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ORIGINAL RESEARCH

Elevated Lipoprotein(a) Predicts Stent Edge Restenosis and Adverse Two-Year Outcomes After PCI: An Intravascular Ultrasound Study

Xi Wu, Mingxing Wu, Haobo Huang, Zhe Liu, He Huang, Lei Wang

Department of Cardiology, Xiangtan Central Hospital (The Affiliated Hospital of Hunan University), Xiangtan, Hunan, 411100, People's Republic of China

Correspondence: Lei Wang, Department of Cardiology, Xiangtan Central Hospital (The Affiliated Hospital of Hunan University), Xiangtan, Hunan, 411100, People's Republic of China, Email heartwl@126.com

Background: Elevated lipoprotein(a) [Lp(a)] is a known contributor to recurrent ischemic events following percutaneous coronary intervention (PCI). Although drug-eluting stents (DES) have significantly advanced coronary revascularization, stent edge restenosis (SER) remains a clinical challenge. However, the relationship between Lp(a) levels and the incidence of SER is not well defined.

Objective: This study aimed to investigate the association between serum Lp(a) levels and the development of SER, and to explore potential pathophysiological mechanisms using intravascular ultrasound (IVUS).

Methods: A total of 211 patients with SER lesions who underwent IVUS-guided PCI were included. Patients were divided into two groups based on their baseline Lp(a) concentrations: elevated Lp(a) (≥50 mg/dL, n=75) and non-elevated Lp(a) (<50 mg/dL, n=136). Clinical characteristics, angiographic features, IVUS findings, and device-oriented clinical endpoints (DoCE) were compared between the two cohorts.

Results: Baseline clinical and angiographic characteristics were similar between the groups ($P > 0.05$). Neoatherosclerosis was significantly more frequent in the elevated Lp(a) group (56.0% vs 44.1%, $P < 0.001$), whereas neointimal hyperplasia was less common (24.0% vs 33.8%, $P < 0.001$). Multivariate analysis identified elevated Lp(a) as an independent predictor of SER (odds ratio: 3.391; 95% confidence interval: 2.030–5.273; $P < 0.001$). During a two-year follow-up, the elevated Lp(a) group showed higher rates of DoCE (16.0% vs 7.4%, $P < 0.001$) and target lesion revascularization (13.3% vs 5.1%, $P = 0.011$).

Conclusion: Elevated Lp(a) is an independent predictor of SER and is associated with adverse two-year clinical outcomes after PCI. These findings underscore the importance of Lp(a) as a potential therapeutic target for improving long-term stent durability.

Keywords: lipoprotein(a), stent edge restenosis, percutaneous coronary intervention, intravascular ultrasound

Introduction

Lipoprotein(a) [Lp(a)] is a unique lipoprotein particle structurally similar to low-density lipoprotein (LDL), consisting of apolipoprotein B-100 covalently linked to apolipoprotein(a) via a disulfide bond.[1] Its plasma concentration varies widely among individuals and is primarily determined by genetic factors through an autosomal co-dominant inheritance pattern.[2] Lp(a) exhibits both atherogenic and thrombogenic properties due to its structural resemblance to plasminogen and LDL.[3] It contributes to lipid deposition, impaired fibrinolysis, inflammation, and smooth muscle cell proliferation,[3] thus playing a significant role in the development of atherosclerosis and thrombosis. Elevated Lp(a) levels have been associated with increased cardiovascular risk and recurrent ischemic events in patients with coronary artery disease (CAD) who have undergone percutaneous coronary intervention (PCI).[4–6]

Drug-eluting stents (DES), particularly newer-generation devices with thinner struts and more biocompatible polymers, have substantially reduced in-stent restenosis (ISR) and thrombosis rates compared to first-generation stents.[7] However, stent edge restenosis (SER)—restenosis occurring at the proximal or distal margins of the stent—remains a relevant limitation.[8] SER is often attributed to mechanical and procedural factors, including vascular injury during

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balloon dilation, residual plaque at the stent edge, mismatches between stent and vessel size, and mechanical stresses at the stent-artery interface.[9–11] Additional contributors include hinge motion, plaque burden, and lipid arc presence.[11,12] Despite these known mechanical factors, the potential biological contributors to SER, particularly the role of elevated Lp(a), have not been well defined. Given Lp(a)'s proatherogenic and prothrombotic properties, it is biologically plausible that elevated Lp(a) may influence the development of SER. Intravascular ultrasound (IVUS), a high-resolution imaging modality, plays a central role in assessing lesion morphology and plaque characteristics and is therefore instrumental in evaluating the underlying mechanisms of SER. Accordingly, this study aimed to investigate the association between elevated Lp(a) levels and the incidence of SER in patients with CAD undergoing PCI, using IVUS to provide detailed lesion characterization. In particular, the study sought to assess whether elevated Lp(a) levels were associated with specific tissue features of restenosis, such as neoatherosclerosis and neointimal hyperplasia(NIH), to better understand potential biological mechanisms underlying SER.

Materials and Methods

Study Population

This single-center, retrospective observational research initially encompassed 211 consecutive CAD patients receiving IVUS-guided treatment for SER lesions from January 1, 2017 to December 31, 2021. Exclusion criteria encompassed bare metal stent (BMS)-related SER (n=12), absence of serum Lp (a) measurement (n=25), suboptimal IVUS image quality (n=6), serious pulmonary, hepatic, or renal insufficiency (n=8), malignant tumor or autoimmune disease (n=2) (Figure 1). The final cohort was stratified into two cohorts based on serum Lp(a) levels: elevated Lp (a) group (≥50 mg/dL, n=75) and non-elevated Lp (a) group (<50 mg/dL, n=136).[13] The study protocol adhered to the Declaration of Helsinki (2013 revision) and received approval from the Research and Ethics Committee of Xiangtan Central Hospital. Written informed consent from all participants or their legal representatives was obtained after they had been fully informed about the objectives of the study (X201863231-3).

Clinical Baseline, Procedures and Angiographic Characteristic Data

A dedicated database captured comprehensive information on patient demographics, comorbidities, and laboratory findings. The choice of interventional strategies, encompassing drug-coated balloon (DCB) angioplasty, second-

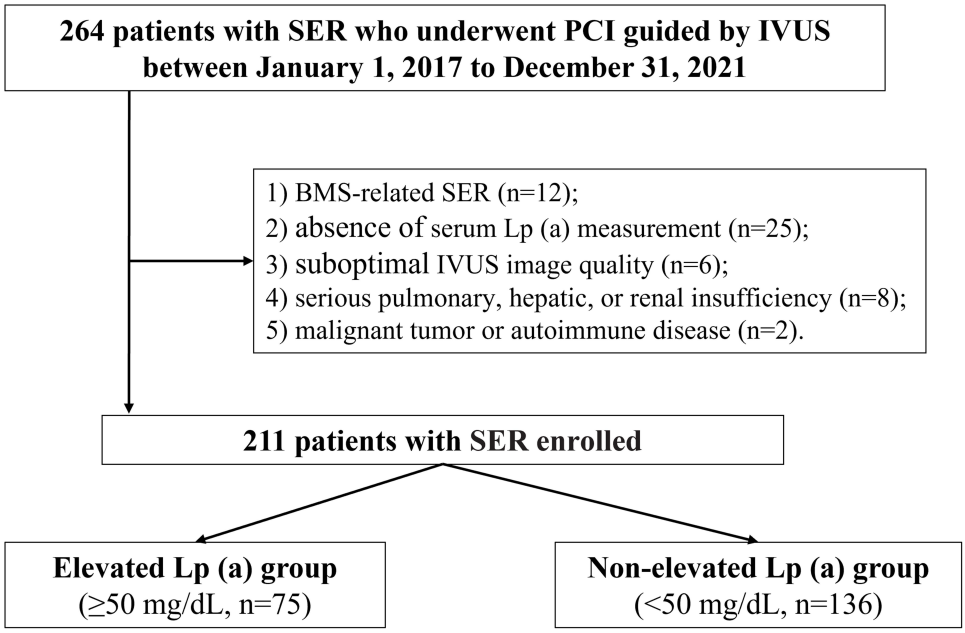

Figure 1 Study flow.
Abbreviations: SER, stent edge restenosis; PCI, percutaneous coronary intervention; IVUS, intravascular ultrasound; BMS, bare metal stent; Lp(a), lipoprotein(a).

generation DES implantation, auxiliary device usage, and pharmacotherapy, was determined by operators based on current guidelines and local best practices.[14,15] Medication regimens at discharge were documented on dual antiplatelet therapy with 100 mg aspirin daily and a P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily), selected according to guideline recommendations and individual bleeding risk assessments. Additional secondary prevention medications, including statins, nitrates, β-blockers, as well as angiotensin-converting enzyme inhibitors, were prescribed in alignment with prevailing guidelines.

Quantitative coronary angiography (QCA) was conducted using QAngio XA software (Medis Medical Imaging Systems, Leiden, the Netherlands). Coronary lesion morphology evaluation followed previously established methodologies.[16] Two experienced angiographers, working independently and blinded to the study details, performed all quantitative measurements using off-line computerized analysis. Lesion images were acquired in at least two orthogonal projections following the administration of 0.5 mg intracoronary nitroglycerin.The major angiographic parameters assessed included minimum lumen diameter (MLD), lesion length, diameter of reference vessel, and percentage diameter stenosis. To minimize procedural variability, all interventions were performed by experienced interventional cardiologists following current PCI guidelines. Decisions on lesion preparation, stent sizing, and landing zone selection were made under IVUS guidance and QCA support. Although lesion preparation techniques (eg, pre-dilation or scoring balloon use) were not uniformly documented, stent deployment adhered to best practices and IVUS-optimized expansion targets.

Lp(a) Measurement

Serum Lp(a) levels were quantified using an immune-turbidimetry assay, with ≥50 mg/dL established as a risk-enhancing threshold in accordance with recent guidelines.[13] For patients with multiple preprocedural Lp(a) measurements, the value closest to the procedure date was selected for analysis.

IVUS Image Acquisition and Assessment

IVUS imaging of SER arteries was performed using a 40-MHz OptiCross™ catheter (Boston Scientific, Marlborough, MA, USA). Following intracoronary nitroglycerin administration (0.1–0.2 mg), automated pullback (0.5 mm/s) was initiated. The IVUS catheter was advanced >10 mm beyond the stent distally and proximally. IVUS image analysis utilized QIvus® software (Medis, Leiden, the Netherlands). SER was defined as >50% diameter stenosis within 5mm proximal or distal to the stent edge.[17] Reference segments, representing the most normal-appearing cross-sections in 5 mm of the SER, were identified for comparative analysis (Figure 2). The minimum lumen area (MLA) and minimum stent area (MSA) sites were determined based on smallest lumen/greatest plaque and smallest stent area, respectively. Two independent, blinded cardiologists performed SER identification and quantitative analyses, with high intra-observer

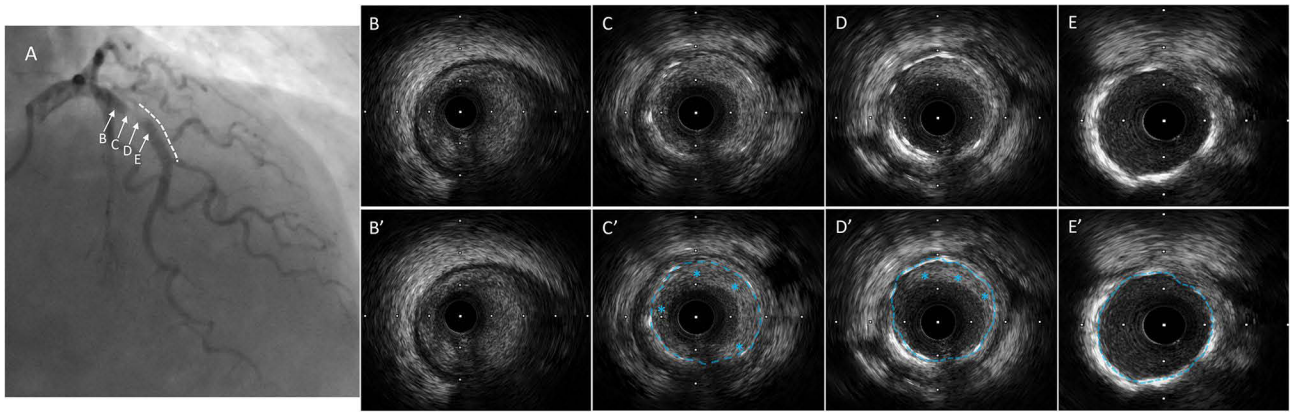

Figure 2 In the example, the coronary angiogram at the time of SER (**A**) is shown accompanied by a white dotted line indicating the old stents. (**B**–**E**) in the coronary angiograms correspond to the IVUS image (**B**–**E**). (**B′**–**E′**) are the same images with annotation compared with (**B**–**E**). IVUS images shown excessive neointimal hyperplasia with good stent expansion; blue dotted lines in the IVUS images indicate old stent struts; the blue asterisks indicate excessive neointimal hyperplasia.
Abbreviations: SER, stent edge restenosis; IVUS, intravascular ultrasound.

as well as inter-observer agreement (κ = 0.92 and 0.90, respectively). NIH area (stent area minus lumen area) and percentage (NIH/stent area) were calculated from stent and lumen areas. Stent expansion was defined as MSA divided via the largest reference lumen,[18] with under-expansion classified as MSA <4 mm^2 or expansion <50%.[19] To further address potential procedural bias, IVUS analysis included parameters related to stent expansion and plaque morphology. The classification of neoatherosclerosis and other SER subtypes was based on consensus definitions and validated by two independent observers. While procedural nuances such as exact lesion preparation were not systematically recorded, the combination of anatomical imaging, blinded review, and high inter-observer agreement (κ = 0.90–0.92) supports the reliability of lesion classification.

Definitions

SER was categorized into five primary patterns: 1) NIH, 2) Neo-atherosclerosis, 3) uncovered lesion, 4) stent under-expansion, and 5) protruding calcified nodule (CN). Neo-atherosclerosis was characterized by atherosclerotic changes at the MLA site within the stent, manifesting as calcified NIH (echogenic tissue with acoustic shadowing), attenuated NIH (ultrasound shadowing without superficial calcium), or ruptured NIH (cavitation within NIH).[20] A neo-atherosclerotic calcified nodule was distinguished from a non-neoatherosclerotic protruding calcified nodule, which presented as an irregular, convex calcium deposit within the old stent, lacking adjacent NIH.[21] In cases of multiple potential causes, the primary factor contributing to in-stent restenosis was determined based on its predominant impact on stenosis severity.

Clinical Follow-up and Outcomes

The study's primary endpoint focused on device-oriented clinical endpoints (DoCE), encompassing cardiac mortality, myocardial infarction (MI) related to the target vessel or stent thrombosis, and target lesion revascularization (TLR). These clinical outcomes were defined in compliance with the Academic Research Consortium guidelines.[22] The investigation prioritized the incidence of DoCE as its main objective, while the secondary goal examined the occurrence of individual DoCE components. Patient monitoring involved periodic assessments at six-month intervals, conducted either through in-person clinical visits or telephone consultations. The follow-up period extended up to two years, with all study participants completing a minimum of one year of observation.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range), and categorical variables in terms of frequencies and percentages for data presentation. Analysis of continuous outcome data was done by comparing data employing the Student's *t*-test or Mann–Whitney *U*-test, based on the data distribution. Fisher's exact test was used to evaluate categorical outcome data when the total number of observations was 9 or fewer; chi-square analysis was used if the total number of observations was greater than 9. Cox regression analysis, both univariate and multivariable, were conducted to ascertain independent determinants of SER, providing odds ratio (OR) with 95% confidence interval (95% CI). Those variables demonstrating P less than 0.10 in univariate analysis were then joined into a multivariable marginal Cox proportional hazards model. Kaplan-Meier survival assessment was utilized to estimate event rates, and hazard ratios (HR) was calculated from Cox regression analysis. For patients for whom multiple DoCEs were applicable, the first was employed for analytical purposes. All analyses were carried out at a statistical significance of $P < 0.05$. The statistical program SPSS 24.0 was used to handle and evaluate the data (SPSS Inc., Chicago, IL, US).

Results

Baseline Clinical Characteristics and Angiography Characteristics

The research encompassed 211 patients (136 males, 75 females; mean age 64.28±10.78 years) presenting with SER and 211 corresponding target lesions. Upon analysis, no noteworthy disparities in baseline clinical or angiographic features were detected between subjects with elevated and non-elevated Lp(a) levels (Tables 1 and 2).

Table 1 Baseline Clinical Characteristics

	Elevated Lp(a) (n=75)	Non-Elevated Lp(a) (n=136)	P value
Age, years	65.55±11.17	64.29±10.39	0.806
Male, %	48 (64.0)	88 (64.7)	0.918
Current smoker, %	27 (36.0)	46 (33.8)	0.750
Hypertension, %	56 (74.7)	95 (69.9)	0.208
Body mass index, kg/m^2	29.27±5.74	28.74±5.76	0.571
Diabetes mellitus, %	19 (25.3)	36 (26.5)	0.428
Hyperlipidemia, %	37 (50.0)	66 (48.5)	0.839
Chronic renal insufficiency, %	1 (1.3)	4 (2.9)	0.793
Chronic cardiac insufficiency, %	12 (16.0)	27 (19.9)	0.490
Prior CABG, %	0(0)	0(0)	0
Prior MI, %	20 (26.7)	38 (27.9)	0.411
Medication at the time of SER			
Aspirin, %	71 (94.7)	136 (100)	0.199
Clopidogrel, %	52 (69.3)	98 (72.1)	0.735
Ticagrelor, %	17 (22.7)	36 (26.5)	0.301
Statin, %	64 (85.3)	122 (89.7)	0.601
β-blocker, %	28 (37.3)	45 (33.1)	0.521
ACEI or ARB, %	20 (26.7)	38 (27.9)	0.505
Nitrates, %	13 (17.3)	30 (22.1)	0.411
Anticoagulant, %	2 (2.7)	2 (1.5)	0.694
Laboratory data			
Hemoglobin, g/dL	11.73 (10.54, 12.54)	11.24 (10.15, 12.46)	0.153
C-reactive protein, mg/dL	0.31 (0.15, 0.84)	0.33 (0.15, 0.81)	0.841
Total cholesterol, mg/dL	141.43 (124.42, 167.65)	150.65 (136.65, 178.66)	0.146
LDL cholesterol, mg/dL	75.54 (54.84, 94.82)	81.01 (62.05, 96.07)	0.208
HDL cholesterol, mg/dL	47.05 (41.03, 56.12)	44.15 (35.63, 54.77)	0.102
Triglyceride, g/dL	79.63 (56.52, 131.37)	82.02 (53.02, 139.06)	0.301

Note: Values are the mean ± standard deviation, number (%), or median [interquartile range].
Abbreviations: CABG, coronary artery bypass grafting; SER, stent edge restenosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MI, myocardial infarction;

IVUS Analysis of SER Lesions

The IVUS findings of SER were not different between the elevated Lp(a) cohort and the non-elevated Lp (a) cohort (Table 3). Between the two cohorts, there was a noticeable difference in the distribution pattern of SER stenotic tissue shape. The elevated Lp(a) cohort exhibited fewer instances of NIH compared to the non-elevated Lp(a) cohort (24.0% vs 33.8%, P<0.001)(Figure 3). Conversely, Neo-atherosclerosis was more prevalent in the elevated Lp(a) cohort than in the non-elevated Lp (a) cohort (56.0% vs 44.1%, P<0.001) (Figure 3).

Prediction of SER

As depicted within Table 4, both univariate (OR: 3.612, 95% CI: 2.226–5.477; *P*<0.001) and multivariate (OR: 3.391, 95% CI: 2.030–5.273; *P*<0.001) assessments show that elevated Lp(a) was independently correlated with the development of SER.

Clinical Outcomes

Table 5 and Figure 4 illustrate the comparative clinical outcomes between participants with elevated and non-elevated Lp(a) levels. Over a 2-year observational follow-up period, the elevated Lp(a) cohort consistently demonstrated higher incidences of DoCE and TLR compared to the non-elevated Lp(a) cohort (16.0% vs 7.4%, P<0.001; 13.3% vs 5.1%, P= 0.011, respectively).

Table 2 Angiography Characteristics

	Elevated Lp(a) (n=75)	Non-Elevated Lp(a) (n=136)	P value
Time since implantation, years	4.63±4.32	5.63±5.53	0.392
Stent type before index procedure			
First generation DES, %	5 (6.7)	6 (4.4)	0.783
Second generation DES, %	70 (93.3)	130 (95.6)	0.761
Culprit vessel, %			
LAD	45 (60.0)	78 (57.4)	0.509
LCX	7 (9.3)	13 (9.6)	0.892
RCA	22 (29.3)	45 (33.1)	0.487
Other lesion	1(1.3)	0	0.820
Proximal location, %	40 (53.3)	70 (51.5)	0.552
Distal location, %	35 (46.7)	66 (48.5)	0.509
QCA analysis of lesion segment			
Restenosis lesion length, mm	6.22 (3.45, 9.86)	5.64 (3.13, 9.53)	0.325
Reference vessel diameter, mm	2.76 (2.34, 3.26)	2.8 (2.51, 3.37)	0.349
Pre-MLD, mm	1.14 (0.86, 1.47)	1.15 (0.74, 1.57)	0.782
Final-MLD, mm	2.43 (1.72, 3.07)	2.44 (1.81, 3.06)	0.746
Pre diameter stenosis, %	62.84 (51.16, 74.23)	62.74 (53.67, 75.34)	0.520
Final diameter stenosis, %	25.64 (20.11, 31.26)	26.14 (20.44, 31.87)	0.373

Note: Values are the mean ± standard deviation, number (%), or median [interquartile range].
Abbreviations: SER, stent edge restenosis; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; QCA, quantitative coronary angiography; MLD, minimum lumen diameter; DES, drug-eluting stents;

Discussion

This study's principal observations can be summarized as follows: 1.Among patients with SER, Neo-atherosclerosis was much more prevalent within the elevated Lp(a) cohort. 2.NIH was less frequent in the elevated Lp(a) cohort. 3.Elevated Lp(a) levels exhibited an independent correlation with SER. 4.The cumulative 2-year incidence of both DoCE and TLR was consistently elevated within the elevated Lp(a) cohort.

Impact of Lp(a) on SER

This real-world investigation reveals a notable disparity in the distribution of SER stenotic tissue structure between the two cohorts. The elevated Lp(a) cohort exhibited fewer instances of NIH but a higher prevalence of neo-atherosclerosis compared to their counterparts with non-elevated Lp(a) levels. Lp(a) promotes atherosclerosis by transporting cholesterol while adhering to macrophages, facilitating foam cell formation, which contributes to atherosclerotic plaque development.[23] In addition, Lp(a) competes for specific binding sites with plasminogen and enhances the activity of plasminogen activator inhibitor, both processes promoting thrombogenesis.[24] The post-stent implantation inflammatory response is badly affected by Lp(a). Through its actions on white blood cells and the immune cascades at sites of injured vessel walls, it stimulates proinflammatory cytokine and matrix metalloproteinase secretion. It triggers a localized inflammatory response and then promotes vascular smooth muscle proliferation and migration towards atherosclerotic lesions.[25] A second potential proatherogenic mechanism of Lp(a) is its inverse association with vascular reactivity. Lp(a) directly binds to the extracellular matrix, is internalized via macrophages, and is associated with lipid accumulation and Neo-atherosclerosis and in-stent restenosis.[26] As a consequence, increased plasma Lp(a) levels result in endothelial dysfunction,[27] a major impetus for SER development.[28]

Table 3 Intravascular Ultrasound Findings

	Elevated Lp(a) (n=75)	Non-Elevated Lp(a) (n=136)	P value
Pre-procedure quantitative assessment			
Distal reference lumen area, mm^2	5.12 (4.14, 6.46)	5.04 (4.04, 6.36)	0.601
Proximal reference lumen area, mm^2	6.74 (5.97, 8.74)	6.78 (5.91, 8.74)	0.148
MLA, mm^2	2.36 (1.44, 3.14)	2.16 (1.53, 2.77)	0.792
Minimum lumen diameter, mm	1.87 (1.55, 2.15)	1.87 (1.55, 2.02)	0.826
Minimum stent area, mm^2	6.07 (4.55, 7.32)	6.45 (5.67, 7.83)	0.111
Minimum stent area <4.0 mm^2, %	18 (24.0)	27 (19.9)	0.481
Maximal NIH area, %	60.14 (43.65, 73.42)	65.67 (50.44, 72.65)	0.421
Minimum stent expansion, %	66.68 (54.97, 77.34)	65.33 (52.73, 76.27)	0.739
Minimum stent expansion <70%, %	38 (50.7)	65 (47.8)	0.755
Minimum stent expansion <50%, %	11 (14.7)	23 (16.9)	0.471
MSA <4.0 mm^2 or stent expansion <50%, %	18 (24.0)	34 (25.0)	0.882
Post-procedure quantitative assessment			
Minimum stent area*, mm^2	6.84 (5.66, 8.35)	7.04 (6.27, 9.03)	0.357
Minimum stent expansion, %	70.66 (60.13, 79.14)	70.68 (60.43, 79.64)	0.837
SER treatment			
New DES, %	45 (60.0)	75 (55.1)	0.229
DCB, %	30 (40.0)	61 (44.9)	0.191

Note: Values are the mean ± standard deviation, number (%), or median [interquartile range]. *New drug-eluting stent area (if new drug-eluting stent was implanted), otherwise, old stent area post drug-coated ballooning;
Abbreviations: SER, stent edge restenosis; NIH, neointimal hyperplasia; MLA, minimum lumen area; DCB, drug-coated balloon; DES, drug-eluting stents;

Predictors of SER

The development, severity, as well as pattern of SER are due to multiple factors, such as mechanical (stent under-expansion, uneven drug distribution, and stent fracture), biological (drug resistance and hypersensitivity), or operator-related technical factors (barotraumas beyond the stented section, stent gaps, and remaining

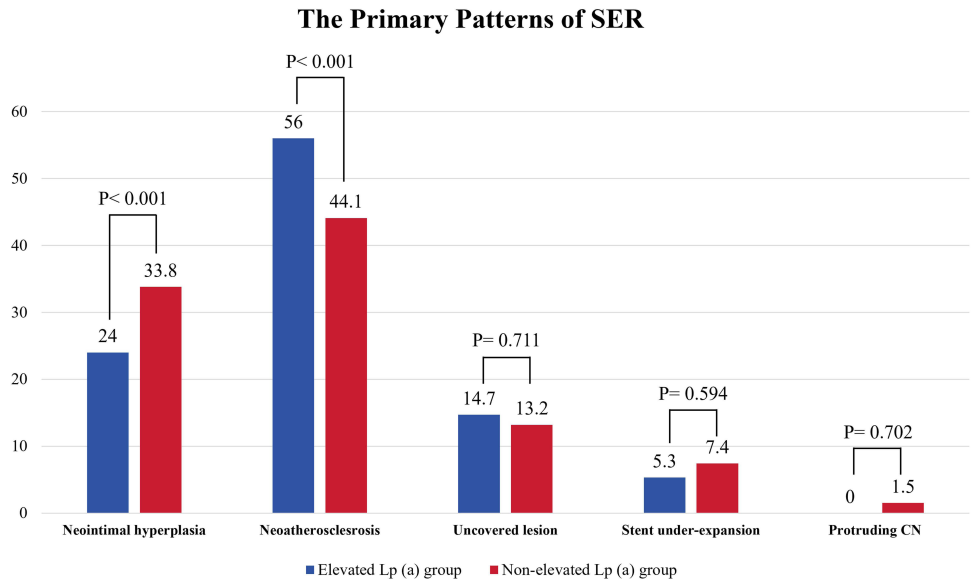

Figure 3 The primary patterns of SER.
Abbreviations: CN,calcified nodule; Lp(a), lipoprotein(a); SER, stent edge restenosis.

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Table 4 Univariate and Multivariate Logistic Regression Analysis to Determine the Independent Factors Affecting the Presence of SER

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age>65 years	2.256	0.823–6.246	0.122			
Male	2.161	0.746–6.354	0.167			
Hypertension	1.662	1.024–2.724	0.041	1.422	0.845–2.418	0.195
Diabetes mellitus	0.995	0.971–1.023	0.564			
LDL cholesterol	1.847	1.155–2.953	0.018	1.176	0.721–1.926	0.543
Absence of statin use at the time of SER	1.549	0.963–2.453	0.073			
NIH>50%	1.493	1.258–4.872	0.012	2.653	0.353–1.237	0.192
Time since implantation	0.952	0.529–1.527	0.843			
Minimum stent area <4.0 mm^2	0.656	0.353–1.239	0.194			
Minimum stent expansion	1.029	0.452–2.203	0.821			
Minimum lumen area	1.718	1.131–2.865	0.024	0.642	0.383–1.130	0.161
Elevated Lp (a)	3.612	2.226–5.477	<0.001	3.391	2.030–5.273	<0.001
Neoatherosclesrosis	1.405	0.373–3.936	0.346			

Abbreviations: OR, odds ratio; CI, confidence interval; SER, stent edge restenosis; LDL, low density lipoprotein; NIH, neointimal hyperplasia; Lp(a), lipoprotein(a).

Table 5 Clinical Outcomes During Follow-up

	Elevated Lp(a) (n=75)	Non-Elevated Lp(a) (n=136)	P value
DoCE	12 (16.0)	10 (7.4)	<0.001
Cardiac death	1 (1.3)	2 (1.5)	0.894
Target vessel-related MI	5 (6.7)	3 (2.2)	0.260
Target vessel-related stent thrombosis	5 (6.7)	4 (2.9)	0.331
TLR	10 (13.3)	7 (5.1)	0.011

Note: Values are number (%).
Abbreviations: DoCE, device-oriented clinical endpoints; MI, myocardial infarction; TLR, target lesion revascularization.

uncovered atherosclerotic plaques).[29] Our study corroborates that elevated Lp(a) levels independently correlate with an elevated SER risk, supporting Lp(a)'s potential impact on restenotic lesions. However, previous IVUS and optical coherence tomography (OCT) studies have highlighted several key risk factors for SER: mechanical injury, hinge motion, stent under-expansion, smaller lumen size, residual plaque at the stent edge PCI, and a larger step-up index (ie, the ratio of stent border to reference minimum lumen area).[11,30,31] A retrospective OCT study of 319 patients immediately after everolimus-eluting stent implantation revealed lipidic plaque (OR: 5.99; 95% CI: 2.89–12.81; P<0.001) and minimum lumen area (OR: 0.64; 95% CI: 0.42–0.96; P=0.029) as independent predictors of SER.[11] For post-PCI patients, intensive management directed toward conventional risk factors (elevated LDL level, lesion morphology, hypertension, and diabetes) is usually performed.[32] Our cohort's lack of correlation between these conventional risk variables and SER could be due to the fact that their potential influence may not be a major driver of SER and that the control of these risk factors through intense treatment interventions following baseline PCI has been effective. In contrast, secondary prevention with Lp(a)-targeted therapies is approved but only in development and not yet standardized, giving us the advantage to study the persistent effect of elevated Lp(a) levels on stent durability.

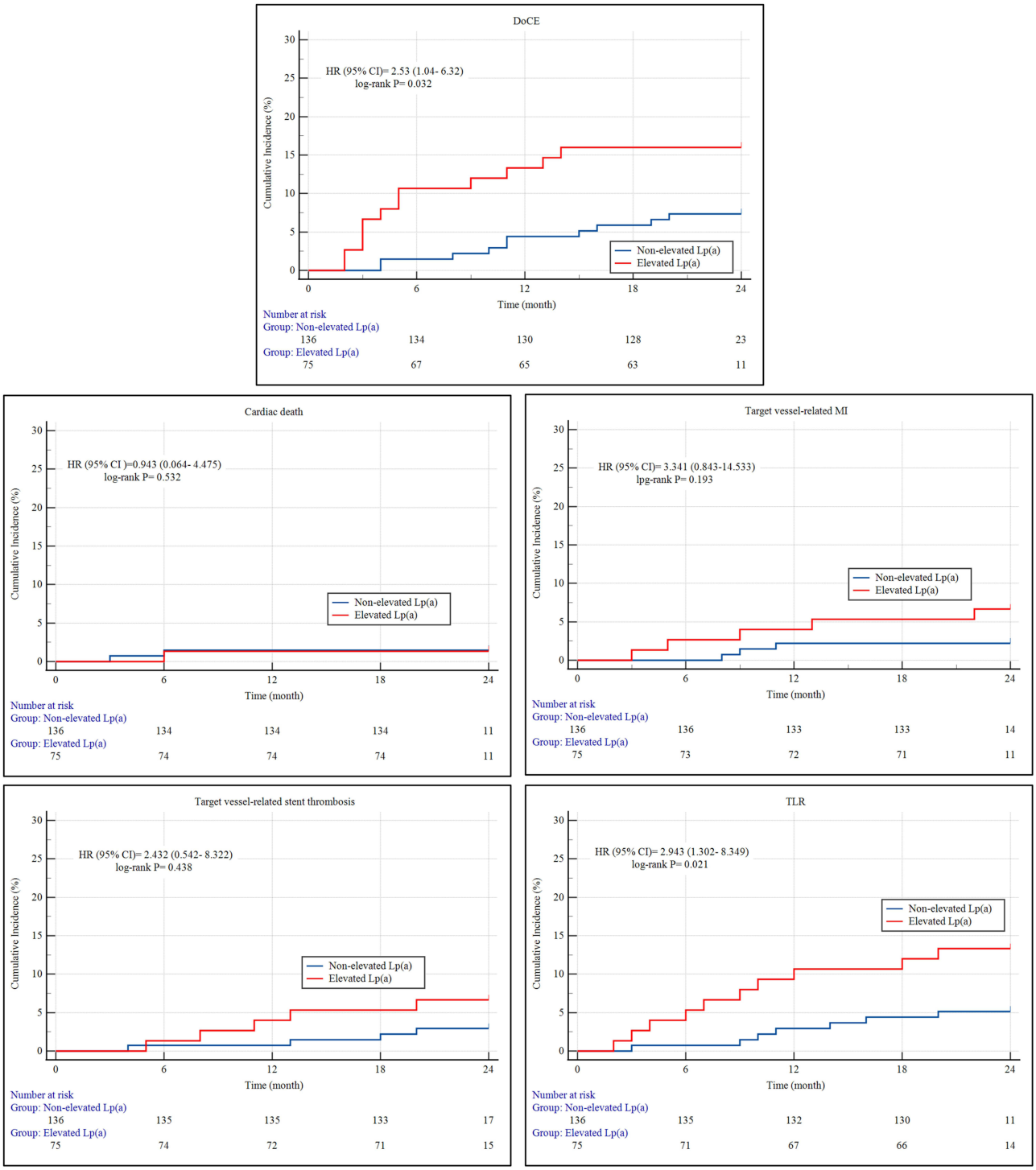

Figure 4 Kaplan-Meier survival curves of DoCE for 2 years.
Abbreviations: DoCE, device-oriented clinical endpoints; MI, myocardial infarction; TLR, target lesion revascularization; 95% CI, 95% confidence intervals; HR, hazard ratio; Lp(a), lipoprotein(a).

Clinical Outcome

Our study revealed consistently higher cumulative 2-year incidences of DoCE and TLR in the elevated Lp(a) cohort in contrast to the non-elevated Lp(a) cohort. The association seen in SER patients with elevated Lp(a) and adverse clinical outcomes following repeat PCI indicated these findings as a potential causal effect even in the DES era. Landmark

assessment showed that the differences in SER in patients with elevated and non-elevated Lp(a) were greatest following the index post-baseline PCI and therefore consistent with Lp(a)'s 2-year clinical effects on SER. In fact, a previous OCT study has shown that 185° of lipid arc and a minimal lumen area of 4.10 mm² at the stent edge predict SER and future adverse clinical events.[11]

Limited data exist on the association involving Lp(a) levels and stent thrombosis risk following PCI with DES. Due to structural homology between apolipoprotein(a) and plasminogen, Lp(a) may compete with and inhibit tissue plasminogen's thrombolytic activity.[33] Park et al reported an association involving higher Lp(a) levels as well as stent thrombosis following PCI with DES,[34] suggesting a more thrombogenic state within patients having high Lp(a) levels. However, our study found no statistically significant difference in cumulative 2-year stent thrombosis incidence involving the two cohorts, possibly due to insufficient sample size. Larger sample size studies are needed to draw definitive conclusions about Lp(a)'s role in stent thrombosis development.

Despite high and similar statin use in both cohorts (85.3% in elevated Lp(a) cohort versus 89.7% in non-elevated Lp(a) group, P=0.601), significant differences in 2-year DoCE outcomes were observed, suggesting that Lp(a) is not modified by statin therapy.[35] Following treatment with a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i), which decreased Lp(a) levels from 71.5 to 47.4 mg/dL, a patient with elevated Lp(a) levels showed no ISR recurrence, according to a case report by Akiyama et al. It is noteworthy that before to starting PCSK9i, this patient had a history of recurrent ISR (6 times) while receiving appropriate traditional antihyperlipidemia medication. Further studies are warranted to investigate potential therapies for preventing SER within patients having high Lp(a) levels undergoing PCI with DES.

Lp(a) is discussed as a promising risk factor and therapeutic target for SER prevention, and research in this area is encouraged. In patients undergoing PCI, elevated Lp(a) levels should be managed meticulously with a corresponding decrease in Lp(a) level. Of particular relevance in this era of emerging Lp(a)-targeted therapies,[36] this approach is important.The clinical importance of Lp(a) in the prevention of SER is amplified because SER is routinely treated by revascularization, which may be complex PCI or surgical intervention and could affect patient prognosis.[29] In addition, though, beyond treatment trials, more prospective studies are necessary to better explore the role of Lp(a) in SER.

Limitations

This study has several limitations. First, the single-center, non-randomized, retrospective design and limited sample size may introduce selection and information bias. Additionally, some patients were excluded due to missing IVUS assessments or Lp(a) measurements, which may have affected representativeness. Second, the types of DES previously implanted at SER sites included both first- and second-generation devices, potentially influencing plaque morphology and confounding the analysis. Third, although patients received guideline-directed medical therapy, detailed information on prior pharmacological interventions—particularly statin and P2Y12 inhibitor use—was not fully available, which may have contributed to observed differences in restenotic tissue characteristics between cohorts. Fourth, while clinical follow-up was performed for up to two years, extended long-term data beyond this period, including major adverse cardiovascular events (MACE) or late revascularization rates, were not collected. This may have limited the ability to fully assess the long-term prognostic implications of elevated Lp(a). In addition, dynamic changes in Lp(a) levels and longitudinal data on stent type during follow-up were not available, which may have further influenced outcomes. Fifth, while IVUS provided detailed structural information, it has intrinsic limitations in accurately characterizing tissue composition, as its imaging features may not fully correspond with histopathological findings. Future studies incorporating multimodal imaging—such as OCT, NIRS, or hybrid imaging platforms—are warranted to improve tissue characterization and validation.

Conclusion

This study demonstrates that elevated Lp(a) is independently associated with the occurrence of neoatherosclerosis and adverse two-year outcomes in patients with SER after PCI. These findings reinforce the biological plausibility of Lp(a) as

a risk factor, given its pro-inflammatory and pro-thrombotic properties that may promote plaque progression and vascular remodeling. The results highlight the potential of Lp(a) not only as a predictor of SER but also as a future therapeutic target or risk stratification tool in post-PCI patient management. While the findings are supported by robust imaging and clinical analysis, the single-center, retrospective design and limited follow-up duration represent inherent limitations. Future prospective, multicenter studies with extended follow-up are warranted to validate these observations and assess the impact of Lp(a)-targeted interventions.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The present research was carried out in accordance with the tenets mentioned in the Helsinki Declaration and was approved by the Ethical Board of Xiangtan Central Hospital (approval number:X201863231-3). Prior to the commencement of the research, our team obtained written informed consent from each patient.

Consent for Publication

Not applicable. No individual patient data will be reported.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. Specifically, X.W. and L.W. conceived the study and critically reviewed the manuscript for important intellectual content. H.B.H. and H.H. performed the literature search and data analysis. X.W., M.X.W., L.W., Z.L., and H.H. contributed to drafting and revising the manuscript. All authors gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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