Prognostic value of novel neutrophil-to-hemoglobin and lymphocyte score in patients with acute myocardial infarction

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Abstract
We developed and assessed whether a novel neutrophil-to-hemoglobin and lymphocyte (NHL) score would improve the ability to predict clinical outcome compared with neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) in acute myocardial infarction (AMI). We examined 13,072 AMI patients from the Korean AMI Registry–National Institute of Health database. NHL score was calculated as follows: NHL score (U) = N/(Hb × L), where N, Hb, and L are baseline blood neutrophil, hemoglobin, and lymphocyte count. The primary outcome was the occurrence of major adverse cerebrocardiovascular events (MACCEs) at 2 years. The NLR, SII, and NHL score were independent predictors of 2-year MACCEs. The area under the curve of the NHL score (0.637) for predicting 2-year MACCEs was significantly higher compared with those of SII (0.589) and NLR (0.607). The NHL score significantly improved the reclassification and integrated discrimination compared with NLR (p < 0.0001) and SII (p < 0.0001). A high NHL score (≥ 0.35 U) was an independent predictor of 2-year MACCEs (adjusted hazard ratio, 1.41; 95% confidence interval, 1.29–1.55; p < 0.001). The NHL score could be a novel model for predicting long-term MACCEs in patients with AMI.

Keywords
acute myocardial infarction, immune, inflammation, prognosis, biomarker

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Introduction
A robust inflammatory response is an integral component of the response to tissue injury in patients with acute myocardial infarction (AMI). The neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) are inflammation-related indicators that integrate neutrophil, platelet, and lymphocyte counts in the early stage of AMI. Therefore, the NLR and SII are available for risk prediction in patients with AMI. However, these have not been compared with other prognostic scoring systems of AMI. Moreover, the infarction-related inflammatory state with excess cytokine production may suppress erythropoiesis and impair intestinal iron absorption. Therefore, anemia is not uncommon in patients with AMI and can influence clinical outcome. However, there has been no simple and effective inflammation-related indicator that integrates neutrophil, lymphocyte, and hemoglobin in patients with AMI. Therefore, we developed the neutrophil-to-hemoglobin and lymphocyte (NHL) score incorporating hemoglobin into NLR as a risk prediction model to determine the long-term prognosis of patients with AMI. We aimed to validate the NHL score as a risk prediction model.
and to assess whether the NHL score would improve the ability to predict clinical outcome compared with the NLR and SII in patients with AMI.

Methods

Study population

The Korean Acute Myocardial Infarction Registry (KAMIR) is a prospective, open, observational, multicenter, online registry of Korean patients with AMI supported by the National Institute of Health (NIH) since November 2011. The main purpose of KAMIR-NIH was to develop novel risk prediction model for AMI in Korea. Sample size calculation was performed based on the previous KAMIR I–III. This study was planned to recruit at least 12,000 AMI patients for 4 years from 20 hospitals. Between November 2011 and December 2015, a total of 13,072 patients from 20 hospitals who were diagnosed with AMI at admission were recruited. The inclusion criteria were all patients who were diagnosed with AMI. AMI was diagnosed based on the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia. Exclusion criteria were patients who refused to participate in this study. Other details about the Korean Acute Myocardial Infarction Registry—National Institute of Health have been published previously.

Clinical assessment

We analyzed baseline demographic and clinical characteristics including age, sex, cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and current smoking), and presenting characteristics at admission. Electrocardiogram was recorded and analyzed in all patients by attending cardiologists. Venous blood samples including neutrophils, lymphocyte, platelets, and hemoglobin were obtained at the time of admission. Biomarkers such as cardiac troponin I (cTnI), CK-MB, and high-sensitivity C-reactive protein (hs-CRP) were also measured at the time of admission.

The NHL score calculation

The NLR was calculated by dividing the neutrophil count by the lymphocyte count. We calculated SII using the equation $SII = P \times N/L$, where $P$, $N$, and $L$ are baseline peripheral blood platelet, neutrophil, and lymphocyte counts per liter, respectively. We calculated the NHL score using the equation $NHL score (U) = N/(Hb \times L)$, where $N$, $Hb$, and $L$ are baseline peripheral blood neutrophil, hemoglobin, and lymphocyte count. The $U$ indicates unit (1/g/dL).

Data analysis

All patient data and procedural details were collected at the time of admission and followed prospectively at each hospital. Data were recorded on a web-based report form with electronic encryption in the National Institute of Health database. This research was supported by the Korea Centers for Disease Control and Prevention (2013-E63005-02). The protocol was approved by the ethics committee of each participating institution, and all patients provided written informed consent to participate in the study. During the follow-up period, clinical outcome data were obtained by reviewing medical records and interviewing patients by telephone. Outcomes were adjudicated by an investigator at each participating hospital, and central adjudication was regularly performed through an audit.

Outcomes

The primary outcome was the occurrence of major adverse cerebrocardiovascular events (MACCEs) at 2 years, defined as the composite of all-cause death; non-fatal MI; repeat revascularization, including repeated percutaneous coronary intervention, and coronary artery bypass grafting; cerebrovascular accident; and rehospitalizations.

Statistical analysis

Data were expressed as mean ± standard deviation for continuous variables and as percentages for categorical variables. Comparisons between baseline variables were assessed using the student’s $t$ test for continuous variables and Pearson’s chi-squared test for categorical variables. Normality test was performed for all continuous variables (Supplementary Table 1). The cumulative incidence rates of 2-year MACCEs according to NLR, SII, and NHL scores were estimated using the Kaplan–Meier method. They were compared using the log-rank test. Univariate analyses were performed to determine the
predictors for 2-year MACCEs. The Cox proportional-hazards model was used to compute the hazard ratio (HR) and 95% confidence intervals (CI) of independent predictors of 2-year MACCEs. Variables with p values < 0.05 on univariate analysis were entered into the Cox proportional-hazards model. The Hosmer–Lemeshow chi-square, a measure of deviation between observed and predicted outcomes in deciles of predicted risk, was used to evaluate the calibration of the model.

The increased discriminative value of the NHL score compared with the NLR or SII was estimated using three measures (Harrell’s C index, net reclassification improvement, and integrated discrimination improvement). Harrell’s C index (c-statistic) is defined as the proportion of usable patient pairs, in which the predictions and outcomes are concordant. We estimated receiver-operating characteristic (ROC) curves and compared the areas under the ROC curves (AUC) of the NHL score, NLR, and SII in corresponding

Table 1. Clinical characteristics of study subjects.

| Variable                                      | Overall          | MACCEs                  | p value |
|-----------------------------------------------|------------------|-------------------------|---------|
| Demographics                                  |                  |                         |         |
| Age (years)                                   | 63.9 ± 12.6      | 62.5 ± 12.3             | 70.6 ± 11.8 | < 0.001 |
| Male                                          | 9665 (73.9%)     | 8227 (75.9%)            | 1438 (64.2%) | < 0.001 |
| Body mass index (kg/m²)                       | 24.0 ± 3.3       | 24.1 ± 3.2              | 23.1 ± 3.4 | < 0.001 |
| Presentation at admission                     |                  |                         |         |
| Systolic blood pressure (mmHg)                | 130.1 ± 30.1     | 131.6 ± 28.6            | 122.8 ± 35.4 | < 0.001 |
| Heart rate (beats/min)                        | 78.6 ± 19.5      | 77.4 ± 18.2             | 84.6 ± 24.1 | < 0.001 |
| Killip class > 1                              | 2874 (22.0%)     | 1881 (17.4%)            | 993 (44.4%) | < 0.001 |
| ST-segment elevation myocardial infarction    | 6290 (48.1%)     | 5277 (48.7%)            | 1013 (45.3%) | 0.003 |
| Left ventricular ejection fraction (%)        | 51.9 ± 11.2      | 52.0 ± 8.8              | 43.3 ± 10.6 | < 0.001 |
| Past history                                  |                  |                         |         |
| Previous myocardial infarction                | 1027 (7.9%)      | 746 (6.9%)              | 281 (12.6%) | < 0.001 |
| Previous angina                               | 1273 (9.7%)      | 945 (8.7%)              | 328 (14.6%) | < 0.001 |
| Hypertension                                  | 6672 (51.0%)     | 5250 (48.5%)            | 1422 (63.5%) | < 0.001 |
| Diabetes mellitus                             | 3738 (28.6%)     | 2826 (26.1%)            | 912 (40.7%) | < 0.001 |
| Hyperlipidemia                                | 1471 (11.3%)     | 1270 (11.7%)            | 201 (9.0%) | < 0.001 |
| Current smoking                               | 5110 (39.1%)     | 4501 (41.5%)            | 609 (27.2%) | < 0.001 |
| Laboratory findings                           |                  |                         |         |
| WBC (*10⁹/μL)                                 | 10.5 ± 4.5       | 10.3 ± 3.8              | 11.3 ± 6.9 | < 0.001 |
| Neutrophil (%)                                | 66.5 ± 15.0      | 65.7 ± 14.8             | 70.3 ± 15.3 | < 0.001 |
| Lymphocyte (%)                                | 24.6 ± 13.0      | 25.4 ± 12.8             | 21.0 ± 13.2 | < 0.001 |
| Platelet (*10⁹/μL)                            | 232.3 ± 67.7     | 232.9 ± 65.0            | 229.1 ± 79.5 | 0.033 |
| Hemoglobin (g/dL)                             | 13.7 ± 2.1       | 14.0 ± 1.9              | 12.5 ± 2.3 | < 0.001 |
| SII (*10⁹ cells/L)                            | 1014.9 ± 1270.4  | 929.8 ± 989.1           | 1426.8 ± 2118.0 | < 0.001 |
| NLR                                           | 4.3 ± 4.9        | 3.9 ± 3.9               | 6.1 ± 8.1 | < 0.001 |
| NHL score (U)                                 | 0.33 ± 0.42      | 0.29 ± 0.31             | 0.52 ± 0.73 | < 0.001 |
| Glucose (mg/dL)                               | 170.0 ± 82.8     | 163.7 ± 74.3            | 200.2 ± 110.4 | < 0.001 |
| eGFR (mL/min/BSA)                             | 79.6 ± 28.8      | 83.1 ± 26.7             | 63.7 ± 32.5 | < 0.001 |
| cTnI (ng/mL)                                  | 46.8 ± 105.5     | 43.8 ± 91.7             | 60.4 ± 153.8 | < 0.001 |
| Serum CK-MB (mg/mL)                           | 110.7 ± 164.5    | 109.2 ± 158.3           | 118.1 ± 191.8 | < 0.001 |
| hs-CRP (mg/dL)                                | 1.55 ± 6.20      | 1.29 ± 5.93             | 2.98 ± 7.34 | < 0.001 |
| Total cholesterol (mg/dL)                     | 185.2 ± 41.2     | 180.6 ± 45.4            | 164.3 ± 48.4 | < 0.001 |
| Triglycerides (mg/dL)                         | 134.5 ± 120.1    | 138.2 ± 124.8           | 114.9 ± 89.5 | < 0.001 |
| HDL-C (mg/dL)                                 | 42.8 ± 12.5      | 43.0 ± 12.3             | 41.7 ± 13.4 | < 0.001 |
| LDL-C (mg/dL)                                 | 111.8 ± 40.5     | 113.8 ± 39.6            | 101.0 ± 43.6 | < 0.001 |
| Percutaneous coronary intervention            | 11,707 (89.6%)   | 9865 (91.1%)            | 1842 (82.3%) | < 0.001 |
| Multivessel disease                           | 6407 (51.8%)     | 5099 (49.4%)            | 1308 (64.0%) | < 0.001 |

Data are expressed as mean ± SD or number (percent).

BSA, body surface area; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiocerebrovascular event; NHL, neutrophil-to-hemoglobin and lymphocyte; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; WBC, white blood cell.
logistic models. The net reclassification improvement and integrated discrimination improvement were calculated by analyzing the differences in individual estimated probability for 2-year MACCEs and mortality of the NHL score compared with the NLR or SII. Because no prior risk categories exist for 2-year MACCEs and mortality, we calculated the category-free net reclassification improvement.

Because the patients were not randomly assigned to NHL score, propensity-score (PS) matching was performed to reduce the effect of treatment-selection bias and potential confounding factors in this observational study. For each patient, a PS indicating the likelihood of a high NHL score was calculated using a nonparsimonious multivariable logistic regression model with covariates including baseline and angiographic characteristics, leaving 3661 NHL score < 0.35 U versus 3661 NHL score ≥ 0.35 U. Goodness of fit of the PS was evaluated using the c-statistic and the Hosmer–Lemeshow test. After PS matching, the cumulative incidence rates of 2-year MACCEs between NHL score < 0.35 U and NHL score ≥ 0.35 U were estimated by the Kaplan–Meier curve using the log-rank test. For all analyses, a 2-sided p value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS software (version 9.3, SAS Institute, Cary, NC) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics and outcome are presented in Table 1. Of these, the mean age was 63 ± 12 years, and 9665 (73.9%) of the participants were men. Among these, GRACE risk score calculation was available in 12,922 patients. NHL score was well correlated with GRACE score (r = 0.284, p < 0.001; Supplementary Figure 1). The NHL score was significantly higher in patients with high GRACE risk score compared with intermediate-to-low GRACE risk score (p for ANOVA < 0.001; Supplementary Figure 2). During the follow-up period, 2239 (17.1%) MACCEs occurred. Among inflammation-related indicators, the SII (929.8 ± 989.1 × 10⁹ cells/L vs 1426.8 ± 2118.0 × 10⁹ cells/L; p < 0.001), NLR (3.9 ± 3.9 vs 6.1 ± 8.1; p < 0.001), and NHL score (0.29 ± 0.31 U versus 0.52 ± 0.73 U; p < 0.001) were significantly greater in patients with MACCEs at 2 years, respectively. In the Cox proportional-hazards model, the log NHL score (HR, 1.23; 95% CI, 1.16–1.29; p < 0.001) as well as age (HR, 1.37; 95% CI, 1.34–1.40; p < 0.001), hypertension (HR, 1.11; 95% CI, 1.01–1.22; p = 0.027), diabetes mellitus (HR, 1.20; 95% CI, 1.09–1.31; p < 0.001), hyperlipidemia (HR, 0.83; 95% CI, 0.71–0.97; p = 0.021), previous myocardial infarction (HR, 1.40; 95% CI, 1.22–1.61; p < 0.001), eGFR < 60 mL/min/BSA (HR, 2.10; 95% CI, 1.90–2.31; p < 0.001), log cTnI (HR, 1.05; 95% CI, 1.03–1.07; p < 0.001), log hs-CRP (HR, 1.14; 95% CI, 1.11–1.18; p < 0.001), and multivessel disease (HR, 1.36; 95% CI, 1.24–1.49; p < 0.001) were independent predictors of 2-year MACCEs after adjusting for confounding variables (Table 2). The log SII (HR, 1.14; 95% CI, 1.09–1.20; p < 0.001) and log NLR (HR, 1.18; 95% CI, 1.12–1.25; p < 0.001) were also independent predictors of 2-year MACCEs after adjusting for confounding variables.

In ROC curve analysis, the AUCs of the SII, NLR, and NHL score for predicting 2-year MACCEs were 0.589,
0.607, and 0.637, respectively (Figure 1(a)). The AUC of the NHL score was significantly higher compared with those of the SII ($p < 0.0001$) and NLR ($p < 0.0001$), as shown in Table 3. The NHL score significantly improved the reclassification (0.459; $p < 0.0001$) and integrated discrimination (0.020; $p < 0.0001$) of patients compared with the SII. The NLR also significantly improved the reclassification (0.227; $p < 0.0001$) and integrated discrimination (0.004; $p < 0.0001$) of patients compared with the SII. The NHL score significantly improved the reclassification (0.540; $p < 0.0001$) and integrated discrimination (0.015; $p < 0.0001$) of patients compared with the NLR. In terms of 2-year mortality, the AUCs of the SII, NLR, and NHL score for predicting 2-year mortality were 0.619, 0.644, and 0.681 in ROC curve analysis, respectively (Figure 1(b)). The NHL score significantly improved the reclassification ($p < 0.0001$) and integrated discrimination ($p < 0.0001$) of patients compared with the SII and NLR, respectively.

The optimum cutoff point for the NHL score for a favorable prognosis was determined to be 0.35 U. The patients were divided into two groups, namely, those with a low NHL score (< 0.35 U) and those with a high NHL score (≥ 0.35 U). High-risk clinical features and risk factors were more frequently observed in the high NHL score group (Table 4). In Kaplan–Meier survival curve analysis, the high NHL score group had significantly higher rates of 2-year MACCEs (26.3% vs 12.9%; log-rank $p < 0.001$) (Figure 2), mainly driven by mortality (18.4% vs 6.6%; log-rank $p < 0.001$), non-fatal MI (2.9% vs 2.1%; log-rank $p = 0.006$), and rehospitalization (5.0% vs 2.4%; log-rank $p < 0.001$). High NHL score (≥ 0.35) was determined to be an

### Table 2. Cox-proportional hazards models for major adverse cardiocerebrovascular events at 2 years.

| Variable                        | HR     | 95% CI       | p value |
|--------------------------------|--------|--------------|---------|
| Ln NHL score                   | 1.23   | 1.16–1.29    | < 0.001 |
| Age, 10-year increase          | 1.37   | 1.34–1.40    | < 0.001 |
| Male                           | 0.99   | 0.89–1.09    | 0.893   |
| Hypertension                   | 1.11   | 1.01–1.22    | 0.027   |
| Diabetes mellitus              | 1.20   | 1.09–1.31    | < 0.001 |
| Hyperlipidemia                 | 0.83   | 0.71–0.97    | 0.021   |
| Current smoking                | 1.01   | 0.91–1.13    | 0.752   |
| Previous myocardial infarction | 1.40   | 1.22–1.61    | < 0.001 |
| eGFR < 60 mL/min/BSA           | 2.10   | 1.90–2.31    | < 0.001 |
| Ln cTnI                         | 1.05   | 1.03–1.07    | < 0.001 |
| Ln hs-CRP                      | 1.14   | 1.11–1.18    | < 0.001 |
| Multivessel disease            | 1.36   | 1.24–1.49    | < 0.001 |

HR, hazard ratio; CI, confidence interval; NHL, neutrophil-to-hemoglobin and lymphocyte ratio; eGFR, estimated glomerular filtration rate; BSA, body surface area; cTnI, cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein.

### Table 3. Discrimination of SII, NLRs, and NHL score in predicting 2-year clinical outcomes.

| Variable        | C-index | p value | NRI      | p value | IDI      | p value |
|-----------------|---------|---------|----------|---------|----------|---------|
| MACCEs          |         |         |          |         |          |         |
| SII             | 0.589   | —       | Reference| —       | —        | —       |
| NLR             | 0.607   | < 0.0001| 0.227    | < 0.0001| 0.004    | < 0.0001|
| NHL score       | 0.637   | < 0.0001| 0.459    | < 0.0001| 0.020    | < 0.0001|
| MACCEs          |         |         |          |         |          |         |
| NLR             | 0.607   | < 0.0001| 0.540    | < 0.0001| 0.015    | < 0.0001|
| NHL score       | 0.637   | < 0.0001| 0.592    | < 0.0001| 0.021    | < 0.0001|
| Mortality       |         |         |          |         |          |         |
| SII             | 0.619   | —       | Reference| —       | —        | —       |
| NLR             | 0.644   | < 0.0001| 0.312    | < 0.0001| 0.004    | < 0.0001|
| NHL score       | 0.681   | < 0.0001| 0.592    | < 0.0001| 0.021    | < 0.0001|
| Mortality       |         |         |          |         |          |         |
| NLR             | 0.644   | < 0.0001| 0.692    | < 0.0001| 0.016    | < 0.0001|
| NHL score       | 0.681   | < 0.0001| 0.692    | < 0.0001| 0.016    | < 0.0001|

The NRI was defined as (Pimproved prediction among patients with major adverse cardiocerebrovascular events or mortality + Pimproved prediction among patients without major adverse cardiocerebrovascular events or mortality) (Pworsened prediction among patients with major adverse cardiocerebrovascular events or mortality + Pworsened prediction among patients without major adverse cardiocerebrovascular events or mortality), where $p = \text{proportion of patients}$. The IDI was defined as (SII)– Pold(j)/ln (Patients with major adverse cardiocerebrovascular events or mortality) (SII)– Pold(j)/ln (Patients with no major adverse cardiocerebrovascular events or mortality), where $p = \text{predicted probability of major adverse cardiocerebrovascular events or mortality}$. IDI, integrated discrimination improvement; MACCE, major adverse cardiocerebrovascular event; NHL, neutrophil-to-hemoglobin and lymphocyte ratio; NLR, neutrophil-to-lymphocyte count ratio; NRI, net reclassification improvement; SII, systemic immune-inflammation index.
independent predictor of 2-year MACCEs after adjusting for confounding variables (HR, 1.41; 95% CI, 1.29–1.55; \( p < 0.001 \)) (Table 5).

After PS matching, there were no significant differences in baseline characteristics (Supplementary Table 2). In Kaplan–Meier survival curve analysis, there were significantly higher rates of 2-year MACCEs (23.9% vs 20.1%; log-rank \( p < 0.001 \)) and mortality (16.1% vs 11.8%; log-rank \( p < 0.001 \)) in patients with NHL score \( \geq 0.35 \) U (Supplementary Table 3 and Supplementary Figure 3).

### Discussion
The main findings of this study are as follows. First, the severity of systemic inflammation is closely associated with prognosis of AMI. Second, the NHL score is a novel inflammatory indicator
in AMI. Third, the NHL score is an independent predictor of long-term outcomes in patients with AMI. Fourth, the NHL score has an ability superior to either the SII or NLR in the prediction of long-term outcome in patients with AMI.

There are two noteworthy findings in our study. First, this is the first risk-prediction model to incorporate anemia as one of the inflammatory markers in patients with AMI. In patients with AMI, the prevalence of anemia varies between 10% and 43%, depending on preexisting comorbidities. A previous large cohort study reported that AMI patients with anemia had more preexisting comorbidities compared with those of normal hemoglobin level. This is consistent

Figure 2. (a) Kaplan–Meier survival curve showing 2-year major adverse cardiocerebrovascular events, (b) death, (c) non-fatal MI, (d) revascularization, (e) CVA, and (f) rehospitalization according to high and low NHL scores. CVA, cerebrovascular accidents; MACCE, major adverse cardiocerebrovascular event; MI, myocardial infarction; NHL, neutrophil-to-hemoglobin and lymphocyte.
with the results of our study. In our study, patients with a high NHL score had greater previous history of hypertension, diabetes mellitus, hyperlipidemia, and current smoking. Accordingly, anemia at baseline should be regarded as a marker of “fragile” patients. Furthermore, anemia in AMI patients should be regarded as “anemia of inflammation” that is a part of the systemic inflammatory response syndrome.\(^5\) Inflammatory response mediated by acute-phase cytokines results in a shorter half-life of red blood cells, antiproliferative action against endothelial progenitor cells, low iron availability for hemopoiesis, reduced erythropoietin production, and minor response of hematopoietic progenitors to stem cell factor and erythropoietin for receptor downregulation.\(^20\) Therefore, the systemic effects of the inflammatory response induced by myocardial necrosis in AMI patients are not just limited to blunted erythroid function but also involve the ability to produce or mobilize endothelial progenitor cells by the bone marrow.\(^5\) This systemic inflammatory response syndrome reduces the vascular healing capacity and contributes to worse clinical outcomes in AMI patients with anemia.\(^21\) This is the reason why we developed the NHL score incorporating anemia into NLR as an inflammatory marker. In our study, the NHL score was an independent predictor of long-term outcomes in patients with AMI after adjusting for other inflammatory markers such as cTnI and hs-CRP.

Second, the NHL score has robust prognostic accuracy compared with the NLR and SII and adds additional prognostic risk stratification in patients with AMI. Many of the hematological indices, as biomarkers related to inflammation, have been studied to establish their prognostic value.\(^22,23\) Hematological indices such as white blood cell, neutrophil, lymphocyte, and platelet counts are relatively simple, rapid, and inexpensive. Previous studies have reported that increased neutrophils were associated with poor clinical outcome in patients with AMI.\(^24-31\)

Neutrophils play a role in the destabilization of atherosclerotic plaque by the formation of neutrophil extracellular traps that contributed to atherothrombosis.\(^32\) Conversely, increased lymphocytes were associated with lower mortality in patients with AMI.\(^33,34\) Therefore, the NLR is useful and better than each separate hematological index for predicting clinical outcome.\(^2\) The SII is another inflammatory marker that incorporates platelets into the NLR. The activation of platelets plays a key role in thrombus formation, and its derivative contributes to sustained inflammation.\(^35\) Recently, some studies have reported that higher SII is independently associated with worse clinical outcomes in patients with coronary artery disease, particularly among elderly AMI patients.\(^3,4\) In our study, we found that the SII was significantly greater in patients with higher MACCEs at 2 years. This result is consistent with previous studies. However, the NLR and SII have not been compared with other inflammation-related prognostic scoring systems in AMI. In our study, we developed a novel NHL score as an inflammation-related indicator in patients with AMI. The NHL score significantly improved the reclassification and integrated discrimination of patients and has an ability superior to either the SII or NLR in the prediction of long-term outcome in patients with AMI. We believe the NHL score might be the best risk-prediction model among inflammation-related indices in patients with AMI.

### Study limitations

This study has certain limitations that should be noted. First, because the Korean Acute Myocardial Infarction Registry—National Institute of Health was an observational study, we could not completely exclude the possibility of residual confounding factors that were not available in our registry. Therefore, our results should only be regarded as hypothesis generating. Second, because some biomarkers were not routinely assessed, we did not compare the NHL score with various inflammatory indicators. However, the limitations of the study should not undermine the strength of this study, namely, that it includes patients encountered in day-to-day clinical practice. Despite these limitations, we believe that the NHL score could provide the clinical insight necessary to determine the future prognosis of patients with AMI.

### Conclusion

An improvement in the ability of the NLR and SII to predict long-term MACCEs can be achieved by combining the NLR with anemia to produce the NHL score. The NHL score is a novel valid model of long-term MACCEs in patients with AMI.
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Ethics approval
The study was approved by the by the Institutional Review Board of Kyungpook National University Hospital (KNUH 2011-11-023) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent
All patients gave written informed consent to participate in this study.

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Supplementary Material
Supplementary material for this article is available online.

References
1. Melamed KH and Goldhaber SZ. Cardiology patient page: inflammation and myocardial infarction. Circulation 2014; 130(24): e334–336.
2. Duffy BK, Gurm HS, Rajagopal V, et al. Usefulness of an elevated neutrophil tolymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. Am J Cardiol 2006; 97(7): 993–996.
3. Huang J, Zhang Q, Wang R, et al. Systemic immune-inflammatory index predicts clinical outcomes for elderly patients with acute myocardial infarction receiving percutaneous coronary intervention. Med Sci Monitor 2019; 25: 9690–9701.
4. Yang YL, Wu C-H, Hsu P-F, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clinical Invest 2020; 50(5): e13230.
5. Stucchi M, Cantoni S, Piccinelli E, et al. Anemia and acute coronary syndrome: current perspectives. Vasc Health Risk Manag 2018; 14: 109–118.
6. AlpertJS, Thygesen K, Antman E, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000; 36(3): 959–969.
7. Lee JH, Yang DH, Park HS, et al. Suboptimal use of evidence-based medical therapy in patients with acute myocardial infarction from the Korea Acute Myocardial Infarction Registry: prescription rate, predictors, and prognostic value. Am Heart J 2010; 159(6): 1012–1019.
8. Harrell FE, Jr, Lee KL and Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15(4): 361–387.
9. DeLong ER, DeLong DM and Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44(3): 837–845.
10. Pencina MJ, D’Agostino Sr RB, D’Agostino RB Jr, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond.. Stat Med 2008; 27(2): 157–212.
11. Archbold RA, Balami D, Al-Hajiri A, et al. Hemoglobin concentration is an independent determinant of heart failure in acute coronary syndromes: cohort analysis of 2310 patients. Am Heart J 2006; 152(6): 1091–1095.
12. Kunadian V, Mehran R, Lincoff AM, et al. Effect of anemia on frequency of short- and long-term clinical events in acute coronary syndromes (from the Acute Catheterization and Urgent Intervention Triage Strategy Trial). Am J Cardiol 2014; 114(12): 1823–1829.
13. Meneveau N, Schiele F, Seronde M-F, et al. Anemia for risk assessment of patients with acute coronary syndromes. Am J Cardiol 2009; 103(4): 442–447.
14. Sulaiman K, Prashanth P, Al-Zakwani I, et al. Impact of anemia on in-hospital, one-month and one-year mortality in patients with acute coronary syndrome from the Middle East. Clin Med Res 2012; 10(2): 65–71.
15. Shiraiishi J, Kohno Y, Nakamura T, et al. Prognostic impact of chronic kidney disease and anemia at admission on in-hospital outcomes after primary percutaneous coronary intervention for acute myocardial infarction. Int Heart J 2014; 55(4): 301–306.
16. Tsujita K, Nikolsky E, Lansky AJ, et al. Impact of anemia on clinical outcomes of patients with st-segment elevation myocardial infarction in relation to gender and adjunctive antithrombotic therapy (from the HORIZONS-AMI trial). Am J Cardiol 2010; 105(10): 1385–1394.
17. Wu W-C, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. New Engl J Med 2001; 345(17): 1230–1236.
18. Yazji K, Abdul F, Elangovan S, et al. Baseline anemia in patients undergoing percutaneous coronary intervention after an acute coronary syndrome—A paradox of high bleeding
risk, high ischemic risk, and complex coronary disease. *J Interventional Cardiol* 2017; 30(5): 491–499.

19. Weiss G and Goodnough LT. Anemia of chronic disease. *New Engl J Med* 2005; 352(10): 1011–1023.

20. Mamas MA, Kwok CS, Kontopantelis E, et al. Relationship between anemia and mortality outcomes in a national acute coronary syndrome cohort: insights from the UK myocardial ischemia national audit project registry. *J Am Heart Assoc* 2016; 5(11): e003348.

21. Solomon A, Blum A, Peleg A, et al. Endothelial progenitor cells are suppressed in anemic patients with acute coronary syndrome. *Am J Med* 2012; 125(6): 604611–611.

22. Budzianowski J, Pieszko K, Burchardt P, et al. The role of hematological indices in patients with acute coronary syndrome. *Dis Markers* 2017; 2017: 3041565.

23. Shiyovich A, Gilutz H and Plakht Y. White blood cell subtypes are associated with a greater long-term risk of death after acute myocardial infarction. *Tex Heart Inst J* 2017; 44(3): 176–188.

24. Barron HV, Cannon CP, Murphy SA, et al. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction. *Circulation* 2000; 102(19): 2329–2334.

25. Dragu R, Huri S, Zukermann R, et al. Predictive value of white blood cell subtypes for long-term outcome following myocardial infarction. *Atherosclerosis* 2008; 196(1): 405–412.

26. Guasti L, Dentali F, Castiglioni L, et al. Neutrophils and clinical outcomes in patients with acute coronary syndromes and/or cardiac revascularisation. a systematic review on more than 34,000 subjects review on more than 34,000 subjects. *Thromb Haemostasias* 2011; 106(4): 591–599.

27. Huang G, Zhong X-N, Zhong B, et al. Significance of white blood cell count and its subtypes in patients with acute coronary syndrome. *Eur J Clin Invest* 2009; 39(5): 348–358.

28. Järemo P and Nilsson O. Interleukin-6 and neutrophils are associated with long-term survival after acute myocardial infarction. *Eur J Intern Med* 2008; 19(5): 330–333.

29. Naruko T, Ueda M, Haze K, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. *Circulation* 2002; 106(23): 2894–2900.

30. Núñez J, Fácil L, Llàcer À, et al. Prognostic value of white blood cell count in acute myocardial infarction: long-term mortality. *Revista Española de Cardiología (English Edition)* 2005; 58(6): 631–639.

31. Taglieri N, Bacchi Reggiani ML, Palmerini T, et al. Baseline white blood cell count is an independent predictor of long-term cardiovascular mortality in patients with non-st-segment elevation acute coronary syndrome, but it does not improve the risk classification of the GRACE score. *Cardiology* 2013; 124(2): 97–104.

32. Döring Y, Soehnlein O and Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. *Circ Res* 2017; 120: 736–743.

33. Núñez J, Núñez E, Bodi V, et al. Low lymphocyte count in acute phase of ST-segment elevation myocardial infarction predicts long-term recurrent myocardial infarction. *Coron Artery Dis* 2010; 21(1): 1–7.

34. Zouridakis EG, Garcia-Moll X and Kaski JC. Usefulness of the blood lymphocyte count in predicting recurrent instability and death in patients with unstable angina pectoris. *Am J Cardiol* 2000; 86(4): 449–451.

35. Croce K and Libby P. Intertwining of thrombosis and inflammation in atherosclerosis. *Curr Opin Hematol* 2007; 14(1): 55–61.