Neutrophil to Lymphocyte Ratio and Long-Term Cardiovascular Outcomes in Coronary Artery Disease Patients with Low High-Sensitivity C-Reactive Protein Level

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Summary

Although an elevated neutrophil to lymphocyte ratio (NLR) has been associated with the adverse outcomes of coronary artery disease (CAD), less is known about its prognostic value among patients with low high-sensitivity C-reactive protein (hs-CRP) levels. We enrolled 2,591 consecutive patients with stable CAD who underwent elective percutaneous coronary intervention (PCI) and had available data on preprocedural hs-CRP and NLR between 2000 and 2016. Of these patients, 1,951 with low-grade hs-CRP levels (< 2.0 mg/L) were divided into quartiles based on the NLR values. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke after the index PCI. Clinical follow-up data were obtained up to 5 years. The median NLR was 1.9 (interquartile range: 1.5-2.5). During the follow-up, 102 events occurred (5.2%), with a cumulative incidence that was significantly higher in the highest NLR group than in the other groups (log-rank, \( P = 0.02 \)). After adjusting for the other cardiovascular risk factors, the risk for the primary endpoint was significantly higher for the highest than in the lowest NLR group (HR 1.97, 95% CI 1.09-3.54, \( P = 0.02 \)). Increasing NLR as a continuous variable was associated with the incidence of adverse cardiovascular events (HR 1.85 per log 1 NLR increase, 95% CI 1.19-2.88, \( P = 0.007 \)). In conclusion, the adverse long-term clinical outcomes of CAD patients with low-grade hs-CRP levels has been independently predicted by increased NLR level. NLR could be useful for risk stratification of CAD patients with increased inflammatory marker levels.

Key words: Inflammation, Atherosclerosis, Long-term outcomes

Inflammation plays an important role in the pathogenesis and progression of atherosclerosis.1-3 Inflammatory markers, including white blood cell count (WBC), C-reactive protein (CRP), and interleukin-6, have been demonstrated to be significantly associated with cardiovascular disease.4-6 Recently, anti-inflammatory drugs have been expected as new therapies for patients with cardiovascular disease.7,8 Inflammation can alter the ratio of peripheral neutrophils to lymphocytes, resulting in an increased neutrophil to lymphocyte ratio (NLR).9 The NLR has been an established nonspecific biomarker of low-grade systemic inflammation and has prognostic utility in several cardiac conditions, such as acute coronary syndrome, stable coronary artery disease (CAD), and heart failure.9-11 The prognostic value of NLR in CAD patients with relatively low inflammatory condition, however, has not been fully investigated. Therefore, in this study, we aimed to investigate the association of preprocedural NLR level with the long-term cardiovascular events in stable CAD patients with low high-sensitivity CRP (hs-CRP) levels.

Methods

This investigation was a single-center, observational, retrospective cohort study. We only included those available preprocedural NLR and hs-CRP data among consecutive patients with CAD and who underwent elective percutaneous coronary intervention (PCI) for the first time at Juntendo University Hospital, Tokyo, Japan, between January 2000 and December 2016. Blood samples were collected in the early morning after an overnight fasting. With both values obtained from the same blood sample, NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. Patients with known malignancy or active inflammatory disease were excluded from the study.
The patients with low-grade hs-CRP levels (< 2.0 mg/L) were finally included and divided into four groups according to the preprocedural NLR (< 1.5, 1.5-1.9, 1.9-2.5, and ≥ 2.5).

Demographic data and information about coronary risk factors, medications, factors related with the revascularization procedure, and comorbidities were prospectively collected and analyzed. Blood pressure (BP) was measured on admission. Patients with BP > 140/90 mmHg or those receiving antihypertensive drugs were regarded as hypertensive. Dyslipidemia was defined as low-density lipoprotein cholesterol of ≥ 140 mg/dL, high-density lipoprotein cholesterol of ≤ 40 mg/dL, triglycerides of ≥ 150 mg/dL, or current treatment with statins and/or lipid-lowering agents. Diabetes mellitus was defined as either hemoglobin A1c ≥ 6.5% or medication with insulin or oral hypoglycemic drugs. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of < 60 mL/minute/1.73 m², as calculated using the Modification of the Diet in Renal Disease equation, which was modified with a Japanese coefficient using baseline serum creatinine. A current smoker was defined as a person who smoked at the time of PCI or who had stopped smoking within 1 year before the PCI. Left ventricular ejection fraction (LVEF) was assessed using left ventricular angiography or echocardiography before the PCI. All patients had symptoms of effort angina, documented myocardial ischemia, or both.

Prior to PCI, written informed consent was obtained from all patients. This study was performed in accordance with the Declaration of Helsinki and with the approval of the institutional review board. The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke during the follow-up period after the index PCI. Cardiovascular death was defined as death from cardiovascular disease, cardiogenic shock, or sudden death. Clinical follow-up comprised analyses of the office visit charts and the responses to the questionnaires sent to the patients or their families and telephone contact. Mortality data were collected from the medical records of patients who died or who were treated at our institution, and the details and causes of death were obtained from other hospitals wherein the patients were admitted. Myocardial infarction was defined as evidence of myocardial necrosis in a clinical setting and consistent with myocardial ischemia.

Quantitative data were presented as mean ± standard deviation or as median and interquartile range (IQR). Categorical variables were presented as frequencies. Continuous variables were compared among groups using one-way analysis of variance or the Kruskal-Wallis test. Categorical variables were compared using the chi-square test. Pearson’s correlation coefficients were used to examine the relationships between NLR and the other variables. Unadjusted cumulative event rates were estimated using Kaplan-Meier curves and were compared among quartiles. Cox proportional hazards models were used to assess the univariate and multivariable covariates, and the hazard ratios (HRs) and confidence intervals (CIs) were calculated for each factor by Cox proportional hazards analysis. Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus hs-CRP level. Model 3 was adjusted for the variables in model 2 plus, hypertension, diabetes mellitus, dyslipidemia, body mass index (BMI), CKD, and statin use. These variables in model 3 were selected by univariate Cox hazard analysis (P < 0.10). The logarithm (log) of the NLR was included in the multivariate model, and the HRs and 95% CIs were calculated. Differences were considered significant at P < 0.05. Statistical analyses were conducted using JMP version 12.0 (SAS Institute, Cary, NC, USA).

Results

Of the 3,149 patients who underwent elective PCI, 10 patients were excluded because of malignant or inflammatory diseases, and 2,584 patients had available data on preprocedural NLR and hs-CRP. Among these, 1,951 patients with low-grade hs-CRP levels (< 2.0 mg/L) were divided into quartiles (Figure 1). For these 1,951 patients, the NLR had a median of 1.9 (IQR: 1.5, 2.5) and a mean of 2.1 ± 1.1. The clinical and procedural characteristics of these patients are shown in Table I. Patients in the higher NLR groups displayed relatively high prevalence of female sex and CKD and relatively lower BMI, total cholesterol, and LVEF. No significant differences were found among the groups in terms of age and prevalence of coronary risk factors, such as diabetes mellitus, dyslipidemia, hypertension, or current smoking. Patients in the higher NLR groups were less likely to be taking statins on admission.

Table II shows the association between the log of NLR and the clinical parameters. The NLR level had a significant inverse correlation with BMI (r = −0.08, P = 0.003) and a positive correlation with hs-CRP levels (r = 0.07, P = 0.004). However, these correlations were relatively weak.

The median duration of follow-up was 5.8 years (IQR, 2.4-10.8 years). Follow-up rate at 5 years was 53.9%. During follow-up, 102 (5.2%) patients developed the primary endpoint; 52 (2.7%) cases were cardiac death. Table III shows the cumulative incidences of the cardiac events. The cumulative incidence of the primary endpoints among patients, which was stratified by quartiles of NLR, is presented in Figure 2. The Kaplan-Meier curves showed that the primary endpoint clearly and significantly increased at higher quartiles of NLR (log-rank test, P = 0.02).

Table IV shows the Cox proportional hazards analysis for the primary endpoint. In the unadjusted Cox model, the rate of cardiovascular events increased progressively at higher NLR quartiles (P = 0.02 for trend). Multivariate Cox hazard analysis also showed the association between NLR value and cardiovascular events. In model 3, the risk for adverse cardiovascular events increased by two-fold in the highest NLR group than in the lowest NLR group (HR 1.97, 95% CI 1.09-3.54, P = 0.02). Furthermore, in the multivariate model, the continuous variables of the NLR values were related with the incidence of the primary endpoint (HR 1.85 per log 1 NLR increase, 95% CI 1.19-2.88, P = 0.007; Table V). Lower
BMI, CKD, and hs-CRP levels were independently associated with adverse cardiovascular events.

Discussion

The major findings of this study were 1) patients with high NLR level were more likely to be women and have CKD and low BMI, although age and the prevalence of the other cardiovascular risk factors were not significantly different among the NLR quartile groups; 2) the cumulative incidence of the primary endpoint increased with higher quartiles of NLR; and 3) even after adjusting for the important covariates, a relatively high preprocedural NLR was strongly associated with cardiovascular events in CAD patients with lower hs-CRP levels.

Several screening markers and scoring systems have been used for CAD patients, but some are relatively costly or difficult to obtain in everyday clinical practice. Conversely, NLR is a simple and inexpensive biomarker that can immediately be obtained. Previous studies have reported the predictive values of NLR in patients with various cardiovascular diseases. For example, relatively high NLR was associated with the incidence of atrial fibrillation,18) heart failure,19) and cardiac death.20) Fest et al. analyzed the data from the Rotterdam Study and reported that NLR levels were independently associated with an increased risk of all-cause mortality and cardiac mortality in the general population.21) In that study, the patients with relatively high NLR were men, older, smokers, had relatively high prevalence of diabetes, and had a history of cardiovascular disease. Compared with that study, this study had, to a certain degree, different baseline characteristics of the patients classified in the high NLR group. Moreover, the relationship between elevated NLR level and cardiovascular events has been shown in patients with acute coronary syndrome.22,23) A recent meta-analysis that included 23 studies on ACS patients demonstrated that a high NLR on admission was associated with relatively high mortality rate and major clinical adverse outcomes.24) In contrast, only few reports were available on the relationship of the NLR values with the clinical outcomes of patients with stable CAD.22,23) To the best of our knowledge, this study was the first to evaluate the association between NLR and the long-term cardiovascular outcomes in stable CAD patients with lower hs-CRP levels. We excluded patients with high CRP level, so the incidence rate of primary endpoint in this study was relatively low. Moreover, the risk of cardiovascular events was not significant between quartiles 1 and 2 groups. However, this study clearly demonstrated that among patients with low CRP levels, those with high NLR value had higher cardiovascular risk compared with those with low NLR. Early risk stratification is important in the management of patients with CAD. Strict guideline-recommended therapies might be considered for these higher-risk patients. Actually, statins or antihypertensive therapies have been reported to decrease NLR.24,25) Although few intervention studies have investigated patients with high NLR and CAD, these treatments could reduce their adverse cardiovascular events.

There are several possible mechanisms to explain the association between elevated NLR and cardiovascular events. The clinical outcomes of CAD patients can be affected by both high neutrophil count and low lymphocyte count. Neutrophils secrete large amounts of inflammatory mediators and regulate the inflammatory response.26) Furthermore, neutrophils reportedly made an atherosclerotic plaque more vulnerable by releasing protective enzymes, myeloperoxidase, and superoxide radicals.27) Conversely, lymphocytes represent the regulatory pathway of the immune system; in particular, inflammatory activation was reported to promote lymphocyte apoptosis.28) Moreover, a decreased lymphocyte count has been reported as an early marker of physiologic stress and systemic collapse secon-
Inflammation and cardiovascular diseases.30,31) NLR level could be better predictor of cardiovascular mortality in the general population.20) The inflammatory components of WBC or platelet-related markers reflect inflammation.30,31 NLR level could be better predictor of cardiovascular events although neutrophils alone are associated with inflammation and cardiovascular diseases.

Among the several biomarkers of inflammation, CRP has been widely used in the clinical setting to assess inflammatory disorders and has been found to be strongly associated with the risk and prognosis of cardiovascular diseases.3,6-8,32-34) Moreover, CRP was reported to strongly correlate with neutrophil, monocyte, and NLR.35 However, in the Rotterdam Study, even with the addition of CRP in the multivariate model, elevated NLR level remained an independent predictor of all-cause mortality and cardiovascular mortality in the general population.26) The inflammatory pathways of NLR and CRP and their impact on CAD might be different, although both of them are useful inflammatory biomarkers. In this study, we demonstrated that the correlation between NLR and hs-CRP was relatively weak, although NLR was strongly associated with inflammatory pathways of NLR and CRP and their impact on CAD.

| Table I. Baseline Clinical and Angiographic Characteristics |
|-------------------------------------------------------------|
| NLR (n = 1951)                                               |
| Overall (n = 543)                                            |
| Q1 1.5-2.5                                                  |
| Q2 2.0-3.3                                                  |
| Q3 2.5-3.6                                                  |
| Q4 ≥ 3.7                                                    |
| P value                                                    |
| NLR                                                        |
| Age, years (n = 0.0001) 1951)                                |
| Male, n (%) (n = 0.01) 1625 (83.3)                           |
| Hypertension, n (%) (n = 0.0001) 1425 (73.0)                 |
| Diabetes mellitus, n (%) (n = 0.01) 882 (45.2)               |
| Dyslipidemia, n (%) (n = 0.001) 1455 (75.0)                  |
| Current smoker, n (%) (n = 0.01) 421 (21.6)                  |
| Family history, n (%) (n = 0.01) 589 (30.6)                  |
| Multivessel CAD, n (%) (n = 0.01) 1183 (61.1)                |
| Body mass index, kg/m^2 (n = 0.001) 24.2 ± 3.2               |
| Chronic kidney disease, n (%) (n = 0.01) 527 (27.0)          |
| LVEF, % (n = 0.001) 63.4 ± 10.8                             |
| TC, mg/dL (n = 0.01) 174.7 ± 35.1                           |
| LDL-C, mg/dL (n = 0.01) 102.6 ± 30.7                        |
| HDL-C, mg/dL (n = 0.01) 45.3 ± 13.1                         |
| TG, mg/dL (n = 0.001) 134.5 ± 70.2                          |
| FBS, mg/dL (n = 0.001) 106.7 ± 29.7                         |
| HbA1c, % (n = 0.01) 6.3 ± 1.1                                |
| Inflammation markers (n = 0.01) 48.3 ± 12.9                 |
| CRP, mg/L (n = 0.001) 0.6 ± 0.3                               |
| White blood cell count, μL (n = 0.0001) 5300                 |
| Hemoglobin, g/dL (n = 0.001) 13.4 ± 1.6                     |
| Platelet count × 1000/μL (n = 0.0001) 195 [163, 227]        |
| Medication                                                  |
| ACE-I/ARB, n (%) (n = 0.001) 924 (47.8)                     |
| β-blocker, n (%) (n = 0.001) 1017 (52.6)                    |
| OHA, n (%) (n = 0.001) 600 (30.8)                           |
| Insulin, n (%) (n = 0.001) 153 (7.8)                        |
| Statin, n (%) (n = 0.001) 1286 (66.3)                       |
| Lesion and procedure characteristics                       |
| Reference lumen diameter, mm (n = 0.001) 2.8 ± 0.3           |
| Stent size, mm (n = 0.001) 3.0 ± 0.3                         |

Table II. Relationship Between Neutrophil to Lymphocyte Ratio and Clinical Parameters

| Area of interest          | r     | P value |
|---------------------------|-------|---------|
| Body mass index           | -0.08 | <0.0001 |
| High-sensitivity C-reactive protein | 0.07  | 0.003   |
| Hemoglobin                | -0.07 | 0.004   |
| Low-density lipoprotein cholesterol | -0.05 | 0.02    |
| Triglycerides             | -0.05 | 0.04    |
| Age                       | 0.05  | 0.045   |
| Fasting blood glucose     | 0.04  | 0.10    |
| High-density lipoprotein cholesterol | -0.0006 | 0.98    |

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; FBB, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NLR, neutrophil to lymphocyte ratio; OHA, oral hypoglycemic agent; TC, total cholesterol; and TG, triglycerides.
the outcomes, despite the analytical adjustments. Second, this study evaluated NLR or hs-CRP only once and did not assess changes over time. Finally, various factors might affect NLR levels and outcomes. In this study, NLR level was significantly related to BMI or hemoglobin; however, these correlations were relatively weak among patients with low CRP levels. Previous studies have reported that NLR is associated with various diseases or clinical outcomes in patients with malignant diseases.35) Some drugs, such as antithyroid drugs, antibacterial drugs, were reported to affect WBC levels.36) In this study, patients with known malignancy or active inflammatory disease were excluded; however, several factors which we could not know might affect NLR levels and results.

### Table III. Cumulative Incidence of Cardiovascular Events

| NLR | Overall | Q1 | Q2 | Q3 | Q4 | P value |
|-----|---------|----|----|----|----|---------|
|     | < 1.5   | 1.5-1.9 | 1.9-2.5 | ≥ 2.5 |
| Primary endpoint | 102 (5.2) | 18 (3.3) | 20 (4.5) | 28 (6.0) | 36 (7.3) | 0.02 |
| Death | 120 (6.2) | 27 (5.0) | 27 (6.0) | 30 (6.5) | 36 (7.3) | 0.48 |
| Cardiovascular death | 52 (2.7) | 8 (1.5) | 10 (2.2) | 17 (3.7) | 17 (3.4) | 0.09 |
| Non-fatal myocardial infarction | 26 (1.3) | 4 (0.7) | 6 (1.3) | 5 (1.1) | 11 (2.2) | 0.22 |
| Non-fatal stroke | 33 (1.7) | 6 (1.1) | 8 (1.8) | 7 (1.5) | 12 (2.4) | 0.42 |

### Table IV. Cox Proportional Hazard Model for the Primary Endpoint

| NLR quartile | Q1 | Q2 | Q3 | Q4 |
|--------------|----|----|----|----|
| Crude        | 1.00 | 1.41 | 0.74-2.68 | 0.29 | 1.94 | 1.08-3.56 | 0.03 | 2.32 | 1.34-4.18 | 0.003 | 0.02 |
| Model 1      | 1.00 | 1.40 | 0.74-2.64 | 0.31 | 1.92 | 1.06-3.47 | 0.03 | 2.25 | 1.27-3.97 | 0.005 | 0.02 |
| Model 2      | 1.00 | 1.38 | 0.73-2.61 | 0.32 | 1.92 | 1.06-3.47 | 0.03 | 2.19 | 1.24-3.88 | 0.007 | 0.03 |
| Model 3      | 1.00 | 1.41 | 0.73-2.69 | 0.3 | 1.83 | 0.99-3.37 | 0.05 | 1.97 | 1.09-3.54 | 0.02 | 0.12 |

95% CI indicates 95% confidence interval; HR, hazard ratio; and NLR, neutrophil to lymphocyte ratio. Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, and high sensitivity C-reactive protein. Model 3, adjusted for age, sex, high sensitivity C-reactive protein, hypertension, diabetes mellitus, dyslipidemia, body mass index, CKD, and statin use.
Conclusions

Increased NLR levels independently predicted the adverse long-term clinical outcomes of stable CAD patients with low-grade hs-CRP levels. NLR could be useful for the risk stratification of CAD patients with increased levels of inflammatory markers.

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Disclosure

Conflicts of interest: The authors have no conflicts of interest to disclose.

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Table V. Multivariate Cox Hazard Analysis for the Factors Affecting the Primary Endpoint

|                | Univariate | Multivariate |
|----------------|------------|--------------|
|                | HR 95% CI  | P value      | HR 95% CI  | P value      |
| NLR (log 1 increase) | 2.34       | 1.51-3.58    | 0.0001     | 1.85        | 1.19-2.88    | 0.007 |
| Age            | 1.02       | 0.996-1.040  | 0.11       | 0.998       | 0.977-1.020  | 0.88  |
| Body mass index | 0.93       | 0.87-0.99    | 0.03       | 0.93        | 0.865-0.996  | 0.04  |
| CKD            | 2.35       | 1.59-3.47    | < 0.0001   | 1.94        | 1.29-2.92    | 0.002 |
| Current smoker | 0.73       | 0.42-1.20    | 0.22       |             |             |       |
| Dyslipidemia   | 0.59       | 0.39-0.89    | 0.01       | 0.68        | 0.43-1.07    | 0.10  |
| Diabetes mellitus | 1.42       | 0.97-2.11    | 0.07       | 1.36        | 0.91-2.02    | 0.13  |
| Family history of CAD | 1.12       | 0.74-1.68    | 0.58       |             |             |       |
| Hypertension   | 1.70       | 1.02-2.83    | 0.04       | 1.71        | 0.992-2.94   | 0.05  |
| Log hs-CRP     | 1.41       | 1.08-1.85    | 0.01       | 1.33        | 1.01-1.75    | 0.04  |
| LVEF           | 0.99       | 0.97-1.01    | 0.26       |             |             |       |
| Male           | 1.26       | 0.74-2.31    | 0.41       | 1.27        | 0.70-2.33    | 0.43  |
| Statin use     | 0.69       | 0.46-1.02    | 0.06       | 0.92        | 0.60-1.43    | 0.72  |

CAD indicates coronary artery disease; 95% CI, 95% confidence interval; CKD, chronic kidney disease; HR, hazard ratio; hs-CRP, high sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; and NLR, neutrophil to lymphocyte ratio.
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