.23–2.58, \(P = 0.002\)) (Fig. 2A). And incidence of MACE in the FIR layering was also higher than that of in the FCR layering (24.0% vs 12.6%, HR = 1.96, 95%CI = 1.35–2.83, \(P < 0.001\)) (Fig. 2B).

In the nondiabetes cohort, kaplan-Meier curves showed that nonDM + FIR patients had a higher 3-year MACE incidence (18.5% vs 9.8%, HR = 1.98, 95%CI = 1.06–3.72, \(P = 0.032\)) as compared to nonDM + FCR (Fig. 3A). In the diabetes cohort, DM + FIR patients also had a higher 3-year MACE incidence (27.9% vs 16.1%, HR = 1.76, 95%CI = 1.11–2.80, \(P = 0.017\)) as compared to DM + FCR (Fig. 3B). In the FCR layering, DM + FCR had a similar incidence of MACE with nonDM + FCR \((P = 0.085)\) (Supplemental Fig. 3A), while in the FIR layering DM + FIR had a little higher incidence than nonDM + FIR \((P = 0.044)\) (Supplemental Fig. 3B).

In addition, components of MACE included cardiac death, TVR, non-TVR, rehospitalization due to UAP, and non-fatal MI were also analysed. On the whole, incidence rate of rehospitalization due to UAP (19.1% vs 8.8%, HR = 2.22, 95%CI = 1.46–3.38, \(P < 0.001\)) and non-fatal MI (4.0% vs 9.0%, HR = 4.01, 95%CI = 1.15–8.75, \(P = 0.026\)) in the diabetes cohort were higher than nondiabetes cohort (Fig. 2A). The incidence rate of non-TVR (7.2% vs 2.3%, HR = 2.83, 95%CI = 1.38–5.80, \(P = 0.004\)), rehospitalization due to UAP (17.3% vs 10.9%, HR = 1.61, 95%CI = 1.06–2.45, \(P = 0.026\)), and non-fatal MI (3.8% vs 1.0%, HR = 3.18, 95%CI = 1.15–8.75, \(P = 0.026\)) in the FIR layering were higher than FCR layering (Fig. 2B).
Among them, nonDM + FIR and nonDM + FCR had difference in incidence rate of non-TVR (7.0% vs 6.9%, HR = 4.34, 95%CI = 1.51–12.51, P = 0.007), and non-fatal MI (5.4% vs 0%, HR = 5.75, 95%CI = 1.64–0.13, P = 0.006) (Fig. 3A), but DM + FIR and DM + FCR had no statistical difference about components of MACE (Fig. 3B). In the FCR layering, DM + FCR had no statistical difference about components of MACE with nonDM + FCR (Supplemental Fig. 3A), while DM + FIR had a higher incidence of rehospitalization due to UAP than nonDM + FIR (22.4% vs 9.9%, HR = 2.24, 95%CI = 1.31–3.82, P = 0.003) in the FIR layering (Supplemental Fig. 3B).

A multivariate Cox regression model was used to find independent predictors of MACE. Results showed that after adjustment for baseline clinical differences, non-infarcted vessel with DS ≥ 90 (HR = 1.56, 95%CI = 1.05–2.32, P = 0.027), DM (HR = 1.60, 95%CI = 1.03–2.49, P = 0.036), and FIR (HR = 1.71, 95%CI = 1.13–2.57, P = 0.011) were independent predictors for overall patients (Fig. 4). Non-infarcted vessel with DS ≥ 90 (HR = 1.70, 95%CI = 1.05–2.76, P = 0.030), and FIR (HR = 1.69, 95%CI = 1.01–2.83, P = 0.045) were independent predictors of 3-year MACE for DM cohort (Fig. 4). There was no independent predictor for nonDM cohort.

Receive operating characteristic curve (ROC) curves were plotted to find a better indicators for discrimination of 3-year MACE. Result showed that when adding clinical risk factors, rSSQFR in the nonDM + FIR group had a statistical difference with clinical risk factors alone ((area under curve) AUC = 0.715, 95%CI = 0.596–0.835 vs AUC = 0.613, 95%CI = 0.474–0.752, P = 0.040) and clinical risk factors + rSS (AUC = 0.715, 95%CI = 0.596–0.835 vs AUC = 0.621, 95%CI = 0.479–0.764, P = 0.045) (Fig. 5A).

Similarly, clinical risk factors + rSSQFR showed the biggest AUC when compare with clinical risk factors alone (AUC = 0.812, 95%CI = 0.750–0.874 vs AUC = 0.666, 95%CI = 0.581–0.751, P < 0.001) and clinical risk factors + rSS (AUC = 0.812, 95%CI = 0.750–0.874 vs AUC = 0.672, 95%CI = 0.587–0.757, P = 0.003) in the DM + FIR group (Fig. 5B). Due to the rSSQFR value of 0 in the FCR group, there is no analyticity in nonDM + FCR group and DM + FCR group.

**Discussion**

To evaluate whether the introduction of QFR will improve the MACE prediction ability for MVD-STEMI and DM patients, we set up a nonDM control group and stratified patients using QFR. Finally, we analyzed the MACE results. The main conclusion is the more severe the vessels, the more suitable for QFR. The major findings obtained from the study are as follows: 1) DM worsens coronary arteries; 2) both DM population and FIR layering are more prone to MACE, and the DM + FIR group (i.e. MVD-STEMI + DM + FIR) has the highest incidence of MACE; DM and FCR were important predictors of MACE; 3) The predictive ability of MACE was significantly improved by adding rSSQFR, however, there was no improvement by adding rSS; the DM (+ FIR) population has the greatest improvement in predictive ability by adding rSSQFR among all populations.

**Diatebes and coronary arteries**
It is well known that DM accelerates development of atherosclerosis and progression of macro- and micro-vascular diseases thereby causing the vessels to become severe [18]. The severity of vessels (before PCI) is mainly reflected in the quantity and complexity of diseased vessels in angiography.

In terms of quantity, some reports showed the ratio of 2-vessel disease in STEMI patients with DM was similar with nonDM (36% vs 35%, \(P = 0.809\)), but 3-vessel disease was different obviously (29% vs 23%, \(P = 0.121\)) [19]. Other study showed 2-vessel disease (31.6% vs 27.6%, \(P\) not displayed) and 3-vessel disease (24.5% vs 15.2%, \(P\) not displayed) of STEMI + DM patients were similar with patients with nonDM [20]. Another study showed 2-vessel disease (31.0% vs 28.0%, \(P\) not displayed) and 3-vessel disease (28.0% vs 16.0%, \(P\) not displayed) of STEMI + DM patients were higher than that of nonDM [21]. Our research subjects were MVD-STEMI + DM patients, both of which are 2-vessel disease. The proportion of 3-vessel releases in 2-vessel disease was 58.8%, which was higher than nonDM (53.2%). This proves the damaging effect of DM on coronary arteries. However, this difference is not statistically significant (\(P = 0.158\)), possibly due to the small sample size. Besides, the proportion in our study was lower than the above report.

In terms of complexity, baseline SS of STEMI + DM patients was higher than nonDM patients (18.0 ± 11.5 vs 15.0 ± 12.5, \(P = 0.013\)) in Burgess et al study [20]. MVD-STEMI + DM patients are more severe than STEMI + DM patients, but there are no reports on the specific situation of SYNTAX score. Our study first reported that MVD-STEMI + DM patients had higher baseline SS (16.0 (12.0–21.0) vs 15.0 (12.0-19.5), \(P = 0.096\)) than nonDM even without statistical differences. This result was also much higher than Burgess et al study.

Apart from the observation from angiography, QFR can bring a different perspective. After QFR improvement, the SYNTAX score showed a significant gap between DM and nonDM population. Baseline SS\(_{QFR}\) before PCI in MVD-STEMI patients with DM was significantly higher than that of without DM (8.0 (6.0–15.0) vs 11.0 (6.0–18.0), \(P<0.001\)). QFR confirms vascular ischemia is more severe in the DM population from a functional perspective.

**Diabetes & FIR and MACE**

Diabetes impairs the prognosis of patients. In a large regional program, STEMI patients with DM had higher rates of 5-year all-cause mortality (16% vs 9%, \(P<0.001\)) when compared to that without DM [27]. Likewise, another trial showed 3.6-year primary endpoint (27% vs 18%, \(P = 0.042\)) including cardiac death (12% vs 4%, \(P = 0.001\)), myocardial infarction (14% vs 13%, \(P = 0.581\)), and cardiovascular accident (7% vs 5%, \(P = 0.124\)) had a higher incidence in STEMI patients with DM than those without DM [20]. Our research revealed the MACE occurred in 22.9% MVD-STEMI patients with DM vs 13.6% with nonDM (\(P = 0.002\)).

Numerous studies have demonstrated that the method of revascularization had an impact on prognosis [22, 23]. In the DANAMI-3-PRIMULTI trial of 1 countries and 627 patients, compared with FFR-guided functional CR, MVD-STEMI patients treated with IRA-only strategy (anatomical IR) had a 1.7-fold increase
in 27-month MACE risk (22% vs 13%, \(P = 0.004\)), mainly including all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation [24]. Likewise, in the COMPARE-ACUTE trial of 8 countries and 855 patients, compared with FFR-guided functional CR, MVD-STEMI patients treated with IRA-only strategy (anatomical IR) had a 2.6-fold increase in 1-year MACCE risk (20.5% vs 7.8%, \(P < 0.001\)), mainly including all-cause mortality, non-fatal reinfarction, ischaemia-driven revascularisation, and cerebrovascular event [25]. Our study revealed FIR guided by QFR had worse prognosis than FCR by almost 2-fold increase of 3-year MACE (24.0% vs 12.6%, \(P < 0.001\)), mainly non-TVR (7.2% vs 2.3%, HR = 2.83, 95%CI = 1.38–5.80, \(P = 0.004\)), rehospitalization due to UAP (17.3% vs 10.9%, HR = 1.61, 95%CI = 1.06–2.45, \(P = 0.026\)), and non-fatal MI (3.8% vs 1.0%, HR = 3.18, 95%CI = 1.15–8.75, \(P = 0.026\)).

When continuing to stratify DM and nonDM cohort using QFR, FCR layering including DM + FCR group and nonDM + FCR group, and FIR layering including DM + FIR group and nonDM + FIR group were obtained (Central Illustration Figure). The order of MACE of the four groups in our study was: 27.9% in DM + FIR group > 18.5% in nonDM + FIR group > 16.1% in DM + FCR group > 9.8% in nonDM + FCR group. When compared highest 27.9% of DM + FIR group with lowest 9.8% of nonDM + FCR group, it can be concluded that both diabetes status and revascularization assignment promote the occurrence of MACE. In Kongyong et al study, order of MACCE (including all-cause death, cardiac death, MI, Stroke and unplanned revascularization) in MVD-STEMI patients was: DM + staged PCI 37.8% > nonDM + culprit-only PCI 35.5% > DM + culprit-only PCI 31.9% > nonDM + staged PCI 31.8% [6]. Using culprit-only PCI can lead to a certain degree of anatomical incomplete revascularization (IR), while staged PCI can lead to a certain degree of anatomical complete revascularization (CR), which is close to the study population set in this article. Even if the order of the MACE was inconsistent, it can still be seen that the risk of MACE with DM + IR was the highest. This is consistent with our study.

However, rate of MACE in our research was difference with other studies. Possible explanations are as follows: 1) different research subjects: Our study focuses on MVD-STEMI patients, while some above studies focuses on only STEMI patients; 2) different MACE composition: Our study had one more MACE composition for rehospitalization caused by unstable or progressive angina than the studies above; 3) different research scope: Our research scope was all revascularization except CR, while the above research is IRA-only revascularization. 4) different sample size: Our size was two hundreds, while above studies was six hundreds; 5) different sample region.

In order to further explore the role of DM and FIR in MACE, the COX regression model was used. Results suggested both DM and FIR was independent predictors of MACE (HR = 1.58, 95%CI = 1.02–2.46, \(P = 0.042\); HR = 1.70, 95%CI = 1.13–2.55, \(P = 0.012\)), which is consistent with other trials. In the FAVOR III China trial, FIR guided by QFR was an independent predictor of 1-year MACE in patients with CHD (HR = 0.31, 95% CI = 0.23–0.40, \(P < 0.001\)) (14).

**rSS\text{QFR} and MACE**

rSS is a marker of the residual ischaemia burden but only consider the anatomic severity. Residual functional SYNTAX score (rFSS) integrates rSS and functionalism, thereby providing both anatomic and
functional information. Research reported rFSS with post-PCI FFR ≤ 0.80 showed significantly higher rate of adverse clinical events than that post-PCI FFR > 0.80 [26]. QFR as a wire-free, faster, and more costeffective assessment of functional significance has been demonstrated substantial correlation with FFR in coronary artery disease [27]. Previous research demonstrated that in FAVOR III China trial rSSQFR can discriminate 1-year MACE than rSS (AUC = 0.66 vs AUC = 0.58; P<0.001) in the CAD patients [14]. Tang et al showed the AUC of rSSQFR was significantly greater than that of rSS for 2-year MACE in patients with STEMI (AUC = 0.738 vs AUC = 0.648, P< 0.001) [28]. Our study showed the predictive ability of rSSQFR for 3-year MACE was significantly improved than the simply model of clinical risk factors (AUC difference − 0.102 and − 0.146; P = 0.004 and P< 0.001). However, rSS did not trigger a change (AUC difference − 0.008 and − 0.006; P = 0.656 and P = 756). This proves the importance of rSSQFR in improving the prediction model. The result was consistent with the above research.

Besides, DM enhanced the discrimination value of rSSQFR. In DM (+ FIR) population, rSSQFR had a biggest AUC difference when compared to the nonDM (+ FIR) population (AUC difference − 0.146 vs -0.102). This proves that the use of QFR by DM population is more valuable than that of nonDM population.

**Study limitations**

First, this study was an observational study with some selective bias. Patients who were not suitable for QFR assessment (such as left-main disease) or unqualified QFR image quality were excluded from this study. Therefore, our conclusion may not be generalized to patients who were excluded. Second, this study was not a randomised study, and the decision for non-infarcted artery revascularisation at index procedure was left to the operator's discretion. Therefore, the optimal treatment strategy for patients with FIR could not be evaluated. We will design randomized controlled trials in the future and do more work. Third, current follow-up was 3 years. Future trials with long-term follow-ups are needed to elucidate long-term outcomes. Fourth, the study population was relatively small. Our study was not powered to detect differences in low-frequency events, such as cardiac death, non-fatal MI and other adverse clinical events.

**Conclusions**

Diabetes status and functional incomplete revascularization strategy increased 3-year rates of MACE in patients with MVD-STEMI. The use of QFR by DM population is more valuable than that of nonDM population.

**Declarations**

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**Authors' contributions**
H.X. contributed to the study design, data analysis, and wrote the manuscript. Y.L. helped data acquisition and data analysis. B.G. and Y.G. contributed to data acquisition and interpretation of results. R.Z. reviewed and edited the intellectual content. All authors reviewed the manuscript.

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The study was approved by the ethics committee of 2nd Affiliated Hospital of Harbin Medical University and complied with the Declaration of Helsinki. All patients signed an informed consent form to participate in this study.

**Consent for publication**

Not applicable.

**Competing interests**

All authors have no potential conflicts of interest to declare.

**References**


Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures
DM = diabetes mellitus; FCR = functional complete complete revascularization; FIR = functional incomplete complete revascularization; MVD-STEMI = multivessel disease and ST-elevation myocardial infarction; NonDM = non-diabetes mellitus; PCI = percutaneous coronary intervention; QFR = quantitative flow ratio.

Figure 1

See image above for figure legend.
Figure 2

See image above for figure legend.
FIGURE 3 3-Year Clinical Outcomes

(A) NonDM+FIR and nonDM+FIR, DM+FIR and DM+FIR of Kaplan-Meier curves for 3-year MACE and (B) bar chart for MACE components

Bold represents significance inside the diabetic cohort and inside the nondiabetic cohort. *P* value <0.05 was considered statistically significant.

MACE = major adverse cardiac events; MI = myocardial infarction; TVR = target vessel revascularization; UAP = unstable angina pectoris.

Other abbreviations as in Figure 1, Figure 2, Table 1.

Figure 3

See image above for figure legend.
A multivariate Cox proportional hazards model was used to analyze independent predictors of 3-year MACE. Bold represents significance in overall and diabetes cohort. *P* value < 0.05 was considered statistically significant.
Abbreviations as in Figure 1, Table 1, and Table 2.

**Figure 4**

See image above for figure legend.

**FIGURES** Discrimination of 3-year MACE

(A) NonDM+FIR group and (B) DM+FIR group of ROC curve to discriminate 3-year MACE through rSS and rSSgPr after adding clinical risk factors. Clinical risk factors included age, gender, smoking history, hypertension, dyslipidemia, CKD, previous MI, previous PCI. Bold represents significance between clinical factors + rSS or clinical factors + rSSgPr and clinical factors. *P* value < 0.05 was considered statistically significant.

AUC = area under the curve, ROC = Receiver operating characteristic curves. Other abbreviations as in Table 1 and Figure 2.
Figure 5
See image above for figure legend.

Figure 6
Unnumbered image in the Discussion section.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Supplementalmaterial4CardiovascularDiabetology.docx
- Tables.docx