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FULL RESEARCH PAPER
Coronary artery disease

Association of neutrophil-to-lymphocyte ratio with clinical outcomes after percutaneous coronary intervention

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See the editorial comment for this article 'Inflammation in the spotlight: neutrophil-to-lymphocyte ratio takes centre stage in atherosclerotic cardiovascular disease', by A. Laino *et al.*, https://doi.org/10.1093/eurjpc/zwaf606.

Aims Inflammation contributes significantly to coronary artery disease (CAD). The neutrophil-to-lymphocyte ratio (NLR) has emerged as a readily available biomarker reflecting both inflammatory and immune cells' activity, potentially enhancing risk stratification of patients with CAD. This study evaluates the clinical impact of baseline NLR in patients undergoing percutaneous coronary intervention (PCI) for both chronic coronary syndrome and acute coronary syndrome (ACS).

Methods and results We conducted a retrospective analysis of patients undergoing PCI at Mount Sinai Hospital between 2012 and 2022. Patients were stratified into NLR quartiles and outcomes were analysed using Cox regression models. The primary endpoint was major adverse cardiovascular events (MACEs) at 1-year follow-up, including all-cause death, myocardial infarction (MI), and stroke. A total of 7287 patients were included in the study. Age, male sex, comorbidities, high-sensitivity C-reactive protein, and complexity of PCI tended to be higher in the highest NLR quartiles. At 1 year, MACE incidence increased across NLR quartiles, from 5.1% (1st quartile) to 9.3% (4th quartile) (P for trend = 0.004). Compared with the 1st quartile, the 4th NLR quartile (NLR > 5.0) was associated with increased adjusted risks of MACE [adjusted hazard ratio (adjHR) 1.52, 95% CI 1.12–2.05], all-cause death (adjHR 1.71, 95% CI 1.10–2.65), MI (adjHR 1.53, 95% CI 1.00–2.35), and bleeding (adjHR 2.01, 95% CI 1.50–2.70). Ischaemic risk associated with high NLR was more pronounced in patients presenting with ACS and chronic kidney disease (CKD).

Conclusion Baseline NLR is associated with adverse cardiovascular outcomes in CAD patients undergoing PCI. Assessment of NLR could enhance risk stratification particularly in patients with ACS and CKD.

Lay summary This study found that a simple blood marker—the neutrophil-to-lymphocyte ratio (NLR)—can help predict the risk of heart attack, death, and bleeding in patients undergoing stent procedures for coronary artery disease.

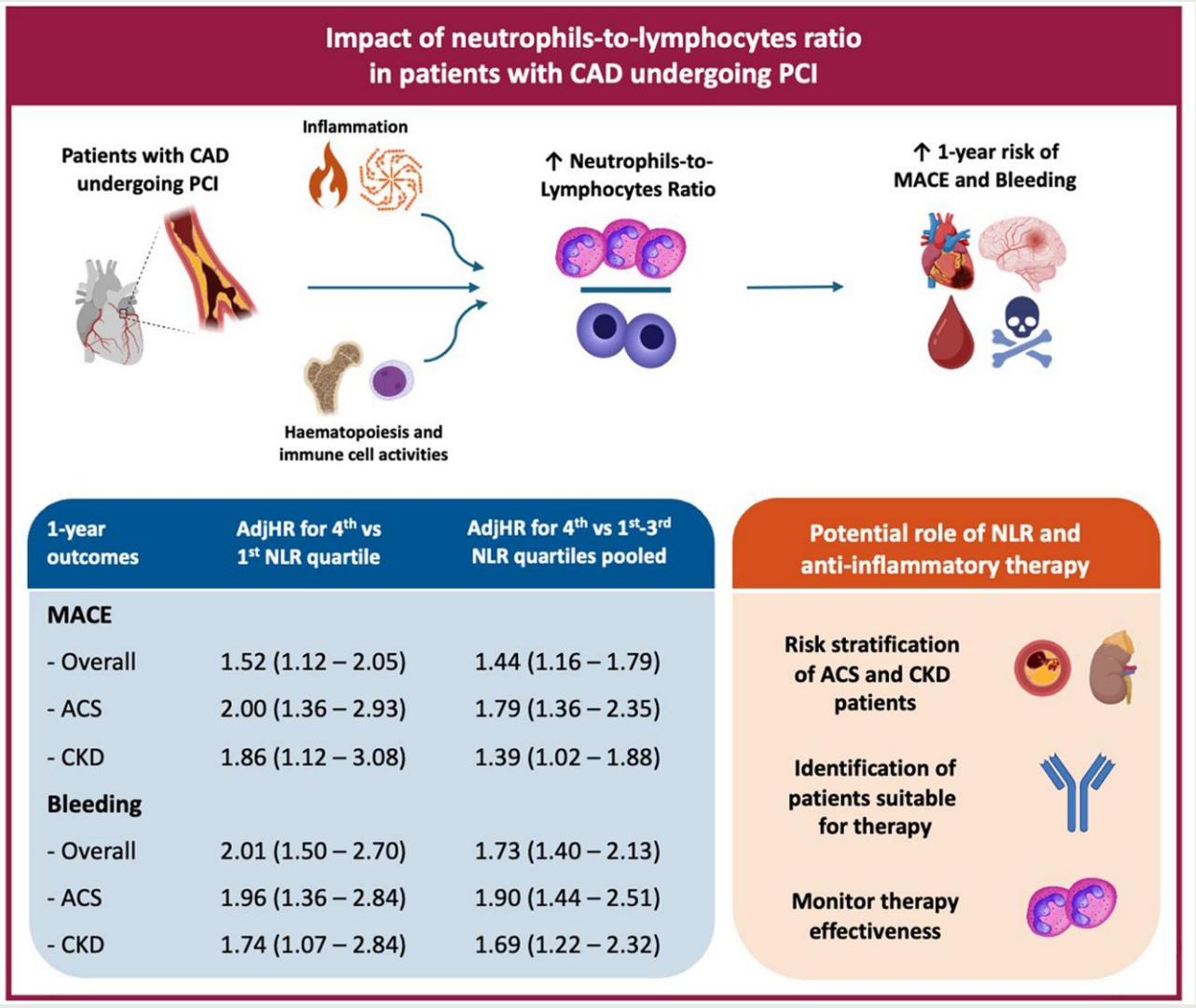
- Patients with higher NLR levels before their procedure had a significantly increased risk of death, heart attack, and major bleeding within 1 year, particularly those presenting with acute chest pain or renal disease.
- Neutrophil-to-lymphocyte ratio could be a low-cost, widely available tool to improve risk assessment and guide new therapies targeting inflammation in patients with coronary artery disease.

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Graphical Abstract



Keywords Inflammation • Coronary artery disease • Percutaneous coronary intervention • Acute coronary syndrome • Chronic kidney disease • Neutrophil-to-lymphocyte ratio

Introduction

Inflammation has been shown to play a pivotal role in coronary artery disease (CAD) and atherosclerosis progression to the extent that it is now considered an emerging cardiovascular risk factor.[1] Acute ischaemic insults such as myocardial infarction (MI) provoke an immediate intense inflammatory response, causing more severe reperfusion injury and unfavourable left ventricular remodeling.[2] Chronic accumulation of cholesterol and immune cells within the plaque stimulates low-grade activation of the cytokines cascade, which has been associated with worse cardiovascular outcomes, even in patients with optimally managed cholesterol levels.[3,4] In this framework, interleukin-1 (IL-1) and interleukin-6 (IL-6) are upstream signal regulators that can be pharmacologically targeted, whereas acute-phase proteins serve as downstream biomarkers of the inflammatory response.[5] Along with high-sensitivity C-reactive protein (hsCRP), the neutrophil-to-lymphocyte ratio (NLR) has recently emerged as an inexpensive and readily available biomarker that may further inform residual risk stratification, reflecting the activity of inflammatory and immune cells.[6,7] The use of NLR relies on large observational studies showing that the absolute neutrophil and lymphocyte counts are positively and negatively—respectively—associated with worse cardiovascular outcomes.[8] Neutrophil-to-lymphocyte ratio is more accurate than absolute counts and has been tested in different clinical settings, including acute coronary syndrome (ACS), diabetes, heart failure, and stroke.[9] In patients with recent MI or chronic kidney disease (CKD), on-treatment reduction of NLR and hsCRP has been observed following anti-inflammatory therapy, suggesting a potential disruption of multiple atherogenic inflammatory pathways, including those mediated by the myeloid cell compartment.[10,11] These high-risk subsets of patients, characterized by elevated atherothrombotic and inflammatory burden, are currently the focus of ongoing clinical trials testing anti-cytokine therapies (NCT05021835, NCT06118281). Recently, a large pooled analysis

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of five randomized clinical trials, encompassing both primary and secondary prevention and including more than 60 000 patients, confirmed that NLR is an independent predictor of cardiovascular events and mortality.[11] Given its potential role in risk stratification of patients with established CAD, we aimed to evaluate the clinical impact of baseline NLR in a large contemporary, real-world cohort of patients undergoing percutaneous coronary intervention (PCI), further stratified by both clinical presentation and presence of CKD.

Methods

Study population

We conducted a retrospective analysis of the Mount Sinai Hospital (New York, NY, USA) PCI registry, which includes baseline and procedural data extracted from the electronic health record system at the time of PCI, as well as clinical outcomes prospectively collected by a dedicated team up to 1 year after the index procedure through records, visits, and phone calls. All clinical events are independently adjudicated and the registry is approved by the local institutional review board.

All patients undergoing PCI between 1 January 2012 and 31 December 2022 with available differential blood count performed within 24 h before or after the index procedure were evaluated for inclusion in the analysis. We excluded patients who were deemed to have active haematological or infective diseases at the time of PCI, as well as patients presenting with extremely low or high lymphocyte ($<0.5 \times 10^3/\mu L$ and $>10 \times 10^3/\mu L$, respectively) or neutrophil counts ($<1 \times 10^3/\mu L$ and $>20 \times 10^3/\mu L$, respectively) and those with hsCRP above 10 mg/L, a threshold that has been suggested to discriminate patients with infectious process or other acute phase response.[7]

Clinical endpoints

The primary endpoint of the analysis was major adverse cardiovascular events (MACE), defined as the composite of all-cause death, MI, or stroke at 1-year follow-up. Secondary endpoints included the individual components of primary endpoint, as well as target vessel revascularization (TVR), stent thrombosis, and any bleeding at 1-year follow-up. We also assessed acute kidney injury (AKI) defined as post-procedure rise of serum creatinine of ≥0.3 mg/dL or ≥50% from the baseline.

Statistical analysis

The NLR was calculated using the following formula: plasma neutrophil count ($\times 10^9$/L) / plasma lymphocyte count ($\times 10^9$/L). Quartiles of NLR were derived in the overall population, and patients were stratified accordingly. The risk of 12-month adverse events, using the lowest NLR quartile as a reference, was assessed. Clinical outcomes were analysed using the Kaplan–Meier (KM) method and compared using the log-rank test. Risk estimates are provided as hazard ratios (HRs) with 95% confidence intervals (CIs). Multivariable adjustment was performed using the Cox regression method, including the following adjustment variables: age, sex, race, smoking status, anaemia, CKD, atrial fibrillation, cholesterol, multivessel disease, baseline hsCRP ≥ 2, and clinical presentation. Analyses were repeated after stratifying patients according to the two pre-specified subgroups of interest: (i) ACS (consisting of patients presenting with unstable angina, non-ST-segment elevation myocardial infarction [NSTEMI], or ST-segment elevation myocardial infarction [STEMI]) vs. chronic coronary syndrome (CCS) and (ii) presence of CKD (defined as baseline estimated glomerular filtrate rate [eGFR] < 60 mL/min/1.73 m^2. We also repeated the analysis using subgroup-specific cut-offs). Categorical data are presented as numbers and percentages and compared using the χ^2 test. Continuous data are presented as means ± standard deviations and compared using the independent-samples *t*-test. *P*-values of <0.05 were considered statistically significant. All statistical analyses were conducted at the Icahn School of Medicine at Mount Sinai, New York, NY, using Stata software version 18.0 (StataCorp) and SAS version 9.4 (SAS Institute, Inc.).

Results

A total of 7287 patients undergoing PCI between 2012 and 2022 were included in the analysis and stratified according to NLR quartiles (1st quartile, NLR < 2.1; 2nd quartile, 2.1 ≤ NLR < 3.2; 3rd quartile, 3.2 ≤ NLR ≤ 5.0; 4th quartile, NLR > 5.0). A detailed patient flow diagram and the distribution of NLR in the study population are presented in Supplementary material online, *Figures S1* and *S2*. Age, male sex, and comorbidities such as CKD, lung disease, peripheral artery disease, and atrial fibrillation increased stepwise across the NLR quartiles (*Table 1*). Conversely, smoking, diabetes, triglycerides, and LDL cholesterol levels were lower in patients with high NLR. Caucasian patients were predominantly in the highest NLR quartiles, while African Americans were mainly in the lowest; Hispanics were more evenly distributed. Elevated hsCRP and complexity of PCI, as indicated by calcification, multivessel disease, use of rotational atherectomy, and mechanical circulatory support, were greater in higher NLR quartiles. Overall, there were no significant differences in the use of statins, beta-blockers, and more potent P2Y12 inhibitors.

Clinical endpoints

At 1-year follow-up, incidence of primary endpoint MACE increased across NLR quartiles, ranging from 5.1% in patients in the 1st quartile to 9.3% in the 4th quartile (*P* for trend = 0.004) (*Figure 1A*). As compared with the lowest quartile, patients with NLR > 5.0 had the highest risk of MACE (HR 1.91, 95% CI 1.46–2.51), which remained statistically significant after multivariable adjustment [adjusted hazard ratio (adjHR) 1.52, 95% CI 1.12–2.05] (*Figure 2*) The 4th NLR quartile was also associated with significantly higher 1-year risk of all-cause death (5.5% vs. 2.2%, HR 2.60, 95% CI 1.76–3.85; adjHR 1.71, 95% CI 1.10–2.65), MI (4.1% vs. 2.8%, HR 1.54, 95% CI 1.04–2.27; adjHR 1.53, 95% CI 1.00–2.35), and bleeding (9.4% vs. 4.8%, HR 2.23, 95% CI 1.70–2.93; adjHR 2.01, 95% CI 1.50–2.70) (*Table 2*, *Figure 2*, and *Figure 3A*). There were no statistically significant differences across the groups with regard to stroke, TVR, and stent thrombosis. NLR was also associated with an increased risk of post-procedure AKI (*P* for trend < 0.001), with patients in the 4th quartile experiencing the highest risks (11.2% vs. 4.8%, HR 2.48, 95% CI 1.90–3.26; adjHR 2.15, 95% CI 1.60–2.92) (*Table 2*).

Subgroup analysis according to clinical presentation (acute coronary syndrome vs. chronic coronary syndrome)

We performed a pre-specified analysis according to the clinical presentation: among the 7287 included patients, 3973 (55.2%) presented with ACS and 3228 (44.8%) with CCS. Patients were stratified using NLR cut-off derived in the overall population, and baseline characteristics are reported in Supplementary material online, *Tables S1* and *S2*. In general, ACS patients tended to be younger and had a lower burden of comorbidities but showed greater inflammatory activity. Within ACS, the prevalence of MI was higher in patients with NLR > 5.0 (STEMI 15.0%, NSTEMI 37.8%). In ACS, results were generally consistent with the primary analysis, showing a significant trend for MACE increase across NLR quartiles (*P* for trend < 0.001) and the highest risk in patients with NLR > 5.0 (adjHR 2.00, 95% CI 1.36–2.93), along with higher risk of all-cause death and MI as compared with the 1st quartile

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Table 1 Baseline clinical and procedural characteristics across neutrophil-to-lymphocyte ratio quartiles

	Overall $n = 7287$	1st quartile NLR < 2.1 $n = 1822$ (25.0%)	2nd quartile 2.1 ≤ NLR < 3.2 $n = 1824$ (25.0%)	3rd quartile 3.2 ≤ NLR ≤ 5.0 $n = 1826$ (25.1%)	4th quartile NLR > 5.0 $n = 1815$ (24.9%)	*P*-value
Patient characteristics						
Age, years	66.0 ± 12.1	62.9 ± 11.6	65.0 ± 11.8	66.9 ± 11.7	69.5 ± 12.4	<0.001
Female sex	2118 (29.1%)	575 (31.6%)	528 (29.0%)	524 (28.7%)	491 (27.1%)	0.027
Race/ethnicity						<0.001
Caucasian	3069 (47.7%)	580 (36.7%)	753 (47.2%)	831 (51.6%)	905 (54.9%)	
African American	789 (12.3%)	295 (18.7%)	166 (10.4%)	175 (10.9%)	153 (9.3%)	
Asian	954 (14.8%)	278 (17.6%)	294 (18.4%)	190 (11.8%)	192 (11.7%)	
Hispanic	1297 (20.2%)	325 (20.6%)	295 (18.5%)	359 (22.3%)	318 (19.3%)	
Others	324 (5.0%)	102 (6.5%)	88 (5.5%)	54 (3.4%)	80 (4.9%)	
Medical history						
Current smoker	1041 (14.3%)	336 (18.4%)	290 (15.9%)	234 (12.8%)	181 (10.0%)	<0.001
Family history of CAD	1462 (20.1%)	409 (22.4%)	404 (22.1%)	326 (17.9%)	323 (17.8%)	<0.001
Anaemia	2935 (40.9%)	651 (36.1%)	688 (38.3%)	756 (42.0%)	840 (47.4%)	<0.001
Diabetes mellitus	3478 (47.7%)	882 (48.4%)	873 (47.9%)	917 (50.2%)	806 (44.4%)	0.005
Hypertension	6603 (90.6%)	1610 (88.4%)	1663 (91.2%)	1670 (91.5%)	1660 (91.5%)	0.002
Hyperlipidaemia	6534 (89.7%)	1617 (88.7%)	1647 (90.3%)	1650 (90.4%)	1620 (89.3%)	0.294
Lung disease	535 (7.3%)	101 (5.5%)	125 (6.9%)	145 (7.9%)	164 (9.0%)	<0.001
Peripheral artery disease	764 (10.5%)	142 (7.8%)	189 (10.4%)	195 (10.7%)	238 (13.1%)	<0.001
Prior stroke	860 (11.8%)	189 (10.4%)	226 (12.4%)	210 (11.5%)	235 (12.9%)	0.085
Atrial fibrillation	706 (9.7%)	119 (6.5%)	136 (7.5%)	195 (10.7%)	256 (14.1%)	<0.001
Chronic kidney disease	2008 (27.6%)	333 (18.3%)	478 (26.2%)	544 (29.8%)	653 (36.0%)	<0.001
Dialysis	268 (3.7%)	36 (2.0%)	52 (2.9%)	70 (3.8%)	110 (6.1%)	<0.001
Prior MI	1906 (26.2%)	431 (23.7%)	473 (25.9%)	497 (27.2%)	505 (27.8%)	0.022
PCI presentation						
CCS	3226 (44.8%)	710 (39.3%)	758 (42.0%)	824 (45.7%)	936 (52.3%)	<0.001
ACS	3973 (55.3%)	1096 (60.7%)	1044 (57.9%)	979 (54.3%)	854 (47.7%)	<0.001
Unstable angina	2272 (31.6%)	692 (38.3%)	616 (34.2%)	560 (31.1%)	404 (22.6%)	<0.001
NSTEMI	1310 (18.2%)	319 (17.7%)	340 (18.9%)	328 (18.2%)	323 (18.0%)	0.821
STEMI	393 (5.5%)	85 (4.7%)	88 (4.9%)	91 (5.0%)	127 (7.1%)	0.004
Laboratory						
Serum creatinine, mg/dL	1.2 ± 1.1	1.1 ± 0.8	1.2 ± 1.0	1.3 ± 1.1	1.4 ± 1.3	<0.001
Haemoglobin, g/dL	12.9 ± 1.8	13.1 ± 1.7	13.1 ± 1.8	12.9 ± 1.8	12.7 ± 1.9	<0.001
Platelets, per mm^3	211.3 ± 76.6	212.9 ± 79.6	212.6 ± 79.5	211.4 ± 72.3	208.1 ± 74.6	0.216
Total cholesterol, mg/dL	143.3 ± 43.0	148.5 ± 42.5	145.4 ± 45.9	140.2 ± 40.4	138.6 ± 42.1	<0.001
Triglycerides, mg/dL	110.7 ± 92.7	121.5 ± 108.1	114.3 ± 83.3	109.2 ± 104.3	96.6 ± 65.9	<0.001
LDL, mg/dL	82.5 ± 34.2	86.3 ± 34.8	83.9 ± 34.0	80.7 ± 33.2	79.1 ± 34.1	<0.001
HDL, mg/dL	40.3 ± 12.3	39.7 ± 12.2	39.4 ± 11.7	40.4 ± 12.3	41.5 ± 12.9	<0.001
hsCRP, mg/L	2.8 ± 2.4	2.6 ± 2.3	2.9 ± 2.5	2.9 ± 2.4	3.0 ± 2.6	<0.001
Procedural characteristics						
Multivessel disease	4686 (64.3%)	1123 (61.6%)	1139 (62.4%)	1174 (64.3%)	1251 (68.9%)	<0.001
B2/C lesion	5215 (71.6%)	1267 (69.5%)	1288 (70.6%)	1299 (71.1%)	1362 (75.0%)	0.001
Calcification	1437 (19.8%)	254 (14.1%)	322 (17.7%)	377 (20.7%)	485 (26.8%)	<0.001
Bifurcation	1274 (17.5%)	291 (16.0%)	319 (17.5%)	319 (17.5%)	345 (19.0%)	0.121
Chronic total occlusion	460 (6.3%)	109 (6.0%)	104 (5.7%)	118 (6.5%)	129 (7.1%)	0.321
Total lesion length, mm	39.3 ± 33.5	36.5 ± 30.1	38.6 ± 33.3	39.5 ± 34.1	42.9 ± 35.9	<0.001
Rotational atherectomy	29 (0.4%)	216 (11.9%)	273 (15.0%)	306 (16.8%)	370 (20.5%)	<0.001
MCS	469 (6.5%)	65 (3.6%)	74 (4.1%)	130 (7.1%)	200 (11.0%)	<0.001
Discharge medication						
Aspirin	6748 (93.0%)	1716 (94.5%)	1721 (94.5%)	1677 (92.0%)	1634 (90.8%)	<0.001
Clopidogrel	4951 (68.2%)	1225 (67.5%)	1223 (67.1%)	1237 (67.9%)	1266 (70.4%)	0.143

Continued

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Table 1 *Continued*

	Overall $n = 7287$	1st quartile NLR < 2.1 $n = 1822$ (25.0%)	2nd quartile 2.1 ≤ NLR < 3.2 $n = 1824$ (25.0%)	3rd quartile 3.2 ≤ NLR ≤ 5.0 $n = 1826$ (25.1%)	4th quartile NLR > 5.0 $n = 1815$ (24.9%)	*P*-value
Prasugrel	744 (10.2%)	201 (11.1%)	201 (11.0%)	185 (10.2%)	157 (8.7%)	0.069
Ticagrelor	1480 (20.4%)	363 (20.0%)	383 (21.0%)	386 (21.2%)	348 (19.3%)	0.466
Oral anticoagulants	716 (9.9%)	129 (7.1%)	152 (8.4%)	194 (10.7%)	241 (13.5%)	<0.001
Statins	6907 (95.2%)	1724 (94.9%)	1738 (95.4%)	1737 (95.3%)	1708 (94.9%)	0.870
Beta blockers	5931 (81.7%)	1475 (81.2%)	1474 (80.9%)	1509 (82.8%)	1473 (81.9%)	0.453

NLR Quartile 1, 0.220 < NLR < 2.094; NLR Quartile 2, 2.094 < NLR < 3.154; NLR Quartile 3, 3.154 < NLR ≤ 5.000; and NLR Quartile 4, NLR > 5.000.
NLR, neutrophil-to-lymphocyte ratio; ACS, acute coronary syndrome; CAD, coronary artery disease; PCI, percutaneous coronary intervention; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; MCS, mechanical circulatory support; CCS, chronic coronary syndrome; hsCRP, high-sensitivity C-reactive protein.

(*Figure 1B* and *Figure 2*). Other clinical endpoints are reported in Supplementary material online, *Table S3*. In patients presenting with CCS, there were no statistically significant differences in the 1-year risk of MACE, death, MI, stroke, or TVR across quartiles (see Supplementary material online, *Table S4* and *Figure 1B*). Patients in the 4th quartile had the highest risk of bleeding, regardless of clinical presentation (*Figure 3B*).

Subgroup analysis according to presence of chronic kidney disease

Across the included patients, a total of 2008 (27.6%) had CKD (mean eGFR 40.8 ± 16.1 mL/min/1.73 m^2), and 268 (3.7%) were on dialysis. Baseline characteristics and clinical outcomes across NLR quartiles in patients with and without CKD are reported in Supplementary material online, *Tables S5–S8*. Chronic kidney disease patients exhibited a higher prevalence of cardiovascular risk factors, comorbidities, inflammation burden, and PCI complexity. However, these features were more uniformly distributed across NLR quartiles in CKD vs. non-CKD patients. The risk of MACE and all-cause death significantly increased with NLR quartiles in CKD (*P* for trend 0.012 and 0.002, respectively) but not in non-CKD patients. After adjustment, CKD patients with NLR > 5.0 compared with the 1st quartile had higher risk of MACE (adjHR 1.86, 95% CI 1.12–3.08) and all-cause death (adjHR 2.44, 95% CI 1.18–5.05) (*Figure 1C* and *Figure 2*). The risk of bleeding was augmented by NLR in both CKD and non-CKD patients (*Figure 3C*). Post-procedure AKI was high in CKD patients across all NLR quartiles, but it was significantly augmented by NLR in non-CKD patients (4th vs. 1st quartile: adjHR 2.80, 95% CI 1.85–4.31).

Secondary analyses

The results remained consistent when patients in the 4th NLR quartile were compared with the pooled 1st, 2nd, and 3rd quartiles in the overall population and in the pre-specified subgroups (see Supplementary material online, *Tables S9–S11* and *Figure 2*). When considered as a continuous variable in a multivariable model including hsCRP and all clinical covariates used for risk adjustment, NLR remained an independent predictor of 1-year MACE (HR per 1-unit increase 1.04; 95% CI 1.02–1.07; $P < 0.0001$). To further assess incremental prognostic value, likelihood ratio testing demonstrated that addition of NLR to a model including hsCRP and the full set of covariates significantly improved model fit (LR $\chi^2 = 12.25$; $P = 0.0005$). Finally, the results were largely unchanged when group-specific NLR quartile cut-offs were used for stratification, compared with cut-offs derived from the overall population.

Discussion

In this study, we investigated the impact of baseline NLR on clinical outcomes across >7000 CAD patients undergoing PCI. The main findings are as follows:

- At 1-year follow-up, the risk of MACE increased stepwise across NLR quartiles, with patients in the 4th quartile (NLR > 5.0) experiencing the highest risk; results remained statistically significant after multivariate adjustment and when NLR was analysed as a continuous variable.
- The excess of ischaemic risk associated with high NLR was more pronounced in patients presenting with ACS and CKD, mainly due to higher incidence of death or MI.
- Patients with high NLR had also a higher risk of bleeding, regardless of clinical presentation and CKD status.

Neutrophil-to-lymphocyte ratio as inflammatory biomarker

Assessment of inflammation in patients with CAD has a great importance for both cardiovascular risk stratification and decision-making regarding adjunctive therapy.[12] In the CANTOS trial, which tested the IL-1β inhibitor canakinumab for reduction of cardiovascular events in patients with a history of MI and inflammation, treatment effect was larger in those who had greater on-treatment reduction of hsCRP and IL-6, highlighting the importance of modulating the inflammation pathway but also the need for readily available markers for assessing treatment effectiveness.[10,13,14] Neutrophil-to-lymphocyte ratio is cheap and accessible and can be easily derived from a blood differential test. From a mechanistic perspective, neutrophils contribute to atherosclerotic plaque progression by promoting LDL deposition, oxidation, and foam cell formation and to plaque destabilization by releasing proteases, myeloperoxidase, and neutrophil extracellular traps (NETs), which stimulate inflammation and endothelial erosion.[15] Additionally, in patients suffering from MI, neutrophil activation results in acute oxidative burst and further myocardial damage.[2] While neutrophilia is more clearly associated with worse outcomes, lymphocytes play a composite role, with different subsets either accelerating or protecting against atherosclerosis.[2,16,17] During acute inflammatory states, for instance, activation of stress response is accompanied by lymphocytes'

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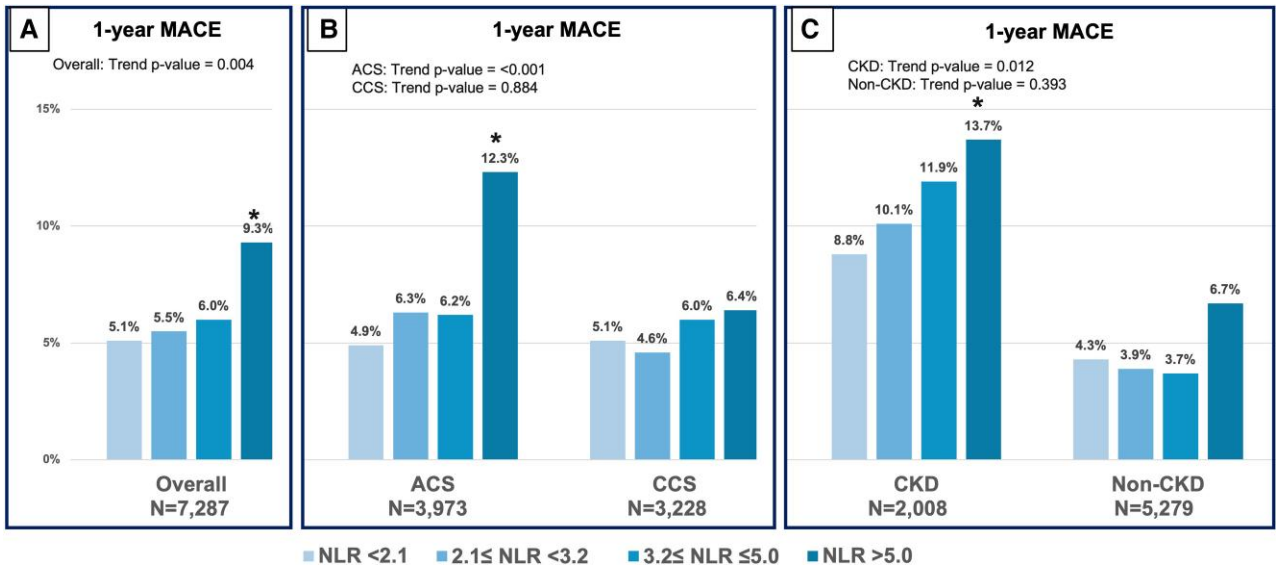


Figure 1 One-year incidence of major adverse cardiovascular event across quartiles of neutrophil-to-lymphocyte ratio in the overall population (*A*) and in patients stratified according to clinical presentation (*B*) and chronic kidney disease (*C*). *Denotes a statistically significant difference as compared with the 1st quartile. % are from KM analysis.

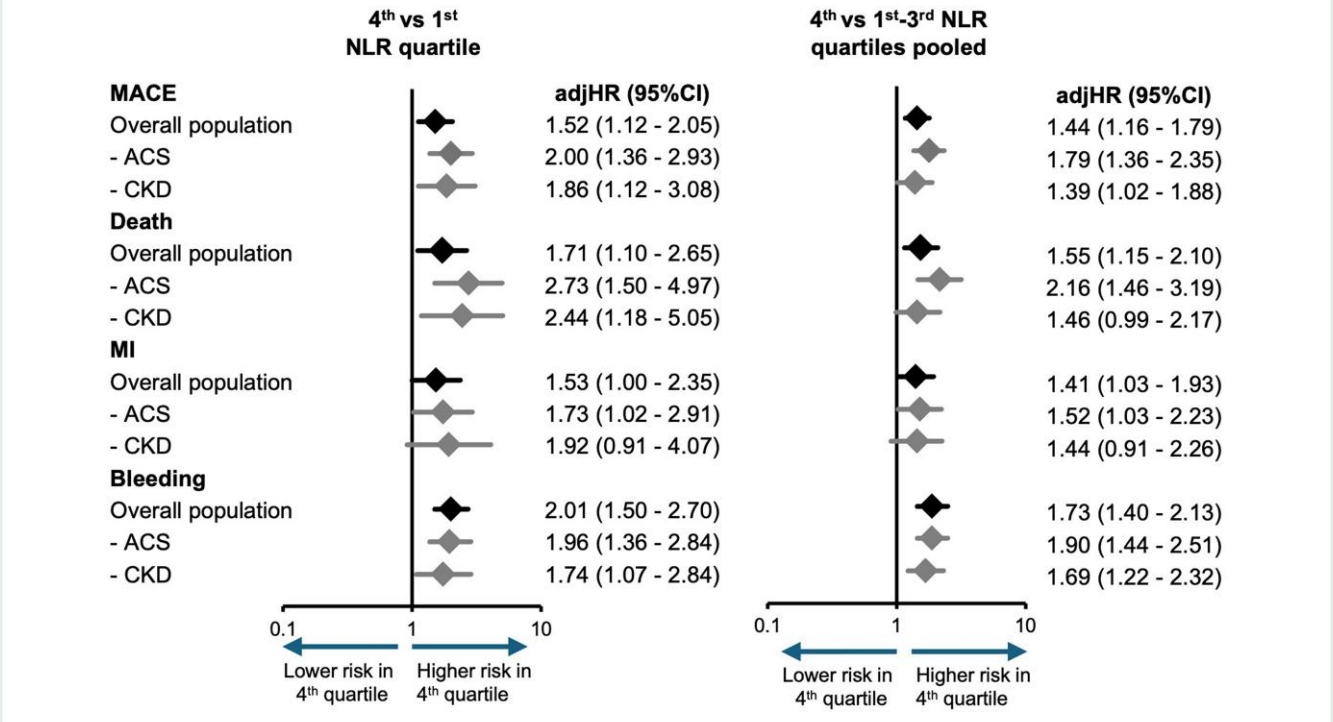


Figure 2 Adjusted hazard ratio for the risk of 1-year of major adverse cardiovascular event, death, myocardial infarction, and bleeding.

apoptosis and relative lymphopenia, which has been associated with worse clinical outcomes.[18,19] In this complex scenario, NLR has demonstrated to outperform absolute white cell count by integrating neutrophils and lymphocytes into a single biomarker reflecting the contributions of the innate inflammatory response and activity of bone marrow and immune cells.[11,16,20] In addition, the relative stability of NLR over time and its responsiveness to anti-inflammatory treatment, like the IL-1β inhibitor canakinumab or the IL-6 inhibitor ziltivekimab, make it a suitable candidate for both assessing residual inflammation and monitoring the effectiveness of anti-inflammatory therapy.[21]

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Table 2 Association between neutrophil-to-lymphocyte ratio and outcomes at 1 year after percutaneous coronary intervention in overall population

	No. of patients	No. of event (%)	HR (95% CI)	*P*-value	AHR† (95% CI)	*P*-value	Trend *P*-value
Death, MI, or stroke							
NLR 1st quartile	1822	80 (5.1%)	Ref.		Ref.		0.004
NLR 2nd quartile	1824	86 (5.5%)	1.08 (0.80–1.47)	0.616	1.05 (0.76–1.44)	0.786	
NLR 3rd quartile	1826	96 (6.0%)	1.20 (0.89–1.62)	0.224	1.10 (0.80–1.51)	0.543	
NLR 4th quartile	1815	147 (9.3%)	1.91 (1.46–2.51)	<0.001	1.52 (1.12–2.05)	0.006	
All-cause death							
NLR 1st quartile	1822	35 (2.2%)	Ref.		Ref.		0.001
NLR 2nd quartile	1824	31 (2.0%)	0.89 (0.55–1.44)	0.631	0.82 (0.49–1.37)	0.448	
NLR 3rd quartile	1826	59 (3.7%)	1.69 (1.11–2.57)	0.014	1.42 (0.91–2.24)	0.126	
NLR 4th quartile	1815	88 (5.5%)	2.60 (1.76–3.85)	<0.001	1.71 (1.10–2.65)	0.017	
MI							
NLR 1st quartile	1822	42 (2.8%)	Ref.		Ref.		0.133
NLR 2nd quartile	1824	53 (3.4%)	1.27 (0.85–1.90)	0.250	1.32 (0.85–2.03)	0.215	
NLR 3rd quartile	1826	39 (2.5%)	0.93 (0.60–1.44)	0.742	0.94 (0.59–1.50)	0.811	
NLR 4th quartile	1815	62 (4.1%)	1.54 (1.04–2.27)	0.031	1.53 (1.00–2.35)	0.050	
Stroke							
NLR 1st quartile	1822	7 (0.5%)	Ref.		Ref.		0.820
NLR 2nd quartile	1824	6 (0.4%)	0.86 (0.29–2.56)	0.785	0.72 (0.24–2.14)	0.550	
NLR 3rd quartile	1826	5 (0.3%)	0.72 (0.23–2.26)	0.570	0.56 (0.18–1.78)	0.324	
NLR 4th quartile	1815	11 (0.7%)	1.64 (0.63–4.22)	0.309	1.10 (0.41–2.96)	0.847	
Stent thrombosis							
NLR 1st quartile	1822	4 (0.2%)	Ref.		Ref.		1.000
NLR 2nd quartile	1824	5 (0.3%)	1.25 (0.34–4.66)	0.738	0.90 (0.22–3.61)	0.880	
NLR 3rd quartile	1826	7 (0.4%)	1.76 (0.51–6.01)	0.368	1.51 (0.44–5.24)	0.516	
NLR 4th quartile	1815	5 (0.3%)	1.29 (0.35–4.82)	0.700	0.82 (0.20–3.36)	0.779	
TVR							
NLR 1st quartile	1822	156 (10.1%)	Ref.		Ref.		0.490
NLR 2nd quartile	1824	171 (11.3%)	1.10 (0.88–1.36)	0.403	1.12 (0.89–1.41)	0.332	
NLR 3rd quartile	1826	140 (9.1%)	0.90 (0.71–1.12)	0.341	0.92 (0.72–1.17)	0.488	
NLR 4th quartile	1815	161 (10.9%)	1.07 (0.86–1.34)	0.525	1.17 (0.92–1.48)	0.205	
All bleeding							
NLR 1st quartile	1822	76 (4.3%)	Ref.		Ref.		<0.001
NLR 2nd quartile	1824	79 (4.5%)	1.04 (0.76–1.43)	0.803	1.03 (0.74–1.43)	0.870	
NLR 3rd quartile	1826	113 (6.3%)	1.49 (1.12–2.00)	0.007	1.42 (1.04–1.93)	0.026	
NLR 4th quartile	1815	166 (9.4%)	2.23 (1.70–2.93)	<0.001	2.01 (1.50–2.70)	<0.001	
AKI							
NLR 1st quartile	1822	81 (4.8%)	Ref.		Ref.		
NLR 2nd quartile	1824	99 (5.9%)	1.23 (0.91–1.66)	0.181	1.12 (0.81–1.56)	0.487	<0.001
NLR 3rd quartile	1826	141 (8.3%)	1.79 (1.35–2.38)	<0.001	1.62 (1.20–2.21)	0.002	
NLR 4th quartile	1815	187 (11.2%)	2.48 (1.90–3.26)	<0.001	2.15 (1.60–2.92)	<0.001	

The percentages mentioned above represent K-M rates at 12 months after index percutaneous coronary intervention procedure.
†Model adjusted for age, sex, race (Caucasian vs. others), smoking, anaemia, chronic kidney disease, atrial fibrillation, LDL, multivessel disease, baseline C-reactive protein ≥ 2, and clinical presentation.
NLR, neutrophil-to-lymphocyte ratio; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; TVR, target vessel revascularization; AKI, acute kidney injury defined by serum creatinine difference ≥ 0.3 mg/dL or ≥50%.

Neutrophil-to-lymphocyte ratio in patients undergoing percutaneous coronary intervention

In our study, we sought to investigate the impact of baseline NLR in patients with established CAD from a large, contemporary, Western cohort of patients undergoing PCI. We observed that patients in the 4th quartile of NLR, corresponding to NLR > 5.0, had a ≈50% increase of adjusted risk of 1-year MACE, mainly due to increased risk of death and MI. These findings are consistent with previous studies investigating the role of NLR in patients with established CAD.[8,20] Notably, NLR remained associated with increased risk after multivariate adjustment, and

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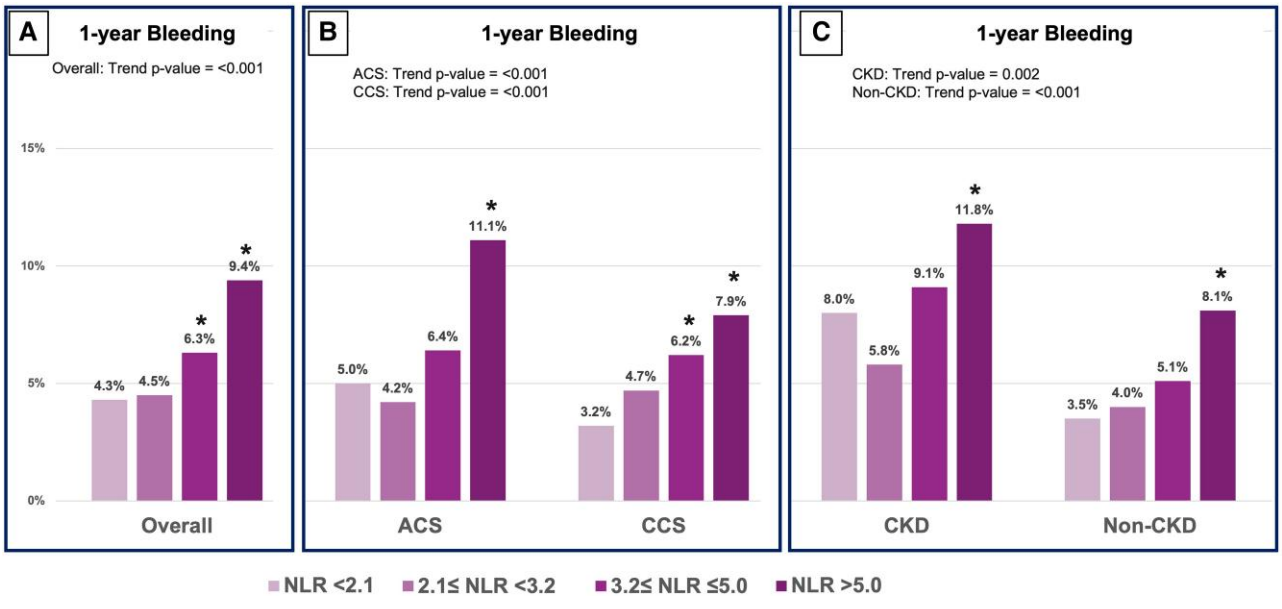


Figure 3 One-year incidence of bleeding across quartiles of neutrophil-to-lymphocyte ratio in the overall population (*A*) and in patients stratified according to clinical presentation (*B*) and chronic kidney disease (*C*). *Denotes a statistically significant difference as compared with the 1st quartile. % are from KM analysis.

likelihood ratio testing confirmed that the addition of NLR to a model including hsCRP and clinical covariates significantly improved model fit, supporting its role as a complementary biomarker for risk stratification. Neutrophil-to-lymphocyte ratio may capture a distinct inflammatory risk component, possibly reflecting the activity of immune cells.

We also focused on patients stratified by clinical presentation and the presence of CKD; these subgroups were chosen because they have been shown to carry the highest inflammatory risk and, consequently, may be those who benefit most from anti-inflammatory therapy.[22]

Neutrophil-to-lymphocyte ratio in patients with acute coronary syndrome and chronic coronary syndrome

When patients were stratified according to clinical presentation, the increased ischaemic risk was more pronounced in patients presenting with ACS and NLR > 5.0, which had a higher incidence of 1-year MACE, death, and MI. Remarkably, baseline NLR measured in ACS patients has been linked to several mechanisms associated with worse prognosis, including the extent of thrombosis, larger final infarct sizes, microvascular obstruction, and ischaemia-reperfusion injury.[8] In the randomized ASSAIL-MI trial, the IL-6 receptor inhibitor tocilizumab significantly improved myocardial salvage and reduced microvascular obstruction and inflammation in patients with STEMI undergoing PCI, a clinical benefit that may have been mediated by reduction of neutrophils and NLR up to 1 week after PCI.[23,24] Similar results were also reported in the VCUART 3, in which interleukin-1 blockade with anakinra in patients with STEMI significantly reduced hsCRP, neutrophils, and NLR.[25] The ongoing Phase 3 ARTEMIS trial (NCT06118281) is now evaluating whether early initiation of the IL-6 inhibitor ziltivekimab in patients with acute MI can reduce MACE, further supporting the role of inflammation as actionable targets in the acute setting.

We did not observe significant differences in adverse cardiovascular events across quartiles of NLR in patients presenting with CCS. Conversely, previous studies found a significant association with NLR and cardiovascular outcomes in patients with stable CAD undergoing elective PCI.[26–28] These studies were smaller or conducted in non-western populations, but reported a longer follow-up, so we cannot exclude that similar findings could be observed in our cohort with longer observation. Of note, our study included 12.3% African Americans, a group of patients who have been shown to have worse outcomes after PCI but are associated with lower levels of NLR, being consistently more represented in the 1st NLR quartile.[29,30] To what extent this might have influenced the results is unknown.

Neutrophil-to-lymphocyte ratio in patients with chronic kidney disease

Our study confirmed the role of NLR in cardiovascular risk stratification in patients with CKD. Of note, CKD patients tended to have higher NLR and elevated hsCRP, and since more than half of the patients presented with CCS, presence of CKD might serve as an enrichment criterion to identify those with stable CAD in whom the contribution of NLR and/or inflammation is relevant. In the CANTOS trials, among 1092 patients with CKD treated with statins, inflammation assessment outperformed cholesterol risk in the prediction of MACE, underscoring the potential role of residual inflammatory risk in this population.[22] Potential mechanisms can be related to persistent low-grade inflammation, which involves cross-talk between the renal and cardiovascular systems and is also exacerbated by recurrent AKI episodes.[31] The IL-1/IL-6 pathway, along with both innate and adaptive immune cells, accelerates atherosclerosis and contributes to immune-mediated renal

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injury, showing a significant correlation with elevated NLR.[32,33] In the Phase 2 RESCUE trial, the inhibition of IL-6 with ziltivekimab in patients with residual inflammatory risk and Stages 3–5 CKD was associated with a significant and sustained reduction of both hsCRP and NLR.[11,34] Whether this reduction can be translated into clinical benefit in terms of cardiovascular outcomes is now being tested in the large, ongoing ZEUS trial (NCT05021835).

Neutrophil-to-lymphocyte ratio and bleeding risk

Finally, we also observed that high levels of NLR are associated with a high risk of bleeding. This finding is consistent with prior studies linking NLR to haemorrhagic events in various clinical settings and may reflect systemic inflammation and immune dysregulation, particularly in patients with comorbidities such as anaemia, atrial fibrillation, or the use of anticoagulant and antiplatelet therapy.[35] Despite the incidence of bleeding being higher in patients with ACS and CKD, the magnitude of the risk increase across the overall population and the subgroups was similar, with a two-fold risk in the 4th quartile of NLR compared with the 1st. Given the prognostic association with bleeding and mortality in patients undergoing PCI, NLR may indirectly inform about the inherent haemorrhagic risk.[36]

Limitations

This study should be interpreted in light of several limitations. First, the analysis is retrospective and based on a single-centre registry which may limit external validity; only patients with available differential blood counts were included and, although considered a routine test, reasons for ordering or omitting differential blood count at the time of PCI were not known. Second, quartiles of NLR were derived from the overall population and applied uniformly to subgroups of interest. While this approach was intended to favour the use of a single and practical threshold (e.g. NLR > 5.0 for the 4th quartile), it may have led to imbalances in patient distribution across subgroups. However, sensitivity analyses using group-specific NLR cut-offs yielded consistent results. Third, patients with active haematological or infectious diseases, extreme lymphocyte or neutrophil counts, or elevated hsCRP were excluded. Nevertheless, high NLR might still reflect additional conditions not accounted for, including underlying inflammatory states, frailty, or medication use. Despite multivariable adjustment for numerous clinical and procedural covariates, residual confounding disproportionately affecting patients with higher NLR and contributing to the observed associations cannot be excluded. Fourth, the study reports 1-year follow-up data; long-term outcomes beyond 1 year, potentially influenced by chronic inflammation and ongoing treatments, are not assessed and might provide further insights into the predictive value of NLR. Fifth, results from subgroups analyses may be unpowered for ischaemic endpoints and should be considered hypothesis generating. Finally, while NLR is a useful biomarker, it is relatively unspecific and does not capture all aspects of inflammation or other relevant biological processes.

Conclusions

Among patients with CAD undergoing PCI, elevated NLR is associated with higher risk of adverse cardiovascular events; this association is more pronounced in patients presenting with ACS and CKD. In these settings, while novel studies with monoclonal antibodies targeting cytokines are underway, NLR may help in risk stratification at the time of PCI, identifying patients who might benefit from anti-inflammatory therapy and potentially serving as a marker to monitor the effectiveness of such treatments.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

A.O. and R.M. conceived and designed the study with input from D.L.B., P.M.R., and G.D. S.Sa. and K.F.S. performed the statistical analysis. S.J.P. provided independent statistical review. D.C., B.V., B.B., M.D., F.M.D.M., and M.G. contributed to data interpretation and methodology. J.S., P.M., G.G.S., A.K., and S.S. provided clinical expertise and contributed to data review. All authors critically reviewed the manuscript for important intellectual content and approved the final version for submission.

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Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Researchers wishing to access the data may contact the corresponding author for further information.

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