Lipids in Health and Disease

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Effects of residual inflammatory and cholesterol risks on cardiovascular events with evolocumab in patients with acute coronary syndrome undergoing percutaneous coronary intervention

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Abstract

Background Evolocumab has shown significant reductions in low-density lipoprotein cholesterol (LDL-C) levels and incident cardiovascular events among acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). Nonetheless, the potential modification of evolocumab's effectiveness by baseline inflammatory risk remains unclear. We aimed to assess evolocumab's effectiveness based on baseline neutrophil-to-lymphocyte ratio (NLR) and evaluate residual inflammatory and cholesterol-related risks across varying on-treatment NLR and LDL-C levels.

Methods This multicentric, retrospective analysis enrolled consecutive patients with ACS undergoing PCI and exhibiting elevated LDL-C at the First Affiliated Hospital of Zhengzhou University and Zhongda Hospital Southeast University between March 2019 and August 2021. Patients were categorized into evolocumab and standard-of-care treatment groups based on evolocumab administration. Hazard ratios for the primary composite outcome—including myocardial infarction, ischemic stroke, cardiac death, unplanned coronary revascularization, and hospitalization due to unstable angina—comparing baseline NLR quartiles were computed using multivariable Cox regression. We assessed evolocumab's impact on the primary outcome across median-based NLR dichotomization and evaluated the outcome across 1-month NLR and LDL-C levels.

Results The median baseline NLR was 2.99 (IQR: 2.14–4.69), remaining stable following evolocumab therapy. Each NLR quartile increase heightened the risk of primary outcome by 29% (95% CI, 17–42%; $P < 0.01$). The relative risk reductions with evolocumab were consistent across NLR categories (P-interaction > 0.05), but absolute risk reductions were higher in high-NLR patients (2.9% vs. 6.2%). Residual inflammatory and cholesterol risks, indicated by on-treatment NLR and LDL-C, independently correlated with the primary outcome ($P < 0.001$).

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Conclusions Higher baseline NLR is associated with increased cardiovascular risk in ACS/PCI patients. Relative risk reductions with evolocumab were consistent across NLR categories, while absolute risk reductions were more significant in high-NLR patients. Minimized risk is observed in patients with the lowest on-treatment NLR and LDL-C levels.

Highlights

1. Neutrophil-to-lymphocyte ratio (NLR) predicts cardiovascular risk in ACS post-PCI.
2. Relative risk reductions from evolocumab were consistent across varying NLR.
3. Absolute risk reductions by evolocumab were higher in patients with elevated NLR.
4. On-treatment NLR and LDL-C independently predict adverse cardiovascular events.
5. Cardiovascular risk minimized in patients with lowest NLR and LDL-C levels.

Keywords Acute coronary syndrome, Cholesterol, Evolocumab, Inflammation, Neutrophil-to-lymphocyte ratio

What new information does this article contribute?

- This investigation identified a significant association between elevated baseline NLR and increased cardiovascular risk in ACS patients undergoing PCI. Furthermore, residual inflammatory risk, as indicated by the 1-month NLR, maintained its predictive capacity even among patients with exceptionally low residual cholesterol risk, as evidenced by 1-month LDL-C concentrations.
- The relative risk reductions attributed to evolocumab remained consistent across varying NLR categories; however, considering the elevated absolute risk associated with higher baseline NLR, the absolute risk reductions conferred by evolocumab were more pronounced in patients with elevated NLR, indicating a greater absolute benefit for those with higher inflammatory risk.
- Both on-treatment NLR and LDL-C levels—reflecting residual inflammatory and cholesterol risks—independently predicted adverse cardiovascular events. These findings imply that the NLR functions as a biomarker for an inflammatory pathway independent of the lipid-lowering effect, while remaining relevant to atherothrombosis and potentially serving as a therapeutic target.
- The cardiovascular risk was minimized in patients who achieved the lowest 1-month NLR and LDL-C levels, thereby reinforcing the necessity of simultaneously targeting both inflammatory and cholesterol-related risk factors to effectively manage and mitigate cardiovascular risk.

Introduction

Atherosclerosis, the principal pathophysiological substrate of acute coronary syndromes (ACS), remains a global health burden despite advances in lipid-lowering therapies [1–3]. The introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors such as evolocumab has enabled unprecedented low-density lipoprotein cholesterol (LDL-C) reduction (median < 0.5 mmol/L in 10% of FOURIER trial participants), substantially modifying residual cardiovascular risk profiles [4]. Contemporary evidence from extended FOURIER-OLE data confirmed sustained clinical benefits over 5-year follow-up [5], while coronary imaging studies demonstrated evolocumab-induced plaque stabilization [6].

Previous investigations have elucidated that, in the absence of therapeutic intervention, inflammation presents a risk comparable to hyperlipidemia in subsequent atherothrombotic events [7, 8]. Although anti-inflammatory therapies like colchicine demonstrate additive benefits to statins [9], practical barriers including statin intolerance and delayed therapeutic onset frequently prevent LDL-C target achievement [10, 11], potentially confounding inflammatory risk stratification. The potent lipid-lowering efficacy of evolocumab provides a unique clinical paradigm to investigate whether systemic inflammation persists as the dominant determinant of residual cardiovascular risk in ACS patients under conditions of ultralow cholesterol exposure.

The neutrophil-to-lymphocyte ratio (NLR), validated in stable atherosclerotic cardiovascular disease cohorts (ASCVD) [12], represents a pragmatic inflammatory biomarker requiring investigation in ACS populations. Our study aimed to address two critical knowledge gaps: ① the interaction between baseline inflammatory status and evolocumab efficacy in ACS patients undergoing percutaneous coronary intervention (PCI), and ② whether

residual inflammatory risk, as indicated by the 1-month NLR, retains prognostic value amidst ultra-low LDL-C levels achievable with evolocumab therapy.

Methods

Study population and procedures

This multicentric, retrospective analysis enrolled consecutive participants with ACS undergoing PCI at the First Affiliated Hospital of Zhengzhou University and Zhongda Hospital Southeast University between March 2019 and August 2021. Eligible patients were recruited based on the following inclusion criteria: admission for ACS within 72 h of symptom onset; undergoing PCI; and exhibiting elevated LDL-C concentrations: LDL-C levels ≥ 1.8 mmol/L under high-intensity statin therapy for at least one month prior to enrollment, LDL-C levels ≥ 2.3 mmol/L on low-to-moderate-intensity statin therapy for at least one month before enrollment, or LDL-C levels ≥ 3.2 mmol/L in the absence of regular statin administration. The intensity of statin therapy was classified according to the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol [13]. Patients meeting any of the following criteria were systematically excluded: New York Heart Association functional class III or IV; documented intolerance to statins, aspirin, or P2Y12 inhibitors; acute cerebrovascular disease; acute infections; cardiomyopathy; any malignancy diagnosed within the preceding five years; severe renal impairment, defined as acute or chronic kidney disease with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 or a condition requiring dialysis; or severe hepatic impairment, classified as Child–Pugh class C.

Given the elevated ischemic vulnerability and plaque instability inherent to ACS patients requiring PCI, the majority of treating physicians treating physicians routinely advised the administration of evolocumab to patients immediately following the PCI procedure. For those patients who consented to this treatment regimen, evolocumab was administered via subcutaneous injection at an initial dose of 140 mg, followed by bi-weekly injections of 140 mg for an 18-month period. The remaining eligible patients who adhered to standard-of-care treatment were classified into the control group. Both cohorts were subjected to routine follow-up assessments over an 18-month period. In both groups, patients were initiated on maximally tolerated statin therapy as soon as feasible post-ACS. If the LDL-C target was unachieved within 4 to 6 weeks, the treating physician recommended escalation to a high-intensity statin in conjunction with ezetimibe. Secondary prevention therapies, in accordance with established professional guidelines, were provided to all enrolled patients. The baseline NLR was determined using the absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) derived from complete blood count data obtained upon admission. Ethical approval for the study protocol was granted by the institutional review boards of both institutions, which additionally waived the requirement for written informed consent.

Clinical outcomes

At the 18-month follow-up, the primary outcome was characterized by a composite of myocardial infarction (MI), ischemic stroke, cardiac death, unplanned coronary revascularization, or hospitalization due to unstable angina (UA). The key secondary outcome consisted of a composite of MI, ischemic stroke, or cardiac death. Additional outcomes encompassed each individual component of the primary composite outcome, along with all-cause death. Cardiovascular Death was defined based on the International Classification of Diseases, 10th Revision (ICD-10) codes I00-I99, encompassing all cardiovascular causes. Ischemic Stroke was defined according to the World Health Organization criteria and ICD-10 codes I63, with all diagnoses confirmed through brain imaging to ensure a robust diagnostic process. Myocardial Infarction was adjudicated using the Fourth Universal Definition of Myocardial Infarction [14]. Data on clinical endpoints were systematically collected through a thorough review of hospital records and follow-up communication via telephone, SMS, WeChat, and email.

Statistical analysis

A priori sample size estimation was conducted to ensure adequate statistical power, with calculation parameters detailed in the Supplementary Methods subsection "Sample Size Estimation". Continuous variables exhibiting normality were expressed as means with standard deviations (SD). Between-group comparisons were conducted using the Student's t-test for pairs of groups or one-way analysis of variance (ANOVA) for more than two groups. For continuous variables deviating from normality, descriptive statistics included medians with interquartile ranges (IQR), and differences were assessed using the Wilcoxon rank-sum test for pairs of groups or the Kruskal–Wallis H test for multiple groups. All intergroup comparisons of continuous variables among multiple groups were adjusted using the Bonferroni method. Categorical variables were presented as frequencies and percentages, with group comparisons facilitated by the Pearson χ^2 test, supplemented by Fisher's exact test for sparse data. The cumulative incidence of clinical endpoints was estimated using the Kaplan–Meier method.

The prognostic significance of baseline NLR in predicting incident cardiovascular events and the stratified effectiveness of evolocumab by NLR were assessed using a multivariable Cox regression model. Adjusted hazard

ratios (HRs) with 95% confidence intervals (CIs) were derived after comprehensive covariate adjustment following our pre-specified analytical framework detailed in the "Covariate Selection and Adjustment Procedures" subsection of Supplementary Methods. The predictive accuracy of our Cox regression models was systematically validated through dual metrics: discrimination capacity quantified by Harrell's concordance index (C-index) and calibration accuracy assessed via Gronnesby-Borgan goodness-of-fit tests, where $P > 0.05$ indicated adequate agreement between model-predicted and observed event probabilities over time.

In the statistical analysis, we assessed the proportional hazards (PH) assumption for the Cox regression models through both graphical and statistical methods. Graphically, we evaluated the PH assumption by plotting log(-log(S(t))) vs. log(t) for each covariate to check for parallelism and by plotting Schoenfeld residuals against time to identify any significant time trends. Statistically, we performed the Schoenfeld residuals test to confirm the PH assumption.

To evaluate the combined effects of ANC and ALC, sixteen distinct strata were established based on all possible quartile combinations of ANC and ALC. Subsequent multivariable-adjusted hazard ratios were calculated for each stratum relative to a reference cohort characterized by the lowest quartiles of both ALC and ANC. Additionally, the influence of baseline NLR on cardiovascular outcomes was examined across nine predefined subgroups through a Cox regression model incorporating baseline NLR, subgroup assignment, and their interaction term.

In the evaluation of evolocumab's effectiveness stratified by NLR, the 95% CIs for absolute risk reductions (ARRs) were derived under the premise that the Kaplan–Meier rates for each group, as well as the ARRs—defined as the differences in Kaplan–Meier estimates across the specified endpoints—conform to a normal distribution. Given the independence of the Kaplan–Meier rates between the two treatment arms, the variance of the ARR was determined by the variances of the Kaplan–Meier rates from each cohort, thereby enabling the determination of the 95% CIs for the ARR.

To evaluate the combined predictive value of residual inflammatory and cholesterol-related risks on adverse cardiovascular events, we employed a landmark approach using 1-month post-PCI achieved NLR and LDL-C levels. Patients experiencing a major adverse cardiovascular event within the initial 30 days or lacking 1-month NLR or LDL-C measurements were excluded. This landmark approach significantly minimized the potential for immortal time bias and ensured the accuracy of the risk assessment. The 18-month Kaplan–Meier estimates and adjusted HRs for both primary and key secondary outcomes were derived from two main analytical frameworks: (1) categorical subgroups characterized by median-based 1-month NLR stratification and quartiles of 1-month LDL-C levels post-intervention, and (2) continuous variables indicating the achieved NLR and LDL-C levels at 1 month. A multivariable Cox regression model with forward stepwise selection was employed to account for potential confounders, with covariates described above.

We employed the Kaplan–Meier method and incorporated the plotly package in R to develop a three-dimensional visualization. This graphical representation was designed to elucidate the combined effect of the 1-month post-intervention achieved NLR and LDL-C levels on the primary outcome during an 18-month follow-up. Additionally, the regression modeling strategies (rms) package in R was employed to generate restricted cubic splines, enabling the investigation of a potential dose–response gradient between the 1-month achieved NLR and LDL-C levels and cardiovascular events. This approach was further applied to visually assess and validate the assumption of linearity within our dataset, thereby enhancing the robustness and reliability of our findings. Statistical analyses were conducted using R software (version 4.2.3), SPSS version 25.0 (IBM Corp., NY, USA), and Stata version 16.0 (Stata Corp., TX, USA). All p-values reported are two-tailed, with a statistical significance threshold established at $p < 0.05$.

Results

Patients

From March 2019 to August 2021, 3399 consecutive patients with ACS undergoing PCI were screened for eligibility. Following rigorous application of predefined inclusion/exclusion criteria, 2876 subjects (84.6% screening success rate) were enrolled in this observational cohort study. The evolocumab group included 823 patients, whereas the control group consisted of 2053 patients. Over the 18-month follow-up period, 5.7% of patients in the evolocumab group and 6.1% of patients in the control group were lost to follow-up. Additionally, 88.2% of the patients had complete NLR and lipid data available post-discharge. Notably, 95.3% of the patients had at least two time points of NLR and lipid data at the 1st, 6th, 12th, and 18th months following discharge.

During follow-up, treatment discontinuation events occurred in 69 evolocumab-treated patients (8.4%) and 53 statin-treated control participants (2.6%). Notably, 80 control group individuals (3.9%) initiated evolocumab therapy during the observation period due to inadequately controlled hypercholesterolemia.

Baseline NLR and cardiovascular outcomes

Patients in the highest baseline NLR quartile were older and exhibited higher prevalences of diabetes, hypertension, and peripheral artery disease, along with increased rates of cardiac arrest and multivessel disease, and received a significantly greater mean number of stents during PCI (Tables 1 and 2). The two lipid-lowering strategies demonstrated no significant difference in the median change of NLR at 1, 6, 12, and 18 months (Supplemental Table 1).

Schoenfeld residuals plots and Log–log plots indicated that the proportional hazards assumption was satisfied for Cox regression models with NLR quartiles as covariates, both for the primary composite outcome and the key secondary outcome (Supplemental Figs. 1 and 2). In our cohort, baseline NLR proved to be a significant predictor of incident cardiovascular events

Table 1 Baseline characteristics across quartiles of baseline NLR levels[a]

Characteristic	NLR 1st Quartile (*N* = 719)	NLR 2nd Quartile (*N* = 719)	NLR 3rd Quartile (*N* = 719)	NLR 4th Quartile (*N* = 719)	$\chi^2_{/F}$	*P* Value
NLR (baseline) range	NLR ≤ 2.138	2.138 < NLR ≤ 2.990	2.990 < NLR ≤ 4.694	NLR > 4.694		
Age, yr	63.9 ± 11.8	64.6 ± 12.3	64.9 ± 12.3	66.1 ± 12.1[†]	4.20	0.01
Weight, kg	75.4 ± 12.2	74.8 ± 12.1	75.0 ± 12.2	74.6 ± 12.0	0.48	0.70
Men, No. (%)	425 (59.1)	425 (59.1)	403 (56.1)	446 (62.0)	5.32	0.15
Clinical presentation, No. (%)					5.87	0.44
NSTEMI	191 (26.6)	189 (26.3)	191 (26.6)	170 (23.6)		
STEMI	141 (19.6)	160 (22.3)	141 (19.6)	168 (23.4)		
Unstable angina	387 (53.8)	370 (51.5)	387 (53.8)	381 (53.0)		
Cardiac arrest, No. (%)	13 (1.8)	19 (2.6)	24 (3.3)	31 (4.3)	8.29	0.04
Current smoker, No. (%)	233 (32.4)	235 (32.7)	232 (32.3)	248 (34.5)	1.04	0.79
Diabetes, No. (%)	223 (31.0)	230 (32.0)	256 (35.6)	268 (37.3)	8.41	0.04
Hypertension, No. (%)	458 (63.7)	469 (65.2)	497 (69.1)	506 (70.4)	9.73	0.02
Previous stroke, No. (%)	53 (7.4)	47 (6.5)	50 (7.0)	58 (8.1)	1.37	0.71
Previous coronary artery bypass grafting, No. (%)	25 (3.5)	21 (2.9)	25 (3.5)	27 (3.8)	0.80	0.85
Prior myocardial infarction, No. (%)	159 (22.1)	157 (21.8)	127 (17.7)	162 (22.5)	6.67	0.08
Previous percutaneous coronary intervention, No. (%)	147 (20.4)	131 (18.2)	150 (20.9)	123 (17.1)	4.48	0.21
Peripheral vascular disease, No. (%)	19 (2.6)	27 (3.8)	30 (4.2)	44 (6.1)	11.34	0.01
Family history of coronary heart disease, No. (%)	181 (25.2)	177 (24.6)	163 (22.7)	165 (22.9)	1.80	0.62
Chronic obstructive pulmonary disease, No. (%)	41 (5.7)	42 (5.8)	57 (7.9)	47 (6.5)	3.68	0.30
Estimated glomerular filtration rate, mL/min/1.73m^2	84.4 ± 21.3	82.5 ± 22.9	83.0 ± 23.0	82.5 ± 22.8	1.15	0.33
Prior thrombolytic treatment, No. (%)	14 (1.9)	29 (4.0)	15 (2.1)	20 (2.8)	7.43	0.06
Lipid-lowering strategy, No. (%)					0.71	0.87
Evolocumab	205 (28.5)	212 (29.5)	198 (27.5)	208 (28.9)		
Control	514 (71.5)	507 (70.5)	521 (72.5)	511 (71.1)		
Anti-inflammatory drugs, No. (%)						
Steroids	13 (1.8)	17 (2.4)	20 (2.8)	28 (3.9)	6.38	0.09
Colchicine	3 (0.4)	6 (0.8)	7 (1.0)	10 (1.4)	3.88	0.27
Lipid profile						
LDL-C	3.31 ± 0.86	3.36 ± 0.85	3.30 ± 0.79	3.34 ± 0.84	0.70	0.55
HDL-C	1.11 ± 0.38	1.10 ± 0.35	1.10 ± 0.38	1.12 ± 0.38	0.37	0.78
Triglyceride	1.74 ± 0.82	1.74 ± 0.79	1.83 ± 0.90	1.73 ± 0.78	2.66	0.05

HDL-C high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *NLR* neutrophil–lymphocyte ratio, *NSTEMI* non-ST-segment elevation myocardial infarction, *STEMI* ST-segment elevation myocardial infarction

[a] Data are mean ± SD or No. (%)

[†] For continuous variables, differences were assessed using ANOVA for normal data and Kruskal–Wallis H test for non-normal data. *P*-values were adjusted using Bonferroni for multiplicity. "†" indicates significant difference versus "NLR 1st Quartile" (Bonferroni-adjusted $p < 0.05$)

Table 2 Procedural characteristics across quartiles of baseline NLR levels[a]

Characteristic	NLR 1st Quartile (*N* = 719)	NLR 2nd Quartile (*N* = 719)	NLR 3rd Quartile (*N* = 719)	NLR 4th Quartile (*N* = 719)	$\chi^2_{/F}$	*P* Value
NLR (baseline) range	NLR ≤ 2.138	2.138 < NLR ≤ 2.990	2.990 < NLR ≤ 4.694	NLR > 4.694		
Access, No. (%)					1.28	0.73
Radial	652 (90.7)	640 (89.0)	647 (90.0)	650 (90.4)		
Femoral	67 (9.3)	79 (11.0)	72 (10.0)	69 (9.6)		
Number of diseased vessels, No. (%)					13.90	0.03
1-vessel disease	228 (31.7)	199 (27.7)	186 (25.9)	168 (23.4)		
2-vessel disease	173 (24.1)	190 (26.4)	197 (27.4)	204 (28.4)		
3-vessel disease	318 (44.2)	330 (45.9)	336 (46.7)	347 (48.3)		
Thrombus lesion, No. (%)	186 (25.9)	205 (28.5)	186 (25.9)	213 (29.6)	3.92	0.27
Thrombus aspiration, No. (%)	13 (1.8)	26 (3.6)	21 (2.9)	26 (3.6)	5.42	0.14
Treated vessel (s), No. (%)						
Right coronary artery	247 (34.4)	257 (35.7)	254 (35.3)	240 (33.4)	1.06	0.79
Left main	56 (7.8)	74 (10.3)	64 (8.9)	49 (6.8)	6.23	0.10
Left circumflex	205 (28.5)	199 (27.7)	203 (28.2)	230 (32.0)	4.00	0.26
Left anterior descending	438 (60.9)	432 (60.1)	412 (57.3)	427 (59.4)	2.14	0.54
Multi-vessel treatment, No. (%)	180 (25.0)	193 (26.8)	201 (28.0)	220 (30.6)	5.85	0.12
TIMI flow 0 to 1 prior to PCI, No. (%)	237 (33.0)	254 (35.3)	271 (37.7)	272 (37.8)	4.96	0.17
Intra-aortic balloon pump, No. (%)	20 (2.8)	22 (3.1)	30 (4.2)	28 (3.9)	2.82	0.42
Revascularization strategy, No. (%)					0.37	0.95
Balloon angioplasty	27 (3.8)	25 (3.5)	24 (3.3)	23 (3.2)		
Stent implantation	692 (96.2)	694 (96.5)	695 (96.7)	696 (96.8)		
Total stent length per patient, mm	44.7 ± 29.3	45.7 ± 29.1	46.7 ± 30.7	47.7 ± 28.5	1.36	0.25
Number of stents per patient	1.78 ± 1.02	1.86 ± 1.02	2.07 ± 1.08[†]	2.23 ± 1.08[†]	26.53	< 0.01
Anticoagulants during PCI					5.18	0.16
Unfractionated heparin	436 (60.6)	454 (63.1)	413 (57.4)	442 (61.5)		
Bivalirudin	283 (39.4)	265 (36.9)	306 (42.6)	277 (38.5)		
Full procedural success, No. (%)	707 (98.3)	697 (96.9)	706 (98.2)	695 (96.7)	6.51	0.09

NLR neutrophil–lymphocyte ratio, *PCI* percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

[a] Data are mean ± SD or No. (%)

[†] For continuous variables, differences were assessed using ANOVA for normal data and Kruskal–Wallis H test for non-normal data. *P*-values were adjusted using Bonferroni for multiplicity. "†" indicates significant difference versus "NLR 1st Quartile" (Bonferroni-adjusted $p < 0.05$)

(Fig. 1). A per-quartile increase in NLR was associated with a 29% increased risk of the primary composite outcome (95% confidence interval [CI] 17–42%, $P < 0.01$), a 35% increase in the key secondary composite outcome (95% CI 21–51%, $P < 0.01$), a 30% increase in MI (95% CI 14–49%, $P < 0.01$), a 33% increase in ischemic stroke (95% CI 3–72%, $P = 0.03$), a 34% increase in cardiac death (95% CI 4–73%, $P = 0.02$), a 19% increase in unplanned coronary revascularization (95% CI 6–34%, $P < 0.01$), a 46% increase in hospitalization due to UA (95% CI 9–97%, $P = 0.01$), and a 32% increase in all-cause mortality (95% CI 5–67%, $P = 0.02$) (Table 3; Supplemental Fig. 3). Sensitivity analyses confirmed the consistency of these effects within the statins-only cohort (Supplemental Table 2).

Hazard ratios for each quartile increase in NLR across various subgroups further substantiated the robustness of the association with both the primary and key secondary outcomes. The relative risk increase for the primary outcome per quartile increase in NLR was significantly higher in patients aged ≥ 65 years (P-interaction = 0.03). Likewise, the relative risk increases for the key secondary outcome were markedly greater in patients aged ≥ 65 years, those with ST-segment elevation myocardial infarction (STEMI), and individuals with three-vessel disease, with all P-interactions < 0.05 (Fig. 2).

Rates of cardiovascular outcomes by baseline ANC and ALC

The baseline and procedural characteristics of participants, stratified according to ascending quartiles

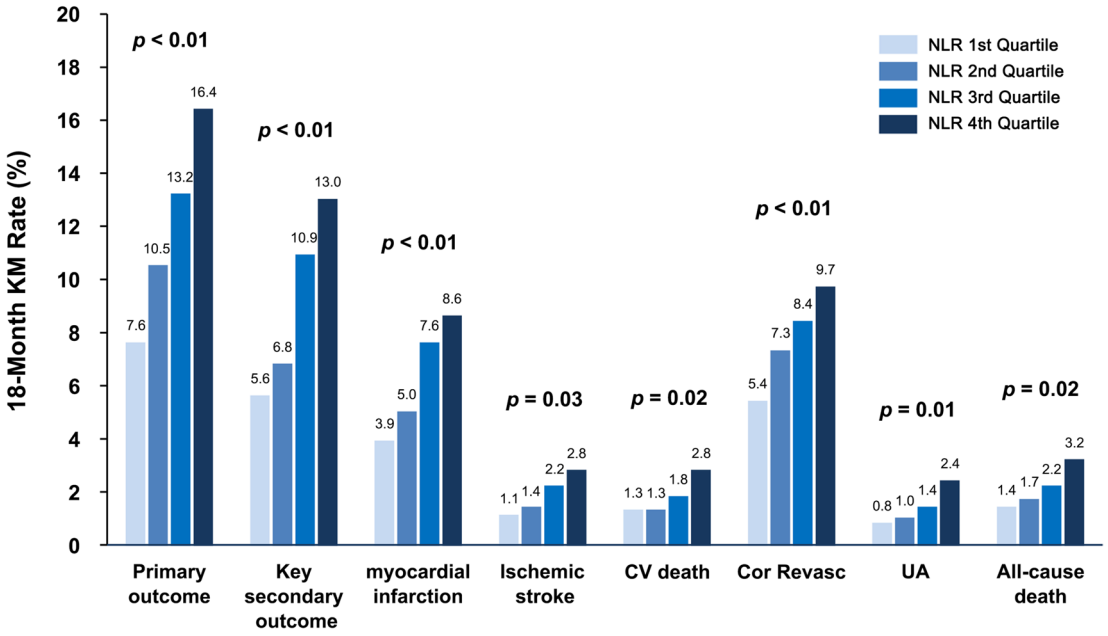

Fig. 1 Cardiovascular risk gradient stratified by baseline NLR quartiles in the entire cohort. Cor Revasc: coronary revascularization; CV: cardiovascular; KM: Kaplan–Meier; NLR: neutrophil–lymphocyte ratio; UA, hospitalization due to unstable angina

of baseline ANC and ALC, respectively, are presented in Supplemental Tables 3–6. Baseline ANC was positively associated with both primary and key secondary outcomes (Supplemental Fig. 4, Supplemental Table 7). However, no significant differences were observed in the incidence of ischemic stroke, cardiac death, and all-cause death with per-quartile increases in ANC (Supplemental Fig. 4, Supplemental Table 7). Conversely, baseline ALC demonstrated an inverse association with primary and key secondary outcomes (Supplemental Fig. 5, Supplemental Table 8). Similarly, per-quartile increases in ALC did not show significant differences in the incidence of MI, cardiac death, unplanned coronary revascularization, hospitalization due to UA, and all-cause death (Supplemental Fig. 5, Supplemental Table 8).

In light of the differential associations observed for ANC and ALC, we established sixteen distinct strata based on all possible quartile combinations of these variables. Within each quartile of ALC, there was a discernible trend of increasing rates for primary and key secondary outcomes with per-quartile increments in ANC (Fig. 3, Supplemental Tables 9 and 10). Conversely, within each quartile of ANC, per-quartile increases in ALC were associated with a decreasing trend in the risk for these outcomes (Fig. 3, Supplemental Tables 9 and 10). The most pronounced risk for primary and key secondary outcomes was observed in participants stratified within the highest quartile of ANC and the lowest quartile of ALC (adjusted hazard ratio [HRadj] 2.48, 95% CI 1.47–4.18, $P<0.01$; HRadj 3.17, 95% CI 1.68–5.99, $P<0.01$, respectively) (Fig. 3, Supplemental Tables 9 and 10).

Risk reduction of evolocumab based on median NLR stratification

The baseline and procedural characteristics of the evolocumab and control groups are presented in Supplemental Tables 11 and 12. The two groups were generally well-balanced, with the exception of a higher prevalence of a family history of coronary heart disease and peripheral vascular disease, as well as a greater average number of stents implanted in the evolocumab group. Additionally, Supplemental Tables 13 and 14 provide detailed baseline and procedural characteristics of the evolocumab and control groups, stratified by median NLR. Evolocumab demonstrated robust lipid-lowering effectiveness in both median NLR-stratified subgroups, consistently reducing LDL-C levels from a baseline of 3.4 mmol/L to 0.8 mmol/L at 18 months and maintaining this effect consistently throughout the follow-up period (Table 4; Supplemental Fig. 6). Notably, LDL-C levels were reduced to below 1.4 mmol/L in approximately 90% of patients in the evolocumab cohort at 18 months, in contrast to less than 20% in the standard-of-care cohort (Table 4).

In the Low NLR group, the relative risk reductions and ARRs with evolocumab compared with standard therapy for both the primary and key secondary outcomes were

Table 3 Association of quartiles of baseline NLR with cardiovascular risk across the entire cohort[a]

Outcome	NLR 1st Quartile (*N* = 719)	NLR 2nd Quartile (*N* = 719)	NLR 3rd Quartile (*N* = 719)	NLR 4th Quartile (*N* = 719)	Effect across groups	C-index	Gronnesby-Borgan Test
NLR (baseline) range	NLR ≤ 2.138	2.138 < NLR ≤ 2.990	2.990 < NLR ≤ 4.694	NLR > 4.694			
Primary composite outcome							
No. (%)	55 (7.6)	75 (10.5)	94 (13.2)	118 (16.4)			
HR (95% CI); *P*	1 (ref)	1.39 (0.98–1.97); 0.06	1.75 (1.26–2.44); < 0.01	2.26 (1.64–3.11); < 0.01	1.30 (1.18–1.44); < 0.01	0.61	*P* = 0.77
HRadj (95% CI); *P*	1 (ref)	1.38 (0.98–1.96); 0.07	1.70 (1.22–2.37); < 0.01	2.20 (1.60–3.03); < 0.01	1.29 (1.17–1.42); < 0.01	0.71	*P* = 0.95
Key secondary composite outcome							
No. (%)	40 (5.6)	49 (6.8)	77 (10.9)	93 (13.0)			
HR (95% CI); *P*	1 (ref)	1.24 (0.82–1.88); 0.32	1.97 (1.35–2.89); < 0.01	2.43 (1.68–3.52); < 0.01	1.37 (1.22–1.53); < 0.01	0.63	*P* = 0.84
HRadj (95% CI); *P*	1 (ref)	1.24 (0.82–1.89); 0.31	1.92 (1.31–2.81); < 0.01	2.37 (1.64–3.44); < 0.01	1.35 (1.21–1.51); < 0.01	0.72	*P* = 0.86
Myocardial infarction							
No. (%)	28 (3.9)	36 (5.0)	54 (7.6)	61 (8.6)			
HR (95% CI); *P*	1 (ref)	1.30 (0.79–2.13); 0.30	1.98 (1.25–3.12); < 0.01	2.27 (1.45–3.55); < 0.01	1.32 (1.16–1.52); < 0.01	0.61	*P* = 0.68
HRadj (95% CI); *P*	1 (ref)	1.29 (0.79–2.12); 0.31	1.90 (1.20–2.99); 0.01	2.18 (1.39–3.41); < 0.01	1.30 (1.14–1.49); < 0.01	0.73	*P* = 0.87
Ischemic stroke							
No. (%)	8 (1.1)	10 (1.4)	15 (2.2)	20 (2.8)			
HR (95% CI); *P*	1 (ref)	1.25 (0.49–3.17); 0.64	1.89 (0.80–4.45); 0.15	2.55 (1.12–5.78); 0.03	1.38 (1.08–1.78); 0.01	0.63	*P* = 0.81
HRadj (95% CI); *P*	1 (ref)	1.25 (0.49–3.17); 0.64	1.92 (0.81–4.52); 0.14	2.58 (1.14–5.86); 0.02	1.33 (1.03–1.72); 0.03	0.76	*P* = 0.96
Death from cardiac causes							
No. (%)	9 (1.3)	9 (1.3)	13 (1.8)	20 (2.8)			
HR (95% CI); *P*	1 (ref)	1.00 (0.40–2.52); 1.00	1.45 (0.62–3.40); 0.39	2.25 (1.03–4.95); 0.04	1.35 (1.05–1.75); 0.02	0.62	*P* = 0.91
HRadj (95% CI); *P*	1 (ref)	0.99 (0.39–2.48); 0.98	1.46 (0.62–3.40); 0.39	2.20 (1.00–4.83); 0.05	1.34 (1.04–1.73); 0.02	0.74	*P* = 0.99
Unplanned coronary revascularization							
No. (%)	39 (5.4)	52 (7.3)	60 (8.4)	69 (9.7)			
HR (95% CI); *P*	1 (ref)	1.35 (0.89–2.05); 0.16	1.56 (1.04–2.34); 0.03	1.83 (1.23–2.71); < 0.01	1.21 (1.07–1.36); < 0.01	0.58	*P* = 0.86
HRadj (95% CI); *P*	1 (ref)	1.33 (0.88–2.02); 0.17	1.51 (1.01–2.26); 0.05	1.76 (1.18–2.60); 0.01	1.19 (1.06–1.34); < 0.01	0.70	*P* = 0.97
Hospitalization due to UA							
No. (%)	6 (0.8)	7 (1.0)	10 (1.4)	17 (2.4)			
HR (95% CI); *P*	1 (ref)	1.17 (0.39–3.49); 0.78	1.68 (0.61–4.62); 0.31	2.90 (1.14–7.37); 0.02	1.47 (1.09–1.97); 0.01	0.63	*P* = 0.91
HRadj (95% CI); *P*	1 (ref)	1.17 (0.39–3.49); 0.78	1.66 (0.60–4.58); 0.33	2.89 (1.13–7.35); 0.03	1.46 (1.09–1.97); 0.01	0.73	*P* = 0.95
All-cause death							
No. (%)	10 (1.4)	12 (1.7)	16 (2.2)	23 (3.2)			
HR (95% CI); *P*	1 (ref)	1.20 (0.52–2.78); 0.67	1.61 (0.73–3.54); 0.24	2.33 (1.11–4.89); 0.03	1.34 (1.06–1.69); 0.01	0.62	*P* = 0.92
HRadj (95% CI); *P*	1 (ref)	1.19 (0.51–2.76); 0.68	1.60 (0.72–3.53); 0.25	2.24 (1.06–4.73); 0.03	1.32 (1.05–1.67); 0.02	0.70	*P* = 0.99

HR hazards ratio, *HRadj* multivariable adjusted hazards ratio, *NLR* neutrophil–lymphocyte ratio, *UA* unstable angina

[a] Percentages were calculated as estimates of cumulative incidence using the Kaplan–Meier method

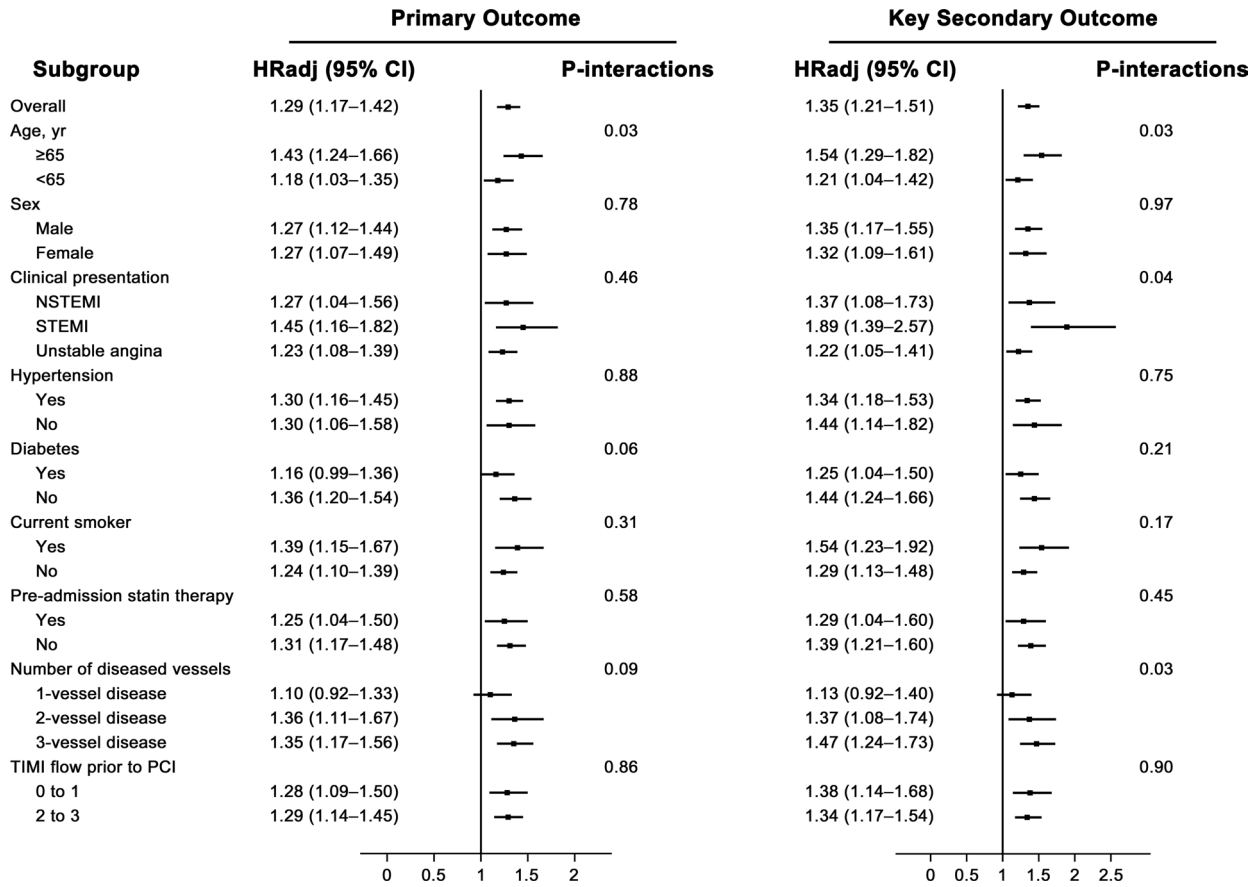

Fig. 2 Association of per-quartile increases in baseline NLR with the primary and key secondary outcomes across sub-groups. HRadj: multivariable adjusted hazards ratio; NLR: neutrophil–lymphocyte ratio; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TIMI: thrombolysis in myocardial infarction

not statistically significant (all P > 0.05). In contrast, in the High NLR group, evolocumab compared to standard therapy significantly reduced both the relative and absolute risks for the primary and key secondary outcomes (all $P < 0.05$) (Fig. 4; Table 5). Subsequently, we incorporated both dimensions—treatment (evolocumab vs. control) and inflammation levels—into a multivariable Cox regression model. The interaction *p*-value for the primary composite outcome was 0.72, which is greater than 0.05. This indicated that the relative risk reductions associated with evolocumab compared to standard therapy were consistent across median-based NLR subgroups (Fig. 4; Table 5). For the key secondary endpoint, the relative risk reductions were also consistent among the NLR subgroups, showing HRs of 0.77 (95% CI, 0.47–1.25) for low NLR and 0.59 (95% CI, 0.40–0.87) for high NLR, with a P-interaction of 0.45 (Fig. 4; Table 5).

Nonetheless, considering the heightened absolute risk associated with elevated baseline NLR, the ARRs for the primary composite outcome with evolocumab were more pronounced among individuals with high baseline NLR (Fig. 4; Table 5). Specifically, it was 2.9% (95% CI, −0.1–6.0) in those with low baseline NLR and 6.2% (95% CI, 2.5–9.9) in those with high baseline NLR, resulting in numbers needed to treat (NNT) of 34 and 16, respectively, to prevent one primary composite outcome at 18 months (Fig. 4; Table 5). Similarly, for the key secondary composite endpoint, the ARRs with evolocumab also favored individuals with high baseline NLR, showing reductions of 1.6% (95% CI, −1.0–4.2) and 5.6% (95% CI, 2.2–8.9) for low and high baseline NLR, respectively (Fig. 4; Table 5). The corresponding NNT were 62 for low baseline NLR and 18 for high baseline NLR to prevent one key secondary composite outcome at 18 months.

Cardiovascular outcomes stratified by NLR and LDL-C levels at 1 month

To assess the effects of residual inflammatory and cholesterol-related risks on cardiovascular event incidence, the 18-month event rates were analyzed based on the achieved NLR and LDL-C levels at 1 month. After excluding patients who experienced a major adverse

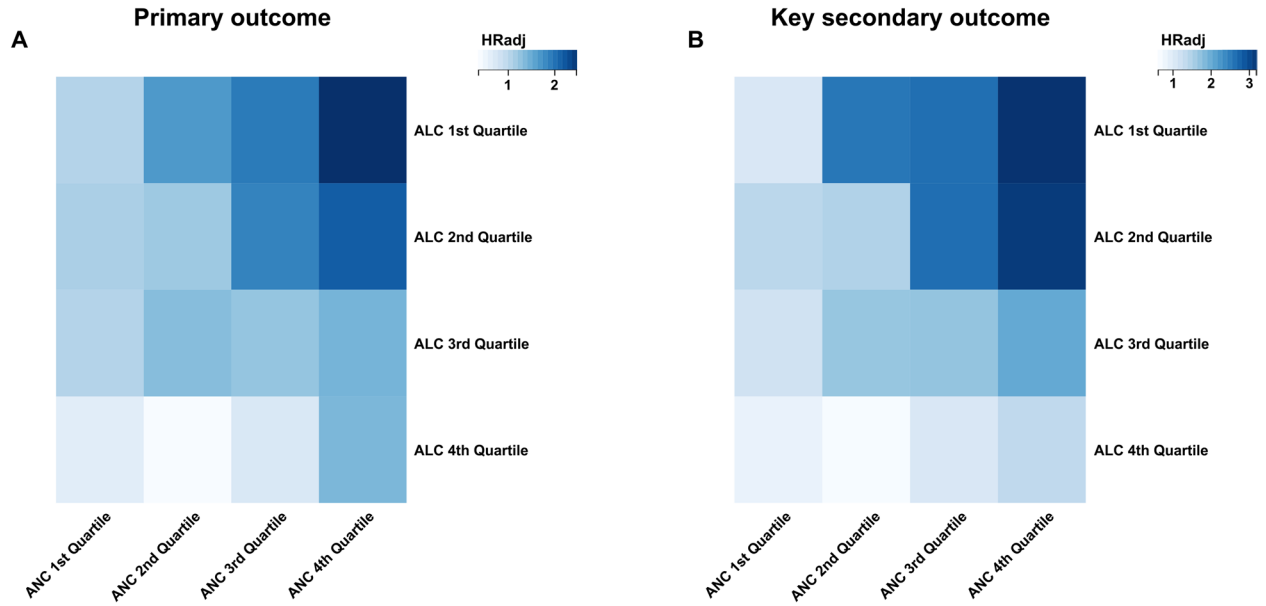

Fig. 3 Combined association of baseline ANC and ALC with the primary and key secondary outcomes. Sixteen strata were defined by all possible quartile combinations of ANC and ALC. Multivariable adjusted hazard ratios (HRadj) for the primary (**A**) and key secondary outcomes (**B**) were subsequently computed for each stratum in comparison to the reference group, which comprised individuals within the lowest quartiles of both ANC and ALC. ALC: absolute lymphocyte count; ANC: absolute neutrophil count

cardiovascular event within the initial 30 days or lacked 1-month NLR or LDL-C data, a cohort of 2732 individuals was incorporated into the subsequent examination. After adjusting for the 1-month NLR and other confounders as detailed in the methods, elevated LDL-C levels at 1 month significantly correlated with increased incidence of both the primary and key secondary composite outcomes, with each additional unit of LDL-C corresponding to a 28% relative increase in risk for the primary outcome (HRadj 1.28, 95% CI 1.14–1.43, $P<0.001$) and a 33% relative increase in risk for the key secondary outcome (HRadj 1.33, 95% CI 1.17–1.51, $P<0.001$) (Supplemental Table 15). Likewise, after adjusting for 1-month LDL-C levels and other confounders, an elevated 1-month NLR exhibited a significant association with increased rates of both the primary and key secondary outcomes, with each unit increase in NLR corresponding to a 15% relative increase in risk for the primary outcome (HRadj 1.15, 95% CI 1.07–1.23, $P<0.001$) and a 16% relative increase in risk for the key secondary outcome (HRadj 1.16, 95% CI 1.07–1.26, $P<0.001$) (Supplemental Table 15). Correspondingly, the incidence of the primary outcome was minimized among patients exhibiting the lowest levels of 1-month achieved NLR and LDL-C (Supplemental Fig. 7).

The dose–response associations between the 1-month post-intervention achieved NLR and LDL-C concentrations and adverse cardiovascular events were examined using restricted cubic splines, as shown in Fig. 5. Significant linear dose–response relationships were observed between 1-month NLR and both the primary outcome (P_overall < 0.001; P_nonlinear = 0.245) and the key secondary outcome (P_overall = 0.001; P_nonlinear = 0.216) (Fig. 5). Similarly, significant linear dose–response relationships were noted between 1-month LDL-C levels and the primary outcome (P_overall = 0.001; P_nonlinear = 0.564) as well as the key secondary outcome (P_overall = 0.001; P_nonlinear = 0.559) (Fig. 5).

In the stratification analysis of the 1-month attained NLR and LDL-C levels, it was observed that elevated 1-month NLR was consistently associated with heightened risks for both the primary and key secondary outcomes across all quartiles of 1-month LDL-C levels (Fig. 6; Supplemental Fig. 8; Supplemental Tables 16 and 17). Even in the subgroup of patients who achieved extremely low LDL-C values (< 0.8 mmol/L) at 1 month post-PCI ($n=465$), a cohort predominantly consisting of those receiving evolocumab, elevated 1-month NLR was significantly associated with increased risks for the primary outcome (HRadj 2.41, 95% CI 1.06–5.52, $P=0.04$) and the key secondary outcome (HRadj 3.23, 95% CI 1.18–8.82, $P=0.02$) (Supplemental Table 18).

Sex-specific rates of cardiovascular outcomes

To evaluate the impact of sex on cardiovascular risk in our cohort, we conducted an additional analysis

Table 4 Effect of evolocumab on LDL-C levels across median baseline NLR stratification[a]

Low-density lipoprotein cholesterol	Low NLR (≤ 2.9897)					High NLR (> 2.9897)				
	Evolocumab (*N* = 417)	Control (*N* = 1021)	Mean Difference (95%CI)[†]	χ^2/t	*P* Value	Evolocumab (*N* = 406)	Control (*N* = 1032)	Mean Difference (95%CI)[†]	χ^2/t	*P* Value
Baseline, mmol/L	3.37 ± 0.76	3.32 ± 0.90	−0.05 (−0.15 to 0.05)	0.97	0.33	3.38 ± 0.77	3.30 ± 0.84	−0.09 (−0.18 to 0.01)	1.78	0.07
18 months, mmol/L	0.78 ± 0.48	2.12 ± 0.84	1.33 (1.26 to 1.41)	36.22	< 0.01	0.75 ± 0.54	2.06 ± 0.78	1.30 (1.23 to 1.38)	34.43	< 0.01
Percentage reduction from baseline, %	−76.55 ± 14.45	−34.50 ± 23.84	42.06 (39.95 to 44.16)	39.18	< 0.01	−77.18 ± 15.43	−36.07 ± 23.13	41.11 (38.96 to 43.26)	37.55	< 0.01
Absolute decrease from baseline, mmol/L	−2.61 ± 0.79	−1.21 ± 0.92	1.39 (1.29 to 1.49)	27.75	< 0.01	−2.62 ± 0.84	−1.25 ± 0.87	1.37 (1.27 to 1.47)	26.53	< 0.01
LDL-C levels < 1.4 mmol/L at month 18, No. (%)	337 (88.7)	147 (15.6)	–	623.78	< 0.01	346 (91.1)	176 (18.8)	–	588.85	< 0.01
LDL-C levels < 1.8 mmol/L at month18, No. (%)	365 (96.1)	375 (39.8)	–	348.14	< 0.01	362 (95.3)	408 (43.6)	–	296.75	< 0.01

LDL-C low-density lipoprotein cholesterol, *NLR* neutrophil–lymphocyte ratio

[a] Data are mean ± SD or No. (%)

[†] Control minus evolocumab

Table 5 Comparative analysis of lipid-lowering strategies on cardiovascular risk stratified by median baseline NLR levels. *

Outcome	Low NLR (≤ 2.9897)								High NLR (> 2.9897)								
	Evolocumab (*N* = 417)	Control (*N* = 1021)	Unadjusted HR (95% CI); *P*	HRadj (95% CI); *P*	C-index	Gronnesby-Borgan Test	ARR	RRR	Evolocumab (*N* = 406)	Control (*N* = 1032)	Unadjusted HR (95% CI); *P*	HRadj (95% CI); *P*	C-index	Gronnesby-Borgan Test	ARR	RRR	*P* Value for Interaction†
	No. (%)						%	%	No. (%)					%	%		
Primary composite outcome	29 (7.0)	101 (9.9)	0.70 (0.46–1.05); 0.09	0.67 (0.44–1.01); 0.06	0.70	*P* = 0.45	2.9 (−0.1–6.0)	33.3	42 (10.4)	170 (16.6)	0.61 (0.44–0.86); < 0.01	0.63 (0.45–0.89); 0.01	0.72	*P* = 0.56	6.2 (2.5–9.9)	36.8	0.72
Key secondary composite outcome	21 (5.0)	68 (6.7)	0.75 (0.46–1.23); 0.26	0.77 (0.47–1.25); 0.29	0.71	*P* = 0.29	1.6 (−1.0–4.2)	23.3	32 (7.9)	138 (13.5)	0.58 (0.39–0.84); < 0.01	0.59 (0.40–0.87); 0.01	0.71	*P* = 0.48	5.6 (2.2–8.9)	40.6	0.45
Components of primary outcome																	
Myocardial infarction	15 (3.6)	49 (4.8)	0.75 (0.42–1.33); 0.32	0.75 (0.42–1.33); 0.32	0.72	*P* = 0.89	1.2 (−1.0–3.4)	25.3	21 (5.2)	94 (9.2)	0.55 (0.35–0.89); 0.01	0.58 (0.36–0.94); 0.03	0.76	*P* = 0.95	4.0 (1.2–6.8)	41.5	0.49
Ischemic stroke	4 (1.0)	14 (1.4)	0.70 (0.23–2.13); 0.53	0.61 (0.20–1.87); 0.39	0.84	*P* = 0.96	0.4 (−0.8–1.6)	38.7	8 (2.0)	27 (2.8)	0.75 (0.34–1.64); 0.47	0.72 (0.33–1.59); 0.41	0.69	*P* = 0.67	0.8 (−0.9–2.5)	28.2	0.28
Death from cardiac causes	4 (1.0)	14 (1.4)	0.70 (0.23–2.13); 0.53	0.73 (0.24–2.21); 0.57	0.78	*P* = 0.92	0.4 (−0.8–1.6)	27.4	6 (1.5)	27 (2.6)	0.56 (0.23–1.36); 0.20	0.57 (0.23–1.38); 0.21	0.71	*P* = 0.68	1.1 (−0.4–2.7)	43.1	0.17
Unplanned coronary revascularization	23 (5.5)	68 (6.7)	0.83 (0.52–1.33); 0.43	0.80 (0.50–1.29); 0.37	0.76	*P* = 0.91	1.1 (−1.5–3.8)	19.6	29 (7.2)	100 (9.8)	0.73 (0.48–1.10); 0.13	0.74 (0.49–1.12); 0.16	0.75	*P* = 0.88	2.6 (−0.5–5.7)	25.6	0.10
Hospitalization due to UA	3 (0.7)	10 (1.0)	0.73 (0.20–2.66); 0.64	0.71 (0.19–2.60); 0.61	0.73	*P* = 0.78	0.3 (−0.8–1.3)	28.8	6 (1.5)	21 (2.1)	0.72 (0.29–1.79); 0.48	0.72 (0.29–1.79); 0.49	0.74	*P* = 0.36	0.6 (−0.9–2.0)	27.6	0.41
All-cause death	5 (1.2)	17 (1.7)	0.72 (0.27–1.95); 0.52	0.74 (0.27–2.01); 0.55	0.71	*P* = 0.85	0.5 (−0.8–1.8)	26.1	8 (2.0)	31 (3.0)	0.65 (0.30–1.42); 0.28	0.66 (0.30–1.44); 0.30	0.70	*P* = 0.60	1.0 (−0.7–2.7)	33.7	0.22

ARR absolute risk reduction, *HR* hazards ratio, *HRadj* multivariable adjusted hazards ratio, *NLR* neutrophil–lymphocyte ratio, *RRR* relative risk reduction, *UA* unstable angina

* Percentages were calculated as estimates of cumulative incidence using the Kaplan–Meier method

† The P-interaction value assessed the statistical significance of the interaction between NLR background (stratified by median) and the type of lipid-lowering therapies (evolocumab vs. statins alone) on the risk of the adverse cardiovascular events

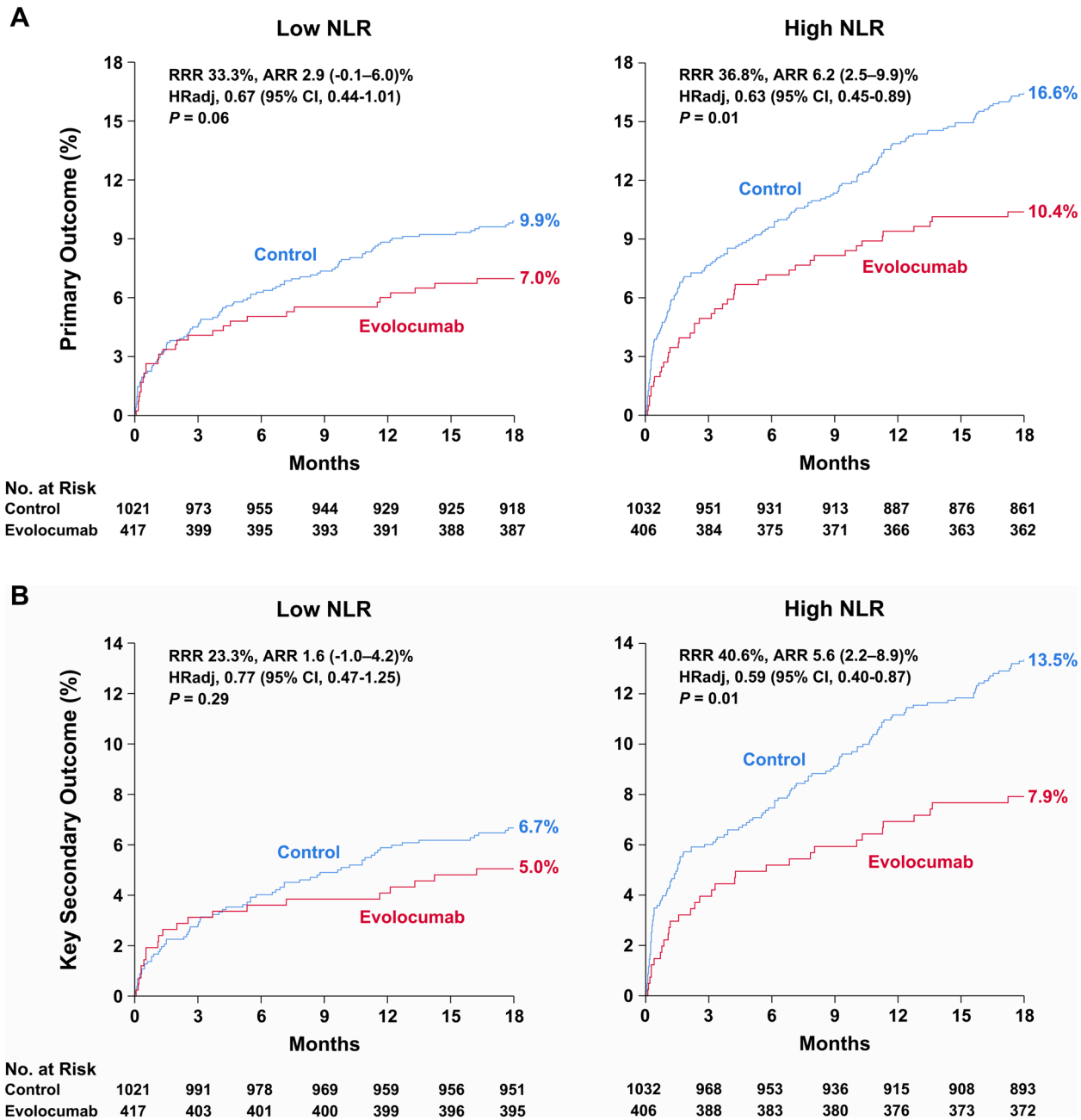

Fig. 4 Kaplan–Meier estimates of cardiovascular risks stratified by median baseline NLR and lipid-lowering strategies. 18-month Kaplan–Meier estimates stratified by median baseline NLR levels and lipid-lowering strategies (evolocumab vs. standard-of-care control group) for the primary (**A**) and key secondary outcomes (**B**). Multivariable adjusted hazards ratio (HRadj), 95% confidence interval (CI), relative risk reduction (RRR), and absolute risk reduction (ARR) are presented for evolocumab versus the control group. The p-interaction value for lipid-lowering interventions by median baseline NLR levels is 0.72 for the primary outcome and 0.45 for the key secondary outcome. NLR: neutrophil–lymphocyte ratio

stratifying patients by sex. Compared to male patients, female patients were older, had a lower body weight, and exhibited a higher prevalence of hypertension. Furthermore, baseline LDL-C levels were significantly higher in female patients. In contrast, fewer female patients were current smokers, and fewer had a history of myocardial infarction, alongside lower HDL-C levels (Supplemental Tables 19 and 20). Prognostic analysis revealed that the incidence of adverse cardiovascular events following PCI in female patients with ACS was statistically comparable to that observed in male patients (Supplemental Table 21).

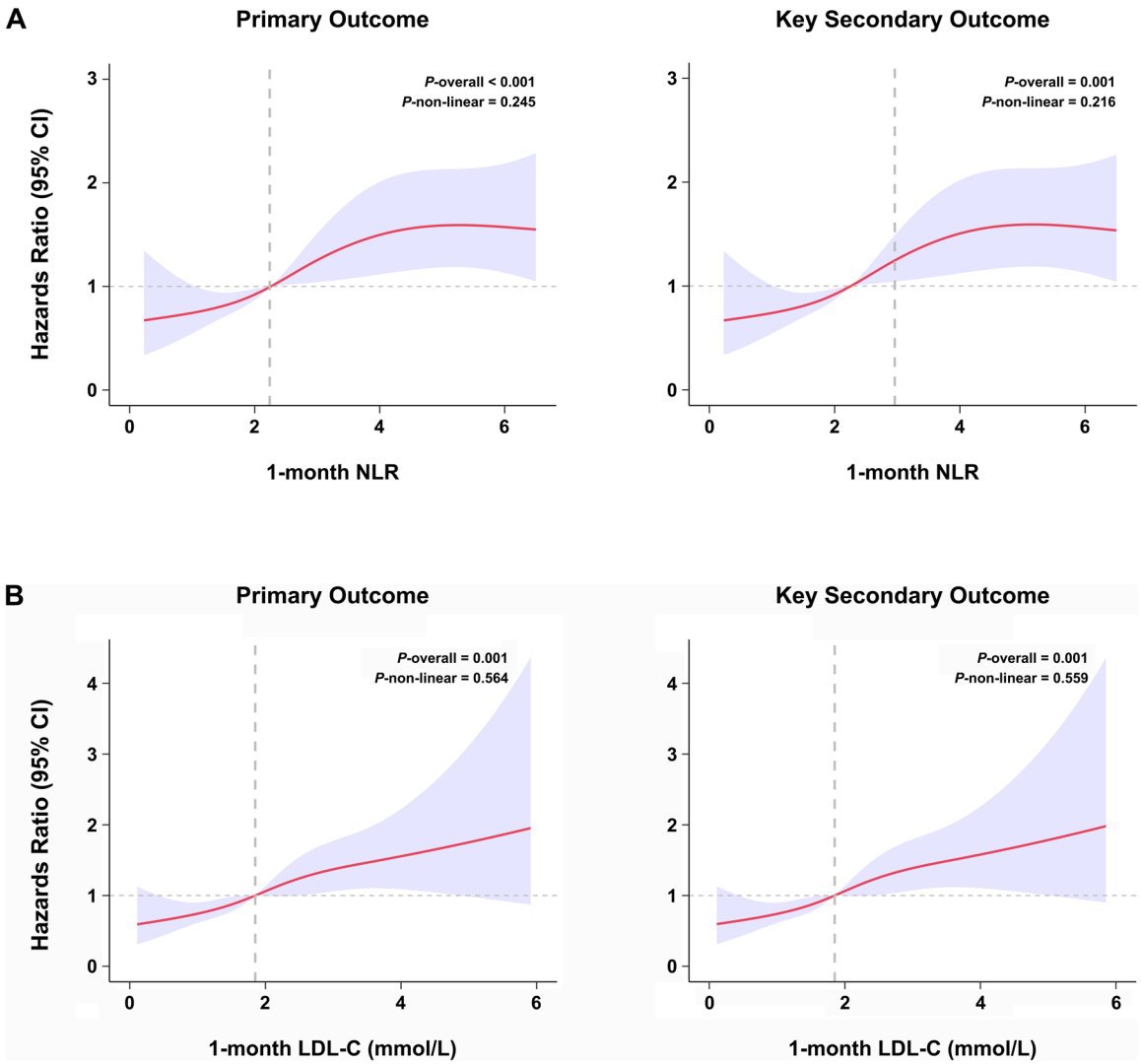

Fig. 5 Dose–response associations of NLR and LDL-C levels at 1 month with the primary and key secondary outcomes. Associations of 1-month achieved NLR (**A**) and LDL-C levels (**B**) with the primary and key secondary outcomes were investigated using multivariable Cox regression models incorporating restricted cubic spline functions. All risk estimates were adjusted for age, weight, sex, current smoking status, diabetes, hypertension, peripheral vascular disease, and estimated glomerular filtration rate. Additionally, the associations of 1-month NLR with the primary and key secondary outcomes were further adjusted for 1-month LDL-C, and similarly, the associations of LDL-C at 1 month with the primary and key secondary outcomes were additionally adjusted for 1-month NLR. LDL-C: low-density lipoprotein cholesterol; NLR: neutrophil–lymphocyte ratio

Discussion

In this analysis, we investigated the prognostic significance of the NLR for predicting adverse cardiovascular events and assessed the effectiveness of evolocumab, a potent LDL-C-lowering therapy, for preventing cardiovascular events, with the analysis stratified by the baseline inflammatory marker NLR among ACS patients undergoing PCI. Additionally, we evaluated the combined prognostic significance of residual inflammatory and cholesterol-related risks across varying on-treatment NLR and LDL-C levels. Within our cohort, the baseline NLR demonstrated a robust predictive capability for adverse cardiovascular events. The relative risk reductions associated with evolocumab compared with standard therapy for the primary and key secondary outcomes exhibited consistency across median-based NLR subgroups. Remarkably, individuals characterized by elevated NLR, who demonstrated a higher propensity for cardiovascular events, also exhibited more substantial absolute benefits from evolocumab treatment. In a comprehensive analysis integrating the 1-month post-intervention achieved NLR and LDL-C levels, both metrics

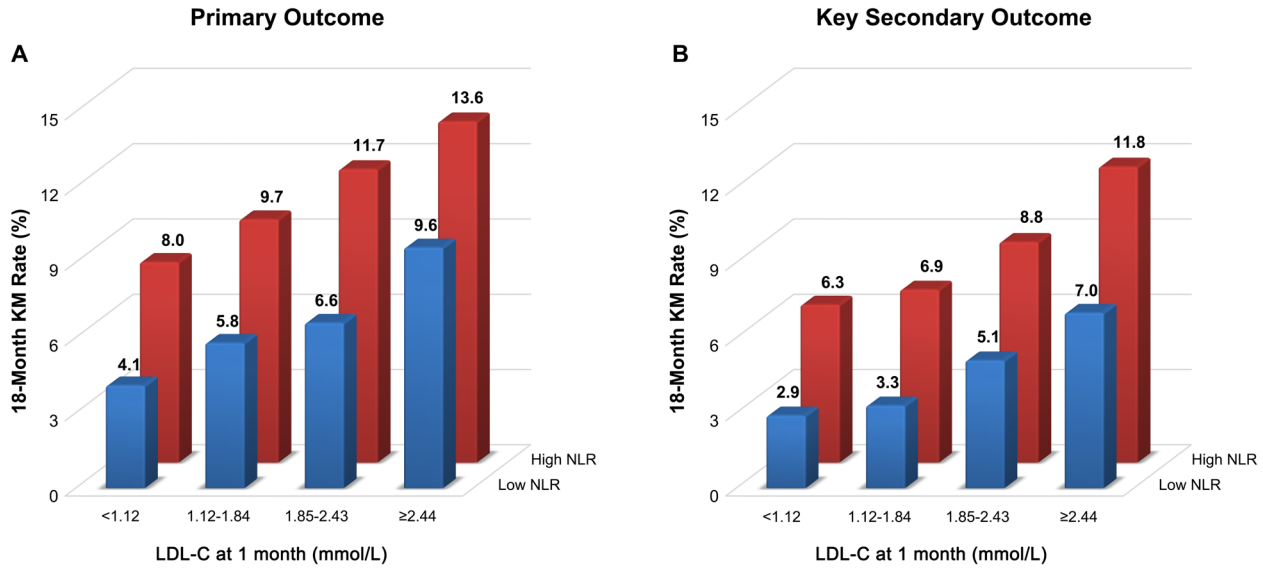

Fig. 6 Primary and key secondary outcomes stratified by NLR and LDL-C levels at 1 month. 18-month Kaplan–Meier estimates for the primary (**A**) and key secondary outcomes (**B**), categorized by median-based 1-month NLR groups and quartiles of 1-month LDL-C levels. KM: Kaplan–Meier; LDL-C: low-density lipoprotein cholesterol; NLR: neutrophil–lymphocyte ratio

were independently associated with cardiovascular event risk, underscoring the significance of residual inflammatory and cholesterol-related risk factors.

Our retrospective analysis adopted principles analogous to intention-to-treat philosophy by retaining participants in their original exposure cohorts—maintaining evolocumab-treated patients (8.4% discontinuation) and statin-treated controls (2.6% discontinuation) in their initial groups, while continuing to classify control subjects initiating evolocumab (3.9%) within their original cohort. This approach mitigated selection bias by avoiding exclusion of non-adherent or crossover patients, preserved statistical power through complete cohort retention, and aligned with pharmacoepidemiologic standards endorsed in STROBE guidelines. Although potentially attenuating effect sizes through inclusion of treatment non-persisters and cross-over cases, this methodology enhanced real-world generalizability by reflecting clinical practice patterns where therapeutic modifications routinely occur, while reducing risks of immortal time bias and informative censoring inherent in observational studies of longitudinal treatment effects.

Five contemporary randomized trials, encompassing a total of 60,087 participants, have consistently demonstrated that the NLR served as a robust predictor of future adverse cardiovascular outcomes and all-cause mortality in patients with stable ASCVD [12]. Nonetheless, data elucidating the predictive value of NLR in ACS patients remains scant. Across our entire cohort, the baseline NLR emerged as a significant predictor of adverse cardiovascular events in ACS patients undergoing PCI, a finding confirmed in the statins-only cohort, thereby excluding any potential confounding by evolocumab. Notably, the relative risk increase for the primary outcome per quartile increase in NLR was significantly higher in patients aged ≥ 65 years. Likewise, the relative risk increase for the key secondary outcome was significantly greater in patients aged ≥ 65 years, those with STEMI, and individuals with multi-vessel disease. These findings underscore the robust predictive value of NLR in stratifying cardiovascular risk in these high-risk subgroups, suggesting that in addition to intensive lipid-lowering strategies, such patients may also benefit from targeted anti-inflammatory therapies. Beyond its prognostic significance for adverse cardiovascular outcomes, prior investigation has established the NLR as a valuable tool for therapeutic monitoring in anti-inflammatory interventions, as demonstrated by the dose-dependent reduction in NLR associated with interleukin-1β inhibitor canakinumab, which notably lowered cardiovascular risk in the CANTOS trial [12, 15]. Consequently, the NLR could potentially serve as a response marker for various anti-inflammatory therapies, thereby facilitating a more precise and economically efficient application of these frequently costly treatments.

Extensive evidence from epidemiologic, genetic, experimental, and clinical investigations has unequivocally established LDL-C as a causative factor in the development of atherosclerosis, and robust data have conclusively demonstrated that cholesterol-lowering

interventions significantly mitigate cardiovascular endpoints in ASCVD patients [16–19]. Current guidelines underscore the necessity of intensifying cholesterol-lowering therapy to achieve significantly low LDL-C concentrations in patients with established cardiovascular disorders [20–22]. The FOURIER trial substantiated the efficacy of evolocumab, revealing a significant 59% reduction in LDL-C levels, with median levels decreasing from 2.38 mmol/L at baseline to 0.78 mmol/L after 48 weeks of treatment. This substantial reduction was accompanied by significant attenuation of major cardiovascular risks over a median follow-up period of 2.2 years [4]. The FOURIER-OLE study further indicated that the benefits associated with evolocumab were sustained when the median follow-up duration was extended to 5.0 years [5]. However, in light of the current economic burden associated with PCSK9 inhibitors, it is essential to identify subgroups of patients with ACS who may achieve greater ARRs. In our cohort, baseline NLR proved to be a significant prognostic marker for future atherothrombotic events, as an elevated NLR effectively identified individuals with nearly a twofold higher incidence of major adverse cardiovascular events. Notably, the relative benefits of evolocumab compared with standard therapy in preventing the cardiovascular event risks were consistent across varying baseline NLR levels, with P-interactions exceeding 0.05 for both comparisons. Nonetheless, given the heightened absolute risk associated with elevated baseline NLR, the ARRs for adverse cardiovascular events with evolocumab were more pronounced among individuals with higher baseline NLR, yielding reductions of 6.2% for the primary outcome and 5.6% for the key secondary outcome, with corresponding NNT of only 16 and 18, respectively, over an 18-month period in ACS and PCI settings.

The present findings contribute substantially to the existing literature on inflammation and ACS. Our data demonstrated that the potent lipid-lowering agent, evolocumab, did not induce a significant effect on the NLR. Consistent with these observations, analyses derived from the SPIRE-1 and SPIRE-2 cardiovascular outcomes trials (Studies of PCSK9 Inhibition and Reduction in Vascular Events) consistently showed that the PCSK9 inhibitor bococizumab had no significant impact on the NLR [12, 23, 24]. Upon stratified analysis based on on-treatment NLR and LDL-C levels, it was determined that elevated NLR consistently associated with an increased risk for both primary and key secondary outcomes across all strata of 1-month LDL-C levels. This association remained significant even among patients who achieved extraordinarily low LDL-C values (<0.8 mmol/L), a cohort predominantly composed of individuals receiving the PCSK9 inhibitor evolocumab. When assessed as continuous variables across the spectrum of the achieved NLR and LDL-C levels at 1 month, both variables emerged as independent prognostic factors for adverse outcomes. These observations underscore the significant residual inflammatory risk in patients treated with evolocumab, even among those achieving ultralow LDL-C levels. Additionally, these findings suggest that the NLR serves as a marker for an inflammatory pathway independent of the lipid-lowering effect of evolocumab, yet it remains pertinent to atherothrombosis and potentially constitutes a therapeutic target.

Emerging therapies targeting both lipid metabolism and inflammation offered new strategies to address residual cardiovascular risk. The recent meta-analysis by De Filippo et al. [25] highlighted the dual benefits of bempedoic acid, an ATP-citrate lyase inhibitor, demonstrating a 22.42% reduction in LDL-C and a 27.83% decrease in hsCRP at 12 weeks, with a subsequent 13% reduction in major adverse cardiovascular events over a median follow-up of 87 weeks. These results aligned with our focus on cholesterol-inflammation interplay in PCI-treated ACS patients. Unlike evolocumab (a PCSK9 inhibitor), bempedoic acid targets upstream cholesterol synthesis while exhibiting anti-inflammatory effects through hsCRP reduction. This dual mechanism supports complementary strategies to address residual cardiovascular risk. Our study further demonstrated that NLR, a practical inflammatory marker, remained prognostically relevant even under ultralow LDL-C achieved with evolocumab. While dual-pathway approaches (lipid-lowering + anti-inflammatory) are promising, bempedoic acid's elevated gout risk necessitates personalized safety assessments. Future research should explore combining PCSK9 inhibitors with upstream agents like bempedoic acid, particularly in high-risk subgroups with elevated NLR or residual CRP.

In contrast to Bohula et al.'s FOURIER sub-analysis [26], which assessed baseline high-sensitivity C-reactive protein (hsCRP)-based inflammatory risk in stable atherosclerotic cardiovascular disease, our study focused on ACS patients undergoing PCI. A key distinction lay in the higher-risk ACS cohort, providing insights into a different clinical scenario. Bohula et al. relied on baseline hsCRP due to limited longitudinal data, which may not have fully captured dynamic inflammation. In contrast, we utilized the NLR from routine complete blood counts (CBC), enabling continuous monitoring of residual inflammatory risk. This approach overcame hsCRP data scarcity and provided a more comprehensive systemic inflammation assessment. Additionally, our design integrated NLR-based residual inflammatory data with residual cholesterol data, enabling a nuanced evaluation of their combined predictive value for adverse

cardiovascular events. While both studies aimed to assess residual risks beyond lipid-lowering therapies, our study extended this to ACS patients and employed NLR for dynamic inflammatory risk evaluation, offering a practical and clinically relevant approach to cardiovascular risk management.

Paolo Calabrò et al. [27] demonstrated that female sex is a predictive factor for unfavorable outcomes in ischemic heart disease, particularly in older women with lower body weight. In our study, female patients were older and had lower body weight compared to males. Despite cardiovascular disease affecting both sexes equally, a higher proportion of women die from cardiovascular causes and coronary heart disease in Europe [28]. Paolo Calabrò [27] also noted that women diagnosed with ACS are less frequently recommended for early cardiac catheterization and revascularization. These factors contribute to poorer outcomes in women with ischemic heart disease. Initial concerns about the benefits of newer-generation Drug-Eluting Stents in women, due to complex anatomy and higher comorbidity rates, have been addressed by recent studies showing similar efficacy and safety in both sexes [29]. Similarly, our findings indicated that the incidence of adverse cardiovascular events following PCI in female patients with ACS was comparable to that in male patients. Therefore, early invasive strategies should be advocated for female ACS patients, as for males, to achieve similar cardiovascular benefits.

Our findings highlight the critical interplay between residual inflammatory risk and cholesterol-related risk in determining cardiovascular outcomes among ACS patients undergoing PCI. However, it is important to acknowledge that residual risk in this population may also stem from non-LDL lipid mediators, particularly lipoprotein(a) [Lp(a)]. Elevated Lp(a) levels have emerged as an independent risk factor for atherosclerotic cardiovascular disease, contributing to both plaque progression and thrombogenicity through pro-inflammatory and pro-atherogenic mechanisms. Recent evidence further underscores the role of Lp(a) in modulating coronary complexity, as higher Lp(a) levels correlate with increased lesion burden, multivessel disease, and calcified plaque morphology—features that may exacerbate ischemic risk even in optimally managed patients [30]. While our study did not specifically assess Lp(a), this observation aligns with the notion that comprehensive risk stratification in post-PCI patients should integrate inflammatory, lipid, and lipoprotein-related biomarkers. Importantly, the relative risk reductions observed with evolocumab in our cohort, though consistent across NLR strata, may not fully address the residual hazard associated with elevated Lp(a). Future studies should explore whether combining aggressive LDL-C lowering with therapies targeting Lp(a) reduction or anti-inflammatory pathways could synergistically mitigate residual risk in high-risk subgroups, particularly those with concurrent elevations in NLR, LDL-C, and Lp(a). Such a multidomain approach may be essential to optimize outcomes in complex ACS/PCI populations.

Several limitations must be acknowledged. Given the retrospective nature of this study, the lipid-lowering regimens (evolocumab versus standard-of-care) stratified by median-based NLR were not subject to randomization. To mitigate potential bias, we implemented several rigorous measures. These included applying strict inclusion and exclusion criteria, adjusting for potential confounding factors (including baseline and procedural characteristics) in multivariable Cox proportional hazards models, and conducting sensitivity analyses to validate the consistent predictive value of baseline NLR for adverse cardiovascular events across multiple subgroups (such as age, sex, clinical presentation, hypertension, diabetes, and multivessel disease). Despite these efforts, residual confounding cannot be entirely ruled out. Therefore, further validation through large-scale randomized controlled trials is warranted to confirm our findings. Additionally, while this study established that evolocumab exerts no significant effect on NLR, it did not assess the effects of various anti-inflammatory agents on NLR. Consequently, it requires future investigations to rigorously validate the hypothesis that NLR could potentially serve as a response marker for diverse anti-inflammatory therapies. Moreover, our study exclusively evaluated the effects of evolocumab, which may limit the generalizability of our findings to other PCSK9 inhibitors, such as alirocumab and inclisiran. Each of these drugs, while targeting the same protein, may have distinct pharmacodynamic and pharmacokinetic profiles, leading to variations in their clinical outcomes. To address this limitation, we propose conducting more comprehensive and sophisticated clinical trials in the future. These trials will aim to include all major PCSK9 inhibitors, thereby enabling a more robust comparison of their effectiveness and safety profiles. Additionally, we plan to incorporate a diverse patient population and extend follow-up periods to gain a more thorough understanding of the long-term benefits and potential adverse effects associated with these medications. Finally, the 18-month follow-up period may be insufficient to fully evaluate the long-term effects of evolocumab. While our study cohort, comprising patients with ACS who underwent PCI, exhibited a higher incidence and earlier onset of cardiovascular events (11.9% event rate over 18 months, with 29.8% of events occurring within the first month and 51.1% within the first six months), longer-term follow-up is necessary to provide a comprehensive assessment of evolocumab's long-term

efficacy and safety. Additionally, the large patient cohort of 2,876 individuals allowed us to detect statistically significant differences within the 18-month period, but future studies should extend follow-up durations, particularly in randomized controlled trials, to address these limitations.

Conclusions

This investigation showed that higher baseline NLR is associated with increased cardiovascular risk in ACS patients undergoing PCI. The relative risk reductions conferred by evolocumab for cardiovascular events were consistent across NLR categories, whereas ARRs were more significant among patients with higher NLR. Both on-treatment NLR and LDL-C levels were independently predictive of cardiovascular risk, with the lowest event rates observed in individuals characterized by the minimal residual inflammatory and cholesterol risk profiles. This highlights the paramount significance of targeting both inflammatory and cholesterol-related risk factors in comprehensive cardiovascular risk management.

Abbreviations

ACS	Acute coronary syndrome
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ARRs	Absolute risk reductions
ASCVD	Atherosclerotic cardiovascular disease
CIs	Confidence intervals
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk
FOURIER-OLE	FOURIER–Open-Label Extension
HRadj	Multivariable adjusted hazards ratio
HRs	Hazard ratios
hsCRP	High-sensitivity C-reactive protein
[Lp(a)]	Lipoprotein(a)
IQR	Interquartile ranges
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
MZ	Marginal zone B
NLR	Neutrophil-to-lymphocyte ratio
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
rms	Regression modeling strategies
RRR	Relative risk reduction
SD	Standard deviations
SPIRE	Studies of PCSK9 Inhibition and Reduction in Vascular Events
STEMI	ST-segment elevation myocardial infarction
TLR2	Toll-like receptor 2
Tregs	Regulatory T cells
UA	Unstable angina

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02537-2.

Supplementary Material 1.

Acknowledgements
None.

Authors' contributions
Y.Z., K.L., and X.B. drafted the manuscript. X.B., Y.Z., and T.X. curated the data. K.L. and H.L. performed the formal analysis and created the visualizations. J.D. secured the funding. Y.Z., T.X., and O.I.R.C.V conducted patient follow-ups. K.C. and J.D. supervised the project. All authors reviewed the manuscript.

Funding
This work was supported by the Jiangsu Provincial Medical Key Discipline (Laboratory) (ZDXK202207) and the Jiangsu Provincial Science and Technology Project (BE2022852).

Data availability
The datasets underlying the findings of this study will be provided by the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval for the study protocol was obtained from the institutional review boards of both Zhongda Hospital Southeast University and the First Affiliated Hospital of Zhengzhou University. The ethics committees deemed the study protocol to be in compliance with the principles outlined in the Declaration of Helsinki and relevant regulatory requirements. Given the retrospective nature of the study, the institutional review boards waived the requirement for written informed consent from the enrolled patients. This waiver was justified by the fact that the study involved the analysis of existing clinical data without any interference with standard medical care or patient treatment protocols. The collected data were anonymized to ensure patient confidentiality, and the study was conducted with the utmost respect for patient privacy and data integrity.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 26 December 2024 Accepted: 17 March 2025
Published online: 31 March 2025

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