

Discordance Between Neutrophil to Lymphocyte Ratio and High Sensitivity C-Reactive Protein to Predict Clinical Events in Patients with Stable Coronary Artery Disease: A Large-Scale Cohort Study

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Purpose: Neutrophil to lymphocyte ratio (NLR), a novel inflammatory biomarker, has been shown to positively predict prognosis independent of high-sensitivity C-reactive protein (hsCRP) in patients with coronary artery disease (CAD). This study aimed to use discordance analysis to evaluate the effectiveness of NLR and hsCRP to predict adverse events in patients with stable CAD.

Patients and Methods: This observational cohort study included 7827 consecutive CAD patients at Fuwai Hospital from March 2011 to April 2017. Discordant NLR with hsCRP was defined by the highest quartiles and medians. The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCEs), including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unplanned revascularization.

Results: During a median 36-month follow-up, 624 (8.0%) MACCEs occurred. Compared with the lowest NLR quartile, a significantly higher risk of MACCEs was observed in the highest NLR quartile after adjusting for confounding factors (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.09–1.71). High NLR and low hsCRP discordance were also associated with an increased risk of MACCEs in the fully adjusted model (HR, 1.39; 95% CI, 1.05–1.84).

Conclusion: This study demonstrated that discordantly elevated NLR levels were associated with a greater risk of adverse clinical events in patients with stable CAD, suggesting the potential clinical significance of NLR as a goal of inflammatory risk management.

Keywords: coronary artery disease, high-sensitivity C-reactive protein, inflammation, neutrophil to lymphocyte ratio, prognosis

Introduction

Inflammation plays a crucial role in the development and progression of coronary artery disease (CAD).¹ As a benchmark biomarker for inflammatory risk, high-sensitivity C-reactive protein (hsCRP) is positively associated with cardiovascular events in both primary and secondary prevention.^{2,4} In the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial, the greatest clinical benefit accrued among participants who attained the lowest tertile of hsCRP levels, whereas individuals with on-treatment hsCRP levels in the highest tertile had comparable clinical outcomes relative to placebo.³⁻⁵ Such observations further support hsCRP as a potential biomarker to guide therapeutic decision-making.

Contemporary studies not only increase interest in conventional inflammatory biomarkers including hsCRP but also in awareness of a simple biomarker widely and readily available to the clinical community.^{5–7} One such biomarker is neutrophil to lymphocyte ratio (NLR), which is derived from the complete blood count.^{8,9} NLR integrated information from both innate immunity, predominately due to neutrophils, and adaptive immune response, supported by lymphocytes. Increasing studies have demonstrated that baseline NLR is positively associated with cardiovascular events and mortality.^{9,10} Of note, data from five large randomized clinical trials, including the CANTOS trial, demonstrated that baseline NLR modestly correlated with hsCRP, interleukin (IL)-6 and fibrinogen, and it could consistently and independently predict cardiovascular events and death after adjusting the effect of hsCRP.⁹ These findings indicated that NLR provide additional insights into the nature of the inflammatory atherosclerotic process, which is not reflected by cytokines or hsCRP. Additionally, NLR has been shown to be stable over time and to be responsive to anti-inflammatory therapy, which may make it an alternative or complementary inflammatory biomarker in clinical practice.^{9–11}

Recently, a previous study by Wada et al¹² has shown that the 5-year adverse outcomes of CAD patients with low-grade hs-CRP levels could be independently predicted by increased NLR level, suggesting that NLR could be useful for risk stratification of CAD patients with low inflammatory marker levels. However, to date, there are no studies comparing the predictive values of the NLR levels with hsCRP levels for the risk of adverse clinical events in patients with stable CAD. Accordingly, the objective of this study is to use discordance analysis to investigate the joint or discordant association of NLR and hsCRP levels with adverse clinical events in patients with stable CAD.

Materials and Methods

Study Design

This study was a single-center, observational cohort study. Between March 2011 and April 2017, a total of 9180 patients who underwent coronary angiography examination due to angina-like chest pain or positive non-invasive tests (such as treadmill exercise test or coronary computed tomography angiography) were consecutively recruited at the Fuwai Hospital, Chinese Academy of Medical Sciences. Patients meeting the following criteria were included:¹ aged of equal to or more than 18 years,² diagnosed with CAD. Patients meeting the following criteria were excluded:¹ patients with missing detailed information (missing Complete blood counts and/or hsCRP measurements),² patients with severe hepatic or kidney dysfunction,³ patients with systematic inflammatory disease,⁴ patients with malignant tumor,⁵ patients with hematological disorder,⁶ patients with acute infection,⁷ patients with acute coronary syndrome (ACS), and⁸ patients lost to follow-up (Figure 1). ACS was determined according to elevated myocardial enzyme levels, typical electrocardiogram changes, positive findings by angiography and medical history.

This study complied with the Declaration of Helsinki and followed the guidelines for reporting cohort studies of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). The STROBE checklist was provided in the [Supplementary Material](#). The study protocol was approved by Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (IRB2012-BG-006). All study patients provided written informed consent before enrollment.

Study Endpoints and Follow-Up

Study patients were routinely followed-up at 6-month intervals through clinical visits and/or telephone contact by well-trained coordinators who were blinded to the aims of this study. All clinical events were carefully adjudicated by two independent and experienced cardiologists. Conflicts were resolved by consulting a third experienced cardiologist. The primary endpoint was major cardiovascular and cerebrovascular events (MACCEs), defined as a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke, and unplanned revascularization. The secondary endpoints of interest were individual components of MACCEs. Cardiovascular death was confirmed by medical records, death certificates, and information provided by the relatives. Non-fatal MI was diagnosed by positive cardiac troponins together with typical chest pain or typical electrocardiogram serial changes. Non-fatal Stroke was defined by persistence of neurological symptoms with acute cerebral infarction as demonstrated by computed

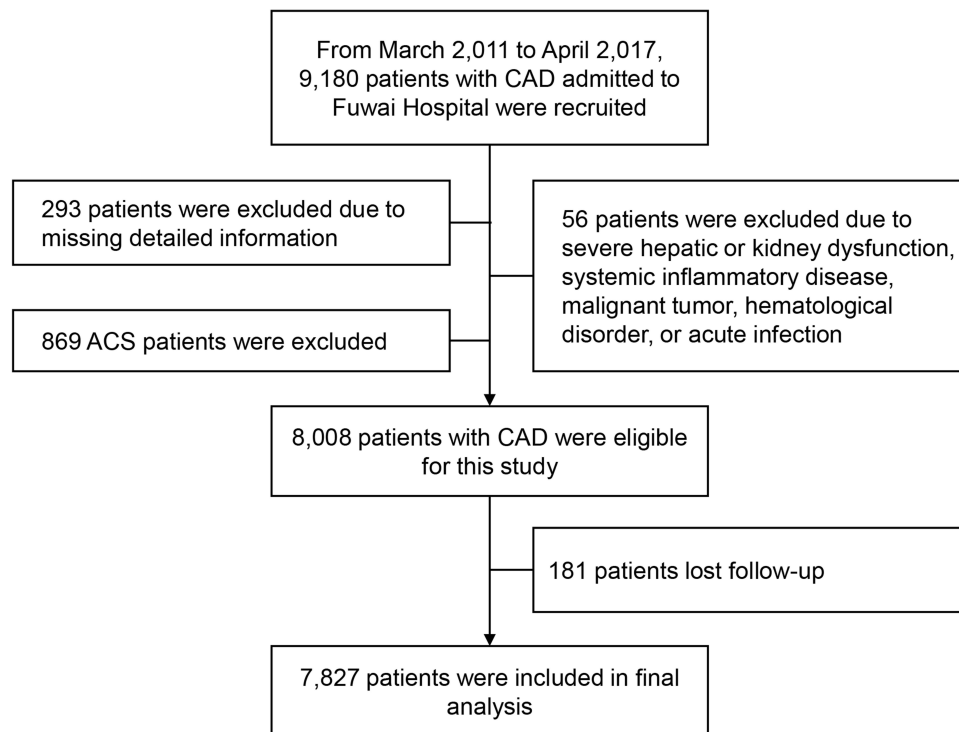


Figure 1 Study flowchart.

Abbreviations: CAD, coronary artery disease; ACS, acute coronary syndrome.

tomography and/or magnetic resonance imaging. Unplanned revascularization was defined as any percutaneous coronary intervention or surgical bypass excluding staged procedures.

Clinical Assessment

Baseline information on personal health habits, demographics, medications, and medical history was collected from each participant. According to the American Diabetes Association criteria, diabetes was determined by a fasting blood glucose (FBG) ≥ 7.0 mmol/L, or 2-h plasma glucose (PG) ≥ 11.1 mmol/L, or HbA1c $\geq 6.5\%$, or currently using hypoglycemic drugs.¹³ Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or currently using antihypertensive drugs. Dyslipidemia was defined by triglyceride ≥ 1.7 mmol/L, total cholesterol ≥ 5.2 mmol/L, LDL-C ≥ 3.4 mmol/L, or high-density lipoprotein cholesterol ≤ 1.0 mmol/L, and/or use of lipid-lowering agents. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Laboratory Tests

On admission, venous blood samples were collected from each participant after at least 12-h fasting and were tested at clinical chemistry department of our hospital. Complete blood counts (including WBC, neutrophils, and lymphocytes) were performed using an automatic blood cell analyzer (XT-1800i; Sysmex Corporation). The NLR value was calculated using the following formula: neutrophils ($\times 10^9/L$)/lymphocytes ($\times 10^9/L$). The hsCRP level was determined using immunoturbidimetry (Beckmann Assay, Bera, California). The HbA1c level was measured by Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tokyo, Japan). All other laboratory measurements were performed according to the standard biochemical techniques. Left ventricular ejection fraction (LVEF) was measured using the modified Simpson's method.

Statistical Analysis

Continuous variables were presented as mean with standard deviation, and categorical variables were expressed as count with percentage. Differences were estimated by Student's *t*-test, Mann–Whitney *U*-test, Chi-square test, and Fisher's

exact test, as appropriate. Distribution of variables was determined by Kolmogorov–Smirnov test. The correlation between NLR and other laboratory parameters was evaluated by Spearman correlation test. Patients were then assigned into the NLR and hsCRP groups according to the quartiles of each measure with the whole population. According to the highest quartile of NLR levels (<2.62 or ≥ 2.62) and the median of hsCRP levels (<1.30 or ≥ 1.30 mg/L), patients were subsequently divided into 4 mutually exclusive concordance/discordance groups, as follows: low/low (less than the highest quartile of NLR and less than the median of hsCRP), high/low (greater than or equal to the highest quartile of NLR and less than the median of hsCRP), low/high (less than the highest quartile of NLR and greater than or equal to the median of hsCRP), high/high (greater than or equal to the highest quartile of NLR and greater than or equal to the median of hsCRP). Discordance was defined as high NLR levels and hsCRP levels being low, or vice versa.

In survival analysis, linearity relationship of hsCRP and NLR for the MACCE risk was illustrated by restricted cubic splines (RCS) analysis. Cumulative incidence of adverse events among groups were presented by Kaplan–Meier curves and compared by Log rank test. Patients were censored at the time of death or last contact, whichever came first. The association of NLR and hsCRP levels with study endpoints was explored in univariable and multivariable Cox proportional hazard models. Hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. In multivariable analysis, age, male sex, diabetes, hypertension, previous CABG, previous stroke, creatinine, TG, LVEF, statins use, and aspirin use were included based on their statistical significance in univariable model or clinical importance. Moreover, sensitivity analysis was performed to confirm our findings by classifying 4 concordance/discordance groups using hsCRP guideline-guide target cutoffs of 2 mg/L.¹⁴ Furthermore, subgroup analyses were performed to assess the association of 4 concordance/discordance groups with MACCEs in specific subsets. Finally, mediation analysis was performed to evaluate the proportional contribution of NLR and hsCRP on the associations of the counterparts with MACCE risk. Mediation analysis models were adjusted for the same set of confounders as in the multivariable model mentioned above. A two-tailed P value <0.05 indicated statistical significance. All statistical analyses were performed with R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Among 9180 consecutively recruited patients, we excluded 293 patients with missing detailed information, 56 patients due to severe hepatic or kidney dysfunction, systematic inflammatory disease, malignant tumor, hematological disorder, or acute infection. Besides, we excluded 869 patients with acute coronary syndrome according to elevated myocardial enzyme levels, typical electrocardiogram changes, positive findings by angiography and medical history. Furthermore, 181 patients lost to follow up. Eventually, a total of 7827 patients were included in final analysis (Figure 1).

Generally, a total of 7827 CAD patients (58.02 ± 10.16 years, 70.6% male) were consecutively included in this study. Baseline characteristics of patients with and without MACCEs are presented in Table 1. Patients experiencing any component of MACCEs tended to be older, with higher prevalence of diabetes and prior CABG compared to those in non-MACCE group (all $P < 0.05$). In addition, higher levels of HbA1c, creatinine, NLR, hsCRP, and lower level of LVEF were noticed in patients with unfavorable prognosis (all $P < 0.05$). Moreover, there was less use of statins, aspirin, and CCB in patients who suffered from MACCEs than those not (all $P < 0.05$).

The baseline characteristics across 4 concordance/discordance groups according to low or high NLR and hsCRP levels are listed in Table 2. There were 803 (10.3%) patients had a discordantly high NLR levels. Significant differences were observed regarding age, sex, diabetes, hypertension, family history, smoking status, prior PCI, prior CABG, prior stroke, and medications (statins, aspirin, ACEIs/ARBs, and β -blocker) across 4 groups (all $P < 0.05$). Moreover, patients with high NLR levels were more likely to have higher levels of FBG, HbA1c, and creatinine (all $P < 0.05$). Among patients with low hsCRP levels, those with increased NLR values were older and more likely to be male with more prevalent hypertension and prior stroke and less prevalent family history of CAD and current smoker. Meanwhile, there were higher levels of FBG, creatinine, WBC and neutrophils, and lower levels of TC, TG, LDL-C and lymphocytes in those with high NLR levels (all $P < 0.05$). In addition, among patients with high hsCRP levels, those with increased NLR values were also older and more likely to be male with a higher prevalence of previous PCI or CABG. And these patients

Table I Baseline Characteristics According to Incidence of MACCEs

	Overall (n = 7827)	Non-MACCE (n = 7203)	MACCE (n = 624)	P value
Age, years	58.02±10.16	57.85±10.13	60.05±10.26	<0.001
Male sex	5527 (70.6)	5073 (70.4)	454 (72.8)	0.239
BMI, kg/m ²	25.76±3.60	25.75±3.62	25.79±3.38	0.784
Diabetes	2876 (36.7)	2597 (36.1)	279 (44.7)	<0.001
Hypertension	5745 (73.4)	5269 (73.2)	476 (76.3)	0.099
Family history of CAD	1077 (13.8)	997 (13.8)	80 (12.8)	0.516
Current smoker	2250 (28.7)	2085 (28.9)	165 (26.4)	0.201
Prior PCI	2177 (27.8)	1998 (27.7)	179 (28.7)	0.645
Prior CABG	207 (2.6)	182 (2.5)	25 (4.0)	0.038
Prior stroke	258 (3.3)	219 (3.0)	39 (6.3)	<0.001
Laboratory tests				
FBG, mmol/L	5.85±1.76	5.85±1.75	5.91±1.79	0.412
HbA1c, %	6.32±1.09	6.30±1.07	6.59±1.28	<0.001
Creatinine, µmol/L	77.44±17.58	77.33±17.58	78.73±17.55	0.026
TC, mmol/L	4.15±1.33	4.15±1.34	4.21±1.24	0.136
TG, mmol/L	1.78±1.28	1.77±1.24	1.87±1.68	0.360
HDL-C, mmol/L	1.07±0.29	1.07±0.29	1.06±0.28	0.571
LDL-C, mmol/L	2.51±1.05	2.51±1.04	2.53±1.06	0.578
Non-HDL-C, mmol/L	3.08±1.29	3.08±1.30	3.14±1.21	0.218
WBC, ×10 ⁹ /L	6.45±7.96	6.44±8.28	6.48±1.68	0.037
Neutrophils, ×10 ⁹ /L	3.85±1.30	3.84±1.30	3.96±1.31	0.040
Lymphocytes, ×10 ⁹ /L	1.90±0.61	1.90±0.61	1.86±0.63	0.087
NLR	2.23±1.19	2.22±1.18	2.39±1.26	0.001
hsCRP, mg/L	2.40±2.90	2.35±2.86	2.90±3.32	<0.001
LVEF, %	63.88±7.76	64.05±7.55	61.86±9.64	<0.001
Medications				
Statins	4772 (61.0)	4439 (61.6)	333 (53.4)	<0.001
Aspirin	4431 (56.6)	4135 (57.4)	296 (47.4)	<0.001
ACEIs/ARBs	1304 (16.7)	1216 (16.9)	88 (14.1)	0.083
β-blocker	2571 (32.8)	2383 (33.1)	188 (30.1)	0.143
CCB	1103 (14.1)	1037 (14.4)	66 (10.6)	0.010

Note: Values are expressed as mean ± standard deviation or n (%).

Abbreviations: MACCEs, major adverse cardiac and cerebrovascular events; BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

had higher levels of creatinine, neutrophils and hsCRP levels, and lower TC, TG, LDL-C and LVEF levels (all $P < 0.05$). The correlation analysis showed that NLR levels are modestly and positively correlated with hsCRP levels ($r = 0.181$, $P < 0.001$) ([Supplementary Table 1](#)).

Association of Inflammatory Status with Adverse Clinical Events

During a median follow-up of 36 months, 107 (1.4%) CV death, 79 (1.0%) non-fatal MI, 155 (2.0%) non-fatal stroke, 330 (4.2%) unplanned revascularization, and 624 (8.0%) MACCEs was documented.

Kaplan–Meier analysis showed that patients with hsCRP levels in the third and fourth quartile had a higher probability of MACCEs compared with those with hsCRP levels in the lowest quartile ($P < 0.001$, [Figure 2A](#)), and that subjects in fourth quartile of NLR had a higher probability of MACCEs than those in first quartile of NLR ($P = 0.002$, [Figure 2B](#)). The crude and adjusted HRs and 95% CIs of MACCEs according to hsCRP or NLR quartiles are

Table 2 Baseline Characteristics of the Concordance/Discordance Groups According to Low or High NLR and hsCRP Categories

	NLR/hsCRP Concordance/Discordance Groups						P value
	Low/Low (n = 3097)	High/Low (n = 803)	P value	Low/High (n = 2767)	High/High (n = 1160)	P value	
Age, Years	57.11±9.99	59.03±9.77	<0.001	58.14±10.28	59.48±10.35	<0.001	<0.001
Male sex	2183 (70.5)	638 (79.5)	<0.001	1826 (66.0)	880 (75.9)	<0.001	<0.001
BMI, kg/m ²	25.37±3.49	25.27±3.16	0.463	26.22±3.80	26.03±3.53	0.134	<0.001
Diabetes	997 (32.2)	268 (33.4)	0.555	1129 (40.8)	482 (41.6)	0.689	<0.001
Hypertension	2133 (68.9)	596 (74.2)	0.004	2110 (76.3)	906 (78.1)	0.226	<0.001
Family history of CAD	441 (14.2)	81 (10.1)	0.002	398 (14.4)	157 (13.5)	0.518	0.014
Current smoker	857 (27.7)	182 (22.7)	0.005	857 (31.0)	354 (30.5)	0.807	<0.001
Prior PCI	944 (30.5)	253 (31.5)	0.595	640 (23.1)	340 (29.3)	<0.001	<0.001
Prior CABG	86 (2.8)	22 (2.7)	1.000	57 (2.1)	46 (4.0)	0.001	0.009
Prior stroke	74 (2.4)	30 (3.7)	0.047	108 (3.9)	46 (4.0)	0.999	0.004
Laboratory tests							
FBG, mmol/L	5.64±1.53	5.87±1.76	<0.001	5.99±1.87	6.08±1.97	0.145	<0.001
HbA1c, %	6.18±0.96	6.15±0.94	0.544	6.47±1.18	6.46±1.21	0.804	<0.001
Creatinine, µmol/L	76.42±17.37	78.74±16.07	0.001	76.81±16.92	80.78±20.07	<0.001	<0.001
TC, mmol/L	4.01±1.13	3.83±0.98	<0.001	4.41±1.61	4.13±1.16	<0.001	<0.001
TG, mmol/L	1.69±1.14	1.48±0.74	<0.001	1.96±1.48	1.80±1.36	<0.001	<0.001
HDL-C, mmol/L	1.09±0.30	1.10±0.31	0.304	1.05±0.28	1.03±0.28	0.153	<0.001
LDL-C, mmol/L	2.41±1.04	2.29±0.86	0.003	2.70±1.06	2.51±1.07	<0.001	<0.001
Non-HDL-C, mmol/L	2.92±1.10	2.73±0.92	<0.001	3.37±1.57	3.10±1.10	<0.001	<0.001
WBC, ×10 ⁹ /L	5.87±1.46	6.65±4.04	<0.001	6.70±13.03	7.24±1.98	0.165	<0.001
Neutrophils, ×10 ⁹ /L	3.32±0.95	4.61±1.28	<0.001	3.70±1.05	5.11±1.56	<0.001	<0.001
Lymphocytes, ×10 ⁹ /L	1.99±0.57	1.36±0.38	<0.001	2.13±0.59	1.47±0.45	<0.001	<0.001
NLR	1.73±0.45	3.54±1.15	<0.001	1.79±0.45	3.71±1.75	<0.001	<0.001
hsCRP, mg/L	0.70±0.33	0.71±0.34	0.398	3.68±2.94	5.03±3.93	<0.001	<0.001
LVEF, %	64.29±7.32	64.39±7.22	0.738	63.72±7.91	62.77±8.71	0.001	<0.001
Medications							
Statins	2004 (64.7)	551 (68.6)	0.043	1523 (55.0)	694 (59.8)	0.006	<0.001
Aspirin	1865 (60.2)	506 (63.0)	0.163	1426 (51.5)	634 (54.7)	0.080	<0.001
ACEIs/ARBs	543 (17.5)	146 (18.2)	0.709	410 (14.8)	205 (17.7)	0.028	0.014
β-blocker	1090 (35.2)	297 (37.0)	0.370	819 (29.6)	365 (31.5)	0.261	<0.001
CCB	437 (14.1)	123 (15.3)	0.418	362 (13.1)	181 (15.6)	0.042	0.138

Note: Values are expressed as mean ± standard deviation or n (%).

Abbreviations: NLR, neutrophil to lymphocyte ratio; hsCRP, high-sensitivity C-reactive protein; BMI, body mass index; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

listed in [Table 3](#). Patients with Q3 or Q4 of hsCRP or Q4 of NLR had significantly higher risk of MACCEs (adjusted HR, 1.29; 95% CI, 1.02–1.64; adjusted HR, 1.38; 95% CI, 1.09–1.74; adjusted HR, 1.36; 95% CI, 1.09–1.71; respectively, all $P < 0.05$) after adjusting confounding factors including age, male sex, diabetes, hypertension, previous CABG, previous stroke, creatinine, TG, LVEF, statins, and aspirin. RCS analysis suggested that there was a linear relationship of hsCRP and NLR with MACCEs after adjusting confounding factors (both P for non-linearity >0.05) ([Supplementary Figure 1](#)).

Association of 4 Concordance/Discordance Groups According to Low or High NLR and hsCRP Levels with Adverse Clinical Events

Patients in the concordant high /high group had the highest incidence of MACCEs, CV death, non-fatal stroke, and unplanned revascularization during follow-up. Meanwhile, no significant difference was observed with regard to the incidence of non-fatal MI across four risk groups ([Figure 3](#)).

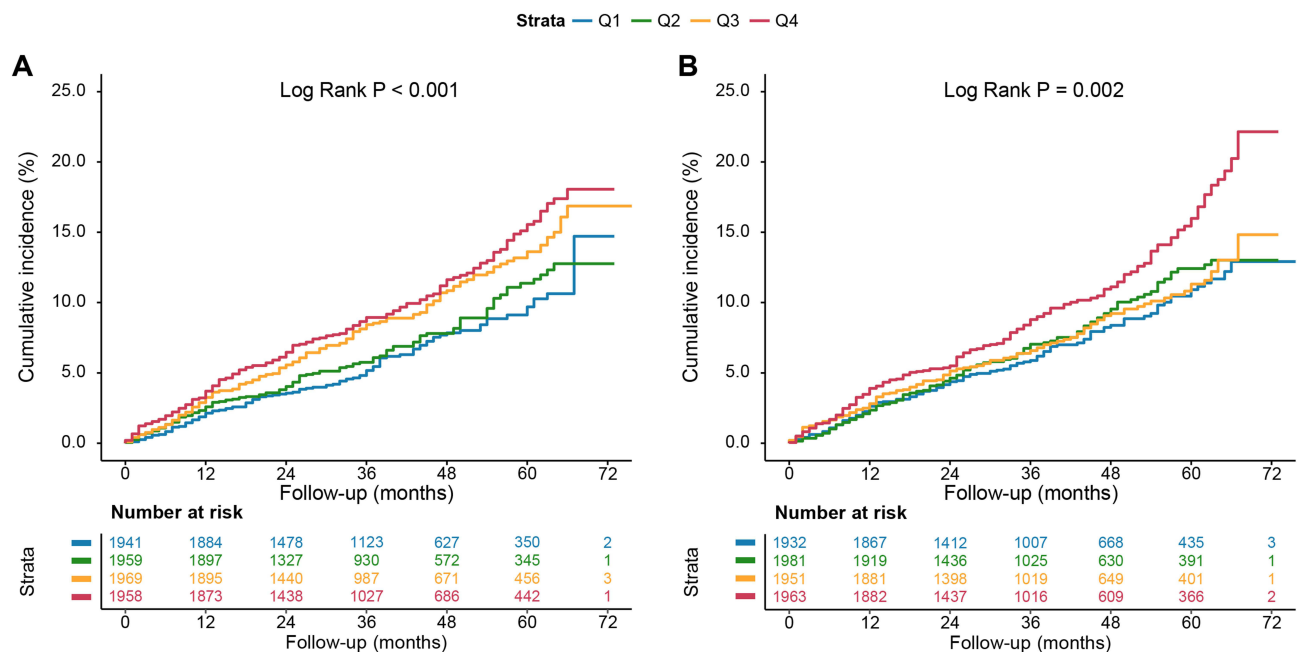


Figure 2 Kaplan–Meier (KM) curves for MACCEs according to different inflammatory biomarkers levels (A) KM curves for MACCEs according to hsCRP levels; (B) KM curves for MACCEs according to NLR levels. MACCEs were defined as a composite of CV death, non-fatal MI, non-fatal stroke, and unplanned revascularization.

Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular events; CV death, cardiovascular death; MI, myocardial infarction; NLR, neutrophil to lymphocyte ratio; hsCRP, high-sensitivity C-reactive protein.

Univariable Cox regression analysis showed that patients in the high/low, low/high, and high/high groups encountered a 42%, 45%, and 87% increase in MACCE risk, respectively, compared to the reference group (the low/low group; all $P < 0.05$, Table 3). Consistently, in the fully adjusted model, the adjusted HRs for MACCEs were 1.39 (95% CI, 1.05–1.84), 1.31 (95% CI, 1.08–1.59), and 1.57 (95% CI, 1.25–1.98) when NLR and hsCRP were elevated discordantly or

Table 3 Univariable and Multivariable Cox Proportional Hazard Analyses for MACCEs

	Events/Totals	Univariable Analysis		Multivariable Analysis*	
		HR (95% CI)	P value	HR (95% CI)	P value
hsCRP quartiles	624/7827				
Q1, <0.72	121/1941	Reference	NA	Reference	NA
Q2, ≥0.72–1.30	129/1959	1.12 (0.87–1.44)	0.367	1.08 (0.84–1.38)	0.554
Q3, ≥1.30–2.63	178/1969	1.45 (1.15–1.83)	0.002	1.29 (1.02–1.64)	0.031
Q4, ≥2.63	196/1958	1.61 (1.28–2.01)	<0.001	1.38 (1.09–1.74)	0.007
NLR quartiles	624/7827				
Q1, <1.54	135/1932	Reference	NA	Reference	NA
Q2, ≥1.54–1.99	148/1981	1.10 (0.87–1.39)	0.438	1.07 (0.85–1.36)	0.549
Q3, ≥1.99–2.62	146/1951	1.10 (0.87–1.38)	0.446	1.06 (0.84–1.35)	0.613
Q4, ≥2.62	195/1963	1.48 (1.19–1.84)	<0.001	1.36 (1.09–1.71)	0.007
NLR/hsCRP[†]	624/7827				
Low/low	183/3097	Reference	NA	Reference	NA
High/low	67/803	1.42 (1.08–1.88)	0.013	1.39 (1.05–1.84)	0.022
Low/high	246/2767	1.45 (1.20–1.75)	<0.001	1.31 (1.08–1.59)	0.007
High/high	128/1160	1.87 (1.49–2.34)	<0.001	1.57 (1.25–1.98)	<0.001

Notes: *Models adjusted for age, male sex, diabetes, hypertension, previous CABG, previous stroke, creatinine, TG, LVEF, statins use, and aspirin use. [†]P for trend between combined levels of NLR and hsCRP and MACCE <0.001.

Abbreviations: MACCEs, major adverse cardiac and cerebrovascular events; HR, hazard ratio; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; NLR, neutrophil to lymphocyte ratio; NA, not applicable.

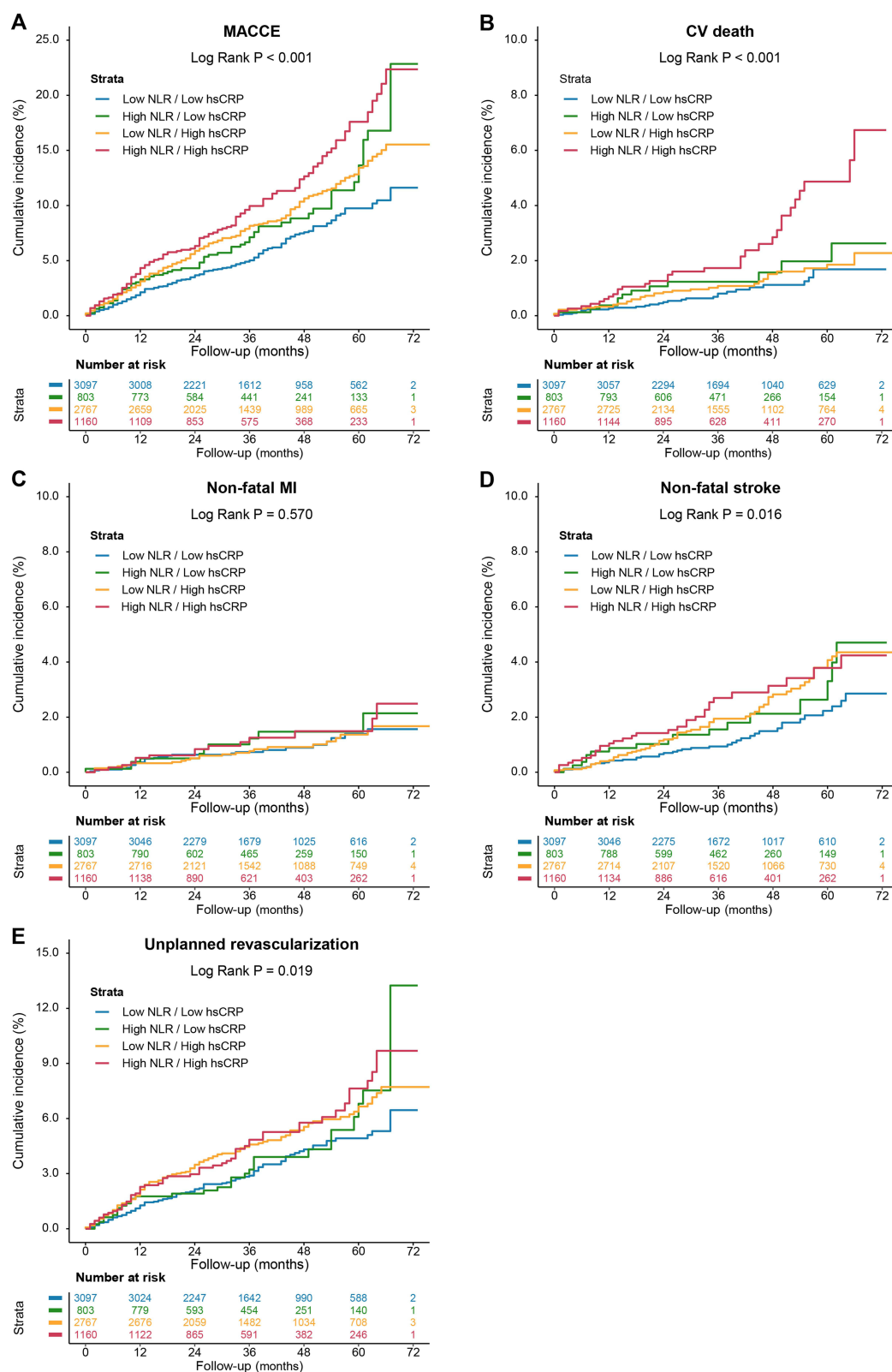


Figure 3 Kaplan-Meier (KM) curves for adverse clinical events according to 4 concordance/discordance groups by NLR and hsCRP levels. KM curves for MACCEs (A), CV death (B), non-fatal MI (C), non-fatal stroke (D), and unplanned revascularization (E) according to 4 concordance/discordance groups by NLR and hsCRP levels. MACCEs were defined as a composite of CV death, non-fatal MI, non-fatal stroke, and unplanned revascularization.

Abbreviations: NLR, neutrophil to lymphocyte ratio; hsCRP, high-sensitivity C-reactive protein; MACCE, major adverse cardiovascular and cerebrovascular events; CV, cardiovascular; MI, myocardial infarction.

concordantly, respectively, compared with the reference group (all $P < 0.05$) ([Supplementary Table 2](#)). In addition, multivariable Cox proportional hazard analysis revealed that patients with concordant elevations of NLR and hsCRP had the highest risk of MACCEs (P for trend <0.001). Cox regression analyses for secondary endpoints are listed in the [Supplementary Table 3](#). NLR and hsCRP elevated concordantly were associated with a 1.73-fold (95% CI, 1.02–2.92), 1.72-fold (95% CI, 1.07–2.76), and 1.45-fold (95% CI, 1.05–2.00) higher risk for CV death, non-fatal stroke, and unplanned revascularization, respectively, compared to the reference group (all $P < 0.05$).

Sensitivity, Subgroup and Mediation Analyses

In an exploratory step, the association of 4 concordance/discordance groups using hsCRP guideline-guided target cutoffs of 2 mg/L with the risk of MACCEs was estimated to test the robustness of our findings. As a result, in fully adjusted models, patients with discordantly increased NLR levels were still at a 1.30-fold higher risk of MACCE (95% CI, 1.03–1.64) ([Supplementary Table 4](#)).

Moreover, As illustrated in [Supplementary Tables 5](#) and [6](#), subgroup analyses demonstrated that the association between four risk groups and MACCEs remained consistent regardless of age (age ≥ 65 years or age < 65 years), sex (male or female), BMI (BMI ≥ 25 kg/m² or BMI < 25 kg/m²), diabetes (with or without diabetes), and hypertension (with or without hypertension) in both crude and fully adjusted models (all P for interaction >0.05).

In mediation analyses ([Supplementary Table 7](#)), NLR accounted for 13.1% (95% CI, 1.5%–42.0%, $P = 0.020$) of the associations between hsCRP and MACCEs. Besides, hsCRP also played a significant mediating role in the associations of NLR with MACCEs (proportions mediated, 17.1%; 95% CI, 4.0%–60.0%, $P = 0.008$).

Discussion

This observational study including large-scale secondary prevention cohort of CAD participants demonstrated that systemic inflammation assessed by elevated NLR levels was strongly associated with an increased risk for MACCEs during long-term follow-up. NLR levels are significantly but modestly correlated with hsCRP levels, and the discordance existed in more than 10% of patients with stable CAD. Discordantly elevated NLR levels were associated with a higher risk of MACCEs in patients with CAD during follow-up. Meanwhile, patients could encounter an increased risk of CV death and non-fatal stroke only when NLR and hsCRP increased concordantly. Specifically, the risk for adverse events may underestimate or overestimate when using hsCRP alone. To our knowledge, this study is the first comparing the effectiveness of NLR and hsCRP to predict the risk of adverse clinical events in patients with stable CAD, and our findings suggested a promising clinical significance for NLR as a goal of inflammatory risk management.

Plasma TC levels in many resource-rich populations have been in steady decline in response to lifestyle interventions and pharmacological treatments by targeting LDL-C.¹⁵ However, despite such efforts, CV events continue to occur frequently, even among subjects with controlled LDL-C.^{16,17} In the recent FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trial using evolocumab, a PCSK9 inhibitor, for secondary prevention after ACS, composite event rates during the median follow-up of 26 months remained at 9.8% in the evolocumab group despite an achieved median LDL-C of 0.78 mmol/L.¹⁷ Although current evidence supports aggressively reducing LDL-C to reduce CV events, further therapeutic strategies may be needed to appropriately reduce remaining CV risk. And systemic inflammation is one of the most mainly focused risk factors among residual CV risk.^{1,5} In secondary prevention of stable atherosclerotic vascular disease, extensive studies demonstrated that hsCRP is also informative and has a positive relationship with adverse cardiovascular events such as MI, revascularization, stroke, heart failure, and mortality.^{1,2,18} Similarly, our findings also indicated that patients with the higher hsCRP levels encountered increased risk of MACCEs compared to those with the lowest hsCRP level during follow-up. In the FOURIER trial, participants with the highest hsCRP levels had the highest event rates and, in turn, the greatest absolute risk reductions.² Supporting this clinical observation, intravascular ultrasonography demonstrated on-statin reductions in hsCRP are significantly associated with the rate of plaque progression after adjusting for changes in lipids.¹⁹ These studies support hsCRP as a reliable biomarker to assess inflammatory risk, and potential biomarker to guide-related therapies.

Although the role of hsCRP as an inflammatory biomarker has been widely studied, contemporary studies have also increased awareness of a simple biomarker that is widely and readily available to the clinical community, such as NLR.^{8,9} Observational studies have suggested that high NLR levels were associated with increased atherosclerotic plaque vulnerability and lesion

severity.^{10,20} Besides, previous studies have demonstrated baseline NLR independently predict future adverse events and CV death after adjusting confounding factors.^{21–23} Of note, a recent analysis of five large contemporary trials, including the CANTOS trial, studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE)-1, SPIRE-2, and Cardiovascular Inflammation Reduction Trial, demonstrated that the association between NLR and clinical outcomes remained significant even after adjusting for hsCRP. Meanwhile, previous studies have reported that NLR levels were modestly correlated with hsCRP levels,^{9,22} which was also observed in this study. Collectively, these observations convey the information that NLR, as an inflammatory biomarker, has important prognostic value and provides additional information on the nature of the inflammatory process, which is not mirrored by hsCRP or cytokines.⁹ And our study provided additional information to support previous research, indicating the clinical significance of NLR for predicting the risk of adverse events in CAD patients.

There are several potential mechanisms for the positive association between NLR and poor prognosis. First, activated neutrophils secrete inflammatory mediators. These molecules could initiate atherosclerosis and promote plaque progression by upregulating inflammatory response, myeloid cell recruitment, oxidative stress, and foam cell formation.^{24,25} In addition, the presence of neutrophils in the arterial intima was positively associated with traits of plaque instability in humans and mice.²⁶ Activated neutrophils release neutrophil extracellular traps (NETs) containing cytotoxic histone H4 and matrix metalloproteinases eventually resulting in the fibrous cap thinning.²⁴ Furthermore, lymphopenia may occur in response to an increase level of cortisol, catecholamines, and proinflammatory cytokines.^{27,28} Besides, lymphocyte apoptosis was shown to be present in atherosclerotic plaques and becomes increasingly frequent with the progression and destabilization of the atherosclerotic lesion.²⁹ The redistribution of T cells from the circulation to lymphoid tissues potentially exacerbate lymphopenia, which could promote compensatory proliferation of antigen-experienced T cells, further resulting in risk of CV events.^{30,31}

In this study, we adopted discordance analysis to compare the effectiveness of NLR and hsCRP levels for the prediction of CAD prognosis. Although the C-statistics have been widely used to evaluate the discriminative performance and could identify diseased patients by sensitivity and specificity, it might be suboptimal and could mistakenly exclude pivotal risk factors. Meanwhile, the improvement in C-statistics by adding new risk factors to the clinical risk models might be small, despite statistically significant.³² By contrast, discordance analysis mainly focused on the clinical consequences, rather than the prediction accuracy. This method is a new approach,^{33,34} which could discriminate additional positive cases and help the clinicians to understand the consequences of NLR through the disagreements between the NLR and hsCRP levels. In this study, there were more than 10% of patients exhibiting discordant elevation in NLR levels who were also at higher inflammatory risk which was underestimated by hsCRP alone. Since previous research has demonstrated that NLR levels markedly decreased during anti-inflammatory treatment with canakinumab,⁹ future prospective studies are also warranted to examine whether monitoring anti-inflammatory treatment response by targets of NLR levels could further reduce CV risks among CAD patients. Furthermore, in the present study, reduced rates of aspirin and statins use were observed in patients experiencing MACCE. According to current guideline, patients with stable CAD could benefit from adequate therapy for secondary prevention (such as aspirin and statins).³⁵ Aspirin acts via irreversible inhibition of platelet cyclooxygenase-1 and thus thromboxane production, and current evidence suggests a daily low-dose aspirin for the prevention of ischemic events in CAD patients with or without a history of MI.^{36,37} Consistently, in this study, univariable Cox proportional hazard model shown that aspirin use and statins use were both inversely associated with the risk of MACCE. And after multivariable adjustment including aspirin use and statins use, high NLR levels remained to predict MACCE in CAD patients, even in those with low hsCRP levels, indicating the association of NLR and hsCRP with risk of MACCE independent of medications for secondary prevention.

Clinical Translations

This study with a sizeable sample size confirmed that increased levels were associated with increased risk of adverse clinical events in CAD populations, even in those with low hsCRP levels. The CANTOS trial illustrated that participants who achieved on-treatment hsCRP in the lowest tertile had a 29% reduction in CV events, whereas participants with on-canakinumab hsCRP in the highest tertile had comparable outcomes with the placebo group.³ The findings support hsCRP as a potential marker of the adequacy of relative therapies. Meanwhile, a post-hoc analysis of the CANTOS trial showed that canakinumab significantly reduced the NLR in a dose-dependent manner, mimicking that for CRP and IL-6.⁹ Since there was an increased risk of adverse events in patients with low hsCRP levels who had high NLR levels, patients

could benefit from anti-inflammatory therapies by targeting both NLR and hsCRP levels. Further prospective studies are needed to investigate such hypothesis.

Study Limitations

Several limitations of this study need to be addressed. First, due to the nature of observational study design, potential confounding factors could not be fully eradicated.^{38,39} Second, information on hsCRP and NLR was not available during follow-up, which possibly provide incremental value for prediction of adverse clinical events. Third, this study only included Chinese patients, and further studies are warranted among individuals from other ethnicities. Fourth, per observation study design, the effect of pharmacological treatments on CV outcomes by targeting NLR levels could not be determined in this study. Further prospective studies are needed to investigate the effect of pharmacological treatments. Fifth, the mechanism between NLR and events remained unclear. Further mechanistic studies aiming to investigate the association between NLR and events are needed.

Conclusion

This study demonstrated discordantly elevated NLR levels were associated with a greater risk of adverse clinical events in patients with stable CAD, suggesting a potential clinical significance for NLR as a goal of inflammatory risk management.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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