Association Between Lipoprotein(a) and Peri-procedural Myocardial Infarction in Patients With Diabetes Mellitus Who Underwent Percutaneous Coronary Intervention

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Background: High lipoprotein(a) (Lp[a]) levels are associated with increased risks of cardiovascular events in Percutaneous Coronary Intervention (PCI) patients with diabetes mellitus (DM). Peri-procedural myocardial infarction (PMI) occurs commonly during the PCI, whereas the relationship between Lp(a) and PMI remains unclear. Our study aimed to evaluate the association between Lp(a) value and the incidence of PMI in a larger-scale diabetic cohort undergoing PCI throughout 2013.

Methods: A total of 2,190 consecutive patients with DM were divided into two groups according to the median Lp(a) level of 175 mg/L: Low Lp(a) group (N = 1095) and high Lp(a) group (N = 1095). PMI was defined based on the 2018 universal definition of myocardial infarction.

Results: Patients with high Lp(a) levels exhibited higher rates of PMI compared to those with low Lp(a) levels (2.3% versus 0.8%, P = 0.006). The multivariable logistic analysis showed that PMI was independently predicted by Lp(a) as a dichotomous variable (OR 2.64, 95%CI 1.22–5.70) and as a continuous variable (OR 1.57, 95% CI 1.12–2.20). However, further investigation found that this association was only maintained in men, whose Lp(a) levels were significantly associated with the frequency of PMI, both as a dichotomous variable (OR 3.66, 95%CI 1.34–10.01) and as a continuous variable (OR 1.81, 95%CI 1.18–2.78). Lp(a) wasn’t a risk factor of PMI in women.

Conclusions: High Lp(a) levels had forceful correlations with the increased frequency of PMI in male diabetic patients undergoing PCI. Lp(a) might act as a marker of risk stratification and a therapeutic target to reduce PCI-related ischemic events.

Keywords: lipoprotein(a), peri-procedural myocardial infarction, diabetes mellitus, percutaneous coronary intervention, coronary artery disease
INTRODUCTION

It is estimated that the number of patients with diabetes mellitus (DM) has doubled in the past two decades (1). DM has become one of the most common metabolic disorders in contemporary PCI practice. DM exerts the pro-thrombotic and pro-inflammatory effects in the pathogenesis of atherosclerosis and increases the risk of cardiovascular consequences (2). It’s noteworthy to identify the risk factors that predict cardiac events in diabetic patients undergoing PCI.

Peri-procedural myocardial infarction (PMI) is a procedure-related ischemic cardiac event following coronary stenting (3). There is a growing body of evidence showing the association between PMI and worse outcomes after PCI over short- and long-term periods (4–6). Previous research proposed that the distal and side-branch thromboembolism, which resulted from lipid-rich plaques rupture, gave rise to the occurrence of PMI (7). Moreover, blood lipid profiles, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fatty acid were demonstrated to have correlations with PCI-related myocardial injury (8–10).

Lipoprotein(a) (Lp[a]) is a LDL-like lipid with additional apolipoprotein(a) attached to apolipoprotein B (11). Epidemiological studies identified Lp(a) as an atherothrombotic risk factor, and prior studies revealed the relationship between the elevation of Lp(a) and the myocardial ischemic events (12, 13). But much less is known about the impact of elevated Lp(a) on the peri-procedural coronary events among patients with DM.

Therefore, our study aimed to investigate whether high Lp(a) status was associated with an increased risk of PMI, defined by the latest 2018 fourth universal definition of myocardial infarction (UDMI) (14), among a large-scale diabetic cohort undergoing PCI. Univariable and multivariable logistic regression models and receiver-operating curve (ROC) analysis were used to investigate the predictive value of Lp(a).

MATERIAL AND METHODS

Study Population

The study enrolled consecutive patients with DM undergoing PCI at Fuwai Hospital (Beijing, China) between January 2013 and December 2013. Patients without available Lp(a) and cardiac biomarker data were excluded. Cardiac markers were generally measured in patients undergoing PCI, while the measurement of Lp(a) wasn’t routinely performed. Therefore, we compared the differences between patients with and without available Lp(a) data. As shown in Supplementary Table S1, most baseline characteristics and procedural features were evenly distributed between patients without available Lp(a) data and with available Lp(a) data. All patients had written informed consent. The study complied with the principles of Helsinki and was approved by the hospital review board. A total of 2,190 subjects were eligible for the present analysis. According to the median Lp(a) level of 175 mg/L, patients were divided into two parts: Low-Lp(a) group (N = 1,095) and High-Lp(a) group (N = 1,095). Baseline clinical and procedural data were extracted from medical records. Venous blood was collected from all patients after fasting overnight. Biochemical analyses were performed in the biochemistry laboratory of Fuwai Hospital. Lp(a) concentrations were measured by immunoturbidimetry (Lasay Lp(a) auto, Shima laboratories, Japan) method following the manufacturer’s instructions.

Procedure

The PCI strategies and stents were determined by treating cardiologists according to patients’ characteristics. A loading dose of 300 mg aspirin and 300 mg clopidogrel was prescribed for the patients before the procedure. After the procedure, all patients received at least 1 year of clopidogrel (75 mg/day) and lifelong aspirin (100mg/day). The Synergy between Percutaneous Coronary Intervention (PCI) with TAXUS and Cardiac Surgery (SYNTAX) score (http://www.syntaxscore.com) was calculated by treating cardiologist at Fuwai Hospital. PCI with a SYNTAX score of more than 22 were considered a high-risk PCI procedure (15). Levels of cardiac biomarkers were assayed before and after procedures. The diagnostic definition of PMI was based on the 2018 UDMI. PMI was defined as a rise of more than five times the 99th percentile upper reference limit (URL) of cardiac biomarker levels when patients showing normal baseline levels or an increase over 20% cardiac biomarker levels when patients showing elevated baseline levels but stable or declining. Additional evidence of ischemic ECG findings, imaging changes, and angiographic complications was required for the diagnosis.

Statistical Methods

Continuous characteristics were presented as mean ± SD and comparisons were made with Student’s t-test. Categorical variables were described as frequencies with percentages and evaluated with the chi-square test or Fisher’s exact test as appropriate. Univariate and multivariate logistic regression evaluations were performed to identify the independent predictors for PMI. Lp(a) was presented as a categorical variable [high Lp(a)] and a continuous variable (natural logarithm) in the analysis. The receiver-operating curve (ROC) was used to assess the prediction for PMI. Kaplan-Meier survival estimate was used to evaluate time-to-event data. All P values were two-sided, and a P-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patients Characteristics

Patients were stratified into high Lp(a) group and low Lp(a) group and major clinical and angiographic variables of the study population are shown in Tables 1 and 2. 75.7% of patients were male and their mean age was 59 years old.
High Lp(a) group were more frequently female, as well as showing more complicated procedural features, compared with low Lp(a) group. As expected, significant worse metabolic profiles exhibited in the high Lp(a) group, which were composed of high LDL levels, and high Haemoglobin A1c (HbA1c) levels.

**Lp(a) and PMI**

Figure 1A demonstrates the proportion of patients with PMI according to the Lp(a) levels. Patients with high Lp(a) levels exhibited an increased occurrence of PMI than those with low Lp(a) levels (2.30% versus 0.80%, \( P=0.006 \)). In male patients, the incidence of PMI was considerably higher in the high Lp(a) group than the low Lp(a) group (1.60% versus 0.46%, \( P=0.006 \)). In female patients, the incidences of PMI between the two groups were not significantly different (0.76% versus 0.36%, \( P=0.456 \)).

Table 3 provides the univariable logistic regression analysis for the prediction of PMI, which summarizes that Lp(a), as a continuous variable (adjusted OR 3.66, 95%CI 1.34–10.01, \( P=0.011 \)) or a dichotomous variable (adjusted OR 1.81, 95%CI 1.18–2.78, \( P=0.007 \)), whereas Lp(a) did not predict PMI events in women.

To further provide an estimate that might be compared against in the future, we conducted ROC analysis in male diabetic patients. Figure 2 shows that the area under the receiver-operating curve (AUC) was 0.680 (95% CI 0.657–0.703, \( P<0.001 \)) for Lp(a) to predict PMI. The optimal cut-off value was 112.4 mg/L (AUC=0.678, sensitivity 95.5%, specificity 40.1%).

**DISCUSSION**

**Major Findings**

The major findings of our research were high Lp(a) was independently associated with the occurrence of PMI and a predictor for PMI in diabetic patients undergoing PCI, but further investigation found the association was only significant in male, and Lp(a) wasn’t a risk factor of PMI for female. Our analysis indicated that high Lp(a) might be a convenient screening marker for the assessment of PMI, and reducing Lp(a) concentrations might be one possible way to improve the outcome of PCI patients with DM.

**The Clinical Implication of Lp(a) and PMI in Patients With DM**

It is reported that diabetic patients had a two-fold higher risk for cardiovascular diseases than non-diabetic patients (16). However, previous studies demonstrated that intensive lowering of glucose levels didn’t reduce the risk of cardiac events (17). Thus, it is of...
great importance to find out the risk factor for diabetic patients to prevent adverse cardiovascular consequences.

Lipid disorders commonly occur in patients with diabetes (2). Notably, lipoprotein abnormalities advance atherosclerosis and are a strong predictor of adverse cardiovascular outcomes. Lp(a) is an inheritable lipoprotein element, which is barely affected by dietary changes and environmental alterations (18). The ability of Lp(a) to engage in cardiovascular diseases mainly depends on its pro-atherosclerotic and pro-thrombotic effect (19). Lp(a) promotes the development of atherosclerosis by advancing foam cell formation, inducing smooth muscle cell proliferation, and activating monocyte chemoattractant (20). Moreover, Lp(a) could be a marker to predict the complexity and severity of the angiographic lesions. Prior studies reported that elevated Lp(a) was significantly associated with severe coronary conditions (21, 22). Besides, Lp(a) had a plasminogen-like function, which could bind to fibrin, inhibit fibrinolysis, and promote thrombosis (20). The increased frequency of PMI in our study provided additional evidence of the association of elevated Lp(a) and post-procedure elevated risk of thrombotic cardiac events. Moreover, the two-year composite outcomes of all-cause mortality and myocardial infarction significantly increased in the PMI group than the non-PMI group (Figure 3). Reducing Lp(a) level might provide a potential way to prevent PMI and subsequent adverse consequences.

Although broadly use of statin therapy (23) markedly decreases the risk of adverse cardiovascular events by targeting LDL (24), statin shows hardly any effect on lowering Lp(a) levels. Conversely, a recent meta-analysis revealed that Lp(a) levels escalated over 10% from baseline after statin treatment (25) and Lp(a) may represent part of the residual risk of the statin therapies (26). Hence, Lp(a) plays a critical role in contemporary lipid-lowering medication administration. In a recent BiomarCaRE (Biomarkers for Cardiovascular Risk Assessment in Europe) study (27), high Lp(a) levels robustly increased the risk of cardiac events in patients with DM, indicating that the Lp(a)-lowering might greatly improve the cardiac outcomes in diabetic patients. Our study further demonstrated that the low Lp(a) population had a reduced risk of procedure-related myocardial infarction and Lp(a) might

TABLE 3 | Univariate logistic regression analysis for peri-procedural myocardial infarction.

|                       | Odds ratio (95% CI) | P Value | Odds ratio (95% CI) | P Value | Odds ratio (95% CI) | P Value |
|-----------------------|--------------------|---------|--------------------|---------|--------------------|---------|
| Total population      |                    |         |                    |         |                    |         |
| Age                   | 2.20 (1.07–4.53)   | 0.033   | 1.05 (1.01–1.10)   | 0.021   | 0.995 (0.93–1.07)  | 0.885   |
| Male                  | 0.58 (0.29–1.19)   | 0.138   | Not applicable     |         | Not applicable     |         |
| BMI                   | 1.09 (0.99–1.20)   | 0.086   | 1.09 (0.97–1.23)   | 0.139   | 1.10 (0.95–1.30)   | 0.283   |
| Hypertension          | 1.18 (0.55–2.55)   | 0.668   | 1.03 (0.42–2.54)   | 0.953   | 1.40 (0.30–6.48)   | 0.667   |
| Current smoking       | 0.56 (0.28–1.11)   | 0.098   | 0.63 (0.27–1.47)   | 0.283   | 0.74 (0.09–5.84)   | 0.775   |
| LVEF                  | 0.97 (0.94–1.02)   | 0.621   | 0.97 (0.92–1.01)   | 0.153   | 0.99 (0.91–1.07)   | 0.760   |
| Previous MI           | 0.92 (0.47–1.99)   | 0.921   | 0.96 (0.40–2.31)   | 0.932   | 1.31 (0.35–4.91)   | 0.693   |
| High LDL              | 1.13 (0.55–2.33)   | 0.884   | 1.05 (0.44–2.51)   | 0.918   | 1.16 (0.31–4.33)   | 0.829   |
| LDL, mmol/L           | 1.06 (0.73–1.53)   | 0.754   | 0.99 (0.60–1.62)   | 0.963   | 1.07 (0.61–1.88)   | 0.814   |
| HbA1c <7%             | 0.60 (0.27–1.33)   | 0.204   | 0.68 (0.26–1.76)   | 0.428   | 0.50 (0.11–2.31)   | 0.374   |
| Low HDL               | 1.17 (0.94–1.44)   | 0.163   | 1.17 (0.89–1.52)   | 0.263   | 1.13 (0.76–1.63)   | 0.527   |
| HDL, mmol/L           | 1.09 (0.55–2.14)   | 0.814   | 1.14 (0.48–2.73)   | 0.769   | 0.84 (0.25–2.81)   | 0.772   |
| High Lp(a)            | 0.76 (0.21–2.72)   | 0.676   | 0.47 (0.08–2.81)   | 0.405   | 0.81 (0.11–5.95)   | 0.833   |
| Ln-Lp(a)              | 2.82 (1.31–6.07)   | 0.008   | 3.74 (1.37–10.17)  | 0.010   | 1.58 (0.47–5.32)   | 0.459   |
| SYNTAX score >22      | 1.64 (1.17–2.30)   | 0.004   | 1.84 (1.20–2.84)   | 0.006   | 1.26 (0.74–2.15)   | 0.395   |
| SYNTAX score          | 2.97 (1.41–6.29)   | 0.004   | 1.07 (0.31–3.63)   | 0.919   | 12.11 (3.71–39.47) | <0.001  |
| Total lesion length   | 1.05 (1.01–1.08)   | 0.017   | 1.01 (0.96–1.06)   | 0.677   | 1.12 (1.05–1.19)   | 0.001   |
| Number of stents      | 0.97 (0.72–1.30)   | 0.842   | 0.94 (0.65–1.37)   | 0.747   | 1.02 (0.99–1.04)   | 0.254   |

*95%CI, 95% confidence interval; Lp(a), lipoprotein(a); LVEF, left ventricular ejection function; MI, myocardial infarction; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HbA1c, Haemoglobin A1c.

High Lp(a), Lp(a) > 175 mg/L; high LDL, LDL > 2 mmol/L; low HDL, HDL < 1 mmol/L; ln-Lp(a), natural log Lp(a).
be a potential evaluation tool for risk management in diabetic patients undergoing PCI.

The most promising Lp(a)-Lowering pharmacologic treatments are hepatocyte-directed antisense oligonucleotide (ASO) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The latest randomized controlled trial of ASO therapy showed that Lp(a) achieved forcefully 35% to 72% reduction in a dose-dependent manner after 32 weeks (28). ODYSSEY OUTCOME (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) randomized trial demonstrated that PCSK9 inhibitor alirocumab reduced Lp(a) by a median 23.5% after 4 months (29). Currently, lipoprotein apheresis is an efficient therapy for lowering Lp(a) levels (30). Recent evidence showed a reduction of 63% for Lp(a) had been achieved by apheresis and cardiovascular events markedly reduced about 94% after treatment (31). The combination of statin and Lp(a)-lowering therapy provides us an insight into future lipid treating therapy in patients with diabetes (32).

TABLE 4 | Multivariate logistic regression analysis for peri-procedural myocardial infarction.

| Total population | Male | Female |
|------------------|------|--------|
| **Lp(a) as categorical variable** | | |
| Age | 1.03 (0.996–1.07) | 0.079 | 1.05 (1.01–1.10) | 0.027 | 0.98 (0.92–1.05) | 0.630 |
| Male | 0.74 (0.35–1.57) | 0.435 | Not applicable | Not applicable | Not applicable | Not applicable |
| High Lp(a) | 2.64 (1.22–5.70) | 0.014 | 3.68 (1.34–10.01) | 0.011 | 1.28 (0.37–4.47) | 0.695 |
| Previous MI | 0.96 (0.45–1.99) | 0.893 | 0.89 (0.37–2.15) | 0.798 | 1.00 (0.25–4.05) | 0.999 |
| SYNTAX score >22 | 2.80 (1.31–5.95) | 0.008 | 0.99 (0.29–3.41) | 0.993 | 12.19 (3.67–40.48) | <0.001 |
| **Lp(a) as continuous variable** | | |
| Age | 1.03 (0.995–1.07) | 0.094 | 1.05 (1.004–1.10) | 0.031 | 0.98 (0.92–1.05) | 0.635 |
| Male | 0.78 (0.37–1.65) | 0.518 | Not applicable | Not applicable | Not applicable | Not applicable |
| Ln-Lp(a) | 1.57 (1.12–2.20) | 0.008 | 1.81 (1.18–2.78) | 0.007 | 1.17 (0.66–2.07) | 0.601 |
| Previous MI | 0.93 (0.44–1.94) | 0.841 | 0.67 (0.36–2.10) | 0.754 | 0.97 (0.24–3.97) | 0.967 |
| SYNTAX score >22 | 2.82 (1.32–5.996) | 0.007 | 0.99 (0.29–3.40) | 0.989 | 12.10 (3.65–40.17) | <0.001 |

*95%CI, 95% confidence interval; Lp(a), lipoprotein(a).
High Lp(a), Lp(a) > 175 mg/L; ln-Lp(a), natural log Lp(a).

FIGURE 2 | Receiver-operating characteristics analysis. AUC, the area under the receiver-operating curve.
**Limitations**

There are several limitations requiring careful consideration. First, this study was conducted in a single center, further multi-center validation is needed to confirm our findings. Second, the study was based on observational data, not on randomized design trials. Thus, the result of the analysis might not indicate final conclusions for the impact of Lp(a). Finally, although we adjusted the traditional risk factors, hidden unadjusted confounders may not be totally eliminated. Moreover, there was a lack of a family history record and genetic background that could allow us to further evaluate the inheritable Lp(a) influence.

**Conclusions**

In conclusion, Lp(a) levels were independently associated with an elevated risk of PMI during PCI in male patients with DM. Lp(a) might be a significant indicator for PCI risk stratification and a potential target for PMI treatment. Further studies should be conducted to investigate the detailed role of Lp(a) in the pathology of PMI.

**DATA AVAILABILITY STATEMENT**

Request to the data of this study can be sent to the corresponding author, who will provide them to vetted and qualified applicants.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital. The patients/participants provided their written informed consent approved by the Ethics Committee of Fuwai Hospital. The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital. The patients/participants provided their written informed consent approved by the Ethics Committee of Fuwai Hospital.

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**AUTHOR CONTRIBUTIONS**

YL: Conceptualization, methodology, investigation, formal analysis, and writing—original draft. WW: Data curation, writing—review and editing, and supervision. JS: Formal analysis, software, and validation. KZ: Project administration. BX: Resources. PL, CS, MY, JC: Investigation. Y-DT: Conceptualization, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.603922/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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