Technology and Health Care -1 (2024) 1–12 1
DOI 10.3233/THC-240005
IOS Press
CORRECTED PROOF

Impact of lipoprotein(a) and fibrinogen on prognosis in patients with coronary artery disease: A retrospective cohort study

Dakai Liang[a,b], Dandan Liang[b], Jin Liu[a], Yiying Zheng[b], Dehua Huang[b], Zeliang Li[a], Xiaoyu Huang[b] and Jiyan Chen[a,*]
[a]*Department of Cardiology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China*
[b]*Department of Cardiology, People's Hospital of Yangjiang, Yangjiang, China*

Received 2 January 2024
Accepted 16 April 2024

Abstract.
BACKGROUND: Despite the considerable progress made in preventative methods, medication, and interventional therapies, it remains evident that cardiovascular events (CVEs) continue to be the primary cause of both death and morbidity among individuals diagnosed with coronary artery disease (CAD).
OBJECTIVE: To compare the connection between lipoprotein a (Lp[a]), fibrinogen (Fib), and both parameters combined with all-cause mortality to detect their value as prognostic biomarkers.
METHODS: This is a retrospective study. Patients diagnosed with CAD between January 2007 and December 2020 at the Guangdong Provincial People's Hospital (China) were involved in the study. 43,367 patients met the eligibility criteria. The Lp(a) and Fib levels were distributed into three tertile groups (low, medium, and high). All of the patients included in the study were followed up for all-cause mortality. Kaplan–Meier and Cox regression were performed to determine the relationship between Lp(a), Fib, and all-cause mortality. A concordance statistics model was developed to detect the impact of Fib and Lp(a) in terms of anticipating poor outcomes in patients with CAD.
RESULTS: Throughout a median follow-up of 67.0 months, 6,883 (15.9%) patients died. Participants with high Lp(a) (above 27.60 mg/dL) levels had a significantly higher risk for all-cause mortality than individuals with low Lp(a) levels (below 11.13 mg/dL; adjusted hazard ratio [aHR] 1.219, 95% confidence interval [CI]: 1.141–1.304, $p < 0.001$). Similarly, patients with high Fib levels (above 4.32 g/L) had a significantly greater risk of developing all-cause mortality compared with those with reduced Fib levels (below 3.41 g/L; aHR 1.415, 95% CI: 1.323–1.514, $p < 0.001$). Patients with raised Lp(a) and Fib levels had the maximum risk for all-cause mortality (aHR 1.702; 95% CI: 1.558–1.859, $p < 0.001$). When considered together, Lp(a) and Fib caused a significant elevation of the concordance statistic by 0.009 ($p < 0.05$), suggesting a higher value for predicting mortality when combining the two indicators.
CONCLUSION: High Lp(a) and Fib levels could be used as predictive biomarkers for all-cause mortality in individuals with CAD. The prediction accuracy for all-cause mortality improved after combining the two parameters.

Keywords: Lipoprotein(a), fibrinogen, coronary artery disease, all-cause mortality

*Corresponding author: Jiyan Chen, Department of Cardiology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, No. 106 Zhongshan Second Road, Guangzhou 510080, China. Tel.: +86 2083827812; Fax: +86 20 83827812 20893; E-mail: laaght@tom.com.

1. Introduction

The prognosis of individuals with coronary artery disease (CAD) varies widely. Despite the considerable progress made in preventative methods, medication, and interventional therapies, it remains evident that cardiovascular events (CVEs) continue to be the primary cause of both death and morbidity among individuals diagnosed with CAD [1]. Accurate early risk stratification could facilitate the delivery of timely treatment for patients with CAD and may improve treatment outcomes in these cases. In recent years, researchers have identified serum biomarkers that are associated with an elevated risk of atherosclerotic events [2]. Many of these biomarkers, such as lipoprotein, C-reactive protein, and others, either alone or in combination, have been integrated into risk prediction models to assess whether their inclusion improves prediction accuracy [3]. However, there remains a lack of large-scale clinical studies on CAD-related biomarkers.

Lipoprotein a (Lp[a]) can increase atherosclerosis progression and promote blood clot formation while inhibiting the dissolution of blood clots (fibrinolysis). As a result, Lp(a) has been acknowledged as an independent atherosclerotic cardiovascular disorder risk factor [4,5,6]. Apolipoprotein a (Apo[a]) is a structural element of Lp(a) [7]. The fourth kringle of Apo(a) shares similarities with the plasminogen domain that binds with fibrin and ultimately interferes with the process of fibrinolysis [8]. Fibrinogen (Fib) is a glycoprotein present in the blood that has a vital function in the blood clotting mechanism. However, high levels of Fib can increase the risk of thrombus formation [9]. Numerous investigations have found a connection between raised Fib and Lp(a) levels and the risk of developing CAD [10,11,12, 13]. Moreover, some studies have revealed that when Fib and Lp(a) are considered in combination (rather than in isolation), they can enhance the predictive value for the occurrence of both stable CAD (SCAD) and acute coronary syndrome (ACS) [14,15]. However, the relationship between these parameters and mortality remains unclear. To address this issue, in this investigation, we aimed to compare the connection between Lp(a), Fib, and both parameters combined with all-cause mortality to detect their value as prognostic biomarkers.

2. Methods

2.1. Study design and participants

This investigation depended on information obtained from the Cardiorenal Improvement study (Clinicaltrials.gov NCT04407936). Patients who underwent coronary angiography (CAG) at Guangdong Provincial People's Hospital (China) between January 2007 and December 2020 were eligible for this study.

Inclusion criteria: (1) aged above 18 years; (2) received a diagnosis of CAD based on the 10^{th} Revision Codes of the International Classification of Diseases (ICD-10; I20.xx–I25.xx, I50.00001, and I91.40001); (3) the standard used for diagnosing CAD was a coronary artery stenosis degree exceeding 50%.

Exclusion criteria: (1) patients with blood diseases (white blood cell count $\leqslant 3.5 \times 10^9$/L or $\geqslant 20 \times 10^9$/L); (2) a history of cancer; (3) patients with renal disease, determined as an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73m^2 or receiving dialysis [16]; (4) patients who lacked Lp(a) and Fib data, or gave up treatment during hospitalisation, or had missing follow-up mortality information. The patient recruitment process is shown in Fig. 1.

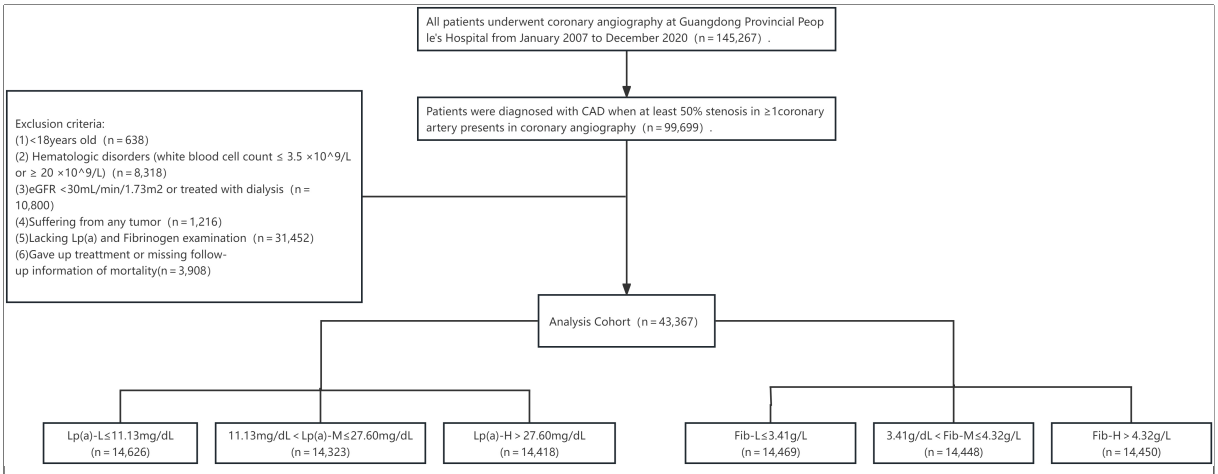

Fig. 1. Study flowchart.

2.2. Ethical considerations

This investigation was authorised by the Ethics Committee of Guangdong Provincial People's Hospital and followed the principles set out in the Declaration of Helsinki.

2.2.1. Grouping

Grouping was conducted based on the data characteristics of this study. All of the patients were divided into three subgroups according to the tertiles of plasma Lp(a) levels as follows: low (L), medium (M), and high (H). The Lp(a)-L levels were 11.13 mg/dL or less; Lp(a)-M levels were between 11.13 and 27.60 mg/dL; and Lp(a)-H levels were above 27.60 mg/dL. Similarly, the participants were distributed into 3 additional groups according to the tertiles of plasma Fib levels as follows: Fib-L, consisting of levels rated 3.41 g/L or less; Fib-M, consisting of Fib levels between 3.41 and 4.32 g/L; and Fib-H, reflecting Fib levels above 4.32 g/L.

To test the link between Fib and Lp(a) with all-cause mortality, the patients were categorised into 9 groups as follows: Group 1: Lp(a)-L + Fib-L; Group 2: Lp(a)-L + Fib-M; Group 3: Lp(a)-L + Fib-H; Group 4: Lp(a)-M + Fib-L; Group 5: Lp(a)-M + Fib-M; Group 6: Lp(a)-M + Fib-H; Group 7: Lp(a)-H + Fib-L; Group 8: Lp(a)-H + Fib-M; Group 9: Lp(a)-H + Fib-H [17].

2.2.2. Basic information

Basic patient information was obtained from the computerised medical managing system of the Guangdong Provincial People's Hospital, which included demographic features, comorbidities, lab investigations, and drugs prescribed upon discharge. The comorbidities extracted from the medical records included a history of arterial fibrillation (AF), chronic kidney disease (CKD), congestive heart failure (CHF), percutaneous coronary intervention, diabetes mellitus (DM), and acute myocardial infarction (AMI). Chronic kidney disease is characterised by an eGFR that falls below 60 ml/min/1.73 m^2 [18] All other comorbidities were defined using the diagnostic codes as determined by the ICD-10.

2.2.3. Lipoprotein a and fibrinogen measurement

Measurements of patients' Lp(a) and Fib levels were taken on admission to the hospital via a blood sample. The Lp(a) concentration was determined using an immunoturbidimetry chemistry analyser

(AU5800 Analyzer, Beckman Coulter, Brea, California), while the Fib concentration was measured via quantitative latex turbidimetric test using a CA-7000 automatic coagulation analyser (Sysmex Corporation, Kobe, Japan).

2.3. Endpoint definitions

The main endpoint was the incidence of all-cause mortality, which was described as any death that took place between the participant's enrolment in the study and the follow-up period's conclusion on 31 December 2023. The median follow-up for patients was 67.0 months (the 25–75 percentile is 41.2–99.8 months). The follow-up records were obtained by qualified nurses during outpatient or telephone consultations and recorded by research assistants according to the ICD-10 nomenclature.

2.4. Statistical analysis

The patients were subsequently divided into the all-mortality and alive groups based on their survival status at the completion of the follow-up period. Whether the variables showed normal distribution was evaluated using visual (histograms, probability curves) and analytical (Kolmogorov–Smirnov or Shapiro–Wilk tests) methods [19]. The means and standard deviation were utilised to summarise the normally distributed continuous variables, which were analysed employing a t-test. Median and interquartile ranges were employed to summarise the non-normally distributed continuous variables, which were compared utilising a non-parametric test. The categorical variables were assessed by measuring them in percentages or absolute numbers; thereafter, they were analysed using Pearson's chi-squared test.

Kaplan–Meier curves were employed to examine patient prognoses, and Cox proportional hazards analysis was conducted to test the connection between Fib and/or Lp(a) in the all-cause mortality among individuals with CAD. A concordance statistics (C-statistic) model was developed to detect the impact of Fib and Lp(a) administration on the original model (based on age, gender, DM, CKD, smoking, hypertension, and lipid levels) as it related to expecting poor outcomes in patients with CAD. The analyses of all data were conducted using version 4.3.2 of the R software program and the riskRegression R package [20]. All of the statistical tests conducted were two-tailed, and $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Typically, 14,5267 patients experienced CAG during the data collection period, 99,699 of whom were diagnosed with CAD. Following the exclusion of cases that did not meet the eligibility criteria of this investigation, 43,367 remained (Fig. 1). The mean participant age was 62.67 $\pm$ 10.59 years, and 10,100 (23.3%) were women. Table 1 illustrates the baseline features of the participants of this cohort study.

Throughout a median follow-up time of 67.0 months (the 25–75 percentile is 41.2–99.8 months), 6,883 patients died. The patients in the all-cause mortality group were older ($p < 0.001$) and had a greater incidence of CHF, DM, AF, CKD, AMI, and stroke ($p < 0.001$ for all). Individuals in the all-cause mortality group exhibited markedly elevated baseline concentrations of Fib and lipid parameters encompassing lip(a), haemoglobinA1c, high-density lipoprotein cholesterol and Apo(a). Moreover, this cohort manifested diminished levels of eGFR compared with their counterparts in the surviving group. No statistically significant variation was detected in the intake of medicines, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, dual antiplatelet drugs, statins, and beta-blockers.

Table 1
Baseline features of the patients

Characteristic*	Total, ($N = 43{,}367$)	Death, ($n = 6{,}883$)	Survival, ($n = 36{,}484$)	p-value
Demographic features				
Age, years, mean (SD)	62.67 (10.59)	66.39 (10.70)	61.97 (10.42)	< 0.0001
Female, n (%)	10,100 (23.3)	1,459 (21.2)	8,641 (23.7)	< 0.0001
Medical history				
Hypertension, n (%)	24,092 (55.6)	3,883 (56.4)	20,209 (55.4)	0.1203
CHF, n (%)	5,250 (12.1)	1,447 (21.0)	3,803 (10.4)	< 0.0001
CKD, n (%)	7,833 (18.1)	2,136 (31.0)	5,697 (15.6)	< 0.0001
Stroke, n (%)	2,363 (5.4)	513 (7.5)	1,850 (5.1)	< 0.0001
PCI, n (%)	32,575 (75.1)	5,085 (73.9)	27,490 (75.3)	0.0101
AMI, n (%)	7,788 (18.0)	1,471 (21.4)	6,317 (17.3)	< 0.0001
Atrial fibrillation, n (%)	1685 (3.9)	428 (6.2)	1,257 (3.4)	< 0.0001
DM, n (%)	14,450 (33.3)	2,497 (36.3)	11,953 (32.8)	< 0.0001
Laboratory tests				
HbA1c, %, mean (SD)	6.51 (1.38)	6.67 (1.49)	6.48 (1.36)	< 0.0001
CHOL, mmol/L, mean (SD)	4.49 (1.21)	4.45 (1.17)	4.50 (1.21)	0.0006
LDLC, mmol/L, mean (SD)	2.80 (0.96)	2.74 (0.95)	2.81 (0.96)	< 0.0001
HDLC, mmol/L, mean (SD)	0.99 (0.25)	0.99 (0.27)	0.99 (0.25)	< 0.0001
TRIG, mmol/L, mean (SD)	1.68 (1.24)	1.53 (1.05)	1.70 (1.27)	< 0.0001
Lipoprotein(a), mg/dL, mean (SD)	29.47 (31.97)	32.16 (34.20)	28.96 (31.51)	< 0.0001
APOA, g/L, mean (SD)	1.11 (0.25)	1.12 (0.25)	0.83 (0.23)	< 0.0001
APOB, g/L, mean (SD)	0.85 (0.24)	0.85 (0.24)	0.66 (0.27)	< 0.0001
Fibrinogen,g/L, mean (SD)	4.08 (1.25)	4.30 (1.38)	4.04 (1.22)	< 0.0001
eGFR, mL/min/1.73 m^2, mean (SD)	79.94 (23.58)	71.79 (22.84)	81.48 (23.41)	< 0.0001
Medications				
Statins, n (%)	40886 (94.3)	6396 (92.9)	34490 (94.5)	0.8611
Dual antiplatelet drugs, n (%)	34322 (79.1)	5429 (78.9)	28893 (79.2)	0.0619
ACEI/ARB, n (%)	30987 (71.5)	5054 (73.4)	25933 (71.1)	0.0812
β-blockers, (%)	34910 (80.5)	5411 (78.6)	29499 (80.9)	0.0748

*The mean value (standard deviation) were utilized to summarize the normally distributed continuous variables, which were analyzed employing the t-test. Median [interquartile range] were employed to summarize the non-normally distributed continuous variables, which were compared utilizing the non-parametric test. The categorical variables were assessed by number of participants (percentage) or absolute numbers and then analyzed utilizing the Pearson chi-squared test. p-value: Comparison between the Death group and the Survival group. LPa, lipoprotein(a); AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; CHO, serum total cholesterol; TG, triglycerides; APOA, apolipoprotein A; CHF, congestive heart failure; APOB, apolipoprotein B; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

3.2. Impact of Lp(a) and Fib on all-cause mortality incidence

The occurrence of all-cause mortality was the lowest in the Lp(a)-L group (13.35%), followed by the Lp(a)-M (14.65%) and Lp(a)-H (19.65%) ($p < 0.0001$) groups. Similarly, the occurrence of all-cause mortality was the lowest in the Fib-L group (14.02%), followed by the Fib-M (16.32%) and Fib-H (17.28%) ($p < 0.0001$) groups. The Kaplan–Meier survival curves (Fig. 2a, b) revealed that the Lp(a)-H and Fib-H groups exhibited the highest rates of all-cause mortality, whereas the Fib-L and Lp(a)-L groups demonstrated the lowest mortality rates ($p < 0.0001$).

The univariate Cox regression models revealed that the Lp(a)-M and Lp(a)-H groups indicated a 1.133 and 1.203-fold greater risk, respectively, of all-cause mortality, compared with the Lp(a)-L and (Lp(a)-M groups (hazard ratio [HR]; 95% confidence interval [CI]: 1.133 [1.067–1.202], $p < 0.001$; Lp(a)-H: HR [95% CI] 1.203 [1.134–1.275], $p < 0.001$). Similarly, the univariate Cox regression models revealed that the Fib-M and Fib-H groups exhibited a 1.129 and 1.548-fold greater risk, respectively, of experiencing

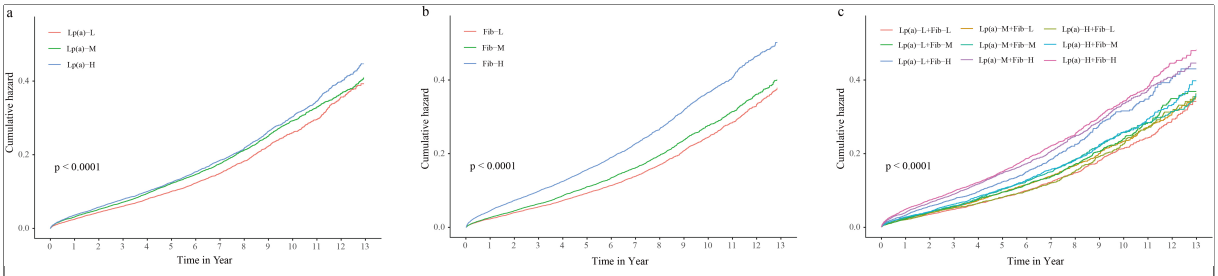

Fig. 2. Kaplan-Meier curves for the cumulative hazard in Fib, Lp(a), and combined groups. (a) Lp(a) groups, (b) Fib groups, (c) combined groups.

all-cause mortality compared with the Fib-L group (Fib-M: HR [95% CI] 1.161 [1.061–1.201], $p < 0.001$; Fib-H: HR (95% CI) 1.548 [1.461–1.640], $p < 0.001$). Following the adjustment of confounding variables, the statistical significance of the relationship between the 2 Lp(a) groups (Lp[a]-M: HR [95% CI] 1.117 [1.044–1.196], $p = 0.001$; Lp[a]-H: HR (95% CI) 1.219 [1.141–1.304], $p < 0.001$) was unchanged in the multivariate Cox regression models. However, in the Fib groups, after adjusting for confounders, the Fib-M group was no longer connected with the risk of developing all-cause mortality (Fib-M: HR [95% CI] 1.072 [0.998–1.15], $p = 0.057$), whereas the Fib-H remained significantly linked with all-cause mortality (Fib-H: HR [95% CI] 1.415 [1.323–1.514], $p < 0.001$).

3.3. Interrelationship of Lp(a), Fib Levels and all-cause mortality

The all-cause mortality was the lowest in the Lp(a)-L and Fib-L models (12.54%), followed by Lp(a)-L + Fib-M (14.31%), Lp(a)-L + Fib-H (13.53%), Lp(a)-M + Fib-L (13.70%), Lp(a)-M + Fib-M (14.96%), Lp(a)-M + Fib-H (15.33%), Lp(a)-H + Fib-L (17.36%), Lp(a)-H + Fib-M (19.51%), and Lp(a)-H + Fib-H (20.96%) ($p < 0.001$). As illustrated in Fig. 2c, the cumulative event frequency reached a maximum in the Lp(a)-H + Fib-H group ($p < 0.001$). The HRs in relation to the Lp(a)-L and Fib-L groups are summarised in Table 2. The Lp(a)-H + Fig-H group had the maximum risk of all-cause mortality (HR [95% CI] 1.592 [1.437–1.736], $p < 0.001$) after adjustment of the confounding variables.

3.4. Constructing the risk prediction model

The C-statistic of the original model was 0.643 (95% CI: 0.635–0.651). The administration of Lp(a) significantly enhanced the C-statistic by 0.008 ($p < 0.05$), while the addition of Fib enhanced the C-statistic by 0.002 ($p < 0.05$). The addition of Fib and Lp(a) to the model significantly improved the C-statistic by 0.009 ($p < 0.05$) (Table 3).

4. Discussion

The impact of Fib and Lp(a) levels on mortality risk in individuals with CAD remains unclear. Accordingly, we conducted a large retrospective cohort study to assess the influence of Lp(a) and Fib on mortality risk and developed a novel prediction model for patients with CAD. To achieve this aim, we first explored the Lp(a) and Fib baseline levels' effect on adverse medical outcomes following CAD. Our results indicated that raised Fib and Lp(a) concentrations were significantly linked with an enhanced risk of developing long-term adverse events, even after adjusting the confounding risk factors. Subsequently,

Table 2
Models of Cox regression for Lp(a) and Fib categories with all-cause mortality

Items		Univariate cox regression			Multivariate cox regression					
			Model 1		Model 2			Model 3		
Categorical variable	Tertile/ range	HR	95%CI	*p*-value	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Lp(a) categories	Lp(a)L ($\leqslant$ 11.13)	Reference								
	Lp(a)-M (11.13–27.60)	1.133	1.067–1.202	$<$ 0.001	1.108	1.044–1.176	0.001	1.117	1.044–1.196	0.001
	Lp(a)-H ($>$ 27.60)	1.203	1.134–1.275	$<$ 0.001	1.207	1.138–1.28	$<$ 0.001	1.219	1.141–1.304	$<$ 0.001
Fibrinogen categories	Fib-L ($\leqslant$ 3.41)	Reference								
	Fib-M (3.41–4.32)	1.129	1.061–1.201	$<$ 0.001	1.086	1.02–1.155	0.009	1.072	0.998–1.151	0.057
	Fib-H ($>$ 4.32)	1.548	1.461–1.64	$<$ 0.001	1.487	1.403–1.575	$<$ 0.001	1.415	1.323–1.514	$<$ 0.001
Combined categories	Lp(a)-L+FibL	Reference								
	Lp(a)-L+Fib-M	1.107	0.999–1.228	0.054	1.087	0.980–1.205	0.115	1.089	0.966–1.227	0.164
	Lp(a)-L+Fib-H	1.047	0.936–1.171	0.421	1.092	0.976–1.222	0.128	1.123	0.987–1.277	0.078
	Lp(a)-M+Fib-L	1.136	1.025–1.259	0.015	1.096	0.989–1.215	0.081	1.084	0.963–1.220	0.184
	Lp(a)-M+Fib-M	1.182	1.069–1.308	0.001	1.135	1.026–1.255	0.014	1.134	1.057–1.336	0.033
	Lp(a)-M+Fib-H	1.226	1.108–1.357	$<$ 0.001	1.195	1.080–1.323	0.001	1.188	1.057–1.336	0.004
	Lp(a)-H+Fib-L	1.467	1.317–1.635	$<$ 0.001	1.447	1.299–1.613	$<$ 0.001	1.351	1.192–1.531	$<$ 0.001
	Lp(a)-H+Fib-M	1.611	1.467–1.770	$<$0.001	1.531	1.394–1.682	$<$ 0.001	1.472	1.321–1.640	$<$0.001
	Lp(a)-H+F ib-H	1.702	1.558–1.859	$<$0.001	1.645	1.506–1.797	$<$ 0.001	1.592	1.437–1.763	$<$ 0.001

Model 1, Unadjusted model. Model 2, Adjusted for age and gender. Model 3, Hyperlipemia, diabetes mellitus, chronic kidney disease, smoking, hypertension, and medications such as drug Statins.

Table 3
C-statistic of Lp(a) and Fib categories for anticipating all-cause mortality

Models	C-statistic (95% CI)	ΔC-statistic (95% CI)	p-value
Original model	0.643 (0.635–0.651)	–	< 0.05
Original model+Lp(a) categories	0.651 (0.643–0.660)	0.008 (0.008–0.009)	< 0.05
Original model + Fib categories	0.645 (0.636–0.653)	0.002 (0.001–0.002)	< 0.05
Original model + combined categories	0.652 (0.644–0.660)	0.009 (0.009–0.009)	< 0.05

The original model included age, gender, diabetes mellitus, chronic kidney disease, smoking, hypertension, and hyperlipidemia as risk factors.

we discovered that high Lp(a) and Fib levels could increase the risk of developing all-cause mortality 1.219 and 1.415-fold, respectively. However, patients in the Lp(a)-H and Fib-H group had a 1.592-fold greater all-cause mortality risk. In addition, the predictive model based on both Lp(a) and Fib promoted the prognostic performance for adverse events by 0.009.

Although several studies evaluated the Fib and Lp(a) effect on the risk of developing main adverse cardiovascular and cerebrovascular events (MACCE) in individuals with CAD, the findings remain controversial. Some investigations revealed the vital function of Fib and/or Lp(a) in promoting cardiovascular disorder development [21,22,23,24,25] and CVEs [26,27,28,29,30,31] The 'PROCAM' study showed that, compared with healthy men with low low-density lipoprotein (LDL) and Fib levels, patients with high LDL and Fib levels had a 6.1-fold raised risk of developing coronary conditions like sudden cardiac mortality, as well as fatal and nonfatal AMI. Additionally, Fib was also an independent CAD risk factor ($P < 0.05$) in the PROCAM study [32]. An observational single-centre investigation showed that, compared to traditional risk factors, raised Lp(a) levels can enhance the risk of developing MACCE by a factor of 2 in patients with suspected CAD who had been subjected to CAG [33]. Conversely, a nested case-control study found no connection between baseline Lp(a) levels and the risk of developing coronary events or ischemic stroke in patients who received dalcetrapib after experiencing acute coronary syndrome [34]. The 'LURIC' study enrolled 3,313 subjects with established coronary heart disease and showed that although coronary heart disease severity was linked with high Lp(a) levels and the presence of Lp (a) single-nucleotide polymorphisms (rs10455872 and rs3798220), no relationship was detected between Lp(a) and all-cause and cardiovascular mortality [35]. The variation in the LURIC study outcomes may have been due to the different study populations and endpoint events.

The present investigation successfully identified raised levels of Lp(a) and Fib as significant risk factors that are associated with the occurrence of long-term adverse outcomes, even after the adjustment of confounders. The effect of inflammation on the development and advancement of atherosclerosis is crucial since it may involve plaque instability and the progression of cardiovascular disorders [36]. In this regard, Lp(a) can impact the anti-inflammatory pathway, trigger vasodilation mediated by nitric oxide, and alter the balance of procoagulant and anticoagulant agents within blood vessel walls [37]. It also participates in the construction of atheromatous plaques, which may cause ischemic and stenosis events. High Fib levels (above 3.5 g/L) have been associated with several inflammatory diseases, including CAD [38, 39]. Additionally, Lp(a) exhibits a significant resemblance to plasminogen and exerts anti-fibrinolytic impacts through its Apo[a] constituent [6]. A crucial component of the fibrinolytic system, Fib adds to the complexity of this relationship. Elevated levels of Lp(a) and Fib can potentially disrupt the inflammatory and coagulation pathways, thereby increasing the risk of CVEs [40].

To date, very few investigations have evaluated the influence of Lp(a) and Fib on prognosis in individuals with CAD. The Quebec Cardiovascular Study showed that high Fib and Lp(a) levels can significantly increase the CAD risk in men who are free of clinical CAD [41]. However, this study exclusively assessed the susceptibility to CAD in an ostensibly healthy male population. In contrast, our investigation

encompassed both male and female patients diagnosed with CAD, revealing a heightened risk of all-cause mortality associated with elevated levels of Lp(a) and Fib-H. Caiyan Cui et al. found that patients with ACS had an elevated risk of developing MACCE, all-cause mortality, nonfatal myocardial infarction and stroke, as well as revascularisation if their Fib levels exceeded 3.08 g/L and their Lp(a) levels were above 300 mg/L [13]. The Lp(a)-and-Fib-based model further enhanced the prediction accuracy for developing adverse events in these patients [14]. Similarly, Yan Zhang et al. showed that combining Fib and Lp(a) can promote the prediction of recurrent CVEs in angiographically proven stable individuals with CAD [15]. Consistent with these studies, we also found that the incorporation of Fib and Lp(a) levels could improve the all-cause mortality prediction. However, compared to previous studies, our research had a larger patient cohort, a longer follow-up time, and different endpoints. In addition, we also included patients with SCAD and ACS.

4.1. Limitations

Our investigation has several restrictions that must be acknowledged. While it is vital to note that this study was observational and conducted within a single centre, which restricted our capacity to draw direct causal effects, the study nonetheless benefitted from a substantial sample size and a lengthy follow-up period. Therefore, the present research still provides a robust representation of patients with CAD in southern China. Additionally, Fib and Lp(a) levels were obtained only at the starting point and may have altered over time. Therefore, further research is necessary to examine the long-term effect of Lp(a) and Fib levels on prognosis.

5. Conclusion

High Lp(a) and Fib levels can significantly increase the all-cause mortality risk in individuals with CAD. However, the combined use of both parameters improved the prediction for all-cause mortality, even after accounting for confounders. Our Lp(a) and Fib model can be used to stratify patients with CAD based on the mortality risk, thereby optimising the monitoring of high-risk patients. However, further longitudinal investigations are essential to confirm the validity of the model.

Ethics statement

The research conducted with human subjects underwent a thorough evaluation and received approval from the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019555H(R1)).

Availability of data and materials

The authors will offer the raw data that supports their findings upon receiving an appropriate request.

Conflict of interest

None of the authors have any personal, financial, commercial, or academic conflicts of interest to report.

Funding

No financial support was received for the research, authorship, or publication of this manuscript.

Author contributions

JL had full accessibility to data and was responsible for its integrity and the precision of the data analysis. DKL, DDL, XYH created the concept and design for the study. YYZ, DHH, ZLL data management. DKL, DDL drafted the manuscript. JL and JYC revised the article. Each author made significant contributions to the collection, analysis, and interpretation of the data. The final version was confirmed by all authors.

Acknowledgments

The authors express their gratitude to the staff and individuals who were involved in this research for their significant contributions.

References

[1] Tsao CW, Aday AW, Almarzooq ZI, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. 2023 Feb 21; 147(8): e93-e621. doi: 10.1161/CIR.0000000000001123.

[2] Della Corte V, Todaro F, Cataldi M, Tuttolomondo A. Atherosclerosis and Its Related Laboratory Biomarkers. Int J Mol Sci. 2023 Oct 24; 24(21): 15546. doi: 10.3390/ijms242115546.

[3] Freitas IA, Lima NA, Silva GBD Jr., Castro RL Jr., Patel P, Lima CCV, Lino DODC. Novel biomarkers in the prognosis of patients with atherosclerotic coronary artery disease. Rev Port Cardiol (Engl Ed). 2020 Nov; 39(11): 667-672. English, Portuguese. doi: 10.1016/j.repc.2020.05.010. Epub 2020 Oct 24. PMID: 33239161.

[4] Ferretti G, Bacchetti T, Johnston TP, et al. Lipoprotein(a): A missing culprit in the management of athero-thrombosis? J Cell Physiol. 2018 Apr; 233(4): 2966-2981. doi: 10.1002/jcp.26050.

[5] Gragnano F, Calabrò P. Role of dual lipid-lowering therapy in coronary atherosclerosis regression: Evidence from recent studies. Atherosclerosis. 2018 Feb; 269: 219-228. doi: 10.1016/j.atherosclerosis.2018.01.012.

[6] From the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), et al. Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke. Int J Stroke. 2018 Aug; 13(6): 612-632. doi: 10.1177/1747493018778713.

[7] Boffa MB. Beyond fibrinolysis: The confounding role of Lp(a) in thrombosis. Atherosclerosis. 2022 May; 349: 72-81. doi: 10.1016/j.atherosclerosis.2022.04.009.

[8] Saeedi R, Frohlich J. Lipoprotein (a), an independent cardiovascular risk marker. Clin Diabetes Endocrinol. 2016 Mar 31; 2: 7. doi: 10.1186/s40842-016-0024-x.

[9] Shabani M, Bakhshi H, Ostovaneh MR, et al. Temporal change in inflammatory biomarkers and risk of cardiovascular events: the Multi-ethnic Study of Atherosclerosis. ESC Heart Fail. 2021 Oct; 8(5): 3769-3782. doi: 10.1002/ehf2.13445.

[10] Gencer B, Mach F. Potential of Lipoprotein(a)-Lowering Strategies in Treating Coronary Artery Disease. Drugs. 2020 Feb; 80(3): 229-239. doi: 10.1007/s40265-019-01243-5. PMID: 31916186.

[11] Cho SMJ, Koyama S, Honigberg MC, Surakka I, Haidermota S, Ganesh S, Patel AP, Bhattacharya R, Lee H, Kim HC, Natarajan P. Genetic, sociodemographic, lifestyle, and clinical risk factors of recurrent coronary artery disease events: a population-based cohort study. Eur Heart J. 2023 Sep 21; 44(36): 3456-3465. doi: 10.1093/eurheartj/ehad380.

[12] Su H, Cao Y, Chen Q, Ye T, Cui C, Chen X, Yang S, Qi L, Long Y, Xiong S, Cai L. The association between fibrinogen levels and severity of coronary artery disease and long-term prognosis following percutaneous coronary intervention in patients with type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2023 Nov 29; 14: 1287855. doi: 10.3389/fendo.2023.1287855.

[13] Kryczka KE, Kruk M, Demkow M, Lubiszewska B. Fibrinogen and a Triad of Thrombosis, Inflammation, and the Renin-Angiotensin System in Premature Coronary Artery Disease in Women: A New Insight into Sex-Related Differences in the Pathogenesis of the Disease. Biomolecules. 2021 Jul 15; 11(7): 1036. doi: 10.3390/biom11071036. PMID: 34356659; PMCID: PMC8301902.

[14] Cui CY, Ye T, Cheng LC, et al. Lipoprotein a Combined with Fibrinogen as an Independent Predictor of Long-Term Prognosis in Patients with Acute Coronary Syndrome: A Multi-Center Retrospective Study. J Cardiovasc Dev Dis. 2022 Sep 23; 9(10): 322. doi: 10.3390/jcdd9100322.

[15] Wang H, Wu P, Jiang D, Zhang H, Zhang J, Zong Y, Han Y. Relationship between serum homocysteine, fibrinogen, lipoprotein-a level, and peripheral arterial disease: a dose-response meta-analysis. Eur J Med Res. 2022 Nov 21; 27(1): 261. doi: 10.1186/s40001-022-00870-1. PMID: 36411481; PMCID: PMC9677707.

[16] Lin J, Reilly MP, Terembula K, et al. Plasma lipoprotein(a) levels are associated with mild renal impairment in type 2 diabetics independent of albuminuria. PLoS One. 2014 Dec 9; 9(12): e114397. doi: 10.1371/journal.pone.0114397.
[17] Zhang Y, Jin JL, Cao YX, Liu HH, Zhang HW, Guo YL, Wu NQ, Gao Y, Hua Q, Li YF, Xu RX, Cui CJ, Liu G, Dong Q, Sun J, Li JJ. Prognostic utility of lipoprotein(a) combined with fibrinogen in patients with stable coronary artery disease: a prospective, large cohort study. J Transl Med. 2020 Oct 1; 18(1): 373. doi: 10.1186/s12967-020-02546-y.
[18] Roth D, Bloom RD, Molnar MZ, et al. KDOQI US Commentary on the 2018 KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C. Am J Kidney Dis. 2020 May; 75(5): 665-683. doi: 10.1053/j.ajkd.2019.12.016.
[19] Guler A, Turkmen I, Atmaca S, Karakurt H, Kahraman S, Aydin S, Sevinc S, Tukenmez Karakurt S, Turkvatan Cansever A, Erturk M, Babur Guler G. Influence of cardiac biomarkers on predicting significant coronary artery disease in hypertrophic cardiomyopathy patients. Heart Vessels. 2023 Nov; 38(11): 1329-1336. doi: 10.1007/s00380-023-02287-0.
[20] Newman JD, Anthopolos R, Ruggles KV, Cornwell M, Reynolds HR, Bangalore S, Mavromatis K, Held C, Wallentin L, Kullo IJ, McManus B, Newby LKK, Rosenberg Y, Hochman JS, Maron DJ, Berger JS, ISCHEMIA Biorepository Research Group. Biomarkers and cardiovascular events in patients with stable coronary disease in the ISCHEMIA Trials. Am Heart J. 2023 Dec; 266: 61-73. doi: 10.1016/j.ahj.2023.08.007.
[21] Gilliland TC, Liu Y, Mohebi R, et al. Lipoprotein(a), Oxidized Phospholipids, and Coronary Artery Disease Severity and Outcomes. J Am Coll Cardiol. 2023 May 9; 81(18): 1780-1792. doi: 10.1016/j.jacc.2023.02.050.
[22] Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, et al. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA. 2009 Jun 10; 301(22): 2331-9. doi: 10.1001/jama.2009.801.
[23] Li JJ, Ma CS, Zhao D, et al. Lipoprotein(a) and Cardiovascular Disease in Chinese Population: A Beijing Heart Society Expert Scientific Statement. JACC Asia. 2022 Nov 15; 2(6): 653-665. doi: 10.1016/j.jacasi.2022.08.015.
[24] Cao YX, Liu HH, Sun D, et al. The different relations of PCSK9 and Lp(a) to the presence and severity of atherosclerotic lesions in patients with familial hypercholesterolemia. Atherosclerosis. 2018 Oct; 277: 7-14. doi: 10.1016/j.atherosclerosis.2018.07.030.
[25] Cui Z, Zhao G, Liu X. Blood fibrinogen level as a biomarker of adverse outcomes in patients with coronary artery disease: A systematic review and meta-analysis. Medicine (Baltimore). 2022 Aug 19; 101(33): e30117. doi: 10.1097/MD.0000000000030117.
[26] Nestel PJ, Barnes EH, Tonkin AM, et al. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. Arterioscler Thromb Vasc Biol. 2013 Dec; 33(12): 2902-8. doi: 10.1161/ATVBAHA.113.302479.
[27] Suwa S, Ogita M, Miyauchi K, et al. Impact of Lipoprotein (a) on Long-Term Outcomes in Patients with Coronary Artery Disease Treated with Statin After a First Percutaneous Coronary Intervention. J Atheroscler Thromb. 2017 Nov 1; 24(11): 1125-1131. doi: 10.5551/jat.38794.
[28] Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. J Am Coll Cardiol. 2017 Feb 14; 69(6): 692-711. doi: 10.1016/j.jacc.2016.11.042.
[29] O'Donoghue ML, Morrow DA, Tsimikas S, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. J Am Coll Cardiol. 2014 Feb 18; 63(6): 520-7. doi: 10.1016/j.jacc.2013.09.042.
[30] Jin JL, Cao YX, Zhang HW, et al. Lipoprotein(a) and Cardiovascular Outcomes in Patients With Coronary Artery Disease and Prediabetes or Diabetes. Diabetes Care. 2019 Jul; 42(7): 1312-1318. doi: 10.2337/dc19-0274.
[31] O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. Circulation. 2019 Mar 19; 139(12): 1483-1492. doi: 10.1161/CIRCULATIONAHA.118.037184.
[32] Kris-Etherton PM, Stewart PW, Ginsberg HN, et al. The Type and Amount of Dietary Fat Affect Plasma Factor VIIc, Fibrinogen, and PAI-1 in Healthy Individuals and Individuals at High Cardiovascular Disease Risk: 2 Randomized Controlled Trials. J Nutr. 2020 Aug 1; 150(8): 2089-2100. doi: 10.1093/jn/nxaa137.
[33] Kwon SW, Lee BK, Hong BK, et al. Prognostic significance of elevated lipoprotein(a) in coronary artery revascularization patients. Int J Cardiol. 2013 Sep 1; 167(5): 1990-4. doi: 10.1016/j.ijcard.2012.05.007.
[34] Schwartz GG, Ballantyne CM, Barter PJ, et al. Association of Lipoprotein(a) With Risk of Recurrent Ischemic Events Following Acute Coronary Syndrome: Analysis of the dal-Outcomes Randomized Clinical Trial. JAMA Cardiol. 2018 Feb 1; 3(2): 164-168. doi: 10.1001/jamacardio.2017.3833.
[35] Moissl AP, Delgado GE, Krämer BK, et al. Gender- and subgroup-specific sensitivity analysis of alcohol consumption and mortality in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Data Brief. 2022 Jan 26; 41: 107873. doi: 10.1016/j.dib.2022.107873.
[36] Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012 Sep; 32(9): 2045-51. doi: 10.1161/ATVBAHA.108.179705.
[37] Enas EA, Chacko V, Senthilkumar A, et al. Elevated lipoprotein(a)–a genetic risk factor for premature vascular disease in people with and without standard risk factors: a review. Dis Mon. 2006 Jan; 52(1): 5-50. doi: 10.1016/j.disamonth.2006.01.002.

[38] Surma S, Banach M. Fibrinogen and Atherosclerotic Cardiovascular Diseases-Review of the Literature and Clinical Studies. Int J Mol Sci. 2021 Dec 24; 23(1): 193. doi: 10.3390/ijms23010193.
[39] Davalos D, Akassoglou K. Fibrinogen as a key regulator of inflammation in disease. Semin Immunopathol. 2012 Jan; 34(1): 43-62. doi: 10.1007/s00281-011-0290-8.
[40] Li H, Zhang P, Yuan S, Tian H, Tian D, Liu M. Modeling analysis of the relationship between atherosclerosis and related inflammatory factors. Saudi J Biol Sci. 2017 Dec; 24(8): 1803-1809. doi: 10.1016/j.sjbs.2017.11.016. Epub 2017 Nov 17.
[41] Cantin B, Després JP, Lamarche B, et al. Association of fibrinogen and lipoprotein(a) as a coronary heart disease risk factor in men (The Quebec Cardiovascular Study). Am J Cardiol. 2002 Mar 15; 89(6): 662-6. doi: 10.1016/s0002-9149(01)02336-0.