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Relationship Between Preoperative Low-Density Lipoprotein Cholesterol and Periprocedural Myocardial Injury in Patients Following Elective Percutaneous Coronary Intervention in Southern China

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Statistical Analysis C
Data Interpretation D
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Background: Periprocedural myocardial injury (PMI) is known to be a predictor of postprocedural cardiovascular morbidity and mortality following a percutaneous coronary intervention (PCI). However, the correlation between low-density lipoprotein cholesterol and periprocedural myocardial injury in patients following elective PCI in southern China remains unclear. Therefore, we aimed to investigate the association of preoperative low-density lipoprotein cholesterol (LDL-C) levels with PMI in patients following elective PCI.

Material/Methods: This study included 1942 consecutive patients who received elective PCI. Cardiac troponin I (cTnI) was used to assess perioperative myocardial injury. The peak cTnI was measured within 24 h after PCI, and the correlation between the cTnI value and the preoperative LDL level was studied.

Results: The data suggest that the PCI patients with preprocedural LDL-C <100 mg/dl were strongly and independently correlated with less risk of PMI. Univariate logistic regression indicated that patients with preprocedural LDL-C of 70~99 mg/dl were correlated with lower risk of postprocedural cTnI elevation above 3×ULN (odds ratio [OR]: 0.762; 95% [CI]: 0.603–0.965; *P*<0.024) up to 20×ULN (OR: 0.730; 95% CI: 0.576–0.924; *P*<0.000) compared to those with preprocedural LDL-C ≥100 mg/dl. Moreover, patients with preprocedural LDL-C of <70 mg/dl were more strongly correlated with lower risk of postprocedural cTnI elevation above 3×ULN (OR: 0.641; 95% CI: 0.436–0.936; *P*<0.021) up to 20×ULN (OR: 0.476; 95% CI: 0.316–0.717; *P*<0.000).

Conclusions: Our study demonstrated that PCI patients with lower preprocedural LDL-C were correlated with a lower risk of PMI in southern China.

MeSH Keywords: Cholesterol, LDL • Percutaneous Coronary Intervention • Troponin I

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Background

In modern interventional therapy, percutaneous coronary intervention (PCI) is the main method of revascularization in patients with coronary heart disease. PCI can significantly improve the symptoms of myocardial ischemia and reduce the incidence of vascular events in patients with coronary heart disease [1]. The incidence of perioperative myocardial injury (PMI), also known as myocardial infarction, did not substantially decreased despite technological advances and effective medical treatment [2]. Many clinical studies have shown that PMI is a predictor of adverse clinical outcomes after PCI. According to the Global Working Group on Myocardial Infarction (ESC/ACC/AHA/EHS/WHO), one of the criteria for definition of myocardial infarction (MI) is serum biomarkers (specifically troponin) elevation. Cardiac troponins are sensitive and specific markers of myocardial necrosis [3,4]. Previous cardiovascular magnetic resonance imaging studies showed that elevation of TnI after PCI indicates new irreversible myocardial injury [5]. They were benefited from the sensitivity, specificity, and prognosis of acute coronary syndrome ACS compare with creatine kinase (CK) and creatine kinase-muscle-brain (CK-MB) [6–9]. Postoperative cTnI> 1x the upper limit of normal (ULN) was interpreted as perioperative myocardial injury. Postoperative cTnI >3×ULN was diagnosed as myocardial infarction after PCI in 2007, and postprocedural cTnI >5×ULN, which was defined as PCI-related myocardial infarction in 2012 [10, 11].

Dyslipidemia is an independent risk factor for coronary heart disease. Clinical trials have shown that elevated LDL is linearly associated with coronary heart disease (CHD) [12]. Cardiovascular events and mortality could be reduced by 20% to 50% by interventions to lower levels of LDL-C. Researchers have suggested that patients with low LDL-C have reduced risk of postoperative myocardial injury in eastern China [13]. Although the lipid metabolism in urban and rural areas of southern China was reported to be associated with the special food culture, as well as genetic variants such as thalassemia, which may contribute to cardiovascular diseases in this area, little is known about whether the PCI patients with lower levels of LDL-C also have lower risk of PMI in southern China [14,15]. In this study, we explored the connection between preprocedural LDL-C levels and PMI in patients following elective PCI in southern China.

Material and Methods

Patient population

Eligibility screening was performed in patients undergoing coronary artery interventional therapy (PCI) at Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University. CHD patients were eligible for inclusion if they exhibited: (1) stable angina, or unstable angina and received elective PCI surgery, and (2) there were no ST segment elevation or non-ST segment elevation acute myocardial infarctions in the 4 weeks before the intervention. The major exclusion criteria were: (1) the patient died after PCI or angiography failed, (2) incomplete data on lipid files for patients, and (3) patients treated with atheroablative, distal protection devices, or aspiration thrombectomy.

From September 2014 to September 2016, a total of 1942 patients without acute myocardial infarction in the past 4 weeks who attempted to undergo elective PCI at Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, were eligible for this study. The present study was performed in accordance with the ethics standards laid down in the updated version of the 1964 Declaration of Helsinki and was approved by Human Ethics Committees of Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, Guangdong province, China. All patients had signed informed consent.

Percutaneous coronary intervention

The indications for PCI were based on recommendations from the ACC/AHA, and all of patients were operated on by experienced interventional cardiologists. Patients were treated with aspirin (100–300 mg/day) and clopidogrel (300–600 mg) at least 2 h before PCI. All patients accepted a bolus of ungraded heparin 5000 U or 70 U/kg just before surgery, and a bolus of 2000–3000 U was added when the procedure lasted more than 1 h. The interventional cardiologist could decide on vascular access and PCI type based on the patient's characteristics. The interventional cardiologist also could decide on total inflation times and inflation pressure of balloon, which is based on the technical properties of the balloon and the stent [16]. All patients continuously received aspirin and clopidogrel daily after PCI. Glycoprotein IIb/IIIa inhibitors were used at the surgeon's discretion [12].

ECG monitoring

The 12-lead electrocardiogram was recorded before and after PCI in all patients, and in case of occurrence of symptoms that were considered as postoperative ischemic events. All patients underwent continuous electrocardiographic monitoring after PCI.

Biochemical measurements

Peripheral venous blood samples were collected before PCI for measuring lipid profiles. cTnI was detected before PCI and 24 h after PCI, as well as in the event of symptoms or signs that

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suggested myocardial ischemia. The LDL-C level was tested by selective solubilization method (AU5400 analyzer, Beckman Coulter, CA). cTnI was determined using the PATHFAST cTnI-II (cardiac troponin I) Test (Mitsubishi Chemical, Tokyo, Japan). The ULN was interpreted as the 99th percentile of normal population with a total imprecision of <10%. The ULN of this test was 0.02 ng/mL. The peak value of cTnI was statistically analyzed within 24 h.

Statistics

The continuous variables and categorical variables are expressed as mean ± standard deviation, as percentage, or as frequencies with percentage, respectively. IBM SPSS Statistics 21.0 (IBM, Armonk, NY, USA) was used for all statistical analyses. Differences between groups based on LDL-C levels were analyzed using the χ^2 test, Kruskal-Wallis test, or one-way ANOVA. The relationship of clinical parameters with postprocedural cTnI levels was tested by univariate linear regression analyses. The variables of P<0.05 in univariate linear regression were used as variables in a stepwise multivariate linear model. Successful normalization of cTnI after log-transformation was analysis using the Kolmogorov-Smirnov test. The correlation between LDL-C levels and the occurrence of postprocedural cTnI elevations above various multiples of ULN were determined by logistic regression. Based on the Guidelines for the Prevention and Treatment of Chinese Adult Dyslipidemia 2016, LDL-C was considered as the cut-off point (<70, 70–99, and ≥100 mg/dl). Additionally, variables were adjusted by the logistic model, and these variables were independently related to postprocedural cTnI levels. A probability value of *P*<0.05 was considered significant for this study.

Results

Clinical characteristics of the PCI patients

The study flow chart is shown in Figure 1. Between September 2014 and September 2016, 1942 patients were enrolled in the study. Table 1 demonstrates the baseline characteristics and lipids level of the PCI patients according to the cut-off point in LDL-C levels. Patients with lower levels of LDL-C tended to be male with a higher proportion of current drinking. Patients with higher LDL-C were less often male, had a history of prior myocardial infarction, and were smokers, and more often had hypercholesterolemia, higher levels of triglycerides, total cholesterol, NT-proBNP, and hemoglobin. However, no significant differences were observed in age, diabetes, hypertension, family history of CAD, preprocedural cTnI, and other medications among groups.

Procedural characteristics of the patients are presented in Table 2 according to the cut-off point in LDL-C levels. We found no significant differences in target vessel, target lesion site, number of vascular lesions, and target lesion type expect target vessels among groups with different LDL-C levels.

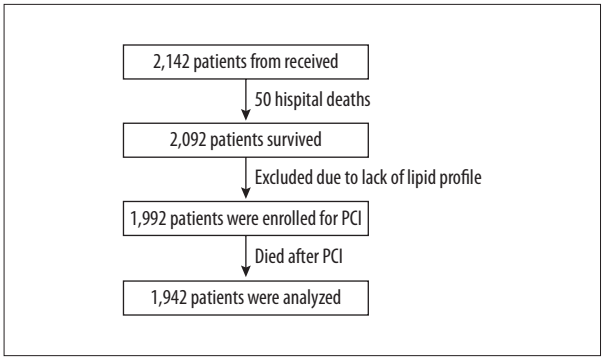

Figure 1. Flowchart of enrolled patients.

Correlation analysis of LDL-C levels with postprocedural cTnI elevation

Peak postprocedural cTnI >1×ULN, >3×ULN, >5×ULN, >10×ULN, and >15×ULN were detected in 1452 (74.8%), 1215 (62.6%), 1119(57.6%), 991 (51.0%), and 908 patients (46.8%), respectively. As shown in Table 3, simple linear regression analysis was performed to study the correlation between postprocedural cTnI (log-transformed) and other variables. The results demonstrated preoperative LDL-C levels were significantly associated with postprocedural cTnI elevation (r=0.077, *P*=0.001), and sex, age, prior CABG, current smoking, systolic blood pressure, diastolic blood pressure, NT-proBNP, and hemoglobin were positively related to postprocedural cTnI. Most importantly, stepwise multivariable analysis revealed that postprocedural cTnI was significantly correlated with sex, prior myocardial infarction, CABG, diabetes, current smoking, systolic blood pressure, diastolic blood pressure, HDL-C, LDL-C, triglyceride, NT-proBNP, preprocedural cTnI, distal, and number of branch target vessels. However, diabetes and triglyceride were inversely correlated with postprocedural cTnI levels.

Logistic regression analyses for LDL-C levels with postoperative cTnI elevation risk

As shown in Table 4, the association of the LDL-C subgroup with risk of postprocedural cTnI elevation were determined by logistic regression. Univariate logistic regression showed that patients with preprocedural LDL-C of 70~99 mg/dl were strongly correlated with lower risk of postprocedural cTnI elevation above 3×ULN up to >20×ULN compared to those with preprocedural LDL-C ≥100 mg/dl. Moreover, patients with preprocedural LDL-C of <70 mg/dl were more strongly associated with lower risk of postprocedural cTnI elevation above 3×ULN up to 20×ULN. In the adjusted logistic regression model, these associations were still present after adjusting for the all confounders according to the baseline of LDL-C levels (Table 4).

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Table 1. Baseline clinical characteristics.

Variable	LDL-C at baseline			P value
	≤70 mg/dl (n=151)	70–99 mg/dl (n=489)	≥100 mg/dl (n=1302)	
Age, y	65.38±9.98	65.50±10.47	63.26±10.85	<0.001
Male, n (%)	122 (80.8%)	385 (78.7%)	972 (74.7%)	0.075
Prior MI, n (%)	19 (12.6%)	38 (7.8%)	42 (3.2%)	0.000
Prior CABG, n (%)	23 (15.2%)	53 (10.8%)	109 (8.4%)	0.013
Diabetes, n (%)	40 (26.5%)	141 (28.8%)	325 (25.0%)	0.249
Hypertension, n (%)	88 (58.3%)	267 (54.6%)	712 (54.7%)	0.692
Hypercholesterolemia, n (%)	23 (15.1%)	92 (18.8%)	453 (34.8%)	0.000
Current smoking, n (%)	61 (40.4%)	189 (38.7%)	490 (37.6%)	0.771
Drinking	15 (9.9%)	25 (5.1%)	53 (4.1%)	0.006
HDL-C, mg/dl	44.58±21.26	44.42±13.85	45.63±16.11	0.001
LDL-C, mg/dl	58.67±9.42	86.68±8.26	137.64±29.96	<0.001
TC, mg/dl	122.38±144.15	395.02±5245.18	330.42±4314.50	<0.001
Triglyceride, mg/dl	136.73±29.47	162.17±145.62	181.88±125.02	<0.001
NT-proBNP, fmol/mL	1981.95±4407.46	2093.51±3787.81	1881.10±8562.90	0.001
hemoglobin, mmol/L	124.41±24.07	132.86±44.24	136.72±17.83	<0.001
Preprocedural cTnI, ng/mL	4.47±9.20	4.92±9.51	5.05±9.99	0.254
Postoperative cTnI, ng/mL	2.17±7.13	3.33±11.49	3.46±8.50	0.004
Medications at study entry				
Statins, n (%)	141 (93.4%)	470 (96.1%)	1254 (96.3%)	0.215
Aspirin, n (%)	136 (90.1%)	436 (89.2%)	1168 (89.7%)	0.927
Clopidogrel, n (%)	135 (894%)	438 (89.6%)	1139 (87.5%)	0.421
β-Blockers, n (%)	126 (83.4%)	384 (78.5%)	1116 (85.7%)	0.001
Calcium blockers, n (%)	17 (11.3%)	63 (12.9%)	189 (14.5%)	0.424
ARBs, n (%)	126 (83.4%)	398 (81.4%)	1076 (82.6%)	0.779
PPI	120 (79.5%)	344 (70.3%)	871 (66.9%)	0.005

ARBs – angiotensin receptor blockers; PPI – proton pump inhibitors CABG – coronary artery bypass graft; cTnI – cardiac troponin I; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; MI – myocardial infarction; NT-proBNP – N-terminal pro-brain natriuretic peptide; PCI – percutaneous coronary intervention. Values are expressed as mean ± standard deviation.

Discussions

To the best of our knowledge, this is the first study reporting the relationship of preprocedural LDL-C levels with PMI in patients undergoing PCI in southern China. The patients were carefully enrolled and sample size was robust in our study. The main finding of this study was that preprocedural LDL-C was correlated with postprocedural cTnI. Patients who had <70 mg/dl or 70–99 mg/dl were strongly and independently associated with less risk of PMI. Therefore, the present study provides0 important information for lipid-lowering therapy in PCI patients.

High LDL-C level is not only a major cause of CAD, but also is related to the development of mature coronary plaques [17]. There are many traditional risk factors for cardiovascular disease, such as smoking, diabetes, obesity, hypertension, and

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Table 2. Procedural characteristics.

Variable	LDL-C at baseline			P value
	≤70 mg/dl (n=151)	70–99 mg/dl (n=489)	≥100 mg/dl (n=1302)	
Target vessel				
LM	19	67	972	<0.001
LAD	141	467	42	<0.001
LCX	114	378	109	<0.001
RCA	119	407	325	<0.001
Lesion location				
Proximal	120	408	1082	0.499
Middle	135	412	1094	0.069
Distal	96	324	843	0.775
Branch	20	55	190	0.183
type B2/C	93	320	863	0.511
Number of target vessel	2.47±0.79	2.56±0.79	2.56±0.75	0.160
Number of stents implanted	1.37±0.52	1.35±0.56	1.39±0.61	0.437
Total stent length, mm	34.66±16.68	35.62±17.55	36.27±19.32	0.966
Bracket diameter	3.13±0.403	3.13±0.44	3.12±0.45	0.759

LM – left main; LAD – left anterior descending; LCX – left circumflex; RCA – right coronary artery; Values are expressed as n (%), mean ± standard deviation or median with interquartile range.

dyslipidemia. LDL-C is a well-established molecular risk factor. Li et al. found that the low preprocedural LDL-C levels were correlated with lower risk of PMI in PCI patients, and the risk of postprocedural cTnI elevation was increased by 12% to 20% due to increased 1-SD in LDL-C [13]. Similarly, Buturak et al. also observed a direct connection between preprocedural LDL-C levels and PMI in PCI patient with stable angina pectoris [18]. A cohort study that enrolled 302 consecutive patients reported that the ratios of LDL-C to high-density lipoprotein cholesterol (LDL-C/HDL-C) were significantly associated with PMI following elective PCI [19]. Furthermore, in recent years, experiments have shown that LDL-C levels <70 mg/dl were related to lower risk of cardiovascular events in secondary prevention populations. Thus, LDL-C plays an important role in secondary prevention and can reduce risk after PCI. According to the results of clinical studies, the hypothesis that "lower and better" in LDL-C level of patients with cardiovascular disease has been generally considered as optimal treatment [20,21].

Numerous studies have shown that statins, by decreasing LDL-C, can significantly reduce the incidence of myocardial injury or infarction after PCI [22]. Previous studies showed that statins have anti-inflammatory effect and anti-thrombotic properties, and improve endothelial function beyond merely decreasing LDL-C levels [23]. The pleiotropic effects of statins are proved by clinical research *in vitro* and *in vivo*, and such effects were obviously beneficial in reducing myocardial injury during PCI. In addition, the effect of lowering LDL-C level on myocardial injury after PCI is mainly due to its effect on plaques.

LDL-C level plays an important role in plaque vulnerability, which is associated with a high risk of periprocedural myocardial injury in patients undergoing elective stent implantation [17]. Clinical evidence showed that elevated LDL-C level is correlated with plaque characteristics and vulnerability, which were examined by intravascular ultrasound [24,25], optical coherence tomography [26], near-infrared spectroscopy [27], and dual-source computed tomography [28]. Vulnerable plaques have a large lipid core and a thin fibrous cap. Vulnerable plaques are prone to transfer, destruction, or exposure of thrombogenic material to the coronary flow, which may lead to thrombosis during and even following PCI. Therefore, intensive lipid-lowering therapy, especially LDL-C reduction, appears to slow plaque growth of minor lesions and reduce the occurrence of cardiovascular events in patients undergoing PCI [29,30].

Our research also revealed that there are some independent factors connected with postoperative myocardial injury, such

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Table 3. Analysis of factors associated with postoperative cTnI levels (log-transformed).

Variable	Simple regression		Multiple regression	
	Standard coefficient	P value	Standard coefficient	P value
Sex (Male, Female)	0.35	0.09	0.050	0.034
Age, y	0.25	0.219		
Prior MI, n (%)	0.23	0.267	0.051	0.03
Prior CABG, n (%)	0.062	0.002	0.059	0.013
Diabetes, n (%)	–0.032	0.081	–0.052	0.014
Hypertension, n (%)	0.970	0.322		
Hypercholesterolemia, n (%)	0.215	0.830		
Current smoking, n (%)	–0.087	<0.001	–0.096	<0.001
Drinking	0.011	0.542		
Systolic blood pressure mmHg	–0.144	<0.001	0.096	0.001
Diastolic blood pressure mmHg	–0.091	<0.001	0.096	<0.001
HDL-C, mg/dl	0.029	0.127	0.075	0.001
LDL-C, mg/dl	0.070	<0.001	0.082	<0.001
TC, mg/dl	–0.015	0.390		
Triglyceride, mg/dl	–0.027	0.173	–0.049	0.026
NT-proBNP, mol/mL	0.073	<0.001	0.089	<0.001
Platelets	0.016	0.366		
hemoglobin, mmol/L	–0.038	0.044		
Preprocedural cTnI, ng/mL	0.199	<0.001	0.276	<0.001
Target vessel				
LM	–0.021	0.248		
LAD	0.001	0.977		
LCX	0.260	0.363		
RCA	–0.011	0.683		
Lesion location				
Proximal	0.01	0.599		
Middle	–0.007	0.714		
Distal	–0.035	0.074	0.075	0.011
Branch	0.036	0.044	0.065	0.002
Number of target vessels	0.054	0.144	0.087	<0.001
Number of type B2/C	–0.028	0.206		
Number of stents	0.004	0.839		
Stent diameter	–0.013	0.472		
Total stent length	–0.022	0.235		

CABG – coronary artery bypass graft; cTnI – cardiac troponin I; HDL-C – high-density lipoprotein cholesterol; LDL-C – lowdensity lipoprotein cholesterol; TC – total cholesterol; MI – myocardial infarction; NT-proBNP – N-terminal pro-brain natriuretic peptide; SBP – systolic blood pressure; DBP – diastolic blood pressure; PCI – percutaneous coronary intervention. Values are expressed as mean ± standard deviation, median with interquartile range or n (%).

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Table 4. Odds ratio (OR) for postprocedural cTnI elevation according to LDL-C levels.

	No. of patients	Unadjusted model		Adjusted model	
		OR (95% CI)	P value	OR (95% CI)	P value
Post-PCI cTnI >1×ULN					
LDL-C ≤70 mg/dl	152	0.802 (0.551–1.167)	0.248	0.786 (0.520–1.189)	0.255
LDL-C 70–99 mg/dl	489	0.863 (0.681–1.093)	0.233	0.776 (0.598–1.006)	0.055
LDL-C ≥100 mg/dl	1302	Reference		Reference	
Post-PCI cTnI >3×ULN					
LDL-C ≤70 mg/dl	152	0.651 (0.464–0.951)	0.013	0.641 (0.436–0.936)	0.021
LDL-C 70–99 mg/dl	489	0.812 (0.656–1.006)	0.057	0.762 (0.603–0.965)	0.024
LDL-C ≥100 mg/dl	1302	Reference		Reference	
Post-PCI cTnI >5×ULN					
LDL-C ≤70 mg/dl	152	0.744 (0.530–1.043)	0.086	0.730 (0.502–1.063)	0.1
LDL-C 70–99 mg/dl	489	0.795 (0.645–0.981)	0.032	0.732 (0.581–0.923	0.008
LDL-C ≥100 mg/dl	1302	Reference		Reference	
Post-PCI cTnI >10×ULN					
LDL-C ≤70 mg/dl	152	0.652 (0.464–0.916)	0.014	0.611 (0.416–0.896)	0.012
LDL-C 70–99 mg/dl	489	0.747 (0.607–0.921)	0.006	0.671 (0531–0.84)	0.001
LDL-C ≥100 mg/dl	1302	Reference		Reference	
Post-PCI cTnI >15×ULN					
LDL-C ≤70 mg/dl	152	0.594 (0.419–0.843)	0.003	0.577 (0.363–0.797)	0.002
LDL-C 70–99 mg/dl	489	0.807 (0.655–0.995)	0.045	0.733 (0.580–0.927)	0.009
LDL-C ≥100 mg/dl	1302	Reference		Reference	
Post-PCI cTnI >20×ULN					
LDL-C ≤70 mg/dl	152	0.545 (0.372–0.770)	0.001	0.476 (0.316–0.717)	0.000
LDL-C 70–99 mg/dl	489	0.797 (0.645–0.984)	0.035	0.730 (0.576–0.924)	0.009
LDL-C ≥100 mg/dl	1302	Reference			

Adjusted model included sex, prior myocardial infarction, CABG, diabetes, current smoking, systolic blood pressure, diastolic blood pressure, HDL-C,LDL-C, Triglyceride, N-terminal pro-brain natriuretic peptide, preprocedural cTnI, number of target vessels, distal, branch. CABG – coronary artery bypass graft; cTnI – cardiac troponin I; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; NT-proBNP – N-terminal pro-brain natriuretic peptide; OR – odds ratio; PCI – percutaneous coronary intervention; ULN – upper limit of normal.

as sex, prior myocardial infarction, CABG, current smoking, systolic blood pressure, diastolic blood pressure, preprocedural cTnI, HDL-C, TC, triglyceride, NT-proBNP, and number of target vessels. Our findings may be important in developing instructions for health care and meditations for PMI patients with LDL-C undergoing PCI.

There are several limitations to this study. First, the presence of possible unmeasured variables might have confused the results, although we tried to adjust for known confounders. Secondly, the cTnI level was not tested continuously after PCI, but each patient received continuous electrocardiography. The cTnI level was additionally measured in the event of the occurrence of symptoms or signs suggestive of myocardial ischemia.

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Conclusions

In summary, PCI patients with low preprocedural LDL-C are independently correlated with a lower risk of PMI. Patients with preprocedural LDL-C of <100 mg/dl had lower risk of periprocedural myocardial injury than those with preprocedural LDL-C of ≥100 mg/dl. Increased attention is needed to control LDL-C in southern China.

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Conflicts of interest

None.

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