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Original Research

Lipoprotein(a) and Prognostic Nutritional Index Levels Exhibit Interactive and Joint Effects on Mortality Risk in Patients With Coronary Artery Disease: Findings From a Real-World Study

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Abstract

Background: Abnormal lipoprotein(a) (Lp(a)) levels and malnutrition are independent cardiovascular risk factors; however, the associated combined effects on mortality in patients with coronary artery disease (CAD) remain incompletely understood. Thus, this study aimed to evaluate the independent and joint associations of Lp(a) and the prognostic nutritional index (PNI) with all-cause and cardiovascular (CV) mortality in patients with CAD, as well as the associated combined interaction. **Methods:** A total of 47,482 patients with CAD from the Southern China multicenter Cardiorenal Improvement II cohort (2007–2020) were enrolled. Patients were stratified according to Lp(a) levels (low: <15 mg/dL; middle: 15 to <30 mg/dL; high: ≥30 mg/dL) and PNI (high: ≥45; low: <45). The primary outcomes were all-cause mortality and CV mortality. Restricted cubic splines were used to assess non-linear associations, while multivariable Cox models and Kaplan–Meier analyses were used for risk assessment; receiver operating characteristic (ROC) curves were used to compare predictive performance, and additive interaction analysis was used to evaluate joint effects. **Results:** During a median follow-up of 5.2 years, 5229 patients (11.01%) died from any cause and 3698 died from CV causes. In fully adjusted models, high Lp(a) combined with low PNI was associated with the highest risk of all-cause mortality (hazard ratio (HR) 1.85, 95% confidence interval (CI) 1.69–2.03) and CV mortality (HR 2.20, 95% CI 1.98–2.46), compared with the low Lp(a)/high PNI reference group. The combined model achieved a higher area under the receiver operating characteristic (AUROC) curve for mortality prediction than either marker alone ($p < 0.05$). Significant additive interactions between Lp(a) and PNI were observed for all-cause mortality (relative excess risk due to interaction, RERI 0.30, 95% CI 0.14–0.43) and CV mortality (RERI 0.32, 95% CI 0.11–0.52). **Conclusions:** Lp(a) and PNI are independently associated with increased long-term mortality in patients with CAD and demonstrate a significant additive interaction. Joint assessment of Lp(a) and PNI may help identify high-risk patients with CAD at hospital discharge and may inform clinical risk stratification, optimized management, and personalized follow-up. **Clinical Trial Registration:** NCT05050877, https://clinicaltrials.gov/study/NCT05050877?cond=NCT05050877&viewType=Card&rank=1.

Keywords: coronary artery disease; lipoprotein(a); prognostic nutritional index; additive interaction; all-cause mortality; cardiovascular mortality; risk stratification; real-world study

1. Introduction

Despite widespread application of percutaneous coronary intervention (PCI) and guideline-directed lipid-lowering therapy, coronary artery disease (CAD) is a major global public burden challenge [1,2]. Traditional low-density lipoprotein cholesterol (LDL-C)-centered management cannot fully eliminate residual cardiovascular risk, and factors beyond conventional lipid targets play critical roles in CAD progression and prognosis [3]. Lipoprotein(a) [Lp(a)] has emerged as an independent, causal risk factor for atherosclerotic cardiovascular disease and as a powerful prognostic marker in CAD [4]. Clinical trials and population studies have demonstrated that elevated Lp(a) is associated with an increased risk of adverse cardiovascular event risk even with well-controlled LDL-C levels [5,6,7].

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In addition to lipid metabolic abnormalities, malnutrition independently predicts worse long-term cardiovascular outcomes [8]. The prognostic nutritional index (PNI), a composite indicator calculated from serum albumin concentration and peripheral lymphocyte count, is one of the most widely used nutritional assessment tools in clinical research [9,10,11]. Compared with other nutritional screening tools, PNI has the advantages of being objective, simple to calculate, and readily available from routine blood tests, making it particularly suitable for large-scale epidemiological studies. Accumulating studies have validated the prognostic value of PNI in various atherosclerotic cardiovascular diseases, including CAD, heart failure and aortic dissection.

Both Lp(a) and PNI are well-recognized independent prognostic biomarkers for CAD, whereas their combined predictive effect on long-term CAD prognosis remains unclear. It is well established that Lp(a) exerts proatherogenic effects by delivering oxidized phospholipids that provoke vascular inflammation and oxidative damage [12]. As a marker of nutritional and immune status, PNI can reflect patients' overall physical conditions to a certain extent [13,14,15]. Malnutrition can increase systemic inflammation, which may further exacerbate vascular injury mediated by Lp(a) [16,17]. These observation suggest a potential pathological interaction between Lp(a) and PNI.

However, most previous studies have only investigated the independent prognostic effects of Lp(a) or PNI in CAD patients separately. The combined effects and potential interaction between Lp(a) and PNI on CAD mortality have not been systematically investigated to date, thus representing a critical research gap. Therefore, the aim of this study was to determine the independent associations of Lp(a) and PNI with all-cause and cardiovascular mortality in CAD patients, and to explore their joint effects on mortality risks. This research was based on a large-scale, multicenter real-world cohort of CAD patients in Southern China. Our findings may offer new perspectives and scientific evidence for developing nutritional interventions and for optimizing prognostic strategies in CAD.

2. Methods

2.1 Study Design and Study Population

This study utilized data from the CardioRenal Improvement II (CIN-II) cohort, a large-scale, multicenter retrospective observational cohort study conducted at 5 major tertiary care centers in Southern China, with consecutive patient enrollment between January 2007 and December 2020 (ClinicalTrials.gov NCT05050877, https://clinicaltrials.gov/study/NCT05050877?cond=NCT05050877&viewType=Card&rank=1). We initially screened 145,267 patients who underwent coronary angiography (CAG) or percutaneous coronary intervention (PCI). Of these screened individuals, 99,699 patients received a definitive diagnosis of CAD, as confirmed by CAG. Diagnostic criteria were defined as ≥50% diameter stenosis in any major epicardial coronary artery, including the left main, left anterior descending, left circumflex, and right coronary arteries. Indications for CAG and PCI procedures were determined by symptoms of ischemia, elevated cardiac markers, or electrocardiographic changes, with all procedures performed in accordance with standardized clinical practice guidelines [18,19]. Coronary angiograms were interpreted by experienced cardiologists following unified diagnostic specifications, ensuring consistent diagnostic standards across multiple centers. Patients were excluded if they met any of the following criteria: (1) aged <18 years (n = 638); (2) incomplete or missing follow-up data (n = 5759); (3) diagnosis of severe sepsis (n = 80) or malignant tumor (n = 1382); (4) lack of data on plasma Lp(a), serum albumin, absolute lymphocyte counts or PNI (n = 44,358). A total of 47,482 patients with CAD were included in the final analysis. The study design and screening process are presented in Fig. 1. This study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (GDREC2019-555H-2) and was conducted in full compliance with the ethical principles of the Declaration of Helsinki.

2.2 Data Acquisition

The primary data sources were the Electronic Clinical Management Systems at the participating institutions, from which baseline clinical data and characteristics (demographics, medical history, procedural details, laboratory findings, and discharge medications) were extracted. Laboratory parameters were acquired at the initial admission, including the key variables of serum albumin, absolute lymphocyte count, and Lp(a). Lp(a) concentrations and serum albumin were analyzed using the AU5800-3 Clinical Chemistry System (Beckman Coulter, Brea, CA, USA). Complete blood count, including absolute lymphocyte count, was performed using the XN9000-1 Hematology Analyzer (Sysmex Corporation, Kobe, Hyogo, Japan). Survival status was determined by linking the ECMS data with local official cause-specific mortality registries from the Public Security Bureau and Centers for Disease Control and Prevention, with a median follow-up of 5.2 years.

2.3 Exposure Definition and Grouping

PNI was used as the primary validated indicator of nutritional status, calculated with the formula: PNI = serum albumin (g/L) + 5 × absolute lymphocyte count ($\times 10^9$/L). Lp(a) was measured as the core non-traditional lipid biomarker.

Patients were stratified into three groups based on their baseline Lp(a) level [20]: Lp(a)-Low (Lpa-L: <15 mg/dL, n = 21,460), Lp(a)-Middle (Lpa-M: ≥15 mg/dL and <30 mg/dL, n = 11,809), and Lp(a)-High (Lpa-H: ≥30 mg/dL, n = 14,213). Patients were also dichotomized according to their baseline PNI level [21]: PNI-High (PNI-H: ≥45, n =

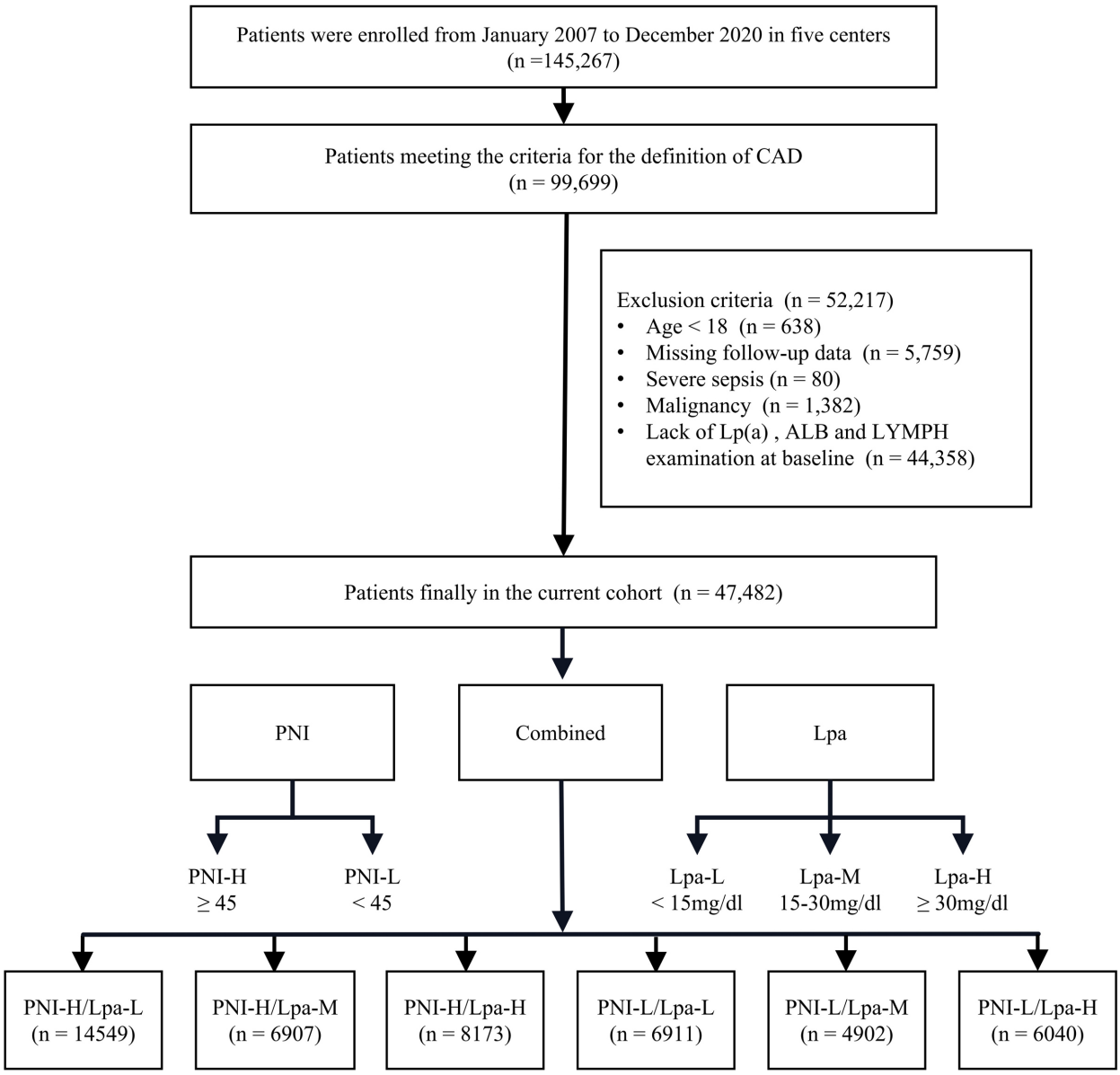


Fig. 1. Flow chart of the study population screening and enrollment process. Abbreviations: CAD, coronary artery disease; Lp(a), lipoprotein(a); PNI, prognostic nutritional index; ALB, albumin; LYMPH, lymphocyte count; L, low; M, middle; H, high.

29,629) and PNI-Low (PNI-L: <45, n = 17,853). For the assessment of joint effects, patients were further divided into 6 mutually exclusive groups based on combined Lp(a) and PNI status: Lp(a)-L/PNI-H, Lp(a)-M/PNI-H, Lp(a)-H/PNI-H, Lp(a)-L/PNI-L, Lp(a)-M/PNI-L, and Lp(a)-H/PNI-L.

2.4 Clinical Definitions and Outcomes

All clinical definitions followed established, standardized criteria. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2, derived from the CKD Epidemiology Collaboration (CKD-EPI) equation [22]. Congestive heart failure (CHF) was considered present with New York Heart Association (NYHA) functional class >2 for chronic CAD and Killip class >1 in those with acute myocardial infarction (AMI) [23]. Anemia was identified by a hematocrit ≤39% in men and ≤36% in women. Dyslipidemia was determined when at least one of the following criteria was met: fasting total cholesterol ≥240 mg/dL, LDL-C >160 mg/dL, triglycerides ≥150 mg/dL, or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL. AMI, diabetes mellitus, and hypertension were classified using the International Classification of Diseases, ICD-10 codes. Coronary angiographic characteristics were classified as single-vessel CAD, multivessel CAD, or left main CAD, defined as ≥50% stenosis in one, two or more, or the left main major epicardial coronary artery, respectively.

Primary endpoints included all-cause and cardiovascular mortality. All-cause mortality was determined through official death registries, while cardiovascular mortality was specifically identified from primary and secondary causes of death classified under ICD-10 codes I00–I99.

2.5 Statistical Analysis

Continuous variables were first tested for normality using the Shapiro-Wilk test. Normally distributed variables were expressed as the means ± standard deviation (SD) and compared using Student's *t*-test or one-way ANOVA, as appropriate. Non-normally distributed variables were expressed as the medians (interquartile ranges [IQR]) and compared using the Wilcoxon rank-sum test or Kruskal-Wallis test. Categorical variables were shown as counts (proportions), with group differences evaluated by chi-square test or Fisher's exact test.

Kaplan-Meier survival curves were constructed to visualize cumulative survival probabilities, and group differences were compared using the log-rank test. Univariable and multivariable Cox proportional hazards models examined associations between baseline PNI and Lp(a) levels and the risks of all-cause and cardiovascular mortality, including both the independent prognostic effects of individual markers and the joint effects of combined Lp(a)-PNI status, with low Lp(a)/high PNI used as the reference. Multivariable models were adjusted for traditional cardiovascular disease risk factors (age, sex, hypertension, diabetes, dyslipidaemia, CKD, AMI, and CHF), coronary angiographic characteristics, and the neutrophil-to-lymphocyte ratio (NLR, calculated as neutrophil count / lymphocyte count) [24,25,26,27].

To further quantitatively evaluate the incremental predictive value, time-dependent receiver operating characteristic (ROC) analyses were performed, with both variables modeled continuously. The area under the curve (AUC) was computed to compare the discriminatory power of Lp(a), PNI, and their combination. Bootstrap internal validation with 1000 resamples was applied to validate model stability and predictive performance. Model calibration was evaluated by comparing predicted risks with observed outcomes, and clinical utility was evaluated using decision curve analysis (DCA).

Potential additive interactions between PNI and Lp(a) on mortality risks were investigated using additive scale models to compute the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and the synergy index (SI), with 95% confidence intervals (CIs) derived via the delta method. An additive interaction was defined as RERI >0, AP >0, and SI >1, indicating that the combined effect surpassed the sum of individual effects. Subgroup analyses were performed according to age (≤65 vs >65 years), sex (male vs female), LDL-C concentration (<1.8 vs ≥1.8 mmol/L) and AMI status (no vs yes). Multiplicative interaction terms were included in multivariable Cox models to test for effect modification. Sensitivity analyses were conducted to prove the robustness of the primary findings: (1) redefining participants according to the median cutoff value of PNI for Cox regression and additive interaction analyses; (2) excluding patients with AMI and those with markedly elevated inflammatory status (high-sensitivity C-reactive protein (hs-CRP) >3.0 mg/L) to reassess the prognostic associations and interaction effects.

Two-tailed p-values < 0.05 were considered statistically significant. All statistical analyses were conducted using R software version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Study Population and Baseline Characteristics

This study included 47,482 participants, 29,629 (7117 women; 62.4%) were classified into the high PNI group (PNI ≥45) and 17,853 (4215 women; 37.6%) into the low PNI group (PNI <45). Table 1 summarizes the baseline demographics, clinical characteristics, biochemical parameters, and discharge medications for the overall cohort and PNI subgroups, with additional stratification by Lp(a) levels (<15 mg/dL, 15 to <30 mg/dL, ≥30 mg/dL).

Compared with patients in the high PNI group, those with low PNI were older, had a lower female proportion, and exhibited higher levels of hs-CRP, NT-proBNP, cardiac troponin T, neutrophil counts and Lp(a), as well as lower levels of eGFR and left ventricular ejection fraction (LVEF). They also had a greater proportion of left main coronary artery involvement. When stratified by Lp(a) levels, patients with higher Lp(a) concentrations were more likely to have higher levels of total cholesterol, LDL-C, and apolipoprotein B (all $p < 0.05$). However, there were no statistically significant differences in the utilization rates of statins and PCSK9 inhibitors across Lp(a) strata. Detailed between-group comparisons of baseline characteristics are presented in Table 1 and **Supplementary Table 1**.

Spearman correlation analysis showed no clinically relevant collinearity between Lp(a) and PNI in the overall CAD cohort ($r = 0.02$, $p < 0.001$), with a correlation coefficient below the pre-specified threshold for multicollinearity ($r < 0.2$) (**Supplementary Fig. 1**).

3.2 Lp(a) and Mortality Risk

We next examined the independent prognostic associations of elevated Lp(a) and reduced PNI with all-cause mortality and cardiovascular mortality. When analyzed as a continuous variable, per 1-SD increase in Lp(a) was consistently associated with increased risks of all-cause and cardiovascular mortality. For all-cause mortality, the hazard ratio (HR) was 1.15 (95% CI 1.12–1.19) in the unadjusted model, 1.16 (95% CI 1.13–1.20) in Model 1, and 1.14 (95% CI 1.10–1.17) in Model 2. For cardiovascular mortality, the association remained significant across all models, with a

Table 1. Baseline clinical characteristics of the study population stratified by lipoprotein(a) and prognostic nutritional index levels.

Characteristic	Overall	PNI ≥45				PNI <45				*p*
		All	Lp(a) <15 mg/dL	Lp(a) 15–30 mg/dL	Lp(a) ≥30 mg/dL	All	Lp(a) <15 mg/dL	Lp(a) 15–30 mg/dL	Lp(a) >30 mg/dL	
	(n = 47,482)	(n = 29,629)	(n = 14,549)	(n = 6907)	(n = 8173)	(n = 17,853)	(n = 6911)	(n = 4902)	(n = 6040)	
Demographic characteristics										
Age, years	62.8 (10.7)	60.70 (10.41)	60.73 (10.46)	61.03 (10.25)	60.35 (10.43)	66.24 (10.19)	66.31 (10.26)	66.59 (10.21)	65.86 (10.09)	<0.001
Female, n (%)	11,332 (23.9)	7117 (24.0)	3345 (23.0)	1621 (23.5)	2151 (26.3)	4215 (23.6)	1603 (23.2)	1102 (22.5)	1510 (25.0)	<0.001
Current smoker, n (%)	12,996 (27.4)	8002 (27.0)	3871 (26.6)	1882 (27.2)	2249 (27.6)	4994 (28.0)	1911 (27.6)	1381 (28.2)	1702 (28.2)	0.519
Coexisting conditions										
AMI, n (%)	9670 (20.4)	4350 (14.7)	1834 (12.6)	1172 (17.0)	1344 (16.4)	5320 (29.8)	1834 (26.5)	1549 (31.6)	1937 (32.1)	<0.001
CHF, n (%)	7363 (15.5)	3227 (10.9)	1381 (9.5)	873 (12.6)	973 (11.9)	4136 (23.2)	1428 (20.7)	1172 (23.9)	1536 (25.4)	<0.001
Hypertension, n (%)	26,514 (55.8)	16,254 (54.9)	8136 (55.9)	3761 (54.5)	4357 (53.3)	10,260 (57.5)	4018 (58.1)	2779 (56.7)	3463 (57.3)	<0.001
Diabetes mellitus, n (%)	17,406 (36.7)	10,829 (36.5)	5562 (38.2)	2441 (35.3)	2826 (34.6)	6577 (36.8)	2572 (37.2)	1771 (36.1)	2234 (37.0)	<0.001
CKD, n (%)	37,594 (79.3)	4206 (14.2)	1959 (13.5)	1010 (14.7)	1237 (15.2)	5584 (31.3)	1933 (28.0)	1565 (32.0)	2086 (34.6)	<0.001
Anaemia, n (%)	14,956 (31.5)	6137 (20.7)	2882 (19.8)	1392 (20.2)	1863 (22.8)	8819 (49.4)	3188 (46.1)	2456 (50.1)	3175 (52.6)	<0.001
Atrial fibrillation, n (%)	1887 (4.0)	946 (3.2)	516 (3.5)	225 (3.3)	205 (2.5)	941 (5.3)	383 (5.5)	266 (5.4)	292 (4.8)	<0.001
Stroke, n (%)	2801 (5.9)	1494 (5.0)	716 (4.9)	321 (4.6)	457 (5.6)	1307 (7.3)	473 (6.8)	350 (7.1)	484 (8.0)	<0.001
NYHA class										0.011
I	4441 (17.1)	3200 (20.4)	1562 (20.7)	780 (21.1)	858 (19.4)	1241 (12.1)	493 (12.5)	345 (12.3)	403 (11.4)	
II	16,825 (64.9)	10,382 (66.2)	5094 (67.4)	2340 (63.3)	2948 (66.7)	6443 (62.8)	2526 (64.3)	1739 (62.2)	2178 (61.7)	
III	3905 (15.1)	1881 (12.0)	805 (10.6)	533 (14.4)	543 (12.3)	2024 (19.7)	729 (18.5)	550 (19.7)	745 (21.1)	
IV	767 (3.0)	219 (1.4)	100 (1.3)	46 (1.2)	73 (1.7)	548 (5.3)	182 (4.6)	163 (5.8)	203 (5.8)	
Laboratory examination										
PNI	46.62 ± 5.82	50.12 ± 3.79	50.36 ± 3.90	49.95 ± 3.68	49.85 ± 3.64	40.82 ± 3.52	41.24 ± 3.24	40.71 ± 3.48	40.42 ± 3.79	<0.0001
Lp(a), mg/dL	16.99 [8.84, 35.60]	15.34 [8.10, 32.94]	8.00 [5.40, 10.97]	20.69 [17.53, 24.60]	54.30 [39.30, 81.10]	19.76 [10.40, 39.41]	8.80 [6.00, 11.66]	21.02 [17.70, 24.80]	54.30 [39.00, 82.92]	<0.001
Lymphocyte, 10^9/L	1.91± 0.69	2.20 ± 0.66	2.21 ± 0.67	2.18 ± 0.65	2.18 ± 0.65	1.45 ± 0.46	1.44 ± 0.45	1.44 ± 0.46	1.46 ± 0.47	<0.001
Albumin, g/L	37.05 ± 4.14	39.14 ± 3.03	39.31 ± 3.01	39.04 ± 3.03	38.92 ± 3.03	33.58 ± 3.35	34.03 ± 3.15	33.49 ± 3.23	33.14 ± 3.59	<0.001
HbA1c, %	6.51 ± 1.42	6.48 ± 1.37	6.51 ± 1.39	6.46 ± 1.36	6.45 ± 1.35	6.56 ± 1.50	6.54 ± 1.48	6.54 ± 1.48	6.60 ± 1.54	<0.001
Hs-CRP	2.63 [0.90, 7.77]	1.93 [0.74, 4.87]	1.67 [0.68, 4.21]	2.14 [0.81, 5.65]	2.30 [0.84, 5.79]	4.94 [1.49, 16.80]	3.71 [1.15, 11.75]	5.72 [1.64, 21.00]	6.54 [1.96, 22.70]	<0.001
NT-proBNP	225.70 [65.14, 920.90]	132.20 [47.71, 470.90]	114.20 [42.75, 392.12]	155.60 [52.20, 565.38]	160.00 [54.57, 547.50]	657.50 [161.07, 2265.25]	452.40 [122.60, 1738.00]	782.61 [180.65, 2565.50]	857.80 [225.85, 2751.50]	<0.001
Cardiac troponin T	13.80 [7.60, 54.70]	11.23 [6.92, 26.63]	10.60 [6.77, 22.13]	11.87 [7.02, 34.75]	12.18 [7.15, 32.77]	28.30 [10.60, 323.42]	20.50 [9.36, 182.35]	30.85 [10.96, 426.75]	38.50 [12.50, 406.20]	<0.001
White blood cells, 10^9/L	7.42 [6.17, 9.03]	7.54 [6.37, 9.01]	7.45 [6.31, 8.89]	7.58 [6.38, 9.10]	7.67 [6.45, 9.10]	7.19 [5.83, 9.08]	7.04 [5.69, 8.90]	7.25 [5.89, 9.16]	7.31 [5.92, 9.16]	<0.001
Neutrophil, 10^9/L	4.53 [3.55, 5.91]	4.42 [3.53, 5.60]	4.34 [3.47, 5.50]	4.49 [3.56, 5.71]	4.50 [3.59, 5.70]	4.76 [3.61, 6.57]	4.62 [3.50, 6.45]	4.82 [3.65, 6.67]	4.87 [3.69, 6.59]	<0.001
Monocyte, 10^9/L	0.59 [0.46, 0.75]	0.59 [0.47, 0.74]	0.58 [0.47, 0.73]	0.59 [0.47, 0.75]	0.59 [0.47, 0.75]	0.59 [0.46, 0.77]	0.58 [0.44, 0.75]	0.60 [0.46, 0.77]	0.60 [0.46, 0.79]	<0.001
NLR	2.43 [1.77, 3.52]	2.07 [1.59, 2.78]	2.03 [1.55, 2.71]	2.13 [1.62, 2.85]	2.12 [1.63, 2.84]	3.34 [2.38, 5.00]	3.27 [2.33, 4.91]	3.37 [2.42, 5.07]	3.40 [2.42, 5.04]	0.002
PLR	119.67 [92.22, 159.24]	106.29 [84.37, 135.00]	102.86 [81.82, 131.10]	108.61 [86.03, 137.85]	110.16 [87.74, 138.76]	151.39 [116.29, 200.83]	145.30 [112.45, 190.65]	151.97 [116.22, 201.96]	158.26 [121.19, 210.34]	<0.001
SII	539.46 [368.74, 827.69]	467.81 [332.82, 71.44]	445.47 [319.53, 636.22]	488.18 [345.17, 699.15]	493.54 [351.11, 705.21]	722.78 [472.51, 1163.69]	681.46 [444.79, 1101.79]	727.19 [487.52, 1175.10]	773.83 [506.52, 1235.28]	<0.001
Total cholesterol, mmol/L	4.55 ± 1.26	4.67 ± 1.30	4.50 ± 1.27	4.78 ± 1.28	4.89 ± 1.31	4.35 ± 1.17	4.16 ± 1.14	4.36 ± 1.12	4.57 ± 1.22	<0.001

Table 1. Continued.

Characteristic	Overall	PNI ≥45				PNI <45				*p*
		All	Lp(a) <15 mg/dL	Lp(a) 15–30 mg/dL	Lp(a) ≥30 mg/dL	All	Lp(a) <15 mg/dL	Lp(a) 15–30 mg/dL	Lp(a) >30 mg/dL	
HDL-C, mmol/L	1.01 ± 0.26	1.02 ± 0.25	1.00 ± 0.25	1.03 ± 0.25	1.04 ± 0.26	0.98 ± 0.27	0.98 ± 0.27	0.98 ± 0.27	0.99 ± 0.28	<0.001
LDL-C, mmol/L	2.86 ± 0.99	2.95 ± 1.02	2.78 ± 0.95	3.06 ± 1.04	3.15 ± 1.05	2.72 ± 0.94	2.52 ± 0.87	2.74 ± 0.90	2.92 ± 0.99	<0.001
Triglyceride, mmol/L	1.69 ± 1.27	1.84 ± 1.36	1.98 ± 1.62	1.70 ± 1.06	1.70 ± 1.02	1.45 ± 1.04	1.54 ± 1.29	1.39 ± 0.92	1.39 ± 0.76	<0.001
Hemoglobin, g/L	134.10 ± 17.46	138.45 ± 15.34	138.96 ± 15.16	138.65 ± 15.49	137.36 ± 15.48	126.89 ± 18.35	128.61 ± 17.80	126.59 ± 18.19	125.15 ± 18.91	<0.001
Apolipoprotein A, g/L	1.13 ± 0.26	1.16 ± 0.25	1.16 ± 0.25	1.17 ± 0.25	1.16 ± 0.26	1.07 ± 0.26	1.08 ± 0.26	1.06 ± 0.26	1.06 ± 0.27	<0.001
Apolipoprotein B, g/L	0.87 ± 0.25	0.89 ± 0.26	0.85 ± 0.25	0.92 ± 0.27	0.94 ± 0.27	0.83 ± 0.23	0.78 ± 0.22	0.84 ± 0.23	0.89 ± 0.24	<0.001
eGFR, mL/min/1.73 m^2	78.2 ± 26.6	82.39 ± 24.93	83.08 ± 24.81	81.84 ± 24.85	81.61 ± 25.18	71.15 ± 27.78	72.82 ± 26.07	70.80 ± 27.87	69.52 ± 29.45	<0.001
Echocardiographic and angiographic data										
LVEF, %	59.1 ± 11.8	60.90 ± 10.69	61.39 ± 10.33	60.76 ± 10.71	60.18 ± 11.22	56.17 ± 12.99	57.47 ± 12.70	55.75 ± 13.00	55.04 ± 13.18	<0.001
Coronary lesion characteristics										
Single-vessel, n (%)	29,358 (61.8)	18,364 (62.0)	9305 (64.0)	4346 (62.9)	4713 (57.7)	10,994 (61.6)	4366 (63.2)	3129 (63.8)	3499 (57.9)	<0.001
Multivessel, n (%)	14,159 (29.8)	9026 (30.5)	4204 (28.9)	2043 (29.6)	2779 (34.0)	5133 (28.8)	1912 (27.7)	1323 (27.0)	1898 (31.4)	
LMCA, n (%)	3965 (8.4)	2239 (7.6)	1040 (7.1)	518 (7.5)	681 (8.3)	1726 (9.7)	633 (9.2)	450 (9.2)	643 (10.6)	
PCI, n (%)	35,300 (74.3)	21,609 (72.9)	10,295 (70.8)	5086 (73.6)	6228 (76.2)	13,691 (76.7)	5087 (73.6)	3808 (77.7)	4796 (79.4)	<0.001
CABG, n (%)	82 (0.2)	50 (0.2)	27 (0.2)	12 (0.2)	11 (0.1)	32 (0.2)	9 (0.1)	12 (0.2)	11 (0.2)	0.349
Medicine										
RASi, n (%)	33,236 (70.8)	20,882 (71.0)	10,208 (70.7)	4905 (71.6)	5769 (71.2)	12,354 (70.5)	4893 (71.9)	3353 (69.9)	4108 (69.4)	0.010
β-blocker, n (%)	37,828 (80.6)	23,972 (81.5)	11,693 (80.9)	5592 (81.6)	6687 (82.5)	13,856 (79.1)	5394 (79.3)	3764 (78.5)	4698 (79.3)	<0.001
Statins, n (%)	44,886 (94.53)	28,235 (96.0)	13,853 (95.9)	6564 (95.8)	7818 (96.4)	16,651 (95.1)	6459 (95.0)	4553 (95.0)	5639 (95.2)	<0.001
PCSK9 inhibitors n (%)	68 (0.1)	48 (0.2)	29 (0.2)	12 (0.2)	7 (0.1)	20 (0.1)	10 (0.1)	4 (0.1)	6 (0.1)	0.186
OAD, n (%)	8850 (18.9)	5774 (19.6)	3052 (21.1)	1272 (18.6)	1450 (17.9)	3076 (17.6)	1260 (18.5)	807 (16.8)	1009 (17.0)	0.027
Aspirin, n (%)	43,174 (90.9)	27,221 (92.6)	13,288 (92.0)	6351 (92.7)	7582 (93.5)	15,953 (91.1)	6159 (90.6)	4370 (91.1)	5424 (91.6)	<0.001

Abbreviations: Lp(a), lipoprotein(a); PNI, prognostic nutritional index; AMI, acute myocardial infarction; CHF, congestive heart failure; CKD, chronic kidney disease; NYHA, New York Heart Association functional classification; HbA1c, glycated hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; HDL-C, high-density lipoprotein cholesterol; LMCA, left main coronary artery; eGFR, Estimated Glomerular Filtration Rate; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; RASi, renin angiotensin system inhibitor; OAD, oral anti-diabetic drugs; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CABG, coronary artery bypass grafting; PCSK9, proprotein convertase subtilisin/kexin type 9. Data are presented as the mean value (standard deviation), median [interquartile range] or number of participants (percentage).

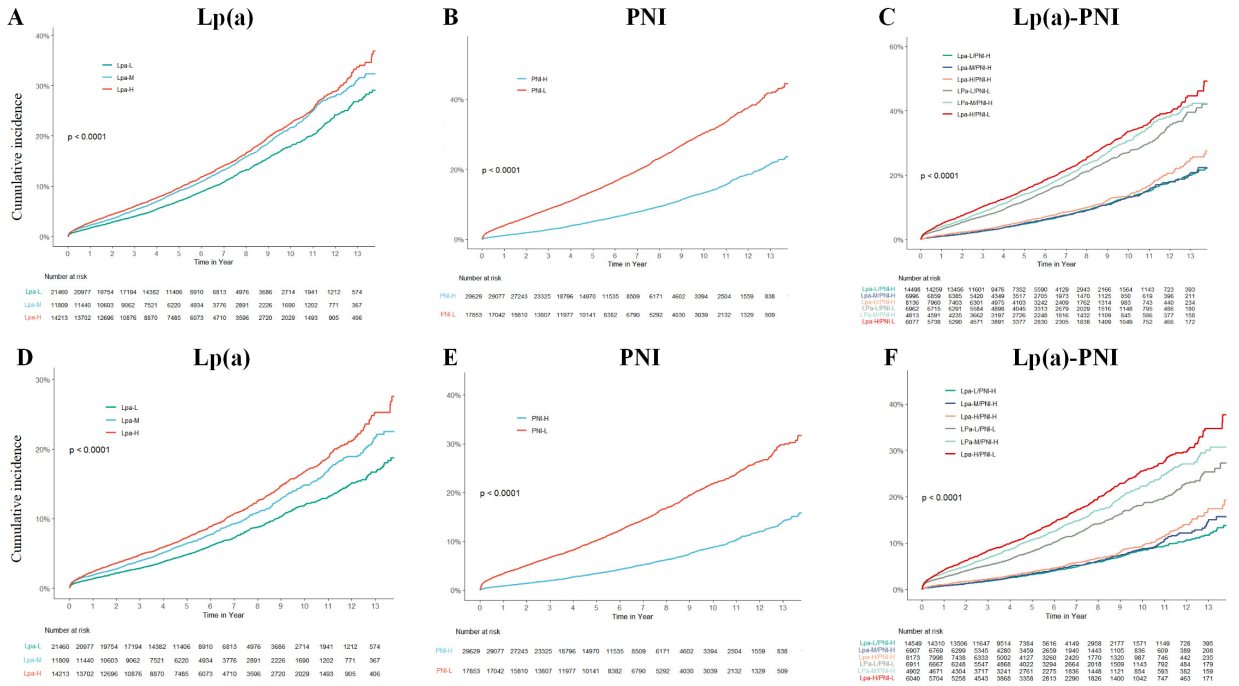


Fig. 2. Kaplan–Meier analysis for all-cause and cardiovascular mortality in coronary artery disease (CAD) patients, stratified by lipoprotein(a) [Lp(a)] and prognostic nutritional index (PNI). (A–C) The Lp(a), PNI and the Lp(a)-PNI combination for all-cause mortality risks. (D–F) The Lp(a), PNI and the Lp(a)-PNI combination for cardiovascular mortality risks. Lp(a), lipoprotein(a); H, high; L, low; PNI, prognostic nutritional index.

fully adjusted HR (aHR) of 1.16 (95% CI 1.10–1.22) per 1-SD increase in Lp(a).

Patients were stratified into three groups according to their Lp(a) level: Lp(a)-Low (<15 mg/dL, n = 21,460), Lp(a)-Middle (15 to <30 mg/dL, n = 11,809), and Lp(a)-High (≥30 mg/dL, n = 14,213). In fully adjusted models, higher Lp(a) levels were associated with a stepwise increase in mortality risk. Compared with the Lp(a)-Low group, the Lp(a)-Middle group had a 14% higher risk of all-cause mortality (aHR 1.14, 95% CI 1.05–1.21) and a 18% higher risk of cardiovascular mortality (aHR 1.18, 95% CI 1.08–1.29), while the Lp(a)-High group had a 24% higher risk of all-cause mortality (aHR 1.24, 95% CI 1.16–1.32) and a 37% higher risk of cardiovascular mortality (aHR 1.37, 95% CI 1.27–1.48) (Table 2).

Restricted cubic spline analysis revealed significant nonlinear relationships between Lp(a) and both all-cause mortality (p for nonlinearity = 0.015) and cardiovascular mortality (p for nonlinearity = 0.001) (**Supplementary Fig. 2**). Kaplan–Meier curves with log-rank tests showed significantly higher cumulative mortality in patients with elevated Lp(a) levels ($p < 0.001$ for both endpoints) (Fig. 2A and 2D). Subgroup analyses revealed no significant multiplicative interaction between Lp(a) levels and age, sex, LDL-C concentration, diabetes, or AMI for all-cause mortality (all p for interaction > 0.05, **Supplementary Table 2**).

3.3 PNI and Mortality Risk

When analyzed as a continuous variable, per 1-point increase in PNI was associated with a 5% lower risk of all-cause mortality (aHR 0.95, 95% CI 0.94–0.95) and an 8% lower risk of cardiovascular mortality (aHR 0.92, 95% CI 0.92–0.93) in the fully adjusted model (both $p < 0.001$). Compared with the high PNI group, patients in the low PNI group had a 61% higher risk of all-cause mortality (aHR 1.61, 95% CI 1.51–1.71) and a 76% higher risk of cardiovascular mortality (aHR 1.76, 95% CI 1.64–1.90) after full adjustment (both $p < 0.001$) (Table 2).

Kaplan–Meier curves with log-rank tests showed significantly higher cumulative mortality in the low PNI group ($p < 0.001$ for both endpoints) (Fig. 2B and 2E). Restricted cubic spline analysis confirmed significant nonlinear associations between PNI and both mortality endpoints after full adjustment (both p for nonlinearity <0.001) (**Supplementary Fig. 2**). Subgroup analyses consistently validated the independent prognostic value of PNI across all predefined patient strata (**Supplementary Table 3**).

3.4 Joint Effects of Lp(a) and PNI on Mortality Risk

Given the significant independent prognostic value of Lp(a) and PNI, we further investigated potential biological interactions between these two biomarkers and quantitatively evaluated their additive interaction effect. Patients were divided into 6 mutually exclusive groups based

Table 2. COX regression models for the association of the prognostic nutritional index and lipoprotein(a) with all-cause and cardiovascular mortality among participants.

Events/Total		All-cause mortality						CV mortality					
		Non-adjusted		Model 1[1]		Model 2[2]		Non-adjusted		Model 1[1]		Model 2[2]	
		HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Lp(a)													
Continuous		1.15 (1.12–1.19)	<0.001	1.16 (1.13–1.20)	<0.001	1.14 (1.10–1.17)	<0.001	1.22 (1.18–1.26)	<0.001	1.23 (1.18–1.27)	<0.001	1.16 (1.10–1.22)	<0.001
<15	1375/21460	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
15–30	971/11809	1.22 (1.13–1.30)	<0.001	1.18 (1.10–1.26)	0.011	1.14 (1.05–1.21)	0.001	1.28 (1.18–1.39)	<0.001	1.24 (1.14–1.35)	<0.001	1.18 (1.08–1.29)	<0.001
≥30	1352/14213	1.31 (1.23–1.39)	<0.001	1.33 (1.25–1.41)	<0.001	1.24 (1.16–1.32)	<0.001	1.47 (1.37–1.59)	<0.001	1.49 (1.38–1.61)	<0.001	1.37 (1.27–1.48)	<0.001
PNI													
Continuous		0.91 (0.91–0.92)	<0.001	0.94 (0.93–0.94)	<0.001	0.95 (0.94–0.95)	<0.001	0.91 (0.90–0.92)	<0.001	0.92 (0.92–0.93)	<0.001	0.92 (0.92–0.93)	<0.001
≥45	1336/29629	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
<45	2362/17853	2.43 (2.30–2.57)	<0.001	1.87 (1.73–1.95)	<0.001	1.61 (1.51–1.71)	<0.001	2.67 (2.50–2.86)	<0.001	2.11 (1.93–2.26)	<0.001	1.76 (1.64–1.90)	<0.001
Combined													
Lpa-L / PNI-H	927/14549	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Lpa-M / PNI-H	465/6907	1.06 (0.95–1.18)	0.321	1.06 (0.95–1.18)	0.322	1.04 (0.93–1.17)	0.475	1.07 (0.94–1.23)	0.307	1.07 (0.94–1.23)	0.307	1.05 (0.91–1.21)	0.486
Lpa-H / PNI-H	605/8173	1.16 (1.04–1.28)	0.006	1.20 (1.08–1.33)	<0.001	1.16 (1.04–1.29)	0.001	1.23 (1.08–1.39)	0.001	1.26 (1.11–1.43)	0.001	1.21 (1.06–1.37)	0.004
Lpa-L / PNI-L	1128/6911	2.29 (2.10–2.50)	<0.001	1.72 (1.58–1.88)	<0.001	1.53 (1.40–1.68)	<0.001	2.40 (2.16–2.67)	<0.001	1.88 (1.69–2.10)	<0.001	1.60 (1.43–1.79)	<0.001
Lpa-M / PNI-L	917/4902	2.66 (2.43–2.91)	<0.001	1.99 (1.82–2.19)	<0.001	1.73 (1.57–1.90)	<0.001	2.95 (2.64–3.29)	<0.001	2.31 (2.06–2.58)	<0.001	1.91 (1.70–2.15)	<0.001
Lpa-H / PNI-L	1187/6040	2.81 (2.58–3.06)	<0.001	2.21 (2.03–2.41)	<0.001	1.85 (1.69–2.03)	<0.001	3.39 (3.06, 3.76)	<0.001	2.76 (2.49, 3.06)	<0.001	2.20 (1.98–2.46)	<0.001

Abbreviations: CV, cardiovascular; HR, hazard ratio; Lp(a), lipoprotein(a); PNI, prognostic nutritional index; H, high; M, middle; L, low.

[1] Model 1 was adjusted for age, gender.

[2] Model 2 was adjusted for age, gender, hypertension, diabetes, dyslipidemia, chronic kidney disease, acute myocardial infarction, congestive heart failure, statin use, PCSK9 inhibitor use, coronary lesion characteristics, and neutrophil-to-lymphocyte ratio.

Table 3. Interactive effects of prognostic nutritional index and lipoprotein(a) on all-cause and cardiovascular mortality among participants.

Interactive items	Interactive effect (95% CI) [1]			
	All-cause mortality	*p*	CV mortality	*p*
RERI	0.30 (0.14–0.43)	<0.001	0.32 (0.11–0.52)	<0.001
AP	0.12 (0.07–0.16)	<0.001	0.12 (0.06–0.18)	<0.001
SI	1.24 (1.15–1.33)	<0.001	1.24 (1.13–1.35)	<0.001

Abbreviations: CV, cardiovascular; AP, proportion attributable to interaction; RERI, relative excess risk due to interaction; SI, synergy index.

[1] All models adjusted for age, gender, hypertension, diabetes, dyslipidemia, chronic kidney disease, acute myocardial infarction, congestive heart failure, statin use, PCSK9 inhibitor use, coronary lesion characteristics, and neutrophil-to-lymphocyte ratio.

on combinations of Lp(a) and PNI status, with Lp(a)-Low/PNI-High (Lpa-L/PNI-H) set as the reference group. As shown in Table 2, compared with the reference group, the isolated high Lp(a) group (Lpa-H/PNI-H) and isolated low PNI group (Lpa-L/PNI-L) both had significantly elevated risks of all-cause mortality after full adjustment in Model 2 (aHR 1.16, 95% CI 1.04–1.29, $p = 0.001$; aHR 1.53, 95% CI 1.40–1.68, $p < 0.001$, respectively). Importantly, patients with combined high Lp(a) and low PNI had the highest risk of all-cause mortality, with a crude HR of 2.81 (95% CI 2.58–3.06, $p < 0.001$) and a fully adjusted HR of 1.85 (95% CI 1.69–2.03, $p < 0.001$) in Model 2.

Kaplan–Meier curves with log-rank tests confirmed the Lp(a)-High/PNI-Low group had the highest cumulative incidence of all-cause and cardiovascular mortality. These were was significantly higher than those of all other groups ($p < 0.001$ for all comparisons) (Fig. 2C and 2F).

To further quantify the additive interaction between PNI and Lp(a), we calculated additive interaction indices (Table 3). Analysis revealed a statistically significant additive interaction for all-cause mortality, with a RERI of 0.30 (95% CI 0.14–0.43), AP of 0.12 (95% CI 0.07–0.16), and SI of 1.24 (95% CI 1.15–1.33). A stronger additive interaction was observed for cardiovascular mortality, with a RERI of 0.32 (95% CI 0.11–0.52), AP of 0.12 (95% CI 0.06–0.18), and SI of 1.24 (95% CI 1.13–1.35). The additive interaction analysis yielded consistent results across all measures, with RERI, AP, and SI each reaching statistical significance (all $p < 0.001$) for both all-cause and cardiovascular mortality.

3.5 Predictive Performance of the Lp(a)-PNI Combination

Considering the interactive effect described above, we subsequently tested whether combining Lp(a) with PNI could further improve predictive discrimination, calibration, and clinical net benefit for long-term mortality. The discriminative performance of Lp(a) alone, PNI alone, and their combination was compared for all-cause and cardiovascular mortality using ROC curve analysis (Fig. 3). For all-cause mortality, the Lp(a)-PNI combination achieved the highest AUC of 0.726 (95% CI 0.718–0.733, $p < 0.001$), followed by PNI alone (AUC 0.681, 95% CI 0.673–0.688, $p < 0.001$), and Lp(a) alone (AUC 0.658, 95% CI 0.650–0.666, $p < 0.001$).

To evaluate the incremental predictive value, the performance of a base risk model (including all covariates in Model 2) was compared with the base model plus the Lp(a)-PNI combination for 5-year and 10-year clinical endpoints. The addition of Lp(a)-PNI combination yielded an evident improvement in model discrimination, with the time-dependent AUC rising from 0.605 to 0.713 for the 5-year endpoint and from 0.648 to 0.750 for the 10-year endpoint (all $p < 0.001$) (Fig. 3C). Calibration curves demonstrated good agreement between predicted and observed mortality risks for both models (Fig. 3D and 3E). DCA further showed that adding Lp(a) and PNI to the base model yielded a significant improvement in clinical net benefit across the full range of threshold probabilities (Fig. 3F).

3.6 Sensitivity Analyses

Sensitivity analyses confirmed the robustness of the primary findings (**Supplementary Table 4** and **Supplementary Table 5**). Reclassifying participants using the median PNI as the cutoff yielded similar prognostic associations and consistent additive joint effects of PNI and Lp(a) on cardiovascular and all-cause mortality. After excluding patients with AMI and those with hs-CRP >3.0 mg/L, the independent prognostic associations of Lp(a) and PNI remained consistent with the primary results, and a significant difference in mortality risk was still observed in the low PNI subgroup. However, no statistically significant additive interaction between Lp(a) and PNI was observed. These findings indicate that the core prognostic value of PNI and Lp(a) is reliable across different subpopulations, while their synergistic effect may be more pronounced in the overall cohort including patients with acute cardiac events and elevated systemic inflammation.

4. Discussion

Based on a large-scale, multicenter real-world cohort of patients with CAD in Southern China, this is the first

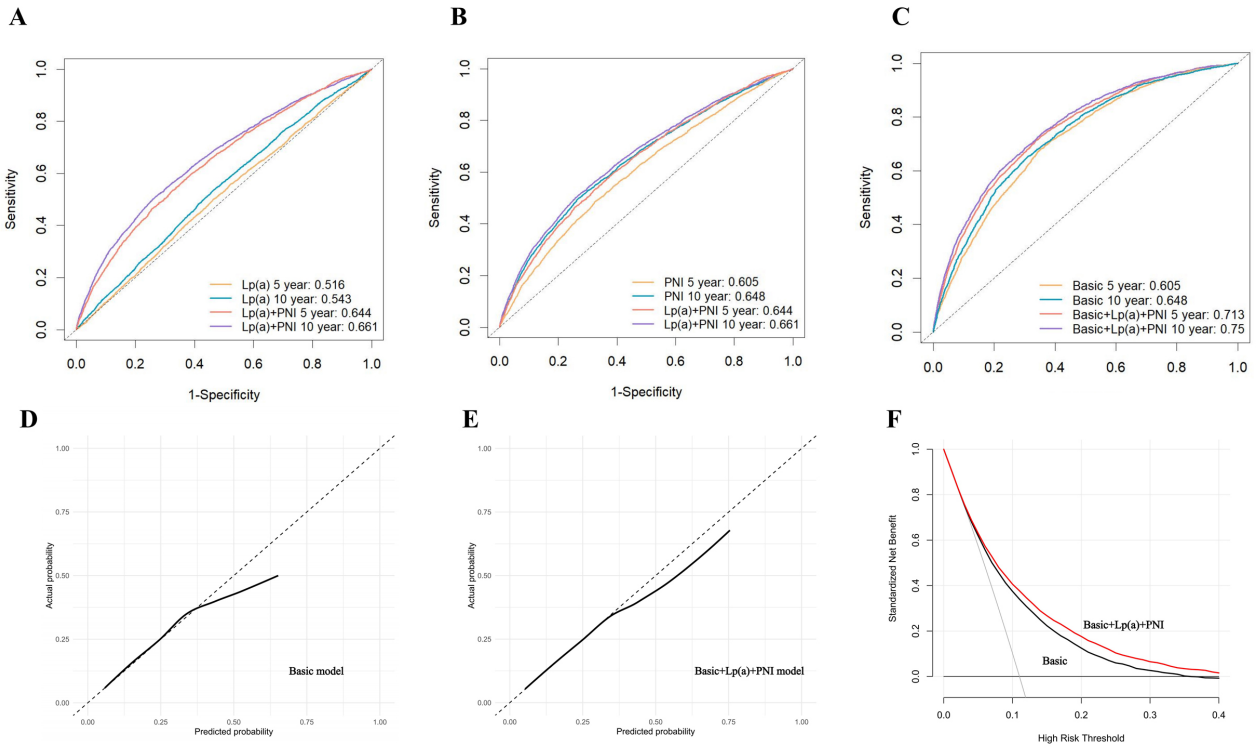


Fig. 3. Predictive performance of the combined lipoprotein(a) [Lp(a)] and prognostic nutritional index (PNI) for all-cause mortality in patients with coronary artery disease (CAD). (A) The ROC curves of the Lp(a)-PNI combination vs. Lp(a) as a marker to predict all-cause mortality risks in patients with CAD. (B) The ROC curves of the Lp(a)-PNI combination vs. PNI as a marker to predict all-cause mortality risks in patients with CAD. (C) The ROC curves of basic risk model vs. + the Lp(a)-PNI combination to predict all-cause mortality. (D) Calibration curves of basic risk model. (E) Calibration curves of basic + Lp(a) + PNI model. (F) The decision curve analysis of basic risk model vs. + the Lp(a)-PNI combination.

study to systematically demonstrate that serum Lp(a) and PNI are not only independent prognostic markers for all-cause and cardiovascular mortality in CAD patients, but also exhibit a statistically significant additive interaction on long-term mortality risk. Specifically, CAD patients with elevated Lp(a) combined with reduced PNI had the highest risk of all-cause and cardiovascular mortality. Joint assessment of the two markers yielded a statistically significant improvement in predictive ability, although the incremental change was relatively small, and its clinical implication should be interpreted with appropriate caution.

However, the precise biological mechanisms underlying the additive interaction between dyslipidemia and nutritional status on mortality risk remain unclear. There may be several mechanism involved: Firstly, lower levels of albumin were observed in both the low PNI subgroup and high Lp(a) subgroup. Lp(a) promotes platelet activation and inhibits fibrinolysis to enhance prothrombotic potential, while hypoalbuminemia compromises the endothelial anticoagulant function. The superposition of these two risk factors may further elevate cardiovascular coagulation tendency, thereby triggering thrombosis, inducing myocardial ischemia and hypoxia, and ultimately progressing to MI [12,28,29]. Secondly, severe malnutrition is associated with increased inflammation [30]. Multiple inflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor-α, exacerbate oxidative stress and vasoconstriction, leading to endothelial dysfunction and impairment of myocardial cell, thereby increasing the long-term risk of adverse outcomes in CAD patients [28,29]. Finally, there is an interaction between nutritional status and dyslipidemia. Lymphopenia directly impairs systemic immune defense and anti-inflammatory regulatory capacity, which may render the body unable to effectively counteract vascular endothelial inflammation and innate immune activation triggered by oxidized phospholipids carried by Lp(a) [31]. In turn, chronic inflammation induced by Lp(a) further accelerates systemic catabolism and increases nutritional consumption, which may further deteriorate nutritional status and lower PNI, and ultimately form a vicious cycle that may promote the progression of atherosclerosis [32].

A large number of previous studies have reported that elevated Lp(a) is an independent, causal risk factor for the onset and adverse prognosis of CAD [7,33,34,35]. Similarly, reduced PNI, a composite biomarker integrating nutritional and inflammatory status, has consistently been shown

to predict adverse cardiovascular events in CAD patients [36,37,38]. However, almost all previous studies have investigated the prognostic role of each of these factors alone, while few have evaluated their joint and interactive effects on CAD outcomes. The importance of the combined assessment of lipid and nutritional biomarkers is illustrated by the "lipid paradox" phenomenon reported in a classic cohort study [39,40,41]. This phenomenon indicates that the prognostic value of lipid biomarkers cannot be interpreted independently of nutritional status, which is consistent with the findings of the present study. Furthermore, the EPIC-Norfolk study demonstrated that isolated Lp(a) has limited long-term cardiovascular predictive value, which is enhanced when combined with hs-CRP and LDL-C to identify the 20-year risk [42]. Several studies have suggested that combined assessment of Lp(a) and the cytokine interleukin-6 more accurately predicts atherosclerotic cardiovascular disease risk than either marker alone [43,44]. This indicates that the interaction between Lp(a) and inflammation is a general phenomenon that may involve the activation of the entire inflammatory pathway. It further suggests that the interaction between Lp(a) and nutritional status may be mediated by the level of systemic inflammation, supporting the key role of inflammation in this synergistic effect.

Our findings have important clinical implications for risk stratification and management of CAD patients. First, both Lp(a) and PNI retained their strong independent prognostic associations, confirming their universal predictive value across the entire hospitalized CAD population. Furthermore, the combined assessment of Lp(a) and PNI can be used for risk stratification in hospitalized CAD patients, helping to identify high-risk patients, and providing a basis for clinicians to develop individualized management strategies. However, it is critical to emphasize that this study exclusively enrolled hospitalized CAD patients, and the prognostic value of this combined assessment strategy in stable outpatient CAD populations has not been validated. This conclusion is supported by our subgroup analyses. Specifically, the statistically significant additive interaction between these two biomarkers observed in the overall cohort was attenuated and no longer detectable after excluding patients with AMI and those with hs-CRP >3.0 mg/L. These findings suggest that the synergistic effect between Lp(a) and malnutrition may be mediated by systemic inflammatory status and is significantly amplified in the context of high inflammation.

The robustness of these conclusions is supported by several strengths of our study. Based on a multicenter, large-sample real-world cohort of 47,482 CAD patients, it is one of the largest studies in this field with sufficient statistical power. Hence, the results are closer to the real-life clinical diagnosis and treatment scenario. Notably, this is the first study to systematically and quantitatively verify the additive interaction between Lp(a) and PNI on all-cause and cardiovascular mortality in CAD patients, thus filling a critical gap in previous studies. Both core biomarkers have excellent clinical accessibility. Lp(a) is a guideline-recommended cardiovascular risk marker [45], and PNI uses only two routine laboratory tests. Their low cost and simplicity ensure that our combined risk stratification strategy is highly applicable to clinical practice. Moreover, this study adopted strict multivariable confounding adjustment, restricted cubic spline nonlinear analysis, quantitative assessment of additive interaction, and sensitivity analyses, which minimized bias and ensured robust and reliable results. Importantly, the present findings offer certain potential value for clinical translation and targeted risk management. It is worth noting that existing clinical evidence has identified multiple pharmacotherapies and surgical interventions with significant regulatory effects on circulating Lp(a) levels, including pioglitazone, raloxifene, and bariatric surgery [46,47,48]. Combined with our finding that low PNI further increases the prognostic risk of elevated Lp(a), this provides a novel rationale for combined risk stratification and targeted intervention strategies in high-risk CAD patients.

5. Limitations

Nevertheless, this work has several limitations that should be acknowledged. First, this retrospective observational study can only establish associations between biomarkers and prognosis, not causal relationships. Although comprehensive adjustment for major confounding factors in multivariate regression and sensitivity analyses confirmed the robustness of our results, both inherent baseline disparities between subgroups and unmeasured residual confounding could not be ruled out entirely. Additionally, the exclusion of patients with incomplete clinical data may have introduced potential selection bias. Second, although this was a multicenter hospital-based cohort, all participants were exclusively hospitalized CAD patients recruited from southern China. This geographic restriction limits nationwide representativeness, and the findings cannot be directly generalized to community residents, asymptomatic populations, other ethnic groups, or different CAD subtypes. Notably, the combined assessment of Lp(a) and PNI appears to be particularly relevant and prognostic in the setting of acute or hospitalized CAD, whereas its clinical predictive value in stable outpatient CAD populations remains uncertain and requires further validation. Third, Lp(a) and PNI were measured only once at admission, and the prognostic significance of longitudinal changes was not evaluated. It is worth noting that multiple pharmacotherapies and surgical interventions have been shown to significantly modulate circulating Lp(a) levels, including pioglitazone, raloxifene, and bariatric surgery [46,47,48]. Despite adjustment for baseline medication use in our multivariable models, we cannot rule out the possibility that initiation, discontinuation, or dose adjustment of these Lp(a)-modifying treat-

ments during follow-up may have affected the observed prognostic relationships. Furthermore, missing data for some body composition indicators limited our ability to adjust for other potential confounding factors, even though multiple imputation was performed and sensitivity analyses confirmed that our core results remained stable. Finally, our primary endpoints were limited to all-cause and cardiovascular mortality, and excluded non-fatal adverse cardiovascular events such as MI, stroke, and heart failure hospitalization. Importantly, whether targeted nutritional interventions can effectively modify cardiovascular risk and improve long-term clinical outcomes among patients with elevated Lp(a) accompanied by low PNI remains largely unknown. This unresolved issue requires further dedicated prospective investigations and clinical trials for confirmation.

Therefore, further large-scale prospective cohort studies, randomized controlled trials, multi-population studies, longitudinal repeated-measurement analyses, and expanded endpoint assessments are warranted. These should help to validate our findings, clarify causal links, confirm the heterogeneous prognostic performance of the Lp(a)-PNI combination across different CAD clinical states, and comprehensively evaluate the prognostic value of combined Lp(a) and PNI assessment, as well as explore the potential clinical benefits of nutritional intervention strategies for high-risk patients.

6. Conclusions

In conclusion, serum Lp(a) and PNI are independent prognostic markers for all-cause and cardiovascular mortality in CAD patients. These two factors exhibit a statistically significant additive interaction on the long-term risk of mortality. Joint assessment of Lp(a) and PNI can improve the incremental predictive value for long-term mortality, and provides reasonable evidence for optimized risk stratification in routine clinical practice.

Availability of Data and Materials

The raw data of this study cannot be publicly shared due to patient privacy protection and institutional ethical policies of the CardioRenal Improvement II (CIN-II) multicenter cohort. Reasonable requests for the relevant study data can be addressed to the corresponding authors.

Author Contributions

JMC conducted the formal statistical analysis of all study data, and contributed to study conceptualization and design, literature search and synthesis, original manuscript drafting and interpretation of study results. XLR and XZL contributed to drafting of the methods and results sections, and assisted in data collation and result verification. ZL contributed to development of the study's core methodology, data curation, and technical support for statistical software application, data quality validation and drafting of the statistical methods subsection. YA contributed to study investigation, on-site implementation, source data validation, and verification of the results section. AAFAM provided critical professional guidance for the study conception and framework design, participated in the collective discussion and interpretation of experimental data, and conducted comprehensive academic revision of the manuscript's discussion section. JL, SQC, and YL contributed to study conception and design, overall supervision, academic guidance throughout the entire research process, and critical revision of the full manuscript. WG, JYC and JYX contributed to study design optimization, critical revision of the full manuscript, and acquisition of research funding. All authors participated in the editorial revision and critical academic review of the manuscript. All authors have read and approved the final version of the 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

This study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (GDREC2019-555H-2) and was conducted in full compliance with the ethical principles of the Declaration of Helsinki. Considering the retrospective nature of our study with fully de-identified data, the ethics committee has approved the protocol and granted a waiver of individual written informed consent.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The authors used Gemini-3.0 for spelling and grammar checking, as well as academic language polishing during the preparation of this manuscript. All content processed by the AI tool was fully reviewed and revised by the

authors, who take full responsibility for the entire content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/RCM51948.

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