Lipids in Health and Disease

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Lipoprotein(a) molar concentrations rather than genetic variants better predict coronary artery disease risk and severity in Han Chinese population

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Abstract

Background It is well established that increased lipoprotein(a) [Lp(a)] is a significant risk factor for coronary artery disease (CAD). Plasma Lp(a) levels are genetically determined and vary widely between different races, regions and individuals. However, most studies on Lp(a) associated genetic variants have focused on the Caucasian population currently. Our study aimed to test the associations among *LPA* genetic variants, Lp(a) concentrations, and CAD in a Han Chinese cohort.

Methods A total of 3779 patients undergoing coronary angiography were recruited from Tongji Hospital. *LPA* Kringle IV type 2 (KIV-2) copies were detected using TaqMan probe real-time quantitative polymerase chain reaction (qPCR) analysis and fifteen single nucleotide polymorphisms (SNPs) within the *LPA* gene were detected using TaqMan probe genotyping analysis. *LPA* genetic risk score (GRS) was computed based on seven SNPs associated with Lp(a). Associations of *LPA* genetic variants with Lp(a) and CAD were evaluated using linear regression analyses and Logistic regression analyses, respectively.

Results Compared with the first quartile of Lp(a), the fourth quartile exhibited a significant association with CAD [odds ratio (OR): 2.08, 95% confidence interval (CI): 1.67–2.59, $p < 0.001$], multivessel CAD [OR: 2.54, 95% CI: 2.06–3.12, $p < 0.001$], and high Gensini scores [OR: 2.17, 95% CI: 1.77–2.66, $p < 0.001$] after multivariable adjustment for cardiovascular risk factors. Both *LPA* GRS and KIV-2 quartiles were associated with Lp(a) concentrations (both p for trend < 0.001). However, after false discovery rate (FDR) correction, there were no significant associations of *LPA* genetic variants with CAD, multivessel CAD or high Gensini scores.

Conclusions Our findings indicate *LPA* genetic variants can affect Lp(a) levels, but do not exceed Lp(a) molar concentrations to predict CAD incidence and severity usefully, highlighting the importance of Lp(a) detection and management.

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Keywords *LPA* gene, Kringle IV type 2 copies, Single nucleotide polymorphism, Genetic risk score, Genetics, Epidemiology

Introduction

Coronary artery diseases (CAD) are the principal causes of morbidity and mortality globally [1, 2]. Dyslipidemia is a vital modifiable risk factor for CAD [3] and has seriously impacted public health [4]. Despite remarkable progress in prevention and treatment, the residual risk for cardiovascular disease remains significant, which can be partly attributed to increased lipoprotein(a) [Lp(a)] concentrations, highlighting the importance of Lp(a) management [5].

Lp(a) consists of one molecule of low-density lipoprotein (LDL)-like particle comprising apolipoprotein B (ApoB)-100 and one molecule of apolipoprotein(a) [Apo(a)], which contains a site that covalently binds oxidized phospholipids [6]. Apo(a) includes circular protein structures called Kringle, Kringle IV and Kringle V, in addition to a non-functional protease domain [7]. Kringle IV has 10 types, from type 1 to type 10, of which the copies of Kringle IV type 2 (KIV-2) are variable and genetically determined [8]. Lp(a) may contribute to CAD by promoting inflammation, enhancing atherosclerosis and inhibiting fibrinolytic reaction [9]. Extensive genetic and epidemiological data confirm a causal relationship between increased Lp(a) concentrations and CAD incidence and severity [10–15]. Currently, several therapeutic agents that reduce the Lp(a) concentrations are in clinical trials [16–18].

Lp(a) levels exhibit strong heritability and differ greatly among various races, regions and individuals [19–21]. Lp(a) variation is primarily explained by the *LPA* gene locus, which codes highly polymorphic Apo(a), including KIV-2 copy number variations (CNVs), single nucleotide polymorphisms (SNPs), and other relevant genetic variants [10, 11, 21]. The negative association between *LPA* KIV-2 CNV and Lp(a) levels has been confirmed [10, 22], while the relationship between KIV-2 copies and cardiovascular outcomes remains controversial. Pia R. Kamstrup et al. found the quartiles of KIV-2 repeats were associated with CAD and myocardial infraction (MI) in European individuals [10, 23], and a mendelian randomization analysis indicated lower *LPA* KIV-2 copies can increase the risk of CAD independently [24]. In addition, a large prospective study showed low KIV-2 copies were associated with cardiovascular and all-cause mortality [22]. Conversely, Daniel F. Gudbjartsson et al. demonstrated Lp(a) molar concentration, rather than Apo(a) isoform size, is the key factor influencing cardiovascular disease risk [25].

Notably, studies regarding Lp(a) and associated genetic variants have primarily been conducted in European and American populations. Given the racial differences in both Lp(a) and the spectrum and risk factors of CAD [20, 26], these research results may not be applicable to the Han Chinese population. However, related studies among the Han Chinese population are scarce, limited by either relatively small sample sizes or the lack of comprehensive coverage of *LPA* genetic variants [27–29].

To clarify the relationship between KIV-2 copies and CAD and to address the issue that relevant studies on Han Chinese population are limited, we tested the associations of *LPA* genetic variants with Lp(a) concentrations and CAD incidence and severity in a Han Chinese cohort, expecting to gain a more comprehensive understanding of Lp(a).

Methods

Research design and participant recruitment

Participants who underwent coronary angiography were selected from Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology in Wuhan, China. Peripheral blood was obtained from arterial catheters placed in the radial or femoral arteries before coronary angiography. All blood samples were centrifuged immediately, divided into plasma and blood cells, and stored at -80 degrees before the present experiment. The study excluded patients lacking Lp(a) data, patients who were not of Han nationality, patients who were pregnant, patients with malignant tumors or severe hematological diseases, and patients lacking valid KIV-2 number of repeats or SNPs phenotyping data. Eventually, a total of 3,779 patients were included in the study, among whom 2528 (66.9%) patients had confirmed CAD. The flow chart of the patient recruitment was shown in Fig. 1.

The research procedures were authorized by the ethics committee of Tongji Hospital (TJ-IRB20211259) and adhered to the Declaration of Helsinki. All patients signed informed consent before inclusion.

Data gathering and definitions

In this study, clinical information was recorded from a large scientific research data center in the hospital. Lp(a) molar concentrations were measured in nanomoles per liter (nmol/L) using latex enhanced immunoturbidimetry. Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (ApoA1), ApoB and Lp(a) levels were all directly measured using the ROCHE COBAS 8000 platform in the central laboratory of the hospital. CAD was defined as at least 1 > 50%

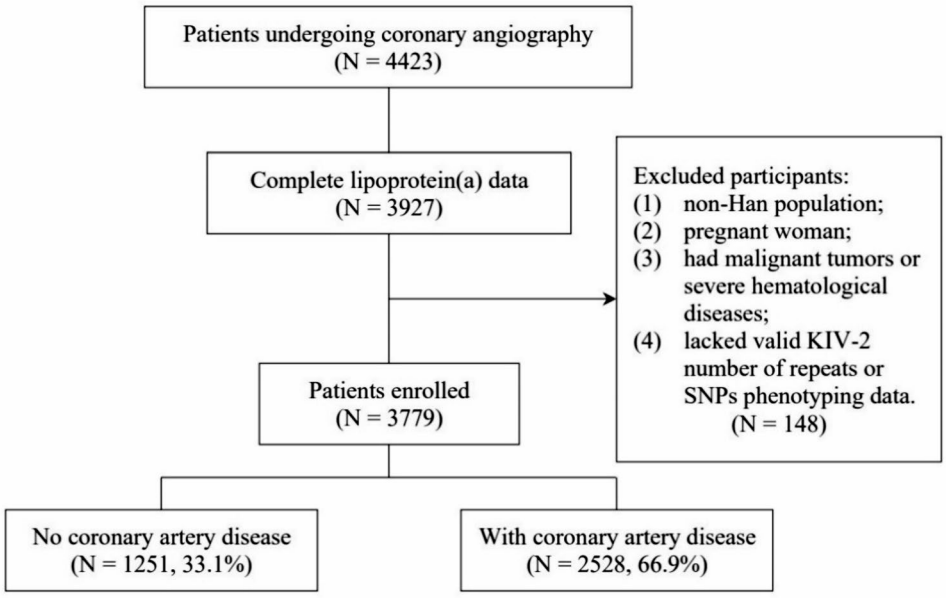

Fig. 1 The flow chart of the patient recruitment. KIV-2, Kringle IV type 2; SNPs, single nucleotide polymorphisms

coronary lesion in the left main (LM), left anterior descending (LAD), left circumflex (LCx), or right coronary artery (RCA). In the LM, lesion over 50% was considered as severe lesion, and in the LAD, LCx, or RCA, lesion over 70% was considered as severe lesion. Multivessel CAD was defined as at least 2 severe coronary lesions [30]. The Gensini score quantifying the severity of CAD was calculated according to an established method [31]. Smoking status was divided into smokers and never smokers, and drinking status was divided into drinkers and never drinkers. Other related diseases were defined based on self-reported medical history, self-reported medication history, laboratory tests, imaging examinations and discharge diagnosis.

Assessment of KIV-2 number of repeats

Genomic DNA was extracted from peripheral blood cells using a Blood DNA Isolation Mini Kit (Vazyme, Nanjing, China). KIV-2 copies of *LPA* were detected by real-time quantitative polymerase chain reaction (qPCR) analysis using the 7900HT Sequence Detection System (Applied Biosystems, California, USA) [10]. The *ALB* gene served as a control gene, and each 384-well plate included a blank control, a calibrator sample and a control sample selected from participants. The intraplate and interplate coefficients of variation of CT values were 0.05% and 2%, respectively. The number of KIV-2 repeats were calculated by ΔΔCt relative quantification. Sequences for primers, TaqMan probes, and a calibrator were presented in Supplementary Table S1 [10]. The doubling dilution standard curves of a DNA sample (Supplementary Figure S1) indicated comparable and acceptable amplification efficiencies for both the KIV-2 and the *ALB* assays.

SNPs ascertainment and phenotyping

Based on SNP data of *LPA* gene (GRCh38 chr6:160531482–160664275) in Southern Han Chinese, China (CHS) and Han Chinese in Beijing, China (CHB) populations from 1000 Genomes, linkage disequilibrium (LD) analysis was performed using Haploview 4.1 (Broad Institute, Cambridge, USA) (Supplementary Figure S2). The study selected SNPs with minor allele frequency (MAF) > 0.05 and Hardy-Weinberg equilibrium *p*-value > 0.05, and then twenty tag SNPs was captured at $r^2 \geq 0.8$. Five SNPs were excluded due to the inability to be accurately genotyped, four of which were located in the CNV sequences and one of which were incorporated in the repetitive CT sequences. Finally, fifteen SNPs (Supplementary Table S2) were genotyped, four of which (rs3798220, rs7765781, rs1801693, and rs3124784) were located in the exon region. Primers and TaqMan probes for the fifteen SNPs in the *LPA* gene (Gene ID: 4018) were designed using Primer Express 3.0.1 (Applied Biosystems, California, USA) (Supplementary Table S3). SNPs were genotyped by TaqMan probe genotyping using the 7900HT Sequence Detection System. To verify the accuracy of the genotyping results, 96 randomly selected DNA samples were analyzed by sanger sequencing for each SNP, and all the genotyping results were consistent.

LPA genetic risk score (GRS) calculation

The *LPA* GRS was calculated by summing the counts of risk alleles for per selected SNP, weighted by the effect size [beta coefficient (β)] from association studies of SNPs with inverse-normal transformed Lp(a) concentrations [11]. The weighted scores were then aggregated to generate an overall GRS for each individual.

Statistical analysis

All statistical analyses were conducted by R software version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). All *p*-values were two-tailed, with a value below 0.05 deemed statistically significant unless stated otherwise.

In describing baseline characteristics, Lp(a) levels were grouped according to quartiles. Body mass index (BMI) data were partially missing, with a missing rate of 0.93%. Date were shown as mean ± standard deviation (SD) for normal distribution continuous variables, median [interquartile range (IQR)] for nonnormal distribution continuous variables, or number (proportion, %) for categorical variables. The trend across these quartile groups was assessed using the linear trend test for normal distribution continuous variables, the Cuzick nonparametric test for nonnormal distribution continuous variables and the Cochran-Armitage trend test for categorical variables.

The associations between Lp(a), as a continuous variable, and CAD, multivessel CAD, or high Gensini scores were assessed using restricted cubic splines under multivariable adjustment. Associations of the Lp(a) quartiles with CAD, multivessel CAD, or high Gensini scores were assessed using logistic regression analyses in unadjusted and multivariable-adjusted models. The Gensini scores were divided into low and high groups according to median Gensini level. In all multivariable-adjusted analyses, age, sex, smoking status, hypertension, diabetes, TC, LDL-C and HDL-C were adjusted. To assess the collinearity among covariates, the variance inflation factors (VIFs) were calculated in all multivariable regression models. The results demonstrated that the VIFs were < 5 for all variables, indicating no significant collinearity issues and confirming the robustness of our models. Further, subgroup analyses were conducted according to age (below and above 45 years) by adjusting sex, smoking status, hypertension, diabetes, TC, LDL-C and HDL-C. The interaction between the Lp(a) quartiles and age was also evaluated.

For statistical analysis, highly skewed Lp(a) data was normalized using inverse-normal transformation method. The LD analysis and Hardy-Weinberg equilibrium tests of SNPs were conducted by Haploview 4.1 (Broad Institute, Cambridge, USA). Associations between twelve SNPs, which conform to the Hardy-Weinberg equilibrium, and Lp(a) levels were evaluated by linear regression. Based on Bonferroni correction, SNPs with *p*-values less than 0.05/12 were included in the GRS calculation. Linear regression analyses were applied to assess the associations of the KIV-2 and GRS quartiles with inverse-normal transformed Lp(a) concentrations, and the trend *p*-values were evaluated. Furthermore, associations of *LPA* genetic variants with CAD, multivessel CAD, and high Gensini scores were evaluated using logistic regression analyses under multivariable adjustment, and subgroup analyses were conducted according to age. In presenting associations of SNPs, the Benjamini-Hochberg correction was used to control the false discovery rate (FDR). Prior to analyzing *LPA* KIV-2 copies and GRS as continuous variables, an inverse normal transformation was applied.

Results

Study subjects and baseline characteristics

Baseline characteristics of the 3,779 research participants were shown according to Lp(a) level quartiles (Table 1). The average age was 58.24 ± 13.25 years and 2,570 (68.0%) were male. The distribution of Lp(a) concentrations was extremely left-skewed (Fig. 2), and the median Lp(a) concentration was 25.30 nmol/L [IQR: 10.90–70.05 nmol/L]. The mean TC concentration was 4.10 ± 1.11 mmol/L and the average LDL-C concentration was 2.41 ± 0.93 mmol/L, both well below the reference value. However, the mean HDL-C concentration was 1.04 ± 0.28 mmol/L, equal to the lower limit of the normal range, and the median TG concentration was 1.61 mmol/L (IQR: 1.06–2.47 mmol/L), slightly below the reference value. Among the study participants, 2,528 (66.9%) patients had CAD and 1,483 (39.2%) patients had multivessel CAD. The median Gensini score was 24 (IQR: 3 to 62). Across the Lp(a) quartiles, age and BMI levels exhibited significant trends (p for trend < 0.01 and p for trend < 0.001, respectively). Similarly, TC, LDL-C, HDL-C, and ApoB levels exhibited significant positive trends with increasing Lp(a) levels (all p for trend < 0.001, except for HDL-C p for trend < 0.01). Notably, the risk of CAD and multivessel CAD, and the Gensini scores showed significant upward trends with increasing Lp(a) quartiles (all p for trend < 0.001).

Lp(a) was associated with coronary artery disease incidence and severity

When Lp(a) was treated as a continuous variable, the odds ratios (ORs) for CAD, multivessel CAD and high Gensini (Gensini > median) increased with elevated concentrations of Lp(a) after adjustment for conventional risk factors and blood lipids, including age, sex, smoking status, hypertension, diabetes, TC, LDL-C and HDL-C (Fig. 2). When the first quartile (Q1) was used as a reference, the unadjusted ORs of the fourth quartile (Q4) Lp(a) levels were 1.83 [95% confidence interval (CI): 1.51–2.23, p < 0.001] for CAD, 2.22 (95% CI: 1.84–2.69, p < 0.001) for multivessel CAD, and 1.94 (95% CI: 1.62–2.33, p < 0.001) for high Gensini scores (Fig. 3A). In multivariable-adjusted models, the corresponding ORs increased to 2.08 (1.67–2.59), 2.54 (2.06–3.12) and 2.17 (1.77–2.66), respectively. Elevated Lp(a) quartiles were significantly associated with a stepwise increased in the

Table 1 Baseline characteristics of the participants stratified by lipoprotein(a) quartiles

		Lipoprotein(a), nmol/L				
	All (*N* = 3779)	**Q1 (*N* = 940)**	**Q2 (*N* = 947)**	**Q3 (*N* = 947)**	**Q4 (*N* = 945)**	***p* for trend**
Age, y	58.24 ± 13.25	57.33 ± 13.58	58.15 ± 13.61	58.44 ± 13.45	59.04 ± 12.27	< 0.01
Male	2570 (0.68)	653 (0.69)	636 (0.67)	652 (0.69)	629 (0.67)	0.30
BMI[a]	24.97 ± 3.63	25.24 ± 3.73	25.05 ± 3.49	24.94 ± 3.64	24.66 ± 3.63	< 0.001
Smokers	1584 (0.42)	378 (0.40)	397 (0.42)	405 (0.43)	404 (0.43)	0.24
Drinkers	1332 (0.35)	348 (0.37)	334 (0.35)	318 (0.34)	332 (0.35)	0.29
Hypertension	2217 (0.59)	541 (0.58)	553 (0.58)	566 (0.60)	557 (0.59)	0.44
Diabetes	1411 (0.38)	382 (0.41)	338 (0.36)	343 (0.36)	348 (0.37)	0.12
TC, mmol/L	4.10 ± 1.11	3.96 ± 1.15	4.06 ± 1.08	4.16 ± 1.12	4.22 ± 1.09	< 0.001
TG, mmol/L	1.61 (1.06–2.47)	1.75 (1.11–2.87)	1.58 (1.05–2.41)	1.60 (1.05–2.38)	1.54 (1.04–2.34)	0.05
LDL-C, mmol/L	2.41 ± 0.93	2.19 ± 0.85	2.38 ± 0.91	2.49 ± 0.97	2.57 ± 0.94	< 0.001
HDL-C, mmol/L	1.04 ± 0.28	1.03 ± 0.28	1.04 ± 0.28	1.04 ± 0.28	1.07 ± 0.27	< 0.01
ApoA1, g/L	1.23 ± 0.25	1.24 ± 0.24	1.23 ± 0.25	1.23 ± 0.25	1.24 ± 0.25	0.97
ApoB, g/L	0.78 ± 0.26	0.74 ± 0.25	0.77 ± 0.26	0.80 ± 0.28	0.82 ± 0.27	< 0.001
Lp(a), nmol/L	25.30 (10.90-70.05)	6.60 (4.50–8.60)	16.70 (13.65–20.15)	40.50 (31.60–53.70)	140.80 (99.50-203.80)	< 0.001
CAD	2528 (0.67)	574 (0.61)	622 (0.66)	631 (0.67)	701 (0.74)	< 0.001
Multivessel CAD	1483 (0.39)	278 (0.30)	347 (0.37)	402 (0.42)	456 (0.48)	< 0.001
Gensini score	24.00 (3.00–62.00)	17.00 (0.00–48.00)	23.00 (2.00–60.00)	26.00 (2.25-65.00)	36.00 (6.00–78.00)	< 0.001

[a] Missing BMI data *N* = 35, and the missing rate was 0.93%

Lp(a) levels overtake 240 nmol/L were calculated as 250 nmol/L, and ApoB levels below 0.2 g/L were calculated as 0.18 g/L. Data were presented as mean ± standard deviation, median (interquartile range), or number (proportion, %). The *p*-values for trend were used to evaluate the trend changes in baseline characteristics across the Lp(a) quartile groups. BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp(a), lipoprotein(a); CAD, coronary artery disease

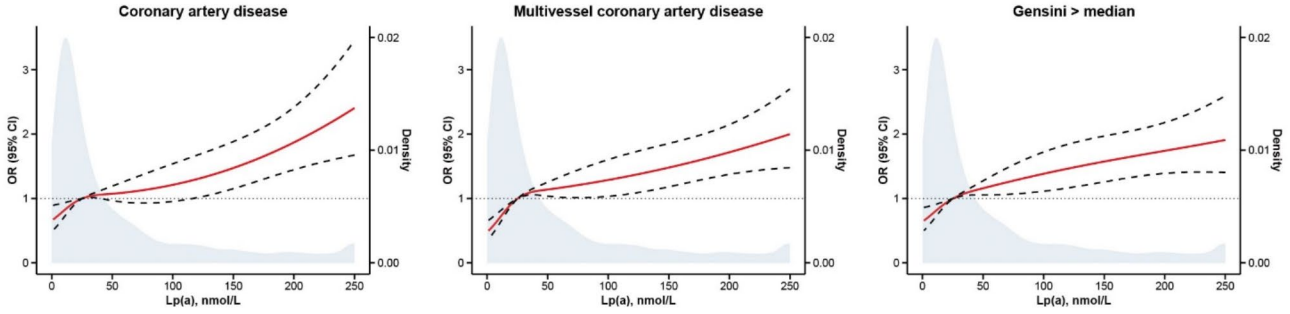

Fig. 2 Risk of CAD, multivessel CAD and high Gensini scores (Gensini > median) by Lp(a) on continuous scales. Lp(a) levels overtake 240 nmol/L were calculated as 250 nmol/L. Kernal density plot (solid) was used to evaluate the distribution of Lp(a) levels. Restricted cubic splines using Logistic regressions were shown with ORs (red solid lines) and 95% CI (black dashed lines). Analyses were multivariable-adjusted for age, sex, smoking status, hypertension, diabetes, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. CAD, coronary artery disease; Lp(a), lipoprotein(a); OR, odds ratio; CI, confidence interval

incidence of CAD, multivessel CAD and high Gensini scores in both unadjusted and multivariable-adjusted models (all *p* for trend < 0.001).

Subgroup analyses based on age were performed under multivariable adjustment (Fig. 3B). For CAD, the OR in Lp(a) Q4 compared with Q1 for patients aged ≤ 45 was 1.72 (95% CI: 1.08–2.73, $p = 0.02$), lower than the OR [2.14 (1.67–2.74), $p < 0.001$] for patients aged > 45. However, the corresponding ORs for those aged ≤ 45 were 3.06 (95% CI: 1.86–5.04, $p < 0.001$) for multivessel CAD and 2.32 (95% CI: 1.46–3.69, $p < 0.001$) for high Gensini, higher than the ORs [2.27 (1.81–2.85) and 2.09 (1.67–2.61), respectively] for those aged > 45. No interaction of the Lp(a) Q4 and age was observed for CAD (*p* for interaction = 0.31), multivessel CAD ($p = 0.43$), and high Gensini scores ($p = 0.94$).

Both *LPA* GRS and KIV-2 copies were associated with lipoprotein(a) level

A total of fifteen SNPs were genotyped in 3,779 participants and three SNPs (rs3124784, rs181039552, and rs9355816) were excluded due to not adhere to Hardy-Weinberg equilibrium. Association studies of twelve SNPs with inverse-normal transformed Lp(a) concentrations were performed, with a *p*-value less than 0.05/12 deemed significant. As shown in Fig. 4A, seven SNPs were significantly associated with inverse normal-transformed Lp(a) levels. Among seven SNPs,

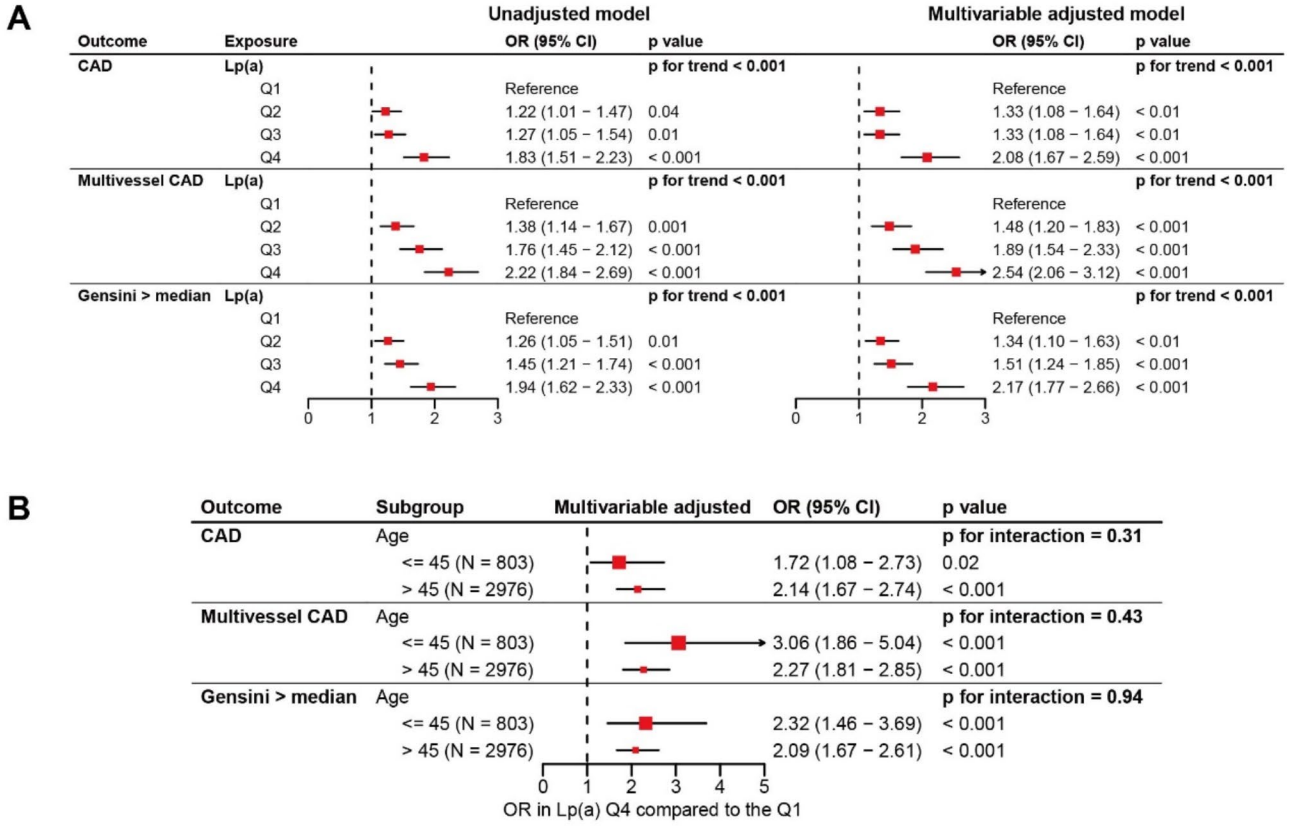

Fig. 3 Risk of CAD, multivessel CAD and high Gensini scores (Gensini > median) by Lp(a) quartiles. **A**: Logistic regressions estimated the ORs (95% CI) of the Lp(a) Q2, Q3 and Q4 compared to Q1 for CAD, multivessel CAD and high Gensini scores in unadjusted and multivariable-adjusted models. In multivariable-adjusted analyses, age, sex, smoking status, hypertension, diabetes, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were adjusted. **B**: ORs (95% CI) of the Lp(a) Q4 compared to Q1 for CAD, multivessel CAD and high Gensini scores in different age subgroups (below and above 45) were shown after adjusting sex, smoking status, hypertension, diabetes, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. The size of box indicates standard error. CAD, coronary artery disease; Lp(a), lipoprotein(a); OR, odds ratio; CI, confidence interval

rs6415084-T [beta coefficient (β) (95% CI): 0.58 (0.52–0.65), $p = 7.06E\text{-}65$] and rs117162385-A [0.22 (0.12–0.33), $p = 3.15E\text{-}5$] showed a positive association with Lp(a). However, rs3798220-C [-0.16 (-0.24 - -0.09), $p = 4.06E\text{-}5$], rs9365171-A [-0.30 (-0.35 - -0.26), $p = 8.27E\text{-}38$], rs77655781-C [-0.33 (-0.37 - -0.29), $p = 6.25E\text{-}48$], rs78363782-C [-0.26 (-0.36 - -0.16), $p = 2.95E\text{-}7$], and rs1367211-T [-0.14 (-0.20 - -0.08), $p = 3.20E\text{-}6$] demonstrated a negative association. The LD analysis of SNPs was performed in Fig. 4B. The *LPA* GRS was defined according to the above seven SNPs. As presented in Fig. 4C, Lp(a) levels exhibited a significant increase across ascending quartiles of the *LPA* GRS (p for trend < 0.001). Moreover, elevated *LPA* KIV-2 quartiles were associated with the decrease in Lp(a) levels (p for trend < 0.001) (Fig. 4D).

No significant associations of *LPA* genetic variants with CAD incidence and severity were found

After Benjamini-Hochberg correction, no statistically significant associations were found between any of twelve SNPs and CAD, multivessel CAD, or high Gensini in multivariable-adjusted models ($p > 0.05$) (Fig. 5). As continuous variables, *LPA* KIV-2 was associated with multivessel CAD [OR (95% CI): 0.92 (0.86–0.99), $p = 0.030$], and after further adjustment of Lp(a) levels, the association was abolished ($p = 0.936$) (Fig. 6A). However, no significant associations were observed between *LPA* KIV-2 and CAD ($p = 0.963$) or high Gensini scores ($p = 0.138$). Likewise, *LPA* GRS on a continuous scale was not associated with CAD ($p = 0.775$), multivessel CAD ($p = 0.642$), and high Gensini ($p = 0.490$) (Fig. 6A). Furthermore, as categorical variables, *LPA* KIV-2 and GRS quartiles showed no significant associations with the occurrence of CAD (p for trend = 0.685 and $p = 0.592$, respectively), multivessel CAD ($p = 0.052$, and $p = 0.900$), and high Gensini scores ($p = 0.287$, and $p = 0.236$) under multivariable adjustment (Supplementary Figure S3). Subgroup analyses demonstrated that regardless of age below or above 45 years, both *LPA* KIV-2 and GRS repeats were not associated with CAD, multivessel CAD and high Gensini

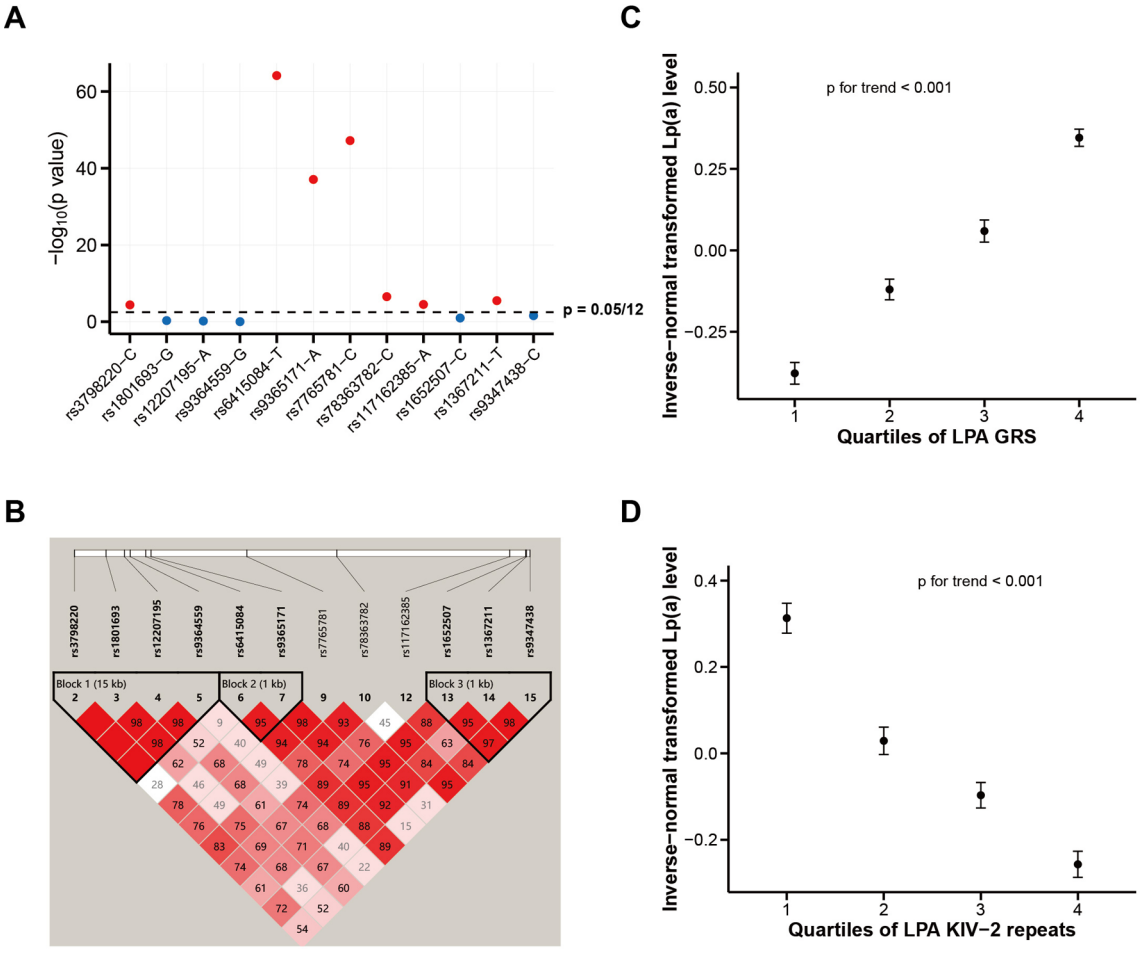

Fig. 4 Associations of *LPA* genetic variants with Lp(a) level. Prior to analysis, Lp(a) data was inverse-normal transformed to reduce skewness. **A**: Association plot of SNPs on Lp(a) levels. The threshold of significance was 0.05/12 (black dashed line). **B**: Linkage disequilibrium analysis of twelve SNPs. The number in the box represents D'. **C**: Mean inverse-normal transformed Lp(a) levels according to the quartiles of *LPA* GRS scores. **D**: Mean inverse-normal transformed Lp(a) levels according to the quartiles of *LPA* KIV-2 repeats. Error bars indicate standard error. Lp(a), lipoprotein(a); SNPs, single nucleotide polymorphisms; GRS, genetic risk score; KIV-2, Kringle IV type 2

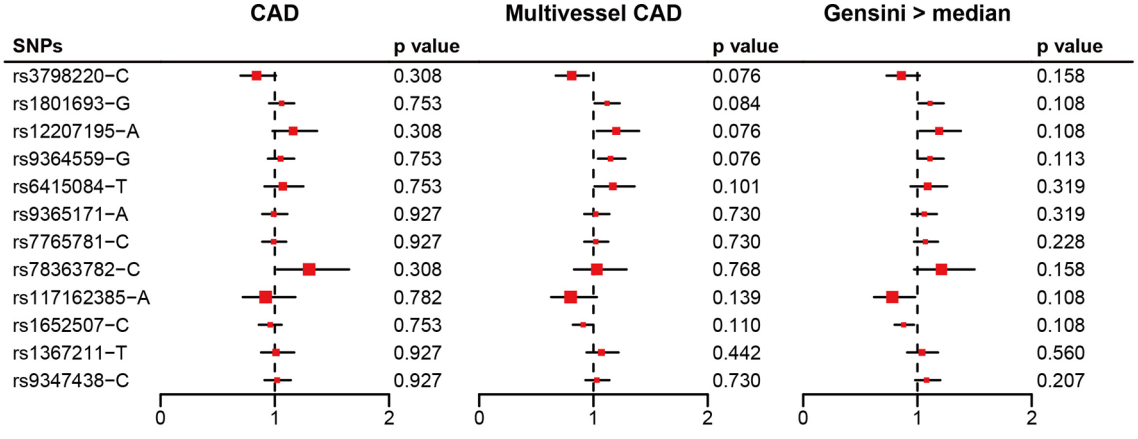

Fig. 5 Associations of twelve SNPs with CAD, multivessel CAD and high Gensini scores (Gensini > median). Analyses were multivariable-adjusted for age, sex, smoking status, hypertension, diabetes, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. *P* values were assessed using the Benjamini-Hochberg correction to control false discovery rate. The size of box indicates standard error. SNPs, single nucleotide polymorphisms; CAD, coronary artery disease

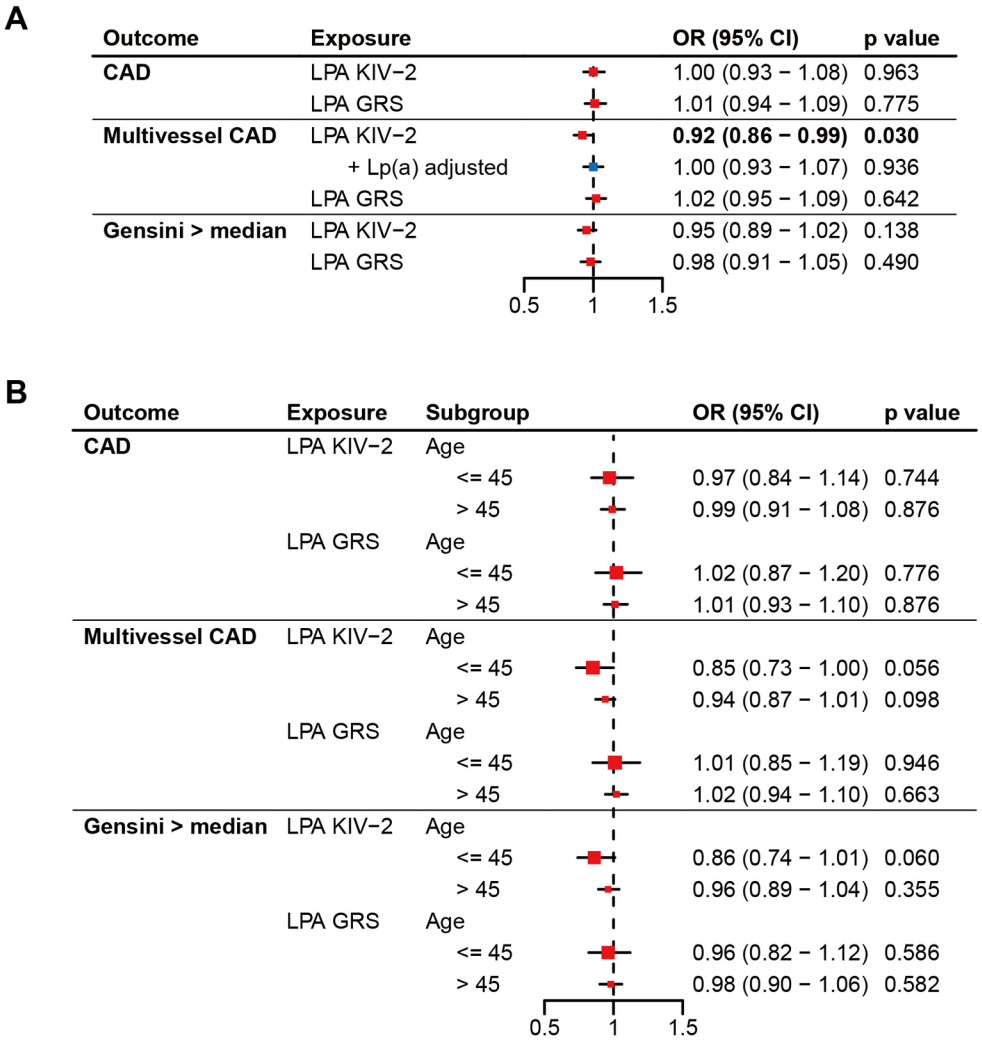

Fig. 6 Risk of CAD, multivessel CAD and high Gensini scores (Gensini > median) by *LPA* KIV-2 and GRS on continuous scales. Prior to analysis, Lp(a), *LPA* KIV-2 and *LPA* GRS data were inverse-normal transformed to reduce skewness. **A**: Logistic regressions estimated the ORs (95% CI). The red box indicates adjusting for age, sex, smoking status, hypertension, diabetes, TC, LDL-C and HDL-C. The blue box indicates adjusting for age, sex, smoking status, hypertension, diabetes, TC, LDL-C, HDL-C and Lp(a). **B**: ORs (95% CI) of the *LPA* KIV-2 and GRS in different age subgroups (below and above 45) were shown. Analyses were adjusted for sex, smoking status, hypertension, diabetes, TC, LDL-C and HDL-C. The size of box indicates standard error. CAD, coronary artery disease; KIV-2, Kringle IV type 2; GRS, genetic risk score; Lp(a), lipoprotein(a); OR, odds ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

after adjusting for confounding factors (all $p > 0.05$) (Fig. 6B, Supplementary Table S4).

Discussion

In our study, we observed the Lp(a) quartiles were strongly associated with the incidence of CAD and the severity of CAD, defined as multivessel CAD and high Gensini scores (Gensini > median), in both unadjusted and adjusted regression analyses, consistent with previous studies [15, 32–34]. Importantly, in adjusted models for age, sex, smoking status, hypertension, diabetes, TC, LDL-C and HDL-C, the associations increased. Moreover, as a continuous variable, the incidence of CAD, multivessel CAD and high Gensini increased progressively with elevated Lp(a) levels. In other ethnic groups, increased Lp(a) levels are also associated with greater complexity of CAD, assessed by SYNTAX I and Gensini scores, consistent with our findings in the Han Chinese population [15, 34].

Our findings further confirm the essential role of Lp(a) in the development of CAD, independent of conventional risk factors and lipids. Despite the pathophysiological mechanisms of Lp(a) remaining unclear, Lp(a) may contribute to CAD incidence and severity through several pathways. As a result of its structural resemblance to LDL, Lp(a) can facilitate the deposition of cholesterol in arterial walls, promoting atherosclerosis [9]. Additionally, the Apo(a) component of Lp(a) resembles plasminogen

and may inhibit the fibrinolytic system, slowing down thrombolysis and increasing the risk of arterial obstruction [35]. Furthermore, Lp(a) may trigger inflammatory responses via oxidized phospholipids, exacerbating atherosclerosis and vascular damage [36].

Unlike other lipoproteins, plasma Lp(a) concentrations are rarely influenced by lifestyle changes or lipid-lowering medications and are mainly affected by the *LPA* gene, which encodes Apo(a) [6]. As acknowledged in previous studies, the larger the KIV-2 number of repeats, the larger the Apo(a) isoform sizes, and thus the lower the Lp(a) concentrations [21]. In accordance with prior researches on Caucasian population [10, 22], we observed that *LPA* KIV-2 copies were negatively associated with Lp(a) concentrations. Interestingly, we observed *LPA* KIV-2 copies as continuous variables were negatively associated with multivessel CAD ($p = 0.030$), and after further adjustment for Lp(a) levels, this association was abolished ($p = 0.936$). This finding indicates that the effect of *LPA* KIV-2 on multivessel CAD is largely due to its influence on Lp(a) levels, rather than an independent relationship. Additionally, no significant associations were observed between *LPA* KIV-2 copies and CAD or high Gensini scores. And as categorical variables, *LPA* KIV-2 quartiles showed no significant associations with CAD risk and severity under multivariable adjustment. These results further support that KIV-2 does not directly contribute to CAD risk and severity beyond its role in modulating Lp(a) levels. Importantly, the research by Daniel F. Gudbjartsson et al. supported our conclusion [25].

In addition to KIV-2 copies, SNPs also have a profound influence on Lp(a) concentrations [21]. Multiple genome-wide association study (GWAS) analyses in Caucasian populations have focused on Lp(a)-related SNPs [12, 37]. Studies in European populations found that two frequent variants in the *LPA* KIV-2 domain were associated with lower Lp(a) levels and decreased coronary risk [38, 39]. A study conducted in four European countries indicated that rs3798220 and rs10455872 were significantly associated with both elevated Lp(a) concentrations and raised cardiovascular risk [12]. Nevertheless, in Han Chinese population, the MAF of rs10455872 is close to zero, and there is no strong positive association observed between rs3798220 and cardiovascular outcomes [27, 28].

In a study of 1,716 CAD patients and 1,572 controls in Southern Han Chinese, rs3798220 was positively associated with CAD, regardless of adjustment for covariates [29]. However, an earlier research of 2,365 MI patients and 2,678 controls in Chinese population found rs3798220 had no association with MI, but was associated with TG [28]. These two studies conducted in Chinese population had different outcomes, CAD and MI, respectively, and none of them evaluated the association among rs3798220 and Lp(a) concentration. In our study, we found rs3798220-C was negatively associated with Lp(a) ($p = 4.06E\text{-}5$), and had no associations with CAD (adjusted $p = 0.308$) and multivessel CAD ($p = 0.076$) after multivariable adjustment. According to a study including 198 people from Hong Kong, China, rs3798220 was not associated with low KIV-2 repeats and high Lp(a) in Asians, unlike the high association between rs3798220-C and low KIV-2 copies in European populations [40]. This likely explained why rs3798220 in *LPA* gene was not associated with high Lp(a) and raised cardiovascular outcomes in Han Chinese population. Based on data from 1000 Genomes, the MAF of rs3798220 in All phase 3 individuals, CHB, CHS and European were 5.1%, 8.7%, 10.5%, 1.0%, respectively. And the MAF of rs3798220 was 9.1% in our study. In addition, a mechanism study demonstrated that the I4399M variant (Ile/Met replacement) resulted by *LPA* rs3798220 influenced fibrin clot structure and fibrinolysis, due to structural differences with wild-type Apo(a) [41]. Therefore, further mechanism and epidemiological studies of rs3798220 are needed.

We detected fifteen SNPs located in the *LPA* gene in 3,779 Han Chinese participants undergoing coronary angiography and defined seven SNPs associated with Lp(a) level. Rs6415084 exhibits LD with rs7770628, and rs7765781 exhibits LD with rs6926458. We found rs6415084-T was positively associated with Lp(a) and rs7765781-C was negatively associated with Lp(a), similar to the study on rs7770628 and rs6926458 [42]. After FDR correction, *LPA* SNPs showed no significant association with CAD incidence and severity. Mark Trinder et al. indicated *LPA* GRS comprising 43 variants was associated with CAD during a median follow-up of 11.1 years in European individuals, and the association was attenuated after adjusting for Lp(a) [11]. In our study, *LPA* GRS was calculated based on the seven SNPs mentioned above. *LPA* GRS was significantly associated with Lp(a) concentration, but was not associated with the risk and the severity of CAD. Thus, further prospective studies with more precise designs, larger sample sizes and more rigorous SNP inclusion are necessary to evaluate the association between *LPA* GRS and cardiovascular outcomes.

Although Lp(a) levels are primarily determined by genetic factors, the specific genetic influences on Lp(a) concentration are likely mediated through complex genetic mechanisms and interactions, varying between populations and individuals [21]. *LPA* genetic variants such as GRS and KIV-2 copies may not fully account for Lp(a) molar concentrations, as Lp(a) levels are also influenced by additional factors such as transcriptional and translational regulation, as well as environmental factors [6]. Consequently, while these genetic variants are associated with Lp(a) levels, they do not appear to directly predict CAD risk. In contrast, Lp(a) molar concentrations

more accurately reflect actual plasma levels and exhibit a stronger, more direct association with CAD risk, highlighting their greater significance in predicting CAD risk.

Our findings emphasize the practicality of directly measuring Lp(a) molar concentrations. Unlike the detection of *LPA* genetic variants, which can be complex and costly, measuring Lp(a) concentrations is convenient, cost-effective, and more accessible in routine clinical settings. This makes Lp(a) useful in identifying high-risk individuals for CAD. Furthermore, emerging therapies targeting Lp(a) reduction, such as antisense oligonucleotides and small interfering RNAs, are showing promise in clinical trials [16–18]. These treatments aim to specifically lower Lp(a) levels and potentially reduce cardiovascular risk, offering a novel and targeted approach for managing patients with elevated Lp(a) levels. As these therapies toward clinical application, integrating Lp(a) measurements into routine clinical assessments is beneficial for cardiovascular disease prevention, risk stratification and lipid-lowering drug selection.

Conclusions

In conclusion, we found increased Lp(a) molar concentrations were significantly associated with CAD incidence and severity, defined as multivessel CAD and high Gensini scores (Gensini > median = 24). However, *LPA* genetic variants associated with Lp(a) levels, including KIV-2 copies and GRS, were not associated with the risk and severity of CAD after FDR correction. Our results indicate compared with *LPA* KIV-2 copies and GRS, Lp(a) molar concentrations (nmol/L) were better for predicting CAD. Thus, the direct detection and effective intervention of Lp(a) molar concentrations are vital.

Strengths and limitations

Firstly, all the participants were from the Han Chinese population and the sample size is relatively large compared with the existing studies on Han population, which is beneficial to the management of Lp(a) in Chinese population. Secondly, our study consisted of many young people under 45, therefore, we can evaluate the role of Lp(a) and relevant genetic variants among the youth population. Thirdly, Lp(a) was detected using a kit from Roche Diagnostics GmbH and was expressed in nmol/L, reducing the deviation caused by the heterogeneity of Apo(a) size. Fourthly, the participants were enrolled from Grade-A tertiary hospital and had the high rates of CAD, hence our conclusions cannot be generalized to low-risk populations. Fifthly, there may be ethnicity specific risk factors unique to the Han Chinese population that were not fully adjusted for in our analysis, which may influence the findings. Sixthly, Lp(a) concentrations were measured through venous blood, while KIV-2 copies and SNPs were detected through arterial blood. We cannot guarantee that it has no influence. In addition, it is difficult to assess the SNPs located in the highly variable KIV-2 repeat region by common genotyping technologies, which may neglect functional variants that influence Lp(a) levels and CAD [38, 39, 43].

Abbreviations

Lp(a)	Lipoprotein(a)
CAD	Coronary Artery Disease
KIV-2	Kringle IV type 2
qPCR	real-time quantitative Polymerase Chain Reaction
SNPs	Single Nucleotide Polymorphisms
GRS	Genetic Risk Score
OR	Odds Ratio
CI	Confidence Interval
FDR	False Discovery Rate
LDL	Low-Density Lipoprotein
ApoB	Apolipoprotein B
Apo(a)	Apolipoprotein(a)
CNV	Copy Number Variation
MI	Myocardial Infraction
TC	Total Cholesterol
TG	Triglyceride
LDL-C	Low-Density Lipoprotein Cholesterol
HDL-C	High-Density Lipoprotein Cholesterol
ApoA1	Apolipoprotein A1
LM	Left Main
LAD	Left Anterior Descending
LCx	Left Circumflex
RCA	Right Coronary Artery
CHS	Southern Han Chinese, China
CHB	Han Chinese in Beijing, China
LD	Linkage Disequilibrium
MAF	Minor Allele Frequency
β	beta coefficient
BMI	Body Mass Index
SD	Standard Deviation
IQR	Interquartile Range
VIF	Variance Inflation Factor
GWAS	genome-Wide Association Study

Supplementary Information

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Supplementary Material 1

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Author contributions

Jie Li, Hu Ding and Yan Wang designed the study. Jie Li, Ben Ma and Jing Wang conducted the experiments. Jie Li, Qin Fang and Yang Sun contributed to the data acquisition and data interpretation. Jie Li drafted the manuscript. Ben Ma, Hu Ding and Yan Wang contributed to the manuscript revision. Hu Ding and Yan Wang supervised the entire research process. All authors read and approved the final manuscript.

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Data availability

SNPs data of LPA gene used for linkage disequilibrium analysis were downloaded from 1000 Genomes (https://www.internationalgenome.org/). Patient data were extracted from a centralized hospital database and are not

publicly available to protect patient privacy. Additional related data during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20211259) and adhered to the Declaration of Helsinki. All patients signed informed consent before inclusion.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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