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Original Article

Prognostic Value of Eosinophil to Leukocyte Ratio in Patients with ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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***Aim*: Leukocyte profile has been related to clinical outcome in patients with ST-segment elevation (STE) myocardial infarction (MI). However, whether eosinophil to leukocyte ratio (ELR) predicts clinical outcome in patients who have undergone primary percutaneous coronary intervention (PCI) remains unclear. Therefore, we examined the prognostic value of ELR in this patient population.**

***Methods*: We retrospectively analyzed the data of 331 consecutive patients who underwent primary PCI for STEMI between January 2009 and March 2015. All leukocyte types were counted and ELR was calculated for all patients 24 h after hospital admission. The primary study endpoint was major adverse cardiac events (MACEs) within up to one year of follow-up duration.**

***Results*: MACEs including cardiac deaths in 9.4% of the patients, MI in 1.5%, and target lesion or vessel revascularization in 10.3%, occurred within one year in 68 patients (20.5%). The mean ELR was significantly lower in patients with MACEs than in patients without MACEs (0.20 ± 0.51 vs. 0.49 ± 0.66, respectively; $p < 0.001$). An ELR < 0.1 at 24 h was identified as the best cut-off value for mortality prediction. Multivariate analysis identified that an ELR < 0.1 (odds ratio [OR] = 0.38; 95% confidence interval [CI] = 0.22–0.67; $p < 0.001$) and chronic kidney disease (OR = 2.38; CI = 1.33–4.24; $p = 0.003$) are independent predictors of MACEs.**

***Conclusion*: In primary PCI patients with STEMI, ELR at 24 h was an independent predictor of MACEs in addition to the usual coronary risk factors and commonly used biomarkers.**

Key words: Eosinophil to leukocyte ratio, ST-segment elevation myocardial infarction, Percutaneous coronary intervention, Major adverse cardiac event

Introduction

Early risk stratification is recommended in daily clinical practice for predicting prognosis in patients presenting with ST-segment elevation (STE) myocardial infarction (MI). Elevated leukocyte and neutrophil counts and decreased lymphocyte counts have been associated with adverse cardiac events after primary percutaneous coronary intervention (PCI) in patients with STEMI[1-4]. More recently, novel cardiac biomarkers or parameters have been identified as predictive indicators of STEMI[5-7]. He *et al.* demonstrated that circulating levels of miR-328 and miR-134 were associated with increased mortality risk and heart failure within 6 months[5]. Wang *et al.* suggested that a high red blood cell distribution width might reflect the severity and instability of acute myocardial infarction[6]. Although some reports have demonstrated that eosinopenia might be a prognostic marker in patients with bacteremia or intensive care unit patients[8, 9], no study has directly examined whether the eosinophil to leukocyte ratio (ELR) and prognosis after primary PCI for STEMI are correlated. It is also uncertain whether ELR is a superior predictor of

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infarct size and clinical outcomes. We designed the present study to examine the prognostic value of ELR in patients who presented with STEMI and underwent primary PCI.

Methods

Data Collection and Follow-Up

We retrospectively analyzed data from 360 consecutive patients who underwent PCI for STEMI at Hokkaido Cardiovascular Hospital between January 2009 and March 2015. Patients were followed-up for one year. We excluded patients who a) presented with infections, allergic diseases, or malignancies; b) were referred to our hospital over 48 h after the onset of STEMI; or c) died within 24 h after hospital admission. Primary PCI was performed using standard techniques. The use of thrombectomy devices, intravascular ultrasound, pre-dilatation, stent choice, post-dilatation, and the initiation of intra-arterial balloon pump or percutaneous cardiopulmonary support were at the operators' discretion.

Park *et al.* suggested that because of delayed response of the patient to the extent of STEMI, the initial leukocyte count obtained in the emergency department might not reliably reflect the inflammatory status[3]. They found that in patients presenting with STEMI, the leukocyte count 24 h after hospital admission is more likely to reflect the severity of inflammation than the leukocyte count at the time of hospital admission. Therefore, in the present study, we chose the 24-h leukocyte count as a predictor of prognosis in STEMI patients who underwent PCI. ELR was calculated as the ratio of the number of eosinophils to the number of leukocytes 24 h after hospital admission. In addition, we evaluated the data from patients presenting with stable angina pectoris (SAP) during the study period. The left ventricular (LV) ejection fraction (EF) was based on measurements of the LV end-diastolic and end-systolic volumes in the apical 4- and 2-chamber views using the modified Simpson method. Informed consent was obtained from patients or their relatives before PCI. The present study protocol was approved by the research ethics committee of the Hokkaido Cardiovascular Hospital.

Study Endpoints and Definitions

Primary endpoints of the present study were major adverse cardiac events (MACEs) at one year defined as death, Q-wave MI, and the need for target lesion revascularization (TLR) or target vessel revascularization (TVR) by coronary artery bypass graft or repeat PCI. Angiographic restenosis was defined as a $>50\%$ diameter stenosis of the target lesion on follow-up angiography. Secondary endpoints were in-hospital mortality and complications, and LVEF. Diabetes mellitus was defined as a) a ≥ 126 mg/dL fasting plasma glucose level, b) a ≥ 200 mg/dL fasting plasma glucose level 2 h after an oral glucose load, c) a $\geq 6.5\%$ plasma hemoglobin A1c, or d) the prescription of insulin or an oral hypoglycemic agent. Hypertension was defined as a ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic blood pressure or by the prescription of an antihypertensive drug. Dyslipidemia was defined as a ≥ 220 mg/dL total or ≥ 140 mg/dL low-density lipoprotein cholesterol, <40 mg/dL high-density lipoprotein cholesterol, ≥ 150 mg/dL triglyceride, or the prescription of a blood lipid-lowering drug. Chronic kidney disease (CKD) was defined by an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Peak creatine kinase (CK) and peak CK-myocardial band (CK-MB), leukocyte count, neutrophil to lymphocyte ratio, and ELR were measured 24 h after hospital admission.

Statistical Analysis

Data were expressed as the mean ± standard deviation. Between-group differences were analyzed using the Pearson chi-square test or Fisher exact test for categorical variables and the Student *t*-test or Mann–Whitney *U* test for continuous variables as appropriate. Receiver-operating characteristic (ROC) curves were constructed to identify the optimal predictor of clinical endpoints. Incidences of clinical events were expressed as Kaplan–Meier estimates and they were compared using the log-rank test. Uni- and multivariate logistic regression analyses were performed to identify the independent predictors of MACEs at one year. Uni- and multivariate logistic regression models including predictors of MACEs identified via univariate analysis were used to define the risk of MACEs. Odds ratio (OR) and 95% confidence interval (CI) were calculated to confirm the significance of between-group differences. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS software version 22.0 (IBM Corporation, Armonk, NY).

Results

Patients and Clinical Characteristics

Among 360 patients who underwent PCI for STEMI, we excluded 13 patients from the analysis because of inflammatory or allergic diseases, six patients because they were admitted >48 h after the onset of STEMI, five patients because they died within 24 h after hospital admission, two patients because of missing data at 24 h after admission, two

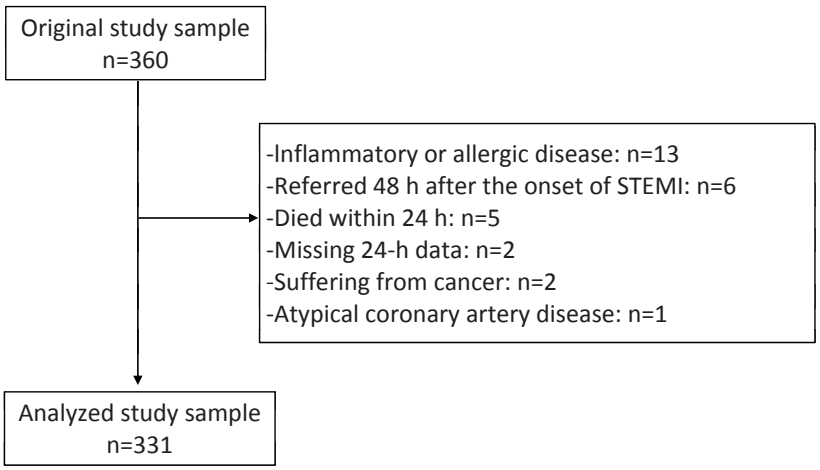


Fig. 1. Population selection flow diagram
Initial cohort and cohort exclusions

patients because they had active cancers, and one patient because he presented with a spontaneous coronary artery dissection that was pathophysiologically different from a typical STEMI. The final patient population included 331 patients with STEMI who underwent PCI (**Fig. 1**).

MACEs developed in 68 patients (20.5%) including cardiac deaths in 31 (9.4%), MI in five (1.5%), and TLR or TVR in 34 (10.3%) patients. The baseline patient characteristics are listed in **Table 1**. The mean age of patients who developed MACEs was higher than that of patients who remained MACE-free (73.1 ± 12.6 years vs. 65.7 ± 12.4 years, respectively; $p < 0.001$). The percentage of women in the MACE group was significantly higher than that in the MACE-free group (37% vs. 21%, respectively; $p = 0.005$). The percentages of CKD (63% vs. 31%; $p < 0.001$) and previous cerebral infarctions (15% vs. 6%; $p = 0.027$) in the MACE group were higher than those in the MACE-free group. The mean LVEF in the MACE group was significantly lower than that in the MACE-free group (50.2 ± 13.6% vs. 54.4 ± 10.5%, respectively; $p = 0.022$). Comparisons of MACE and MACE-free patients showed significantly higher peak CK (3,959 ± 3,458 IU/L vs. 2,669 ± 2,504 IU/L, $p = 0.005$), peak CK-MB (334 ± 282 vs. 228 ± 188 IU/L; $p = 0.004$), leukocyte count (11,634 ± 3,661/μL vs. 10,481 ± 3,356/μL; $p = 0.021$), and neutrophil to lymphocyte ratio (10.8 ± 7.0 vs. 6.6 ± 4.6; $p < 0.001$), and a significantly lower ELR for MACE patients (0.20 ± 0.51 vs. 0.49 ± 0.66; $p < 0.001$) at 24 h after hospital admission. A ROC curve was constructed to identify the best cut-off ELR value that predicted the primary endpoint calculated as an area < 0.1 under ROC curve with sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of 68, 64, 32, 88 and 64%, respectively (**Fig. 2**). Similarly, a ROC curve was constructed to determine the best cut-off value for peak CK-MB that predicted the primary study endpoint. The best cut-off value for peak CK-MB was calculated as ≥ 189 with sensitivity, specificity, and positive and negative predictive values of 68, 57, 29, and 87%, respectively, and a diagnostic accuracy of 59%. The ELR of patients with peak CK-MB ≥ 189 IU/L was significantly lower than that of patients with peak CK-MB < 189 IU/L (0.13 ± 0.28 vs. 0.71 ± 0.76; $p < 0.001$). Patients with 24-h ELRs < 0.1 were older, more likely to be women and less likely to be hypertensive, more often suffered from CKD or underwent bare metal stent implantation or simple balloon angioplasty, had lower LVEFs; and higher peak CK, peak CK-MB, leukocyte count, and neutrophil to lymphocyte ratios than patients with 24-h ELRs ≥ 0.1 (**Table 2**).

Incidence of MACEs in the ELR < 0.1 versus ELR ≥ 0.1 groups

Kaplan–Meier survival analysis (**Fig. 3A**) showed that patients with 24-h ELRs < 0.1 had significantly higher incidence of MACEs than patients with 24-h ELR ≥ 0.1 (32.4% vs. 11.6%, respectively; $p < 0.001$). On day 30 after PCI (**Fig. 3B**), patients with 24-h ELRs < 0.1 had significantly higher MACE incidence rates than patients with ELRs ≥ 0.1 (16.9% vs. 1.1%, respectively; $p < 0.001$). However, beyond 30 days, the outcomes were similar (15.5% vs. 10.6%, respectively; $p = 0.184$) in both groups (**Fig. 3C**).

Independent Predictors of MACEs in Patients with Acute Myocardial Infarction after PCI

Uni- and multivariate logistic regression analyses were performed to identify independent predictors of

Table 1. Baseline patient characteristics

	MACE		
	Absent $n=263$	Present $n=68$	p
Age, years	65.7 ± 12.4	73.1 ± 12.6	< 0.001
Women	54 (21)	25 (37)	0.005
Anterior myocardial infarction	127 (48)	38 (56)	0.276
Body mass index (kg/m^2)	24.3 ± 3.9	23.5 ± 4.3	0.268
Diabetes mellitus	95 (36)	25 (37)	0.922
Hypertension	186 (71)	43 (63)	0.233
Dyslipidemia	219 (84)	51 (74)	0.065
Chronic kidney disease	82 (31)	43 (63)	< 0.001
Current smoker	158 (60)	35 (51)	0.199
Family history of coronary artery disease	10 (4)	4 (6)	0.447
Sleep apnea syndrome*	58 (50)	11 (61)	0.399
Intima-media thickness (mm)**	2.4 ± 1.1	2.7 ± 1.1	0.259
Peripheral artery disease	36 (14)	11 (16)	0.600
History of:			
Percutaneous coronary intervention	28 (11)	8 (12)	0.792
Coronary artery bypass graft	2 (1)	2 (3)	0.142
Cerebral infarction	17 (6)	10 (15)	0.027
Prior aspirin or clopidogrel use	40 (15)	12 (18)	0.622
Prior ACE inhibitor or ARB use	42 (16)	15 (22)	0.235
Prior statin use	32 (12)	6 (9)	0.441
Prior β blockers use	18 (7)	8 (12)	0.179
Door to balloon time (min)	85 ± 39	90 ± 41	0.398
Admission systolic blood pressure (mmHg)	127 ± 30	130 ± 28	0.474
Admission diastolic blood pressure (mmHg)	76 ± 18	79 ± 17	0.216
Use of bare metal stent or simple balloon angioplasty	138 (52)	34 (50)	0.716
Left ventricular ejection fraction (%)	54.4 ± 10.5	50.2 ± 13.6	0.022
Peak, (IU/l)			
Creatine kinase	2,669 ± 2,504	3,959 ± 3,458	0.005
Creatine kinase myocardial-band	228 ± 188	334 ± 282	0.004
Hemoglobin (g/dl)	13.9 ± 2.3	13.7 ± 2.3	0.583
White blood cell count (/μl)	10,481 ± 3,356	11,634 ± 3,661	0.021
Neutrophil count (/μl)	8,284 ± 3,093	9,647 ± 3,417	0.002
Lymphocyte count (/μl)	1,709 ± 1,278	1,201 ± 711	0.002
Eosinophil count (/μl)	47 ± 68	17 ± 36	< 0.001
Ratio			
Neutrophil to lymphocyte	6.6 ± 4.6	10.8 ± 7.0	< 0.001
Eosinophil to leukocyte	0.49 ± 0.66	0.20 ± 0.51	< 0.001
Platelets ($\times 10^6$/μl)	20.7 ± 6.3	19.3 ± 6.5	0.105

Values are means ± SD or numbers (%) of observations.
*$n=133$; **$n=159$

MACEs (**Table 3**). Patient age, female sex, CKD, history of cerebral infarction, ELR, and platelet counts were included in the multivariate model. Because the LVEF ($r=0.270$, $r^2=0.073$; $p<0.001$), peak CK ($r=-0.402$, $r^2=0.162$; $p<0.001$), peak CK-MB ($r=-0.370$, $r^2=0.137$; $p<0.001$), leukocyte count ($r=-0.271$, $r^2=0.073$; $p<0.001$), and neutrophil to lymphocyte ratio ($r=-0.450$, $r^2=0.203$; $p<0.001$) were directly or inversely correlated with ELR, they were excluded from the multivariate analysis. Multivariate analysis identified CKD and ELR as independent predictors of MACEs (**Table 3**). An ELR < 0.1 was associated with the risk of MACEs (OR = 0.38; 95% CI, 0.22–0.67; $p<0.001$).

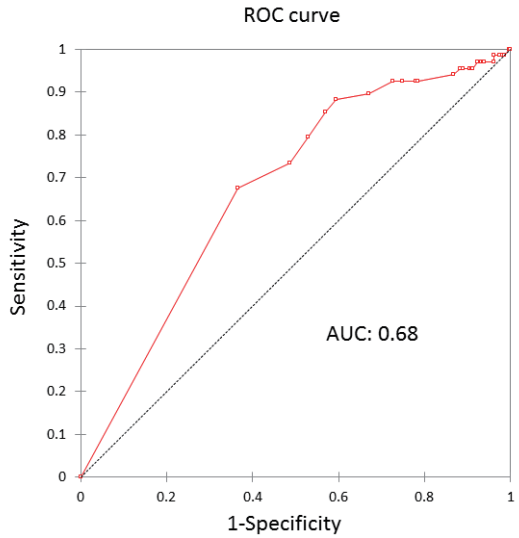


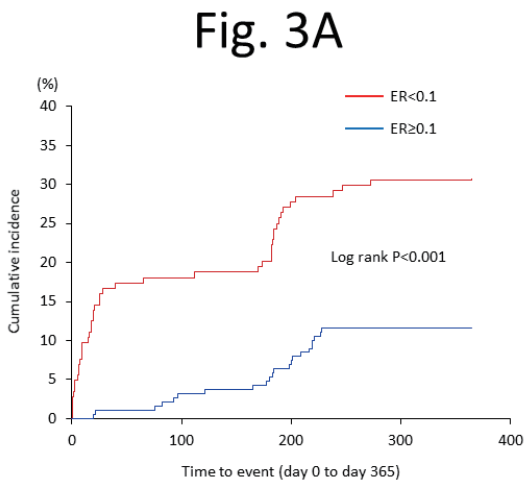
Fig. 2. Diagnostic characteristics of eosinophil to leukocyte ratio (ELR) for the prediction of clinical outcomes

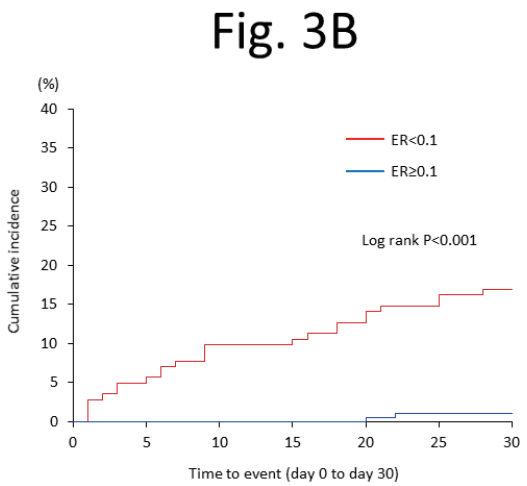
A receiver-operating characteristic (ROC) curve analysis was performed to determine the best cut-off ELR value for predicting the primary endpoints. The best cut-off ELR value was calculated as <0.1. The area under the ROC curve was 0.68 and the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 68%, 64%, 32%, 88%, and 64%, respectively.

Table 2. Baseline characteristics according to eosinophil/leukocyte ratio <0.1

	ELR		*p*
	≥ 0.1 *n* = 189	<0.1 *n* = 142	
Age. years	65.9 ± 12.7	69.1 ± 12.7	0.025
Women	36 (19)	43 (30)	0.018
Anterior myocardial infarction	92 (49)	73 (51)	0.623
Body mass index (kg/m^2)	24.5 ± 3.4	23.7 ± 3.9	0.069
Diabetes mellitus	68 (36)	52 (36)	0.904
Hypertension	139 (74)	90 (63)	0.047
Dyslipidemia	151 (80)	119 (84)	0.364
Chronic kidney disease	53 (28)	72 (51)	<0.001
Current smoker	118 (62)	75 (53)	0.079
Family history of coronary artery disease	6 (3)	8 (6)	0.410
Sleep apnea syndrome*	51 (56)	18 (43)	0.157
Intima-media thickness (mm)**	2.4 ± 1.1	2.5 ± 1.0	0.809
Peripheral artery disease	27 (14)	20 (14)	0.959
History of:			
Percutaneous coronary intervention	23 (12)	13 (9)	0.383
Coronary artery bypass graft	1 (1)	3 (2)	0.426
Cerebral infarction	12 (6)	15 (11)	0.166
Prior aspirin or clopidogrel use	35 (19)	17 (12)	0.105
Prior ACE inhibitor or ARB use	33 (17)	24 (16)	0.894
Prior statin use	22 (12)	16 (10)	0.653
Prior β blockers use	16 (8)	10 (7)	0.634
Door to balloon time (min)	86 ± 40	87 ± 39	0.795
Admission systolic blood pressure (mmHg)	128 ± 26	128 ± 29	0.939
Admission diastolic blood pressure (mmHg)	76 ± 17	77 ± 19	0.658
Use of bare metal stent or simple balloon angioplasty	83 (44)	89 (63)	<0.001
Left ventricular ejection fraction (%)	56.2 ± 9.5	49.8 ± 12.3	<0.001
Peak, (IU/l)			
Creatine kinase	1,843 ± 1,441	4,385 ± 3,391	<0.001
Creatine kinase myocardial-band	167 ± 124	359 ± 257	<0.001
Hemoglobin (g/dl)	14.0 ± 2.3	13.6 ± 2.3	0.134
White blood cell count (/μl)	9,620 ± 2,851	12,179 ± 3,634	<0.001
Neutrophil to lymphocyte ratio	4.7 ± 2.3	11.2 ± 6.1	<0.001
Platelet count (/μl)	20.6 ± 6.3	20.1 ± 6.4	0.441

Values are means ± SD or numbers (%) of observations.
*n = 133; **n = 159





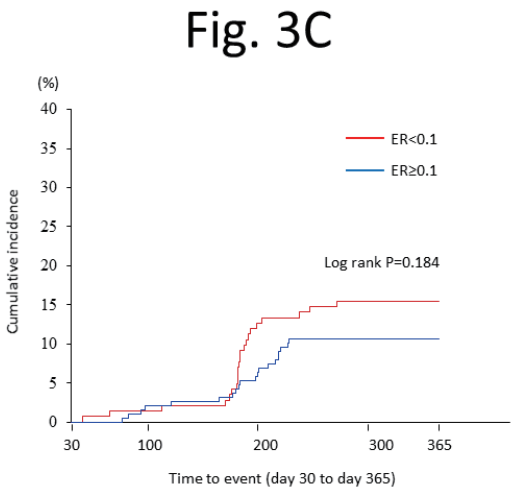


Fig. 3. Cumulative incidence of MACEs according to ELR

A. Outcomes in all patients according to ELR. Patients with 24-h ELR <0.1 showed higher incidences of primary endpoints compared to patients with 24-h ELRs ≥ 0.1 (32.4% vs. 11.6%, respectively; $p<0.001$).

B. Landmark analysis showed that patients with 24-h ELRs <1.0 had higher MACE rates during the first 30 days than patients with 24-h ELRs ≥ 0.1 (16.9% vs. 1.1%, respectively; $p<0.001$).

C. After 30 days, there was no statistically significant difference in outcomes between patients with ELRs <1.0 and patients with ELRs ≥ 0.1 (15.5% vs. 10.6%, respectively; $p=0.184$).

Instead of ELR, we included the LVEF, peak CK, peak CK-MB, leukocyte count, and neutrophil to lymphocyte ratio in the multivariate model and found that the peak CK, peak CK-MB, leukocyte count, and neutrophil to lymphocyte ratio were also significant predictors of MACEs (**Table 3**).

Rates of Cardiac Death, TLR or TVR, and MI according to ELR

The incidence of cardiac death in patients with 24-h ELRs <0.1 was significantly higher than that in patients with 24-h ELRs ≥ 0.1 (19.7% vs. 1.6%, respectively; $p<0.001$). However, the rates of MI (2.8 vs. 0.5%; $p=0.217$) and TLR or TVR (10.6 vs. 10.1%; $p=0.880$), were similar in both groups. Congestive heart failure (CHF) was the cause of cardiac death in 25 patients, cardiac ruptures (two ventricular septal perforations and three LV free wall ruptures) in five patients, and ventricular fibrillation (VF) in one patient. Death incidences due to CHF (15.5% in 22 patients vs. 1.6% in 3 patients) and cardiac rupture (3.5% in five patients vs. 0% in 0 patients) were significantly higher in patients with 24-h ELRs <0.1 compared to patients with 24-h ELRs ≥ 0.1 ($p<0.001$ and $p=0.032$, respectively; **Fig. 4A** and **4B**). The incidence of VF ($n=1$; 0.7% vs. $n=0$; 0%; $p=0.886$) was similar in both groups.

ELR <0.1 and Secondary Clinical Endpoints

The secondary clinical endpoints are shown in **Fig. 5**. In-hospital deaths occurred in 23 patients, including 17 deaths due to CHF, five due to cardiac ruptures, and one due to VF. In-hospital mortality (**Fig. 5A**) was significantly higher among patients with 24-h ELRs <0.1 compared to patients with 24-h ELRs ≥ 0.1 (15.5% vs. 0.7%, $p<0.001$). In-hospital complications occurred in 117 patients. The rate of in-hospital complications (**Fig. 5B**) was significantly higher in patients with 24-h ELRs <0.1 than in patients with 24-h ELRs ≥ 0.1 (55.6% vs. 20.1%, $p<0.001$). The in-hospital complications observed are listed in **Table 4**. The incidences of cardiogenic shock

Table 3. Logistic regression analysis of MACE

	Analysis			
	Single variable		Multiple variable	
	OR (95% CI)	*p*	OR (95%CI)	*p*
Age	2.78 (1.58-4.88)	<0.001	1.61 (0.89-2.92)	0.116
Female sex	2.25 (1.26-4.01)	0.008	1.45 (0.78-2.68)	0.239
Anterior myocardial infarction	1.36 (0.79-2.32)	0.327		
Body mass index	0.74 (0.38-1.41)	0.447		
Diabetes mellitus	0.99 (0.58-1.73)	0.891		
Hypertension	0.71 (0.41-1.25)	0.296		
Dyslipidemia	0.54 (0.29-1.02)	0.081		
Chronic kidney disease	3.80 (2.17-6.63)	<0.001	2.38 (1.33-4.24)	0.003
Current smoker	0.70 (0.41-1.20)	0.252		
Family history of coronary artery disease	1.58 (0.48-5.21)	0.673		
Sleep apnea syndrome	1.54 (0.60-4.26)	0.556		
History of cerebral infarction	2.49 (1.09-5.73)	0.049	1.63 (0.68-3.89)	0.273
Intima-media thickness	1.20 (0.48-3.01)	0.877		
Peripheral artery disease	1.22 (0.58-2.54)	0.742		
Previous percutaneous coronary intervention	1.12 (0.49-2.58)	0.963		
Previous coronary artery bypass grafting	3.95 (0.55-28.6)	0.398		
Prior aspirin or clopidogrel use	1.19 (0.59-2.43)	0.759		
Prior ACE inhibitor or ARB use	1.49 (0.77-2.89)	0.315		
Prior statin use	0.70 (0.28-1.75)	0.577		
Prior β blockers use	1.81 (0.75-4.32)	0.275		
Door to balloon time	1.92 (0.95-3.86)	0.092		
Admission systolic blood pressure	1.91 (0.93-3.91)	0.114		
Admission diastolic blood pressure	1.02 (0.57-1.86)	0.955		
Use of bare metal stent or simple balloon angioplasty	0.91 (0.53-1.54)	0.820		
Left ventricular ejection fraction	0.47 (0.27-0.81)	0.009	0.60 (0.35-1.05)	0.073
Peak				
Creatine kinase	4.04 (2.31-7.05)	<0.001	2.34 (1.34-4.09)	0.003
Creatine kinase myocardial-band	2.73 (1.56-4.80)	<0.001	2.51 (1.43-4.42)	0.001
Hemoglobin concentration	0.69 (0.34-1.39)	0.397		
White blood cell count	2.62 (1.49-4.64)	0.001	2.43 (1.38-4.29)	0.002
Neutrophil to lymphocyte ratio	4.41 (2.52-7.73)	<0.001	3.78 (2.15-6.67)	<0.001
Eosinophil to leukocyte ratio (ELR)	0.27 (0.16-0.48)	<0.001	0.38 (0.22-0.67)	<0.001
Platelet count	1.85 (1.04-3.27)	0.046	0.74 (0.41-1.32)	0.310

CI=confidence interval; OR=odd ratio.

(28.2% vs. 9.0%; $p<0.001$), CHF (31.7% vs. 6.9%; $p<0.001$), continuous hemofiltration (8.5% vs. 1.1%, $p=0.002$), tracheal intubation (5.6% vs. 1.1%, $p=0.037$), sustained ventricular tachycardia (VT) or VF (12.0% vs. 4.2%, $p=0.008$), and blood transfusion (5.6% vs. 0.0%, $p=0.003$) were significantly higher in patients with 24-h ELRs <0.1 than in patients with 24-h ELRs ≥ 0.1, respectively. LVEF (**Fig. 5C**, **Table 2**) was significantly lower in patients with a 24-h ELRs <0.1 than in patients with 24-h ELRs ≥ 0.1 (49.8±12.3% vs. 56.2±9.5%, respectively; $p<0.001$).

ELR in Patients Presenting with STEMI versus Patients with Stable Angina Pectoris

During the present study, 1,461 patients presenting with SAP underwent PCI, of whom 1,276 patients free from inflammatory or allergic diseases or cancers were included in the analyses. Mean ELR (**Supplementary Fig. 1**) was significantly lower in patients with STEMI than in patients presenting with SAP (0.4±0.7% vs. 3.8±3.2%, respectively; $p<0.001$).

Discussion

The main observations of the present study were

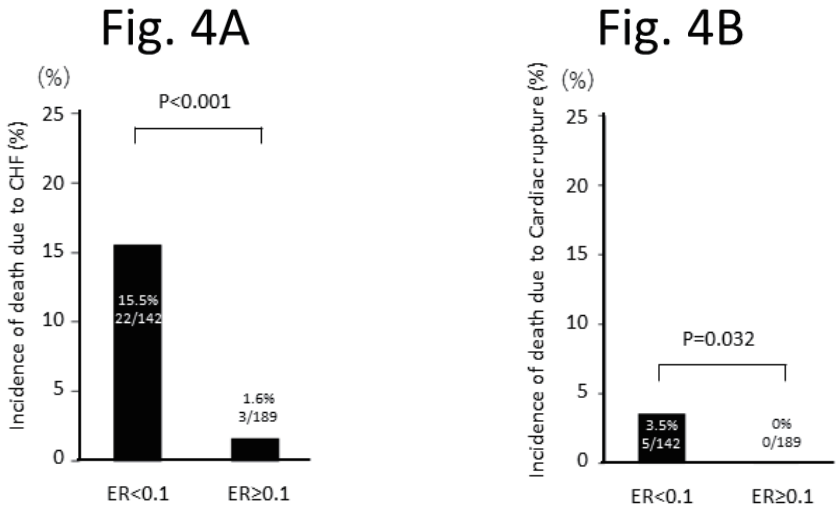


Fig. 4. Comparison of cardiac death in patients with ELRs <0.1 and patients with ELRs ≥ 0.1

A. The incidence of death due to CHF was significantly higher in patients with ELRs <0.1 than in patients with ELRs ≥ 0.1 ($p<0.001$). CHF: congestive heart failure.
B. The incidence of death due to cardiac rupture was significantly higher in patients with ELRs <0.1 than in patients with ELRs ≥ 0.1 ($p=0.032$).

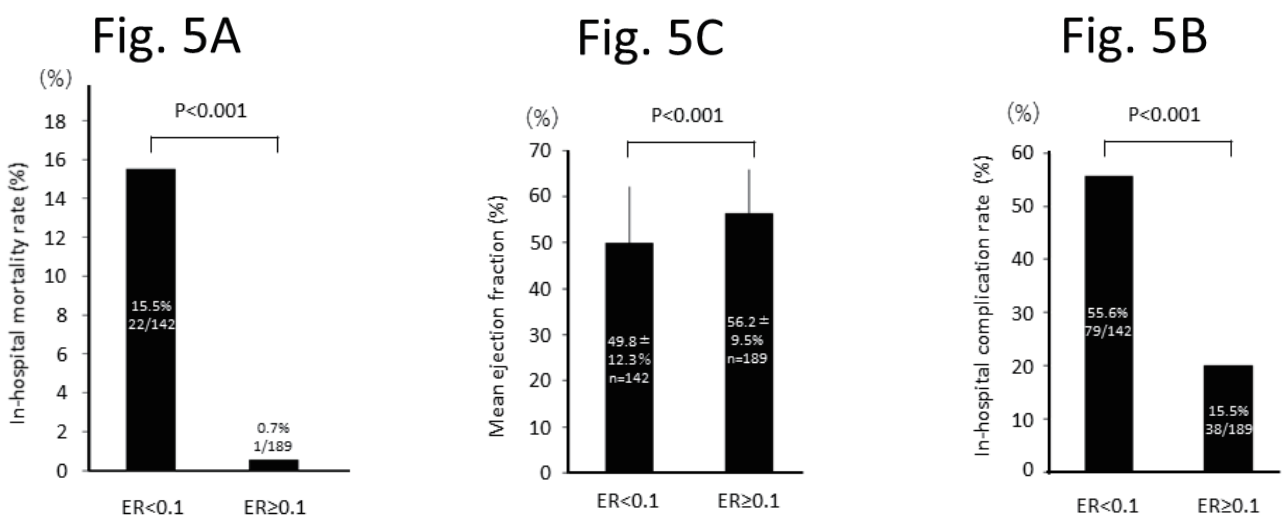


Fig. 5. Comparison of secondary endpoints between patients with ELRs <0.1 and patients with ELRs ≥ 0.1

A. In-hospital mortality was significantly higher in patients with ELRs <0.1 than in patients with ELRs ≥ 0.1.
B. In-hospital complication rate was significantly higher in patients with ELRs <0.1 than in patients with ELRs ≥ 0.1.
C. Mean LVEF was significantly lower in patients with ELRs <0.1 than in patients with ELRs ≥ 0.1. See text for details of individual measurements

1) in patients presenting with STEMI, 24-h ELR, CKD, peak CK, peak CK-MB, leukocyte count, and neutrophil to lymphocyte ratio were independent predictors of MACEs at one-year after PCI; 2) the incidence of MACE at one year was higher in patients with 24-h ELRs <0.1 than in patients with 24-h ELRs ≥ 0.1, mainly attributable to the higher 30-day death rates due to CHF; and 3) consistent with larger infarct sizes, the peak CK and CK-MB were higher and the LVEF was lower in patients with 24-h ELR < 0.1 than in patients with 24-h ELRs ≥ 0.1. The present study adds an important clinical factor to the list of hematological predictors of outcome after PCI in patients presenting with STEMI.

Relationship between ELR and Cardiac Enzyme Concentration

After performing PCI in patients with STEMI,

Table 4. In-hospital complications recorded in 117 patients

	Eosinophil/leukocyte ratio		*p*
	< 0.1 *n* = 142	≥ 0.1 *n* = 189	
Cardiogenic shock/need for intra-aortic balloon pump or percutaneous cardiopulmonary support	40 (28.2)	17 (9.0)	< 0.001
Congestive heart failure	45 (31.7)	13 (6.9)	< 0.001
Continuous hemofiltration	12 (8.5)	2 (1.1)	0.002
Tracheal intubation	8 (5.6)	2 (1.1)	0.037
Arrhythmias or temporary pacemaker	28 (19.7)	17 (9.0)	0.005
Sustained ventricular tachycardia, ventricular fibrillation	17 (12.0)	8 (4.2)	0.008
Profound bradycardia/need for temporary pacing	13 (9.2)	11 (5.8)	0.247
Acute or subacute stent thrombosis	4 (2.8)	0	0.070
Coronary artery bypass graft	5 (3.5)	3 (1.6)	0.440
Cerebral infarction	2 (1.4)	0	0.358
Blood transfusion	8 (5.6)	0	0.003

Values are numbers (%) of observations.

early risk stratification is of utmost importance in the prevention of adverse cardiac events. Several recent studies have shown that the leukocyte profile in patients with acute MI is related to prognosis[3, 4, 10-13]. Jiang *et al*. found that the peripheral eosinophil counts were lowest in patients presenting with the largest acute MIs. They observed that patients who presented with troponin I ≥ 20 ng/mL had significantly lower ELRs than patients who presented with troponin I < 20 ng/mL. In the present study, the ELR of patients with peak CK-MB ≥ 189 IU/L was significantly lower than that of patients with peak CK-MB <189 IU/l. This result appears to be consistent with the results reported by Jiang *et al*.

Decreased ELR Reflecting a Large Infarct Size

The higher one-year cardiac death incidence, and in-hospital mortality and complications in patients with 24-h ELRs <0.1 might be explained by a larger infarct size compared to that of patients with 24-h ELRs ≥ 0.1. In the present study, LVEF was lower and peak CK and peak CK-MB were higher in patients with 24-h ELRs <0.1 than in patients with 24-h ELRs ≥ 0.1. An impaired LV function after MI is consistent with a large infarcted area and it is associated with the development of adverse cardiac events[14]. Peak CK and CK-MB are well-known enzymatic markers of infarct size and important predictors of one-year mortality in patients with STEMI[15, 16]. Sustained VT and VF are more likely to develop in patients with extensive myocardial injuries[17, 18]. Therefore, higher prevalences of cardiogenic shock, CHF, and sustained VT and VF were expected in patients with 24-h ELRs <0.1, who had larger myocardial infarctions and higher in-hospital and one-year cardiac mortalities compared to patients with 24-h ELRs ≥ 0.1, mainly attributable to CHF.

Mechanisms of Decreased ELR in STEMI

In patients presenting with STEMI, a decrease in peripheral circulating eosinophils has recently been reported (**Supplementary Fig. 1**)[19]. At least three mechanisms might explain the reduction in ELR in patients presenting with STEMI:

Eosinophil Adherence to Coronary Thrombi

Because eosinophils may aggregate to form coronary thrombi in STEMI, their numbers are reduced in the peripheral circulation. A relationship between eosinophils and increased risk of thrombosis was confirmed in patients presenting with hypereosinophilic syndrome[20-22]. The activity of circulating eosinophils on the endothelium is mediated primarily by P-selectin, while that of the neutrophils is mediated primarily by E-selectin[23, 24]. In patients with acute MI, P-selectin concentrations have been measured to be higher in the infarcted coronary artery than in the circulation[25]. Some studies have suggested that eosinophils and their by-products affect the evolution of MI adversely. Eosinophils play an important role in the initiation of thrombosis, with platelets adhering to the injured intravascular wall[26]. Tissue factor is released upon degranulation of the eosinophils and is crucial in the initiation of blood coagulation[27, 28]. The eosinophil granule proteins, particularly major basic proteins, may contribute to hypercoagulation by inhibiting the thrombomodulin function[29, 30]. The serum concentrations of cortisol predict the infarct size and patient mortality. Sakai *et al*. examined the histopathology of aspirated thrombi obtained from patients with acute

coronary syndrome and showed that the largest red thrombi were observed in the group with the greatest eosinophilic infiltration into thrombi[31]. The concentration of plasma IL-5, which stimulates the release of eosinophils from the bone marrow[32], was significantly elevated in patients with acute MI[26]. The half-life of eosinophils *in vivo* ranges between 8 and 18 h[33], although IL-5 and IL-3 prolong the survival of eosinophils[34, 35]. Therefore, within 24-h after the onset of STEMI, the peripheral counts of eosinophils may remain low due to the aggregation of eosinophils within thrombi until the cells are fully released from the bone marrow into the peripheral circulation to recover their original concentrations.

Increased Cortisol Concentrations

A second potential mechanism is an increase in the cortisol concentration caused by an acute stress response to STEMI, which might lower the peripheral eosinophil counts[36]. Bain *et al.* observed that the mean serum cortisol concentrations were significantly higher in patients with MI than in patients with angina pectoris, both at the time of admission to the hospital and on the next day[37]. Furthermore, in patients presenting with MI, high cortisol concentrations have been associated with poor prognosis[37, 38]. In response to STEMI, the majority of eosinophils tend to migrate to tissues such as the spleen, lymph nodes, peritoneum, gastrointestinal tract, thymus, mammary glands, and uterus[39-42].

Eosinophil Aggregation at the Site of Inflammation

The third putative mechanism is the migration of peripheral eosinophils to the site of inflammation. In acute, non-infectious inflammatory stimulation, a reduction in eosinophil counts has been observed, which persisted for several days[42]. Since the rupture of atherosclerotic plaques in STEMI is associated with inflammation, some of the eosinophils might adhere to the intravascular plaques and thrombi[43, 44]. The infiltration of eosinophils into the infarcted myocardium occurs during the acute phase of MI[45, 46], although the presence of eosinophils has been observed in only 24% of the infarcts[45]. Therefore, by compared ELR in STEMI to SAP (**Supplementary Fig. 1**), one might hypothesize that the circulating eosinophils in the acute phase of STEMI migrate to the coronary thrombi, infarcted myocardium, or other organs such as the spleen, lymph nodes, and peritoneum owing to an increased secretion of cortisol.

Eosinopenia and Cardiac Rupture

Peripheral eosinopenia may be a predictor of cardiac rupture. Miyazato *et al.* reported a case of eosinophil infiltration in a patient who died of ruptured myocardium after acute MI[47]. Similarly, Atkinson *et al.* observed significantly higher numbers of eosinophils in ruptured hearts than in control infarcted hearts[48]. Eosinophils are potentially collagenolytic and cytotoxic. Their granules contain a variety of substances including a collagenase that cleaves type I and Ⅲ collagens, peroxidase, major basic protein, acid phosphatase, alkaline phosphatase, aryl sulphatase B that can degrade some glycosaminoglycans and proteoglycans, ribonuclease, and β-glucuronidase[49, 50]. Major basic protein is cytotoxic and it is associated with myocyte injury[48]. Since the specific activity of arylsulfatase B is augmented by acidic conditions, the non-reperfused myocardium accompanied by eosinophil infiltration is susceptible to rupture owing to tissue vulnerability[51]. An eosinophil contains 2.65 times as much peroxidase, 2.44 times as much β-glucuronidase, and approximately twice as much acid β-glycerophosphatase as a neutrophil[52]. In a previous study of eosinophilic myocarditis, eosinophil granule components were detected within degraded collagen[53]. In the present study, patients with 24-h ELRs <0.1 had significantly higher risks of cardiac rupture than patients with 24-h ELRs ≥ 0.1 (**Fig. 4B**). This observation and those of previous studies support the hypothesis that eosinophils in the peripheral circulation are targeting severely necrotic myocardium, causing further tissue vulnerability. Therefore, the reduction in peripheral eosinophil counts might be more prominent in patients with STEMI complicated by cardiac rupture than in patients without cardiac ruptures. Such high-risk patients should receive more intensive management of blood pressure, including the administration of angiotensin-converting enzyme inhibitors and β-adrenergic blockers, and they should avoid strenuous cardiac rehabilitation that increases the blood pressure.

The ideal marker of mortality should be easily and rapidly measurable, inexpensive, correlate with the severity of prognosis, and predict mortality in the coronary care unit. To the best of our knowledge, the present study is the first to examine whether eosinopenia predicts MACEs after PCI in patients presenting with STEMI, suggesting that ELR is indeed one of the reliable and inexpensive monitoring tools for patients at high risk for MACEs. Early identification of eosinopenia might aid the caregivers in their initial decision-making process, and help identifying patients in need of vigorous diagnostic and therapeutic interventions.

Limitations of the Present Study

The present retrospective, observational study,

conducted at a single medical center had a small sample size. The reported findings should be confirmed in a larger prospective multicenter study. Furthermore, because we excluded patients who died within the first 24 h after hospital admission, the data of a few critically ill patients might have been omitted. Irrespective of these limitations, the findings of the present study demonstrated that after PCI for STEMI, eosinopenia is a reliable predictor of higher MACE risk. ELR should contribute to the prevention of MACE through identification of patients with eosinopenia who should receive intensive medical management.

Conclusion

ELR measured 24 h after hospital admission was an independent predictor of MACEs in patients with STEMI who underwent primary PCI.

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Disclosure

The authors have no potential conflicts of interest to disclose.

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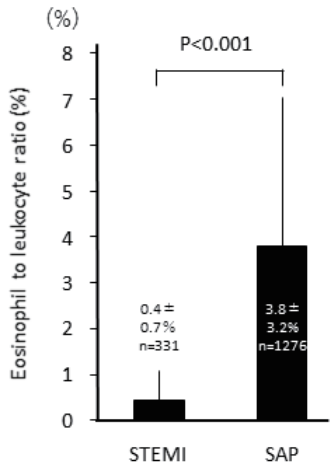

Supplementary Fig. 1.

The STEMI group had significantly lower eosinophil percentages than the SAP group (0.4 ± 0.7% vs. 3.8 ± 3.2%, respectively; $p < 0.001$). STEMI: ST-segment elevation myocardial infarction, SAP: stable angina pectoris.