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Original Article

The association of platelet-to-lymphocyte ratio with in-hospital acute stent thrombosis in non-st elevated acute coronary syndromes

Non-ST eleve akut koroner sendromda platelet/lenfosit oranının akut stent trombozunu öngörmedeki rolü

Mustafa KARANFIL*, Sefa UNAL

University of Health Sciences, Ankara City Hospital, Department of Cardiology, Ankara/TURKEY

Abstract

Aim: Cardiovascular diseases are the leading causes of mortality in the world. Interventional methods used in the treatment of coronary artery disease have revolutionized the treatment of the disease. Balloon angioplasty and coronary stenting are two miraculous treatment methods of the disease. Acute stent thrombosis(ST) is a serious and mortal complication of stent thrombosis. Platelet-to-lymphocyte ratio (PLR), a novel inflammatory marker, has previously been shown to be associated with cardiac problems. In this study, we aimed to investigate the association of PLR with in hospital acute stent thrombosis.

Material and Methods: 1300 patients without ST elevated myocardial infarction (NSTEMI)who underwent stent implantation between January 2013 and December 2013 in our hospital were included in the study. Demographic, clinical, angiographic and laboratory parameters of all participants were recorded.

Results: In the ST+ group hypertension, diabetes mellitus rates were higher, clopidogrel loading time was shorter. The mean PLR value was significantly higher in the ST+ group as compared to ST- group (133.3 ± 75.0 vs 110.1 ± 47.0, p= 0.005). In the multivariate analyses hypertension, diabetes mellitus, shorter clopidogrel loading time and PLR was found to be independent predictors of acute stent thrombosis.

Conclusion: Our results demonstrated that PLR is an independent predictor of acute stent thrombosis in Non-ST elevated acute coronary syndrome patients.

Keywords: acute stent thrombosis; platelet-to-lymphocyte ratio; coronary artery disease; inflammation

Corresponding author*: Mustafa Karanfil, University of Health Sciences, Ankara City Hospital, Department of Cardiology, Ankara/TURKEY
E-mail: mkaranfil42@yahoo.com
ORCID: 0000-0002-5401-1149
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Öz

Amaç: Kardiyovaskuler hastalıklar dünyada önde gelen mortalite nedenidir. Akut stent trombozu (ST) stent implantasyonunun çok ciddi ve mortal bir komplikasyonudur. Yeni bir enflamatuar belirteç olan platelet/lenfosit oranının (PLR) daha önce kalp problemleriyle ilişkili olduğu gösterilmiştir. Bu çalışmada, ST- segment yükselmesiz akut koroner sendromlarda (ST- segment yükselmesiz myokard enfarktüsü ve kararsız angina) PLR ile akut stent trombozunun (ST) ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamıza Ocak 2013- Aralık 2013 tarihleri arasında stent implantasyonu yapılan, ST- segment yükselmesiz akut koroner sendrom hastası 1300 hasta dahil edildi. Tüm hastaların demografik, klinik, anjiyografik ve laboratuvar parametreleri kaydedildi.

Bulgular: ST (+) grupta hipertansiyon, diabetes mellitus oranları daha yüksekti, klopidogrel yükleme süresi daha kısaydı. Ortalama PLR değeri ST (+) grupta ST (-) gruba göre anlamlı olarak daha yüksekti (133.3 ± 75.0'a karşı 110.1 ± 47.0, p = 0.005). Çok değişkenli analizlerde hipertansiyon, diabetes mellitus, kısa klopidogrel yükleme süresi ve PLR'nin akut stent trombozunun bağımsız öngördürücüleri olduğu bulundu.

Sonuç: Bulgularımız PLR' nin, ST- segment yükselmesiz akut koroner sendrom hastalarında akut stent trombozunun bağımsız bir öngördürücüsü olduğunu göstermiştir.

Anahtar kelimeler: akut stent trombozu; platelet/lenfosit oranı; koroner arter hastalığı; inflamasyon

Introduction

Cardiovascular diseases including coronary artery disease, cerebrovascular disease, peripheral artery disease and aortic arteriosclerosis are the leading causes of mortality in the world. Especially coronary artery disease is the most lethal disease of this group. In the United States, coronary artery disease is still responsible for about one third of deaths in people over 35 years of age. In Europe, 47% (52% in females and 42% in males) of deaths that occur each year are due to cardiovascular diseases, mainly CAD and stroke.

In the study of Heart Disease and Risk Factors in Turkish adults (TEKHARF), coronary artery disease was found to be responsible for 42.5% of the deaths which has a known cause. The prevalence of heart disease in adults in Turkey were found to be 6.7%.[1]

Interventional methods used in the treatment of coronary artery disease have revolutionized the treatment of the disease. Balloon angioplasty was used for the first time in 1977 by Gruentzig and colleagues in the treatment of coronary artery disease in 1986(4), Puel and colleagues performed intracoronary stent implantation, which is the second important invention of interventional treatment of coronary artery disease .[2, 3]

Stent implantation has been the main treatment for acute coronary syndrome due to improvements in stent technology and operator techniques, the use of dual antiplatelet therapy and positive results with acute intracoronary stenting in patients with acute occlusions due to dissection during PTCA, AMI and other acute coronary syndromes.

In this miraculous treatment method, stent restenosis and stent thrombosis are the major obstacles to treatment.

Acute stent thrombosis, which occurs in the first 24 hours after stent implantation, is a serious and mortal complication. Stent thrombosis and stent restenosis are the major problems of stent implantation. Despite advances in pharmacological treatment, stent technology and implantation techniques, stent thrombosis is still seen about 1-2% after stent implantation.PLR, a novel inflammatory marker, has previously been shown to be associated with cardiac problems such as stent restenosis, plaque fragility, and no-reflow phenomena. To the best of our knowledge, there is no study that previously examined the association of acute stent thrombosis with PLR. Our aim in this study is to investigate the relationship between acute stent thrombosis and PLR.

Material and Methods

Patients who underwent percutaneous coronary intervention between January 2013 and December 2013 at Turkey Yuksek Ihtisas Training and Research Hospital were screened retrospectively. Patients who had only balloon angioplasty and stent thrombosis after 24 hours of stent implantation were not included in the study. STEMI patients were also excluded. 1300 patients who underwent stent implantation were included in the study. 35 of these patients had in

hospital acute stent thrombosis. These patients were divided into 2 groups according to whether acute stent thrombosis developed. Risk factors (age, gender, hypertension, diabetes mellitus, dyslipidemia, family history for CAD, cigarette use) for coronary artery disease were recorded at the time of admission. In addition, risk factors for stent thrombosis (stent length, stent diameter, stent type, when ADP receptor antagonist was administered to the patient, and indication for stent implantation) were recorded. Patients with hypertension and hyperlipidemia were defined as either receiving treatment for these diseases at the time of the procedure or having the disease according to the ESC / ESH criteria at that time. Diabetes was defined as meeting the American Diabetes Association criteria or receiving antidiabetic treatment at the time of the procedure. Fifteen patients included in our study were randomly selected to determine the universality of the diagnosis of acute stent thrombosis. These patients were evaluated by different operators under the same conditions. Complete blood count, renal function tests and lipid profile were studied in venous blood samples taken immediately before percutaneous coronary intervention. The white blood cell components were determined by the Coulter counter method (Coulter LH780 Hematology Analyzer, Beckman Coulter Corp., Hileh, Fla.). The PLR value was obtained by dividing the number of platelets by the number of lymphocytes. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Statistical Analysis

All calculations were done using the SPSS 22.0 "Statistical Package for Social Sciences" program. The Shapiro Wilk test was used to determine the distributions of the data. Continuous variables were expressed mean ± standard deviation or median (interval between quarters); categorical variables were expressed in percentage and number. Continuous variables were compared using Student's t test or Mann Whitney U test and categorical variables were compared using Chi-Square or Fisher's test. Univariate logistic regression analysis was used to determine the association between variables and stent thrombosis.By the variables which were found associated with stent thrombosis and had a p value smaller than 0,05, multivariate logistic regression analyses were performed. The results of the regression analysis were expressed by the risk ratio (HR) and 95% confidence interval. Ap value less than 0,05 was considered as statistically significant.

Results

796 of 1300 patients included in the study were males. The average age was 59,7. Acute stent thrombosis was seen in 35 of these patients.

Table 1 shows demographic characteristics, presence of diseases that are risk factors for atherosclerosis, ejection fractions, which vessels were diseased, which vessels were intervened, clopidogrel loading time, implanted stent length and diameter, or stent type (DES or BMS) of ST + and ST- patients. There was no difference between ST + and ST- groups in terms of age, gender, smoking status, stent diameter and length. In the ST + group, it was seen that diabetes (60% vs 33,6%, p: 0,001), hypertension (77,1% vs. 40%, p: 0,001), lower ejection fraction (44,6± 8.5 vs. 54.1 ± 7.8, p: 0,001) were more frequent and clopidogrel loading time was shorter.

Table 2 shows the results of regression analysis. Univariable regression analysis showed that DM (2.954 (1.487-5.868), p: 0,002), HT (5.062 (2.282-11.232), p<0,001), pre-procedural EF (0.903 (0.875-0.932), p<0,001), clopidogrel loading time (0.122 (0.037-0.401), p: 0,001), acute coronary syndrome as indication for stent implantation (0.292 (0.186-0.458), p<0,001) and PLR(1.008 (1.002-1.014), p: 0,005) was associated with stent thrombosis. In multivariate regression analysis, DM (4.045 (1.684-9.719), p: 0,002), HT (7.223 (2.725-19.150), p<0,001), clopidogrel loading time (0.067 (0.019-0.237), p<0,001) and PLR (1.008 (1.001-1.015), p: 0,018) were found to be independent predictors for stent thrombosis.

Discussion

PLR, a novel inflammatory marker is an independent predictor of acute stent thrombosis.

Early stent thrombosis (generally defined as stent thrombosis within 30 days of stent placement, first 24 hours acute, 1-30 days subacute stent thrombosis) develops in approximately 0.5% to 1% of patients with well-placed stent and receiving dual antiplatelet therapy (aspirin and clopidogrel). More than 50% of patients with stent thrombosis develop myocardial infarction. The mortality rate in acute stent thrombosis is 10-15%.[4, 5]

Shorter clopidogrel loading time is an independent marker for stent thrombosis. If stent is implanted before clopidogrel is effective stent is prone to thrombosis. Systemic diseases such

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Table1. Comparisons of demographic and clinical characteristics

Parameters	ST+ (N=35)	ST– (N=1265)	P value
Age, years	60.8 ± 12.3	59.7 ± 8.6	0.457
Male, n (%)	25 (73.7)	771 (61.5)	0.209
Diabetes Mellitus, n (%)	21 (60.0)	426 (33.6)	0.001
Hypertension, n (%)	27 (77.1)	506 (40.0)	<0.001
Smoking, n (%)	24 (68.5)	933 (73.7)	0.492
Preprocedural LVEF, n (%)	44.6 ± 8.5	54.1 ± 7.8	<0.001
LAD disease, n (%)	16 (45.7)	493 (38.9)	0.388
LCX disease, n (%)	4 (11.4)	279 (22.0)	0.284
RCA disease, n (%)	14 (40.0)	434 (34.3)	0.863
Clopidogrel loading time < 2h, n (%)	32 (91.4)	716 (56.7)	<0.001
Clopidogrel loading time > 2h, n (%)	3 (8.5)	549 (43.3)	<0.001
BMS/DES, n	28/7	567/698	0.094
Elective PCI, n (%)	8 (22.8)	699 (55.2)	<0.001
Stent diameter (mm)	3.05 ± 0.33	2.99 ± 0.45	0.453
Stent length (mm)	19.0 ± 6.2	19.3 ± 5.7	0.784
Glucose, mg/dl	126.4 ± 55.1	136.1 ± 66.3	0.322
Creatinine, mg/dl	0.88 ± 0.19	1.01 ± 0.52	0.149
Hemoglobin, g/dL	13.7 ± 1.6	13.4 ± 2.2	0.381
Platelet count, $10^3/mm^3$	233.8 ± 92.9	227.24 ±67.9	0.584
WBC count, $10^3/mm^3$	10.2 ± 3.6	10.2 ± 4.5	0.974
Neutrophil,$10^3/mm^3$	6.9 ± 3.2	7.9 ± 3.0	0.461
Lymphocyte, $10^3/mm^3$	2.0 ± 0.9	2.2 ± 0.7	0.096
Total cholesterol, mg/dL	183.4 ± 50.2	182.9 ± 47.0	0.952
Triglyceride, mg/dL	181.7 ± 126.4	170.5 ± 121.1	0.588
LDL-cholesterol, mg/dL	120.8 ± 35.5	116.6 ± 33.9	0.478
HDL-cholesterol, mg/dL	37.6 ± 10.1	39.0 ± 9.1	0.373
PLR	133.3 ± 75.0	110.1 ± 47.0	0.005

Abbreviations: Data are presented as mean ±SD, or number (%). BMS, bare-metal stent; DES, drug-eluting stent; LAD, left anterior descending; LCX, left circumflex; LVEF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PLR, platelet to lymphocyte ratio.; RCA, right coronary artery; STEMI, ST segment elevation myocardial infarction; WBC, White blood cell; PLR, Platelet to lymphocyte ratio

Table 2. Multivariate logistic regression analysis to predicting the acute stent thrombosis.

	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Diabetes Mellitus	2.954 (1.487-5.868)	0.002	4.045 (1.684-9.719)	0.002
Hypertension	5.062 (2.282-11.232)	<0.001	7.223 (2.725-19.150)	<0.001
Preprocedure LVEF	0.903 (0.875-0.932)	<0.001	0.969 (0.921-1.020)	0.224
Clopidogrel loading time	0.122 (0.037-0.401)	0.001	0.067 (0.019-0.237)	<0.001
Stent diameter	1.296 (0.659-2.550)	0.453	-	-
ACS(high troponin) or elective	0.292 (0.186-0.458)	<0.001	0.556 (0.299-1.033)	0.063
Stent length	0.992 (0.934-1.053)	0.784	-	-
PLR	1.008 (1.002-1.014)	0.005	1.008 (1.001-1.015)	0.018

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; PLR, platelet to lymphocyte ratio.

as diabetes mellitus and hypertension are also independent predictors for stent thrombosis. These diseases are increasing the complexity of the disease and tendency to thrombosis.

Active increased inflammation can increase thrombosis. Atherosclerosis is a systemic chronic inflammatory disease. It is known that inflammatory markers such as hsCRP, P selectin, IL-6 are also effective in stent restenosis as well as in atherosclerosis. The association of increased platelet count with major adverse cardiac event and low lymphocyte count with adverse outcome in CAD have been shown in previous studies .[6-9]

A new inflammatory marker, platelet to lymphocyte ratio (PLR), was found to be related to atherosclerosis, to plaque vulnerability, and to no-reflow after primary PCI. [10-12]PLR has also been shown to be associated with mitral annular calcification, coronary slow flow, poor collateral vessel amount, occlusive peripheral disease and non-dipper HT.[13-15]

The effect of inflammation on acute stent thrombosis has been shown in previous studies .[16]

Initiation and progression of the atherosclerosis is associated with inflammation.[10] The association between inflammation, thrombosis, and atherogenesis is multifactorial and platelets has a major effect on this interaction.[17] Interaction between platelets, leukocytes, and endothelial cells cause autocrine and paracrine activation and leukocyte migration into the vascular wall.[18, 19] Chronic inflammatory processes induced by platelets at the vascular wall cause development of atherosclerosis.[20] Arterial thrombi which is an important partof the atherosclerotic process is also related with platelets.

Lymphopenia is associated with adverse cardiac outcomes. [21, 22] As a result of acute stres, cortisol is secreted and it can decrease lymphocyte production.[23] PLR is an independent predictor of worse outcomes in patients with CHD.[15, 24, 25] In non-ST-segment elevated myocardial infarction patients, the impact of PLR on all-cause mortalitywas independent of the platelet or lymphocyte counts alone. Twohypothesis was thought to be responsible from the superiority of PLR compared with separate individual platelet or lymphocyte counts. First, platelet and lymphocyte count can be affected from many conditions alone so the ratio is more stable. Second, PLR is the combination of two inversely related predictor and immune pathway

But best of our knowledge our study is the first to investigate the value of PLR as a predictor of in-hospital acute stent thrombosis in non-ST segment elevated acute coronary syndrome.

PLR is an easy, inexpensive, and fast independent predictor of stent thrombosis. Patients with a high PLR score can be followed up more closely for ST, giving priority for providing more favorable conditions for the procedure to this group of patients, and thus reducing mortality and morbidity rates.

The major limitation of our study is that the number of patients is small, the study is carried out in one center and the study design is retrospective.

Conclusion

Our study is the first study to show that high PLR value is an independent predictor of in-hospital acute stent thrombosis in non-ST segment elevated acute coronary syndrome patients. PLR, an easy, inexpensive and fast-achievable marker, may lead to follow-up of a particularly risky patient group for foreseeing acute stent thrombosis. Prospective, multicenter studies are needed to better understand PLR's predictive value for acute stent thrombosis in non-ST segment elevated acute coronary syndrome patients.

Declaration of conflict of interest

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