Usefulness of Platelet-Lymphocyte Ratio to Predict Stent Thrombosis in Patients with ST Elevation Myocardial Infarction

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ABSTRACT

Introduction: Stent thrombosis, an iatrogenic disease, is an important complication of percutaneous coronary intervention (PCI). The platelet to lymphocyte ratio (PLR) has been recently proposed to be a marker of thrombosis and inflammation, mainly in cancer patients. The aim of this study was to determine whether PLR in patients presenting with acute ST elevation myocardial infarction (STEMI) is predictive of the development of stent thrombosis.

Patients and Methods: We retrospectively analyzed the clinical, hematologic, and angiographic data of total 201 patients (mean age 59.8±13.1 years, 3 out of 4 were males) who had undergone PCI for acute STEMI and a further control coronary angiography. 54 of them were diagnosed as stent thrombosis and formed the patient group and 147 patients matched with patient group in terms of age, gender, traditional coronary risk factors, stent implantation procedure, and stent type and length formed the control group in whom the stent implanted during primary PCI was found patent in the repeat coronary angiography.

Results: The pre-procedural PLR was significantly higher in patients with stent thrombosis compared to patients without stent thrombosis (176±68 vs. 135±62; p<0.001). Based on multiple logistic regression analysis, pre-procedural PLR was a significant and independent predictor of stent thrombosis (OR: 1.009, 95% confidence interval: 1.004-1.014, p<0.001). Using a receiver operating characteristics (ROC) analysis, a PLR > 150 had 63% sensitivity and 70% specificity for predicting stent thrombosis (ROC area under curve: 0.692, 95% CI: 0.614-0.771, p<0.001).

Conclusion: A high pre-procedural PLR is a significant and independent predictor of stent thrombosis in patients with acute STEMI.

Key Words: Percutaneous coronary intervention; platelet to lymphocyte ratio; ST elevation myocardial infarction; stent thrombosis

ST Yükselmeli Miyokard İnfarktüslü Hastalarda Stent Trombozunu Öngörmede Trombosit-Lenfosit Oranının Kullanışlılığı

ÖZET

Giriş: İyatrojenik bir hastalık olan stent trombozu, perkutan koroner girişimin (PCI) önemli bir komplikasyonudur. Trombosit lenfosit oranının (PLR) son zamanlarda daha çok kanser hastalarında, tromboz ve inflamasyonun bir belirteci olduğu gösterilmiştir. Bu çalışmanın amacı akut ST yükselmeli miyokard infarktüsü (STYMİ) ile başvuran hastalarda PLR'nin stent trombozu gelişiminin bir öngördürücüsü olup olmadığını araştırmaktır.

Hastalar ve Yöntem: Akut ST yükselmeli miyokard infarktüsü tanısıyla primer PCI yapılan ve daha sonra stabil anjina veya Akut koroner sendrom tanısıyla tekrar koroner anjiyografi yapılarak stent trombozu tanısı alan 54 olgu çalışmanın hasta grubunu oluştururken; bunlarla yaş, cinsiyet, koroner risk faktörleri, stent uygulama prosedürü ile stent tipi ve boyu bakımından benzer olup primer PCI sonrası yapılan koroner anjiyografide stenti patent bulunan 147 hasta kontrol grubunu oluşturdu. Toplam 201 hastanın (ortalama yaş 59,8±13,1 yıl, ¾'ü erkek) klinik, hematolojik ve anjiyografik verilerini retrospektif olarak inceledik.

Bulgular: İşlem öncesi PLR, stent trombozu gelişen hastalarda gelişmeyenler ile karşılaştıldığında anlamlı olarak daha yüksekti (176±68'e karşı 135±62; p<0,001). Çoklu lojistik regresyon analizinde, işlem öncesi PLR, stent trombozunun önemli bir bağımsız öngördürücüsü idi (OR:1,009, %95 güven aralığı:1,004-1,014, p<0,001). ROC analizi kullanılarak PLR >150 değerinin %63 duyarlık ve %70 özgüllük ile stent trombozunun öngördürücüsü olduğu bulundu (ROC eğri altında kalan alan: 0,692, GA %95: 0,614-0,771, p<0,001).

Sonuç: İşlem öncesi yüksek bulunan PLR, akut STYMİ'li hastalarda stent trombozunun önemli ve bağımsız bir öngördürücüsüdür.

Anahtar Kelimeler: Perkutan koroner girişim; trombosit lenfosit oranı; ST yükselmeli miyokard infarktüsü; stent trombozu

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Submitted: 11.02.2014
Accepted : 13.03.2014

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INTRODUCTION

Rapidly restoring coronary blood flow to the myocardium is critical after sustaining an acute myocardial infarction. The standard of care for ST segment elevation myocardial infarction (STEMI) is percutaneous coronary intervention (PCI), which is safe, effective, and the preferred modality of cardiac muscle reperfusion[1]. However, PCI is associated with a 1.4% - 4.4% incidence of developing stent thrombosis, which is a serious complication[2]. Several factors significantly impact the likelihood of stent thrombosis (ST) including stent type, patient's concomitant diseases, inadequate inhibition of platelets with anti-platelet drugs, coronary artery disease severity, and whether there were complications during PCI. Despite advances in technology that aid in preventing ST, it still remains a significant cause of mortality.

Inflammation plays a pivotal role in initiating and propagating atherosclerotic disease[3]. Several studies have examined whether the elevation of inflammatory markers is associated with the development of poorer outcomes in certain cardiovascular disease[4-9]. The platelet to lymphocyte ratio (PLR) was introduced recently as a biological indicator that demonstrates the balance between thrombosis and inflammation, and this measure is utilized mostly in patients diagnosed with malignancies[10,11]. Little is known about whether elevated PLR levels are associated with adverse outcomes in patients with cardiovascular diseases[12,13]. Thus, we investigated whether high pre-procedural PLR values before performing primary PCI with stent placement in patients presenting with acute STEMI predicts the development of future ST or not.

PATIENDS and METHODS

Study Sample

We retrospectively analyzed clinical and angiographic imaging data of patients presented with acute STEMI and treated with PCI (primary PCI) with stent placement within 12 hours of symptom onset. All of the patients had undergone repeat coronary angiography (CAG) due stable angina or acute coronary syndrome after discharge. Fifty-four patients were diagnosed as stent thrombosis (ST group). Academic Research Consortium definitions were used to define the timing and diagnosis of stent thrombosis[14]. Of these 54 patients; 2 were acute ST (within 24 hours), 28 were subacute ST (between 1-30 days), 21 were late ST (between 1-12 months), and 3 were very late ST (>1 year).

The control group was selected randomly among patients admitted with STEMI and treated with primary PCI plus stent implantation who were comparable with ST group in terms of age, gender, traditional coronary risk factors, stent implantation procedure, and stent type and length. During repeat CAG, the implanted stent was found patent in the control group which is consisted of 147 patients. The mean age of the study population (n=201) was 59.8±13.1 years and 3/4 of the study population was male. Exclusion criteria from the study included patients with high thrombus burden, residual thrombus proximal or distal to the implanted stent, prior coronary artery bypass grafting, active infectious disease, hematologic disease, cirrhosis, chronic obstructive pulmonary disease, chronic kidney disease, malignancy, and recent cessation of antiplatelet drugs. Also patients with improper stent apposition and coronary occlusion requiring more than one stent during primary PCI were not included in the study. PLR was calculated by dividing the absolute pre-procedural platelet count to the lymphocyte count for each patient. STEMI was defined as the presence of chest pain lasting longer than 20 minutes associated with ST segment elevation ≥ 1 mm in at least two successive limb leads, or ≥ 2 mm in at least 2 contiguous precordial leads, or the presence of a new left bundle branch block on electrocardiogram. The local ethics committee reviewed and approved the study protocol.

Biochemical Measurements

Venous blood samples were drawn during the initial emergency department admission or just before undergoing coronary angiography for primary PCI. A complete blood count with differential was routinely performed and measured via commercially available methods for each patient.

Percutaneous Coronary Intervention and Angiographical Analysis

Coronary angiography and PCI with stent placement were performed via the femoral artery approach using the Judkins technique. Almost 3 out of 4 stents implanted during primary PCI were drug eluting stents (DES) with rapamycin or everolimus. Rests of the stents were bare metal stents (BMS). Only one stent was implanted for each patient. Coronary angiograms were digitally recorded and quantitatively analyzed. All patients received 300 mg of oral acetylsalicylic acid, a 600 mg loading dose of oral clopidogrel, and a 100 U/kg dose of intravenous unfractionated heparin before undergoing PCI. Two blinded cardiologists assessed the pre- and post-procedural coronary angiograms.

Statistical Analysis

Data were analyzed with SPSS version 16.0 for Windows® software (SPSS Inc., Chicago, Illinois). Data were expressed as the mean ± one standard deviation (SD) or as frequency percentages. The independent samples t-test or the Mann-Whitney U-test were utilized to analyze continuous variables, and the chi-square test was used to analyze categorical variables. Pearson's or Spearman's tests were used for correlation analysis. Statistical significance was defined as a p-value less than 0.05. Multivariate logistic regression analysis was performed to assess the independent predictors of ST. Variables with a p-value less than 0.1 in univariate analysis were included in the logistic regression model, and the results were expressed as the odds ratio (OR) with a 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was utilized to determine the optimum cutoff level of the association of PLR with ST.

RESULTS

Baseline demographic, laboratory, and angiographic imaging data were organized based on whether or not the subjects developed ST in Table 1. Age, gender, hemoglobin level, stent type and length, and pre- and post- stent dilatation did not significantly differ between groups. The time interval between stent implantation and ST development was in range of 0 to 412 days with a median of 26th day. Pre-procedural PLR was obtained before primary PCI with stent placement was significantly higher in patients with ST as compared to patients who did not develop ST (176±68 versus 135±62, p<0.001, Figure 1). Neutrophil lymphocyte ratio (NLR) was positively correlated with the PLR (r=0.623, p<0.001). However, NLR did not differ significantly between the two groups (p=0.702). Based on multiple logistic regression analysis, the pre-procedural PLR was found to be a significant independent predictor of ST with an OR of 1.009 and a 95% CI of 1.004-1.014 (p<0.001). Using a ROC analysis, a PLR >150 had 63% sensitivity and 70% specificity for predicting ST, with an area under the curve of 0.692 and a 95% CI of 0.614-0.771 (p<0.001, Figure 2).

DISCUSSION

Coronary stent thrombosis (ST) is a rare acute event associated with patient comorbidities and anatomic risk factors that continue to be elucidated. Our findings suggested that an increased PLR taken before PCI with stent placement was a significant and independent predictor of ST in patients presenting with acute STEMI. A pre-procedural PLR >150 had 63% sensitivity and 70% specificity in predicting ST.

Having a STEMI is one of the most significant predictors of developing ST, which may be due to the atherosclerotic plaque itself and/or the subsequent inflammatory response to the stent[15,16]. Stent strut penetration by the underlying plaque may augment inflammation and fibrin deposition and inhibit new intimal growth, which results in uncovered stent struts. This phenomenon is especially common in DES relative to other stent types[17]. Reduced blood flow through the stented

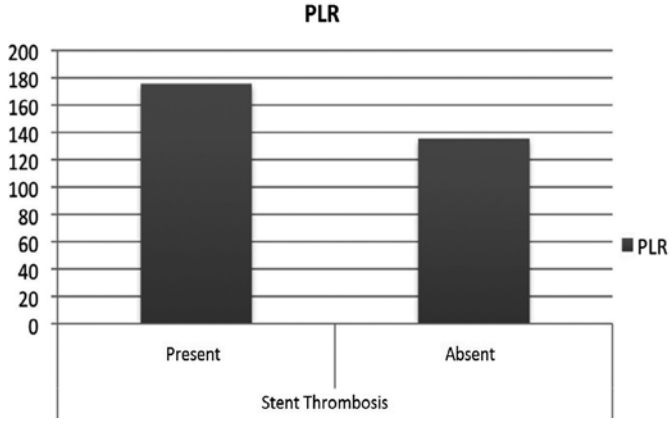

Figure 1. The pre-procedural platelet to lymphocyte ratio (PLR) in patients with stent thrombosis (ST) as compared to control group

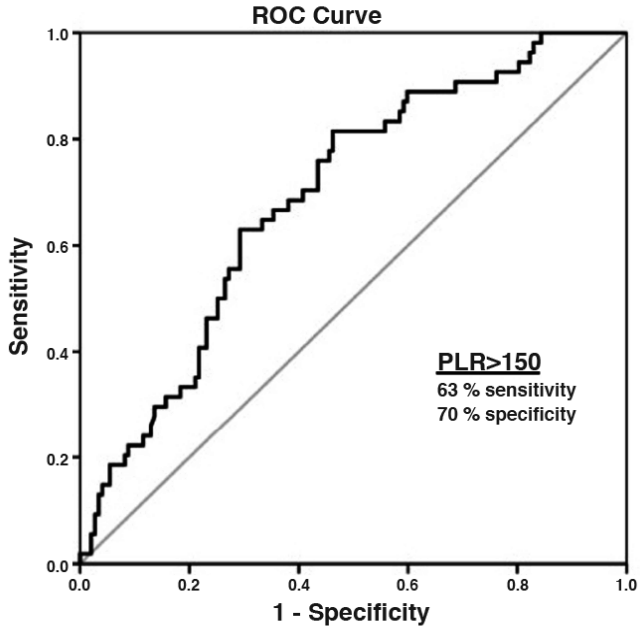

Figure 2. Receiver operating characteristics (ROC) curve of platelet to lymphocyte ratio (PLR) for predicting stent thrombosis in patients presenting with acute STEMI

Table 1. Patient demographics based on the development of stent thrombosis

	Stent thrombosis		
Variables	**Absent n=147**	**Present n=54**	**p-value**
Age (years)	60.5±13.5	57.9±11.9	0.202
Male gender (n %)	110 (74.8)	40 (74.1)	0.913
Hypertension (n %)	49 (33.3)	25 (46.3)	0.091
Diabetes mellitus (n %)	30 (20.4)	12 (22.2)	0.775
Smoking (n %)	76 (51.7)	26 (48.1)	0.655
Glucose (mg/dl)	157±73	158±90	0.202
Creatinine (mg/dl)	0.89±0.21	0.86±0.20	0.408
Total cholesterol (mg/dl)	171±38	170±38	0.872
High-density lipoprotein (mg/dl)	35±9	35±9	0.933
Low-density lipoprotein, (mg/dl)	108±29	104±29	0.369
Hemoglobin (g/L)	14.0±1.2	14.2±1.5	0.455
Platelet count (10^9/L)	251±63	293±71	< 0.001
White blood cell count (10^9/L)	12.20±2.82	11.55±2.86	0.152
Neutrophil count (10^9/L)	9.20±2.72	8.83±2.83	0.361
Lymphocyte count (10^9/L)	2.13±0.90	1.85±0.63	0.077
Neutrophil to lymphocyte ratio	5.09±2.73	5.60±3.50	0.702
Platelet to lymphocyte ratio	135±62	176±68	< 0.001
Drug eluting stents (n %)	61 (41.5)	20 (37)	0.568
Stent diameter (mm)	3.0±0.4	3.0±0.4	0.980
Stent length (mm)	22.15±5.65	22.98±6.62	0.533
Pre-dilatation (n %)	118 (80.3)	44 (81.5)	0.848
Post-dilatation (n %)	80 (54.4)	29 (53.7)	0.928

coronary vessel and the presence of a friable atheroma indicate incomplete stent apposition, which leads to suboptimal coronary artery expansion[18]. The incidence of acquired incomplete stent apposition together with atherosclerotic remodeling is greater in patients with a history of acute coronary syndrome and STEMI and is most often observed in patients with DES[19]. Even though our study does not fully elucidate the mechanism by which PLR is associated with ST, possible explanations include that the PLR reflects platelet and clotting system activation, local vessel wall inflammation, endothelial dysfunction, hypersensitivity reactions, and new plaque rupture either adjacent to or within the stented site. All of these aforementioned mechanisms also contribute to DES-related thrombosis[20-22].

Several studies have demonstrated an association between elevated platelet counts and adverse outcomes in cardiovascular disease[20,22,23]. Higher platelet counts may represent a greater degree of antiplatelet drug resistance and an increased propensity to form platelet rich thrombi on atherosclerotic plaques leading to worse outcomes[24]. Furthermore, increased platelet counts may reflect underlying inflammation as many inflammatory mediators stimulate megakaryocytic proliferation and produce relative thrombocytosis. In fact, a study by Dangas et al. showed that elevated baseline platelet counts were associated with stent thrombosis[2]. Furthermore, patients with coronary artery disease (CAD) tend to have increased levels platelet monocyte aggregates (PMA) in their bloodstream, which is associated with increased plaque instability[25]. It follows that elevated PMA levels in NON-STEMI patients is correlated with worse health outcomes and an increased risk of future cardiac events[21].

There is a relationship between low lymphocyte counts and adverse outcomes in patients with chest pain, stable CAD, unstable angina, and congestive heart failure[26-28]. The histological basis of this relative lymphopenia is due to the release of cortisol in response to the stress of myocardial ischemia[27,29]. Similarly, ST has been associated with low lymphocyte counts in our study as well. The advantage of PLR is that it reflects both activated coagulation and inflammatory pathways, and so it may be superior to platelet or lymphocyte counts alone in predicting adverse outcomes such as ST. The significance of PLR as a prognostic indicator has been demonstrated in patients with various cancers[10,30,31]. In a study by Azab et al., higher PLR values were associated with increased long-term mortality in patients with non-ST segment elevation myocardial infarctions[12]. Sunbul et al. reported that PLR was a significant predictor of not having decreased blood pressures at night for hypertensive patients, which is also known as "non-dipper" hypertension[32]. Moreover, higher PLR levels were found to be related to poor coronary collateral circulation in patients with stable angina pectoris and chronic total coronary artery occlusion[13].

The major limitation of our study was its retrospective design and small sample size in a single-center. Our study also provided no data regarding causality between PLR and the development of ST. It would be more valuable if we could measure the level of platelet aggregation in order to evaluate aspirin and/or clopidogrel resistance in the patients and control subjects. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) might have given us more detailed information about stent apposition after stent implantation, however this data is not available for our study population since these imaging methods are not routinely applied after primary PCI. Measuring laboratory markers that are established indicators of cardiovascular disease such as CRP was lacking as well. Despite these limitations, to our knowledge this is the first study that evaluated the relationship between pre-procedural PLR and stent thrombosis in patients admitted with acute STEMI.

In conclusion, high pre-procedural PLR before PCI with stent placement is a significant and independent predictor of ST in patients presenting with acute STEMI. Large-scale, prospective, and multicenter studies will be necessary to clarify the relationship between PLR and ST. Future studies should be performed that combine clinical, imaging and laboratory results in addition to the PLR in determining whether a patient with previous PCI with stenting is especially at high risk for developing ST.

Acknowledgement

We are grateful to Dicle University DUBAP for their sponsorship about English editing of this manuscript.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

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