Preprocedural Neutrophil To Lymphocyte Ratio Predicts Coronary Artery Perforation

Abdulmelik Yıldız[1], Cennet Yıldız[2], Fatih Tekiner[1], Bayram Bağırtan[3],

[1]Medical Park Hospital, Cardiology, İstanbul, Turkey
[2] Ekotom Medical Center, Cardiology, İstanbul, Turkey
[3]Safak Hospital, Cardiology, İstanbul, Turkey

Corresponding author and contact details.
Abdulmelik Yıldız
Balıklı Çırpıcı Yolu Seyitnizam Mah. Kiptaş Merkez Evleri 2. Etap A: 7 Blok, No: 25 Zeytinburnu / İstanbul/Turkey
E-mail: drmelik {at} hotmail.com

ABSTRACT---- ***Objectives: Coronary artery perforation is a rare, but potentially serious, complication of the percutaneous coronary intervention that can result in death. Our aim is to define the parameters that show the CP risk before the coronary intervention. Neutrophil/lymphocyte ratio is a novel parameter for assessing inflammation. In this study, our aim is to evaluate the predictive value of NLR for coronary artery perforation.***
Method and Results: We retrospectively reviewed 3542 patients who were performed percutaneous coronary intervention (PCI) in our clinic in the period between 2008 and 2012. The group I, consisted of 17 patients diagnosed with CP. The control group (group II) consisted of 358 patients implanted with bare metal stents (BMS) in the same period. The blood samples obtained from the patients prior to the procedure were tested for NLR, C- reactive protein (CRP) and biochemical analysis. There was no statistically significant difference between the groups with regard to age, gender and vessel in which the procedure was done.
NLR and CRP levels were analyzed before percutanous coronary intervention (PCI). NLR and CRP levels in group I was significantly higher than that in group II (3.64±1.3 and 2.5±1.3 p<0.002; 4.1±1.3 and 2.8±1.1 p<0.01 respectively). Multivariate logistic regression analysis showed that NLR, CRP, neutrophil and LDL levels were independently predicted the coronary artery perforation. ROC curve analysis showed that NLR had a sensitivity of 76.5% and a specificity of 77.8% for predicting coronary perforation when the cut-off value of NLR was 3.05.
Conclusion: It has been demonstrated that NLR which are calculated from the whole blood count, a simple and cheap test, before the procedure statistically has a predictive value to anticipate CP.

Keywords--- Coronary Perforation, Neutrophil to Lymphocyte Ratio, Percutaneous Coronary Intervention

1. INTRODUCTION

The role of inflammation in the formation of atherosclerosis is increasingly being understood better. It is known that inflammation plays an important role in many steps from the beginning of atherosclerosis, plaque formation, destabilization of plaque, plaque rupture to the formation of thrombosis.[1,5] The numbers of leukocytes and neutrophils rise in acute inflammation and they cause edema and fragility in the area of inflammation through proteolytic enzymes. Leukocyte subgroups and neutrophils play a role in destabilization of a stable plaque, rupture of plaque, thrombocyte aggregation and in formation of thrombosis. Proteolytic enzymes released in inflamed tissue make the vessel be fragile and therefore it may easily be ruptured during PCI [6,8]. It has been showed that NLR is an indicator of acute inflammation and has predictive value in acute coronary syndrome (ACS). Likewise, it has been disclosed that increased number of leukocytes is a prognostic factor in revascularization processes performed with PCI [9,12]. The studies indicates that NLR can be used to anticipate coronary rupture and further work on this issue is needed [5].

2. METHODS

Patient population*:* In our clinic, we retrospectively reviewed 3542 patients who were performed PCI in the period between 2008 and 2012. The group I, consisted of 17 patients (10 men, 7 women; ages; min. 44, max. 84 and median 62.8± 8.3 years) who were diagnosed with CP. The control group, group II, consisted of 358 patients (251 men and 107 women; ages, min. 50, max. 79 and median 61.8±7.7 years). Patients treated with BMS in the same period and whose follow-up coronary angiography showed less than 50% stenosis included in the control group. Median time interval between percutanous intervention and coronary angiography was 12.9±11.6 months.

Major potential confounding factors, such as active infection, inflammatory disease, acute myocardial infarction, malignancy, tyroid function disorders, renal or hepatic dysfunction, that might affect the NLR excluded from the study.

Hematologic and biochemical measurements: Blood samples were obtained under standardized conditions before coronary angiograms were performed and stored at -70°C until analysis. Fasting plasma glucose, triglycerides, total cholesterol, Low density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, were determined by using standardized methods. C-reactive protein level was immunologically determined by immunoturbidimetric method. Blood samples were analyzed for leukocyte, neutrophil, and lymphocyte counts using Swelab Alfa (Stockholm, Sweden) hematologic analyzer. Biochemical analyses were done on Architec ci4100 (Abbott Laboratories, Abbott Park, Illinois, USA) autoanalyzer.

Evaluation of coronary angiograms: Coronary cineangiography were evaluated by two cardiologist who were not aware of patients' clinical and demographic characteristics, biochemical and hematologic data. The classification was made on the basis of the vessel in which the procedure was performed, type of lesion, cause of perforation and the degree of coronary perforation. Degree of coronary perforation was described according to Ellis classification.

3. STATISTICAL ANALYZES

Continuous variables are expressed as mean±SD. Categorical variables are expressed as percentages. To compare parametric continuous variables, the Student's t test was used; to compare nonparametric continuous variables, the MannWhitney U wasused; to compare categorical variables, the chi-square test was used. Multivariate logistic regression analysis was used to identify the independent predictor of CP. All variables showing significance values <0.05 The receiver operating characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of NLR and its respective optimal cut-off value for predicting CP. Two tailed p values <0.05 were considered as significant, and confidence interval (CI) was 95%. All statistical studies were carried out with the SPSS program (version 20.0, SPSS, Chicago, Illinois, USA).

4. RESULTS

There were no significant differences in age, gender, lessioned vessel, stented segment, number of stent used, size, length and type of the stent and baloon used between two groups. Coronary lesion type (according to ACC/AHA classification), type of the guide wire used, smoking and unstable angina was found to be significantly higher in group I (Table 1). Biochemical analysis revealed that LDL and creatinine levels significantly higher in coronary perforation group (p<0.042 and p<0.001 respectively). Blood samples taken before coronary intervention showed that neutrophil, NLR and CRP levels were significantly elevated in coronary perforation group (p<0,05).

On the analyzes done before PCI, in grup I and grup II respectively; neutrophil counts were 7.56±1.54 and 5.77±1.81, p=0.000, NLR values were 3.64±1.3 and 2.5±1.3, p=0.002, CRP values 4.1±1.3 and 2.8±1.1 p=0.001, LDL values 127.1±28.2 and 105.1±20.1, p=0.042. There was statistically significant differences between group I and group II patients. (Table 2). In multivariate logistic regression analysis; preprocedural NLR, CRP, LDL independently predict CP. (Table 3). ROC curve analysis showed that NLR had a sensitivity of 76.5% and a specificity of 77.8% for predicting CP when the cut-off value of NLR was 3.05. (Figure 1).

5. DISCUSSION

Coronary artery perforation, although a rare event, remains as a nightmare in the catheter laboratory. Several clinical, angiographic, and technical risk factors for coronary perforation were defined. Clinical risk factors involve age, gender, hypertension, low creatinine clearance; angiographic risk factors involve coronary artery calcification, tortuosity, type C lesions; technique-associated risk factors are a choice of large balloon, stent post dilatation with high pressure, the use of hydrophilic guide wire.[13,15] New parameters have been added to these risk factors.[8,12] There are trials indicating the predictive value of NLR to anticipate coronary perforation.[5] In the present study we aimed to ascertain the predictive values of leukocyte count, neutrophil count, NLR and CRP level to anticipate CP.

In the process from emergence of atherosclerosis to destabilization of coronary plaque, there is a complex interaction between leukocyte subgroups in all steps of inflammation until the release of proteolytic enzymes and cytokines that make vascular wall fragile. Likewise, leukocytes and neutrophils play a role in thrombocyte aggregation. Macrophages dominate plaque destabilization, whereas activation of neutrophils is more prominent in acute coronary events. High leukocyte count, neutrophilia, high NLR and CRP are considered as indicators of acute inflammation. [1,8] This complex interaction occurring in inflammation eases coronary perforation. [5] For this reason, NLR has been proposed as a parameter that has predictive value to indicate CP. The association of neutrophils with clinical outcomes in ACS and/or coronary revascularization was investigated in a review article including more than 34000 patients. Many studies mentioned in that article have shown that neutrophil count is an independent predictor for cardiovascular outcomes. [11] The CAPRI study in which 5974 post MI patients were evaluated showed that neutrophilia had a strong predictive value for recurrent vascular ischemic events and vascular mortality.[12] It has been showed that NLR is correlated with the severity of coronary artery disease and is an independent predictor of coronary artery disease (CAD).[16] In ACS, MI with elevated ST, revascularization by PCI and coronary bypass, high NLR is correlated with poor prognosis, mortality, occurrence of cardiac failure, development of major cardiac events during hospitalization, life-threatening ventricular

arrhythmias and no reflow.[16,22] Likewise. It is reversely correlated with TIMI flow ensured by PCI. It has also been showed that in acute MI, NLR is correlated with CK-MB and troponin T.[22]

The neutrophil-lymphocyte ratio (NLR) has been proposed as an indicator of systemic inflammatory response. In addition to cardiovascular disorders, elevated levels of neutrophil lymphocyte ratio (NLR) were found associated with hepatic and renal dysfunction, malignancy, tyroid function disorders, local and systemic infections (23). Patients with these disorders excluded from the study.

CRP induces synthesis of tissue factor in monocytes and endothelial cells and tissue factor activates the extrinsic coagulation cascade, providing a link between inflammation and thrombosis. İnflammation contributes to endothelial dysfunction while endothelial dysfunction promotes inflammation. It has been shown that patient with unstable angina and increased level of CRP (>3 mg/dl) experienced more ischemic episodes and more often developed an acute MI than with lower CRP level. Mulvihill et al. evaluated the predictive value of CRP in the prognosis of patients with unstable angina pectoris (UAP). Raised concentrations of CRP were found to be predictive of an increased risk of major adverse cardiovascular events in these patients with UAP with CRP levels above 3mg/L.[24]

Studies showed that CRP is an inflammatory marker and elevated acute coronary syndromes. Treatment with acetylsalicylic acid, statins and fibrates affect the CRP levels. For this reason, before coronary intervention, it is more reasonable to consider it with NLR to predict the coronary perforation risk.

In the literature, several risk factors that place patients at higher risk for coronary perforation has been defined; such as clinical presentation (stable, unstable angina), materials used during percutanous intervention, operator experience, coronary lesion type. But there is no study about predictive value of NLR, leukocytosis neutrophilia and CRP levels in coronary perforation .

These parameters show acute inflammation before coronary intervention. In our opinion, it would be helpful to use these parameters to asses coronary fragility, unstable coronary artery disease and predict coronary perforation.

6. CONCLUSION

In conclusion, NLR is a parameter possessing predictive value to reveal the existence and severity of CAD. NLR is also an indicator of inflammation. Inflammation exists in every phase of coronary artery disease and it may lead to increased coronary fragility and predispose coronary perforation. The NLR value calculated from the whole blood count before PCI procedure may imply the risk of coronary perforation.

7. REFERENCES

1. Ross R. Atherosclerosis; an inflammatory disease. N Engl J Med. 1999;340(2):115-26
2. Lind L. Circulating markers of inflammation and atherosclerosis. Atherosclerosis. 2003;169(2):203-14.
3. Libby P, Ridker PM, Hansson GK. Leducq Transatlantic Network on atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54:2129-38.
4. Baetta R, Corsini A. Role of polymorphonuclear neutrophils in atherosclerosis: current state and future perspectives. Atherosclerosis. 2010;210:1-13.
5. Chandra P, Chatterjee S, Koradia N, et al. Predisposing factors, demographics, angiographic features, and the possible role of inflammation in coronary perforations. A 10-year single-center experience. Am Heart Hosp J. 2011; 9(2): 87-9
6. Harlan JM, Killen PD, Harker LA, et al. Neutrophil mediated endothelial injury in vitro mechanisms of cell detachment. The Journal of Clinical Investigation. 1981; 68(6):1394-403.
7. Sabatine MS, Morrow DA, Cannon CP, et al. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 trial) substudy. J Am Coll Cardiol. 2002;40(10):1761-8.
8. Tamhane UU, Aneja S, Montgomery D, et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102(6):653-7.
9. Palmerini T, Marzocchi A, Marrozzini C, et al. Preprocedural levels of C-reactive protein and leukocyte counts predict 9-month mortality after coronary angioplasty for the treatment of unprotected left main coronary artery stenosis. Circulation. 2005;112(15):2332-8.
10. Wheeler JG, Mussolino ME, Gillum RF, et al. Associations between differential leucocyte count and incident coronary heart disease: 1764 incident cases from seven prospective studies of 30 374 individuals. Eur Heart J. 2004; 25(15):1287-92.
11. Guasti L, Dentali F, Castiglioni L, et al. Neutrophils and clinical outcomes in patients with acute coronary syndromes and/or cardiac revascularisation. A systematic review on more than 34.000 subjects. Thromb Haemost. 2011;106(4):591-9.

12. Grau AJ, Boddy AW, Dukovic DA, et al. Leukocyte count as an independent predictor of recurrent ischemic events. Stroke. 2004;35(5):1147-52.
13. Ellis SG, Ajluni S, Arnold AZ, et al. Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. Circulation. 1994;90(6):2725-30.
14. Ajluni SC, Glazier S, Blankenship L, et al. Perforations after percutaneous coronary interventions: clinical, angiographic, and therapeutic observations. Cathet Cardiovasc Diagn. 1994;32(3):206-12.
15. Gruberg L, Pinnow E, Flood R, et al. Incidence, management, and outcome of coronary artery perforation during percutaneous coronary intervention. Am J Cardiol. 2000;86(6):680-2.
16. Selcuk H, Dinc L, Selcuk MT, et al. The relation between differential leukocyte count, neutrophil to lymphocyte ratio and the presence and severity of coronary artery disease. Open Journal of Internal Medicine. 2012;2:163-9
17. Prasad A, Stone GW, Stuckey TD, et al. Relation between leucocyte count, myonecrosis, myocardial perfusion, and outcomes following primary angioplasty. Am J Cardiol. 2007;99(8):1067-71.
18. Chia S, Nagurney JT, Brown DF, et al. Association of leukocyte and neutrophil counts with infarct size, left ventricular function and outcomes after percutaneous coronary intervention for ST-elevation myocardial infarction. Am J Cardiol. 2009;103(3):333-7.
19. Rashidi F, Rashidi A, Golmohamadi A, et al. Does absolute neutrophilia predict early congestive heart failure after acute myocardial infarction? A cross-sectional study. Southern medical journal. 2008;101(1):19-23.
20. O'Donoghue M, Morrow DA, Cannon CP, et al. Association between baseline neutrophil count, clopidogrel therapy, and clinical and angiographic outcomes in patients with ST elevation myocardial infarction receiving fibrinolytic therapy. Eur Heart J. 2008;29(8):984-91.
21. Takahashi T, Hiasa Y, Ohara Y, et al. Relationship of admission neutrophil count to microvascular injury, left ventricular dilation, and long-term outcome in patients treated with primary angioplasty for acute myocardial infarction. Circ J. 2008;72(6):867-72.
22. Dogan I, Karaman K, Sonmez B, et al. Relationship between serum neutrophil count and infarct size in patients with acute myocardial infarction. Nucl Med Commun. 2009;30(10):797-801.
23. Balta S, Demirkol S, Unlu M, et al. Neutrophil to lymphocyte ratio may be predict of mortality in all conditions. Br J Cancer. 2013 Oct 1. doi: 10.1038/bjc.2013.598.
24. Mulvihill NT, Foley JB, Murphy RT, et al. Risk stratification in unstable angina and non-Q wave myocardial infarction using soluble cell adhesion molecules. Heart 2001; 85: 623-7

Table: 1. Baseline Characteristics of Patients

Parameters	Group I (n:17)	Group II (n:358)	p
Gender			NS
Male, n (%)	10(58.8)	251(70.1)	
Female, n (%)	7(41.2)	107(29.9)	
Risk Factors			NS
Diabetes Mellitus, n (%)	8(47.1)	115(32.1)	NS
Hypertension, n (%)	5(29.4)	117(32.6)	
Hyperlipidemia, n (%)	8(47.1)	70(19.5)	NS
Current smoker (%)	8(47.0)	86(24.0)	**0.04***
LV EF (%)	65.9±8.2	64.5±8.6	NS
In hospital medical treatment			
ACE-I/ARB	14(82.3)	310(86.5)	NS
Beta blocker	13(76.4)	280(78.2)	NS
Ca-canal blocker	4(23.5)	63(17.5)	NS
Statins	8(47.0)	145(40.5)	NS
Acetylsalicylic acid	14(82.3)	292(81.5)	
Lesioned Vessels			NS
Left anterior descending, n (%)	10(58.8)	187(52.2)	
Circumflex, n (%)	7(41.2)	118(32.9)	
Multivessel intervention, n (%)	5(29.4)	84(23.4)	
Cause of stent implantation			**0.02***
Stable angina pectoris	12(70.6)	320 (89.4)	
Unstable angina pectoris	5(29.4)	38(10.6)	
Lesion Types			**0.04***
Type A, n (%)	0	55(15.3)	
Type B, n (%)	10(58.8)	229(63.9)	
Type C, n (%)	7(41.2)	74(20.6)	
Type of balloon			NS
Non-compliant	5(29.4)	26(16.5)	
Type of Guide Wire			**0.03***
Hydrophilic	2(11.7)	25(6.9)	
Floopy	1(0.05)	95(26.6)	
Standard	14(82.3)	238(66.5)	
Balloon pressure (atm)	14.3±2.0	13.8±3,1	NS
Stent diameter (mm)	3.29±0.74	3.04±0.50	NS

LAD: Left anterior descending, CX: Circumflex, NS: No significant.

Table: 2. Difference between biochemical and hematological parameters of groups

Parameters	Group I, (n:17)	Group II, (n:358)	p
Leukocyte (10^3 μL)	9.8±2.3	8.7±2.3	NS
Hemoglobin (g/L)	13.8±1.9	14.3±1.7	NS
Neutrophil (10^3 μL)	7.56±1.54	5.77±1.81	**0.000***
Lymphocyte (10^3 μL)	2.4±0.9	2.6±0.87	NS
Creatinine (mg/dl)	1.12±0.19	0.86±0.12	**0.001***
Glucose (mg/dl)	128.24±41.55	123.41±31.49	NS
LDL (mg/dl)	127.1±28.2	105.1±20.1	**0.042***
HDL (mg/dl)	42.1±12.9	40.1 ±11	NS
Triglycerides (mg/dl)	168.3±121	133.2±53	NS
CRP (mg/dl)	4.1±1.3	2.8±1.1	**0.001***
NLR	3.64±1.3	2.5±1.3	**0.002***

NLR: Neutrophil/Lymphocyte ratio; LDL: Low density lipoprotein; CRP: C- reactive protein;
LDL: Low density lipoprotein, NS: No significant.

Table 3: Multivariate Logistic Regression Analysis according to risk of Coronary Perforation

	OR	95% CI		P
Neutrophil	0.425	0.235	0.842	NS
LDL	0.932	0.888	0.978	**0.04***
CRP	0.365	0.182	729	**0.04***
NLR	0.668	0.502	0.888	**0.05***

NLR: Neutrophil/Lymphocyte ratio; LDL: Low density lipoprotein; CRP: C- reactive protein;
LDL: Low density lipoprotein, NS: No significant.

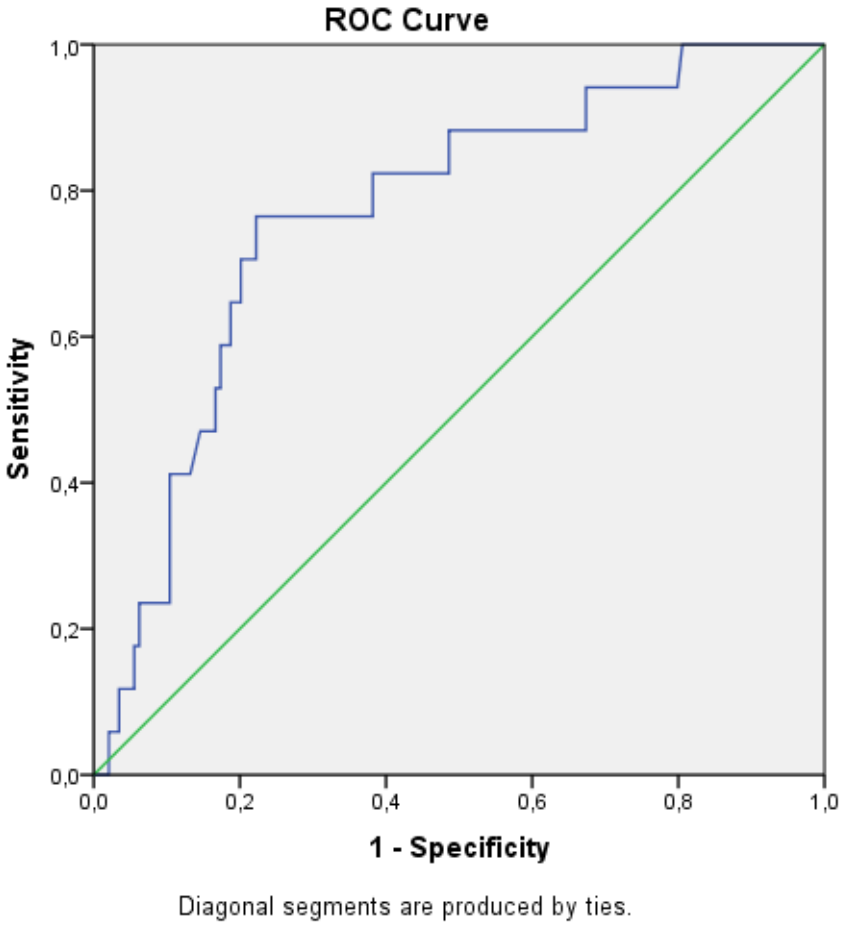

Figure 1. Identification of a cut off value for NLR in coronary perforation by a receiver operating characteristic curve analysis.