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Original Article

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Prognostic Value of Baseline Neutrophil-to-Lymphocyte Ratio Combined With Anemia in Patients With ST-Segment Elevation Myocardial Infarction: A Nationwide Prospective Cohort Study

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ABSTRACT

Objective: Data pertaining to the prognostic value of the combination of high neutrophil-to-lymphocyte ratio (NLR) and anemia on admission in patients with ST-segment elevation myocardial infarction (STEMI) are limited. The objective of this study was to investigate the clinical value of baseline NLR in combination with anemia in predicting clinical outcomes after STEMI.
Methods: A total of 5,194 consecutive patients with STEMI within 12 hours of symptom onset from the Korea Acute Myocardial Infarction Registry-National Institute of Health database between 2011 and 2015 were categorized into 4 groups according to their NLR and hemoglobin levels: low NLR (<4) without anemia (n=2,722; reference group); high NLR (≥4) without anemia (n=1,527); low NLR with anemia (n=508); and high NLR with anemia (n=437). The co-primary outcomes were 180-day and 3-year all-cause mortality.
Results: Mortality rates significantly increased at the 3-year follow-up across the groups (3.3% vs. 5.4% vs. 16.5% vs. 21.7% for 180-day mortality and 5.3% vs. 9.0% vs. 23.8% vs. 33.4% for 3-year mortality; all p-trends <0.001). After adjusting for baseline covariates, the combination of high NLR and anemia was a significant predictor of 180-day mortality after STEMI with low NLR and no anemia as the reference (adjusted hazard ratio, 2.16; 95% confidence interval, 1.58–2.95; p<0.001). Similar findings were observed for the 3-year mortality.
Conclusions: This nationwide prospective cohort study showed that the combination of high NLR (≥4) and anemia is a strong predictor of all-cause mortality after STEMI.

Keywords: Anemia; Lymphocytes; Neutrophils; ST elevation myocardial infarction

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Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

Conceptualization: Cho KH, Jeong MH; Data curation: Cho KH, Kim JH, Ahn Y, Chae SC, Seong IW, Park JS, Yoon CH, Hur SH, Lee SR, Jeong MH; Formal analysis: Cho KH, Kim MC, Sim DS, Hong YJ; Funding acquisition: Cho KH, Kim JH, Chae SC, Seong IW, Park JS, Yoon CH, Hur SH, Lee SR, Jeong MH; Investigation: Cho KH, Kim MC, Kim JH; Methodology: Cho KH, Shin MH; Project administration: Cho KH, Shin MH, Hong YJ, Kim JH, Ahn Y, Jeong MH; Supervision: Sim DS, Hong YJ, Kim JH, Ahn Y, Jeong MH; Visualization: Cho KH, Shin MH, Kim MC, Jeong MH; Writing - original draft: Cho KH, Shin MH, Jeong MH; Writing - review & editing: Kim MC, Sim DS, Hong YJ, Kim JH, Ahn Y, Chae SC, Seong IW, Park JS, Yoon CH, Hur SH, Lee SR, Jeong MH.

INTRODUCTION

All patients with ST-segment elevation myocardial infarction (STEMI) should undergo early risk assessment, which can guide the acuity, intensity, and location of care and provide patients and families with a more informed understanding of the potential adverse clinical outcomes.[1,2] Furthermore, during the coronavirus disease 2019 (COVID-19) pandemic, robust early risk assessment for STEMI can reduce the risk of viral infection.[3] The primary percutaneous coronary intervention (PCI) is the reperfusion therapy of choice when performed within 120 minutes of STEMI diagnosis, however, a blanket policy of primary PCI for all patients with STEMI may be difficult to justify when health care resources are limited, and system delays shifted the balance in favor of fibrinolytic strategies during the COVID-19 pandemic.[4]

Thrombolysis in myocardial infarction (TIMI) score is a well-known bedside risk score for patients with STEMI; however, some variables, such as past medical history, body weight, or symptom-to-treatment time may not be available or reliable for selected patients owing to the patient-oriented approach. On the other hand, complete blood count (CBC) data are readily available and reliable in the early period after STEMI for almost all the patients across various levels of the health care system, and maybe the only laboratory data obtainable before primary PCI for STEMI.

A high neutrophil-to-lymphocyte ratio (NLR) and anemia have both been shown to be associated with worse clinical outcomes in patients with coronary artery disease (CAD), including STEMI.[5-8] However, current guidelines do not recommend the use of CBC data as a predictive factor for clinical outcomes after STEMI.[1,2] Furthermore, data regarding the clinical use of the combination of high NLR and anemia in early risk stratification for STEMI are limited. In 2011, a single-center study involving 739 patients undergoing PCI for STEMI, the combination of high NLR and baseline anemia was an independent predictor of 180-day mortality, with low NLR and no anemia as the reference.[9]

This study aimed to validate the combination of NLR and anemia on admission, which are available in the early period where the critical decision is made before myocardial revascularization, for predicting mortality in patients with STEMI, using a large Korean prospective cohort.

MATERIALS AND METHODS

The study population was selected from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) database involving 20 tertiary university hospitals in Korea between November 2011 and December 2015.[10] The details of the participating sites and exclusion criteria are described in the **Supplementary Data 1**. A trained clinical research coordinator collected clinical, laboratory, and outcome data online. The completeness rates at 180-day follow-up (≥150 days) and 3-year follow-up (≥1,005 days) were 98% (5,202/5,300) and 93% (4,824/5,194), respectively. The study was conducted in accordance with the principles embodied in the Declaration of Helsinki, revised in 2013, and the study protocol was approved by the ethics committee of each participating center (approval number of the Chonnam National University Hospital: CNUH-2011-172). Written informed consent was obtained from all participants, and no stipend was provided. The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology statement. Of

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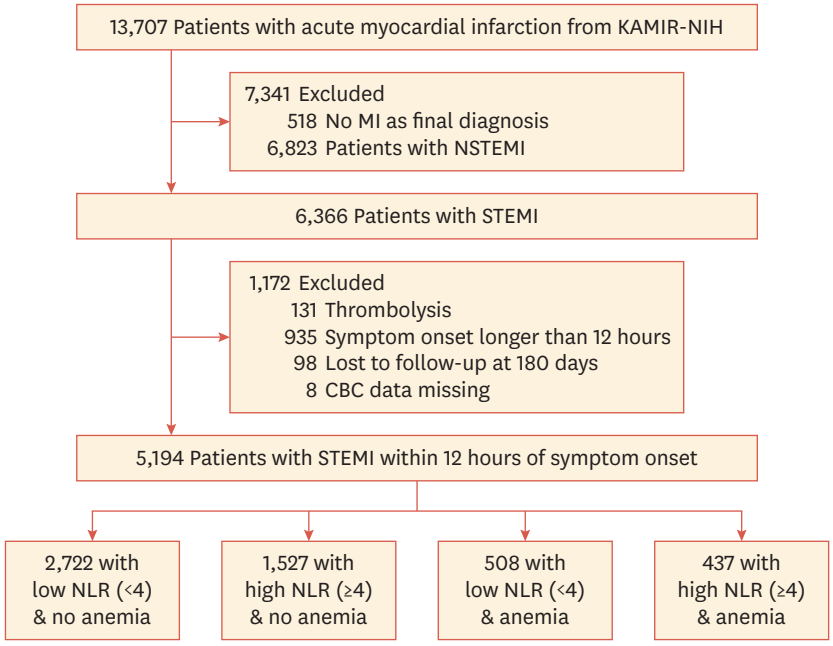

Fig. 1. Study flowchart. The study population was derived from the nationwide, prospective KAMIR-NIH. KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institutes of Health; CBC, complete blood count; MI, myocardial infarction; NLR, neutrophil-to-lymphocyte ratio; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

the 13,707 patients enrolled in the KAMIR-NIH registry, 6,366 diagnosed with STEMI were identified. We excluded those who received thrombolysis with symptom onset longer than 12 hours, and were lost to follow-up at 180 days, or had missing CBC data (**Fig. 1**). The remaining 5,194 patients with STEMI (mean ± standard deviation [SD] age, 62.2±12.7 years; 4,123 men [79.4%]) were categorized into the following 4 groups using an NLR cutoff value of 4 and the presence of anemia (hemoglobin <13 g/dL in men and <12 g/dL in women): low NLR (<4) without anemia (n=2,722; reference group); high NLR (≥4) without anemia (n=1,527); low NLR (<4) with anemia (n=508); and high NLR (≥4) with anemia (n=437).

PCI was performed according to the current standard guidelines. Prior to PCI, all patients received loading doses of aspirin (300 mg) and a $P2Y_{12}$ inhibitor (ticagrelor [180 mg], prasugrel [60 mg], or clopidogrel [300–600 mg]). Route selection for catheterization and the use of thrombus aspiration, adjunctive drugs to support the procedure, or intravascular imaging devices were employed at the discretion of the operator. After PCI, patients received aspirin indefinitely plus a $P2Y_{12}$ inhibitor for more than 12 months. Renin–angiotensin–aldosterone system blockers, beta-blockers, and statins were prescribed according to the practice guidelines.

The co-primary outcomes were 180-day and 3-year all-cause mortality. The secondary outcomes were in-hospital mortality, major adverse cardiocerebrovascular events (a composite of all-cause mortality, nonfatal MI, coronary revascularization via PCI or coronary artery bypass grafting, or nonfatal stroke), and its individual components at 180 days and 3 years. Death from cardiac causes was defined as any death without a clear non-cardiac cause. All events were identified by the patients' physicians and confirmed by the principal investigator of each hospital. All data were collected by trained clinical research coordinators using a web-based case report form on the Internet-based Clinical Research and

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Trial management system (iCReaT), a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Korea (iCReaT Study No. C110016). CBC data were obtained immediately after admission and before coronary catheterization. STEMI was defined as new ST-segment elevation of ≥1 mm in at least 2 contiguous leads (≥2 mm in V2–3 leads) or a new left bundle branch block (LBBB) with a concomitant increase in cardiac biomarker levels (troponin or fraction of biochemical marker creatinine kinase). The discriminatory performance of either NLR or hemoglobin levels as continuous values for 180-day mortality was analyzed using receiver operating characteristic curves (**Supplementary Fig. 1**). The median and mean ± SD NLR values were 2.95 (interquartile range, 1.42–5.50) and 4.15 ± 4.65, respectively. The cutoff value between high and low NLR was established as 4 after considering practical applicability and future external validation (**Supplementary Data 1**). Anemia was defined as a hemoglobin level <12 g/dL for females and <13 g/dL for males based on the World Health Organization's definition. Off-hour admission was defined as arrival at the hospital during weekends, holidays, and during night shifts (6 pm to 8 am) on weekdays. PCI was considered successful if the final stenosis was <30% with TIMI flow grade II or III. Automated analyzers at each center were used for hematological measurements.

R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis from November 2010 to March 2021. The optimal cutoff value of NLR for 180-day mortality was calculated using receiver operating characteristic curve analysis. Linear regression analysis between NLR or hemoglobin levels as a continuous variable and age, symptom-to-door time, and creatinine levels was performed. Kaplan–Meier survival analysis was performed across the 4 groups, which were categorized on the basis on NLR and baseline anemia. The survival curves of each group were then compared using log-rank test. Multivariable Cox regression analysis was performed using the backward stepwise method and included the baseline variables with $p<0.1$ in the univariable analysis and other clinically relevant variables based on the previously published reports including age, sex, off-hour admission, emergency medical service arrival, body weight, Killip class, heart rate, systolic blood pressure, anterior ST-elevation or LBBB, diabetes mellitus, hypertension, previous angina pectoris, previous MI or revascularization, symptom-to-door time, CBC data, creatinine clearance, left ventricular ejection fraction (LVEF), total cholesterol, high-sensitivity C-reactive protein, family history of premature CAD, current smoker status, previous heart failure, previous cerebrovascular accident, and no primary PCI strategy. Furthermore, the following variables with missing data were included in the multivariable analysis: creatinine clearance (n=6), systolic blood pressure (n=19), heart rate (n=19), body weight (n=192), total cholesterol (n=207), LVEF (n=295), and high-sensitivity C-reactive protein (n=1,837). Missing data were imputed using the multiple imputation method with the "mice" package in R. The proportionality assumption was checked by log-minus-log plots. The linearity assumption was assessed by the cumulative sum of martingale-based residuals. Collinearity diagnostics were assessed using the variance inflation factor and eigensystem analysis. As a result, continuous variables, except for age and LVEF, were changed to categorical variables. A 2-sided *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Of 5,194 patients with STEMI (mean [SD] age, 62.2 [12.7] years; 4,123 men [79.4%]), 945 (18.2%) had anemia and 1,964 (37.8%) belonged to the high NLR (≥4) group. The results of

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simple linear regression analysis between CBC data and age, symptom-to-door time, and creatinine levels are presented in **Supplementary Fig. 2**. The NLR increased with age (r=0.131; p<0.001), whereas the hemoglobin levels decreased with age (r=−0.502; p<0.001).

1. Baseline clinical and angiographic characteristics

Baseline clinical characteristics are listed in **Table 1**. Patients with high NLR and baseline anemia were older, females more often, less likely to be obese, less likely to be admitted at off-hours, more likely to have longer symptom-to-door times, had a low systolic blood pressure, an elevated heart rate, a high Killip class, and a low LVEF as compared to those with low NLR and no anemia. They had frequent comorbidities, including hypertension, diabetes mellitus, heart failure, cerebrovascular disease, and renal insufficiency. Moreover, they were more likely to have high levels of glucose, high-sensitivity C-reactive protein, and low lipid profile levels (total cholesterol, low-density lipoprotein cholesterol, and triglycerides). Coronary angiographic characteristics and medical treatments administered are listed in **Supplementary Table 1**. Most of our patients (99.7%) underwent coronary angiography. Patients with high NLR and anemia were more likely to have longer door-to-balloon times, the right coronary artery as the culprit lesion, and multivessel coronary disease. They were less likely to have undergone successful PCI, and have rarely received aspirin, potent $P2Y_{12}$ inhibitors, beta-blockers, renin–angiotensin–aldosterone blockers, and statins at discharge.

2. Clinical outcomes

Clinical outcomes were evaluated up to 3 years (1,095 days; interquartile range, 1,051–1,095 days) after discharge. Death occurred in 6.8% (353/5,194) and 10.6% (550/5,194) of patients at 180 days and 3 years, respectively. **Fig. 2** shows the cumulative incidence of mortality across the 4 groups over 180 days and 3 years. There were significant differences in mortality rates across the 4 groups (3.3% vs. 5.4% vs. 16.5% vs. 21.7% for 180-day mortality and 5.3% vs. 9.0% vs. 23.8% vs. 33.4% for 3-year mortality; p-trend <0.001). All log-rank p-values between any 2 groups were <0.001. Detailed clinical outcomes across the 4 groups, based on NLR and baseline anemia at 3-year follow-up, are listed in **Supplementary Table 2**. Mortality rates stratified by the combined NLR value and baseline anemia were assessed in diverse risk subgroups based on hemodynamic profiles (**Fig. 3**). There were significant differences in clinical outcomes in both the high-risk (patients presenting with Killip class II or III, systolic blood pressure <100 mmHg, or heart rate >100 beats/minute) and low-risk (presenting with Killip class I, systolic blood pressure ≥100 mmHg, or heart rate ≤100 beats/minute) subgroups (all p-trends <0.001). Mortality rates stratified by the combined NLR value and baseline anemia in other risk subgroups are provided in **Supplementary Fig. 3**.

3. Prognostic predictive value of CBC data

The combination of NLR and hemoglobin levels was a strong predictor of 180-day mortality in the multivariable Cox proportional hazards model (high NLR with anemia: hazard ratio [HR], 2.16, 95% confidence interval [CI], 1.58–2.95; low NLR with anemia: HR, 1.81, 95% CI, 1.32–2.48; high NLR without anemia: HR, 1.41, 95% CI, 1.04–1.90) (**Fig. 4**). Crude and adjusted HRs of variables for 180-day and 3-year mortality in the Cox proportional hazards model are shown in **Supplementary Tables 3** and **4**. In multivariable Cox regression analysis applied to assess correlates of 180-day mortality in STEMI patients treated with primary PCI (n=4,941), the adjusted HRs were as follows: high NLR with anemia: HR, 2.31, 95% CI, 1.65–3.24; low NLR with anemia: HR, 1.61, 95% CI, 1.14–2.27; and high NLR without anemia: HR, 1.38, 95% CI, 1.00–1.91 (**Supplementary Table 5**).

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Table 1. Baseline clinical characteristics

Characteristic	Overall (n=5,194)	Low NLR without anemia (n=2,722)	High NLR without anemia (n=1,527)	Low NLR with anemia (n=508)	High NLR with anemia (n=437)	*p*-value*	Group (4th vs. 1st) *p*-value†	*p*-trend‡
Demographics								
Age (yr)	62.2±12.7	59.4±11.6	61.2±12.6	71.4±10.4	72.7±10.9	<0.001	<0.001	
Sex, male	4,123 (79.4)	2,286 (84.0)	1,274 (83.4)	299 (58.9)	264 (60.4)	<0.001	<0.001	<0.001
Initial presentation								
Symptom-to-door time (min)	120 (60–220)	79 (44–146)	183 (119.5–294.0)	104.5 (58.5–197.5)	181 (107–310)	<0.001	<0.001	
Off-hour admission	3,164 (60.9)	1,715 (63.0)	895 (58.6)	316 (62.2)	238 (54.5)	<0.001	0.001	0.001
Means of arrival								
Emergency medical service	1,136 (21.9)	781 (28.7)	150 (9.8)	157 (30.9)	48 (11.0)	<0.001	<0.001	<0.001
Direct visit	1,463 (28.2)	917 (33.7)	344 (22.5)	108 (21.3)	94 (21.5)	<0.001	<0.001	<0.001
Transferred from another hospital	2,595 (50.0)	1,024 (37.6)	1,033 (67.6)	243 (47.8)	295 (67.5)	<0.001	<0.001	<0.001
Weight (kg)	66.7±11.9	69.1±11.6	67.1±11.3	60.1±10.2	57.1±10.5	<0.001	<0.001	
Systolic blood pressure (mmHg)	125.4±32.2	127.4±32.7	129.1±28.0	111.5±37.9	116.4±29.8	<0.001	<0.001	
Heart rate (beats/minute)	76.1±20.4	74.7±20.2	79.2±17.6	70.3±24.9	80.7±22.5	0.001	<0.001	
Killip class on admission								
I	4,003 (77.1)	2,192 (80.5)	1,219 (79.8)	323 (63.6)	269 (61.6)	<0.001	<0.001	<0.001
II	391 (7.5)	181 (6.6)	134 (8.8)	31 (6.1)	45 (10.3)	0.005	0.008	0.023
III	278 (5.4)	114 (4.2)	82 (5.4)	35 (6.9)	47 (10.8)	<0.001	<0.001	<0.001
IV	522 (10.1)	235 (8.7)	92 (6.0)	119 (23.4)	76 (17.4)	<0.001	<0.001	<0.001
Anterior ST-elevation or LBBB on electrocardiogram	2,566 (49.4)	1,343 (49.3)	791 (51.8)	229 (45.1)	203 (46.5)	0.032	0.285	0.176
LVEF (%)	50.7±10.3	52.2±9.8	49.3±9.8	49.7±11.6	46.8±11.2	<0.001	<0.001	
Medical history								
Hypertension	2,396 (46.1)	1,160 (42.6)	638 (41.8)	322 (63.4)	276 (63.2)	<0.001	<0.001	<0.001
Diabetes mellitus	1,252 (24.1)	543 (19.9)	358 (23.4)	189 (37.2)	162 (37.1)	<0.001	<0.001	<0.001
Previous myocardial infarction or revascularization	471 (9.1)	250 (9.2)	108 (7.1)	70 (13.8)	43 (9.8)	<0.001	0.727	0.159
Angina pectoris	338 (6.5)	190 (7.0)	68 (4.5)	47 (9.3)	33 (7.6)	<0.001	0.740	0.543
Dyslipidemia	559 (10.8)	319 (11.7)	150 (9.8)	52 (10.2)	38 (8.7)	0.107	0.076	0.027
Heart failure	39 (0.8)	12 (0.4)	10 (0.7)	7 (1.4)	10 (2.3)	<0.001	<0.001	<0.001
Cerebrovascular disease	268 (5.2)	109 (4.0)	72 (4.7)	37 (7.3)	50 (11.4)	<0.001	<0.001	<0.001
Current smoker	2,341 (45.1)	1,372 (50.4)	752 (49.2)	114 (22.4)	103 (23.6)	<0.001	<0.001	<0.001
Family history of premature coronary artery disease	329 (6.3)	210 (7.7)	90 (5.9)	14 (2.8)	15 (3.4)	<0.001	0.002	<0.001
MDRD eGFR <60 mL/min/1.73 m^2	855 (16.5)	273 (10.0)	190 (12.5)	206 (40.7)	186 (42.8)	<0.001	<0.001	
Laboratory findings								
White blood cell count (×10^3/μL)	10.9 (8.7–13.6)	10.1 (8.2–12.5)	12.7 (10.4–15.6)	8.8 (7.1–11.6)	11.3 (9.3–14.3)	<0.001	<0.001	
NLR	3.0 (1.4–5.5)	1.7 (1.0–2.6)	6.3 (5.0–8.5)	2.0 (1.3–3.0)	7.0 (5.3–10.0)	<0.001	<0.001	
Hemoglobin level (g/dL)	14.5 (13.0–15.6)	14.9 (13.9–15.9)	14.8 (13.7–15.7)	11.4 (10.5–12.1)	11.5 (10.5–12.1)	<0.001	<0.001	
Glucose (mg/dL)	180.0±81.5	172.9±74.5	179.7±76.4	197.2±97.4	205.5±108.6	<0.001	<0.001	
Total cholesterol (mg/dL)	181.8±45.6	187.2±45.6	185.3±44.0	160.7±42.3	158.2±41.0	<0.001	<0.001	
HDL cholesterol (mg/dL)	42.4±11.6	42.2±10.9	44.0±12.2	40.3±11.5	40.9±12.5	0.045	0.051	
LDL cholesterol (mg/dL)	114.7±38.7	117.7±37.7	118.6±39.4	100.6±37.0	96.5±35.7	<0.001	<0.001	
Triglyceride (mg/dL)	143.7±128.7	163.3±147.9	129.3±104.7	112.0±87.0	103.3±81.5	<0.001	<0.001	
High sensitivity C-reactive protein (mg/dL)	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.6)	0.2 (0.1–1.0)	0.4 (0.1–2.2)	<0.001	<0.001	

Values are presented as mean ± standard deviation, median (interquartile range), or number (%).
SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259. To convert triglycerides to mmol/L, multiply by 0.01129. Values for body weight are missing in 192 cases, systolic blood pressure in 19, heart rate in 19, LVEF in 295, creatinine in 6, glucose in 193, total cholesterol in 207, triglycerides in 370, HDL cholesterol in 326, and LDL cholesterol in 638.
eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; NLR, neutrophil-to-lymphocyte ratio.
*Values are from the chi-square test or Fisher's exact test for categorical variables (when appropriate) and one-way analysis of variance F test or Kruskal–Wallis test for continuous variables, to compare across the 4 groups.
†Values are from the chi-square test or Fisher's exact test for categorical variables (when appropriate) and one-way analysis of variance F test or Kruskal–Wallis test for continuous variables, to compare between patients with low NLR and no anemia and those with high NLR and anemia.
‡Values for linear trend across the groups of categorical variables.

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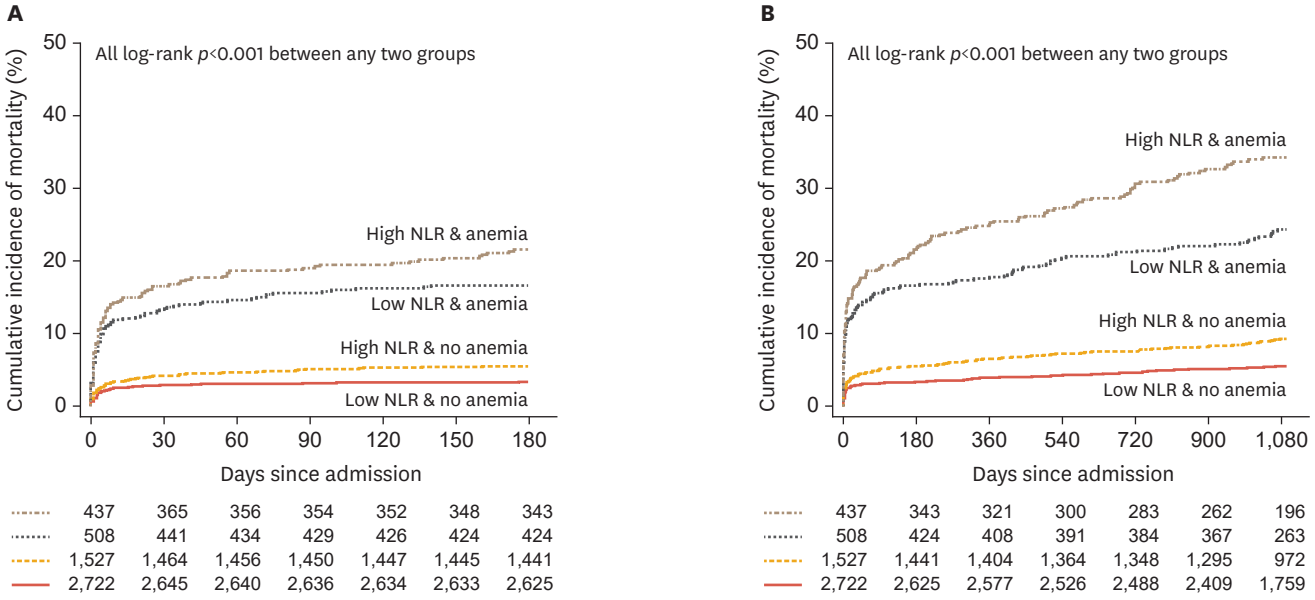

Fig. 2. Cumulative incidence of mortality over (A) 180 days and (B) 3 years. Kaplan–Meier curves show the cumulative incidence of mortality across the 4 groups stratified by the combination of NLR and anemia.
NLR, neutrophil-to-lymphocyte ratio.

DISCUSSION

In a Korean nationwide prospective cohort, there were significant differences in mortality rates after STEMI across the 4 groups stratified by the combination of NLR (high, ≥4; low, <4) and the presence of anemia on admission in all patients with diverse risk subgroups including low-risk populations (patients presenting with Killip class I, systolic blood pressure ≥100 mmHg, or heart rate ≤100 beats/minute). CBC data are readily available and reliable in the early period after STEMI for almost all patients across various levels of the health care system and maybe the only laboratory data obtainable when the critical decision is made before primary PCI for STEMI; the significant prognostic value of this combination may contribute to the early risk stratification of STEMI in real-world practice solely or when combined with other known risk prediction factors. In this study, we observed that the HRs of the combination of high NLR and anemia on admission for all-cause mortality after STEMI were striking after adjusting for baseline variables. To the best of our knowledge, this is the first large-scale nationwide cohort study to investigate the clinical value of the combination of NLR and anemia in the acute phase of STEMI.

Inflammation plays an important role in the pathogenesis of atherosclerosis and is an important risk factor for the development of cardiovascular disease.[11,12] Elevated white blood cell count or neutrophil count has been associated with reduced epicardial blood flow, myocardial reperfusion, and a higher incidence of congestive heart failure and death in patients with acute coronary syndrome.[13,14] Lymphocytes are both proatherogenic and pro-inflammatory cells participating in regulatory pathways of the immune system.[15] Lymphopenia may be a common finding during the stress response.[16] Among the total white blood cell count and its subtypes, the NLR appears to be the greatest predictor of clinical outcomes after acute coronary syndrome.[17] Two cohort studies involving consecutive patients undergoing coronary angiography for various indications revealed that high NLR was an independent predictor of CAD severity.[18,19] Recent meta-analyses have shown that a high NLR on admission appears

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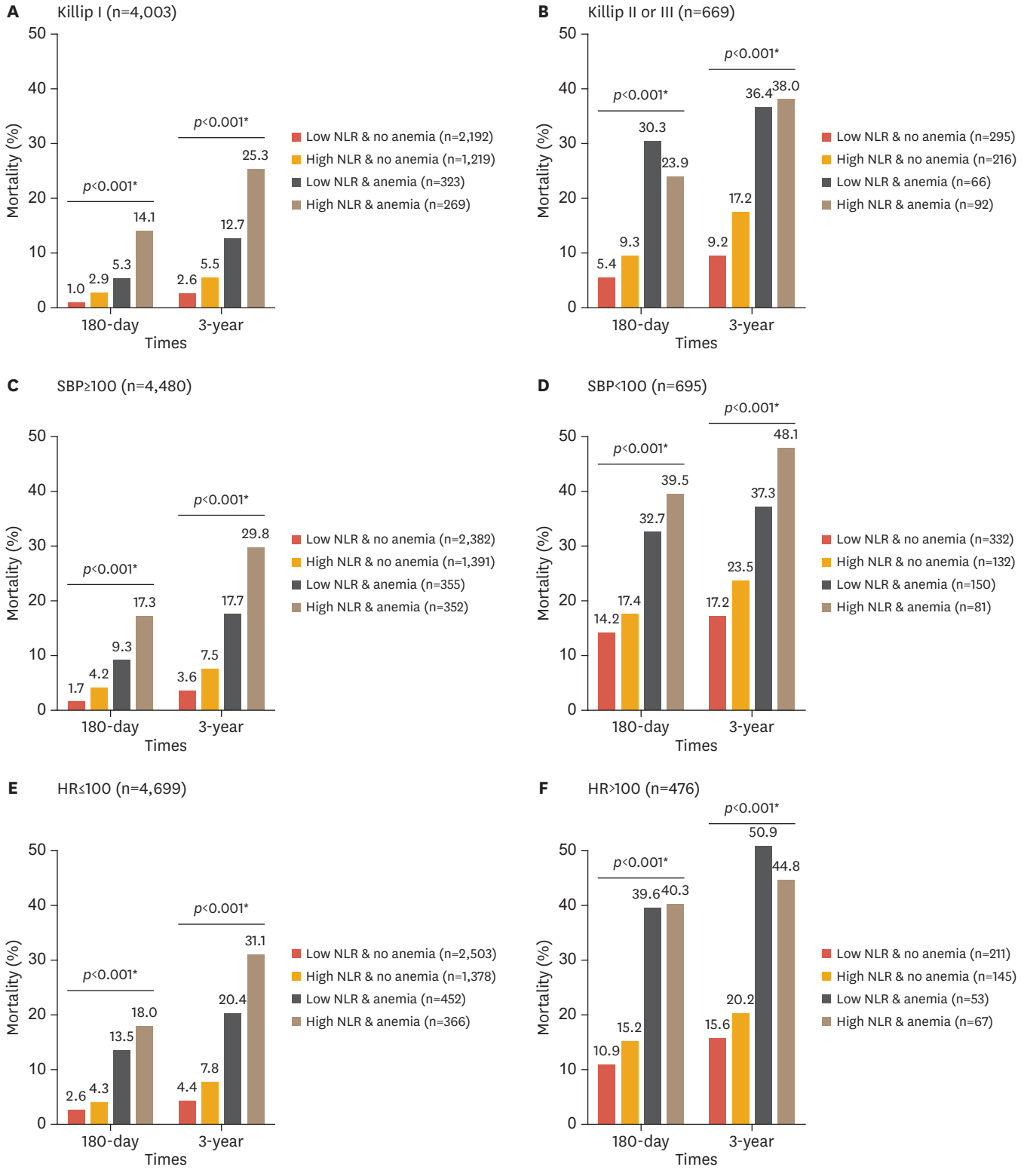

Fig. 3. Mortality rates at 180-day follow-up in diverse risk subgroups. Mortality rates across the 4 groups stratified by the combination of NLR and anemia at 180-day follow-up in diverse risk subgroups based on hemodynamic parameters.
NLR, neutrophil-to-lymphocyte ratio; HR, heart rate; SBP, systolic blood pressure.
*The *p*-values for linear trend across the groups.

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	HR (95% CI)	*p*-value
Age, yr	1.04 (1.03–1.05)	<0.001
LVEF, %	0.96 (0.96–0.97)	<0.001
Killip IV	4.68 (3.38–6.49)	<0.001
Killip III	2.40 (1.67–3.45)	<0.001
Killip II	1.49 (0.98–2.26)	0.065
High NLR and anemia*	2.16 (1.58–2.95)	<0.001
Low NLR and anemia*	1.81 (1.32–2.48)	<0.001
High NLR and no anemia*	1.41 (1.04–1.90)	0.025
Systolic blood pressure<100	1.89 (1.41–2.53)	<0.001
No PPCI	1.85 (1.33–2.57)	<0.001
eGFR<60	1.75 (1.38–2.21)	<0.001
Heart rate>100	1.68 (1.30–2.18)	<0.001
hsCPR>2	1.56 (1.22–1.99)	<0.001
Ant. STE or LBBB	1.27 (1.03–1.58)	0.029

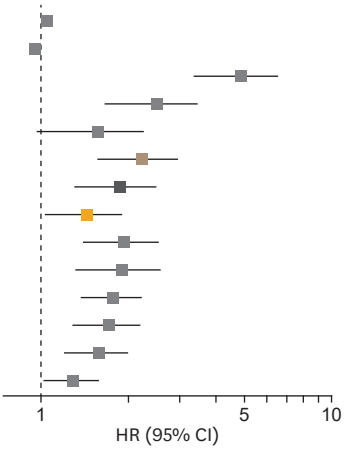

Fig. 4. Adjusted predictive values of variables for 180-day mortality. Cox regression analysis was performed using the backward elimination method.
CI, confidence interval; eGFR, estimated glomerular filtration rate; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NLR, neutrophil-to-lymphocyte ratio; PPCI, primary percutaneous coronary intervention; hsCRP, high sensitivity C-reavtive protein; STE, ST-segment elevation; HR, hazard ratio; CI, confidence interval.
*Variables were analyzed with the low NLR and no anemia group as the reference.

to be associated with all-cause mortality and cardiovascular events in patients with CAD, including STEMI.[6] The prevalence of anemia in patients undergoing PCI for CAD is reported to be approximately 16%.[8] Anemic patients with CAD are prone to oxygen demand and supply mismatch during or after PCI. Pilgrim et al.[20] analyzed 6,528 consecutive patients undergoing PCI and reported that anemia was associated with worse clinical outcomes after PCI. Furthermore, patients with anemia in their study were older and had more comorbidities (e.g., diabetes mellitus and renal insufficiency) than those without anemia. In a national registry of 92,686 patients with STEMI, anemia was associated with an increased prevalence of other preexisting comorbidities and decreased use of guideline-based pharmacological treatment.[7] A recent meta-analysis examined a total of 44 studies with 230,795 patients undergoing PCI and showed that anemia was associated with a significant increase in postprocedural mortality, major adverse cardiac events, reinfarction, and bleeding.[8]

The results of previous studies suggest that a combination of NLR and anemia represents a hematologically integrated assessment of health status, CAD severity, and host responsiveness to acute stress. However, data regarding the clinical use of this combination in the early risk stratification of patients with STEMI are limited. Furthermore, most previous studies regarding NLR in patients with CAD have employed tertiles or quartiles of distribution, which hinders consistent external validation and limits the generalizability of the findings.[6] Although Niu et al.[21] developed a risk stratification tree model using white blood cell count, hemoglobin, and mean platelet volume, it did not include the NLR. Recently, Oh et al.[22] analyzed 1,057 patients with STEMI and demonstrated that the addition of elevated serum transaminase, dysglycemia, anemia, and high NLR improved the prognostic performance of the TIMI risk score for the prediction of 1-year mortality. Previously verified predictors in the early risk stratification for STEMI include not only the indicators of health status or CAD severity, such as older age, renal insufficiency, and previous angina or MI, but also hemodynamic parameters, such as low blood pressure, elevated heart rate, and high Killip class at presentation. The latter may involve CAD severity, health status, and host responsiveness to acute stress. The combination of high NLR and anemia may be a valuable marker for the

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prediction of future atherosclerotic cardiovascular disease events in a manner similar to that observed with hemodynamic parameters. In 2018, a previous study from KAMIR-NIH investigated the prognostic value of the combination of NLR and anemia on 180-day clinical outcomes in 6,157 patients with non-STEMI.[23] It demonstrated that there were significant differences in clinical outcomes during 180-day follow-up among 3 groups stratified by NLR and the presence of anemia. The combination of high NLR and anemia was found to be independently associated with an increased incidence of major adverse cardiac events at 180 days with the combination of low NLR and no anemia as the reference (HR, 2.47; 95% CI, 1.50–4.07; p<0.001). In our study, the patients with high NLR and baseline anemia were more likely to have longer symptom-to-door times and multivessel coronary disease, and were less likely to receive PCI, stenting, successful PCI, aspirin, potent $P2Y_{12}$ inhibitors, beta-blockers, renin–angiotensin–aldosterone blockers, and statins. In conclusion, the combination of high NLR and anemia appears to be associated with worse health status, more severe CAD, later presentation, consequent unfavorable responsiveness to acute stress and less effective treatments, which result in poor prognosis after STEMI. Herein, the HRs for the combination of high NLR and anemia for prediction were striking after adjusting for key variables, such as old age, high Killip class, low blood pressure, elevated heart rate, and renal insufficiency.

Many risk stratification tools have been developed for initial triage after acute coronary syndrome or STEMI.[24-29] Examples of these are presented in **Supplementary Table 6**. The TIMI and Global Registry of Acute Coronary Events (GRACE) scores are recommended by the guidelines in the acute phase of STEMI.[1,2] The TIMI score is a bedside risk score for patients with STEMI.[24] It was developed 20 years ago and was derived from the InTIME-II trial, which was not a real-world prospective cohort study, but a randomized controlled trial.[30] The trial was performed to investigate the efficacy and safety of a thrombolytic agent in patients presenting within 6 hours of symptom onset and did not include patients with previous cerebrovascular accidents or concomitant use of oral anticoagulants. The GRACE score was developed and validated from the multinational registry of acute coronary events study involving patients with or without ST-segment elevation between 1999 and 2005.[28] Patients presenting with Killip class IV comprised approximately 1% of the population, and optimal medical therapy and mechanical revascularization were underutilized.[31,32] In the KAMIR-NIH cohort, 10% of patients had Killip class IV at presentation, and the rates of receiving aspirin, a $P2Y_{12}$ inhibitor, and statins were 99.5%, 97.5%, and 90.8%, respectively. Furthermore, the rates of receiving coronary angiogram and PCI were 99.5% and 97.3%, respectively.

When a patient with STEMI arrives at a health care unit, some known risk factors such as past medical history, body weight, or symptom-to-treatment time may not be available or reliable for selected patients owing to the patient-oriented approach. Conversely, CBC data are available and reliable in the early period after STEMI for almost all patients. Furthermore, it is feasible in terms of cost at any level of the health care system, even in low socioeconomic areas where hospital resources are scarce. In this study, 2.7% (141/5,194) of patients had missing body weight data, whereas only 0.2% (8/5,202) had missing CBC data. Moreover, CBC data may help primary health care facilities to assess the prognosis of patients with STEMI and maybe the only laboratory data available during hospital transfers at lower levels of the health care system before primary PCI for STEMI.

Our study has several limitations. First, the contributing hospitals in the KAMIR-NIH tended to be larger volume centers than the average hospital. Thus, the mortality rates may not be generalizable to all hospitals dealing with patients with STEMI. Second, automated analyzers

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for hematological measurements were used at each center, not the core center, and using a cutoff value of 4 for the NLR may be arbitrary. Third, our study lacked data regarding comorbidities associated with high NLR, the cause of baseline anemia, and bleeding outcomes. Furthermore, despite adjusting for 24 baseline variables, residual confounders may have been omitted. Fourth, our study was based on a single-country registry and not a multinational registry; thus, the results need to be validated in other countries. However, compared with multinational registries, single-country registries appear to have more homogeneity in unmeasured variables that may affect clinical outcomes, such as genetics, hospital resources, and procedural techniques. Moreover, the combination of NLR and anemia on admission is a harmonized mixture of potential prognostic risk factors, rather than a newly developed tool from a restricted dataset.

In conclusion, in a Korean nationwide prospective cohort study, the combination of NLR and anemia on admission was strongly associated with all-cause mortality after STEMI, even in diverse low-risk subgroups. This study indicates that CBC data, which are readily available regarding time and cost across diverse levels of the health care system, may contribute significantly to early risk stratification of patients with STEMI. Further studies are warranted to develop a novel risk scoring system involving CBC data in the acute phase of STEMI.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1
Methods

Click here to view

Supplementary Table 1
Angiographic characteristics and medical treatments across the 4 groups

Click here to view

Supplementary Table 2
Clinical outcomes across the 4 groups

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Supplementary Table 3
Cox proportional hazards models of 180-day mortality

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Supplementary Table 4

Cox proportional hazards models of 3-year mortality

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Supplementary Table 5

Cox proportional hazards models of 180-day mortality in STEMI patients treated with primary PCI (n=4,941)

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Supplementary Table 6

Risk score models for initial triage after presentation with acute coronary syndrome and their components

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Supplementary Fig. 1

ROC curves of NLR and hemoglobin levels for 180-day mortality. (A) NLR and 180-day mortality and (B) hemoglobin levels and 180-day mortality. The optimal cutoff value of NLR for 180-day mortality was 4.87 by ROC curve analysis. The optimal cutoff value of hemoglobin levels for 180-day mortality was 13.7 mg/dL by ROC curve analysis.

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Supplementary Fig. 2

Linear regression analysis. Simple linear regression analysis of (A) age and NLR (r=0.131; $p<0.001$), (B) age and hemoglobin levels (r=−0.502; $p<0.001$), (C) S2DT and NLR (r=0.257; $p<0.001$), (D) S2DT and hemoglobin levels (r=−0.080; $p<0.001$), (E) creatinine and NLR (r=0.031; $p=0.024$), and (F) creatinine and hemoglobin levels (r=−0.170; $p<0.001$).

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Supplementary Fig. 3

Mortality rates across the 4 groups during the 180-day follow-up in diverse risk subgroups. Mortality rates at 180 days stratified by the combination of NLR and baseline anemia in diverse risk subgroups: (A) age <65 years, (B) age ≥65 years, (C) eGFR ≥60 mL/min/1.73 m^2, (D) eGFR <60 mL/min/1.73 m^2, (E) LVEF ≥40%, and (F) LVEF <40%.

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