ORIGINAL RESEARCH

LDL-C and Total Stent Length are Independent Predictors of Periprocedural Myocardial Injury and Infarction for Unstable Angina Patients Undergoing Elective Percutaneous Coronary Intervention

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Background: To investigate the predictive value of low-density lipoprotein cholesterol (LDL-C), total stent length and number of implanted stents in patients with unstable angina (UA) regarding myocardial injury and infarction during perioperative period.

Methods: Three hundred and fifteen consecutive UA patients between January 2015 and June 2018 were retrospectively recruited from two cardiac centers of Hebei Province, China. These patients had normal preprocedural cardiac troponin I (cTnI) and underwent uneventful revascularizations. The predictive value of baseline LDL-C level and total stent length was investigated by linking to post procedural cTnI value in this cohort. Meanwhile, other related clinical and procedural variables were analyzed.

Results: Baseline LDL-C level or LDL-C grade was correlated with post percutaneous coronary intervention (PCI) cTnI levels (r = 0.120, P = 0.01; r = 0.157, P = 0.004). LDL-C grade was an independent risk factor of perioperative myocardial injury and infarction (P < 0.05) after multivariable adjustment. The risk increased with the elevation of baseline LDL-C level. Compared to the lowest level group (<70 mg/dl), the group with 70–99 mg/dl carried three times higher risk (OR = 3.318; 95% CI: 1.167–9.436; P < 0.05). And, patients with LDL-C level ≥100 mg/dl had the worst prognosis (OR = 4.783; 95% CI: 1.736–13.180; P = 0.002). Besides, the study also found that the total length of stent was predictive of perioperative myocardial injury and infarction independently (OR = 1.037; 95% CI: 1.017–1.058; P = 0.001).

Conclusion: Baseline LDL-C level and total stent length were independent predictors of periprocedural myocardial injury and infarction in UA patients undergoing elective PCI.

Keywords: low-density lipoprotein cholesterol, percutaneous coronary intervention, prognosis, stent length, myocardial injury and infarction

Introduction

Coronary artery disease (CAD) remains the leading cause of death worldwide.[1] With techniques advances, PCI (percutaneous coronary intervention) has become the most widely used treatment of revascularization in CAD patients over the past decades,[2] and the post-PCI mortality rate in hospitalization has decreased to less than 2%.[3] However, up to 33% of patients will develop periprocedural myocardial injury, and approximately 6% may have myocardial infarction.[4–6] These patients have been found with increased morbidity and mortality in few years.[6–9] Therefore, the early identification of patients who are at relatively high risk of developing

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myocardial injury and infarction during perioperative period is important in preventing adverse cardiovascular events.

Perioperative myocardial injury and infarction may be caused by microvascular perfusion impairment, thrombus micro-embolization, or slow blood flow.[10] During PCI, debris is often detached from plaque fragmentation and then released into the coronary circulation, which can form coronary thrombosis. The length and number of inserted stents are associated with the debris and thrombus burden.[11,12] Therefore, the length and number of stents may be the potential risk factors of perioperative myocardial injury and myocardial infarction.

Besides, hyperlipidemia is a well-established risk factor of cardiovascular disease development, especially low-density lipoprotein cholesterol (LDL-C).[13,14] Previous studies have also shown that LDL-C level plays a vital role in PCI prognosis having an association with infarction size.[15,16] And, lipid-lowering therapy can prevent cardiovascular risk effectively in the long term.[17–19] Lipid management is also recommended in various patients after PCI, such as in patients with diabetic patients and acute coronary syndrome.[16] Taken together, LDL-C is also an important risk factor for patients undergoing PCI.

The length and number of stents and the baseline LDL-C level are potential risk factors of PCI patients developing perioperative myocardial injury and infarction; however, the associations are not well understood. Therefore, the study will investigate the predictive value of low-density lipoprotein cholesterol (LDL-C), total stent length and number of implanted stents in patients with unstable angina (UA) regarding myocardial injury and infarction during perioperative period. The expected results aim to provide evidence with clinicians to manage lipid levels before PCI better and optimize the procedures of PCI.

Patients and Methods
Patient Population
Consecutive UA patients who were referred to undergoing elective PCI between January 2015 and June 2018 at Heart Centre of Hebei General Hospital and Department of Cardiology, Handan Central Hospital were retrospectively collected and screened for eligibility. The patient underwent elective PCI because PCI was not performed in time. The clinical diagnosis and interventional decisions were made by qualified interventional cardiologists. All the patient data were accessed from the electronic patient resource system of the hospital. The local ethics Institution Review Board of Hebei General Hospital has approved the study with ethic number (No. 202011).

Inclusion Criteria
The inclusion criteria were (1) 18–80 years old; (2) without prior myocardial injury, which was determined by normal cTnI and creatine kinase-MB (CK-MB); (3) UA patients scheduled for elective PCI. Patients with UA were characterized as having ischemic symptoms at rest or minimal exertional without myocardial infarction.[20]

Exclusion Criteria
The patients with (1) failed revascularization or iatrogenic death within 24 hours after PCI; (2) thrombotic lesions and severe calcification treated with coronary artery rotation, or surgical complications such as coronary artery dissection and side branch loss; (3) liver failure defined by the European Association of Hepatology (EASL-CLIF[21]) or renal failure according to KDIGO criteria in 2012;[22] (4) cardiac valvular diseases, myocardial diseases and NYHA class III–IV heart failure were excluded. Successful revascularization was achieved when patients had residual stenosis less than 20% with stents or less than 50% following balloon angioplasty only.[23]

Perioperative Anticoagulant and Lipid Treatment
All the revascularization interventions were performed by experienced interventional cardiologists. Aspirin (100 mg/day) was administrated in patients with regular daily intake of aspirin. However, if the patients have not taken aspirin as the daily therapy, loading dose of 300 mg was applied. Identically, the subjects received clopidogrel on 75 mg daily or a loading dose of 300 mg if they have not taken it daily for a long term before PCI. 5000 U or 70U/kg bolus of unfractionated heparin was injected just before starting the procedure. If the operation lasted for more than one hour, an additional bolus of 2000–3000 U/hour was administrated. Aspirin and clopidogrel therapy daily were managed post PCI after revascularization as regular. Besides, glycoprotein IIb/IIIa receptor antagonists and anticoagulants were prescribed in case. All patients were treated with 20 mg of atorvastatin calcium tablets every night before and after surgery.

Biochemical Measurements and Adverse Myocardial Events Definitions

Biochemical tests including lipid, liver, and renal profiles were performed on admission or the next morning with a fasting state. CTnI levels were detected before PCI and 20~24 h after PCI. According to the linear relationship between LDL-C level and CAD risk, LDL-C was also divided into 3 grades as following, <70, 70–99, and ≥100 mg/dl.[24,25] The upper limit of the normal range (ULN) was interpreted as the 99th percentile of normal population with a total imprecision of <10%. The ULN of this test was 1.0ng/mL. The peak value of cTnI within 24 hours was recorded for statistical analysis. Postoperative cTnI >1×ULN was interpreted as a perioperative myocardial injury. Postoperative cTnI >5×ULN was defined as PCI-related myocardial infarction after PCI.[26]

Statistical Analysis

Clinical and procedural characteristics between groups with and without post-PCI myocardial injury and infarction were assessed by Chi-square test, t-test, and Kruskal–Wallis test. Kendall's tau-b correlation was applied to evaluate the correlation of baseline clinical parameters and postprocedural cTnI levels. Univariable and multivariable logistic regression models were applied to investigate the impact of clinical parameters on patients having post-PCI myocardial injury and infarction. The variable with a P<0.1 in the univariate logistic regression was taken together to do the multivariable analysis by stepwise pattern. A probability value of P<0.05 was considered significant for this study. All the biostatics tests were conducted by IBM SPSS Statistics 26.0 (IBM, Armonk, NY, USA).

Results
Clinical Characteristics

Three hundred and fifteen patients were recruited into the study (Figure 1). The overall demographics and baseline clinical characteristics of the cohort are summarized in Table 1. During perioperative period, 71 (22.5%) patients had myocardial injury and infarction with significantly higher baseline LDL-C levels (104.25 vs 92.66 mg/dL; P = 0.01), compared to those without adverse events. In addition, the data showed that more than 50% of events occurred in patients with baseline LDL-C higher than 100 mg/dl which indicated a detrimental impact of LDL-C on myocardium once it reached into a critical stage.

Coronary Lesions and PCI Characteristics

Patients with and without perioperative myocardial injury and infarction did not show different in coronary lesion severity. The number of diseased vessels, occlusion lesions, SYNTAX score, target vessels, and disease locations had no statistical significance (P > 0.05). However, patients with more stents or longer total stent length were more likely to have myocardial injury and infarction (P =0.005; P=0.001). The information about coronary lesions and PCI are shown in Table 2.

Correlation of LDL-C, Total Stent Length, Inserted Stent Number with Postprocedural cTnI Elevation

As showed in Table 3, Kendall's tau-b correlation analysis demonstrated that LDL-C, as a continuous or dichotomous variable, was positively related to postprocedural cTnI elevation (r = 0.12, P = 0.01; r = 0.157, P = 0.004). Additionally, total stent length and number of inserted stents were positively related to cTnI elevation (r = 0.184, P < 0.001; r = 0.167, P = 0.003).

Regression Analyses of Risk Factors in Postoperative cTnI Elevation

The logistic univariable analysis identified three significant predictors, which were LDL-C grade, number of stents and total stent length (P<0.05). The variables with P < 0.1 were entered into a stepwise multivariable analysis model. The result revealed LDL-C grade and total stent length were independent predictors of myocardial injury and infarction after PCI (P < 0.05). The detailed logistic regression analyses are shown in Table 4.

In the odds ratio (OR) analysis, patients with baseline LDL-C levels between 70 and 99 mg/dl had an appropriate three-fold risk of developing postprocedural myocardial injury and infarction than these with LDL-C less than 70 mg/dl (OR = 3.318; 95% CI:1.167–9.436; P = 0.025). Moreover, the risk for patients with LDL-C higher than 100 mg/dl increased to 4.8 times, compared to patients with <70 mg/dl (OR = 4.783; 95% CI: 1.736–13.180; P = 0.002). Total stent length was also the independent risk factor; the risk increased 3.7% when the stent length increased one in unit (OR = 1.037; 95% CI: 1.017–1.058; P = 0.001). The OR result is displayed in Table 5.
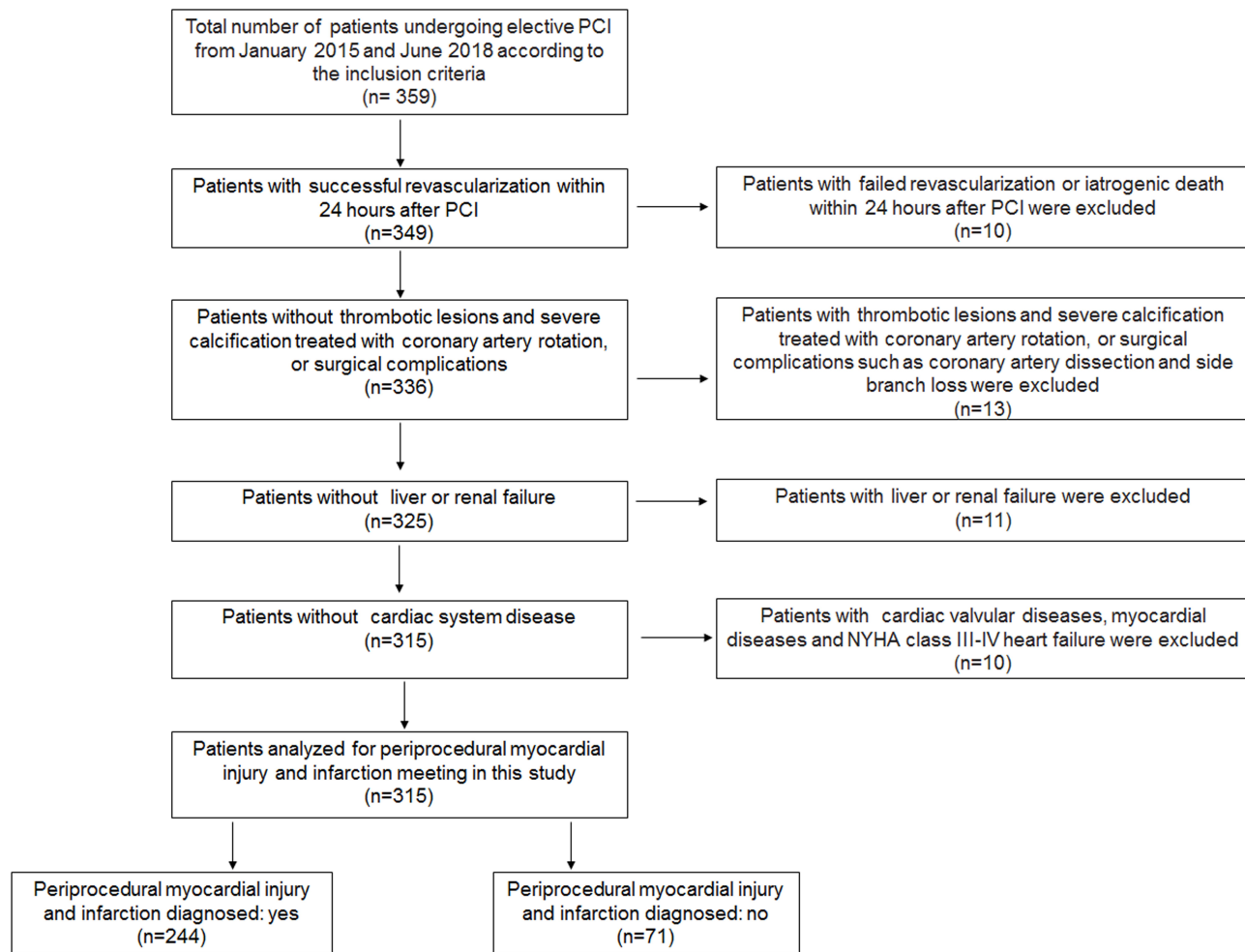
Figure 1 A recruitment flowchart in the study: number of patients undergoing elective PCI from January 2015 and June 2018 at each stage of the study.

Discussion

The study found that baseline LDL-C level and total stent length were independent risk factors of perioperative myocardial injury and infarction in UA patients. Of importance, patients with an LDL-C level greater than 70 mg/dL carried significantly higher risk, which was up to 5 times, than subjects with LDL-C <70 mg/dL. This result strongly suggested the importance of LDL-C management in patients before undergoing revascularization. The result was supported by Zhong et al and Li et al's studies.[20,23] In addition, the independent predictive value of total stent length was demonstrated, which also provided evidence with interventional cardiologists when making procedural plans to prevent UA patients from adverse myocardial injury and neurosis. Other studies have found that postoperative LDL-C is associated with perioperative myocardial infarction and long-term prognosis,[11,20,23] but in this

study, the OR value was statistically analyzed after the classification of LDL-C. In addition, the relationship between total stent length and perioperative myocardial infarction was found in this study, which has hardly been reported in other studies.

There are various mechanisms of perioperative myocardial injury and infarction. For example, acute branch occlusion, target vessel vasospasm, vascular dissection, and slow coronary blood flow or no-reflow after the operation can result in microcirculation blockage and myocardial injury as a result.[10,27] The damaged myocardial location can also tell the mechanisms of post-PCI myocardial injury and infarction. A contrast-magnetic resonance imaging study showed two common sites, adjacent to the target lesion and distal downstream area, which were caused by minor side-branch occlusion and distal embolization, respectively.[4,28] Our study excluded patients with

Table I Demographics and Baseline Clinical Characteristics

Variable	All Patients (n=315)	Perioperative Myocardial Infarction and Myocardial Injury		P value
		No (n=244)	Yes (n=71)	
Age, y	56.4±10.01	55.85±10.12	58.27±9.46	0.740
Male, n (%)	243 (77.1%)	191 (78.3%)	52 (73.2%)	0.373
Body mass index, kg/m^2	25.39 (23.99, 27.36)	25.53 (23.78, 27.34)	25.25 (24.22, 27.53)	0.920
Hypertension (%)	213 (67.6%)	164 (67.2%)	49 (69.0%)	0.775
Diabetes, n (%)	63 (20.0)	46 (18.9%)	17 (23.9%)	0.345
Current smoking, n (%)	157 (49.8%)	128 (52.5%)	29 (40.8%)	0.085
Statins, n (%)	180 (57.1%)	136 (55.7%)	44 (62.0%)	0.350
GFR (mL/min)	79.63 (66.87, 93.83)	79.46 (67.44, 93.64)	80.29 (65.48, 95.30)	0.943
TG (mmol/L)	1.70 (1.18, 2.29)	1.68 (1.15, 2.28)	1.82 (1.20, 2.29)	0.792
HDL-C (mmol/L)	1.15 (1.00, 1.31)	1.14 (1.00,1.31)	1.18 (1.00,1.31)	0.430
LDL-C (mg/dL)	96.53 (77.22, 115.83)	92.66 (73.75, 111.97)	104.25 (84.94, 105.29)	0.01
LDL-C grade, n (%)				
<70 mg/dL	58 (18.4%)	53 (21.7%)	5 (7.0%)	0.008
70–99 mg/dL	114 (36.2%)	89 (36.5%)	25 (35.2%)	
≥100 mg/dL	143 (45.4%)	102 (41.8%)	41 (57.8%)	

Notes: Values were presented as n (%), mean ± standard deviation or median with interquartile range. Statins represented that the patients took atorvastatin calcium tablets for 20 mg per night.
Abbreviations: GFR, glomerular filtration rate; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

acute brachial occlusion, vasospasm, acute thrombosis, and vascular dissection, and thus adverse myocardial injury in the present study was due to distal embolization particularly.

Up to 75% of patients undergoing PCI have been found to have distal embolization.[29,30] Plaque disruption, fragmentation, and dissection are common reasons to cause coronary microvascular obstruction, and, ultimately myocardial injury and necrosis. The underlying mechanism is complicated. For example, plaque disruption is able to stimulate macrophages and activated platelets to release the tissue factor and potent vasoconstrictors. As a result, coagulation cascade was activated, and subsequent thrombin was generated, which can induce the activation and aggregation of platelet. Moreover, the microvascular thrombi was formed to further proceed the damaged area with microvascular obstruction and dysfunction.[31–34] Overall, myocardial injury is attributed to plaque vulnerability and its induced inflammatory reactions.

LDL-C in high level was associated with plaque vulnerability based on different assessment modalities reported by prior studies.[35–37] Our study also provided evidence of LDL-C's negative impact on myocardial reperfusion after PCI, and the underlying mechanism may be due to LDL-C-induced plaque vulnerability, as discussed above. A previous study has reported that the

decrease of LDL-C level was related to plaque regression within coronary arteries evaluated by conventional intravascular ultrasound (IVUS).[38] A meta-analysis study including 4 IVUS randomized control trials also showed the agreement on the effect of LDL-C-lowering therapy, which was given by the good management of LDL-C and LDL-C/high-density lipoprotein-cholesterol (HDL-C) ratio (L/H ratio) by statin contributed to the regression of the total atheroma volume in patients with CVD.[38] These studies conversely supported the finding of our study, that LDL-C is a detrimental risk factor of plaque vulnerability beyond traditional CAD.

Vulnerable plaques were characterized as shift and disruption, and more debris were released into coronary circulation as a consequence to form thrombus and embolization during and even after PCI, also known as myocardial injury and infarction.[23] In addition to high LDL-C level, longer-length stent implantation may disrupt more vulnerable plaques, which induced the release of procoagulants, consequently increasing the risk of perioperative myocardial infarction and myocardial injury. This may also explain that total stent length was also the independent predictor discovered by the present study. The additional predictor value of total stent length over LDL-C needs further investigation in patients with PCI.

Table 2 Coronary Lesions and PCI Characteristics

Variable	All Patients (n=315)	Perioperative Myocardial Infarction and Myocardial Injury		P value
		No (n=244)	Yes (n=71)	
Transracial vascular access, n (%)	224 (71.1%)	179 (73.4%)	45 (63.4%)	0.102
Number of diseased vessels, n (%)				0.065
Single lesion	110 (34.9%)	91 (37.3%)	19 (26.8%)	
Double lesions	118 (37.5%)	93 (38.1%)	25 (35.2%)	
Triple lesions	87 (27.6%)	60 (24.6%)	27 (38.0%)	
Occlusion lesions, n (%)	40 (12.35%)	32 (12.8%)	8 (10.8%)	0.648
SYNTAX score	9.00 (7.00, 14.5)	9.00 (6.00, 14.00)	10.00 (8.00, 15.00)	0.104
Target vessel, n (%)				0.643
LM	1 (0.3%)	1 (0.3%)	0 (0%)	
LAD	190 (50.67%)	149 (51.74%)	41 (47.13%)	
LCX	83 (22.13%)	60 (20.83%)	23 (26.44%)	
RCA	101 (26.93%)	78 (27.08%)	23 (26.44%)	
Number of target vessels, n (%)				0.267
1 target vessel	254 (80.6%)	200 (82%)	54 (76.1%)	
2 target vessels	61 (19.4)	44 (18%)	17 (23.9)	
Lesion location				0.554
Proximal	147 (37.22%)	114 (38.13%)	33 (34.38%)	
Middle	187 (47.34%)	137 (45.82%)	50 (52.08%)	
Distal	40 (10.13%)	33 (11.04%)	7 (7.29%)	
Branch	21 (5.35%)	15 (5.02%)	6 (6.25%)	
Maximum inflation pressure, atm	14.0 (12.0, 14.0)	14.0 (12.0, 14.0)	14.0 (12.0, 14.0)	0.412
Maximum inflation time, s	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)	0.242
Number of stents implanted, n (%)				0.005
1 stent	227 (72.1%)	185 (75.8%)	42 (59.2%)	
2 stents	71 (22.5%)	51 (20.9%)	20 (28.2%)	
3 stents	14 (4.4%)	7 (2.9%)	7 (9.9%)	
4 stents	3 (1.0%)	1 (0.4%)	2 (2.8%)	
Total stent length, mm	18.00 (14.00, 30.00)	18.00 (14.00, 28.00)	24.00 (18.00, 41.00)	0.001
Time of PCI (min)	17.00 (14.00, 23.00)	17 (14.00, 21.00)	18.00 (13.00, 28.00)	0.376

Notes: Diseased vessels: diameter stenosis greater than 50%. Values are expressed as n (%), median with interquartile range.
Abbreviations: LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Finally, this study would like to suggest a reference value for LDL-C management before PCI to clinicians to prevent perioperative myocardial injury and infarction. The preoperative LDL-C should be reduced to below 70 mg/dL as we found patients with LDL-C under this threshold had much lower risk, compared to the counterparts (OR = 3.318;4.783) beyond enough antiplatelet and anticoagulation therapy. Furthermore, the number of stent and total stent length should be reduced within reasonable limits to prevent myocardial injury and infarction after revascularization.

Study Limitations

The study had several limitations. Firstly, it was a retrospective study performed on two different medical centres. The findings should be confirmed on prospective studies in the future. Secondly, cTnI was tested twice only

Table 3 Correlation Between Variable with Postprocedural cTnI Elevation

Variable	Kendall's Tau-b	P
LDL-C (mg/dL)	0.120	0.01
LDL-C grade	0.157	0.004
Total stent length	0.184	0.001
Number of stents (1–4)	0.167	0.003

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Table 4 Logistic Regression Analysis of Risk Factors in Postoperative cTnI Elevation

Variables	Univariable Regression		Multivariable Regression	
	Standard Coefficient	P value	Standard Coefficient	P value
Age	0.025	0.075		0.104
Male	−0.275	0.374		
Body mass index	0.013	0.779		
Hypertension	0.083	0.775		
Diabetes	0.304	0.346		
Current smoking	−0.469	0.086		
Statins	0.258	0.351		
GFR	−0.001	0.884		
TG	0.041	0.629		
HDL-C	0.899	0.077		0.137
LDL-C	0.423	0.01		
LDL-C grade				
<70mg/dL		0.013		0.009
70–99 mg/dL	1.091	0.036	1.199	0.025
≥100 mg/dL	1.449	0.004	1.565	0.002
SYNTAX score	0.040	0.070		0.594
Maximum inflation pressure	−0.024	0.764		
Maximum inflation time	0.065	0.197		
Number of stents implanted	0.673	0.001		0.684
Total stent length	0.034	0.001	0.037	0.001
Number of diseased vessels				
Single lesion	0.069			0.486
Double lesions	0.455			0.727
Triple lesions	0.025			0.245
Number of target vessels	0.269			0.356

Note: Values were presented as mean ± standard deviation, median with interquartile range or n (%).
Abbreviations: cTnI, cardiac troponin I; GFR, glomerular filtration rate; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

before and after PCI, but not monitored continuously, which may less accurately reflect the myocardial injury and infarction at the most severe status. Thirdly, as a matter of fact, not many patients met the inclusion and exclusion criteria of this study. Therefore, our sample size was small, and the sample size sample size will be increased in the following studies. Fourthly, the study lacked the clinical outcome data out of hospital. The study should further follow up these patients in the long term to determine the prognostic value of baseline LDL-C level and procedural factors. Lastly, sample size should be increased in future research.

Table 5 Odds Ratio (OR) Analysis of Independent Risk Factors

	N	Unadjusted Model		Adjusted Model	
		OR (95% CI)	P value	OR (95% CI)	P value
LDL-C grade					
<70mg/dL	58 (18.4%)				
70–99 mg/dL	114 (36.2%)	2.978 (1.075–8.246)	0.036	3.318 (1.167~9.436)	0.025
≥100 mg/dL	143 (45.4%)	4.261 (1.590–11.421)	0.004	4.783 (1.736–13.18)	0.002
Total stent length	18.0 (14.0; 30.0)	1.035 (1.015–1.054)	0.001	1.037 (1.017~1.058)	0.001

Abbreviations: LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

Conclusions

Baseline LDL-C level and total stent length were independent predictors of periprocedural myocardial injury and infarction in UA patients undergoing elective PCI.

Abbreviations

cTnI, cardiac troponin I; CAD, coronary artery disease; CK-MB, creatine kinase-MB; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PCI, percutaneous coronary intervention; UA, unstable angina; ULN, upper limit of the normal range.

Data Sharing Statement

All data generated or analyzed during this study are available from the corresponding author Yi Dang upon reasonable request.

Ethics Approval and Consent to Participate

The local ethics Institution Review Board of Hebei General Hospital has approved the study with ethic number (No. 202011). All participants provided written informed consent and the procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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