

Systematic Review

The Association of Lipoprotein(a) with Major Adverse Cardiovascular Events after Acute Myocardial Infarction: A Meta-Analysis of Cohort Studies

Huiruo Liu¹, Liangshan Wang¹, Hong Wang¹, Xing Hao¹, Zhongtao Du¹, Chenglong Li¹, Xiaotong Hou^{1,*} ¹Centre for Cardiac Intensive Care, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing Anzhen Hospital, Capital Medical University, 100029 Beijing, China*Correspondence: xt.hou@ccmu.edu.cn (Xiaotong Hou)

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Abstract

Background: Despite evidence suggesting a link between lipoprotein(a) (Lp(a)) and the occurrence of acute myocardial infarction (AMI), the relationship regarding prognoses related to AMI remains unclear. This meta-analysis was conducted to summarize the association between Lp(a) and the risks of major adverse cardiovascular events (MACEs) among populations surviving AMI. **Methods:** We searched PubMed, Embase, Web of Science, MEDLINE, and Cochrane Library databases until February 14, 2024. Cohort studies reporting multivariate-adjusted hazard ratios (HRs) for the correlation of Lp(a) with MACEs in AMI populations were identified. The Lp(a) level was analyzed using categorical and continuous variables. Subgroup analyses were conducted based on gender, type of AMI, diabetic and hypertensive status. Publication bias was assessed using funnel plots. A random-effect model was utilized to pool the results. **Results:** In total, 23 cohorts comprising 30,027 individuals were recruited. In comparison to those categorized with the lowest serum Lp(a), individuals in the highest category showed higher risks of MACEs after AMI (HR: 1.05, 95% confidence interval (CI): 1.01–1.09, $p = 0.006$). Similar findings were exhibited when Lp(a) was analyzed as a continuous variable (HR: 1.14, 95% CI: 1.02–1.26, $p = 0.02$). Subgroup analyses indicated that this correlation persisted significantly among females (HR: 1.23, $p = 0.005$), diabetes mellitus (DM) (HR: 1.39, $p = 0.01$), hypertension (HR: 1.36, $p < 0.00001$), ST-segment elevation myocardial infarction (STEMI) (HR: 1.03, $p = 0.04$), non-STEMI (HR: 1.40, $p = 0.03$), and long-term (>1 year) MACE (HR: 1.41, $p = 0.0006$) subgroups. **Conclusions:** Higher Lp(a) levels might be an independent indicator for MACE risks after AMI, especially among female populations with DM and/or hypertension, and more suitable for evaluating long-term MACEs. **The PROSPERO Registration:** CRD42024511985, https://www.crd.york.ac.uk/prosp/record/display_record.php?ID=CRD42024511985.

Keywords: lipoprotein(a); acute myocardial infarction; major adverse cardiovascular events; meta-analysis

1. Introduction

Even after undergoing optimal medical treatment in line with the latest guidelines, individuals who survive an acute myocardial infarction (AMI) continue to face a less-than-favorable prognosis globally [1,2]. Consequently, identifying valid residual risk indicators for major adverse cardiac events (MACEs) following AMI is paramount [3]. Indeed, poorly controlled dyslipidemia has been highlighted among the primary drivers of subsequent MACEs since it is significantly influenced by the accumulation of not only low-density lipoprotein (LDL) cholesterol but also other cholesterol-rich apolipoproteins within the vessel wall, such as lipoprotein(a) (Lp(a)) [4,5].

Lp(a) possesses a core composition similar to that of LDL, containing approximately 30% to 46% cholesterol and oxidized phospholipids, which promotes cholesterol deposition in coronary walls, triggers inflammatory responses, and enhances thrombogenic potential [6]. Recent studies have confirmed that elevated Lp(a) levels are

associated with increased risks and adverse coronary artery disease outcomes [7,8], which remains readily comprehensible for the established correlations of Lp(a) with in-stent restenosis [9], accelerated progression of atherosclerotic plaques, and more severe coronary calcification [10,11]. Moreover, higher Lp(a) levels have also been linked to other various cardiovascular disorders, such as aortic valve calcification [12] and left ventricular hypertrophy [13]. Notably, as demonstrated in a previous meta-analysis, elevated Lp(a) levels were associated with an increased prevalence of MACEs among individuals with coronary heart disease [14] and higher rates of all-cause and cardiac mortality in the general population [15]. More importantly, Bittner *et al.* [16] found that reductions in the baseline Lp(a) level could predict the risk of MACEs after recent acute coronary syndrome. However, despite these findings, the clinical significance of Lp(a) in the prognosis of AMI remains controversial. Relevant studies have reported inconsistent results [17–39]; some concluded that elevated Lp(a) levels



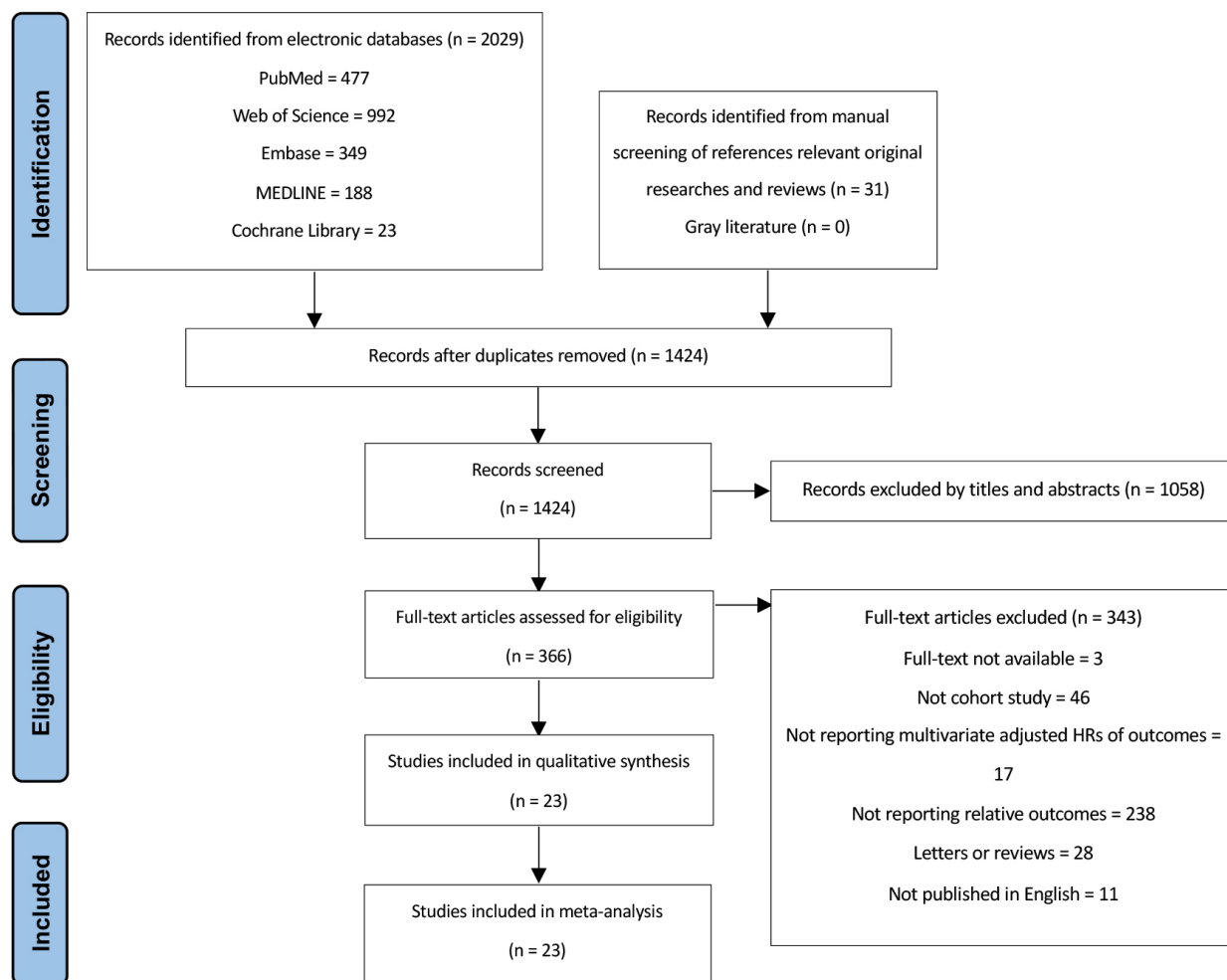


Fig. 1. PRISMA flowchart for study selection. HRs, hazard ratios.

are associated with an increased risk of MACEs following AMI, whereas others found no significant association between the two.

Given the potential of Lp(a) as a modifiable risk factor, this meta-analysis aimed to synthesize existing cohort studies concerning the relationship between baseline Lp(a) levels and the subsequent risk of MACEs in the AMI population. The objective was to provide a comprehensive understanding of the role of serum Lp(a) levels in AMI prognosis, evaluate its potential as a prognostic marker, and lay the foundation for further validation regarding any underlying mechanisms.

2. Materials and Methods

The current review was reported per the PRISMA guidelines [40] (PROSPERO: CRD42024511985).

2.1 Literature Search

A systematic search was performed in PubMed, Embase, Web of Science, MEDLINE, and Cochrane Library databases from inception to February 14, 2024, without language restriction, using the combination of search terms:

(1) “Lipoprotein(a)” OR “Lipoprotein Lp(a)” OR “Lipoprotein (a)” OR “Lipoprotein a” OR “Lp(a)” and (2) “heart infarction” OR “myocardial infarction” OR “myocardial infarct” OR “cardiovascular stroke” OR “heart attack” OR “MINOCA” OR “cardiogenic shock”. Manual hand-searching of gray literature and reference lists from relevant studies was complemented. An elaborate search strategy is presented in **Supplementary Table 1**.

2.2 Selection Criteria

Two reviewers conducted an independent screening of the literature. Disagreements between the reviewers were resolved through discussion, and a third reviewer was consulted if necessary. Studies satisfying the below criteria were incorporated: (P) population: adult individuals with AMI at admission; (E) exposure and (C) comparator: high (higher than cut-off values of 10.3 mg/dL or the highest tertile ranging from 28.7 to 134.4 mg/dL) versus low serum Lp(a) level; (O) outcomes: MACEs, cardiovascular death, recurrent myocardial infarction (MI), or all-cause death. A MACE was defined as a composite of all-cause death, non-fatal MI, nonfatal stroke, hospitalization for heart failure

Table 1. Baseline characteristics of included studies.

Study, publication year	Design	Follow-up duration (months)	Number of participants	Data source	Median age (years)	Male (%)	STEMI (%)	Revascularization (%)	Serum Lp(a) analysis and stratification criteria for Lp(a)	Outcomes	Variables adjusted
Stubbs, 1998 [17]	PC	36.0	266	London (1995–1998)	63.0	77.0	100	27.0	Median (30 mg/dL)	Cardiac mortality	Age, prior MI, infarct size, HP, thrombolysis, revascularization, beta-blocker, aspirin, intravenous heparin on CCU
Igarashi, 2003 [18]	PC	35.0	127	Japan (1996–2001)	61.0	81.9	100	100.0	Median (47 mg/dL)	MACEs	Age, sex, DM, HP, smoking, hypercholesterolemia drinking, number of diseased vessels, Killip class, reperfusion time, door to balloon time, LVEF
Gómez, 2009 [19]	PC	6.0	1271	Spanish (N/A)	57.1	83.9	77.1	71.8	T3:T1 (48 mg/dL)	MACEs	Age, sex, hypercholesterolemia, DM, HP, oxidized-LDL, smoking
Cho, 2010 [20]	RC	12.0	832	Korea (2005–2007)	62.8	72.1	N/A	100.0	T3:T1 (31 mg/dL)	MACEs	Age, sex, smoking, TC, LDL, Apo B
Ikenaga, 2011 [21]	RC	60.0	410	Japan (1999–2007)	63.2	82.4	100.0	100.0	Median (40 mg/dL)	MACEs, ReMI	Age, sex, DM, HP, smoking, prior MI, Killip class >1, time to angiography, anterior MI, initial TIMI 0–1flow, final TIMI 3, CKD, MVD
Peng, 2017 [22]	PC	12.0	175	China (N/A)	59.6	82.9	100.0	100.0	Median (30 mg/dL)	MACEs	Age, sex, smoking, SBP, DBP, TC, Cr
Mitsuda, 2019 [23]	RC	36.0	668	Japan (2007–2014)	65.8	80.5	100.0	100.0	Median (50 mg/dL)	MACEs	Age, sex eGFR, CRP, prior CAD
Sumarjaya, 2020 [24]	PC	Length of hospital stay	66	Indonesia (2018)	59.2	80.3	63.6	48.4	Median (10.3 mg/dL)	MACEs	Age, sex, HP, DM, dyslipidemia, smoking, obesity, CKD, reperfusion therapy
Cao, 2021 [25]	PC	50.4	3864	China (2009–2019)	61.7	79.7	58.6	74.9	Q4:Q1 (41 mg/dL) continuous	MACEs, cardiac mortality	Age, sex, BMI, family history of CAD, HP, smoking, DM, pre-revascularization, Gensini score, LDL-C, TG, FBG, hs-CRP, baseline statin use
Galasso, 2021 [26]	PC	66.9	724	Italy (2014–2019)	62.1	77.3	100.0	100.0	Median (50 mg/dL)	ReMI	Age, sex, DM, history of CAD, multivessel disease, restenosis lesion
Gao, 2021 [27]	PC	41.7	1179	China (2015–2019)	55.7	74.0	53.0	73.5	T3:T1 (30 mg/dL) continuous	MACEs	Age, sex, AMI type, HP, DM, dyslipidemia
Liu, 2021 [28]	RC	60.0	8295	China (2007–2018)	N/A	N/A	N/A	N/A	Median (15 mg/dL)	All-cause mortality	Age, sex, HP, prior MI, DM, prior PCI, Hb, WBC, CHF, TC, TG, Apo A, LDL-C, HDL-C, CKD, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, β -blockers, statins
Wang, 2021 [29]	RC	30.0	2318	China (2012–2017)	58.8	79.8	100.0	100.0	T3:T1 (T3 ranging from 28.7 to 134.4 mg/dL) continuous	MACEs	Age, sex, HP, DM, TC, TG, LDL-C, HDL-C

Table 1. Continued.

Study, publication year	Design	Follow-up duration (months)	Number of participants	Data source	Median age (years)	Male (%)	STEMI (%)	Revascularization (%)	Serum Lp(a) analysis and stratification criteria for Lp(a)	Outcomes	Variables adjusted
Wohlfahrt, 2021 [30]	PC	19.0	851	Czech (2017–2020)	65.1	75.4	57.8	92.1	T3:T1 (56.3 mg/dL)	All-cause mortality	Age, sex, BMI, smoking, LDL-C, HP, DM, Cr, Killip class
Xue, 2021 [31]	PC	31.0	1359	China (2015–2018)	63.4	79.5	100.0	100.0	T3:T1 (19.1 mg/dL)	All-cause mortality	Age, sex, HP, dyslipidemia, smoking, DM, CKD, symptom onset to balloon, BMI, SBP, HbA1c, TG, TC, HDL-C, LDL-C, CK-MB, Cr, hs-CRP, LVEF, prehospital thrombolysis, lipid-lowering medication
Yoon, 2021 [32]	PC	88.8	1650	Korea (2003–2013)	N/A	N/A	N/A	100.0	Median (30 mg/dL)	MACEs	Age, sex, initial presentation, BMI, HP, DM, smoking, prior MI, prior stroke, prior PAD, CKD, baseline LVEF, left main disease, multivessel disease, enrollment period (year), LDL, HDL-C, antithrombotic and statin prescription at discharge
Silverio, 2022 [33]	PC	37.4	1018	Italy (2013–2019)	63.0	75.7	75.7	100.0	Q5:Q1 (70 mg/dL) continuous	All-cause mortality, ReMI	Age, sex, HP, hyperlipidemia, smoking, DM, history of CAD, obesity, AMI type, GFR at admission, TC, HDL-C, LDL-C, multivessel disease, treated vessel by PCI/CABG
Wang, 2022 [34]	RC	60.0	171	China (2014–2017)	N/A	N/A	N/A	100.0	continuous	MACEs	LVEF and eGFR
Dai, 2023 [35]	RC	55.2	262	Japan (2015–2018)	67.7	74.8	100.0	100.0	Median (32 mg/dL)	MACEs	Age, prior MI, Killip 2-4, TG, HbA1c, NT-proBNP, Hb, ACEI/ARB use, loop diuretic use, MRA use, LVEF
Park, 2023 [38]	PC	36.5	1908	Korea (2011–2015)	65.2	70.5	36.4	87.7	T3:T1 (50 mg/dL)	MACEs	Age, sex, BMI, HP, DM, smoking, family history of CAD, prior MI, prior HF, prior CVD, SBP, LVEF, Killip class >2, anemia, TC, LDL-C, eGFR, PCI, high-intensity statin
Rigattieri, 2023 [36]	RC	36.0	634	Italy (2018–2020)	N/A	N/A	N/A	100.0	Median (30 mg/dL)	MACEs	PAD, number of diseased coronary vessels, coronary chronic total occlusion
Zhang, 2023 [37]	RC	48.0	436	China (2018–2020)	65.0	71.4	49.5	100.0	T3:T1 (T3 ranging from 34.2 to 120 mg/dL)	All-cause mortality	Age, sex, hospitalization time, heart rate, DM, prior PCI, Hb, Apo-A, eGFR, uric acid, FBG
Li, 2023 [39]	PC	48.2	1543	China (2017–2020)	61.8	80.9	100.0	100.0	Median (30 mg/dL) continuous	MACEs, cardiac mortality, all-cause mortality, ReMI	Age, sex, BMI, HP, dyslipidemia, PAD, CKD, prior MI or PCI, Killip class, GRACE score, multivessel disease, eGFR, LVEF, TC, LDL-C, hs-CRP, cTnI, NT-proBNP

AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; ReMI, recurrent myocardial infarction; DM, diabetes mellitus; Lp(a), lipoprotein(a); RC, retrospective cohort; PC, prospective cohort; BMI, body mass index; MACEs, major adverse cardiovascular events; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cells; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; PAD, peripheral vascular disease; CAD, coronary artery disease; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MRA, magnetic resonance angiography; TC, total cholesterol; TG, triglyceride; HP, hypertension; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; cTnI, cardiac troponin I; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; Cr, creatinine; Apo A, apolipoprotein A; Apo B, apolipoprotein B; CCU, cardiac care unit; MVD, microvascular disease; TIMI, thrombolysis and thrombin inhibition in myocardial infarction; HF, heart failure; CHF, chronic heart failure; N/A, not applicable; CK-MB, creatine kinase-MB; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

(HF), and revascularization. Exclusion criteria included: (1) cross-sectional research or conference abstracts; (2) studies not reporting multi-adjusted hazard ratios (HRs) for the correlation of serum Lp(a) with the above-mentioned outcomes; (3) studies not in English. In instances where there was an overlap in the populations of different studies derived from the same registry or group, only the sample with the largest size was included.

2.3 Data Extractions and Quality Assessments

Two investigators independently extracted and cross-checked data from retrieved articles, with any discrepancies resolved through discussion or reference by a third investigator. Data extracted were as follows: (1) first author's name, publication year, study design, stratification criteria for Lp(a) levels, and follow-up duration; (2) patient characteristics, including research region, sample size, age, sex, AMI subtype, and revascularization rate; (3) patterns of serum Lp(a) analysis, confounders adjusted, and outcomes reported. The quality (article selection (a maximum of 4 points, with 2 points for the representativeness of the exposed cohort and 2 points for the selection of the non-exposed cohort and the ascertainment of exposure), comparability (a maximum of 2 points, with 1 point for the adjustment of age and 1 point for the adjustment of other confounding factors), and outcomes (a maximum of 3 points, with 2 points for the assessment of outcomes and 1 point for the duration of follow-up)) of enrolled cohorts were evaluated via the Newcastle–Ottawa scale (NOS) [41]. No minimum inclusion score threshold was set for the NOS.

2.4 Statistics Analysis

HRs and 95% confidence intervals (CIs) were used to indicate the relationship between serum Lp(a) and outcomes of individuals with AMI. For studies analyzing Lp(a) as categorical variables, HRs comparing the occurrence of outcomes in populations in the highest Lp(a) category to those in the lowest Lp(a) category were collected. For studies analyzing Lp(a) as continuous variables, HRs for incidences of outcomes per 1-unit increment in Lp(a) level were collected. The HRs were logarithmically transformed, and the standard errors were derived from the 95% CIs. Cochran's Q test and I^2 statistics assessed the heterogeneity, with statistical significance considered when $I^2 > 50$ or $p < 0.10$. Subgroup and sensitivity analyses were conducted to control potential heterogeneity further, and a random-effects model was employed to synthesize the HR data. Subgroup analyses were conducted based on population characteristics, such as sex, type of AMI, and diabetic and hypertensive status, as well as the association between serum Lp(a) level and MACE risks. Publication bias was assessed visually using funnel plots. RevMan (Version 5.4, The Cochrane Collaboration, Copenhagen, Denmark) software was used to carry out these analyses.

3. Results

3.1 Literature Search

Fig. 1 illustrates the progress of conducting a comprehensive literature search. Initially, a sum of 2060 articles were searched. After removing duplicate articles, 366 papers were thoroughly examined in full-text format. Of those, 23 cohorts were recruited for subsequent analyses [17–39].

3.2 Study Characteristics and Quality Assessment

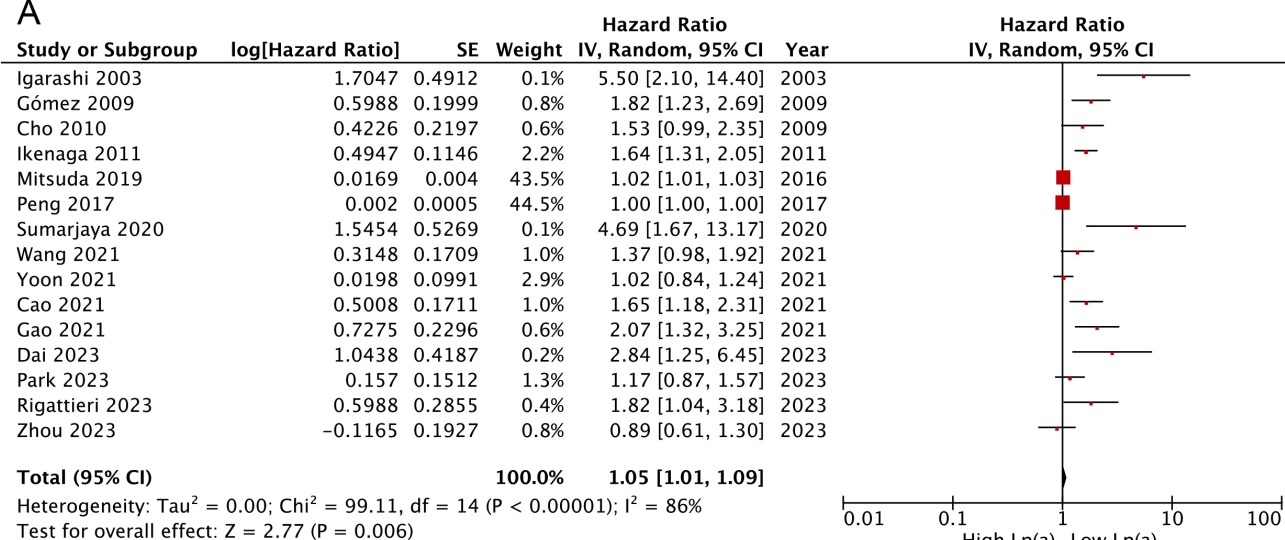
The characteristics of cohorts enrolled in our analysis are presented in Table 1 (Ref. [17–39]). In total, 23 cohorts (14 prospective and nine retrospective) were recruited in the current review, comprising 30,027 individuals diagnosed with acute myocardial infarction (AMI) upon admission. Studies included in the meta-analysis were published between 1998 and 2023; 17 were performed in Asian countries, while another six were carried out in Europe. Across the 23 trials, sample sizes varied from 66 to 8295, and median age varied between 55.7 and 67.7 years, with the proportions of males ranging from 70.5% to 83.9%, ST-segment elevation myocardial infarction (STEMI) diagnosis ranging from 36.4% to 100.0%, and the population receiving revascularization ranging from 27.0% to 100.0%. The median follow-up varied from the length of stay in the hospital to 88 months. Baseline serum Lp(a) was calculated as categorical variables in 17 cohorts [17–24,26,28,30–32,35–38], as a continuous variable in only one cohort [34], and as both in five cohorts [25,27,29,33,39]. HRs for the association between prognosis and Lp(a) were adjusted utilizing age, sex, body mass index, blood pressure, medical history, laboratory and angiographic findings, and in-hospital medications to varying degrees. The NOS score for all cohorts enrolled was 9, demonstrating high levels of quality (Table 2, Ref. [17–39]).

3.3 Serum Lp(a) and the Occurrence of MACEs

Overall, the combined findings of 15 cohorts [18–25,27,29,32,35,36,38,39] indicated that AMI patients categorized with the lowest serum Lp(a) presented a lower likelihood of experiencing MACEs, in comparison to those in the highest category (HR: 1.05, 95% CI: 1.01–1.09, $I^2 = 86\%$, $p = 0.006$) (Fig. 2A). Similar findings were observed when analyzing Lp(a) as a continuous variable (HR: 1.14, 95% CI: 1.02–1.26, $I^2 = 47\%$, $p = 0.02$; Fig. 2B) [27,29,34,39].

Subgroup analyses revealed that AMI patients with a higher Lp(a) category presented significantly increased risks of MACEs, regardless of the AMI subtype (STEMI: HR: 1.03, 95% CI: 1.00–1.06, $p = 0.04$; non-STEMI: HR: 1.40, 95% CI: 1.03–1.90, $p = 0.03$) (Fig. 3B); however, this elevated risk remained apparent only among female individuals and those with DM or hypertension (Fig. 3A,C,D). Further, pooled findings indicated a significant correlation between Lp(a) and long-term (>1 year)

A



B

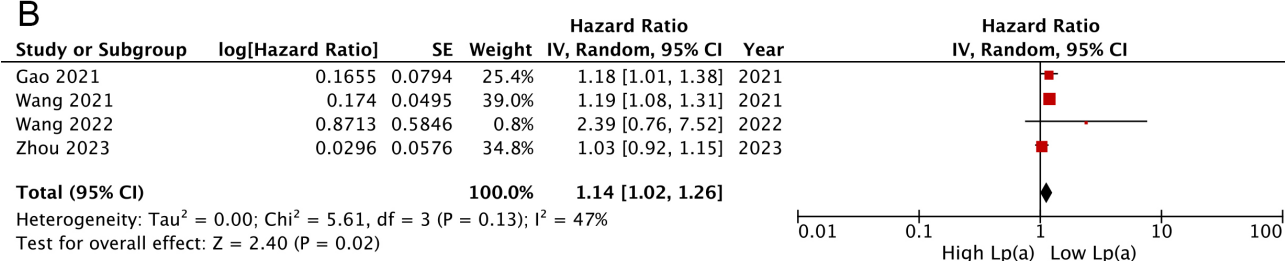


Fig. 2. Forest plots regarding meta-analyses of the links of Lp(a) with risks of composite MACEs. (A) Meta-analyses with Lp(a) pooled as categorical variables. (B) Meta-analyses with Lp(a) pooled as continuous variables. IV, inverse variance; CI, confidence interval.

MACEs (HR: 1.41, 95% CI: 1.16–1.72, $I^2 = 84\%$, $p = 0.0006$), but not short-term (≤ 1 year) MACEs (HR: 1.62, $p = 0.05$) (**Supplementary Fig. 1**). Sensitivity analysis indicated that these associations remained relatively robust (**Supplementary Fig. 2**). In the subgroup analysis where Lp(a) was calculated as continuous variables, only studies with stratified populations based on the AMI type or diabetic status could be pooled for analysis; meanwhile the exhibited results aligned with those for when Lp(a) was calculated as a categorical variable (**Supplementary Fig. 3**).

3.4 Serum Lp(a) and the Occurrence of All-Cause Death, Cardiac Death, and ReMI

Overall, the combined findings of three studies [17, 25,39] demonstrated that AMI patients categorized with the lowest serum Lp(a) tended to experience less cardiac death than those in the highest category (HR: 1.58, 95% CI: 1.07–2.34, $I^2 = 42\%$, $p = 0.02$) (Fig. 4B). Further, trends toward increased all-cause death [28,30,31,33,37,39] (HR: 1.22, $p = 0.20$) and ReMI [21,26,33,39] (HR: 1.20, $p = 0.28$) were also presented in those with the highest Lp(a), but not to levels of statistical significance (Fig. 4A,C). These results were consistent with findings when Lp(a) pooled as a con-

tinuous variable (cardiac death: HR: 1.27, 95% CI: 1.14–1.42, $I^2 = 0\%$, $p < 0.0001$; all-cause death: HR: 1.02, $p = 0.79$; ReMI: HR: 1.30, $p = 0.48$) (Fig. 5A–C).

3.5 Publication Bias

Supplementary Fig. 4 presents funnel plots illustrating the relationship between Lp(a), calculated as a categorical or continuous variable, and MACEs. An apparent asymmetry was obtained, indicating a high risk of publication biases.

4. Discussion

In the current systematic review, we comprehensively analyzed the association between Lp(a) and the risk of MACEs after AMI. Our findings firstly indicated that higher Lp(a) levels correlated with an increased incidence of MACEs. Further, among subgroup analyses, significant associations between elevated Lp(a) and MACE prevalence among female individuals with DM or hypertension were observed; these links were not observed in the remaining subgroups. In addition, elevated Lp(a) was more seemingly related to long-term rather than short-term MACE occur-

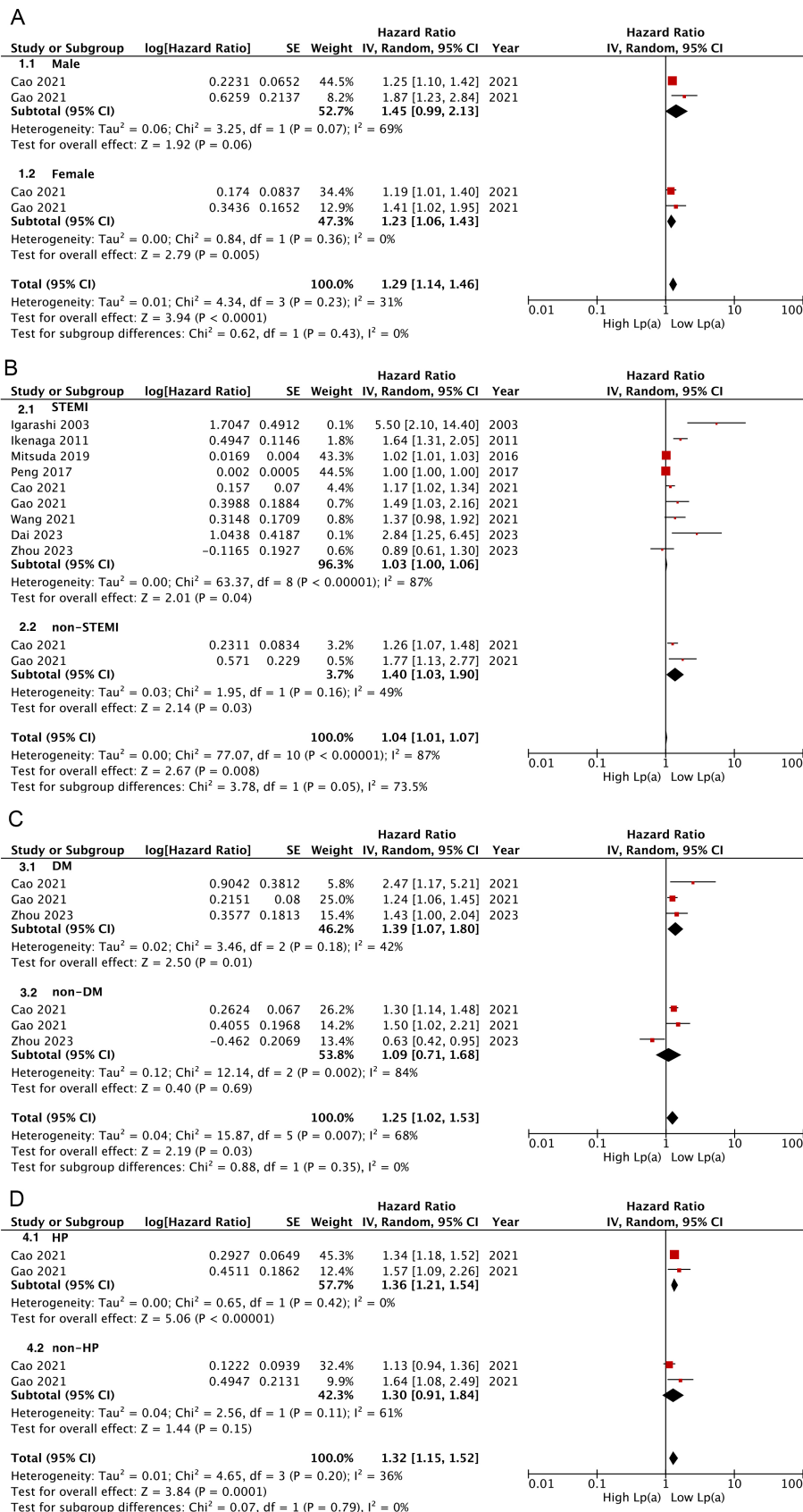


Fig. 3. Subgroup analysis for Lp(a) links analyzed as categorical variables with risks of composite MACEs. (A) Subgroup analysis according to sex (A), AMI type (B), diabetes (C), and hypertension (D).

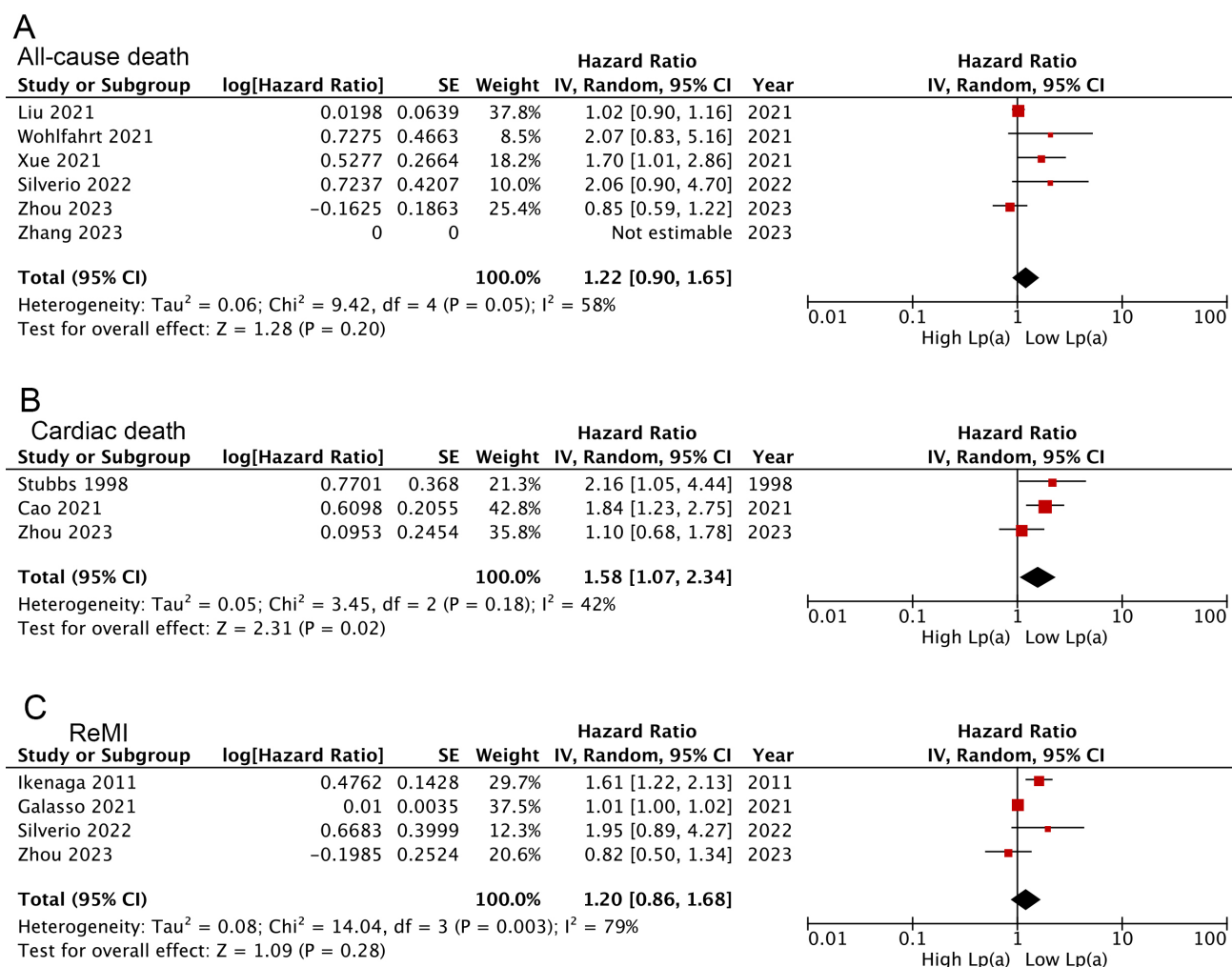


Fig. 4. Forest plots regarding meta-analyses for the links of Lp(a) analyzed as a categorical variable with the risk of all-cause death (A), cardiac death (B), and ReMI (C).

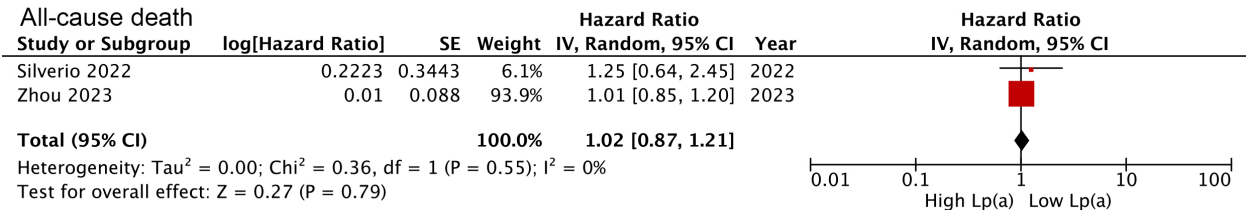
rences. Altogether, these findings are likely more applicable to female populations with coincident DM or hypertension and more suitable to evaluate the prolonged prognosis following AMI.

No prior systematic reviews and meta-analyses have specifically addressed this topic solely relating to populations surviving AMI, despite substantial evidence illustrating the great harms of elevated Lp(a) in the secondary prevention of recurrent cardiovascular events. Willeit *et al.* [42] pooled seven randomized controlled trials with 29,069 patients in a review and highlighted those high levels of both baseline and on-statin Lp(a) exhibited an independent approximately linear relation with incident cardiovascular disease in the general population receiving lipid-lowering therapy. In addition, Wang *et al.* [43] performed a systematic review enrolling 17 studies that indicated a similar relationship between Lp(a) and cardiovascular risks for populations with established coronary artery disease. Notably, a large percentage of the population with dyslipidemia could not gain noticeable benefits from statins or proprotein con-

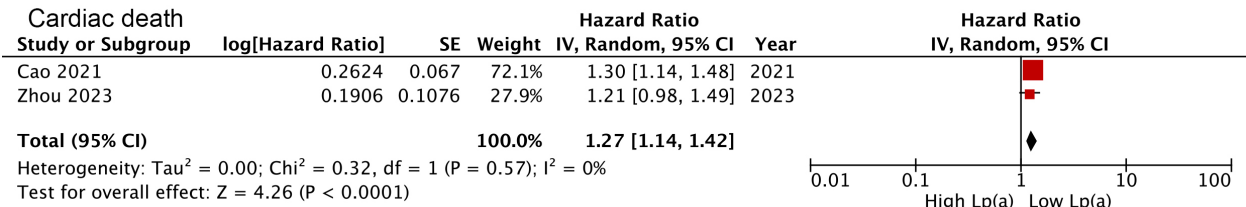
vertase subtilisin/kexin type 9 (PCSK9) inhibitors in secondary prevention therapies [42]. However, these might involve one Lp(a)-associated mechanism that requires an absolute reduction in Lp(a) levels for a clinically apparent decrease in cardiac risk, as highlighted by the Mendelian randomization study [44,45]. In contrast, routine lipid-lowering drugs could not sufficiently eliminate elevated Lp(a) levels. Moreover, a meta-analysis published in 2020 demonstrated that LDL-C content exhibited an apparent association with incident cardiovascular disease only when the Lp(a) cholesterol content was incorporated into its measurement [46]. Notably, the ODYSSEY OUTCOMES trial has recently demonstrated that alirocumab-related MACE reductions might be mediated via decreased Lp(a) levels [47]. These results indirectly indicate the significant increase in Lp(a)-related risk for recurrent MACEs, which aligns with our findings in the current comprehensive meta-analysis among patients surviving AMI.

Regarding the Lp(a) positive relationship with MACEs after AMI, we found that it might be primarily

A



B



C

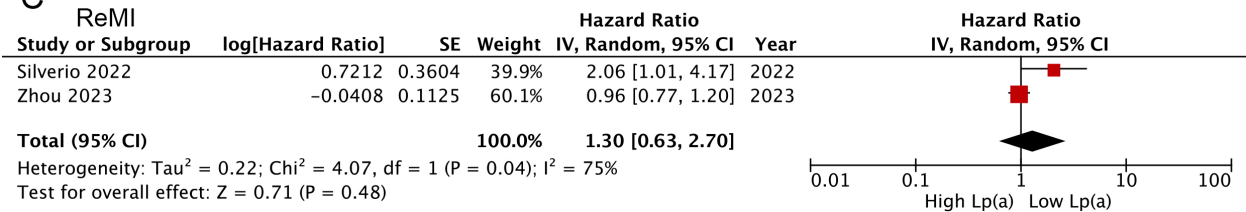


Fig. 5. Forest plots related to meta-analyses for the Lp(a) links following analysis as a continuous variable with the risk of all-cause death (A), cardiac death (B), and ReMI (C).

Table 2. Newcastle–Ottawa Scale appraisal of included studies.

Study, publication year	Selection	Comparability	Outcome	Total
Stubbs, 1998 [17]	4	2	3	9
Igarashi, 2003 [18]	4	2	3	9
Gómez, 2009 [19]	4	2	3	9
Cho, 2010 [20]	4	2	3	9
Ikenaga, 2011 [21]	4	2	3	9
Peng, 2017 [22]	4	2	3	9
Mitsuda, 2019 [23]	4	2	3	9
Sumarjaya, 2020 [24]	4	2	3	9
Cao, 2021 [25]	4	2	3	9
Galasso, 2021 [26]	4	2	3	9
Gao, 2021 [27]	4	2	3	9
Liu, 2021 [28]	4	2	3	9
Wang, 2021 [29]	4	2	3	9
Wohlfahrt, 2021 [30]	4	2	3	9
Xue, 2021 [31]	4	2	3	9
Yoon, 2021 [32]	4	2	3	9
Silverio, 2022 [33]	4	2	3	9
Wang, 2022 [34]	4	2	3	9
Dai, 2023 [35]	4	2	3	9
Park, 2023 [38]	4	2	3	9
Rigattieri, 2023 [36]	4	2	3	9
Zhang, 2023 [37]	4	2	3	9
Li, 2023 [39]	4	2	3	9

mediated by the increased cardiovascular mortality in relation to elevated Lp(a); these findings conformed to the Emerging Risk Factors Collaboration, which reported that an elevation in Lp(a) of 3.5-fold correlated with an approximately 14% increase in cardiovascular death; meanwhile, no apparent association was presented for the risk of non-vascular mortality [48]. Overall, these analyses strongly demonstrated that Lp(a)-mediated coronary damage is potentially mainly responsible for the worse prognosis after AMI. Some genetic and epidemiological studies have shown that elevated Lp(a) was associated with the prevalence and progression of myocardial infarction [49], atherosclerotic stenosis [50,51], as well regarding aortic valve calcification [52,53]; however, certain mechanisms related to these conditions may contribute to the link between higher Lp(a) levels and an augmented risk of cardiovascular events [47]. Briefly, Lp(a) has been implicated in promoting aortic valve sclerosis and calcification [12], which may contribute to developing aortic stenosis and increasing the burden on the cardiovascular system in AMI patients. Additionally, Lp(a) could aggravate left ventricular hypertrophy [13], a common complication of AMI, by promoting inflammation and fibrosis, which might worsen myocardial function and increase the risk of adverse outcomes. Possible pathophysiological mechanisms might explain these observed correlations. The

lipotoxic composition of Lp(a) (low-density lipoprotein-like core, etc.) could be transmitted to the injured vessel walls, causing endothelial dysfunction, inflammation, and consequential atherosclerosis [54,55]. However, some researchers have also elucidated the prothrombotic roles [56] and anti-fibrinolytic functions of Lp(a) [57]. Lp(a) might interfere with plasminogen activity owing to molecular similarity, leading to a deceleration in fibrinolysis and an indirect promotion of thrombosis. A recent study has shown that combining Lp(a) with fibrinogen and hs-CRP can significantly improve the accuracy of cardiovascular risk prediction [58].

Conversely, the connection between Lp(a) and MACEs seems to exist in females and individuals with DM or hypertension. In diabetic patients, the synergistic effect of high blood glucose and elevated Lp(a) may amplify pro-inflammatory and prothrombotic pathways. High blood glucose contributes to increased oxidative stress and endothelial dysfunction, which may enhance the proinflammatory properties of Lp(a) and promote thrombogenesis, further increasing the risk of adverse cardiovascular outcomes [59]. Similarly, high Lp(a) may worsen the effects of elevated blood pressure in hypertensive patients by increasing vascular stiffness and promoting plaque formation in the arteries, thereby exacerbating the progression of cardiovascular disease. In females, the potential hormonal influence on Lp(a) levels should be considered, as postmenopausal women tend to have higher Lp(a) levels, which may increase their risk of cardiovascular events compared to matched male counterparts [60]. These findings made it easy to understand why the effects of Lp(a) on incident MACEs varied in subgroup populations with or without certain risk factors. Notably, the varying prognostic significance of Lp(a) implied that Lp(a) might act differently in promoting cardiovascular events in populations with and without these above-mentioned risk indicators. Hence, heightened emphasis should be placed on Lp(a) within clinical practice owing to its intricate impact on cardiovascular disorders.

Our meta-analysis still possessed some limitations. Firstly, the included studies had diverse cut-off values of Lp(a), definitions of MACEs, and enrolled populations with varying characteristics, potentially leading to evident heterogeneity. Thus, the pooled findings regarding the relationship between Lp(a) and MACE incidents should be interpreted cautiously. Secondly, due to varied Lp(a) cut-off values among included studies, we could not establish a suitable threshold to distinguish elevated Lp(a). Thirdly, all included studies were cohorts, which limited the ability to establish a causal association between Lp(a) and the occurrence of MACEs. Lastly, factors such as variations in in-hospital management across institutions may have potential prognostic implications for populations surviving AMI, which could partly impact the significance of the conclusions drawn in this review.

5. Conclusions

In conclusion, Lp(a) was positively associated with MACE incidents, which might primarily be mediated by increased cardiovascular death. This finding seems more applicable to evaluating the long-term prognosis after AMI among female individuals with concomitant DM and/or hypertension. Hence, it is imperative to ascertain further whether Lp(a)-lowering treatment could reduce MACEs and ultimately improve the prognosis of patients surviving AMI. Meanwhile, a rationale for popularizing Lp(a) measurements in patients suffering from AMI should be provided.

Availability of Data and Materials

All data generated can be obtained from this published article and its additional information files.

Author Contributions

HRL contributed to literature review, writing, conception and design, acquisition of data, and analysis and interpretation of data. LSW contributed to investigation, data curation, and drafting the manuscript. XH and ZTD contributed to creating figures, tables, and revising the manuscript critically for important intellectual content. CLL and HW contributed to conception, design, acquisition of data, drafting the manuscript. XTH contributed to drafting of the manuscript, analysis and interpretation of data. All authors have revised the manuscript critically for important intellectual content, also read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/RCM27376>.

References

- [1] Danchin N. Improved long-term survival after acute myocardial infarction: the success of comprehensive care from the acute stage to the long term. *European Heart Journal*. 2023; 44: 499–501. <https://doi.org/10.1093/eurheartj/ehac714>.
- [2] Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al.* Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. 2020; 141: e139–e596. <https://doi.org/10.1161/CIR.0000000000000757>.
- [3] Mahтта D, Khalid U, Misra A, Samad Z, Nasir K, Virani SS. Premature Atherosclerotic Cardiovascular Disease: What Have We Learned Recently? *Current Atherosclerosis Reports*. 2020; 22: 44. <https://doi.org/10.1007/s11883-020-00862-8>.
- [4] Li JJ, Ma CS, Zhao D, Yan XW, Beijing Heart Society and Expert Committee. Lipoprotein(a) and Cardiovascular Disease in Chinese Population: A Beijing Heart Society Expert Scientific Statement. *JACC. Asia*. 2022; 2: 653–665. <https://doi.org/10.1016/j.jacasi.2022.08.015>.
- [5] Littmann K, Hagström E, Häbel H, Bottai M, Eriksson M, Parini P, *et al.* Plasma lipoprotein(a) measured in the routine clinical care is associated to atherosclerotic cardiovascular disease during a 14-year follow-up. *European Journal of Preventive Cardiology*. 2022; 28: 2038–2047. <https://doi.org/10.1093/eurjpc/zwab016>.
- [6] Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *European Heart Journal*. 2017; 38: 2459–2472. <https://doi.org/10.1093/eurheartj/ehx144>.
- [7] Gilliland TC, Liu Y, Mohebi R, Miksenas H, Haidermota S, Wong M, *et al.* Lipoprotein(a), Oxidized Phospholipids, and Coronary Artery Disease Severity and Outcomes. *Journal of the American College of Cardiology*. 2023; 81: 1780–1792. <https://doi.org/10.1016/j.jacc.2023.02.050>.
- [8] Enas EA, Varkey B, Dharmarajan TS, Pare G, Bahl VK. Lipoprotein(a): An independent, genetic, and causal factor for cardiovascular disease and acute myocardial infarction. *Indian Heart Journal*. 2019; 71: 99–112. <https://doi.org/10.1016/j.ihj.2019.03.004>.
- [9] Mahmoud AK, Farina JM, Awad K, Ali NB, Pereyra M, Scalia IG, *et al.* Lipoprotein(a) and long-term in-stent restenosis after percutaneous coronary intervention. *European Journal of Preventive Cardiology*. 2024; 31: 1878–1887. <https://doi.org/10.1093/eurjpc/zwac212>.
- [10] Tsimikas S. Lipoprotein(a) and Coronary Calcium: Clinical Management and Potential Design of Primary Prevention Trials. *Journal of the American College of Cardiology*. 2022; 79: 769–771. <https://doi.org/10.1016/j.jacc.2021.12.018>.
- [11] Kaiser Y, Daghem M, Tzolos E, Meah MN, Doris MK, Moss AJ, *et al.* Association of Lipoprotein(a) With Atherosclerotic Plaque Progression. *Journal of the American College of Cardiology*. 2022; 79: 223–233. <https://doi.org/10.1016/j.jacc.2021.10.044>.
- [12] Pantelidis P, Oikonomou E, Lampsas S, Zakynthinos GE, Lysandrou A, Kalogeris K, *et al.* Lipoprotein(a) and calcific aortic valve disease initiation and progression: a systematic review and meta-analysis. *Cardiovascular Research*. 2023; 119: 1641–1655. <https://doi.org/10.1093/cvr/cvad062>.
- [13] Yan X, Gong J, Wang Z, Wang F, Qi C. Association of lipoprotein(a) with left ventricular hypertrophy assessed by electrocardiogram in adults: a large cross-sectional study. *Frontiers in Endocrinology*. 2023; 14: 1260050. <https://doi.org/10.3389/fendo.2023.1260050>.
- [14] Zhao X, Wang D, Qin L. Lipid profile and prognosis in patients with coronary heart disease: a meta-analysis of prospective cohort studies. *BMC Cardiovascular Disorders*. 2021; 21: 69. <https://doi.org/10.1186/s12872-020-01835-0>.
- [15] Amiri M, Raeesi-Dehkordi H, Verkaar AJCF, Wu Y, van Westing AC, Berk KA, *et al.* Circulating lipoprotein (a) and all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis. *European Journal of Epidemiology*. 2023; 38: 485–499. <https://doi.org/10.1007/s10654-022-00956-4>.
- [16] Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, *et al.* Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome. *Journal of the American College of Cardiology*. 2020; 75: 133–144. <https://doi.org/10.1016/j.jacc.2019.10.057>.
- [17] Stubbs P, Seed M, Lane D, Collinson P, Kendall F, Noble M. Lipoprotein(a) as a risk predictor for cardiac mortality in patients with acute coronary syndromes. *European Heart Journal*. 1998; 19: 1355–1364. <https://doi.org/10.1053/ehj.1998.1043>.
- [18] Igarashi Y, Aizawa Y, Satoh T, Konno T, Ojima K, Aizawa Y. Predictors of adverse long-term outcome in acute myocardial infarction patients undergoing primary percutaneous transluminal coronary angioplasty: with special reference to the admission concentration of lipoprotein (a). *Circulation Journal*. 2003; 67: 605–611. <https://doi.org/10.1253/circj.67.605>.
- [19] Gómez M, Valle V, Arós F, Sanz G, Sala J, Fiol M, *et al.* Oxidized LDL, lipoprotein (a) and other emergent risk factors in acute myocardial infarction (FORTIAM study). *Revista Española De Cardiología*. 2009; 62: 373–382. [https://doi.org/10.1016/s1885-5857\(09\)71664-0](https://doi.org/10.1016/s1885-5857(09)71664-0).
- [20] Cho JY, Jeong MH, Ahn Y, Hong YJ, Park HW, Yoon NS, *et al.* High Lipoprotein(a) Levels are Associated With Long-Term Adverse Outcomes in Acute Myocardial Infarction Patients in High Killip Classes. *Korean Circulation Journal*. 2010; 40: 491–498. <https://doi.org/10.4070/kcj.2010.40.10.491>.
- [21] Ikenaga H, Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Miura F, *et al.* Usefulness of Lipoprotein (a) for predicting progression of non-culprit coronary lesions after acute myocardial infarction. *Circulation Journal*. 2011; 75: 2847–2852. <https://doi.org/10.1253/circj.cj-11-0365>.
- [22] Peng Y, Shao ZY, Jiang JQ, Chen ZN, Li ZG, Gong ZG, *et al.* Association between serum lipoprotein (a) levels and major adverse cardiovascular events in Chinese patients with ST-segment elevation myocardial infarction. *International Journal of Clinical and Experimental Medicine*. 2017; 10: 897–904.
- [23] Mitsuda T, Uemura Y, Ishii H, Tanaka A, Takemoto K, Koyasu M, *et al.* Prognostic impact of lipoprotein(a) levels during lipid management with statins after ST-elevation acute myocardial infarction. *Coronary Artery Disease*. 2019; 30: 600–607. <https://doi.org/10.1097/MCA.0000000000000798>.
- [24] Sumarjaya IDGD, Nadha IKB, Lestari AAW. High Lipoprotein(a) Levels as a Predictor of Major Adverse Cardiovascular Events in Hospitalized-Acute Myocardial Infarction Patients. *Vascular Health and Risk Management*. 2020; 16: 125–132. <https://doi.org/10.2147/VHRM.S233503>.
- [25] Cao YX, Zhang HW, Jin JL, Liu HH, Zhang Y, Zhang M, *et al.* Lipoprotein(a) and Cardiovascular Outcomes in Patients with Previous Myocardial Infarction: A Prospective Cohort Study. *Thrombosis and Haemostasis*. 2021; 121: 1161–1168. <https://doi.org/10.1055/a-1340-2109>.
- [26] Galasso G, De Angelis E, Silverio A, Di Maio M, Cancro FP, Esposito L, *et al.* Predictors of Recurrent Ischemic Events in

- Patients With ST-Segment Elevation Myocardial Infarction. *The American Journal of Cardiology*. 2021; 159: 44–51. <https://doi.org/10.1016/j.amjcard.2021.08.019>.
- [27] Gao S, Ma W, Huang S, Lin X, Yu M. Effect of Lipoprotein (a) Levels on Long-term Cardiovascular Outcomes in Patients with Myocardial Infarction with Nonobstructive Coronary Arteries. *The American Journal of Cardiology*. 2021; 152: 34–42. <https://doi.org/10.1016/j.amjcard.2021.05.003>.
- [28] Liu J, Liu L, Wang B, Chen S, Liu B, Liang J, *et al*. Coronary Artery Disease: Optimal Lipoprotein(a) for Survival-Lower Is Better? A Large Cohort With 43,647 Patients. *Frontiers in Cardiovascular Medicine*. 2021; 8: 670859. <https://doi.org/10.3389/fcvm.2021.670859>.
- [29] Wang Y, Zhao X, Zhou P, Liu C, Chen R, Sheng Z, *et al*. Impact of Postprocedural High-Sensitivity C-Reactive Protein on Lipoprotein(a)-Associated Cardiovascular Risk with ST-Segment Elevation Myocardial Infarction With Percutaneous Coronary Intervention. *The American Journal of Cardiology*. 2021; 150: 8–14. <https://doi.org/10.1016/j.amjcard.2021.03.038>.
- [30] Wohlfahrt P, Jenča D, Melenovský V, Franeková J, Jabor A, Šramko M, *et al*. Very low lipoprotein(a) and increased mortality risk after myocardial infarction. *European Journal of Internal Medicine*. 2021; 91: 33–39. <https://doi.org/10.1016/j.ejim.2021.04.012>.
- [31] Xue Y, Jian S, Zhou W, Zhou Q, Xiang J, Zhu Y, *et al*. Associations of Lipoprotein(a) With Coronary Atherosclerotic Burden and All-Cause Mortality in Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention. *Frontiers in Cardiovascular Medicine*. 2021; 8: 638679. <https://doi.org/10.3389/fcvm.2021.638679>.
- [32] Yoon YH, Ahn JM, Kang DY, Lee PH, Kang SJ, Park DW, *et al*. Association of Lipoprotein(a) With Recurrent Ischemic Events Following Percutaneous Coronary Intervention. *JACC. Cardiovascular Interventions*. 2021; 14: 2059–2068. <https://doi.org/10.1016/j.jcin.2021.07.042>.
- [33] Silverio A, Cancro FP, Di Maio M, Bellino M, Esposito L, Centore M, *et al*. Lipoprotein(a) levels and risk of adverse events after myocardial infarction in patients with and without diabetes. *Journal of Thrombosis and Thrombolysis*. 2022; 54: 382–392. <https://doi.org/10.1007/s11239-022-02701-w>.
- [34] Wang L, Cong HL, Zhang JX, Li XM, Hu YC, Wang C, *et al*. Prognostic performance of multiple biomarkers in patients with acute coronary syndrome without standard cardiovascular risk factors. *Frontiers in Cardiovascular Medicine*. 2022; 9: 916085. <https://doi.org/10.3389/fcvm.2022.916085>.
- [35] Dai K, Shiode N, Yoshii K, Kimura Y, Matsuo K, Jyuri Y, *et al*. Impact of Lipoprotein (a) on Long-Term Outcomes in Patients With Acute Myocardial Infarction. *Circulation Journal*. 2023; 87: 1356–1361. <https://doi.org/10.1253/circj.CJ-23-0221>.
- [36] Rigattieri S, Cristiano E, Tempestini F, Lo Monaco M, Cava F, Bongiovanni M, *et al*. Lipoprotein(a) and the risk of recurrent events in patients with acute myocardial infarction treated by percutaneous coronary intervention. *Minerva Cardiology and Angiology*. 2023; 71: 406–413. <https://doi.org/10.23736/S2724-5683.22.06213-5>.
- [37] Zhang J, Jia L, Yang Y, Xiao A, Lin X. Lipoprotein (a) and myocardial infarction: impact on long-term mortality. *Lipids in Health and Disease*. 2023; 22: 70. <https://doi.org/10.1186/s12944-023-01841-z>.
- [38] Park JS, Cho KH, Hong YJ, Kim MC, Sim DS, Kim JH, *et al*. Baseline Lipoprotein(a) Levels and Long-Term Cardiovascular Outcomes After Acute Myocardial Infarction. *Journal of Korean Medical Science*. 2023; 38: e102. <https://doi.org/10.3346/jkms.2023.38.e102>.
- [39] Li N, Zhou J, Chen R, Zhao X, Li J, Zhou P, *et al*. Prognostic impacts of diabetes status and lipoprotein(a) levels in patients with ST-segment elevation myocardial infarction: a prospective cohort study. *Cardiovascular Diabetology*. 2023; 22: 151. <https://doi.org/10.1186/s12933-023-01881-w>.
- [40] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*. 2021; 372: n71. <https://doi.org/10.1136/bmj.n71>.
- [41] Lo CKL, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Medical Research Methodology*. 2014; 14: 45. <https://doi.org/10.1186/1471-2288-14-45>.
- [42] Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, *et al*. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet*. 2018; 392: 1311–1320. [https://doi.org/10.1016/S0140-6736\(18\)31652-0](https://doi.org/10.1016/S0140-6736(18)31652-0).
- [43] Wang Z, Zhai X, Xue M, Cheng W, Hu H. Prognostic value of lipoprotein (a) level in patients with coronary artery disease: a meta-analysis. *Lipids in Health and Disease*. 2019; 18: 150. <https://doi.org/10.1186/s12944-019-1092-6>.
- [44] Burgess S, Ference BA, Staley JR, Freitag DF, Mason AM, Nielsen SF, *et al*. Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis. *JAMA Cardiology*. 2018; 3: 619–627. <https://doi.org/10.1001/jamacardio.2018.1470>.
- [45] Lamina C, Kronenberg F, Lp(a)-GWAS-Consortium. Estimation of the Required Lipoprotein(a)-Lowering Therapeutic Effect Size for Reduction in Coronary Heart Disease Outcomes: A Mendelian Randomization Analysis. *JAMA Cardiology*. 2019; 4: 575–579. <https://doi.org/10.1001/jamacardio.2019.1041>.
- [46] Willeit P, Yeang C, Moriarty PM, Tschiderer L, Varvel SA, McConnell JP, *et al*. Low-Density Lipoprotein Cholesterol Corrected for Lipoprotein(a) Cholesterol, Risk Thresholds, and Cardiovascular Events. *Journal of the American Heart Association*. 2020; 9: e016318. <https://doi.org/10.1161/JAHA.119.016318>.
- [47] Szarek M, Reijnders E, Jukema JW, Bhatt DL, Bittner VA, Diaz R, *et al*. Relating Lipoprotein(a) Concentrations to Cardiovascular Event Risk After Acute Coronary Syndrome: A Comparison of 3 Tests. *Circulation*. 2024; 149: 192–203. <https://doi.org/10.1161/CIRCULATIONAHA.123.066398>.
- [48] Emerging Risk Factors Collaboration, Danesh J, Erqou S, Walker M, Thompson SG, Tipping R, *et al*. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. *European Journal of Epidemiology*. 2007; 22: 839–869. <https://doi.org/10.1007/s10654-007-9165-7>.
- [49] Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009; 301: 2331–2339. <https://doi.org/10.1001/jama.2009.801>.
- [50] Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, *et al*. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *The New England Journal of Medicine*. 2009; 361: 2518–2528. <https://doi.org/10.1056/NEJMoa0902604>.
- [51] Arsenault BJ, Boekholdt SM, Dubé MP, Rhéaume E, Wareham NJ, Khaw KT, *et al*. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. *Circulation. Cardiovascular Genetics*. 2014; 7: 304–310. <https://doi.org/10.1161/CIRCGENETICS.113.000400>.
- [52] Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, *et al*. Genetic associations with valvular calcifica-

- tion and aortic stenosis. *The New England Journal of Medicine*. 2013; 368: 503–512. <https://doi.org/10.1056/NEJMoa1109034>.
- [53] Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *Journal of the American College of Cardiology*. 2014; 63: 470–477. <https://doi.org/10.1016/j.jacc.2013.09.038>.
- [54] Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, *et al*. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *European Heart Journal*. 2022; 43: 3925–3946. <https://doi.org/10.1093/eurheartj/ehac361>.
- [55] Pirro M, Bianconi V, Paciullo F, Mannarino MR, Bagaglia F, Sahebkar A. Lipoprotein(a) and inflammation: A dangerous duet leading to endothelial loss of integrity. *Pharmacological Research*. 2017; 119: 178–187. <https://doi.org/10.1016/j.phrs.2017.02.001>.
- [56] Martínez C, Rivera J, Loyau S, Corral J, González-Conejero R, Lozano ML, *et al*. Binding of recombinant apolipoprotein(a) to human platelets and effect on platelet aggregation. *Thrombosis and Haemostasis*. 2001; 85: 686–693.
- [57] Gardener H, Della Morte D, Elkind MSV, Sacco RL, Rundek T. Lipids and carotid plaque in the Northern Manhattan Study (NOMAS). *BMC Cardiovascular Disorders*. 2009; 9: 55. <https://doi.org/10.1186/1471-2261-9-55>.
- [58] Wang Z, Tang J, Shi Q, Fang L, Liu N, Zhang J. Synergistic effect of lipoprotein(a) and high-sensitivity C-reactive protein on the risk of all-cause and cardiovascular death in patients with acute myocardial infarction: a large prospective cohort study. *Frontiers in Endocrinology*. 2024; 15: 1392859. <https://doi.org/10.3389/fendo.2024.1392859>.
- [59] Shang R, Rodrigues B. Lipoprotein lipase as a target for obesity/diabetes related cardiovascular disease. *Journal of Pharmacy & Pharmaceutical Sciences: a Publication of the Canadian Society for Pharmaceutical Sciences, Societe Canadienne des Sciences Pharmaceutiques*. 2024; 27: 13199. <https://doi.org/10.3389/jpps.2024.13199>.
- [60] Bruschi F, Meschia M, Soma M, Perotti D, Paoletti R, Crosignani PG. Lipoprotein(a) and other lipids after oophorectomy and estrogen replacement therapy. *Obstetrics and Gynecology*. 1996; 88: 950–954. [https://doi.org/10.1016/s0029-7844\(96\)00349-3](https://doi.org/10.1016/s0029-7844(96)00349-3).