Platelet-to-lymphocyte ratio is a predictor of in-hospital mortality patients with acute coronary syndrome

Mustafa Oylumlu, Abdülkadir Yıldız, Muhammed Oylumlu[1], Murat Yüksel, Nihat Polat, Mehmet Zihni Bilik, Abdurrahman Akyüz, Mesut Aydın, Halit Acet, Serdar Soydinç

Department of Cardiology, Faculty of Medicine, Dicle University; Diyarbakır-*Turkey*
[1]Department of Cardiology, Faculty of Medicine, Dumlupınar University; Kütahya-*Turkey*

Abstract

Objective: Platelets and inflammatory cells are vital elements of acute coronary syndromes (ACS). Recent studies have shown that the platelet-to-lymphocyte ratio (PLR) is associated with several malignancies; however, there are not enough data in cardiovascular diseases. Therefore, the aim of this study was to explore the association between PLR and in-hospital mortality in patients with ACS.

Methods: We retrospectively collected patients with ACS undergoing coronary angiography. Total and differential leukocyte counts were measured by an automated hematology analyzer.

Results: This study is single-centered and observational. In total, 587 patients with a mean age of 61.8±13.1 years (68.4% male) were enrolled in the study. Patients were divided into 3 tertiles based on PLR levels. In-hospital mortality was significantly higher among patients in the upper PLR tertile when compared with the middle and lower PLR tertile groups [29 (14.8%) vs. 17 (8.7%) and 2 (1.0%); p<0.001]. In the multiple logistic regression analysis, a high level of PLR was an independent predictor of in-hospital mortality, together with age, total leukocyte count, and creatinine. Using a cutoff point of 142, the PLR predicted in-hospital mortality with a sensitivity of 69% and specificity of 63%.

Conclusion: Different from other inflammatory markers and assays, PLR is an inexpensive and readily available biomarker that may be useful for cardiac risk stratification in patients with ACS. *(Anatol J Cardiol 2015; 15: 277-83)*

Keywords: acute coronary syndrome, coronary heart disease, mortality, platelet-to-lymphocyte ratio

Introduction

Despite advances in diagnosis and treatment, coronary heart disease (CHD) is most common cause of mortality in both developing and developed countries. Among the common and severe forms of CHD is acute coronary syndrome (ACS), which includes unstable angina pectoris, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction (1). Atherosclerosis is a chronic inflammatory process, and inflammation is a vital element of ACS (2). Platelets are a source of inflammatory mediators (3). Increased platelet activation is known to trigger atherosclerosis and plays a major role in its progression (4). Elevated peripheral blood platelet count is closely related to major adverse cardiovascular outcomes (5, 6). Lymphocytes have been shown to modulate the immunologic response at all stages of the atherosclerotic process (7). The association between low lymphocyte count and major adverse cardiovascular outcomes was also shown in several studies (8-10).

Previous studies revealed a significant relationship between hematologic parameters, especially neutrophil-to-lymphocyte ratio (NLR), and CHD. The predictive and prognostic value of the NLR has been demonstrated in several cardiovascular diseases (11-15). Although preliminary data have shown that the platelet-to-lymphocyte ratio (PLR) is associated with major adverse cardiovascular outcomes and some cancers, there are not enough data, especially in cardiovascular disease (16-18). Therefore, the aim of this study was to explore the association between PLR and in-hospital mortality in patients with acute coronary syndrome.

Methods

Study population

The present study is a single-center, observational study. We retrospectively collected patients with ACS undergoing coronary angiography between January 2012 and August 2013.

Address for Correspondence: Dr. Mustafa Oylumlu, Dicle Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 21280 Diyarbakır-*Türkiye*
Phone: +90 412 248 80 01 Fax: +90 412 248 85 23 E-mail: dr.oylumlu@yahoo.com

Accepted Date: 13.11.2013 **Available Online Date:** 08.04.2014

DOI:10.5152/akd.2014.5366

Exclusion criteria were cardiogenic shock, significant valvular heart disease, hematological disease, malignancy, severe liver or renal disease, systemic inflammatory disease or active infection, and autoimmune disease. The study was approved by the local ethics committee.

Definitions

Acute coronary syndrome was defined as presentation with symptoms of ischemia in association with electrocardiographic changes or positive cardiac enzymes (1). Arterial hypertension was considered in patients with repeated blood pressure measurements >140/90 mm Hg or active use of antihypertensive drugs. Diabetes mellitus was defined as fasting plasma glucose levels more than 126 mg/dL in multiple measurements or active use of antidiabetic medications. Smoking was defined as current smoking. Patients having fever or symptoms or signs of urinary tract or respiratory system infection (leukocytosis or nitrite positivity in urine, infiltration in chest x-ray) were defined as active infection. PLR was calculated as the ratio of platelet count to lymphocyte count.

Biochemical and hematological parameters

Peripheral venous blood samples were drawn on admission to the emergency room. Total and differential leukocyte counts were measured by an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois, USA). Routine biochemical tests were performed by standard techniques.

Statistical analysis

Data were analyzed with SPSS software, version 18.0 for Windows (SPSS Inc, Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Continuous variables were defined as means±standard deviation; categorical variables were given as percentages. Comparison among multiple groups was performed by Kruskal-Wallis test or one-way analysis of variance (ANOVA) test, and the chi-square Fisher exact test was carried out for categorical variables as appropriate. For the post-hoc analysis, either the Scheffe or Mann-Whitney U test was performed. Statistical significance was defined as $p<0.05$. Variables for which the p value was <0.05 in the univariate analysis were assessed by multiple logistic regression analysis to evaluate the independent predictors of in-hospital mortality. All variables found to be significant in the univariate analysis were included in the logistic regression model, and the results are shown as odds ratio (OR) with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of the PLR in association with in-hospital mortality.

Results

In total, 587 patients with a mean age of 61.8±13.1 years (68.4% male) were enrolled in the study. Patients were divided into 3 tertiles based on PLR levels: 83.9±15.4 in tertile 1, 127.0±13.8 in tertile 2, and 214.0±71.8 in tertile 3. According to the PLR tertiles, the baseline demographic, hematological, and angiographic parameters of the patients are shown in Table 1. In-hospital mortality was significantly higher among patients in the upper PLR tertile when compared with the middle and lower PLR tertile groups [29 (14.8%) vs. 17 (8.7%) and 2 (1.0%); $p<0.001$, respectively; Fig. 1].

In the multiple logistic regression analysis, a high level of PLR was an independent predictor of in-hospital mortality (OR: 1.012, 95% CI: 1.005-1.019, $p<0.001$), together with age (OR: 1.045, 95% CI: 1.005-1.087, $p=0.027$), WBC count (OR: 1.251, 95% CI: 1.108-1.412, $p<0.001$), and creatinine (OR: 3.541, 95% CI: 1.558-8.047, $p=0.003$; Table 2). In the ROC analysis, PLR >142 had 69% sensitivity and 63% specificity (ROC area under curve: 0.756, 95% CI: 0.691-0.822, $p<0.001$) and NLR >4.55 had 79% sensitivity and 61%

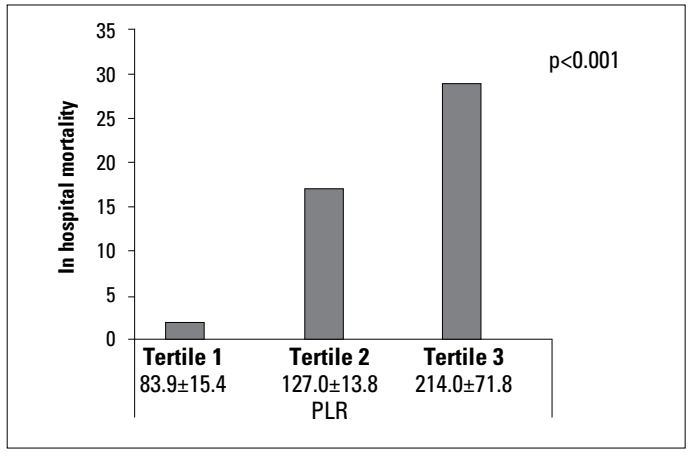

Figure 1. Percentage of patients developing in-hospital mortality stratified by tertile of platelet to lymphocyte ratio

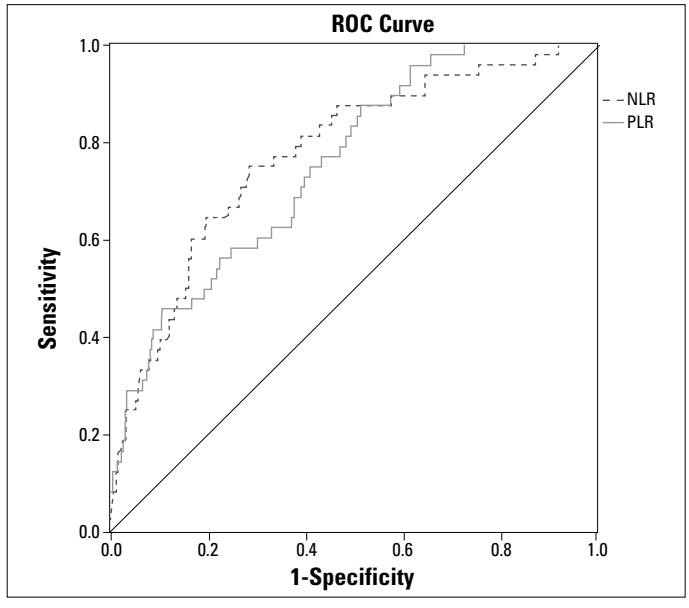

Figure 2. Receiver operating characteristics curve of platelet-to-lymphocyte ratio and neutrophil-lymphocyte ratio for predicting in-hospital mortality in acute coronary syndrome

Table 1. Clinical, hematologic, and angiographic characteristics of population with acute coronary syndrome according to platelet-to-lymphocyte ratio tertiles

	PLR			
Variables	**Tertile 1 83.9±15.4 (n=195)**	**Tertile 2 127.0±13.8 (n=196)**	**Tertile 3 214.0±71.8 (n=196)**	***P**
Age, years (%)	59.0±12.2	61.7±12.7	64.7±13.7	<0.001[a]
Male gender, n (%)	139 (71.3)	133(67.9)	129 (66.2)	0.540
Hypertension, n (%)	84 (43.1)	82 (41.8)	101 (51.5)	0.111
Diabetes mellitus, n (%)	38 (19.5)	54 (27.6)	59 (30.1)	0.043
Smoking, n (%)	74 (37.9)	81 (41.3)	77 (39.3)	0.789
Previous MI history, n (%)	23 (11.8)	32 (16.3)	27 (13.8)	0.432
Hemoglobin, g/dL	14.0±1.5	14.0±1.6	13.6±1.7	0.008[b]
White blood cell count, 10^3/μL	11.5±3.2	11.4±3.5	12.1±4.3	0.133
Neutrophil count, 10^3/μL	7.6±2.9	8.5±3.3	9.9±4.3	<0.001[c]
Lymphocyte count, 10^3/μL	2.8±0.8	2.0±0.5	1.4±0.5	<0.001[d]
Platelet count, 10^3/μL	232.0±53.9	257.1±54.5	286.1±67.5	<0.001[e]
Creatinine, mg/dL	0.79 (0.72-0.94)	0.81 (0.70-0.94)	0.83 (0.72-1.05)	0.133
NLR	2.50 (1.86-3.57)	4.11 (2.88-5.46)	7.04 (4.57-10.15)	<0.001[f]
CRP, mg/dL	0.52 (0.31-1.08)	0.62 (0.35-1.00)	0.64 (0.39-1.39)	0.287
Total cholesterol, mg/dL	179.3±39.3	181.3±44.1	173.7 ± 38.0	0.168
Triglyceride, mg/dL	138 (91-205)	135 (91-195)	116 (80-170)	0.008[g]
LDL, mg/dL	110.9±31.3	114.0±36.9	111.0±32.0	0.595
HDL, mg/dL	34.6±8.2	36.3±9.7	35.1±10.3	0.207
Left ventricular EF, %	50 (45-55)	46 (40-55)	45 (40-50)	<0.001[h]
Number of stenosed coronary arteries, n (%)				0.888
Single vessel	84 (43.1)	81 (41.3)	80 (40.8)	
Two vessel	64 (32.8)	59 (30.1)	63 (32.1)	
Three vessel	47 (24.1)	56 (28.6)	53 (27.0)	
Type of acute coronary syndrome, n (%)				<0.001
USAP	28 (14.4)	18 (9.2)	18 (9.2)	
NSTEMI	71 (36.4)	54 (27.6)	36 (18.4)	
STEMI	96 (49.2)	124 (63.3)	142 (72.4)	
Culprit vessel, n (%)				0.298
LAD	86 (44.1)	89 (45.4)	95 (48.5)	
Cx	55 (28.2)	55 (28.1)	39 (19.9)	
RCA	54 (27.7)	52 (26.5)	62 (31.6)	
In-hospital mortality, n (%)	2 (1.0)	17 (8.7)	29 (14.8)	<0.001

Data are presented as number (percentage) and mean±standard deviation or median (interquartile range) values
For post hoc analysis either Scheffe or Mann-Whitney U test was performed
*ANOVA and Kruskal-Wallis tests
([a]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p=0.134, p<0.001, and p=0.064, respectively)
([b]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p=0.893, p=0.015, and p=0.051, respectively)
([c]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p=0.051, p<0.001, and p=0.001, respectively)
([d]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p<0.001, p<0.001, and p<0.001, respectively)
([e]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p<0.001, p<0.001, and p<0.001, respectively)
([f]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p<0.001, p<0.001, and p<0.001, respectively)
([g]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p=0.583, p=0.004, and p=0.013, respectively)
([h]: 1 vs. 2, 1 vs. 3, and 2 vs. 3 p=0.014, p<0.001, and p=0.057, respectively)
CRP - C-reactive protein; Cx - circumflex; EF - ejection fraction; HDL - high-density lipoprotein; LAD - left anterior descending; LDL - low-density lipoprotein; MI - myocardial infarction; NLR - neutrophil-to-lymphocyte ratio; NSTEMI - non-ST-segment elevation myocardial infarction; PLR - platelet-to-lymphocyte ratio; RCA - right coronary artery; STEMI - ST-segment elevation myocardial infarction; USAP - unstable angina pectoris.
CRP values were available for 247 patients

Table 2. Significant predictors of in-hospital mortality in univariable and multiple logistic regression analyses

Variables	Univariate analysis		Multiple logistic regression analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.060 (1.033-1.088)	<0.001	1.045 (1.005-1.087)	0.027
Male gender	0.541 (0.296-0.990)	0.046	0.546 (0.217-1373)	0.198
Left ventricular EF	0.924 (0.895-0.954)	<0.001	0.980 (0.935-1.028)	0.414
PLR	1.014 (1.009-1.019)	<0.001	1.012 (1.005-1.019)	<0.001
Hypertension	0.750 (0.415-1.354)	0.339		
LAD as the infarct-related artery	1.191 (0.660-2.150)	0.562		
STEMI as the cause of ACS	3.370 (1.547-7.339)	0.002	0.446 (0.128-1.549)	0.203
Multivessel disease	3.924 (1.802-8.542)	<0.001	1.959 (0.717-5.349)	0.190
Diabetes mellitus	2.020 (1.097-3.721)	0.024	1.099 (0.436-2.775)	0.841
Smoking	0.748 (0.400-1.396)	0.361		
Previous MI history	2.530 (1.275-5.019)	0.008	0.395 (0.122-1.285)	0.123
Hemoglobin	0.914 (0.763-1.096)	0.332		
White blood cell	1.180 (1.096-1270)	<0.001	1.251 (1.108-1412)	<0.001
RDW	1.204 (0.975-1.487)	0.084		
Creatinine	2.859 (1.550-5.273)	0.001	3.541 (1.558-8.047)	0.003
LDL	0.987 (0.975-0.998)	0.019	0.993 (0.978-1.009)	0.382
HDL	0.934 (0.895-0.974)	0.002	0.963 (0.923-1.004)	0.080
Triglyceride	0.997 (0.992-1.001)	0.166		

ACS - acute coronary syndrome; EF - ejection fraction; HDL - high-density lipoprotein; LAD - left anterior descending; LDL - low-density lipoprotein; MI - myocardial infarction; OR - odds ratio; PLR - platelet-to-lymphocyte ratio; RDW - reticulocyte distribution width; STEMI - ST-segment elevation myocardial infarction.

specificity in accurately predicting a diagnosis of in-hospital mortality (ROC area under curve: 0.778, 95% CI: 0.709-0.847, p<0.001; Fig. 2).

Discussion

The present study focused more on the assessment of the relation between admission PLR and in-hospital mortality in patients with ACS. We demonstrated that higher PLR is a significant independent predictor of in-hospital mortality in patients with ACS. Moreover, our study showed that a PLR >142 predicted in-hospital mortality with a sensitivity of 69% and specificity of 63%. Although there was a higher frequency of several cardiovascular risk factors among patients with high PLR, this did not influence the significant association between PLR and in-hospital mortality in the multiple logistic regression analysis.

There are multiple factors in the development and progression of atherosclerosis. Inflammation has a major role at all stages of atherosclerosis, including initiation, progression, and in the thrombotic complications of this disease (2). As the understanding of the role of inflammation in the atherosclerotic process gets better, studies have focused on inflammatory markers for improved evaluation of the risk (19). White blood cell (WBC) count, leukocyte subtype, platelet, C-reactive protein (CRP), and the NLR are some of the inflammatory markers that have been demonstrated to have predictive and prognostic significance in cardiovascular diseases (5-7, 11-15, 20, 21).

The relationship between white blood cell count and increased cardiovascular risk is well established. While high neutrophil counts reflect the inflammatory response, low lymphocyte counts reflect poor general health and physiologic stress (22). Zouridakis et al. (23) studied patients with unstable angina and reported that a low lymphocyte count is associated with a significantly higher risk of future cardiac events. There is no clear understanding of the pathogenetic mechanisms underlying these findings. However, lymphocyte count was shown to be an early marker of physiologic stress and systemic failure, secondary to myocardial ischemia mediated by cortisol release (8, 24). On the other hand, an elevated lymphocyte count may also show a more appropriate immune response that leads to a better outcome in unstable angina patients (25).

The role of platelets in the pathogenesis of ACS has been proven by studies that have shown significant clinical improvement associated with antiplatelet therapy (26-28). The mechanisms underlying the association of high platelet counts and poor clinical outcomes seem to be multifactorial. High platelet counts may indicate a higher degree of antiplatelet drug resistance and a higher tendency to form platelet-rich thrombi in atherosclerotic plaques, resulting in poor outcomes. Moreover, higher platelet counts may reflect underlying inflammation, as several inflammatory mediators stimulate megakaryocyte prolif-

eration and lead to relative thrombocytosis. Recent researchers have stated that platelets interact with endothelial cells and leukocytes and release inflammatory mediators that cause adhesion and transmigration of monocytes (29, 30). These monocytes are also reported to propagate inflammatory processes in the vessel wall, promoting atherosclerotic lesions (31).

PLR is derived from the number of platelets and lymphocytes, and it is accepted as a new inflammatory marker (16-18). It reflects both hyperactive coagulation and inflammatory pathways; it may be a better predictor of impaired perfusion than either the individual platelet or lymphocyte count. More recent studies have stated that higher platelet and lower lymphocyte counts play a major role in adverse cardiovascular outcomes. Azab et al. (16) demonstrated a higher value of the PLR as a marker of long-term mortality in patients with non-ST-segment elevation myocardial infarction. Furthermore, Sünbül et al. (32) found that the PLR was a significant predictor of non-dipper status in patients with hypertension. Gary et al. (33) revealed that increased PLR is significantly associated with patients at high risk for critical limb ischemia. In addition to its prognostic significance, the PLR has also been demonstrated in patients with various cancers (34, 35). In a relatively recent study in patients with small cell carcinoma of the esophagus, PLR was proven to be superior to NLR in terms of relapse-free survival and overall survival (36).

In our study, age, presence of DM, left ventricular ejection fraction, and NLR were significantly different among patients in the upper PLR tertile when compared with the lower PLR tertile group. This difference can be explained by inflammation, as all of these conditions are associated with increased inflammatory status of the body. Aging is related with increased levels of serum IL-6 and TNF alpha, so that this chronic low-grade inflammation is often called inflammaging (37). Similarly, inflammation has a crucial role in the pathogenesis and progression of DM and heart failure (38, 39).

In previous studies, higher levels of NLR were demonstrated to be a predictor of short- and long-term mortality in patients with ACS (15, 40). Various inflammatory stimuli cause neutrophils to produce different cytokines and cytotoxic/proteolytic enzymes. Through certain mechanisms, including induction of damage to endothelial cells, induction of the coagulation system, aggregation with leukocytic cells, plugging the microvasculature, increasing infarct expansion, and leading to cardiac electrical instability, these enzymes affect the cardiovascular system (41). The relative lymphopenia seen in ischemia was attributed to increased cortisol levels as a result of physiological stress (8, 24). Therefore, NLR may be considered an inflammatory marker in patients with cardiovascular disease.

Patients with chronic renal disease who present with ACS are at increased risk for both adverse cardiovascular outcomes and death compared to those with normal renal function (42-44). Ahmed et al. (45) demonstrated that older patients had a higher risk of adverse hospital outcomes and short- and long-term mortality rates with respect to younger patients. As shown in previous studies, we found that renal dysfunction, together with age and PLR, is independently related with in-hospital mortality.

The determination of high-risk patients in terms of in-hospital mortality in acute coronary syndrome is crucial in daily practice. These risky patients require close follow-up and aggressive treatment in order to decrease their mortality. In this context, PLR may contribute to the traditional predictors being used in current risk scoring systems to estimate the in-hospital mortality risk of patients admitted with ACS.

Study limitations

Our study had some limitations. This study was conducted on a retrospective basis and represented a single-center experience. It would be better if we had followed the patients and explored the association between adverse long-term cardiac events and PLR in these patients. The use of a single blood sample at admission does not anticipate the persistence of PLR over time.

Conclusion

We found PLR to be a risk variable for in-hospital mortality in patient with ACS. Further large-scale, prospective, and multicenter studies are needed to clarify and confirm the association between the PLR and in-hospital mortality in patients with ACS. In conclusion, different from other inflammatory markers and assays, PLR is an inexpensive and readily available biomarker that may be useful for cardiac risk stratification in patients with ACS.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - Mustafa O., A.Y., S.S.; Design - Mustafa O., M.O., M.Y.; Supervision - M.O., S.S.; Resource - S.S., M.O.; Material - A.A., M.Z.B., M.A.; Data collection and/or processing - M.Y., N.P., M.Z.B.; Analysis and/or interpretation - Mustafa O., M.O., S.S., M.Y., A.Y.; Literature search - A.A., M.A., H.A.; Writing - Mustafa O., M.O., A.Y., M.Y.; Critical review - S.S.

References

1. Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes: A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 2001; 38: 2114-30. [CrossRef]
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-95. [CrossRef]
3. Wagner DD, Burger PC. Platelets in inflammation and thrombosis. Arterioscler Thromb Vasc Biol 2003; 23: 2131-7. [CrossRef]

4. Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictor of vascular risk: is there a practical index of platelet activity? Clin Appl Thromb Hemost 2003; 9: 177-90. [CrossRef]
5. Nikolsky E, Grines CL, Cox DA, Garcia E, Tcheng JE, Sadeghi M, et al. Impact of baseline platelet count in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction (from the CADILLAC trial). Am J Cardiol 2007; 99: 1055-61. [CrossRef]
6. Iijima R, Ndrepepa G, Mehilli J, Bruskina O, Schulz S, Schömig A, et al. Relationship between platelet count and 30 day clinical outcomes after percutaneous coronary interventions. Pooled analysis of four ISAR trials. Thromb Haemost 2007; 98: 852-7. [CrossRef]
7. Taleb S, Tedgui A, Mallat Z. Regulatory T-cell immunity and its relevance to atherosclerosis. J Intern Med 2008; 263: 489-99. [CrossRef]
8. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol 1997; 79: 812-4. [CrossRef]
9. Zouridakis EG, Garcia-Moll X, Kaski JC. Usefulness of the blood lymphocyte count in predicting recurrent instability and death in patients with unstable angina pectoris. Am J Cardiol 2000; 86: 449-51. [CrossRef]
10. Ommen SR, Hammill SC, Gibbons RJ. The relative lymphocyte count predicts death in patients receiving implantable cardioverter defibrillators. Pacing Clin Electrophysiol 2002; 25: 1424-8. [CrossRef]
11. Sönmez O, Ertaş G, Bacaksız A, Taşal A, Erdoğan E, Aşoğlu E, et al. Relation of neutrophil -to- lymphocyte ratio with the presence and complexity of coronary artery disease: an observational study. Anatol J Cardiol 2013; 13: 662-7. [CrossRef]
12. Kaya H, Ertaş F, İslamoğlu Y, Kaya Z, Atılgan ZA, Çil H, et al. Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. Clin Appl Thromb Hemost 2014; 20: 50-4. [CrossRef]
13. Öztürk S, Erdem A, Özlü MF, Ayhan S, Erdem K, Özyaşar M, et al. Assessment of the neutrophil to lymphocyte ratio in young patients with acute coronary syndromes. Turk Kardiyol Dern Ars 2013; 41: 284-9. [CrossRef]
14. Yıldız A, Kaya H, Ertaş F, Oylumlu M, Bilik MZ, Yüksel M, et al Association between neutrophil to lymphocyte ratio and pulmonary arterial hypertension. Türk Kardiyol Dern Arş 2013; 41: 604-9. [CrossRef]
15. Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008; 102: 653-7. [CrossRef]
16. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis 2012; 34: 326-34. [CrossRef]
17. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010; 200: 197-203. [CrossRef]
18. Wang D, Yang JX, Cao DY, Wan XR, Feng FZ, Huang HF, et al. Preoperative neutrophil-lymphocyte and platelet-lymphocyte ratios as independent predictors of cervical stromal involvement in surgically treated endometrioid adenocarcinoma. Onco Targets Ther 2013; 6: 211-6.
19. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-43. [CrossRef]
20. Momiyama Y, Kawaguchi A, Kajiwara I, Ohmori R, Okada K, Saito I, et al. Prognostic value of plasma high-sensitivity C-reactive protein levels in Japanese patients with stable coronary artery disease: the Japan NCVC-Collaborative Inflammation Cohort (JNIC) Study. Atherosclerosis 2009; 207: 272-6. [CrossRef]
21. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease. Meta-analyses of prospective studies. JAMA 1998; 279: 1477-82. [CrossRef]
22. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 2010; 105: 186-91. [CrossRef]
23. Zouridakis EG, Garcia-Moll X, Kaski JC. Usefulness of the blood lymphocyte count in predicting recurrent instability and death in patients with unstable angina pectoris. Am J Cardiol 2000; 86: 449-51. [CrossRef]
24. Thomson SP, McMahon LJ, Nugent CA. Endogenous cortisol: a regulator of the number of lymphocytes in peripheral blood. Clin Immunol Immunopathol 1980; 17: 506-14. [CrossRef]
25. Caligiuri G, Liuzzo G, Biasucci LM, Maseri A. Immune system activation follows inflammation in unstable angina: pathogenetic implications. J Am Coll Cardiol 1998; 32: 1295-304. [CrossRef]
26. Montalescot G, Van de Werf F, Gulba DC, Avezum A, Brieger D, Kennelly BM, et al. Stenting and glycoprotein IIb/IIIa inhibition in patients with acute myocardial infarction undergoing percutaneous coronary intervention: findings from the global registry of acute coronary events (GRACE). Catheter Cardiovasc Interv 2003; 60: 360-7. [CrossRef]
27. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494-502. [CrossRef]
28. Boersma E, Harrington RA, Moliterno DJ, White H, Théroux P, Van de Werf F, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002; 359: 189-98. [CrossRef]
29. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. J Clin Invest 2005; 115: 3378-84. [CrossRef]
30. Lindemann S, Kramer B, Seizer P, Gawaz M. Platelets, inflammation and atherosclerosis. J Thromb Haemost 2007; 1: 203-11. [CrossRef]
31. Huo Y, Schober A, Forlow SB, Smith DF, Hyman MC, Jung S, et al. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. Nat Med 2003; 9: 61-7. [CrossRef]
32. Sünbül M, Gerin F, Durmuş E, Kıvrak T, Sarı I, Tigen K, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. Clin Exp Hypertens 2013 Jun 20. [Epub ahead of print]
33. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013; 8: e67688. [CrossRef]
34. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010; 200: 197-203. [CrossRef]

35. Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Srijaipracharoen S, Thavaramara T. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. J Gynecol Oncol 2012; 23: 265-73. [CrossRef]
36. Feng JF, Huang Y, Zhao Q, Chen QX. Clinical significance of preoperative neutrophil lymphocyte ratio versus platelet lymphocyte ratio in patients with small cell carcinoma of the esophagus. ScientificWorldJournal 2013; 2013: 504365. [CrossRef]
37. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 2007; 128: 92-105. [CrossRef]
38. Högye M, Mándi Y, Csanády M, Sepp R, Buzás K. Comparison of circulating levels of interleukin-6 and tumor necrosis factor-alpha in hypertrophic cardiomyopathy and in idiopathic dilated cardiomyopathy. Am J Cardiol 2004; 94: 249-51. [CrossRef]
39. Festa A, D'Agostino Jr R, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic sub-clinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102: 42-7. [CrossRef]
40. Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, et al. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non ST elevation myocardial infarction. Am J Cardiol 2010; 106: 470-6. [CrossRef]
41. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Intermountain Heart Collaborative Study Group. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005; 45: 1638-43. [CrossRef]
42. Santopinto JJ, Fox KA, Goldberg RJ, Budaj A, Piñero G, Avezum A, et al. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). Heart 2003; 89: 1003-8. [CrossRef]
43. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296-305. [CrossRef]
44. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol 2003; 41: 47-55. [CrossRef]
45. Ahmed E, Alhabib KF, El-Menyar A, Asaad N, Sulaiman K, Hersi A, et al. Age and clinical outcomes in patients presenting with acute coronary syndromes. J Cardiovasc Dis Res 2013; 4: 134-9. [CrossRef]