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Article

A Significant Correlation Between Lipoprotein(a) Levels and Peripheral Arterial Disease in Patients With Type 2 Diabetes Mellitus: A Retrospective Study

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Abstract

Aims/Background: Lipoprotein(a) [Lp(a)] is recognized as a cardiovascular risk indicator; however, its connection to peripheral arterial disease (PAD) in individuals with type 2 diabetes mellitus (T2DM) is not well established. This research seeks to explore how Lp(a) concentrations relate to the occurrence of PAD in T2DM patients. **Methods**: A retrospective analysis was conducted on 590 patients diagnosed with T2DM who were admitted to Hefei First People's Hospital from January 2022 to August 2024. Participants were grouped into tertiles according to their Lp(a) levels. The diagnosis of PAD was made using the ankle-brachial index (ABI), with an ABI <0.9 considered indicative of PAD. The association between Lp(a) concentrations and PAD was examined using multivariate logistic regression models, subgroup analyses, receiver operating characteristic (ROC) curves, and restricted cubic spline (RCS) plotting. **Results**: Compared to lower Lp(a) levels, the group with higher Lp(a) levels exhibited a higher prevalence of PAD ($p = 0.001$). Multivariate logistic regression analysis indicated that, after stepwise adjustment for all confounding factors, the risk of PAD in the higher Lp(a) group was 1.961 times that of the lower Lp(a) group (odds ratio [OR] = 1.961, 95% confidence interval [CI]: 1.071–3.588, $p = 0.029$). Additionally, for each 1 standard deviation increase in Lp(a) or each unit increase in the normalized Lp(a) (Log_{10}Lp(a)), the risk of PAD increased by 25.7% and 80.3%, respectively (OR: 1.257, 95% CI: 1.016–1.555, $p = 0.035$; OR: 1.803, 95% CI: 1.013–3.209, $p = 0.045$). Subgroup analysis revealed a stratified association between Lp(a) and PAD risk across multiple subgroups ($p < 0.05$). ROC analysis demonstrated that Lp(a) had a certain predictive ability for PAD prevalence (area under the curve (AUC): 0.622, 95% CI: 0.568–0.677, $p < 0.001$). RCS analysis indicated that there was no evidence of a nonlinear relationship between Log_{10}Lp(a) and PAD risk, regardless of the logistic regression model used (p for nonlinearity > 0.05). **Conclusion**: A significant correlation was observed between elevated Lp(a) levels and an increased risk of PAD in patients with T2DM.

Keywords: lipoprotein(a); type 2 diabetes mellitus; peripheral arterial disease; ankle brachial index; cross-sectional study

1. Introduction

Peripheral arterial disease (PAD) is a frequently encountered vascular condition involving impaired blood circulation to the extremities, which can result in discomfort and restricted mobility [1,2]. The incidence of PAD is notably elevated in individuals with type 2 diabetes mellitus (T2DM) due to the combined effects of hyperglycemia, oxidative stress, and vascular inflammation accelerating atherosclerosis [3–6]. T2DM, which comprises more than 90% of all diabetes cases, is defined by a combination of insulin resistance and insufficient insulin production [7]. The diagnosis of T2DM is established according to recognized thresholds: fasting plasma glucose $\geq$7.0 mmol/L, 2-hour plasma glucose $\geq$11.1 mmol/L following an oral glucose tolerance test (OGTT), hemoglobin A1c (HbA1c) $\geq$6.5%, or random plasma glucose $\geq$11.1 mmol/L in individuals presenting with classic hyperglycemic symptoms [8]. Major risk factors include excess adiposity, physical inactivity, genetic predisposition, and advanced age [7]. PAD in T2DM patients impairs limb function and significantly raises the risk of cardiovascular diseases (CVDs) and amputation, severely reducing quality of life [3,9]. Since the early symptoms of PAD are often subtle, many patients are diagnosed at an advanced stage of the disease [10]. Unlike type 1 diabetes, T2DM develops slowly in adults and is more often linked to macrovascular complications like PAD [7]. Therefore, this study focuses on T2DM patients to identify key risk factors and biomarkers for PAD, which are essential for early diagnosis and improved outcomes.

Lipoprotein(a) [Lp(a)] is increasingly recognized for its contribution to CVD and mortality, due to its low-density lipoprotein (LDL)-like structure and unique pro-inflammatory and pro-thrombotic properties [11–14]. Structurally, Lp(a) consists of an LDL-like particle covalently bound to apolipoprotein(a) [apo(a)], a glycoprotein homologous to plasminogen, enabling it to interfere with fibrinolysis and promote thrombosis while simultaneously driving atherosclerosis through endothelial dysfunction, oxidative stress, inflammatory cytokine and adhesion molecule expression, impaired endothelial repair, and thrombus formation [15]. Clinically, elevated Lp(a) lev-

els have been identified as an independent risk factor for a range of cardiovascular conditions, including atherosclerotic CVD and heart valve disease [11–13]. Furthermore, numerous studies have linked high Lp(a) concentrations to a greater likelihood of developing PAD and its related complications, such as amputation and revascularization, and these associations vary across different sexes, ethnicities, and types of diabetic foot [16–19]. This implies that Lp(a) could be actively involved in the pathogenesis and advancement of PAD and warrants further investigation as a potential therapeutic target. However, despite the established correlation between Lp(a) and PAD, its specific impact on PAD in the T2DM population remains insufficiently explored [16]. In the context of T2DM, where vascular complications are more common due to chronic hyperglycemia and oxidative stress, Lp(a) may play a more pronounced role [20]. Given that PAD shares common pathophysiological pathways with other atherosclerotic conditions, investigating the role of Lp(a) in this specific context may offer new insights into early diagnosis and risk stratification in PAD patients [21].

Given the existing research context, this study investigates how Lp(a) concentrations relate to the prevalence of PAD among individuals with T2DM, with the aim of identifying a potential biomarker for early diagnosis and risk stratification, ultimately aiding in the prevention of severe complications such as cardiovascular events and limb amputations.

2. Methods

2.1 Study Population

This study retrospectively analyzed 590 individuals diagnosed with T2DM who received treatment at Hefei First People's Hospital between January 2022 and August 2024 (Fig. 1). The inclusion criteria were as follows: (1) a verified diagnosis of T2DM according to the 2025 American Diabetes Association (ADA) guidelines, (2) age of 18 years or older, and (3) availability of complete clinical data, including Lp(a) measurements and PAD status. Exclusion criteria included (1) history of cardiovascular events not related to PAD (such as myocardial infarction, stroke), (2) presence of severe hepatic or renal dysfunction (such as decompensated liver cirrhosis and uremia), (3) active infection or malignancy, and (4) presence of serious diabetic complications, including diabetic ketoacidosis, diabetic foot ulcers, or advanced diabetic retinopathy. Eligible participants were identified using T2DM diagnostic codes extracted from the hospital's electronic medical record system. After initial electronic screening, all cases underwent manual verification to ensure conformity with the defined inclusion and exclusion parameters. The research was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki. The study protocol received approval from the Ethics Committee of Hefei First People's Hospital [Approval No. 2022 (74)], and all subjects provided informed consent before participation.

2.2 Covariate Collection and Definition

In this study, essential patient information—including age, gender, smoking habits, clinical characteristics, and laboratory test results—was obtained. Smoking status was determined through the patients' electronic medical records and classified as smoker (yes) or non-smoker (no). Hypertension was identified either by a prior diagnosis or by elevated blood pressure measured during hospitalization—defined as systolic blood pressure (SBP) $\geq$140 mmHg or diastolic blood pressure (DBP) $\geq$90 mmHg [22]. Hyperlipidemia was determined based on either current lipid panel results or previously documented clinical history. Medication history, including the use of lipid-lowering drugs and antihypertensive drugs, was extracted from the patients' past medical records and recorded as yes or no. Chronic kidney disease (CKD) was determined by either a sustained estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 or the presence of kidney damage markers lasting over three months [23]. Blood pressure (SBP and DBP), heart rate, and body mass index (BMI) were obtained using established protocols and documented. Fasting glucose (mmol/L) and HbA1c (%) were used to assess the patients' glycemic control. Blood lipid analysis included evaluation of triglycerides, total cholesterol, and both low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), with results expressed in mmol/L. Kidney function was assessed via the eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [24]. Serum uric acid was measured in μmol/L and included as a continuous variable in the analysis.

2.3 Diagnosis of PAD

PAD was diagnosed based on a combination of clinical symptoms, physical examination, and objective diagnostic tests, with the ankle-brachial index (ABI) being the primary assessment tool [25]. ABI was calculated by dividing the SBP at the ankle by the SBP at the brachial artery. Following a minimum 10-minute rest in the supine position, SBP was assessed bilaterally at the upper limbs and at the posterior tibial and dorsalis pedis arteries in the lower limbs, using a handheld Doppler ultrasound device (Bidop ES-100V3, Hadeco Inc., Kawasaki, Japan). An ABI value of less than 0.90 was diagnostic of PAD [25].

2.4 Lp(a) Measurement

To assess Lp(a), an immunoturbidimetric assay was employed, utilizing antigen–antibody interactions that produce a turbidity signal proportional to Lp(a) content [26]. Participants provided fasting blood samples following an overnight fast of $\geq$8 hours. Absorbance at 340 nm was recorded using an automated analyzer (Hitachi 7600, Hi-

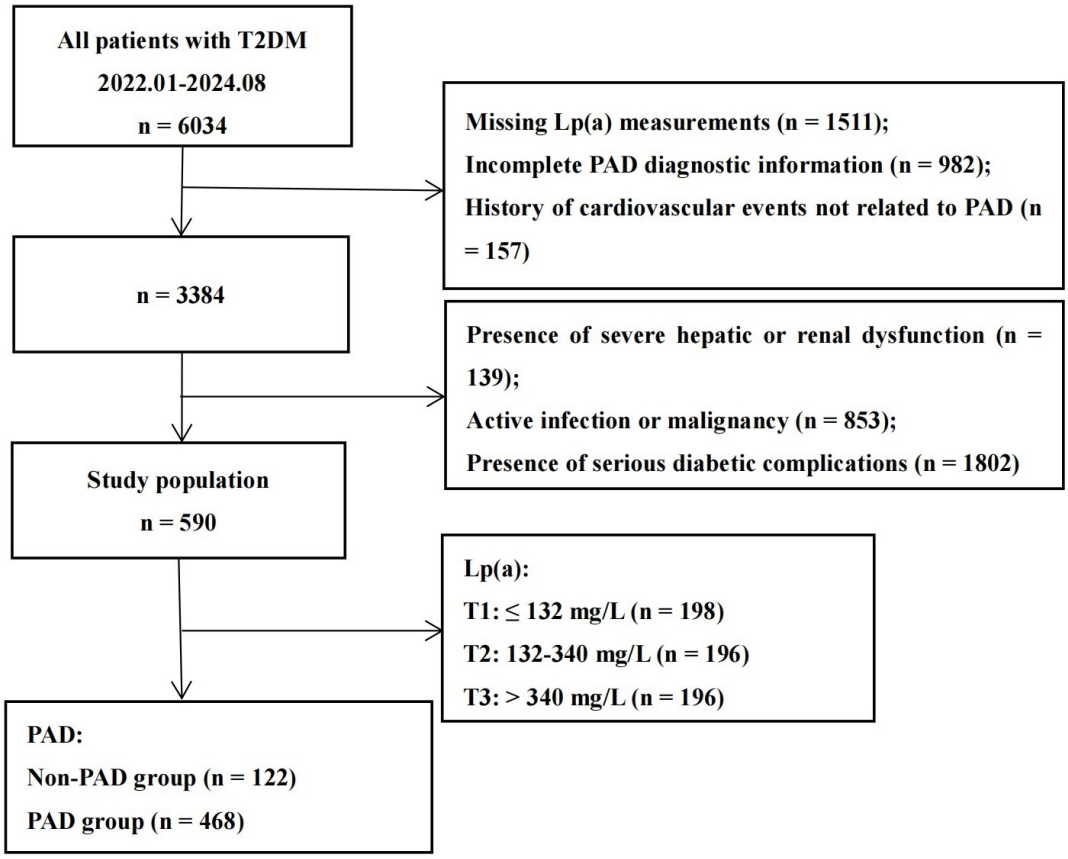

Fig. 1. Flowchart of patient selection and grouping process. T2DM, type 2 diabetes mellitus; PAD, peripheral arterial disease; Lp(a), lipoprotein(a).

tachi High-Technologies Corporation, Tokyo, Japan), with measurements processed via a commercial kit (KAI-017, Sekisui Medical Co., Ltd., Tokyo, Japan). Based on measured values, individuals were categorized into tertiles: T1 (≤132 mg/L), T2 (132–340 mg/L), and T3 (>340 mg/L), ensuring comparable group sizes. This stratification enabled exploration of Lp(a)-related variation in PAD risk, supporting detection of potential dose-dependent relationships.

2.5 Statistics

Data analyses were executed by R (version 4.1.4, R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 26.0, IBM Corp., Armonk, NY, USA). The Shapiro-Wilk procedure was utilized to assess the normality assumption for continuous variables. For variables that followed a normal distribution, results were described using means and standard deviations (SDs), and group differences were evaluated through one-way analysis of variance (ANOVA). Levene's test was employed to examine equality of variances. In contrast, skewed data were summarized as medians and interquartile ranges (IQR), and nonparametric comparisons were conducted via the Kruskal-Wallis method. Categorical variables were expressed as counts (n) and percentages (%), and group differences were assessed using the chi-square (χ^2) test.

The relation between Lp(a) and PAD was assessed through a four-step hierarchical logistic-regression strategy that produced odds ratios (ORs) and 95% confidence intervals (CIs): Model 1 (baseline): no covariate adjustment; Model 2 (+demographics): Model 1 plus age and sex; Model 3 (+lifestyle/clinical): Model 2 plus smoking status, hypertension, antihypertensive treatment, and CKD; Model 4 (full adjustment): Model 3 plus heart rate, BMI, DBP, fasting glucose, HbA1c, triglycerides, eGFR, and uric acid. Covariates were chosen from univariable analyses in which $p < 0.05$ signified potential confounding. Multicollinearity was checked with variance-inflation factors (all <2.5), confirming variable independence. Robustness was probed by repeating the analysis within strata defined by age (≤60 vs. >60 years), sex and the presence of hypertension, hyperlipidemia or CKD. Predictive performance of Lp(a) for PAD was quantified with receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC). Possible non-linear dose-response patterns were investigated with a restricted cubic spline (RCS). Statistical significance was set at a two-tailed p-value < 0.05.

Table 1. Baseline characteristics stratified by Lp(a).

Variables	Total patients	T1	T2	T3	F/H/χ^2	*p*-value
N	590	198	196	196		
Age, years	63.94 ± 12.50	61.92 ± 13.05	64.93 ± 11.70	64.99 ± 12.54	3.915	0.020
Sex, n (%)					4.176	0.124
Male	429 (72.7%)	154 (77.8%)	140 (71.4%)	135 (68.9%)		
Female	161 (27.3%)	44 (22.2%)	56 (28.6%)	61 (31.1%)		
Smoking, n (%)					2.320	0.314
Yes	292 (49.5%)	105 (53.0%)	98 (50.0%)	89 (45.4%)		
No	298 (50.5%)	93 (47.0%)	98 (50.0%)	107 (54.6%)		
Hypertension, n (%)					6.575	0.037
Yes	423 (71.7%)	155 (78.3%)	136 (69.4%)	132 (67.3%)		
No	167 (28.3%)	43 (21.7%)	60 (30.6%)	64 (32.7%)		
Antihypertensive drugs, n (%)					8.100	0.017
Yes	349 (59.2%)	133 (67.2%)	106 (54.1%)	110 (56.1%)		
No	241 (40.8%)	65 (32.8%)	90 (45.9%)	86 (43.9%)		
Hyperlipidemia, n (%)					3.015	0.221
Yes	305 (51.7%)	110 (55.6%)	92 (46.9%)	103 (52.6%)		
No	285 (48.3%)	88 (44.4%)	104 (53.1%)	93 (47.4%)		
Lipid-lowering drugs, n (%)					0.297	0.862
Yes	7 (1.2%)	2 (1.0%)	2 (1.0%)	3 (1.5%)		
No	583 (98.8%)	196 (99.0%)	194 (99.0%)	193 (98.5%)		
Chronic kidney disease, n (%)					23.891	<0.001
Yes	143 (24.2%)	28 (14.1%)	46 (23.5%)	69 (35.2%)		
No	447 (75.8%)	170 (85.9%)	150 (76.5%)	127 (64.8%)		
BMI, kg/m^2	25.54 ± 3.57	25.58 ± 3.17	25.86 ± 3.52	25.18 ± 3.98	1.789	0.168
Heart rate, bpm	83.29 ± 15.43	83.45 ±15.13	82.26 ±14.06	84.17 ± 16.98	0.764	0.466
SBP, mmHg	134.50 ± 22.80	132.69 ± 22.60	136.72 ± 24.35	134.12 ± 21.27	1.582	0.206
DBP, mmHg	79.09 ± 14.64	79.51 ± 13.70	79.70 ± 14.58	77.92 ± 15.59	0.930	0.395
Fasting glucose, mmol/L	8.71 (7.12, 11.75)	8.70 (7.19, 11.88)	8.93 (7.26, 12.00)	8.26 (6.96, 11.57)	2.042	0.360
HbA1c, %	8.04 ± 1.74	7.91 ± 1.66	8.04 ± 1.73	8.16 ± 1.83	1.008	0.366
Total cholesterol, mmol/L	4.69 ± 1.31	4.46 ± 1.25	4.66 ± 1.22	4.95 ± 1.42	6.876	0.001
Triglyceride, mmol/L	1.63 (1.14, 2.40)	1.76 (1.22, 2.66)	1.56 (1.13, 2.19)	1.63 (1.08, 2.30)	5.441	0.066
LDL-C, mmol/L	2.83 ± 0.96	2.54 ± 0.81	2.83 ± 0.84	3.12 ± 1.12	18.672	<0.001
HDL-C, mmol/L	1.14 ± 0.27	1.14 ± 0.28	1.14 ± 0.27	1.13 ± 0.25	0.073	0.929
eGFR, mL/min/1.73 m^2	88.12 ± 40.43	100.38 ± 41.99	85.93 ± 37.88	77.91 ± 38.20	16.461	<0.001
Uric acid, µmol/L	358.22 ± 116.24	352.94 ± 112.30	356.22 ± 114.28	365.55 ± 122.18	0.622	0.537
PAD, n (%)					13.504	0.001
Yes	122 (20.7%)	27 (13.6%)	39 (19.9%)	56 (28.6%)		
No	468 (79.3%)	171 (86.4%)	157 (80.1%)	140 (71.4%)		

T1: ≤132 mg/L, T2: 132–340 mg/L, and T3: >340 mg/L. Lp(a), lipoprotein(a); BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; PAD, peripheral arterial disease.

3. Results

3.1 Baseline Characteristics

Table 1 summarized baseline data: participants were separated into Lp(a) tertiles (T1–T3), and their baseline profiles were contrasted across these categories. First, the incidence of PAD differed significantly between the groups with varying Lp(a) levels (p = 0.001). The prevalence of PAD rose with higher Lp(a) concentrations. Specifically, in the T1 group (Lp(a) ≤132 mg/L), the PAD incidence was 13.6%, while in the T3 group (Lp(a) >340 mg/L), the incidence increased to 28.6%. Second, age likewise varied by tertile (p = 0.020): participants in T1 averaged 61.92 years, whereas those in T2 and T3 were, on average, older than 64 years. Additionally, hypertension and the use of antihypertensive drugs differed significantly between the groups (p = 0.037 and p = 0.017, respectively), with the T1 group showing a higher proportion of hypertension (78.3%) compared to the other groups. Notably, CKD also showed a clear step-wise rise with higher Lp(a) (p < 0.001), climbing from 14.1% in T1 to 35.2% in T3. Moreover, LDL-C and

Table 2. Univariate logistic regression analysis of peripheral arterial disease.

	β	SE	Wald	OR (95% CI)	p-value
Age	0.084	0.011	58.394	1.088 (1.065, 1.112)	<0.001
Male	–0.526	0.217	5.896	0.591 (0.386, 0.904)	0.015
Smoking	–0.476	0.207	5.301	0.622 (0.415, 0.932)	0.021
Hypertension	0.713	0.256	7.772	2.041 (1.236, 3.369)	0.005
Antihypertensive drugs	0.622	0.219	8.037	1.862 (1.212, 2.862)	0.005
Hyperlipidemia	–0.334	0.204	2.681	0.716 (0.480, 1.068)	0.102
Chronic kidney disease	1.549	0.218	50.444	4.707 (3.070, 7.218)	<0.001
Body mass index	–0.085	0.030	8.163	0.919 (0.867, 0.974)	0.004
Heart rate	0.019	0.006	9.074	1.020 (1.007, 1.032)	0.003
Systolic blood pressure	0.005	0.004	1.132	1.005 (0.996, 1.014)	0.287
Diastolic blood pressure	–0.017	0.007	5.299	0.984 (0.970, 0.998)	0.021
Fasting glucose	0.054	0.023	5.519	1.055 (1.009, 1.104)	0.019
Hemoglobin A1c	0.171	0.056	9.320	1.187 (1.063, 1.325)	0.002
Total cholesterol	–0.094	0.080	1.366	0.911 (0.778, 1.065)	0.242
Triglyceride	–0.219	0.088	6.217	0.803 (0.676, 0.954)	0.013
Low-density lipoprotein cholesterol	–0.060	0.107	0.308	0.942 (0.763, 1.163)	0.579
High-density lipoprotein cholesterol	0.056	0.381	0.022	1.058 (0.502, 2.231)	0.882
Estimated glomerular filtration rate	–0.025	0.003	60.283	0.975 (0.969, 0.982)	<0.001
Uric acid	0.003	0.001	13.569	1.003 (1.001, 1.005)	<0.001

OR, odds ratio; CI, confidence interval; SE, standard error.

total cholesterol levels significantly increased with higher Lp(a) levels, while eGFR showed a significant decline as Lp(a) levels increased ($p < 0.05$). No inter-group variation was observed in sex distribution, smoking prevalence, BMI, heart rate, blood pressure, plasma glucose, or HbA1c ($p > 0.05$).

3.2 Univariate Logistic Regression Analysis of Peripheral Arterial Disease

Univariate logistic regression (Table 2) revealed that age, sex, smoking, hypertension, use of antihypertensive drugs, CKD, BMI, heart rate, DBP, fasting glucose, HbA1c, triglycerides, eGFR, and uric acid were all significantly associated with PAD risk ($p < 0.05$).

3.3 Association Between Lp(a) and Peripheral Arterial Disease

As presented in Table 3, higher Lp(a) concentrations were independently correlated with an increased likelihood of PAD. Without covariate adjustment (Model 1), individuals in the highest tertile (T3) exhibited a markedly greater risk of PAD relative to those in the lowest group (T1), with an OR of 2.533 (95% CI: 1.520–4.222; $p < 0.001$). This association persisted even after comprehensive adjustment in Model 4, which accounted for demographic factors, clinical conditions, and biochemical markers—including age, sex, smoking, hypertension, antihypertensive drugs, CKD, heart rate, BMI, DBP, glucose, HbA1c, triglycerides, eGFR, and uric acid—yielding an adjusted OR of 1.961 (95% CI: 1.071–3.588; $p = 0.029$).

Treating Lp(a) as a continuous metric—whether assessed per unit, on a logarithmic scale, or standardized by SD—consistently revealed a robust link with PAD risk across all regression models. In the crude analysis (Model 1), each 1 mg/L increase in Lp(a) corresponded to an OR of 1.001 (95% CI: 1.001–1.002, $p < 0.001$), with this effect persisting after successive adjustments in Models 2 through 4 ($p < 0.05$). Log-transformation of Lp(a) further strengthened the association, yielding an OR of 2.585 (95% CI: 1.582–4.225, $p < 0.001$) in Model 1. Although attenuation was noted in the fully adjusted model, statistical significance was maintained (OR = 1.803, 95% CI: 1.013–3.209, $p = 0.045$). Similarly, when analyzed per SD, Lp(a) remained a significant predictor of PAD, with Model 1 showing an OR of 1.423 (95% CI: 1.186–1.707, $p < 0.001$), and Model 4 yielding a slightly lower but still meaningful OR of 1.257 (95% CI: 1.016–1.555, $p = 0.035$).

3.4 Stratified Association Between Lp(a) and PAD

As presented in the subgroup analysis (Table 4), elevated Lp(a) levels were significantly linked to increased PAD risk within multiple population strata. In individuals older than 60, those in the highest tertile (T3) exhibited a markedly greater likelihood of developing PAD relative to the lowest tertile (T1), with an OR of 1.869 (95% CI: 1.006–3.469, $p = 0.048$). In male patients, the PAD risk in the T3 group also significantly increased (OR = 2.131, 95% CI: 1.087–4.177, $p = 0.028$). Similarly, in patients with hypertension, the PAD risk in the T3 group was significantly elevated (OR = 1.996, 95% CI: 1.080–3.690, $p = 0.028$). For patients with hyperlipidemia, the OR for PAD in the highest

Table 3. Multivariable logistic regression analysis of Lp(a) and PAD.

	Model 1				Model 2				Model 3				Model 4			
	β	SE	OR (95% CI)	*p*-value	β	SE	OR (95% CI)	*p*-value	β	SE	OR (95% CI)	*p*-value	β	SE	OR (95% CI)	*p*-value
Lp(a): T1			Ref	-			Ref	-			Ref	-			Ref	-
Lp(a): T2	0.453	0.274	1.573 (0.920, 2.690)	0.098	0.322	0.289	1.379 (0.782, 2.432)	0.266	0.226	0.305	1.254 (0.690, 2.278)	0.458	0.296	0.321	1.345 (0.717, 2.522)	0.355
Lp(a): T3	0.930	0.261	2.533 (1.520, 4.222)	<0.001	0.838	0.278	2.311 (1.340, 3.985)	0.003	0.666	0.292	1.947 (1.098, 3.454)	0.023	0.673	0.308	1.961 (1.071, 3.588)	0.029
Lp(a) (per 1-unit)	0.001	0.000	1.001 (1.001, 1.002)	<0.001	0.001	0.000	1.001 (1.000, 1.002)	0.003	0.001	0.000	1.001 (1.000, 1.002)	0.020	0.001	0.000	1.001 (1.000, 1.002)	0.035
Log_{10}Lp(a)	0.950	0.251	2.585 (1.582, 4.225)	<0.001	0.815	0.265	2.259 (1.344, 3.799)	0.002	0.615	0.273	1.850 (1.084, 3.156)	0.024	0.589	0.294	1.803 (1.013, 3.209)	0.045
Lp(a) (per 1-SD)	0.353	0.093	1.423 (1.186, 1.707)	<0.001	0.300	0.101	1.350 (1.108, 1.645)	0.003	0.238	0.102	1.268 (1.038, 1.550)	0.020	0.229	0.108	1.257 (1.016, 1.555)	0.035

Model 1 (baseline): no covariate adjustment; Model 2 (+demographics): Model 1 plus age and sex; Model 3 (+lifestyle/clinical): Model 2 plus smoking status, hypertension, antihypertensive treatment, and CKD; Model 4 (full adjustment): Model 3 plus heart rate, BMI, DBP, fasting glucose, HbA1c, triglycerides, eGFR, and uric acid. Lp(a), lipoprotein(a); PAD, peripheral arterial disease; CKD, chronic kidney disease; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Table 4. Multivariable stratified association between Lp(a) and PAD.

	T2 vs. T1			T3 vs. T1			*p* for trend	*p* for interaction
	β	SE	OR (95% CI) *p*-value	*β*	SE	OR (95% CI) *p*-value		
Age								0.397
≤60 years	–0.058	0.823	0.944 (0.188, 4.738) 0.944	0.986	0.665	2.681 (0.728, 9.874) 0.138	0.203	
>60 years	0.335	0.322	1.398 (0.744, 2.627) 0.298	0.625	0.316	1.869 (1.006, 3.469) 0.048	0.138	
Sex								0.212
Male	–0.175	0.380	0.839 (0.398, 1.769) 0.645	0.756	0.344	2.131 (1.087, 4.177) 0.028	0.013	
Female	0.912	0.539	2.488 (0.866, 7.151) 0.090	0.542	0.544	1.719 (0.591, 4.996) 0.320	0.234	
Hypertension								0.041
Yes	0.088	0.333	1.092 (0.569, 2.098) 0.791	0.691	0.314	1.996 (1.080, 3.690) 0.028	0.045	
No	0.818	0.858	2.267 (0.422, 12.177) 0.340	0.647	0.854	1.909 (0.358, 10.178) 0.449	0.634	
Hyperlipidemia								0.039
Yes	–0.166	0.434	0.847 (0.362, 1.983) 0.702	0.860	0.384	2.364 (1.115, 5.013) 0.025	0.014	
No	0.718	0.426	2.050 (0.890, 4.724) 0.092	0.669	0.430	1.953 (0.841, 4.534) 0.119	0.198	
CKD								0.786
Yes	0.116	0.522	1.123 (0.404, 3.124) 0.824	0.177	0.491	1.194 (0.456, 3.128) 0.718	0.936	
No	0.289	0.389	1.336 (0.623, 2.863) 0.457	0.908	0.375	2.479 (1.189, 5.170) 0.015	0.040	

OR, odds ratio; CI, confidence interval; PAD, peripheral arterial disease; Lp(a), lipoprotein(a); CKD, chronic kidney disease.

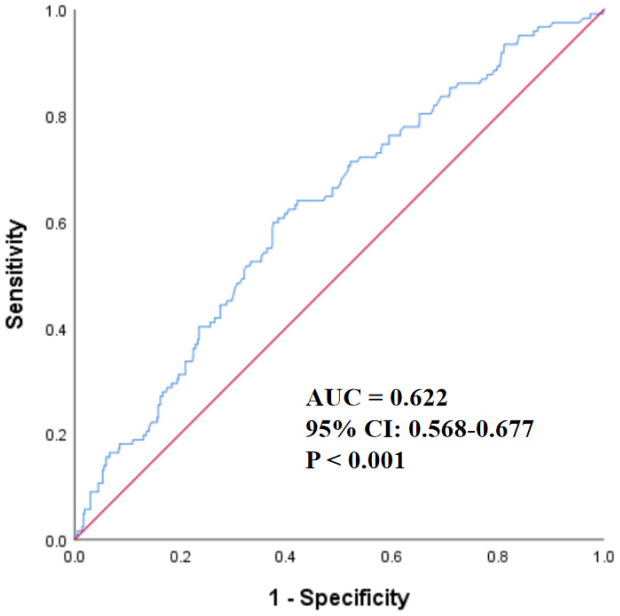

Fig. 2. The ROC curve of Lp(a) for predicting PAD. The ROC curve, depicted in blue, reflected the diagnostic performance of Lp(a), whereas the red diagonal served as the reference line (AUC = 0.5). With an AUC of 0.622 (95% CI: 0.568–0.677; $p < 0.001$), Lp(a) demonstrated limited but statistically significant capacity to distinguish individuals with PAD. ROC, receiver operating characteristic; PAD, peripheral arterial disease; Lp(a), lipoprotein(a); AUC, area under the curve; CI, confidence interval.

Lp(a) tertile (T3) was 2.364 (95% CI: 1.115–5.013, p = 0.025). Likewise, among those without CKD, the T3 group showed a similarly elevated PAD risk, with an OR of 2.479 (95% CI: 1.189–5.170, p = 0.015).

3.5 ROC Analysis of Lp(a) for Predicting PAD

As shown in Fig. 2, the ROC curve demonstrated the discriminative capacity of Lp(a) for identifying PAD. The AUC reached 0.622 (95% CI: 0.568–0.677; $p < 0.001$), suggesting a statistically significant yet modest predictive performance. An optimal threshold of 279 mg/L was identified, corresponding to 59.8% sensitivity and 62.4% specificity.

3.6 The Linear Association Between Lp(a) and PAD

As illustrated in Fig. 3, a strong linear relationship between Log_{10}Lp(a) and PAD risk was observed in Model 1 (unadjusted), with statistical significance ($p < 0.001$) and no indication of nonlinearity (p for nonlinearity = 0.437). This pattern remained evident after controlling for age and sex in Model 2 (p = 0.004; p for nonlinearity = 0.386). Even with further adjustments in Model 3—including smoking status, hypertension, antihypertensive therapy, and CKD—the association persisted (p = 0.029), and the linear trend remained (p for nonlinearity = 0.367). Finally, in Model 4, which included full adjustments for heart rate, BMI, DBP, fasting glucose, HbA1c, triglycerides, eGFR, and uric acid, the significant association continued (p = 0.031) without nonlinearity (p for nonlinearity = 0.266).

4. Discussion

In individuals with T2DM, higher Lp(a) levels were independently linked to a greater prevalence of PAD. Multivariate logistic regression, adjusted for relevant confounders, revealed that those with elevated Lp(a) had nearly twice the odds of developing PAD (OR = 1.961). Notably, the risk increased by 25.7% with each SD rise in Lp(a), and by approximately 80.3% for every unit increment in its log-

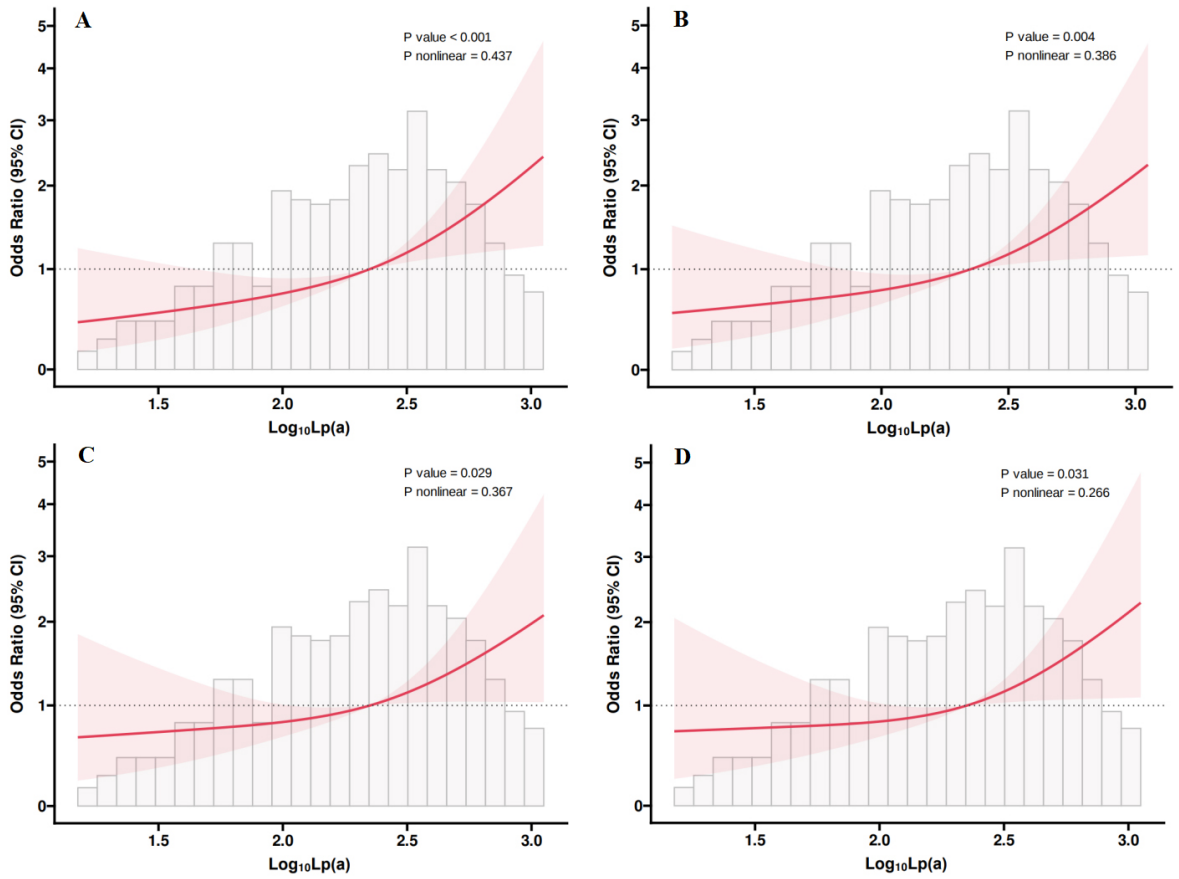

Fig. 3. The restricted cubic spline plots of Lp(a) with PAD in four models. The x-axis represented Log_{10}-transformed Lp(a) concentrations, while the y-axis showed the OR with 95% CI for PAD. The red solid lines indicated the fitted spline curves, shaded areas represented the 95% CI, and the grey bars displayed the distribution of participants. A significant association between Lp(a) and PAD risk was found in all models, with no indication of nonlinearity (p for nonlinearity > 0.05). (A) Model 1 (baseline): no covariate adjustment. (B) Model 2 (+demographics): Model 1 plus age and sex. (C) Model 3 (+lifestyle/clinical): Model 2 plus smoking status, hypertension, antihypertensive treatment, and CKD. (D) Model 4 (full adjustment): Model 3 plus heart rate, body mass index, diastolic blood pressure, fasting glucose, hemoglobin A1c, triglycerides, estimated glomerular filtration rate, and uric acid. Lp(a), lipoprotein(a); PAD, peripheral arterial disease; OR, odds ratio; CI, confidence interval.

transformed form. Subgroup analysis confirmed this association across sex, age, hypertension, and hyperlipidemia. ROC analysis showed weak but statistically significant predictive power. RCS analysis further confirmed a significant relationship between Log_{10}Lp(a) and PAD risk, with no evidence of non-linearity.

Extensive evidence supports the role of Lp(a) in promoting atherosclerotic disease and implicates it as a standalone contributor to cardiovascular pathology [27–29]. However, studies on the relationship between Lp(a) and PAD are relatively few, particularly in T2DM patients. For example, Laschkolnig *et al.* [16] found that Lp(a) concentration, low molecular weight apo(a) phenotype, and the rs10455872 polymorphism were significantly associated with PAD across three cohorts. Mendelian randomization further supported a causal link driven by genetically determined apo(a) traits and single nucleotide polymorphism (SNP) variants. Forbang *et al.* [17] also showed that despite higher Lp(a) levels in African Americans, a significant independent association with PAD was found only in Hispanic Americans, highlighting the need for further research on Lp(a)-lowering interventions in this population. Additionally, in a dose-response meta-analysis, Wang *et al.* [30] identified a linear increase in PAD risk, estimating a 6% elevation for every 10 mg/dL increment in Lp(a). Yi *et al.* [31] reported that this relationship was sex-specific, showing statistical significance exclusively in women. In a large-scale cohort comprising 108,146 participants, Thomas *et al.* [32] reported a two- to threefold heightened risk of both PAD and major adverse limb events among individuals with elevated Lp(a). Besides, Okubo *et al.* [33], studying patients with acute coronary syndrome, noted that increased Lp(a) concentrations were linked to both the presence and severity of lower-limb PAD. A comprehensive systematic review by Masson *et al.* [18], covering over 490,000 subjects, further established associations between

elevated Lp(a) and a wide spectrum of PAD-related complications, including intermittent claudication, restenosis, disease progression, amputation, revascularization, hospital admissions, and PAD-related mortality. And, Gazzaruso *et al.* [19] found that Lp(a) levels varied by diabetic foot type, being elevated in vascular diabetic foot with PAD and decreased in neuropathic diabetic foot, suggesting a bidirectional role of Lp(a) in both vascular damage and impaired wound healing. Moreover, although Tseng [34], in a limited-sample investigation focused on individuals with T2DM, reported a link between elevated Lp(a) and both greater risk and severity of PAD. However, the analysis did not incorporate systematic subgroup evaluations or explore potential nonlinear associations. In conclusion, prior investigations have not definitively established a positive link between Lp(a) and PAD among individuals with T2DM. In contrast, the present study reinforces this association using robust multivariable approaches, thereby addressing an existing gap in the literature. By integrating multiple statistical techniques, the analysis offers a more nuanced perspective on how elevated Lp(a) relates to PAD prevalence in this patient population. Importantly, RCS modeling indicated a linear association, with no evidence of nonlinearity, underscoring the need for future research to explore this relationship across broader demographic and clinical subgroups.

Several biological mechanisms may underlie the relationship between Lp(a) and PAD. First, Lp(a), as a lipoprotein particle, is structurally similar to LDL but contains the specific apo(a) protein [15]. This makes Lp(a) not only atherogenic like LDL but also capable of promoting thrombosis through its apo(a) component [35]. Studies have shown that Lp(a) can accelerate the atherosclerotic process by enhancing lipid deposition, inducing endothelial dysfunction, and promoting inflammation [15,35–37]. Moreover, Lp(a) impairs fibrinolysis, thereby enhancing thrombosis risk [15]. In diabetic patients, the risks of atherosclerosis and thrombosis are higher, likely due to vascular damage and inflammation caused by long-term elevated blood glucose levels [38]. Lp(a) may aggravate these pathological mechanisms, which could help explain the pronounced link observed between elevated Lp(a) and PAD in individuals with T2DM. This outcome indicates that patients with T2DM—especially those exhibiting high Lp(a) concentrations—are potentially more susceptible to developing PAD.

Several limitations should be acknowledged in this study. First, its retrospective nature precludes any inference of causality between Lp(a) levels and PAD. Future longitudinal research is necessary to explore the temporal sequence of this relationship. Second, important confounding variables—such as lifestyle factors and dietary behaviors—were not evaluated and may have influenced the outcomes. Third, although a significant association between Lp(a) and PAD was observed, its ability to discriminate PAD cases was suboptimal. The area under the ROC curve was 0.622, reflecting limited predictive strength. This may be due to the multifactorial nature of PAD pathogenesis, which involves numerous metabolic, inflammatory, and vascular mechanisms. As Lp(a) represents only one of these factors, its predictive capacity on its own is inherently limited. Therefore, Lp(a) may not be sufficient as a standalone predictive tool for PAD but could serve as a supportive risk factor when used in combination with other clinical indicators. Moreover, as the study population was limited to individuals with T2DM, the results may not be applicable to non-diabetic groups. Future research should aim to broaden the sample scope to investigate the Lp(a)–PAD relationship across more diverse populations.

5. Conclusion

In summary, this investigation highlights a clear link between increased Lp(a) concentrations and the prevalence of PAD among individuals with T2DM. Further studies are warranted to assess this relationship in broader populations and to examine whether reducing Lp(a) levels could contribute to PAD prevention.

Key Points

- A significant relationship has been identified between Lp(a) levels and PAD prevalence among T2DM patients.
- Multivariable logistic regression and RCS analyses confirm an independent relationship between Lp(a) and PAD risk.
- Subgroup analyses show consistent associations across age, sex, and comorbidity groups.
- The use of Lp(a) as a risk stratification tool for PAD in T2DM populations may offer clinical value.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

CC designed and performed the research. CC analyzed the data and drafted the manuscript. FL designed the research, reviewed and revised the manuscript. Both authors contributed to revising the manuscript critically for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of Hefei First People's Hospital [Approval No. 2022 (74)], and all participants provided written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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