Biscetti *et al. Cardiovascular Diabetology* (2025) 24:271
https://doi.org/10.1186/s12933-025-02833-2

Cardiovascular Diabetology

RESEARCH Open Access

Prognostic value of lipoprotein(a) for cardiovascular events after lower limb revascularization in diabetic patients with chronic limb-threatening ischemia

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Abstract

Background Chronic limb-threatening ischemia (CLTI) presents a major clinical challenge in patients with Type 2 Diabetes Mellitus (T2DM), requiring lower extremity revascularization (LER) to mitigate adverse cardiovascular and limb outcomes. Lipoprotein(a) (Lp(a)) has been implicated in cardiovascular risk, but its role in patients with T2DM and CLTI undergoing revascularization remains unclear. Thus, this study aimed to investigate the prognostic value of Lp(a) levels in diabetic CLTI patients for major adverse cardiovascular events (MACE), major adverse limb events (MALE), or both after LER.

Methods In this prospective cohort study of 158 individuals with T2DM and CLTI undergoing LER, baseline clinical data were collected, including Lp(a) levels. Patients were followed for occurrence of MACE, MALE, or both over a 12-month period.

Results During follow-up, 74 patients (46.8%) experienced events (MACE, MALE, or both). Patients with events had significantly higher median Lp(a) levels than those without (48.0 vs. 8.1 mg/dL, $p < 0.01$). Lp(a) was independently associated with adverse events (HR 1.07, 95% CI 1.04–1.10; $p < 0.01$). In multivariable analysis, elevated Lp(a) was independently associated with both MACE (HR 1.08, 95% CI 1.03–1.13; $p < 0.01$) and MALE (HR 1.05, 95% CI 1.02–1.07; $p < 0.01$). An empirical Lp(a) cutoff of 29.6 mg/dL conferred a 3.8-fold increased risk of events ($p < 0.01$). Kaplan–Meier survival analysis further confirmed a significantly higher cumulative incidence of events in patients with Lp(a) levels above cutoff ($p < 0.01$). ROC curve comparison analysis showed that the inclusion of Lp(a) significantly improved the predictive performance of the base clinical model (AUC from 0.74 to 0.98, $p < 0.01$ for composite outcome; from 0.81 to 0.89, $p = 0.03$ for MACE; and from 0.78 to 0.92, $p < 0.01$for MALE).

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Conclusions This study demonstrated that Lp(a) is a strong independent predictor of both cardiovascular and limb events in patients with T2DM undergoing LER for CLTI. These findings support the potential role of Lp(a) as a marker of residual risk in this high-risk population and suggest its utility in risk stratification.

Keywords Peripheral artery disease (PAD), Lipoprotein(a) (Lp(a)), Major adverse cardiovascular events (MACE), Major adverse limb events (MALE)

Background

Peripheral artery disease (PAD) affects over 235 million individuals globally and it is characterized by atherosclerosis of non-coronary arteries [1]. Type 2 Diabetes Mellitus (T2DM) exacerbates PAD progression and severity, heightening the risk of ischemic events and amputations [2]. Consequently, early detection of PAD in patients with T2DM is crucial to mitigate cardiovascular complications [3, 4]. A primary complication of PAD is chronic limb-threatening ischemia (CLTI), often leading to tissue loss and major amputations, necessitating revascularization and complex medical management [3]. Even with optimal treatment, individuals with PAD and CLTI face an elevated risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) after lower extremity revascularization (LER) [5, 6].

In recent years, identifying determinants of residual cardiovascular risk has become pivotal for implementing innovative and personalized treatment strategies aimed at reducing adverse cardiovascular outcomes [7]. Our prior research has highlighted the association between inflammation, factors related to calcium homeostasis, and adverse cardiovascular events [3, 4, 8–14]. Additionally, non-LDL-cholesterol (LDL-c) lipids particles have emerged as residual cardiovascular risk factors [7].

There is compelling evidence that Lipoprotein(a) (Lp(a)) is one of the key lipid molecules responsible for initiation and progression of the atherosclerotic process [15, 16]. Initially studied in the 1970s, the utility of Lp(a) as a biomarker predictor of disease faced setbacks due to measurement challenges and uncertainty about its biological role [17]. However, the advent of large-scale epidemiological studies, genome-wide association studies (GWAS), and Mendelian randomization analyses—together with advancements in immunoassay techniques—prompted a renewed recognition of Lp(a) as a significant cardiovascular risk factor [17, 18]. Lp(a) levels remain stable throughout life, being genetically determined and not influenced by lifestyle [17]. Its plasma concentration is determined by the Lp(a) gene alleles, encoding the apolipoprotein(a) (apo(a)) unit. The size of apo(a) is dependent on the number of kringle IV repeats encoded in the Lp(a) gene, with larger particles associated with lower plasma levels of Lp(a) [17]. Studies have demonstrated the association between elevated Lp(a) levels and increased risk of coronary heart disease, stroke, and adverse cardiovascular events [19, 20]. High Lp(a) levels have been linked to the incidence and progression of PAD, as well as restenosis after endovascular revascularization too [21–27]. In addition, higher Lp(a) concentration are associated with an increased risk of cardiovascular events in patients with T2DM [28, 29].

These considerations suggest it is plausible that Lp(a) levels contribute to the risk of atherosclerotic disease progression and the occurrence of major adverse events in diabetic patients with PAD and CLTI requiring LER. Therefore, this prospective study was designed to investigate the potential role of Lp(a) as a prognostic biomarker for cardiovascular outcomes after LER in diabetic patients with PAD and CLTI.

Methods

Aim and study design

This is a prospective cohort study that aimed at evaluating the association between Lp(a) serum levels and the incidence of MACE and MALE in a population of diabetic patients with PAD and CLTI, requiring LER. The Ethics Committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS approved the study that adhered to the principles of the Declaration of Helsinki. All included patients gave informed consent to participate.

Study population and clinical assessment

A total of 172 consecutive patients with T2DM and CLTI admitted to Internal Medicine Cardiovascular Unit of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, from October 23, 2019, to November 26, 2022, were initially screened for inclusion. Of these, 9 patients were excluded based on predefined inclusion/exclusion criteria, and 5 patients were excluded due to failed revascularization procedures. The final study population consisted of 158 patients who successfully underwent LER and were prospectively followed.

Patients over 18 years old who were diagnosed with T2DM for at least 1 year were included in the study if they met the following inclusion criteria: patients with ankle/brachial index (ABI) less than 0.80 and lower-limb stenosis greater than 50% documented by color Doppler Ultrasonography (US), PAD category 4 or 5 according to the Rutherford classification [30], the presence of CLTI as already defined [11], and indication for endovascular treatment. Exclusion criteria were pregnancy; diabetic neuropathy; chronic kidney disease with an estimated glomerular filtration rate (eGFR) less than 30 ml/min

according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; lower extremity surgical or endovascular revascularization in the last month; active solid tumor or hematologic malignancy; organ or bone marrow transplant; life expectancy less than 12 months; acute infectious diseases at enrollment or within the last two weeks; autoimmune diseases; liver disease classified as Child–Pugh B or C; known or suspected monogenic hereditary dyslipidemias; acquired or congenital thrombocytopenia or thrombophilia; contraindications to antiplatelet therapy; known congenital bleeding disorders or acquired coagulation disease; presence of atrial fibrillation or other clinical indications requiring chronic full-dose anticoagulation (e.g., venous thromboembolism, pulmonary embolism), which would have precluded the safe administration of dual antiplatelet therapy (DAPT); contraindications to endovascular revascularization; and failure of the revascularization procedure to address the targeted lesion.

To exclude patients with neuropathic diabetic foot, all participants underwent a standardized evaluation for diabetic neuropathy, as previously described [11]. Briefly, vibration perception threshold was measured using a biothesiometer, and peripheral neuropathy was diagnosed based on a Neuropathy Disability Score > 5 and abnormal nerve conduction velocity. Autonomic neuropathy was assessed using the cardiovascular reflex tests described by Ewing and Clarke [31].

When suspected, radiographic imaging was performed to rule out osteomyelitis. The definition of PAD conformed to the standards of the Society for Vascular Surgery and the International Society of Cardiovascular Surgery [32]. Lower extremity ultrasonography was performed on all patients in the study. In individuals with an ABI of 1.40 or higher, ultrasound was used to confirm the presence of severe lower extremity stenosis.

Data collected included age, sex, body mass index (BMI), duration of T2DM, smoking status, history of hypertension (defined as blood pressure ≥ 140/90 mmHg or antihypertensive treatment), hypercholesterolemia (defined as total cholesterol > 200 mg/dL or lipid-lowering therapy), coronary artery disease (CAD) (defined as defined as prior MI, angina, or coronary revascularization), cerebrovascular disease (CVD) (prior ischemic or hemorrhagic stroke), ABI, Rutherford classification, medications and laboratory test results. On admission, the patient received single antiplatelet therapy, which was expanded to DAPT one month after revascularization. All patients received statins, ezetimibe, or both as part of lipid-lowering therapy. According to the ESC/EAS dyslipidemia treatment guidelines, after revascularization, the goal of lipid-lowering therapy modification is an LDL-c target level of less than 55 mg/dL [33].

Lower-limb endovascular revascularization and follow-up after the procedure

LER was performed by balloon angioplasty, stent placement, or both, as previously described [11, 34, 35]. Revascularization was considered successful if the residual stenosis of the arterial vessel after treatment was less than 30%. No complications related to endovascular procedures were recorded according to the Society of Interventional Radiology definition [36].

The incidence of MACE, MALE, or both was determined during a 12-month follow-up period, evaluating patients 1, 3, 6, and 12 months after the revascularization. MACE was defined as the combination of cardiovascular death, stroke, or myocardial infarction [37]. MALE was defined as the combination of acute limb ischemia, major vessel amputation, and limb-threatening ischemia leading to urgent revascularization [37, 38].

Blood test and biochemical assays

All patients participating in the study had blood tests performed after an overnight fast at baseline before revascularization. Total cholesterol, LDL-c, triglycerides, fasting blood glucose (FBG), creatinine, and glycated hemoglobin were assessed. eGFR was calculated by the CKD-EPI formula. Serum was separated by centrifugation of blood samples and stored at − 80 °C before each analysis. Lp(a) levels were determined using a commercially available ELISA kit EH0660 (Finetest, Wuhan Fine Biotech) according to its protocol. Samples exceeding the assay range were diluted, and final concentrations were adjusted accordingly. The precision of these measurements was reflected in the intra-assay and inter-assay coefficients of variation, which were 3.5% and 10.5%, respectively. The assay's sensitivity was determined to be 0.188 ng/mL, based on the mean ± 3 standard deviations of the 0 standard. Serum levels were quantified twice for each patient, and the measurements were averaged for accuracy.

Statistical analysis

The required sample size was estimated based on the assumption of a medium effect size (Cohen's $f^2 = 0.15$), an alpha level of 0.05, a power of 80%, and the inclusion of up to 15 predictors in multivariable analysis. This yielded a minimum required sample of 149 participants. In the descriptive analyses, continuous variables were summarized as means with standard deviations (SD) when normally distributed, or as medians with interquartile ranges (IQR, 25th–75th percentile) for non-normal distributions. Categorical variables were expressed as absolute and relative frequencies. Between-group comparisons (event vs. no event) were performed using the two-sample t test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normal

variables, and the Pearson chi-squared test for categorical variables. Univariable logistic regression models were constructed to explore associations between each baseline variable and the composite endpoint. Variables with $p < 0.05$ in univariable analyses, and variance inflation factor (VIF) < 5, along with clinically relevant covariates, were included in multivariable logistic regression models to identify independent predictors of outcome. A Cox proportional hazards model was also applied for time-to-event analyses, with proportionality of hazards assessed through Schoenfeld residuals and global tests. Missing data were handled using a complete case approach. For all multivariable models (logistic and Cox regression), only patients with complete information on the covariates included in each model were considered. For Cox models, complete data on follow-up time and event status were also required. No imputation was performed. To reduce the risk of overfitting, stepwise backward selection based on the Akaike Information Criterion (AIC) was applied. Lp(a) was retained in all models as a pre-specified variable of interest. To account for the non-normal distribution of Lp(a), multivariable logistic regression was additionally performed using log-transformed Lp(a) as a covariate. The discriminative performance of baseline Lp(a) levels was evaluated using receiver operating characteristic (ROC) curve analysis, with area under the curve (AUC) reported. Internal validation of the model's discriminative performance was performed using bootstrap resampling with 1,000 iterations, based on the Somers' D transformation of the ROC area. The optimal threshold for Lp(a) was derived using the Youden index to maximize sensitivity and specificity. Kaplan–Meier survival curves were generated to visualize time to events stratified by the optimal Lp(a) cutoff, and statistical differences between groups were tested using the log-rank test. Furthermore, a Cochran–Armitage test for trend was conducted to assess the presence of a linear association between increasing Lp(a) tertiles and the proportion of patients experiencing events. To evaluate the added predictive value of baseline Lp(a) levels for adverse cardiovascular outcomes, we constructed two logistic regression models. The baseline model included conventional cardiovascular risk factors: age, sex, BMI, duration of T2DM, history of smoking, hypertension, hypercholesterolemia, CAD, CVD, ABI, Rutherford classification, FBG, HbA1c, LDL-c, and renal function. The extended model included all these variables plus baseline Lp(a) as a continuous predictor. The AUCs were then compared using the roccomp command in STATA, which implements DeLong's test for two correlated ROC curves. Model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test, with patients grouped into deciles of predicted risk. All analyses were performed using STATA version 18.0 for MacOS (Statistics/Data Analysis, Stata Corporation, College Station, TX, USA) and SPSS version 25.0 for MacOS (IBM Corporation, Armonk, NY, USA). Statistical significance was determined at $p < 0.05$.

Results

Characteristics of the study population

The final study cohort included 158 patients with T2DM and CLTI, of whom 68% were male. The mean age was 74.8 ± 9.2 years, and the median duration of T2DM was 15.5 years (IQR 5–29.2). Most patients had significant cardiovascular risk factors, including hypertension (79.7%), hypercholesterolemia (91.8%), CAD (46.8%), and CVD (18.6%). Regarding glycemic control, 45.5% were on insulin therapy, and 48.8% were taking oral antidiabetic agents. Statins were used in 70.9% of patients, while 32.3% were on ezetimibe. Antiplatelet therapy included aspirin in 58.2%, and clopidogrel in 30.4% of patients. The median HbA1c was 7.0% (IQR 6.2–8.0), and the median FBG was 121 mg/dL (IQR 96.5–150.0). Renal function was moderately preserved with a median eGFR of 84.4 mL/min/1.73 m^2. PAD severity was advanced, with a median ABI of 0.39 (IQR 0.33–0.45), and most patients presented with Rutherford stage III-5 (59.5%). The median Lp(a) level at baseline was 19.9 mg/dL (IQR 7.4–46.7). All baseline demographic and clinical characteristics are summarized in Table 1.

Lp(a) levels and incidence of cardiovascular events after LER

Among the 158 patients included in the study, 74 (46.8%) experienced MACE, MALE, or both during follow-up. Table 2 presents a comparison of baseline clinical characteristics between these two groups. Patients who experienced adverse events had a significantly longer duration of T2DM (20 vs. 11.5 years, $p = 0.01$), were more frequently treated with insulin (60.3% vs. 32.5%, $p < 0.01$), and had higher prevalence of CVD (26.4% vs. 11.9%, $p = 0.02$). Conversely, oral antidiabetic drug use was more frequent among those without events (56.6% vs. 38.4%, $p = 0.04$). Regarding disease severity, patients with MACE, MALE, or both were more likely to present with Rutherford stage III-5 (72.9% vs. 47.6%, $p < 0.01$), indicating more advanced limb ischemia. HbA1c levels were significantly higher in the event group (7.5% vs. 6.8%, $p < 0.05$), and serum creatinine was also elevated (1.1 vs. 0.9 mg/dL, $p = 0.03$). A notable difference was observed in Lp(a) levels, which were substantially higher in individuals who experienced MACE, MALE, or both (48.0 vs. 8.1 mg/dL, $p < 0.01$).

In the multivariable logistic regression model assessing predictors of the composite outcome (MACE, MALE, or both), Lp(a) levels emerged as a significant independent predictor ($p < 0.01$), confirming a strong association

Table 1 Demographic characteristics and clinical data of the study cohort at baseline

Number of patients	158
Men/female, n	108:50
Age, years ± SD	74.8 ± 9.2
Diabetes duration, years (IQR)	15.5 (5–29.2)
BMI, Kg/m^2 (IQR)	25.6 (23.1–28.7)
Smoking (current), n (%)	35 (22.3)
Smoking (former), n (%)	84 (53.5)
Never smoked, n (%)	39 (24.8)
Hypertension, n (%)	126 (79.7)
Hypercholesterolemia, n (%)	145 (91.8)
CAD, n (%)	74 (46.8)
CVD, n (%)	29 (18.6)
Insulin, n (%)	71 (45.5)
Oral antidiabetics, n (%)	75 (48.8)
Statins, n (%)	112 (70.9)
Ezetimibe, n (%)	51 (32.3)
ACEi/ARB, n (%)	93 (58.9)
Other antihypertensive, n (%)	74 (46.8)
Aspirin, n (%)	92 (58.2)
Clopidogrel, n (%)	48 (30.4)
Low dose rivaroxaban, n (%)	3 (1.9)
ABI, (IQR)	0.39 (0.33–0.45)
Rutherford II-4, n (%)	63 (39.9)
Rutherford III-5, n (%)	94 (59.5)
HbA1c, % (IQR)	7.0 (6.2–8.0)
FBG, mg/dL (IQR)	121.0 (96.5–150.0)
Total cholesterol, mg/dL (IQR)	127.0 (109.0–152.0)
LDL cholesterol, mg/dL (IQR)	65.5 (47.0–84.0)
Triglycerides, mg/dL (IQR)	105.0 (82.2–137.7)
Creatinine, mg/dL (IQR)	1.0 (0.8–1.5)
eGFR, mL/min/1.73m^2 (IQR)	84.4 (67.5–93.3)
Lp(a), mg/dL (IQR)	19.9 (7.4–46.7)

The data are reported as the means ± standard deviations or median (interquartile range, IQR, 25–75) for continuous variables and as numbers (percentages) for categorical variables, without the percent symbol, for consistency with other data formats. BMI, Body Mass Index; CAD, Coronary Artery Disease; CVD, Cerebrovascular Disease; ACEi/ARB, angiotensin converting enzyme inhibitors / angiotensin receptor blockers; ABI, Ankle Brachial Index; FBG, Fasting Blood Glucose; eGFR, estimated Glomerular Filtration Rate

Table 2 Demographic and clinical data of study participants without or with events

	NO EVENTS (*n* = 84)	EVENTS (*n* = 74)	*p* value
Male: female, n	58:26	50:24	0.84
Age, years ± SD	75.6 ± 8.7	73.8 ± 9.7	0.23
Diabetes duration, years (IQR)	11.5 (1.25–23)	20 (9.25–30)	0.01
BMI, Kg/m^2 (IQR)	25.6 (22.7–28.7)	25.9 (23.3–28.5)	0.29
Smoking (current), n (%)	18 (21.7)	17 (22.3)	0.85
Smoking (former), n (%)	44 (53.0)	40 (47.6)	0.89
Never smoked, n (%)	22 (26.5)	17 (22.9)	0.60
Hypertension, n (%)	67 (79.8)	59 (79.7)	0.99
Hypercholesterolemia, n (%)	75 (89.3)	70 (94.6)	0.22
CAD, n (%)	35 (41.7)	39 (52.7)	0.16
CVD, n (%)	10 (11.9)	19 (26.4)	0.02
Insulin, n (%)	27 (32.5)	44 (60.3)	< 0.01
Oral antidiabetics, n (%)	47 (56.6)	28 (38.4)	0.04
Statins, n (%)	57 (67.9)	55 (74.3)	0.37
Ezetimibe, n (%)	26 (30.9)	25 (33.8)	0.70
ACEi/ARB, n (%)	52 (61.9)	41 (55.4)	0.40
Other antihypertensive, n (%)	41 (48.8)	33 (44.6)	0.59
Aspirin, n (%)	45 (53.6)	47 (63.5)	0.20
Clopidogrel, n (%)	20 (23.8)	28 (37.8)	0.06
Low dose rivaroxaban, n (%)	3 (3.6)	0	0.10
ABI, (IQR)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.71
Rutherford II-4, n (%)	43 (51.2)	20 (27.0)	< 0.01
Rutherford III-5, n (%)	40 (47.6)	54 (72.9)	< 0.01
HbA1c, % (IQR)	6.8 (6.2–7.8)	7.5 (6.5–8.4)	< 0.05
FBG, mg/dL (IQR)	118 (95–142)	123 (99.75–159)	0.16
Total cholesterol, mg/dL (IQR)	132 (114–159)	122.5 (105.25–140)	0.12
LDL cholesterol, mg/dL (IQR)	70 (52–89.75)	58.5 (42.5–78.75)	0.07
Triglycerides, mg/dL (IQR)	107 (75–141)	105 (86–130)	0.91
Creatinine, mg/dL (IQR)	0.9 (0.8–1.3)	1.1 (0.9–1.9)	0.03
eGFR, mL/min/1.73m^2 (IQR)	87.5 (74.7–94.8)	79.3 (62.9–91.5)	0.09
Lp(a), mg/dL (IQR)	8.1 (3.7–18.5)	48.0 (27.6–59.9)	< 0.01

The data are reported as the means ± standard deviations or median (interquartile range 25–75) for continuous variables and as numbers (percentages) for categorical variables, without the percent symbol, for consistency with other data formats. Variables expressed as mean ± SD were compared using Student's t test; those expressed as median (IQR) were compared using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-square test. BMI, Body Mass Index; CAD, Coronary Artery Disease; CVD, Cerebrovascular Disease; ACEi/ARB, angiotensin converting enzyme inhibitors / angiotensin receptor blockers; ABI, Ankle Brachial Index; FBG, Fasting Blood Glucose; eGFR, estimated Glomerular Filtration Rate

with adverse events. Among the other covariates, insulin therapy was also significantly associated with the occurrence of events ($p < 0.05$), whereas the other variables did not show statistically significant associations. All regression coefficients and confidence intervals are detailed in Table 3. To address potential overfitting in the multivariable analysis, we performed a stepwise logistic regression based on the AIC, retaining Lp(a) as a pre-specified covariate of interest. The final model included only Lp(a) and insulin therapy as independent predictors of the composite outcome (Table S1). Lp(a) remained significantly associated with adverse events (OR: 1.15 per 1 mg/dL, 95% CI: 1.10–1.22, $p < 0.001$), supporting the robustness of our primary findings. When modelled as a log-transformed variable, Lp(a) remained strongly associated with the composite outcome (OR: 11.7; 95% CI: 4.4–30.9; $p < 0.001$), confirming the robustness of the association (Table S2).

In the multivariable Cox regression analysis evaluating time-to-event for the composite outcome, Lp(a) levels remained independently associated with an increased risk of events, with a hazard ratio (HR) of 1.07 per 1 mg/dL increase ($p < 0.01$; 95% CI: 1.04–1.10). Other

Table 3 Multivariable logistic regression for events

	Coef.	St.Err.	t-value	*p*-value	[95% Conf	Interval]	Sig
Diabetes duration	−0.012	0.035	-0.35	0.724	−0.082	0.057	
CVD	1.397	0.981	1.42	0.154	−0.525	3.32	
Insulin	1.843	0.939	1.96	0.05	0.003	3.683	*
Oral antidiabetics	−0.017	0.789	-0.02	0.983	-1.564	1.53	
Rutherford II-4	-1.004	0.791	-1.27	0.204	-2.554	0.545	
Rutherford III-5	0	.	.	.	.	.	
HbA1c	0.174	0.334	0.52	0.602	−0.48	0.828	
Creatinine	0.414	0.341	1.22	0.224	−0.254	1.082	
Lp(a)	0.141	0.028	4.95	0	0.085	0.197	**
Constant	-6.069	2.682	-2.26	0.024	-11.326	−0.813	*
Mean dependent var		0.474			SD dependent var		0.502
Pseudo r-squared		0.657			Number of obs		114
Chi-square		103.559			Prob > chi2		0.000
Akaike crit. (AIC)		72.162			Bayesian crit. (BIC)		96.788

Table 4 Regression results for events

	Haz. ratio	St.Err.	z	*p*-value	[95% Conf	Interval]	Sig
Diabetes duration	1.041	.019	2.20	.028	1.004	1.078	*
CVD	2.673	1.183	2.22	.026	1.123	6.362	*
Insulin	.778	.36	-0.54	.588	.314	1.929	
Oral antidiabetics	1.043	.399	0.11	.912	.493	2.208	
Rutherford II-4	.239	.119	-2.88	.004	.09	.633	**
Rutherford III-5	1	.	.	.	.	.	
HbA1c	.916	.106	-0.76	.447	.73	1.149	
Creatinine	.999	.071	-0.02	.984	.869	1.147	
Lp(a)	1.07	.013	5.43	0	1.044	1.096	**
Mean dependent var		122.173			SD dependent var		87.989
Pseudo r-squared		0.164			Number of obs		52
Chi-square		51.050			Prob > chi2		0.000
Akaike crit. (AIC)		276.122			Bayesian crit. (BIC)		291.732

significant predictors included T2DM duration, with an HR of 1.041 ($p = 0.03$), and history of CVD, associated with a 2.67-fold increased risk ($p = 0.03$). All hazard ratios, confidence intervals, and significance values are reported in Table 4.

Figure 1 shows the ROC curve assessing the predictive performance of Lp(a) levels for the composite outcome of MACE, MALE, or both. The AUC was 0.90 (95% CI: 0.85–0.95), indicating good discriminative ability of Lp(a) in identifying patients at higher risk of adverse events. Using the ROC analysis, a cutoff value for Lp(a) was identified at 29.6 mg/dL for predicting the occurrence of MACE, MALE, or both. At this threshold, the sensitivity was 73% and the specificity was 71%, with a corresponding discriminative value of 0.72. Figure 2 illustrates the Kaplan-Meier event-free survival curves for patients stratified by Lp(a) cutoff of 29.6 mg/dL. Individuals with higher Lp(a) levels experienced a significantly faster decline in event-free survival compared to those with lower levels. The log-rank test confirmed a statistically significant difference in survival distributions between the two groups ($p < 0.01$), indicating that higher Lp(a) is a strong predictor of reduced event-free survival. The cutoff of 29.6 mg/dL for Lp(a) was incorporated into the Cox model to assess its prognostic impact on MACE, MALE, or both (Table 5). Patients with Lp(a) > 29.6 mg/dL had a 3.79-fold increased risk of adverse events compared to those below this threshold (95% CI 1.55–9.27; $p = 0.004$), confirming its independent predictive value. Among other variables, T2DM duration (HR 1.04, 95% CI 1.00–1.07; $p = 0.03$) and CVD (HR 2.35, 95% CI 0.96–5.74; $p = 0.06$) showed associations with the composite outcome, while Rutherford II-4 staging was linked to a significantly lower risk (HR 0.18, $p < 0.01$).

To further evaluate the relationship between Lp(a) levels and the risk of adverse events, patients were stratified into three tertiles based on Lp(a) concentrations. The Cochran–Armitage test for trend confirmed a significant progressive increase in event rates across tertiles. Event rates increased progressively across Lp(a) tertiles, from 10.2% in the lowest to 40.8% in the middle, reaching 93.8% in the highest tertile. The trend test was highly significant ($Z = 8.23$, $p < 0.01$), indicating a strong association between increasing Lp(a) levels and adverse outcomes.

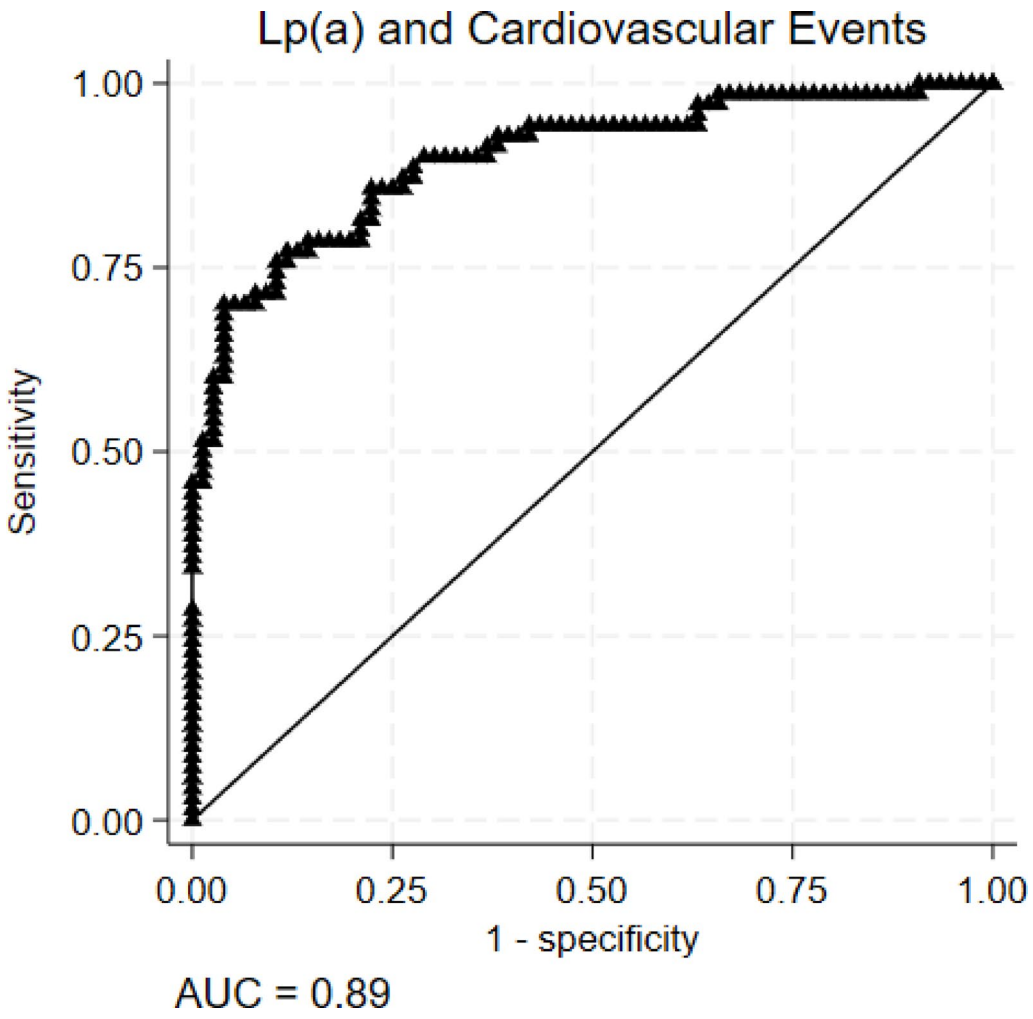

Fig. 1 Receiver operating characteristic (ROC) curve showing the predictive performance of baseline Lp(a) levels for the occurrence of major adverse events (MACE, MALE, or both) in the study population. The area under the curve (AUC) was 0.89 (95% CI: 0.85–0.95), indicating a good discriminatory ability

Figure 3a illustrates the ROC curves comparing two predictive models for the occurrence of MACE, MALE, or both. The first model, based solely on conventional cardiovascular predictors, demonstrated a moderate discriminative ability, with an area under the curve (AUC) of 0.74 (95% CI: 0.64–0.83). When Lp(a) was added to the model, the predictive performance improved substantially, with the AUC increasing to 0.98 (95% CI: 0.96–1.00) (χ^2 = 26.83, $p < 0.01$). Calibration assessed by the Hosmer–Lemeshow test showed good fit for both models: χ^2 = 1.67 ($p = 0.99$) for the full model including Lp(a), and χ^2 = 11.79 ($p = 0.16$) for the clinical model.

Lp(a) levels and incidence of MACE after LER

Among the 158 patients included, 33 (20.9%) experienced MACE. Patients who developed MACE had a longer duration of T2DM (25 vs. 15 years, $p < 0.01$) and were more frequently treated with insulin (72.7% vs. 38.2%, $p < 0.01$). Conversely, they were less frequently on oral antidiabetic agents (27.2% vs. 53.6%, $p = 0.02$). A higher prevalence of CAD was observed in the MACE group (63.6% vs. 42.4%, $p = 0.03$), and clopidogrel use was more common among these patients (48.5% vs. 25.6%, $p = 0.01$). Furthermore, patients with MACE had poorer renal function (creatinine 1.4 vs. 1.0 mg/dL, $p < 0.01$; eGFR 68.9 vs. 87.4 mL/min/1.73 m^2, $p = 0.01$), and lower total cholesterol (116 vs. 129 mg/dL, $p = 0.04$). Notably, in the MACE group, Lp(a) levels were significantly higher (50.8 vs. 15.9 mg/dL, $p < 0.01$). All values and comparisons are detailed in Table S3a.

The multivariable logistic model assessing predictors of MACE is reported in Table S3b and shows that both insulin therapy ($p = 0.02$) and higher Lp(a) levels ($p = 0.01$) were independently associated with an increased risk of MACE. Table S3c presents the results of the Cox regression model for the occurrence of MACE. Among the variables included, Lp(a) was the only independent predictor that reached statistical significance (HR 1.08, 95%

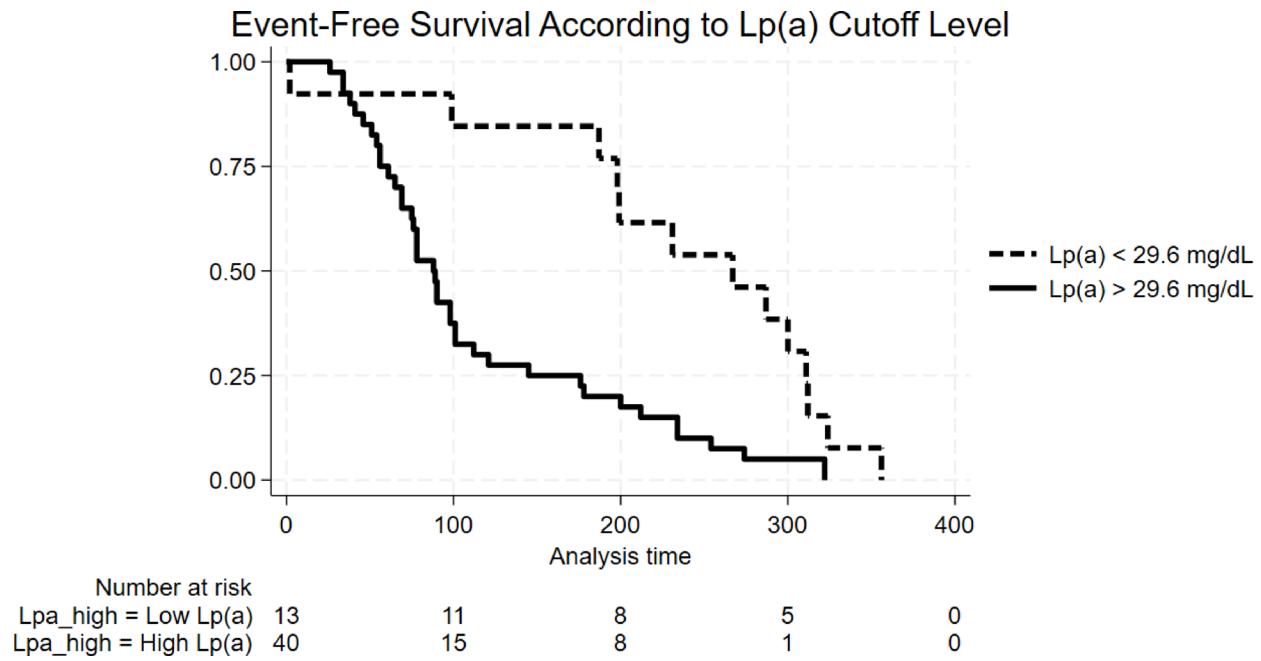

Fig. 2 Kaplan–Meier curves for event-free survival according to baseline Lp(a) levels. Patients were stratified based on the optimal cutoff of Lp(a) (29.6 mg/dL) identified through ROC analysis. Individuals with Lp(a) > 29.6 mg/dL had a significantly lower probability of remaining free from major adverse events (MACE, MALE, or both) during follow-up compared to those with Lp(a) ≤ 29.6 mg/dL (log-rank test $p < 0.01$). The number of patients at risk at each time interval is reported below the x-axis

Table 5 Regression results for events

	Haz. ratio	St.Err.	z	*p*-value	[95% Conf	Interval]	Sig
Diabetes duration	1.034	0.018	1.94	0.052	1	1.069	
CVD	2.368	1.035	1.97	0.049	1.005	5.578	*
Insulin	0.77	0.345	-0.58	0.559	0.32	1.853	
Oral antidiabetics	0.781	0.286	-0.68	0.499	0.381	1.599	
Rutherford II-4	0.215	0.106	-3.12	0.002	0.082	0.564	**
Rutherford III-5	1	.	.	.	.	.	
HbA1c	0.955	0.106	-0.41	0.681	0.769	1.187	
Creatinine	1.028	0.07	0.41	0.684	0.9	1.174	
Lp(a) > 29.6 mg/dL	4.09	1.952	2.95	0.003	1.605	10.421	**
Mean dependent var		**122.173**		**SD dependent var**			**87.989**
Pseudo r-squared		0.082		Number of obs			52
Chi-square		25.558		Prob > chi2			0.001
Akaike crit. (AIC)		301.614		Bayesian crit. (BIC)			317.224

CI: 1.03–1.13; $p < 0.01$). Figure 3b illustrates the ROC curves comparing two predictive models for the occurrence of MACE. The model that includes conventional clinical variables showed a reliable discriminative ability (AUC: 0.81, 95% CI: 0.71–0.91). The second model that incorporates Lp(a), in addition to classical predictors, demonstrated a marked improvement in predictive performance, with a ROC area of 0.89 (95% CI: 0.80–0.98). The comparison between the two models showed a statistically significant difference ($\chi^2 = 4.69$, $p = 0.03$), confirming that the inclusion of Lp(a) significantly enhances the ability to predict MACE in this population. Calibration was acceptable, as indicated by the Hosmer–Lemeshow test ($\chi^2 = 10.45$, $p = 0.23$).

Lp(a) levels and incidence of MALE after LER

Out of 158 patients, 54 (34.2%) experienced a MALE. Individuals who developed MALE were younger (72.4 vs. 76.7 years, $p < 0.01$) and more frequently treated with insulin (58.5% vs. 39.4%, $p = 0.03$). Patients with MALE had more advanced PAD at baseline, with a significantly higher proportion in Rutherford stage III-5 (74.1% vs. 48.9%, $p < 0.01$). Glycemic control was also worse in the MALE group, with higher HbA1c values (7.5% vs. 6.8%, $p < 0.01$). Interestingly, Lp(a) levels were markedly higher

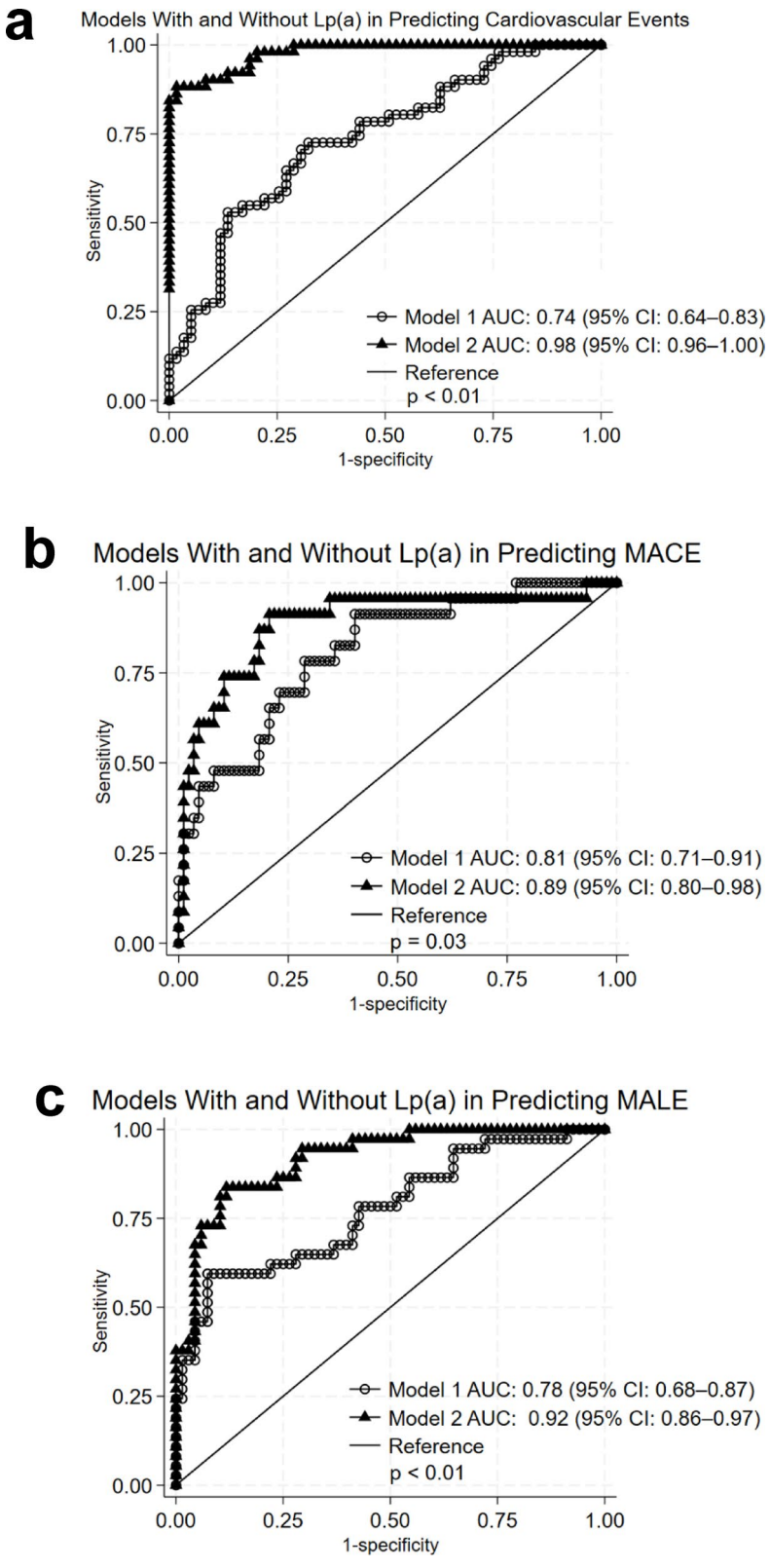

Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 ROC curves comparing predictive models with and without Lp(a). **a** Discrimination for the composite outcome (MACE and/or MALE). The addition of Lp(a) to conventional clinical predictors significantly improved the AUC from 0.74 (95% CI: 0.64–0.83) to 0.98 (95% CI: 0.96–1.00) ($\chi^2 = 26.83$, $p < 0.01$). **b** Discrimination for MACE. The AUC increased from 0.81 (95% CI: 0.71–0.91) to 0.89 (95% CI: 0.80–0.98) with the inclusion of Lp(a) ($\chi^2 = 4.69$, $p = 0.03$). **c** Discrimination for MALE. The model including Lp(a) showed a significantly higher AUC of 0.92 (95% CI: 0.86–0.97), compared to 0.78 (95% CI: 0.68–0.87) for the conventional model ($\chi^2 = 10.90$, $p < 0.01$). Model 1 included conventional cardiovascular risk factors: age, sex, BMI, duration of diabetes, history of smoking, hypertension, hypercholesterolemia, CAD, CVD, ABI, Rutherford classification, FBG, HbA1c, LDL-c, and renal function. Model 2 included all variables in Model 1 plus baseline Lp(a) as a continuous predictor. The addition of Lp(a) significantly improved the predictive accuracy of the model, as reflected by the increase in AUC. All model comparisons were performed using DeLong's test. ROC: receiver operating characteristic; AUC: area under the curve; MACE: major adverse cardiovascular events; MALE: major adverse limb events

in patients who experienced MALE (48.0 mg/dL vs. 13.1 mg/dL, $p < 0.01$), supporting its role as a potential predictor of limb-related complications. All variables and comparisons are summarized in Table S4a.

Table S4b reports the results of the multivariable logistic regression analysis exploring independent predictors of MALE during follow-up. Among the variables included, Lp(a) levels were strongly and independently associated with an increased risk of MALE ($p < 0.01$; 95% CI: 0.041–0.098). Younger age was also significantly associated with MALE ($p = 0.02$), and Rutherford II-4 staging at presentation was associated with a significantly lower risk of MALE ($p = 0.04$). The Cox regression model evaluating predictors of MALE is reported in Table S4c. Among the variables included, Lp(a) was the only factor significantly associated with MALE, with HR 1.05 (95% CI: 1.02–1.07; $p < 0.01$). These findings reinforce the role of Lp(a) as an independent predictor of adverse limb events following LER.

Figure 3c shows the results of the ROC analysis comparing two models for predicting MALE. The model based on conventional risk factors alone showed a fair discriminative performance, with an AUC of 0.78 (95% CI: 0.68–0.87). When Lp(a) was included in the model, the predictive accuracy improved significantly, with the AUC rising to 0.92 (95% CI: 0.86–0.97). The difference between the two models was statistically significant ($\chi^2 = 10.90$, $p < 0.01$), highlighting the incremental value of Lp(a) in improving the identification of patients at higher risk for limb-related adverse outcomes following LER. Calibration was also acceptable (Hosmer–Lemeshow $\chi^2 = 8.37$, $p = 0.40$).

Discussion

Our findings suggest that elevated Lp(a) levels independently predict cardiovascular and limb events in diabetic patients with PAD and CLTI undergoing revascularization. The association was confirmed in sensitivity analyses, including a stepwise model and a log-transformed specification of Lp(a), both of which showed consistent and significant results. This is highly consistent with the established role of Lp(a) in atherosclerosis progression and as a cardiovascular risk determinant from biological, genetic and epidemiological studies [15, 39–41]. Our findings align with the concept that incorporating Lp(a) into risk models improves prediction accuracy beyond traditional factors, highlighting its potential as a valuable prognostic biomarker in diabetic patients undergoing revascularization. Given the high rate of complications despite optimal medical therapy, early identification of high-risk individuals remains essential to improve outcomes.

In line with previous studies involving patients with advanced PAD, our study population exhibited a high burden of cardiovascular risk factors [3, 4, 11, 12, 16, 34, 35, 42–44]. The prevalence of hypertension, hypercholesterolemia, and established atherosclerotic disease reflects the elevated cardiovascular and limb risk typical of this population.

Despite relatively well-controlled LDL-c levels, consistent with current European guidelines threshold of LDL < 55 mg/dl [45, 46], a high rate of cardiovascular events was observed.

This finding highlights the presence of residual cardiovascular risk and supports the hypothesis that non-traditional factors, such as elevated Lp(a), may contribute to adverse outcomes in high-risk individuals [16, 47].

In the first part of the study, the analysis of the composite outcome encompassing both cardiovascular and limb events showed that individuals who experienced complications tended to have a more complex clinical profile. They were more likely to have a longer history of T2DM, require insulin therapy, and present with comorbidities such as CVD. Despite similar rates of hypertension, hypercholesterolemia, and smoking status, patients with cardiovascular and limb events more often presented with severe limb ischemia, as indicated by the higher proportion of Rutherford III-5 classification and the lower frequency of Rutherford II-4. Furthermore, patients who experienced events had significantly worse glycemic control, as reflected by higher HbA1c levels. Although lipid levels were relatively well-controlled in both groups, creatinine levels were higher among those who experienced complications. Notably, these patients also had higher baseline levels of Lp(a), which emerged as an independent predictor of adverse outcomes. Even after accounting for conventional cardiovascular risk factors, Lp(a) remained significantly associated with the development of cardiovascular and limb events, reinforcing its potential role as a meaningful biomarker in this

setting. Our findings are consistent with those reported by Sánchez Muñoz-Torrero et al., who reported that in patients with stable CAD, CVD, and PAD, Lp(a) levels between 30 and 50 mg/dL were associated with a higher risk of myocardial infarction, stroke, or limb amputation over a 36-month follow-up period [19]. Furthermore, in our cohort, individuals with the highest Lp(a) levels experienced a greater incidence of cardiovascular events and tended to develop them earlier during follow-up. This observation highlights a gradient of risk, where increasing Lp(a) levels are associated with a progressively higher likelihood of adverse outcomes. We found that higher Lp(a) levels were associated with MACE, MALE, or both after LER, with a cut-off of 29.6 mg/dL predicting events-free survival. Although this threshold is lower than the 30–50 mg/dL commonly cited in the literature [48, 49], similar findings have been reported in other high-risk populations. For example, Tseng et al. identified 13.3 mg/dL as a predictive threshold for PAD in Chinese patients with T2DM [50]. These results suggest that in individuals with T2DM or systemic inflammation, even moderately elevated Lp(a) levels may contribute to increased cardiovascular risk. Supporting this, Puri et al. showed that the cardiovascular risk associated with Lp(a) becomes more evident in patients with CRP > 2 mg/L, with risk rising at concentrations above 25–30 mg/dL [51]. These findings suggest that Lp(a) contributes not only to atherosclerotic burden but also to the progression of both cardiac and peripheral ischemic complications in patients with T2DM and PAD. Our findings also align with previous evidence suggesting a role for Lp(a) in ischemic diabetic foot complications. In fact, in a study comparing patients with vascular and neuropathic diabetic foot, Lp(a) levels were significantly higher in those with ischemic ulcers and showed an association with vascular diabetic foot [52]. Moreover, in the ROC analysis, baseline Lp(a) levels showed a strong ability to discriminate individuals at higher risk of cardiovascular events. Remarkably, the addition of Lp(a) to conventional cardiovascular risk factors significantly improved the accuracy of the predictive model, highlighting its potential role in refining individual risk stratification. These results suggest that Lp(a) may offer meaningful clinical information beyond traditional risk factors in identifying patients who are more likely to experience adverse outcomes.

When focusing specifically on MACE, our analysis revealed that patients experiencing these events had a longer duration of T2DM, were more likely to be on insulin therapy, and were less likely to be treated with oral antidiabetics, reflecting a more advanced stage of metabolic disease. These individuals also had a higher prevalence of CAD and a trend toward more CVD, suggesting a more widespread atherosclerotic burden. Among the most relevant laboratory findings, those with MACE had higher baseline creatinine and lower eGFR, indicating worse renal function, a known predictor of poor cardiovascular outcomes [53]. Additionally, lower total cholesterol levels were observed in the MACE group, which may reflect either a response to more intensive lipid-lowering therapy in higher-risk individuals or the presence of reverse epidemiology, hypothesized in advanced cardiovascular disease [54]. In individuals with MACE, Lp(a) levels were more than three times higher in the MACE group, reinforcing its potential utility in risk stratification. Importantly, elevated baseline levels of Lp(a) remained independently associated with MACE after multivariable adjustment, supporting their role as predictors of adverse outcomes in this high-risk population. In our high-risk cohort of patients, each 10 mg/dL increase in baseline Lp(a) levels was associated with a twofold higher risk of MACE, independent of traditional cardiovascular risk factors. This finding is particularly remarkable when compared to the general population, where Mendelian randomization studies have estimated a 5.8% increase in the risk of CAD for every 10 mg/dL rise in Lp(a) levels [55]. The stronger association observed in our study likely reflects the increased susceptibility of individuals with advanced atherosclerosis to the atherothrombotic effects of Lp(a), suggesting that even moderate elevations in Lp(a) may have greater clinical relevance in this population. The predictive capacity of Lp(a) for MACE was further supported by its performance in discriminative models, in which baseline Lp(a) levels showed a good ability to identify patients at higher risk of experiencing adverse events during follow-up.

When analyzing limb-related outcomes specifically, baseline Lp(a) levels emerged as a significant independent predictor of MALE. Interestingly, patients with MALE were younger than patients without a MALE, suggesting a greater impact of other cardiovascular risk factors besides the age in determining cardiovascular complications. They had even higher levels of HbA1c, confirming that uncontrolled T2DM promotes vascular complications of the lower limbs [56]. They had also more severe PAD at baseline, as expected. Even after adjusting for conventional cardiovascular risk factors and indicators of disease severity, such as Rutherford classification and ABI, higher Lp(a) levels remained associated with increased risk. The lack of association in the logistic regression between traditional cardiovascular risk factors and MALE after LER was unexpected and may be explained by the limited sample size, short follow-up, and the high-risk nature of our cohort with established atherosclerotic disease. Nonetheless, the significant link between Lp(a) levels and outcomes highlights its potential pleiotropic role in driving short-term complications.

In fact, these findings highlight the potential role of Lp(a) in contributing not only to systemic atherosclerosis

but also to the progression of PAD and the occurrence of acute limb-threatening ischemic events. This reinforces the concept that Lp(a) may play a broader role in vascular pathology than previously appreciated, extending its impact beyond coronary events to include adverse outcomes in the peripheral vascular territory. Several lines of evidence support our findings. Elevated Lp(a) levels have been associated with both the presence and progression of PAD in multiple studies [21–24]. Notably, higher Lp(a) concentrations have been linked to lower ABI values and symptomatic PAD [23]. Furthermore, a retrospective study of patients undergoing endovascular revascularization for PAD found that Lp(a) levels above 30 mg/dL were associated with more severe femoropopliteal atherosclerotic lesions [25]. Moreover, Tomai et al. found that patients undergoing LER who experienced MACE or MALE over a 1.7-year follow-up had elevated Lp(a) levels (> 30 mg/dL) [57]. In contrast, a study by Yi et al. found that elevated Lp(a) levels were linked to PAD severity only in female patients undergoing coronary artery bypass graft (CABG), but not in males, suggesting a possible sex-related difference in Lp(a)'s role [58].

However, the predictive value of Lp(a) in our cohort consistently emerged as a robust and clinically meaningful finding. When added to models already including conventional risk factors, Lp(a) significantly improved the ability to discriminate patients at risk not only for MACE but also for MALE. The improvement was statistically significant in both settings, reinforcing the role of Lp(a) as a marker of vulnerability in this already high-risk population. These findings suggest that baseline Lp(a) levels may help identify patients at particularly elevated risk of both systemic and limb complications, offering an opportunity for more tailored monitoring and preventive strategies. These observations are consistent with recent data showing that the association between elevated Lp(a) levels and MACE is stronger in patients with T2DM compared to those without, highlighting the potential amplifying effect of diabetes on Lp(a)-related cardiovascular risk [59]. Moreover, diabetes-related mechanisms—such as inflammation and expansion of epicardial adipose tissue—may further contribute to cardiovascular vulnerability in this population, offering new opportunities for risk stratification and targeted therapies [60].

Several pathophysiological mechanisms may explain the association between elevated Lp(a) levels, and the increased risk of cardiovascular and limb events observed in our cohort. Lp(a) is known to exert proatherogenic, proinflammatory, and prothrombotic effects. The apo(a) component of Lp(a) structurally resembles plasminogen and plasmin, interfering with fibrinolysis and promoting thrombogenesis [61]. In addition, Lp(a) acts as a preferential carrier of oxidized phospholipids, which contribute to vascular inflammation and endothelial dysfunction [62].

In diabetic patients with CLTI, these mechanisms may be amplified by the coexisting inflammatory milieu, endothelial injury, and altered lipid metabolism typical of this population. Lp(a) has been shown to promote the expression of adhesion molecules, stimulate the recruitment of inflammatory cells, and contribute to plaque instability [63]. Imaging studies have shown that high Lp(a) levels are associated with increased carotid artery inflammation (SPECT/MRI) [62] and, on coronary CT angiography, with greater plaque burden, faster progression, and enhanced perivascular inflammation [64]. The dual proatherogenic and prothrombotic Lp(a) properties [17] may be especially harmful in patients with T2DM and CLTI, who already exhibit vascular inflammation and endothelial dysfunction [58]. Moreover, in the context of PAD, elevated Lp(a) could exacerbate plaque instability and thrombotic occlusion, accelerating the onset of both cardiac and limb ischemic events.

The stronger association of Lp(a) with adverse outcomes in our high-risk cohort reinforces its role as a residual risk factor in advanced vascular disease. Elevated Lp(a) has been associated with cardiovascular events across risk categories, including low- and high-risk individuals [48], and its contribution to atherosclerosis progression is supported by a growing body of evidence [49].

These findings may have important implications not only for risk stratification but also from a therapeutic standpoint. Beyond its role as a biomarker, Lp(a) is emerging as a potential therapeutic target. PCSK9 inhibitors, such as alirocumab, have been shown to reduce Lp(a) levels, and novel therapies—including antisense oligonucleotides and small interfering RNAs—are currently under investigation for their ability to selectively and substantially lower Lp(a). Interestingly, it has been shown that while a reduction of 38.67 mg/dL in LDL cholesterol is required to achieve a 22–25% reduction in cardiovascular risk over 3–5 years, an approximate 100 mg/dL reduction in Lp(a) is needed to attain a similar benefit [55]. This has led to the hypothesis that such a reduction may be clinically meaningful, primarily in individuals with markedly elevated Lp(a) levels or in populations already at high cardiovascular risk—such as the one included in this study—where the contribution of Lp(a) to overall risk may be more pronounced. Notably, Shwartz and colleagues demonstrated that in patients with a recent acute coronary syndrome treated with statins, the risk of critical lower limb ischemia, amputations, or lower-limb revascularization was associated with Lp(a) levels and was significantly reduced by treatment with alirocumab [20]. Our results suggest that Lp(a) may help identify a specific subgroup of diabetic patients in whom traditional biomarkers such as LDL-c

or HbA1c are not sufficient to fully capture cardiovascular risk. In these individuals, Lp(a) could serve as an additional marker of residual risk, guiding more tailored and intensive treatment strategies. If future studies confirm that Lp(a) lowering leads to improved MACE and MALE, Lp(a) assessment could become an essential component of personalized therapeutic strategies, particularly in high-risk patients such as those with T2DM and PAD.

This study had several limitations. The investigation was conducted at a single center and involved a highly selected cohort defined by stringent inclusion and exclusion criteria; thus, the generalizability of the results may be restricted to patient populations with comparable high-risk profiles. While the prospective design and detailed clinical characterization strengthen the internal validity, the relatively small sample size may have limited the statistical power to detect more subtle associations and to explore effect modification or stratified analyses. Due to limited sample size and drug heterogeneity, we were not able to evaluate the impact of specific pharmacological subclasses (e.g., SGLT2 inhibitors, metformin, DPP-4 inhibitors) or treatment dosages. Moreover, although multiple conventional cardiovascular risk factors were accounted for, residual confounding from unmeasured variables cannot be excluded, such as medication adherence, post-revascularization lifestyle modifications, or inflammatory status. Furthermore, Lp(a) levels were measured only at baseline. While this is common in clinical studies and justified by the known stability of Lp(a), longitudinal measurements could offer insights into the dynamic relationship between Lp(a) and outcomes, especially in patients receiving lipid-lowering therapies. Additionally, although the multivariable models included a range of conventional risk factors, the absence of an analysis of other inflammatory cytokines and coagulation markers did not allow us to determine whether the observed association between Lp(a) and adverse outcomes remained significant after adjusting for these potential biological mediators. Moreover, the use of a complete case approach in multivariable models reduced the effective sample size, particularly due to missing HbA1c values, which may have impacted statistical power and the generalizability of results. In addition, the 12-month follow-up, although sufficient to observe early cardiovascular and limb events, may not capture the full burden of long-term complications. Furthermore, the study period overlapped with the COVID-19 pandemic, which may have influenced the incidence of MACE and MALE during follow-up [65, 66]. While symptomatic infections were excluded at baseline, asymptomatic SARS-CoV-2 infections cannot be ruled out. Reduced access to healthcare services during lockdowns may also have contributed to adverse outcomes [67]. Although no systematic assessment of COVID-19 status was performed, the entire study population was similarly exposed to pandemic-related factors, making a differential bias unlikely. Notably, Lp(a) concentrations were measured in using a commercially available ELISA kit, which does not specify isoform independence. This represents a further limitation, as the variability in apo(a) isoform size may affect the accuracy and comparability of Lp(a) levels expressed in mass units across individuals. In addition, although internal validation confirmed model robustness, the lack of external validation may limit the generalizability of our findings. Likewise, the Lp(a) cutoff of 29.6 mg/dL, though consistent with prior studies, should be considered exploratory pending independent validation. Finally, although all patients underwent duplex ultrasound and ABI assessment, we did not collect perfusion-based parameters such as transcutaneous oxygen pressure ($TcPO_2$), which could have allowed a more precise quantification of ischemia severity at baseline and a deeper understanding of its potential interaction with Lp(a) levels. Although microvascular complications such as diabetic retinopathy and albuminuria were not assessed in this study, we included eGFR as an indirect marker of renal microvascular damage. However, eGFR was not significantly associated with outcomes in our analysis. Further studies are needed to explore the potential interaction between Lp(a), microvascular disease, and adverse events in patients with diabetic foot and CLTI.

The main strength of this study lies in the identification of Lp(a) as a potential prognostic biomarker for adverse cardiovascular and limb events in patients with T2DM, PAD, and CLTI undergoing LER. The prospective design, rigorous patient selection, and systematic follow-up enhance the reliability of the results. Moreover, the comprehensive collection of clinical, demographic, and laboratory data allowed for robust multivariable analyses. These methodological strengths improve the internal validity of the study and support its potential clinical applicability. Notably, the finding that Lp(a) improves the predictive performance of traditional risk models underscores the importance of integrating emerging biomarkers into current risk-stratification strategies.

Conclusions

This study highlights the role of Lp(a) as an independent predictor of cardiovascular and limb events in diabetic patients with PAD and CLTI undergoing LER. Incorporating Lp(a) into the baseline risk assessment may improve the identification of patients at heightened risk and guide more tailored therapeutic strategies. These findings support the integration of Lp(a) in future risk-stratification models for this high-risk population. Further research is needed to clarify the biological mechanisms underlying this association and to assess

the clinical benefit of interventions targeting Lp(a) in the context of PAD and T2DM.

Abbreviations

PFKFB-3	6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase
ABI	Ankle/brachial index
apo(a)	Apolipoprotein(a)
AUC	Area under the curve
BMI	Body mass index
CKD-EPI	Chronic kidney disease epidemiology collaboration
CLTI	Chronic limb-threatening ischemia
CVD	Cerebrovascular disease
CV	Coefficient of variation
CCTA	Computed tomography angiography
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
DAPT	Dual antiplatelet therapy
eGFR	Estimated glomerular filtration rate
FBG	Fasting glucose
GWAS	Genome-wide association studies
ICAM	Intercellular adhesion molecule
LDL-c	LDL-cholesterol
Lp(a)	Lipoprotein(a)
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
OxPL	Oxidized phospholipids
PAD	Peripheral artery disease
ROC	Receiver operating characteristic
SD	Standard deviations
TSPI	Toe systolic blood pressure index
T2DM	Type 2 diabetes mellitus
US	Ultrasonography

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02833-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Acknowledgements
The authors thank the Italian Ministry of Health, Ricerca Corrente 2025.

Author contributions
Conceptualization, F.B, M.M.R.; methodology, M.M.R, F.B.; data collection, M.A.N; immunoassays, F.A.; data analysis, F.B.; resources, A.F., D.P; endovascular procedures R.I., data curation, A.F.; writing—original draft preparation, M.M.R., F. B.; review and editing, F.B., A.F, P.D., L.E.; supervision, M.M., A.G., A.F. All authors read and approved the final manuscript.

Funding
This research received no external funding.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy. Informed consent was obtained from all subjects involved in the study.

Consent for publication
All authors have read the document and agree to its publication.

Competing interests
The authors declare no competing interests.

Guarantor's statement
Dr. Andrea Flex is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for data integrity and data analysis accuracy.

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Received: 3 April 2025 / Accepted: 18 June 2025
Published online: 10 July 2025

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