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Platelet/lymphocyte ratio and risk of in-hospital mortality in patients with ST-elevated myocardial infarction

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Background: Platelet-to-lymphocyte ratio (PLR) is a new prognostic marker in coronary artery disease. We aimed to evaluate the relationship between PLR and in-hospital mortality in patients with ST-elevated acute myocardial infarction (AMI).

Material/Methods: The present study included 636 patients with ST-elevated AMI. The study population was divided into tertiles based on their admission PLR. Patients having values in the third tertile was defined as the high PLR group (n=212) and those having values in the lower 2 tertiles were defined as the low PLR group (n=424).

Results: Risk factors of coronary artery disease and treatments administered during the in-hospital period were similar between the groups. Male patient ratio was found to be lower in the high PLR group (73% *vs.* 82.8%, p=0.004). In-hospital mortality was increased in the high PLR group when compared to the low PLR group (12.7% *vs.* 5.9%, p=0.004). The PLR >144 was found to be an independent predictor of in-hospital cardiovascular mortality (HR: 2.16, 95% CI: 1.16–4.0, p=0.014).

Conclusions: This study showed that PLR is an independent predictor of cardiovascular mortality in patients with ST-elevated AMI.

MeSH Keywords: Myocardial Infarction • Hospital Mortality • Platelet/Lymphocyte Ratio

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Background

Acute myocardial infarction (AMI) results from total coronary artery occlusion, usually due to thrombus formation on complicated atherosclerotic plaque [1]. The patients with AMI have higher mortality rates, especially during the first 30 days [2]. Platelets play an important role in development, destabilization, and rupture of the atherosclerotic plaque, as well as in formation of platelet-fibrin plug at the complicated atherosclerotic plaque [3,4]. Platelet count is associated with increased risk of AMI and short- and long-term mortality after AMI [5–8]. Lymphocytes play a dominant role in chronic inflammation of atherosclerosis, and lower lymphocyte count is associated with increased cardiovascular risk and mortality in AMI [9,10]. Platelet/lymphocyte ratio (PLR) has been reported as a novel marker of long-term mortality in patients with non-ST-elevated AMI [11].

In the present study, we tested the hypothesis that PLR is associated with in-hospital cardiovascular mortality in patients with ST-elevated AMI (STEMI).

Material and Methods

Study population

Records of patients with AMI who were admitted to the coronary care unit between January 2009 and November 2011 were evaluated retrospectively. We consecutively evaluated 645 patients who were diagnosed with STEMI and excluded 4 patients with intracranial hemorrhage because of the intravenous thrombolytic treatment (streptokinase, tissue plasminogen activator, or tenecteplase) and 5 patients without eligible laboratory results. A total of 636 patients were enrolled into this study. A diagnosis of STEMI was defined as >30 minutes of continuous typical chest pain and ST-segment elevation ≥2 mm in 2 contiguous electrocardiography leads within 12 hours of symptom onset or within up to 18 hours if there was evidence of continuing ischemia or hemodynamic instability. From medical records, we obtained demographic information, cardiovascular history and risk factors for coronary artery disease (CAD), and treatment received during the in-hospital period. Patients who had been treated with antihypertensive drugs or those whose baseline blood pressure exceeded 140/90 mmHg were diagnosed with hypertension (HT). Diabetes mellitus (DM) was defined as fasting blood sugar level above 126 mg/dl or the use of anti-diabetic medications. The admission glomerular filtration rate (GFR) was estimated by the simplified MDRD (Modification of Diet in Renal Disease) equation [12]. Renal failure was defined as a glomerular filtration rate (GFR) <60 ml/min/m^2.

Cardiovascular events during the in-hospital period were investigated from patient records. Ventricular tachycardia or ventricular fibrillation were defined at least 24 hours after the beginning of the symptoms, advanced heart failure was defined as Killip classification ≥2, and cardiovascular death was defined as death due to AMI, heart failure, or arrhythmia. The mean follow-up period was 7 days.

Analysis of blood samples

Complete blood counts and biochemical values were evaluated retrospectively from blood samples obtained by antecubital vein puncture upon admission to the emergency department. Total and differential leukocyte counts were determined with the BeckmanCoulterLH 780device (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland). Other biochemical measurements and electrolyte levels were determined by standard laboratory methods.

Statistical analysis

The study population was divided into tertiles based on admission PLR values. The high PLR group (n=212) was defined as having values in the highest tertile (PLR >144), and the low PLR group (n=424) was defined as having values in the lower 2 tertiles (PLR ≤144).

Quantitative variables are expressed as the mean value ±SD or median (interquartile range), and qualitative variables are expressed as percentages (%). All measurements were evaluated with the Kolmogorov-Smirnov test. A comparison of parametric values between high and low PLR groups was performed using the t test or the Mann-Whitney U-test. Categorical variables were compared by the likelihood-ratio χ^2 test or Fisher's exact test. A backward stepwise multivariate logistic regression analysis, which included variables with p<0.1, was performed to identify independent predictors of in-hospital cardiovascular mortality. Age ≥70, female sex, renal failure (GFR <60 ml/min/m^2), time of chest pain, not receiving thrombolytic treatment, NLR>4.1, and PLR>144 were entered into the model. A p value <0.05 was considered statistically significant. All statistical studies were carried out with the SPSS program (version 17.0, SPSS, Chicago, IL, USA).

Results

A total of 636 patients (505 men and 131 women) were enrolled into the present study. No differences were found between the groups regarding thrombolytic and other treatments received during the in-hospital period. Tobacco use, HT, DM, and CHD history were not significantly different between the groups. Table 1 shows the clinical characteristics of the groups. The rate of male patients ratio was lower in the high PLR group

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Table 1. Clinical data, risk factors and treatments of study population.

Variable	High PLR (n=212) n (%)		Low PLR (n=474) n (%)		P value
Male	154	(73.0)	351	(82.8)	0.004
Hypertension	68	(32.1)	122	(28.8)	0.401
Diabetes Mellitus	79	(37.3)	167	(39.4)	0.604
Current smoker	79	(37.3)	146	(34.5)	0.495
Prior CHD	34	(16.0)	51	(12.0)	0.161
Thrombolytic	138	(65.9)	283	(66.7)	0.678
LMWH	208	(98.6)	413	(97.9)	0.536
ASA	208	(98.6)	410	(97.2)	0.268
Clopidogrel	208	(98.6)	413	(97.9)	0.546
Beta blocker	191	(91.4)	370	(87.5)	0.142
ACE inhibitor	170	(80.6)	355	(83.9)	0.291
Statin	183	(86.7)	366	(86.7)	1.000
Nitrate	25	(11.8)	32	(7.6)	0.076

n – number of patients; CHD – coronary heart disease; LMWH – low molecular weight heparin; ASA – acetyl salicylic acid; ACE – angiotensin converting enzyme.

Table 2. Patient's laboratory findings.

Variable	High PLR (n=424)		Low PLR (n=212)		P Value
Age	63.7±12.1		61.4±12.0		**0.022**
Blood glucose	124	(56–508)	123	(58–520)	0.801
GFR (MDRD) ml/min/m^2	75.8	(5.8–133.4)	79.6	(19.6–240)	0.166
MI hour	5.1±3.9		5.4±3.3		0.367
T. cholesterol(mg/dl)	187±43		186±41		0.119
LDL (mg/dl)	122	(28–246)	121	(43–228)	0.441
HDL (mg/dl)	33	(14–212)	38.0±21.3		**0.02**
Triglyceride (mg/dl)	112	(21–394)	130	(29–987)	**0.001**
Leucocyte (10^3/mm^3)	11.6	(1.2–30.4)	11.0	(5.0–22.8)	0.205
Neutrophil (10^3/mm^3)	9.6	(3.2–25.1)	7.3	(2.2–18.4)	**0.001**
Platelet (10^3/mm^3)	245	(121–779)	215	(43–419)	**0.001**
Lymphocyte (10^3/mm^3)	1.2	(0.4–3.7)	2.4	(0.6–91)	**0.001**
NLR	7.66	(1.36–44.2)	2.96	(0.6–20.0)	**0.001**
PLR	196.8	(144.1–175.0)	87	(21.4–143.8)	**0.001**

n – number of patients; GFR – glomerular filtration rate; MDRD – modification of diet in renal disease; LDL – low density lipoprotein; HDL – high density lipoprotein; PLR – platelet/lymphocyte ratio.

(73% *vs.* 82.8%, p=0.004). The patients in the high PLR group were older (63.7±12.1 *vs.* 61.4±12.0, p=0.022). Baseline platelet and neutrophil levels were significantly higher in the high PLR group than in the low PLR group (9.6 [3.2–25.1]×10^3/mm^3 *vs.* 7.3 [2.2–18.4]×10^3/mm^3, p<0.001; 245 [121–779]×10^3/mm^3 *vs.* 215 [43–419]×10^3/mm^3, p=0.001), whereas the baseline lymphocyte level was significantly lower in the high PLR group than in the low PLR group (1, 2 [0.4–3.7]×10^3/mm^3 *vs.* 2.4 [0.6–9.1]×10^3/mm^3, p=0.001). Neutrophil-to-lymphocyte ratio (NLR) was higher in high PLR group (p<0.001) (Table 2).

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Table 3. In-hospital cardiovascular events.

	PLR >144 (n=212)		PLR ≤144 (n=424)		P value
In-hospital mortality% (n)	12.7	(27)	5.9	(25)	**0.003**
Serious ventricular arrhythmia % (n)	3.8	(8)	3.5	(15)	0.770
Advanced heart failure% (n)	18.9	(40)	12.3	(52)	**0.026**
Complete atrioventricular block% (n)	2.8	(6)	1.9	(8)	0.445
Post-MI angina% (n)	6.6	(14)	6.4	(27)	0.909

n – number of patients.

Table 4. Univariate analyses for risk factors of in-hospital cardiovascular mortality.

Variable	HR (%95 CI)	P value
Age ≥70 years	4.03 (2.25–7.23)	<0.001
No thrombolytic treatment	5.67 (3.03–10.60)	<0.001
Hypertension	1.51 (0.84–2.73)	0.163
Diabetes mellitus	1.52 (0.86–2.68)	0.149
CHD history	1.39 (0.65–2.98)	0.385
Chest pain time >6 hours	2.55 (1.43–4.53)	0.001
GFR (MDRD) <60 ml/min	3.24 (1.78–5.91)	<0.001
Female gender	2.44 (1.34–4.46)	0.004
NLR >4.1	2.39 (1.29–4.40)	0.005
HDL	1.02 (0.99–1.06)	0.151
PLR >144	2.32 (1.31–4.12)	0.004

CHD – coronary heart disease; GFR – glomerular filtration rate; MDRD – modification of diet in renal disease; PLR – platelet/lymphocyte ratio.

Cardiovascular events are shown in Table 3. The high PLR group had a significantly higher incidence of in-hospital cardiovascular mortality than the low PLR group (12.7% *vs.* 5.9%, p=0.003). Advanced heart failure (Killip class ≥2) was more frequent in patients with high PLR values (18.9% *vs.* 12.3%, p=0.026).

Independent predictors of in-hospital cardiovascular mortality were determined by backward stepwise multivariate logistic regression. Chest pain duration more than 6 hours, female sex, not receiving thrombolytic treatment, renal failure, age ≥70 years, NLR >4.1, and PLR >144 were found to be associated with increased in-hospital cardiovascular mortality in a logistic regression analysis (Table 4). PLR >144 was found to be an independent predictor of in-hospital cardiovascular mortality in multivariate analyses (hazard ratio: 2.16, 95% confidence interval: 1.16–4.0, p=0.014). Table 5 shows other independent predictors of cardiovascular mortality. In ROC curve analyses, an PLR value of 144 was determined as an effective cut-off point in STEMI of in-hospital mortality, with a sensitivity of 51% and a specificity of 69% (area under the curve=0.59, 95% confidence interval 0.50–0.67) (Figure 1).

Table 5. Independent predictors of in-hospital cardiovascular mortality.

Variable	HR (%95 CI)	P value
High PLR (>144)	2.16 (1.16–4.0)	0.014
Age ≥70	2.39 (1.23–4.65)	0.01
No thrombolytic treatment	4.17 (2.1–8.3)	0.001
GFR <60 ml/m^2	2.11 (1.1–4.04)	0.024

PLR – platelet/lymphocyte ratio; HR – hazard ratio; CI – confidence interval.

Discussion

In this study we show that high PLR at admission to hospital is an independent predictor of early cardiovascular mortality in patients with AMI. Older age, renal failure, and not treated with thrombolytic treatment are other independent predictors of mortality. To our knowledge this is the first study to investigate the relationship between PLR and mortality in STEMI.

Atherosclerotic CAD is still the most common cause of mortality and morbidity in developed countries. Inflammation plays a pivotal role in formation and complication of atherosclerosis [13]. Activated platelets precipitate to produce inflammatory substances from endothelial cells and leucocytes that cause monocyte adhesion and transmigration, and thereby increase the inflammatory process and progression of atherosclerotic

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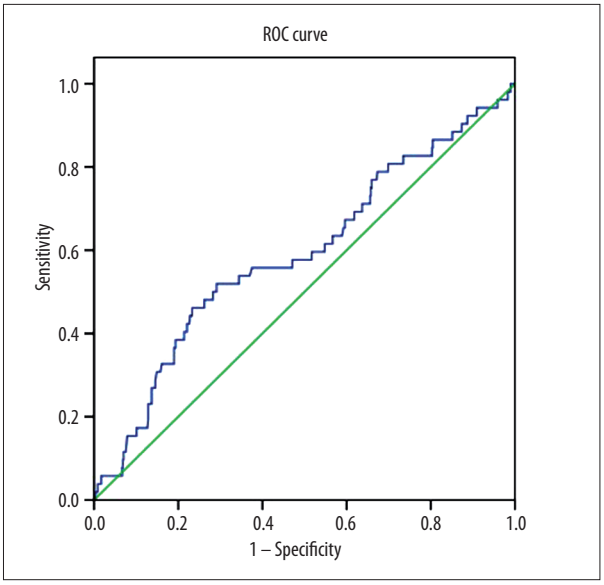

Figure 1. ROC curve for the platelet/lymphocyte ratio.

plaque [14,15]. Furthermore, these activated adhesion molecules and chemokines increase the activation of leucocytes, and produce reactive oxygen molecules and matrix metalloproteinase that cause plaque destabilization in atherosclerotic plaque [16]. AMI usually occurs as a result of coronary artery occlusion due to complication of an atherosclerotic plaque. Platelets play a dominant role in pathogenesis of acute coronary syndromes by formation of platelet-fibrin complexes [17]. Platelet count was found to be associated with development of AMI and presence of CAD [5,17]. Gary et al. concluded that higher platelet volume may change blood viscosity and increase inflammation [18]. Healy et al. reported that expression of CD-49 and plasma myeloid protein in platelets is increased in patients with ST-elevated MI [19]. Davi et al. showed that higher platelet activity is related to higher rates of cardiovascular events [4]. In addition, it was found that platelet count is associated with short- and long-term mortality in patients with ST-elevated and non-ST-elevated AMI, and unstable angina pectoris [20–22]. Nikolsky et al. showed a relationship between platelet count and mortality in patients with recurrent AMI in the first year after primary percutaneous intervention [23]. In addition, fibrinogen levels and platelet counts are positively correlated and related to inflammation in AMI patients. These findings suggest that platelets are one of the most important components of CAD and cardiovascular events.

Lymphocytes are an important part of chronic inflammation in the atherosclerotic process [9]. In AMI, lymphocytes infiltrate to the ischemic and reperfused myocardium and express interleukin-10, which may play a significant role in transmigration of mononuclear cells, and induce the expression of tissue inhibitor of metalloproteinase-1 [24]. Recent studies showed that higher PLR is related to presence of CAD and is correlated with C-reactive protein and fibrinogen levels [18]. Azab et al. reported that PLR above 170 is an independent predictor of long-term mortality in non-ST-elevated AMI patients [11]. In our study, we found that high PLR (above 144) is an independent predictor of in-hospital mortality in patients with STEMI who received thrombolytic treatment.

Prevalence of AMI is increased and prognosis worsens with aging. Complications of AMI, including heart failure, shock, and ventricular rupture, are more frequent in older AMI patients [25,26]. In the present study, patients in the high PLR group were older than in the low PLR group. Additionally, advanced heart failure was more frequent in the high PLR group. Neutrophil count was increased in the high PLR group, suggesting high inflammatory activity. Neutrophils may cause plaque rupture as a result of stimulating the release of proteolytic enzymes, superoxide radicals, and arachidonic acid derivates, and exacerbates the inflammatory condition. Microvascular obstruction due to neutrophil-platelet plug, vasoconstriction due to thromboxanes, and vasoactive molecules may cause no-reflow and cause further myocardial injury. These high inflammatory processes appear to be responsible for high rates of heart failure and mortality. NLR was higher in the high PLR group and was strongly related to cardiovascular mortality in our population, in line with results of previous studies. In multivariate analyses, we found that NLR was not an independent predictor and that PLR is an independent predictor of mortality.

The present study has some limitations. First, this was a retrospective study. Patient long-term survival and cardiac conditions could not be assessed because the patient records and the coronary angiography results of patients were not known. Anti-platelet treatment before AMI is an important factor affecting in-hospital mortality [27], but our data were not able to demonstrate previous antiplatelet use.

Conclusions

AMI is the most important cause of mortality (especially in the first month) and morbidity worldwide. This study showed that high PLR is an independent predictor of in-hospital cardiovascular mortality in patients with STEMI. Complete blood count analysis is a routine and inexpensive method that may be useful for the identification of high-risk patients.

PLR and other inflammatory markers and clinical findings might be helpful in identifying high-risk patients and treatment strategies.

Conflict of Interest

There are no conflicts of interest.

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