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Incremental predictive value of the combined use of the neutrophil-to-lymphocyte ratio and systolic blood pressure difference after successful drug-eluting stent implantation

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Abstract

Background: *Previous work has highlighted the importance of the neutrophil-to-lymphocyte ratio (NLR) and the difference in the ward-to-catheterization laboratory systolic blood pressure (ΔSBP) in prognostic stratification after acute coronary syndrome. However, there is paucity of data regarding the added value of combining these two variables to predict 5-year major clinical outcomes after percutaneous coronary intervention.*

Methods: *A total of 1188 patients were classified into four groups according to the NLR and ΔSBP (high vs. low) using cutoffs derived from an analysis of receiver operating characteristic curves. A NLR > 3.0 and a ΔSBP > 25 mmHg were considered high values. The primary endpoint was the composite of all-cause death, cardiac death, and non-fatal myocardial infarction. The secondary endpoint was the composite of target lesion revascularization, target vessel revascularization, and incidence of cerebrovascular accidents.*

Results: *The incidence of the primary endpoint was significantly higher in the high NLR and ΔSBP group than in the other three groups (2.2% vs. 4.7% vs. 4.3% vs. 13.2%, $p < 0.001$). The incidence of the secondary endpoint was similar among the four groups. Incorporation of high NLR and high ΔSBP into a model with conventional and meaningful clinical and procedural risk factors increased the C-statistics in predicting the primary endpoint (0.575 to 0.635, $p = 0.002$).*

Conclusions: *The power to predict the primary endpoint after drug-eluting stent implantation at the 5-year follow-up was improved by combining NLR and ΔSBP.* (Cardiol J)

Key words: blood pressure difference, drug-eluting stent, neutrophil-to-lymphocyte ratio, outcomes, percutaneous coronary intervention

Introduction

The fundamental mechanism of coronary artery disease (CAD) is stenosis caused by inflammation and atherosclerosis [1]. The earliest type of atherosclerotic lesion observed is a pure inflammatory lesion composed mainly of monocyte-derived macrophages and T-lymphocytes [2]. Arbel et al. [3] demonstrated that a high neutrophil-to-lymphocyte ratio (NLR) is significantly associated with higher

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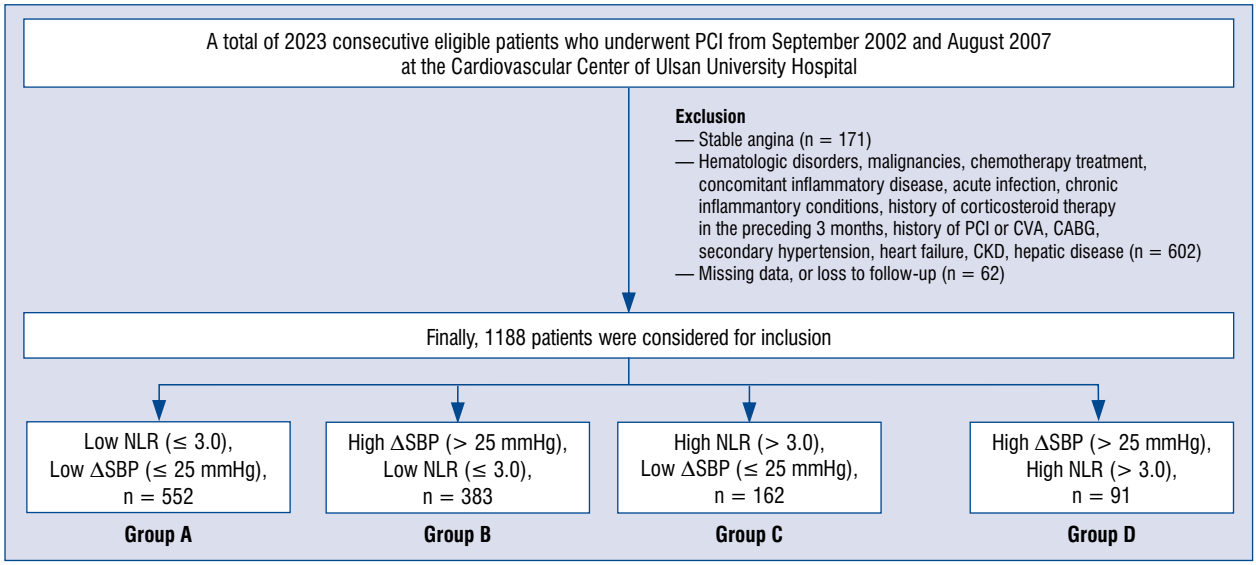

Figure 1. Flow chart; CABG — coronary artery bypass grafting; CKD — chronic kidney disease; CVA — cardiovascular accidents; NLR — neutrophil-to-lymphocyte ratio; PCI — percutaneous coronary intervention; ΔSBP — differences in ward-to-catherization laboratory systolic blood pressure.

rates of 5-year mortality; therefore, the NLR could potentially be used to formulate prognosis in addition to conventional risk factors. Many other reports also emphasize the valuable role of NLR in CAD [4–6].

Another important causative factor of CAD is systolic arterial hypertension, which is associated with adverse cardiac events including such as death; as it is also associated with stress and other known psychosocial risk factors for CAD, it elevates the risk of cardiovascular sequelae [7, 8]. Coronary angiography (CAG) or percutaneous coronary intervention (PCI) may be accompanied by stress in healthy individuals. A meta-analysis suggested that greater responsiveness to acute mental stress has an adverse effect on future cardiovascular risk status; for example, a composite of elevated blood pressure (BP), increased left ventricular mass, subclinical atherosclerosis, and clinical cardiac events [9]. It would be very informative if we could predict long-term prognosis of the patients who are going to have CAG or PCI before these operations begin. Her et al. [10] suggested that changes in peri-procedural BP may be significantly associated with major adverse cardiac events and reported that a difference in the ward-to-catheterization laboratory systolic BP (SBP) (ΔSBP) of > 20 mmHg was related to an increased rate of all-cause death and cardiac death (CD) after drug-eluting stent (DES) implantation. In actual clinical practice, minimally invasive or non-invasive, inexpensive diagnostic tools are preferred over invasive diagnostic tools in view of cost and patient safety [11]. In this regard, the NLR and ΔSBP are very useful non-invasive diagnostic tools for predicting adverse cardiac events. However, most previous studies [4–6, 10, 12] focused only on one of those two parameters. Moreover, data showing the complementary actions and combined usefulness of NLR and ΔSBP in patients diagnosed with acute coronary syndrome (ACS) are limited. Therefore, we investigated the additional predictive power of the NLR and ΔSBP in comparison with that of conventional clinical and procedural risk factors in predicting 5-year major clinical outcomes after DES implantation.

Methods

Study design and population

This retrospective observational study enrolled 2023 consecutive eligible patients who underwent PCI for ACS between September 2002 and August 2007 at the Cardiovascular Center of Ulsan University Hospital, Ulsan, South Korea. Data on cardiovascular risk factors and medical histories were self-reported by the patients. Patients were excluded if they had (1) stable angina (n = 171, 8.5%); (2) any systemic diseases or treatment modality potentially affecting the white blood cells as shown in Figure 1 (n = 602, 29.8%); and (3) missing data or patients were lost to follow-up (n = 62, 3.1%). Finally, 1188 patients were included in the study (Fig. 1). The study protocol complied

with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ulsan University Hospital Institutional Review Board. Written informed consent was obtained from all participants. The enrolled patients were required to visit the cardiology out-patient department at the end of the first month and every 3 to 6 months thereafter for 5 years for clinical follow-up data to be collected through face-to-face interviews, medical chart reviews, and telephone contact.

Study method and medical treatment

During admission, venous blood samples were taken to assess the following: (1) complete blood cell counts, which included total white blood cells, differential counts (neutrophils, lymphocytes, monocytes, eosinophils), red blood cell, and platelet counts; (2) cardiac enzymes (creatine kinase myocardial band [CK-MB] and cardiac troponin T); and (3) other blood chemistry parameters (high-sensitivity C-reactive protein, serum creatinine, estimated glomerular filtration rate [eGFR], and lipid profiles). NLR was defined as the ratio of the neutrophil count to the lymphocyte count. The method of BP measurement has been described previously [10]. In brief, patients were measured with the resting right arm BP in the supine position in a ward setting, before transfer to the catheterization laboratory, where it was measured again after the patients had laid down on the catheterization laboratory table prior to any arterial puncture or PCI (ward-to-catheterization laboratory BP difference). Differences were estimated in the systolic and diastolic BP and heart rate obtained in the ward and catheterization laboratory, with the measurements taken by trained nurses using an auscultatory sphygmomanometer. The BP and heart rate were measured twice for each location, with at least a 1-minute interval between recordings and the mean values were used in the analysis. The stents were deployed using standard PCI techniques [13]. A successful PCI was defined as an angiographic residual stenosis diameter of < 30% in the presence of thrombolysis in myocardial infarction (TIMI) grade 3 flow. After DES implantation, a minimum of 1 year of dual antiplatelet therapy was administered (100 mg acetylsalicylic acid daily and 75 mg clopidogrel daily).

Study definitions and clinical endpoints

The primary endpoint was the composite of all-cause death, CD, and non-fatal myocardial infarction (MI). The secondary endpoint was the composite of target lesion revascularization (TLR), target vessel revascularization (TVR), and cerebrovascular accidents at 5-year follow-up. All-cause death was defined as either of CD or non-CD. Non-fatal MI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI, combined with an increase in the CK-MB fraction above the upper normal limits or an increase in troponin-T/troponin-I to greater than the 99th percentile of the upper normal limit after index PCI [14–16]. The definitions of TLR and TVR have been previously described [17]. The mean eGFR was calculated using the Modification of Diet in Renal Disease equation [18].

Statistical analysis

All statistical analyses were performed using SPSS v20 (IBM; Armonk, NY, USA). For continuous variables, differences among the three groups were evaluated using the analysis of variance or the Jonckheere-Terpstra test, and post-hoc analysis between the two groups was carried out using the Hochberg test or Dunnett-T3 test. Data are expressed as the means ± standard deviations. For discrete variables, the differences between two out of the three groups were analyzed using the χ^2 test or the Fisher exact test, as appropriate; data are expressed as counts and percentages [19]. In a multivariable Cox proportional hazard regression analysis, the baseline confounding covariates were selected if they were significantly different ($p < 0.001$) among the four groups or between the two groups or had predictive values. The multivariable Cox proportional hazard regression analysis including baseline confounding factors, was used to compare the clinical endpoints among the four groups or between the two groups. Survival analysis among the four groups was performed using the Kaplan-Meier method, and differences between the two groups were assessed using the log-rank test. Receiver operating characteristic (ROC) curves were used to differentiate the ability of the NLR and ΔSBP to predict primary endpoint (Fig. 2). After evaluating the relationship of the NLR and ΔSBP with the clinical outcomes using Cox proportional hazard regression analysis, we compared the incremental value of combining a high NLR and a high ΔSBP into the context of conventional and meaningful clinical and procedural characteristics for prediction of the primary endpoint. Estimates of the C-statistics for the Cox regression models were computed using the method of Pencina and D'Agostino [20]. Differences in the C-statistics (with 95% confidence interval [CI])

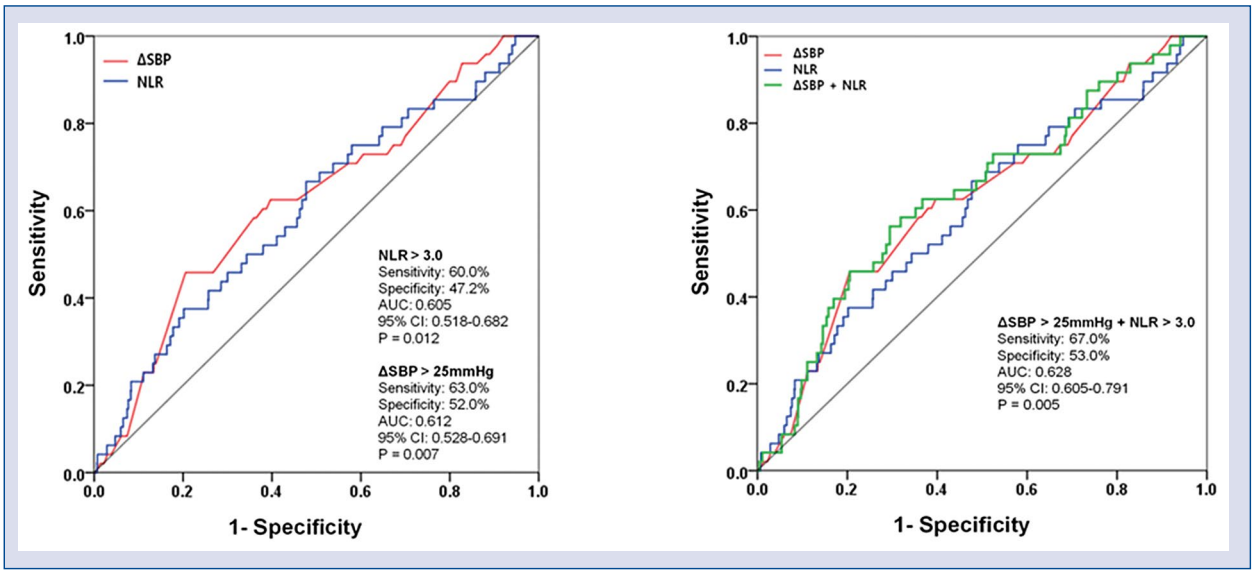

Figure 2. Receiver operating characteristic curve of neutrophil-to-lymphocyte ratio (NLR) and difference in the ward--to-catheterization laboratory systolic blood pressure (ΔSBP) for primary endpoints.

after the addition of the high NLR and high ΔSBP to a model with conventional and meaningful clinical and procedural risk factors were obtained using the bootstrap percentile method (200 replicates) [21]. The statistical significance level was set at a p-value of < 0.05 using a two-tailed test.

Results

Cutoff values for the NLR and ΔSBP

Analysis of the ROC curve was performed to detect the best NLR cutoff value that predicted the primary endpoint. This yielded a cutoff NLR of 3.0, with a sensitivity of 60.0%, a specificity of 47.2%, and an area under the ROC curve of 0.605 (95% CI: 0.518–0.682) (Fig. 2). Therefore, NLRs of > 3.0 (n = 253, 21.3%) and ≤ 3.0 (n = 935, 78.7%) were considered to be high and low values, respectively. Thereafter, the subjects were sub-divided according to ΔSBP. In the same manner, an ROC curve analysis was used to detect the best cutoff value of ΔSBP for predicting the primary endpoint. This yielded a cutoff ΔSBP of 25 mmHg, with a sensitivity of 63.0%, a specificity of 52.0%, and an area under the ROC curve of 0.612 (95% CI: 0.528–0.691; Fig. 2). ΔSBP > 25 mmHg (n = 474, 39.9%) and ≤ 25 mmHg (n = 714, 60.1%) were considered to be high and low values, respectively. The patients were classified into four groups according to the NLR and ΔSBP (high vs. low) using the cutoffs derived from the analysis of the ROC curves: group A (low NLR [≤ 3.0] and low ΔSBP [≤ 25 mmHg], n = 552, 46.5%), group B (high ΔSBP [> 25 mmHg] and low NLR [≤ 3.0], n = 383, 32.2%), group C (high NLR [> 3.0] and low ΔSBP [≤ 25 mmHg], n = 162, 13.6%), and group D (high ΔSBP [> 25 mmHg] and high NLR [> 3.0], n = 91, 7.7%).

Baseline clinical and angiographic characteristics

The baseline laboratory and angiographic characteristics according to the NLR and ΔSBP are summarized in Table 1. The mean age of the total study population was 60.5 ± 10.3 years, and the oldest patient was included in group D. The mean left ventricular ejection fraction (LVEF) of the total study population was 61.6 ± 10.3%. The number of patients with hypertension and unstable angina was the highest in group B. The number of acute MI was the highest in group C. The mean serum creatinine level was the highest in group D. However, the number of patients with a history of diabetes mellitus, dyslipidemia, and MI; number with left anterior descending artery, left circumflex artery, and right coronary artery as the treated vessels; American College of Cardiology/ /American Heart Association lesion type; extent of CAD; number of deployed stents; mean diameter of deployed stents; and mean length of deployed stents were not significantly different among the four groups.

Table 1. Baseline clinical, laboratory, angiographic and procedural characteristics.

Variables	Group A Low NLR ≤ 3.0 Low ΔSBP ≤ 25 mmHg (n = 552)	Group B High ΔSBP > 25 mmHg Low NLR ≤ 3.0 (n = 383)	Group C High NLR > 3.0 Low ΔSBP ≤ 25 mmHg (n = 162)	Group D High ΔSBP > 25 mmHg High NLR > 3.0 (n = 91)	P value						
					Group A vs. B	Group A vs. C	Group A vs. D	Group B vs. C	Group B vs. D	Group C vs. D	Group A vs. B vs. C vs. D
Men	164 (29.7%)	168 (43.9%)	47 (29.0%)	32 (35.2%)	< 0.001	0.922	0.326	0.001	0.156	0.325	< 0.001
Age [years]	58.9 ± 10.1	62.4 ± 9.9	60.2 ± 11.5	62.8 ± 10.0	< 0.001	0.214	0.001	0.039	0.704	0.063	< 0.001
BMI [kg/m^2]	24.4 ± 2.9	24.7 ± 3.0	24.0 ± 3.2	23.9 ± 3.3	0.066	0.271	0.280	0.023	0.046	0.837	0.036
Hypertension	248 (44.9%)	228 (59.5%)	78 (46.9%)	52 (57.1%)	< 0.001	0.655	0.032	0.008	0.722	0.149	< 0.001
Diabetes mellitus	137 (24.8%)	91 (23.8%)	38 (23.5%)	21 (23.0%)	0.757	0.756	0.793	0.939	0.890	0.945	0.956
Dyslipidemia	170 (30.8%)	136 (35.5%)	40 (24.7%)	28 (30.8%)	0.137	0.142	0.996	0.016	0.462	0.305	0.090
Previous MI	9 (1.6%)	8 (2.1%)	4 (2.5%)	2 (2.2%)	0.623	0.505	0.660	0.756	0.948	0.892	0.898
Current smokers	114 (20.7%)	79 (20.6%)	18 (11.1%)	16 (17.6%)	0.992	0.006	0.574	0.007	0.563	0.179	0.041
Unstable angina	420 (76.1%)	308 (80.4%)	67 (41.3%)*	53 (58.2%)	0.128	< 0.001	0.001	< 0.001	< 0.001	0.013	< 0.001
NSTEMI	87 (15.8%)	52 (13.6%)	55 (34.0%)*	21 (23.1%)	0.400	< 0.001	0.096	< 0.001	0.035	0.086	< 0.001
STEMI	45 (8.1%)	23 (6.0%)	40 (24.7%)*	17 (18.7%)	0.249	< 0.001	0.003	< 0.001	< 0.001	0.347	< 0.001
LVEF [%]	62.1 ± 6.9	62.2 ± 6.7	59.3 ± 8.4*	60.0 ± 7.3	0.866	< 0.001	0.010	< 0.001	0.009	0.487	< 0.001
White blood cell [×10^9/L]:	7.5 ± 2.3	7.3 ± 2.2	10.2 ± 3.3*	9.6 ± 3.2	0.040	< 0.001	< 0.001	< 0.001	< 0.001	0.160	< 0.001
Neutrophil [%]	54.9 ± 8.4	54.8 ± 8.5	75.5 ± 6.3*	75.1 ± 7.2	0.787	< 0.001	< 0.001	< 0.001	< 0.001	0.634	< 0.001
Lymphocyte [%]	33.9 ± 7.7	34.0 ± 7.7	16.6 ± 4.4*	16.7 ± 4.4	0.816	< 0.001	< 0.001	< 0.001	< 0.001	0.923	< 0.001
Monocyte [%]	5.8 ± 2.4	5.6 ± 2.0	4.6 ± 2.2*	4.4 ± 1.8	0.096	< 0.001	< 0.001	< 0.001	< 0.001	0.400	< 0.001
Eosinophil [%]	3.3 ± 3.0	3.4 ± 3.0	1.9 ± 1.7*	2.4 ± 2.8	0.949	< 0.001	0.003	< 0.001	0.003	0.100	< 0.001
Hemoglobin [g/dL]	14.0 ± 1.6	13.4 ± 1.7	13.9 ± 2.8	13.1 ± 2.1	< 0.001	0.690	< 0.001	0.062	0.110	0.009	< 0.001
Hematocrit [%]	41.0 ± 15.6	38.9 ± 4.7	39.8 ± 4.9	38.0 ± 6.0	0.003	0.119	0.001	0.042	0.158	0.011	0.011
Platelet [×10^9/L]	254.8 ± 67.9	256.4 ± 62.6	260.8 ± 82.0	258.1 ± 73.5	0.716	0.402	0.692	0.546	0.839	0.792	0.803
NLR	1.75 ± 0.60	1.74 ± 0.59	5.26 ± 3.20	5.41 ± 3.31	0.754	< 0.001	< 0.001	< 0.001	< 0.001	0.735	< 0.001
Ward SBP [mmHg]	131.3 ± 18.8	126.3 ± 19.5	125.4 ± 18.4	125.3 ± 19.0	< 0.001	0.001	0.006	0.598	0.644	0.972	< 0.001
Cath lab SBP [mmHg]	140.0 ± 20.6	162.3 ± 24.4	131.4 ± 21.0	159.4 ± 22.4	< 0.001	< 0.001	< 0.001	< 0.001	0.277	< 0.001	< 0.001
ΔSBP [mmHg]	12.4 ± 7.5	42.2 ± 14.5	11.1 ± 7.5†	41.1 ± 12.3	< 0.001	0.060	< 0.001	< 0.001	0.462	< 0.001	< 0.001
hs-CRP [mg/dL]	0.55 ± 2.09	0.40 ± 0.93	1.79 ± 3.55	1.51 ± 3.23	0.234	< 0.001	0.019	< 0.001	0.006	0.581	< 0.001
Serum creatinine [mg/L]	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.4	1.3 ± 1.1	0.389	0.170	0.028	0.064	0.021	0.072	< 0.001
eGFR [mL/min/1.73 m^2]	71.4 ± 16.0	68.6 ± 14.8	70.2 ± 16.6	64.7 ± 19.5	0.005	0.423	0.002	0.272	0.078	0.024	0.001
Peak CK-MB [mg/dL]	18.7 ± 2.9	14.7 ± 2.8	78.1 ± 8.0	68.4 ± 5.6	0.166	< 0.001	0.003	< 0.001	0.001	0.632	< 0.001

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Table 1 (cont.). Baseline clinical, laboratory, angiographic and procedural characteristics.

Variables	Group A Low NLR ≤ 3.0 Low ΔSBP ≤ 25 mmHg (n = 552)	Group B High ΔSBP > 25 mmHg Low NLR ≤ 3.0 (n = 383)	Group C High NLR > 3.0 Low ΔSBP ≤ 25 mmHg (n = 162)	Group D High ΔSBP > 25 mmHg High NLR > 3.0 (n = 91)	P value						
					Group A vs. B	Group A vs. C	Group A vs. D	Group B vs. C	Group B vs. D	Group C vs. D	Group A vs. B vs. C vs. D
Peak troponin-T [ng/mL]	0.87 ± 0.15	0.71 ± 0.09	3.88 ± 1.65	2.46 ± 0.43	0.311	< 0.001	0.007	< 0.001	0.003	0.064	< 0.001
Total cholesterol [mg/dL]	193.5 ± 39.3	195.1 ± 44.2	192.0 ± 43.4	186.3 ± 42.5	0.569	0.693	0.133	0.449	0.080	0.311	0.329
Triglyceride [mg/L]	150.0 ± 86.1	151.9 ± 101.7	129.7 ± 87.9,	116.2 ± 62.0	0.777	0.012	< 0.001	0.013	< 0.001	0.162	0.001
HDL cholesterol [mg/L]	41.8 ± 16.2	41.5 ± 10.3	46.0 ± 53.4	40.8 ± 53.4	0.702	0.324	0.480	0.294	0.626	0.245	0.184
LDL cholesterol [mg/L]	114.5 ± 36.1	117.3 ± 37.7	111.0 ± 34.7	110.1 ± 34.7	0.286	0.276	0.281	0.070	0.093	0.855	0.194
Discharge medications:											
Acetylsalicylic acid	548 (99.3%)	378 (98.7%)	162 (100.0%)	89 (97.8%)	0.499	0.579	0.203	0.329	0.624	0.128	0.265
Clopidogrel	544 (98.6%)	377 (98.4%)	161 (99.4%)	90 (98.9%)	0.885	0.692	0.792	0.680	0.740	0.678	0.832
Beta-blocker	220 (39.9%)	152 (39.7%)	56 (34.6%)	42 (46.2%)	0.959	0.234	0.300	0.289	0.286	0.081	0.339
CCB	121 (21.9%)	97 (25.3%)	36 (22.2%)	24 (26.4%)	0.239	0.915	0.345	0.513	0.894	0.538	0.564
Nitrate	266 (1.7%)	186 (1.6%)	60 (2.1%)	47 (2.3%)	0.947	0.015	0.572	0.014	0.641	0.034	0.047
ACEI	177 (32.1%)	143 (37.3%)	43 (26.5%)	33 (36.3%)	0.107	0.208	0.469	0.018	0.904	0.117	0.076
ARB	53 (9.6%)	45 (11.7%)	33 (20.4%)	16 (17.6%)	0.329	0.001	0.028	0.011	0.162	0.623	0.001
Lipid lowering agents	452 (81.9%)	314 (82.0%)	140 (86.4%)	70 (76.9%)	0.969	0.193	0.251	0.258	0.298	0.058	0.290
Treated vessels:											
LAD	252 (45.7%)	197 (51.4%)	80 (49.4%)	51 (56.0%)	0.084	0.421	0.070	0.708	0.484	0.359	0.159
LCx	204 (37.0%)	130 (33.0%)	61 (37.7%)	32 (35.2%)	0.367	0.926	0.815	0.433	0.902	0.786	0.767
RCA	224 (1.7%)	146 (1.6%)	54 (2.1%)	35 (2.3%)	0.456	0.100	0.731	0.331	0.952	0.415	0.416
Left main	24 (4.3%)	20 (5.2%)	3 (1.9%)	4 (4.4%)	0.534	0.166	0.983	0.101	0.747	0.255	0.368
ACC/AHA lesion type:											
Type B1	102 (18.5%)	77 (20.1%)	21 (13.0%)	19 (20.9%)	0.555	0.124	0.565	0.047	0.885	0.108	0.231
Type B2	159 (28.8%)	123 (32.1%)	52 (32.1%)	32 (35.2%)	0.278	0.434	0.218	0.997	0.619	0.677	0.516
Type C	114 (20.7%)	88 (23.0%)	30 (18.5%)	20 (22.0%)	0.419	0.280	0.781	0.258	0.890	0.515	0.670
Extent of CAD:											
1 vessel disease	439 (79.5%)	310 (80.9%)	134 (82.7%)	68 (74.7%)	0.618	0.432	0.332	0.718	0.193	0.143	0.454
2 vessel disease	75 (13.0%)	42 (11.0%)	20 (12.3%)	15 (16.5%)	0.269	0.793	0.514	0.659	0.153	0.448	0.458
≥ 3 vessel disease	38 (6.9%)	31 (8.1%)	8 (4.9%)	8 (8.8%)	0.526	0.468	0.510	0.209	0.832	0.283	0.545

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Table 1 (cont.). Baseline clinical, laboratory, angiographic and procedural characteristics.

Variables	Group A	Group B	Group C	Group D	P value						
	Low NLR ≤ 3.0 Low ΔSBP ≤ 25 mmHg (n = 552)	High ΔSBP > 25 mmHg Low NLR ≤ 3.0 (n = 383)	High NLR > 3.0 Low ΔSBP ≤ 25 mmHg (n = 162)	High ΔSBP > 25 mmHg High NLR > 3.0 (n = 91)	A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D	A vs. B vs. C vs. D
Number of stent	1.53 ± 0.81	1.58 ± 0.85	1.50 ± 0.76	1.72 ± 0.91	0.501	0.821	0.158	0.522	0.306	0.186	0.438
Stent diameter [mm]	3.19 ± 0.32	3.16 ± 0.30	3.18 ± 0.31	3.49 ± 2.77	0.305	0.789	0.441	0.741	0.398	0.423	0.104
Stent length [mm]	40.3 ± 25.1	41.3 ± 23.9	40.4 ± 21.9	45.6 ± 28.1	0.638	0.967	0.206	0.794	0.310	0.297	0.554
Median follow-up duration [days]	1889.5 ± 828.5	1987.5 ± 870.5	1901.5 ± 791.8	1895.5 ± 948.5	0.100	0.412	0.542	0.114	0.112	0.640	0.132

Values are means ± standard deviation or numbers and percentages. The p value for continuous data was obtained from the analysis of variance or the Jonckheere-Terpstra test. The p value for categorical data was obtained from the chi-square or the Fisher exact test.
NLR — neutrophil-to-lymphocyte ratio; ΔSBP — difference in ward-to-catheterization laboratory systolic blood pressure; BMI — body mass index; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction; LVEF — left ventricular ejection fraction; hs-CRP — high sensitivity-C-reactive protein; eGFR — estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease equation); CK-MB — creatine kinase myocardial band; HDL — high-density lipoprotein; LDL — low-density lipoprotein; CCB — calcium channel blocker; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II type 1 receptor blocker; LAD — left arterior descending artery; LCx — left circumflex artery; RCA — right coronary artery; ACC/AHA — American College of Cardiology/American Heart Association; CAD — coronary artery disease

Clinical outcomes

The cumulative incidence of the primary endpoint, all-cause death, CD, and secondary endpoint are summarized in Table 2, Figure 3, and **Supplemental Online Material 1**. After adjustment, the cumulative incidence of the primary endpoint in group D was significantly higher than that in group A (adjusted hazard ratio [aHR]: 1.920; 95% CI: 1.462–2.522; $p < 0.001$), group B (aHR: 1.751; 95% CI: 1.186–2.584; $p = 0.005$), and group C (aHR: 3.514; 95% CI: 1.481–9.640; $p = 0.015$) (Table 2, Fig. 3A). Similarly, the cumulative incidence of all-cause death was significantly higher in group D than in group A (aHR: 2.466; 95% CI: 1.721–3.532; $p < 0.001$), group B (aHR: 1.767; 95% CI: 1.168–2.603; $p = 0.007$), and group C (aHR: 3.191; 95% CI: 1.065–9.557; $p = 0.038$) (Table 2, Fig. 3B). The cumulative incidence of CD in group D was significantly higher than that in group A (aHR: 3.394; 95% CI: 1.627–7.079; $p = 0.001$) and group B (aHR: 3.185; 95% CI: 1.228–7.014; $p = 0.017$) (Table 2, Fig. 3C). The cumulative incidence of secondary endpoint was not significantly different among the four groups (**Suppl. Online Material 1**, Fig. 3D). Table 3 summarizes improvements in C-statistics in predicting the primary endpoint when high NLR and high ΔSBP were added into the model with conventional and meaningful clinical and procedural risk factors. The addition of high NLR and high ΔSBP led to significant improvements in C-statistics from 0.575 to 0.602 ($p = 0.017$) and 0.622 ($p = 0.004$), respectively. However, the greatest improvement in C-statistics was seen when both high NLR and high ΔSBP were combined into the model, with C-statistics increasing significantly to 0.635 ($p = 0.002$). Table 4 shows independent predictors of the primary and secondary endpoints at 5 years. Low LVEF (< 50%), hypertension, lymphocyte count, and catheterization laboratory SBP were found to be meaningful independent predictors of the primary endpoint. Additionally, diabetes mellitus was found to be a meaningful independent predictor of the secondary endpoint.

Discussion

The main findings of this study are the follows. The cumulative incidence of the primary endpoint in group D was significantly higher than that in the other three groups and the incorporation of high NLR and high ΔSBP into the model with conventional and meaningful clinical and procedural risk factors synergistically increased the ability to predict the primary endpoint.

Table 2. Comparison of clinical outcomes at 5 years.

Outcomes	Group A (n = 552)	Group D (n = 91)	Log-rank	Unadjusted HR (95% CI)	P value	Adjusted* HR (95% CI)	P value
Primary endpoint:	12 (2.3%)	12 (13.9%)	< 0.001	1.869 (1.431–2.440)	< 0.001	1.920 (1.462–2.522)	< 0.001
All-cause death	5 (1.0%)	11 (12.7%)	< 0.001	2.420 (1.701–3.442)	< 0.001	2.466 (1.721–3.532)	< 0.001
Cardiac death	1 (0.2%)	5 (5.8%)	< 0.001	3.170 (1.550–6.486)	0.002	3.394 (1.627–7.079)	0.001
Non-fatal MI	7 (1.4%)	1 (1.4%)	0.970	1.041 (0.128–8.456)	0.970	1.061 (0.522–9.160)	0.869
Secondary endpoint:	52 (10.1%)	10 (12.8%)	0.464	1.088 (0.868–1.363)	0.466	1.121 (0.891–1.411)	0.330
TLR	39 (7.5%)	7 (9.4%)	0.705	1.053 (0.805–1.377)	0.706	1.111 (0.847–1.459)	0.446
TVR	49 (9.9%)	8 (11.2%)	0.780	1.036 (0.807–1.329)	0.783	1.086 (0.843–1.401)	0.522
CVA	3 (0.6%)	2 (2.4%)	0.083	1.623 (0.894–2.946)	0.112	1.765 (0.936–3.329)	0.079
Outcomes	**Group B (n = 383)**	**Group D (n = 91)**	**Log–rank**	**Unadjusted HR (95% CI)**	**P value**	**Adjusted* HR (95% CI)**	**P value**
Primary endpoint:	18 (5.1%)	12 (13.9%)	0.003	1.704 (1.182–2.455)	0.004	1.751 (1.186–2.584)	0.005
All-cause death	15 (4.3%)	11 (12.7%)	0.002	1.782 (1.208–2.630)	0.004	1.767 (1.168–2.603)	0.007
Cardiac death	2 (0.5%)	5 (5.8%)	< 0.001	3.271 (1.441–7.426)	0.005	3.185 (1.228–7.014)	0.017
Non-fatal MI	3 (0.8%)	1 (1.4%)	0.754	1.197 (0.386–3.712)	0.755	1.469 (0.407–5.308)	0.557
Secondary endpoint:	37 (10.8%)	10 (12.8%)	0.615	1.094 (0.771–1.551)	0.616	1.171 (0.811–1.692)	0.399
TLR	24 (6.9%)	7 (9.4%)	0.598	1.120 (0.735–1.706)	0.598	1.129 (0.725–1.759)	0.591
TVR	32 (10.0%)	8 (11.2%)	0.764	1.060 (0.719–1.561)	0.769	1.127 (0.750–1.694)	0.565
CVA	6 (1.8%)	2 (2.4%)	0.628	1.217 (0.547–2.709)	0.630	1.434 (0.616–3.342)	0.403
Outcomes	**Group C (n = 162)**	**Group D (n = 91)**	**Log–rank**	**Unadjusted HR (95% CI)**	**P value**	**Adjusted* HR (95% CI)**	**P value**
Primary endpoint:	7 (4.4%)	12 (13.9%)	0.007	3.378 (1.329–8.582)	0.011	3.514 (1.481–9.640)	0.015
All-cause death	5 (3.2%)	11 (12.7%)	0.003	4.311 (1.497–12.41)	0.007	3.191 (1.065–9.557)	0.038
Cardiac death	2 (1.2%)	5 (5.8%)	0.041	4.700 (0.912–24.24)	0.044	3.546 (0.594–21.18)	0.165
Non-fatal MI	2 (1.3%)	1 (1.4%)	0.990	1.015 (0.092–11.20)	0.990	4.323 (0.195–95.89)	0.355
Secondary endpoint:	14 (9.1%)	10 (12.8%)	0.326	1.498 (0.665–3.375)	0.329	1.508 (0.647–3.518)	0.342
TLR	7 (4.5%)	7 (9.4%)	0.164	2.071 (0.726–5.909)	0.173	2.392 (0.772–7.410)	0.131
TVR	9 (5.9%)	8 (11.2%)	0.165	1.924 (0.742–4.988)	0.178	2.311 (0.803–6.655)	0.120
CVA	3 (2.0%)	2 (2.4%)	0.742	1.349 (0.225–8.081)	0.743	1.273 (0.200–7.810)	0.798

→

Table 2 (cont.). Comparison of clinical outcomes at 5 years.

Outcomes	Cumulative events according to the level of NLR						
	Low NLR (≤ 3.0) Group A + B (n = 935)	High NLR (> 3.0) Group C +D (n = 253)	Log–rank	Unadjusted HR (95% CI)	P value	Adjusted† HR (95% CI)	P value
Primary endpoint:	30 (3.5%)	19 (7.8%)	0.003	2.315 (1.303–4.112)	0.004	2.499 (1.285–4.857)	0.007
All-cause death	20 (2.3%)	16 (6.5%)	0.001	2.917 (1.512–5.629)	0.001	2.816 (1.326–5.982)	0.007
Cardiac death	3 (0.2%)	7 (2.0%)	0.001	8.535 (2.207–33.00)	0.002	9.509 (2.238–40.41)	0.001
Non-fatal MI	10 (1.1%)	3 (1.6%)	0.517	1.463 (0.459–4.666)	0.520	1.833 (0.444–7.570)	0.403
Secondary endpoint:	89 (10.4%)	24 (10.4%)	0.915	1.025 (0.653–1.608)	0.915	1.034 (0.623–1.717)	0.896
TLR	63 (7.3%)	14 (6.1%)	0.448	1.251 (0.701–2.232)	0.449	1.163 (0.633–2.139)	0.626
TVR	81 (9.9%)	17 (7.6%)	0.274	1.331 (0.789–2.246)	0.283	1.002 (0.571–1.757)	0.996
CVA	9 (1.0%)	5 (2.1%)	0.188	2.051 (0.687–6.120)	0.198	1.229 (0.230–5.864)	0.809
Outcomes	**Cumulative events according to the ΔSBP**						
	Low ΔSBP (≤ 25 mmHg) Group A + C (n = 714)	High ΔSBP (> 25 mmHg) Group B + D (n = 474)	Log–rank	Unadjusted HR (95% CI)	P value	Adjusted‡ HR (95% CI)	P value
Primary endpoint:	19 (2.8%)	30 (6.8%)	0.001	2.499 (1.407–4.440)	0.002	2.379 (1.262–4.218)	0.007
All-cause death	10 (1.5%)	26 (5.9%)	< 0.001	4.125 (1.989–8.554)	< 0.001	4.098 (1.819–7.471)	0.001
Cardiac death	3 (0.4%)	7 (1.6%)	0.046	3.620 (0.936–14.00)	0.062	5.763 (1.116–29.76)	0.037
Non-fatal MI	9 (1.4%)	4 (0.9%)	0.576	1.397 (0.430–4.538)	0.578	1.651 (0.425–6.409)	0.469
Secondary endpoint:	66 (9.9%)	47 (11.1%)	0.457	1.152 (0.793–1.675)	0.458	1.207 (0.810–1.799)	0.355
TLR	46 (6.8%)	31 (7.4%)	0.745	1.078 (0.684–1.701)	0.745	1.068 (0.659–1.731)	0.790
TVR	58 (9.0%)	40 (10.2%)	0.558	1.126 (0.752–1.684)	0.564	1.155 (0.753–1.772)	0.510
CVA	6 (0.9%)	8 (1.9%)	0.152	2.130 (0.739–6.139)	0.162	3.177 (0.775–13.03)	0.108

*Adjusted by men, age, hypertension, unstable angina, STEMI, LVEF, white blood cell, neutrophil, lymphocyte, monocyte, eosinophil, hemoglobin, NLR, ward SBP, catheterization laboratory SBP, ΔSBP, hs-CRP, serum creatinine, peak CK-MB, peak troponin-T; †Adjusted by BMI, unstable angina, STEMI, LVEF, white blood cell, neutrophil, lymphocyte, monocyte, eosinophil, ward SBP, cath lab SBP, ΔSBP, hs-CRP, serum creatinine, peak CK-MB, peak troponin-T, triglyceride, ARB; ‡Adjusted by men, age, hypertension, current smoker, unstable angina, NSTEMI, white blood cell, lymphocyte, hemoglobin, hematocrit, eGFR, ACEI, LAD; Group A — low NLR (≤ 3.0)/low ΔSBP (≤ 25 mmHg); Group B — high ΔSBP (> 25 mmHg)/low NLR (≤ 3.0); Group C — high NLR (> 3.0)/low ΔSBP (≤ 25 mmHg); Group D — high ΔSBP (> 25 mmHg)/high NLR (> 3.0); STEMI — ST-segment elevation myocardial infarction; LVEF — left ventricular ejection fraction; NLR — neutrophil-to-lymphocyte ratio; SBP — systolic blood pressure; ΔSBP — difference in ward-to-catheterization laboratory SBP; hs-CRP — high sensitivity-C-reactive protein; CK-MB — creatine kinase myocardial band; BMI — body mass index; ARB — angiotensin II type 1 receptor blocker; eGFR — estimated glomerular filtration rate; ACEI — angiotensin converting enzyme inhibitor; LAD — left anterior descending artery; HR — hazard ratio; CI — confidence interval; MI — myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization; CVA — cerebrovascular accidents

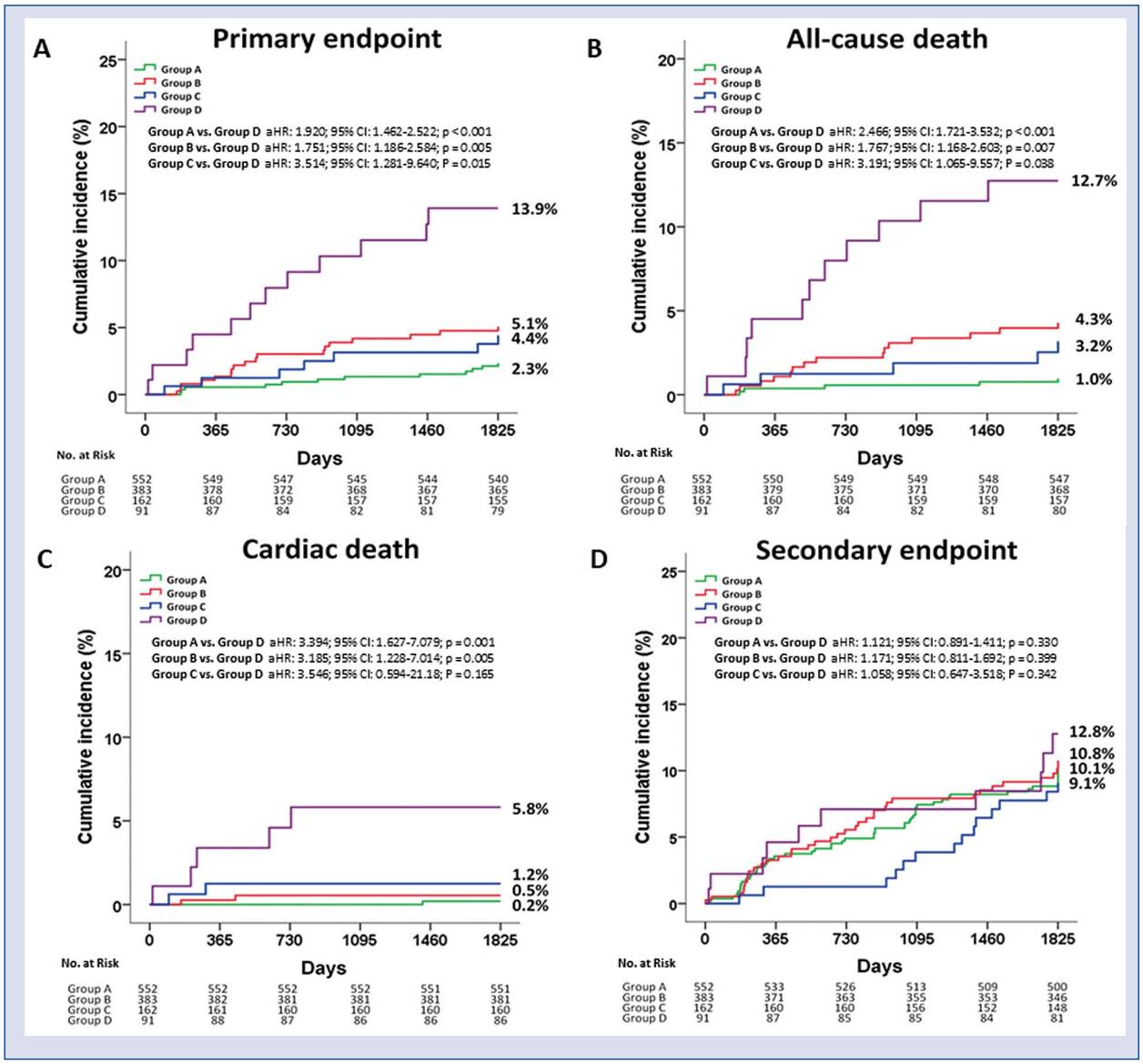

Figure 3. Kaplan-Meier analysis for primary outcome (**A**), all-cause death (**B**), cardiac death (**C**), and secondary end--point (**D**).

Table 3. C-statistics for Cox regression models for prediction of primary endpoint.

Meaningful risk factors, NLR and ΔSBP	C-statistics	Estimated difference (95% CI)	P value
Meaningful clinical and procedural risk factors*	0.575	Reference	Reference
Meaningful clinical and procedural risk factors plus high NLR	0.602	0.055 (–0.107 to 0.108)	0.017
Meaningful clinical and procedural risk factors plus high ΔSBP	0.622	0.050 (–0.099 to 0.099)	0.004
Meaningful clinical and procedural risk factors plus high NLR and high ΔSBP	0.635	0.048 (–0.093 to 0.094)	0.002

*Meaningful clinical and procedural risk factors composed of men, age, hypertension, unstable angina, non-STEMI, STEMI, left ventricular ejection fraction, white blood cell, neutrophil, lymphocyte, monocyte, eosinophil, hemoglobin, NLR, ward SBP, catheterization laboratory SBP, ΔSBP, hs-CRP, serum creatinine, peak CK-MB, peak troponin-T; NLR — neutrophil-to-lymphocyte ratio; SBP — systolic blood pressure; ΔSBP — difference in ward-to-catheterization laboratory SBP; STEMI — ST-segment elevation myocardial infarction; hs-CRP — high sensitivity-C--reactive protein; CK-MB — creatine kinase myocardial band; CI — confidence interval

Table 4. Independent predictors for primary and secondary endpoints at 5 years.

Variables	Primary endpoint				Secondary endpoint			
	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
NLR	2.630 (2.021–3.422)	< 0.001	2.154 (1.948–3.125)	0.030	1.985 (0.982–2.563)	0.009	1.862 (0.672–2.874)	0.028
ΔSBP	2.288 (1.332–3.931)	< 0.001	2.018 (1.012–3.321)	0.018	2.036 (1.245–2.763)	0.002	1.961 (1.028–3.012)	0.010
Age ≥ 65 years	2.015 (1.153–3.521)	0.014	2.517 (1.264–5.011)	0.009	1.615 (1.073–2.432)	0.022	1.544 (0.921–2.590)	0.100
Gender (men)	1.654 (0.949–2.885)	0.076	1.309 (0.637–2.688)	0.464	1.073 (0.724–1.589)	0.727	1.543 (0.897–2.654)	0.117
LVEF < 50%	1.809 (0.814–4.021)	0.146	2.893 (1.196–6.997)	0.018	1.195 (0.642–2.227)	0.547	1.416 (0.602–3.331)	0.426
Hypertension	1.986 (1.014–3.125)	0.028	2.372 (1.105–5.984)	0.023	1.217 (0.840–1.763)	0.298	1.461 (0.899–2.372)	0.126
Diabetes mellitus	1.231 (0.664–2.283)	0.509	1.474 (0.744–2.921)	0.266	1.667 (1.128–2.462)	0.010	1.872 (1.150–3.048)	0.012
Dyslipidemia	2.226 (1.278–3.876)	0.005	1.374 (0.718–2.629)	0.337	1.695 (1.164–2.467)	0.006	1.037 (0.655–1.641)	0.878
Neutrophil	1.027 (1.003–1.051)	0.025	0.931 (0.859–1.008)	0.078	1.004 (0.988–1.020)	0.645	1.052 (0.977–1.133)	0.181
Lymphocyte	0.960 (0.933–0.987)	0.004	0.869 (0.787–0.959)	0.005	0.852 (0.681–0.954)	0.035	1.056 (0.971–1.148)	0.203
Cath. Lab. SBP	1.013 (1.002–1.024)	0.018	1.031 (0.998–1.025)	0.009	1.236 (1.023–1.432)	0.021	1.007 (0.997–1.017)	0.202
Ward SBP	1.005 (0.991–1.020)	0.468	1.005 (0.987–1.022)	0.604	1.001 (0.991–1.010)	0.904	0.998 (0.985–1.012)	0.796
Beta-blocker	1.431 (0.822–2.493)	0.205	1.056 (0.556–2.006)	0.869	1.004 (0.688–1.465)	0.985	1.216 (0.767–1.929)	0.405
Calcium channel blocker	1.407 (0.768–2.576)	0.269	1.836 (0.888–3.796)	0.101	1.121 (0.735–1.710)	0.595	1.088 (0.635–1.864)	0.760
Lipid-lowering agent	2.632 (1.466–4.726)	0.001	1.092 (0.569–2.095)	0.791	2.107 (1.399–3.173)	< 0.001	1.226 (0.766–1.962)	0.396
Current smoker	1.264 (0.663–2.411)	0.477	0.953 (0.444–2.044)	0.901	1.281 (0.799–2.054)	0.305	1.303 (0.761–2.232)	0.335

HR — hazard ratio; NLR — neutrophil-to-lymphocyte ratio; SBP — systolic blood pressure ΔSBP — difference in ward-to-catheterization laboratory SBP; LVEF — left ventricular ejection fraction; Cath. Lab. SBP — catheterization laboratory systolic blood pressure

Because previous work has highlighted the importance of the NLR and ΔSBP in predicting long-term major clinical outcomes in patients with ACS who underwent PCI, we investigated combined usefulness of these two non-invasive, inexpensive, relatively simple, not to mention the little time required employing the diagnostic tools in this study. The present study showed the additive value and combined usefulness of the NLR and ΔSBP in predicting the primary endpoint in patients with ACS after DES implantation. According to available research, this study is the first to report the additive benefit of the NLR and ΔSBP in predicting the 5-year follow-up of clinical outcomes in patients with ACS undergoing PCI with DES implantation.

Vascular inflammation plays a critical role in the initiation, evolution, and rupture of atherosclerotic plaques [22]. The circulating biomarkers of this process predict morbidity and mortality in patients with established CAD [23, 24]. To date, there has been diverse evidence regarding the role of the NLR, which suggests that it has an association with CAD [25, 26] and that it could predict adverse in-hospital mortality and long-term mortality up to 3 years [26]. In this study, the NLR had an additional good prognostic value for predicting the primary endpoint during the 5-year follow-up (increase in C-statistics from 0.575 to 0.602; $p = 0.017$). In addition, the cumulative incidence of the primary endpoint was higher in the high NLR group than in the low NLR group (aHR: 2.499; 95% CI: 1.285–4.857; $p = 0.007$; Table 2). These results are compatible with those of previous reports [3, 5, 25]. In patients with ACS, a low lymphocyte count is common and can be explained by the elevated cortisol level, which induces apoptosis [27]. This low lymphocyte count (i.e., high NLR) is associated with adverse clinical outcomes [6]. In this study, the frequency of the primary endpoint was significantly higher in the high ΔSBP group than in the low ΔSBP group at 5 years (aHR: 2.379; 95% CI: 1.262–4.218; $p = 0.007$; Table 2). It is well known that target organ damage in patients with hypertension and cardiovascular complications is related to elevated BP, which is determined from the average of multiple BP readings (mean BP) [28]. ΔSBP may not be a good substitute of 24-hour ambulatory BP monitoring (ABPM). However, ABPM is an additional diagnostic test with inherent costs and takes more time to get results compared to ΔSBP. Therefore, we thought that ΔSBP may be the preferred technique for the patients with ACS. Moreover, BP measurement in the ward and before catheterization is already done in routine clinical practice.

Although the NLR and ΔSBP have a different pathophysiological mechanism, they both lead to accelerated atherosclerosis. In patients with ACS, an increased total leukocyte count predicts mortality and recurrence of MI [29, 30]. ACS is most commonly caused by disruption of atherosclerotic plaques with superimposed thrombus formation; thus, inflammation plays a crucial role in the pathogenesis of acute coronary events [31]. To date, the precise mechanism of acute transient BP elevation is less well known. Under stressful situations (e.g., CAG or PCI), increased activity of the hypothalamic-pituitary-adrenal axis culminating in release of with catecholamine play a vital role in initiating acute deviations from normal physiology such as hypertension. Through changes in the circulating catecholamine levels, emotional or psychosocial stress evokes negative effects on autonomic and hormonal homeostasis, which can lead to inflammation, metabolic abnormalities, endothelial dysfunction, hypertension, and insulin resistance [32]. From a different perspective, increased cardiac output and arterial stiffness under stressful circumstances are related to acute BP responses; the latter are associated with atherosclerosis [33, 34]. Her et al. [10] proposed that an acute elevation of BP under stress might contribute to an increased risk of adverse clinical outcomes, with this BP elevation representing significant arterial atherosclerosis and increased arterial stiffness. Another possible interaction between BP and NLR is that an elevated BP increases the formation of hydrogen peroxide and free radicals in the plasma [35], and these substrates cause decreased production of nitric oxide from the endothelium [36] and increased leukocyte adhesion [37]. Therefore, these two parameters are associated with each other. Because atherosclerosis is an inflammatory disease and an important causative factor of BP variations, early detection and modification of these reversible factors may reduce the frequency and severity of adverse cardiac events during long-term follow-up after implantation of DESs. In this regard, the combined use of the NLR and ΔSBP as a predictive tool for adverse cardiac events is a rational approach, especially in patients undergoing PCI. Finally, although in this study shows the additional combined usefulness of the NLR and ΔSBP in predicting long-term outcomes after implantation of DESs, other laboratory (e.g., GFR, hemoglobin), clinical features, or well-established risk assessment tools (e.g., Global Registries of

Acute Coronary Events [GRACE] or TIMI risk scores) could also be used as alternatives for these two parameters in further studies.

Limitations of the study

This study has some limitations. First, the NLR was checked only once; thus, it was not known whether there was any change in its value. Second, even though there was an attempt to perform a multivariable Cox proportional hazard regression analysis including baseline confounding factors, as this study was a non-randomized retrospective single-center study with several exclusion criteria, selection bias cannot be excluded. Third, the sample size may not be sufficiently large enough to accurately estimate the study results. Larger randomized prospective studies are required to confirm these results. Fourth, group D was composed of a stringently selected population. Therefore, this may have led to selection bias. Fifth, because 24-hour ABPM was not performed in this study, assessment of any BP variability was not possible. Finally, the patients in this study were enrolled between September 2002 and August 2007; this limited study period can be considered to be the main limitation.

Conclusions

In conclusion, in this retrospective observational study of the patients with ACS, the incorporation of both high NLR and high ΔSBP into the model with conventional and meaningful clinical and procedural risk factors increased the ability to predict the primary endpoint during the 5-year follow-up period.

Conflict of interest: None declared

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