Original Article

Predictors of recurrent angina in patients with no need for secondary revascularization

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BACKGROUND: Approximately 20% to 30% of patients with coronary artery disease (CAD) develop recurrent angina pectoris following successful and complete coronary revascularization utilizing percutaneous coronary intervention (PCI). We aim to investigate predictors of recurrent angina pectoris in patients who have undergone successful coronary revascularization using PCI, but on repeat coronary angiography have no need for secondary revascularization.

METHODS: The study comprised 3,837 patients with CAD, who were enrolled from January 2007 to June 2019. They had undergone successful PCI; some of them redeveloped angina pectoris within one year after the procedure, but on repeat coronary angiography had no need for revascularization. Thrombolysis in myocardial infarction (TIMI) frame count was used to evaluate the velocity of coronary blood in the follow-up angiogram. Multivariate logistic regression was used to investigate risk factors for recurrent angina pectoris. Similarly, predictors of recurrent angina according to the TIMI frame count were assessed using multivariate linear regression.

RESULTS: In this retrospective study, 53.5% of patients experienced recurrent angina pectoris. By multivariate logistic regression, the following characteristics were statistically identified as risk factors for recurrent angina pectoris: female sex, older age, current smoking, low-density lipoprotein cholesterol (LDL-C) ≥1.8 mmol/L, and an elevated TIMI frame count (*P* for all <0.05). Similarly, using multivariate linear regression, the statistical risk factors for TIMI frame count included: female sex, older age, diabetes, body mass index (BMI), post-procedural treatment without the inclusion of dual antiplatelet therapy.

CONCLUSIONS: Patient characteristics of female sex, older age, diabetes, and elevated BMI are associated with an increased TIMI frame count, coronary microcirculation dysfunction, and recurrent angina pectoris after initially successful PCI. In addition, current smoking and LDL-C ≥1.8 mmol/L are risk factors for recurrent angina pectoris. In contrast, the treatment with dual antiplatelet therapy is negatively correlated with a higher TIMI frame count and the risk of recurrent angina pectoris.

KEYWORDS: Recurrent angina; Thrombolysis in myocardial infarction frame count; Predictors

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INTRODUCTION

Percutaneous coronary intervention (PCI) is currently an effective and widely accepted treatment for patients with coronary artery disease (CAD). Despite advances in medical and interventional treatment modalities, many patients develop angina pectoris due to myocardial underperfusion.[1] In previously published reports, recurrent angina developed in 20%–30% of patients within one year following bare-metal stent (BMS) implantation.[2,3] Similar findings were observed in patients treated with drug-eluting stent (DES)[1] or bioresorbable vascular scaffold (BVS).[4,5]

Stent thrombosis and in-stent restenosis (ISR) are the two major causes of stent failure. However, DES registries and randomized trials have typically reported

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stent thrombosis rates less than 1% at one-year follow-up. Moreover, the rate of clinically relevant ISR was only 5% at one-year follow-up.[6] These structural mechanisms do not provide an adequate explanation for the striking 50% rate of persistent or recurrent angina following successful PCI.[7]

Then why do patients develop recurrent angina pectoris without restenosis after PCI? Previous studies have demonstrated that endothelial dysfunction[8] or microcirculation disorders[9] could reduce myocardial perfusion in patients without stent thrombosis or ISR. Such coronary microvascular impairment, as detected by increased microvascular resistance, has been verified as a pathogenetic factor of myocardial ischemia and as an independent predictor of poor clinical outcome in patients with cardiovascular disease.[10,11] There are several methods to assess coronary flow tardiness caused by microcirculation disorders. The index of microcirculatory resistance (IMR) is a new but somewhat invasive method commonly used in clinical practice to evaluate functional coronary microcirculation.[12,13] Notably, IMR requires coronary catheterization at a moderately high cost. In contrast, thrombolysis in myocardial infarction (TIMI) frame count is a relatively simple and economic procedure[14,15] that can be performed by a standardized review of the coronary angiogram. In addition to the assessment of epicardial coronary circulation, it has been reported to effectively and accurately evaluate functional microcirculation.[16]

The study is to investigate predictors of recurrent angina pectoris within one year in patients who have undergone successful coronary revascularization using PCI, but on repeat angiography have no need for secondary revascularization.

METHODS

Inclusion and exclusion

The cohort study comprised 3,837 patients with CAD, enrolled in Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, China, from January 2007 to June 2019. They had undergone successful PCI; some of them had redeveloped angina pectoris within one year after the procedure, but had no need for revascularization on repeat coronary angiography.

The inclusion criteria were: (1) using PCI, patients underwent complete coronary revascularization; (2) repeat coronary angiography was performed within one year± three months following PCI; (3) the TIMI flow grade at initial PCI reached level 3; (4) on repeat angiography, there was no stent restenosis or new stenosis, and no additional stent implantation was required. Exclusion criteria were: (1) severe heart failure, defined by an ejection fraction (EF) <40% or N-terminal pro-B-type natriuretic peptide (NT-proBNP) >2,000 pg/mL; (2) patients with co-morbidities that may have resulted in angina pectoris, such as left ventricular hypertrophy, valvopathy, or cardiomyopathy; (3) patients with atrial fibrillation or severe uncontrolled rhythm disturbance on an electrocardiogram.

The study was conducted according to the *Declaration of Helsinki* and was approved by the ethics committee of Sir Run Run Shaw Hospital.

Procedures and the primary and secondary endpoints

The initial PCI procedure was performed as per accepted, current general guidelines. All patients were treated according to standard guidelines with statin, aspirin, clopidogrel, or ticagrelor. The types of stents, implantation techniques, and the techniques of intravascular imaging were determined by operator preferences. All patients were followed up with telephone interview after PCI, but 18.7% of patients were lost due to the wrong telephone number or refusal. We consecutively enrolled the patients with follow-up angiogram, and vessel diameter stenosis <70% without the evidence of ischemia or fractional flow reserve (FFR) >0.80 was defined for this study as "no PCI intervention indicated".

The TIMI frame count method was used to quantify blood flow through the coronary circulation and coronary microvasculature function.[16] Current studies have used TIMI frame counts of the left anterior descending (LAD) to determine the coronary flow velocity, because TIMI frame counts of the left circumflex and right coronary artery could confuse the results as patients might have either left crown dominant or right crown dominant coronary arteries. The TIMI frame count was performed using the methods as described in the literature.[17] Two investigators extracted the data independently, and the average of the two results was recorded. If the difference between the two measurements was greater than 10%, a third researcher would provide input, and the average of the two closest results was recorded.

The primary endpoint was defined as the development of recurrent angina pectoris within one year following PCI. The secondary endpoint was defined as the TIMI frame count in the follow-up angiogram.

Definitions

The TIMI frame count was defined as the number of cineframes required for contrast to the first reach standardized distal coronary landmarks in the artery.[17] Angina pectoris was a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin.[18]

Statistical analysis

Statistical analysis was performed using the SPSS statistical package, version 24.0 (Chicago, Illinois, USA). Categorical variables were expressed as numbers (percentage) and compared using Chi-square test. Continuous variables were expressed as mean±standard deviation (SD) or median and interquartile range and compared using Student's *t*-test or non-parametric Mann-Whitney *U*-test according to whether the continuous variables conformed to a normal distribution. Univariate and multivariate logistic regressions were performed to assess the risk factors for recurrent angina pectoris. In addition, multivariate linear regression was performed to identify the risk factors of TIMI frame counts. All reported *P*-values were two-sided, and the *P*-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of patients with and without recurrent angina

Notably, 53.5% of patients in our cohort developed recurrent angina pectoris within one year following PCI; patients were 64.3±10.1 years old, 72.0% were male, 65.4% had hypertension, 22.8% had diabetes mellitus, and 24.7 % were current smokers.

Compared with patients who did not suffer recurrent angina pectoris, those who did were significantly older (62.97±10.10 years old vs. 65.45±9.90 years old, *P*<0.001), and had a higher incidence of hypertension (62.7% vs. 67.7%, *P*=0.002). In the group with recurrent angina pectoris, patients had a higher level of C-reactive protein (CRP), fewer of them achieved a low-density lipoprotein cholesterol (LDL-C) target goal of <1.8 mmol/L (*P* for both <0.05), and fewer were taking ezetimibe (4.3% vs. 2.7%, *P*=0.007). Specifically, the TIMI frame count was higher (coronary flow was slower) in the patients with recurrent angina pectoris (20.78±7.29 frames vs. 21.98±7.06 frames, *P*<0.001).

Predictors of post-PCI angina pectoris

Multivariate logistic regression showed that female sex (adjusted odds ratio [*OR*] 1.236, 95% confidence interval [*CI*] 1.044–1.464, *P*=0.014), older age (*OR* 1.313, 95% *CI* 1.221–1.412, *P*<0.001), current smoking (*OR* 1.210, 95% *CI* 1.026–1.428, *P*=0.024), and LDL-C level ≥1.8 mmol/L (*OR* 1.194, 95% *CI* 1.036–1.376, *P*=0.015) were associated with an increased risk of recurrent angina pectoris within one year following PCI. It was also demonstrated that a higher TIMI frame count (*OR* 1.026, 95% *CI* 1.017–1.036, *P*<0.001) was significantly correlated with post-PCI angina pectoris (Table 1).

Quite impressively, a higher TIMI frame count of the LAD was consistently correlated with the incidence of post-PCI angina pectoris irrespective of the subgroup examined. This proved true (*P* for all <0.05, Figure 1) in patients whether they had hypertension (*OR* 1.019, 95% *CI* 1.007–1.032, *P*=0.002) or not (*OR* 1.039, 95% *CI* 1.023–1.056, *P*<0.001), diabetes (*OR* 1.043, 95% *CI* 1.020–1.066, *P*<0.001) or not (*OR* 1.022, 95% *CI* 1.011–1.033, *P*<0.001), female (*OR* 1.040, 95% *CI* 1.019–1.061, *P*<0.001) or male (*OR* 1.022, 95% *CI* 1.011–1.033, *P*<0.001), smoking (*OR* 1.018, 95% *CI* 1.003–1.037, *P*=0.050) or not (*OR* 1.030, 95% *CI* 1.018–1.041, *P*<0.001), and whether they achieved the LDL-C target goal (*OR* 1.026, 95% *CI* 1.014–1.038, *P*<0.001) or not (*OR* 1.027, 95% *CI* 1.010–1.044, *P*=0.002).

Predictors of TIMI flow frame count

The univariate linear regression analysis revealed that the older age, female sex, body mass index (BMI), current smoking, diabetes mellitus, serum uric acid (SUA), and dose of beta-blocker were associated with a higher TIMI frame count, but hypertension and dual antiplatelet treatment were negatively correlated with a higher TIMI frame count (Table 2).

After correction for the confounding factors screened from the univariate analysis, the multivariable linear regression analysis revealed that the female sex, older age, diabetes, and BMI were associated with a higher TIMI frame count. Patients with hypertension and patients that received standard dual antiplatelet therapy were negatively correlated with a higher TIMI frame count (Table 2).

DISCUSSION

This is a large study to investigate the incidence of recurrent angina pectoris and statistically identify risk factors for recurrent angina in patients without restenosis following successful and complete coronary revascularization at initial PCI. The major findings were: (1) the TIMI frame count was significantly correlated with post-PCI angina pectoris; (2) female sex, older age, current smoking, and LDL-C level ≥1.8 mmol/L were associated with an increased risk of recurrent angina pectoris following PCI; (3) female sex, older age, diabetes, and an elevated BMI were correlated with an increased TIMI frame count, while hypertension and standard dual antiplatelet therapy were negatively correlated with a higher TIMI frame count.

Despite advances in medical and interventional treatments, many patients develop recurrent angina pectoris without coronary artery stenosis following complete coronary revascularization at initial PCI.[19] In the present study, 53.5% of patients developed recurrent angina pectoris

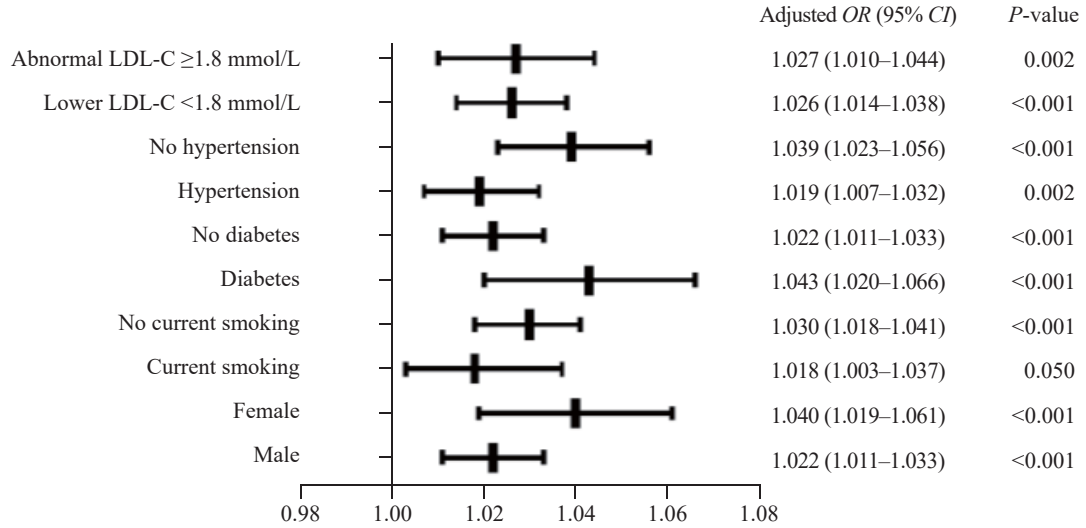

Figure 1. Multiple logistic regression of TIMI frame count of LAD and post-PCI angina in predefined subgroups. LDL-C: low-density lipoprotein cholesterol; *OR*: odds ratio; *CI*: confidence interval; LAD: left anterior descending; TIMI: thrombolysis in myocardial infarction; PCI: percutaneous coronary intervention.

Table 1. Logistics regression for post-PCI angina pectoris at one-year follow-up

Variables	Univariate regression			Multivariate regression		
	OR	95% *CI*	*P*-value	*OR*	95% *CI*	*P*-value
Age	1.281	1.201–1.367	<0.001	1.313	1.221–1.412	<0.001
Female	1.150	0.996–1.328	0.057	1.236	1.044–1.464	0.014
BMI	1.011	0.990–1.033	0.299	1.018	0.995–1.041	0.135
Current smoking	1.015	0.875–1.177	0.842	1.210	1.026–1.428	0.024
Diabetes	0.894	0.767–1.040	0.147	0.865	0.738–1.014	0.073
Hypertension	1.243	1.087–1.422	0.002	1.120	0.967–1.297	0.130
CRP	1.008	0.998–1.018	0.112	1.004	0.993–1.015	0.472
PLT	0.999	0.998–1.000	0.079	0.999	0.998–1.000	0.125
LDL-C ≥1.8 mmol/L	1.172	1.024–1.341	0.022	1.194	1.036–1.376	0.015
SUA	1.001	1.000–1.001	0.115	1.000	1.000–1.001	0.414
Beta blocker	1.150	1.012–1.306	0.032	1.210	1.057–1.386	0.006
CCB	1.130	0.909–1.405	0.271	1.088	0.862–1.375	0.447
Dual antiplatelet	0.989	0.862–1.134	0.873	1.025	0.887–1.185	0.737
TIMI frame count	1.024	1.015–1.033	<0.001	1.026	1.017–1.036	<0.001
Multiple vessels PCI	0.890	0.731–1.085	0.250	0.867	0.697–1.079	0.202
Total stent length	1.000	0.997–1.002	0.730	1.000	0.997–1.003	0.951
Stent size >2.5 mm	1.103	0.888–1.370	0.377	1.181	0.939–1.486	0.154
EF	0.997	0.990–1.003	0.307	0.998	0.991–1.006	0.680

BMI: body mass index; CRP: C-reactive protein; PLT: platelet; LDL-C: low-density lipoprotein cholesterol; SUA: serum uric acid; CCB: calcium channel blocker; EF: ejection fraction; TIMI: thrombolysis in myocardial infarction; PCI: percutaneous coronary intervention; *OR*: odds ratio; *CI*: confidence interval.

Table 2. Linear regression for TIMI frame count of LAD at one-year follow-up

Variables	Simple regression			Multiple regression		
	β	95% *CI*	*P*-value	*β*	95% *CI*	*P*-value
Age	0.558	0.350–0.767	<0.001	0.317	0.074–0.560	0.011
Female	1.877	1.397–2.357	<0.001	1.651	1.079–2.223	<0.001
Body mass index	0.199	0.124–0.275	<0.001	0.155	0.077–0.233	<0.001
Current smoking	0.863	0.333–1.394	0.001	0.042	–0.522–0.607	0.884
Diabetes	0.722	0.272–1.295	0.010	0.717	0.178–1.256	0.009
Hypertension	–0.930	–1.412– –0.448	<0.001	–0.712	–1.215– –0.209	0.006
CRP	–0.007	–0.040–0.027	0.692	–0.013	–0.045–0.020	0.440
PLT	0.000	–0.004–0.004	0.928	0.001	–0.004–0.005	0.814
LDL-C ≥1.8 mmol/L	0.199	–0.286–0.684	0.420	0.017	–0.467–0.501	0.946
SUA	0.005	0.002–0.007	<0.001	0.001	–0.002–0.003	0.593
Beta blocker	0.389	–0.068–0.847	0.095	0.050	–0.526–0.627	0.864
CCB	–0.193	–0.971–0.585	0.626	0.096	–0.699–0.891	0.813
Dual antiplatelet	–0.427	–0.921–0.066	0.089	–0.537	–1.035– –0.040	0.034
Multiple vessels PCI	0.241	–0.470–0.951	0.506	0.104	–0.636–0.845	0.783
Total stent length	–0.005	–0.014–0.005	0.332	–0.002	–0.012–0.008	0.689
Stent size >2.5 mm	0.424	–0.357–1.204	0.287	0.281	–0.502–1.064	0.482
EF	0.003	–0.021–0.027	0.825	0.015	–0.009–0.040	0.216

TIMI: thrombolysis in myocardial infarction; LAD: left anterior descending; CRP: C-reactive protein; PLT: platelet; LDL-C: low-density lipoprotein cholesterol; SUA: serum uric acid; CCB: calcium channel blocker; PCI: percutaneous coronary intervention;EF: ejection fraction; *CI*: confidence interval.

following PCI without revascularization at one-year follow-up.

In recent studies, an elevated BMI[20] and a higher number of stents[19] increased the risk of developing recurrent angina pectoris after PCI, whereas the administration of nicorandil reduced the risk.[21] The current study is consistent with this report as we found that an elevated BMI correlated with a higher TIMI frame count. Nicorandil was not included in the present study due to its extremely low usage in patients following PCI.

A study reported cardiac pain after PCI in the absence of ischemic events.[7] A more intense long-term endothelial dysfunction[8] was proposed as a possible mechanism. Similarly, microcirculation disorders[9] after coronary artery stenting have also been indicated. The TIMI frame count has been demonstrated to be useful in detecting coronary flow changes in patients with stent implantation[22] or impaired coronary microcirculation in patients who have impaired flow and increased burden of coronary atherosclerosis.[23] Previous observations have reported that females,[11,24,25] elderly patients, diabetes mellitus patients,[26,27] and patients with an elevated BMI[28] have been more likely to develop coronary microcirculation dysfunction. These reports are consistent with our study. Angina pectoris without recurrent coronary artery occlusion had a significant correlation with microcirculation disorders. After PCI, the reperfusion of ischemic tissue can cause widespread microvascular dysfunction that significantly exacerbates cardiovascular damage.[29] Platelets are critical mediators of inflammation during reperfusion injury, and a hyperactive platelet phenotype may contribute to exaggerated microcirculation dysfunction. Standard dual antiplatelet therapy can effectively inhibit platelet activation, reduce damage to microcirculation function, and improve myocardial blood perfusion.[30] This could provide the basis for our finding that dual antiplatelet therapy reduced the TIMI frame count. Hypertensive patients have been shown to have higher baseline coronary velocity as compared with healthy controls,[31] again consistent with this study.

The study intended to identify risk factors for recurrent angina pectoris following PCI. Some patient factors cannot be altered, such as sex and age. However, the risk of developing post-PCI recurrent angina might be altered by quitting smoking to decrease endothelial inflammation and improve coronary microcirculation. Additionally, changes in diet, lifestyle, and pharmacological treatments to control weight and reduce both LDL-C and blood glucose are realistic and valuable. These measures have been shown to be effective in improving coronary microcirculation, and reduce the incidence of recurrent angina. As noted previously, standard dual antiplatelet therapy can effectively inhibit platelet activation, reduce damage to microcirculation function, and improve myocardial perfusion.

This study has several limitations. First, as a single-center retrospective study, residual confounding or selection bias cannot be completely ruled out. Second, as a retrospective study, not all patients underwent follow-up angiography. Patients who developed post-PCI angina pectoris reliably returned not only for follow-up, but for remedial action. Patients without recurrent angina pectoris were less likely to return. Third, a part of patients without angina would like to take non-invasive examinations such as coronary CTA in the one-year follow-up. These would lead to a certain degree of selection bias.

CONCLUSIONS

Female sex, older age, diabetes mellitus, and elevated BMI are associated with a higher TIMI frame count, which could develop coronary microcirculation dysfunction and recurrent angina pectoris after PCI. In addition, risk factors of current smoking and LDL-C level ≥1.8 mmol/L are statistically associated with recurrent angina pectoris. Treatment with dual antiplatelet therapy is negatively correlated with a higher TIMI frame count and the risk of recurrent angina pectoris.

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