NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET-TO-LYMPHOCYTE RATIO IN CARDIAC AND NON-CARDIAC ARREST DISTINCTION: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

***Introduction**: Cardiopulmonary arrest (CPA) is a major cause of death in developed countries. While 80% of the arrests occur due to cardiac pathologies, 20% occur due to non-cardiac pathologies. Determining the underlying pathology is very important. In this retrospective study, we examined the potential utilities of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in cardiac and non-cardiac arrest distinction.*

***Materials and methods**: We enrolled the following participants: 136 patients with cardiac arrests and 152 patients with non-cardiac arrests between January 2012 and December 2015. The distinction was made primarily on whether cardiac pathology was present. The cardiac pathology was determined by using cardiac enzyme levels, electrocardiographic and echocardiographic findings, angiographic results, and patient history.*

***Results**: Cardiac arrests were observed more frequently in male patients, while the number of non-cardiac arrests was greater in female patients (p=0.018). PLR and NLR were higher in non-cardiac arrests than in cardiac arrests (p<0.001 for PLR and p=0.001 for NLR). None of these parameters showed any effect on the 30-day mortality. The sensitivities, specificities, positive predictive values (PPV), and negative predictive values (NPV) of the PLRs and NLRs were 80.1%, 42.2%, 64.0%, and 62.3% and 49.7%, 73.5%, 68.8%, and 55.4%, respectively. The area under the curve (AUC) for the PLR was 61.7%, and the AUC for the NLR was 61.0%.*

***Conclusion**: We suggest that the NLR and PLR can be helpful in the differential diagnosis of cardiac and non-cardiac arrest. Thus, the NLR and PLR should be evaluated in addition to the clinical examination.*

***Keywords**: Cardiac arrest, clinical markers, emergency, NLR, PLR.*

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Introduction

Cardiopulmonary arrest (CPA), a major cause of death in developed countries, is defined as the sudden and unexpected clinical entity characterized by the cessation of cardiac function or the failure to obtain a pulse in large arteries, respiratory arrest, and unconsciousness[1]. Determining the etiology of CPA is very important because it plays a major role in determining treatment. However, etiology cannot always be clearly determined.

Currently, while 80% of CPAs have a cardiac cause, such as acute coronary syndrome and myocardial scars, connected to heart failure and myocardial infarction, 20% occur because of non-cardiac causes including respiratory problems, cerebrovascular accident, trauma, and metabolic disorders[2,3].

There have been no comprehensive studies to determine the etiology of CPA or to distinguish between cardiac and non-cardiac causes. To date, it has been shown that various parameters of the complete blood count (CBC), including white blood cell

count (WBC), neutrophil count, platelet count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are associated with the prognosis of many diseases, especially malignancies and cardiovascular events[4-7]. In many of these diseases, it is thought that inflammatory processes and excessive thrombotic activity play a role in the pathogenesis[8].

In a study that investigated the relation between changes in CBC subtypes and inflammation, a huge increase in neutrophil counts and a pronounced decrease in monocyte and lymphocyte counts were detected[9]. In studies conducted in recent years, it has been reported that these changes are associated with mortality in acute compensated congestive heart failure, acute coronary syndrome and pulmonary embolism[10-12]. On the other hand, in addition to the relation between inflammation and neutrophils, there is a positive correlation in nonspecific inflammatory conditions between the acute phase reactants and proinflammatory proteins and an elevated platelet count[13]. Furthermore, the PLR has been suggested as a potential indicator to determine excess thrombotic activity and inflammation in oncologic and cardiac disorders[14,15].

The primary goal of this study was to evaluated the ability of PLR and NLR to distinguish between cardiac and non-cardiac arrest to identify the etiologies of patients with CPA admitted to the emergency department and to plan the emergency treatment of patients according to the etiologic distinction.

Materials and methods

Study groups and study design

This study was retrospectively planned and conducted after ethical committee approval at a single center, the Konya Education and Research Hospital (high-level hospital with 1096 beds that serves approximately 300,000 patients annually), between 01 January 2012 and 31 December 2015. The study enrolled patients presenting with arrest who were admitted to the emergency room and with cardiac arrest that occurred during emergency observation. Cardiopulmonary resuscitation (CPR) was performed on all patients according to the up-to-date American Heart Association Cardiopulmonary Resuscitation Guidelines. CPR was considered successful when the heartbeat was continuous and blood pressure was stable. Prehospital patient data were obtained from the emergency medical record system.

Patients below 18 years of age, patients who were pregnant, patients with either traumatic or toxicological arrest, patients with hematologic diseases, and patients with incomplete records were excluded from the study. A total of 288 patients enrolled in the study were divided into two groups according to the etiologies of arrest, cardiac and non-cardiac. The distinction was made based primarily on whether there was cardiac pathology. In particular, the cardiac arrest group (n=136) included patients with elevated cardiac enzymes, significant cardiac pathology detected in the electrocardiogram, echocardiography and coronary angiography, and a history of cardiac disease in the patient record. Patients in the non-cardiac arrest group (n=152) included patients with pulmonary disease, cerebrovascular events and renal failure.

Laboratory analysis

All laboratory data were obtained from the laboratory results of blood samples taken when patients were admitted. CBC analysis was performed by automated CBC device (Sysmex XE-2100, Kobe, Japan) on venous blood samples and evaluated neutrophil count, lymphocyte count, red cell distribution width (RDW), hemoglobin and platelet count. The NLR and PLR were then calculated, biochemical tests were analyzed by fully automatic analyzers (Abbott C-16000, Abbott Laboratories, Abbott Park, Illinois, USA), and the urea, creatinine, lactate levels, and cardiac biomarkers were recorded. Furthermore, venous blood gases were analyzed. The normal values for all parameters were determined based on reference values accepted by hematology laboratories.

Statistical analysis

All statistical analyses were performed using statistical package for the social sciences (SPSS) version 19.0 software (SPSS Inc., Chicago, IL, USA). The data distribution was evaluated using the Kolmogorov-Smirnov test. Descriptive variables are expressed as the mean ± SD for data that is normally distributed and as the median and interquartile range (IQR) for variables that are not normally distributed. The chi-square or Fisher's exact test was used to compare categorical values. The significance of each difference between continuous variables was examined using the independent sample t-test or the Mann-Whitney U-test. The significance of each difference between categorical variables was compared using Pearson's chi-squared test. Four quartile groups were created according to the number of patients and clinical and laboratory characteristics

and were evaluated according to the PLR quartile via one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal-Wallis test for variables without normal distribution. When necessary, the Mann-Whitney U-test with the Bonferroni correction was used to compare variables. Kaplan-Meier survival estimates were also calculated. Univariate Cox regression models were used to assess the independent associations of laboratory parameters with 30-day mortality. Receiver operating characteristic (ROC) curve analysis was used to define the optimal cut-offs for the PLR and NLR. The specificities, sensitivities, positive and negative predictive values, and overall accuracies were also calculated for the PLR and NLR. Youden's index was used to optimize the accuracies of all calculations. A p-value <0.05 was considered to be statistically significant.

Results

We enrolled 288 patients in the study. Patients were evaluated separately according to the cause of arrest (cardiac or non-cardiac), factors affecting the 30-day mortality and factors related to the PLR quartiles during admission to the emergency room.

Evaluation results according to the cause of arrest

Demographic and laboratory parameters of cardiac and non-cardiac arrest distinction are summarized in Table 1. While cardiac arrests were observed more in male patients, arrests associated with non-cardiac causes were greater in female patients (p=0.018). Whereas the vast majority of arrests occurring outside the hospital were due to induced cardiac causes, arrests inside the hospital were due more to non-cardiac causes (p=0.035). The number of patients with pulseless electrical activity (PEA) was similar in both groups. However, in cardiac arrests, ventricular tachycardia was more pronounced, while asystole rhythm was dominant in non-cardiac arrests (p<0.001).

There was a statistically significant difference between the two groups according to the hemoglobin, RDW, lymphocyte count, urea levels, and creatinine levels (p=0.044 for creatinine and p<0.001 for others). The PLR and NLR were higher in non-cardiac arrests than in cardiac arrests (p<0.001 for PLR and p=0.001 for NLR). When the PLRs were divided into 4 equal quartiles, from low to high, there was a positive correlation between an increase in the PLR and an increase in the number of non-cardiac arrests (p<0.001).

		Cardiac arrest (n=136)	Non-cardiac arrest (n=152)	p
Age (year)		67.76 ± 1.21	69.78 ± 1.23	0.08
Gender (Male/Female)(n)		77/55	69/87	**0.018**
Arrest location (n/%)				**0.035**
	Hospital	78 (41%)	111 (59%)	
	Non-hospital	54 (54%)	45 (45%)	
Arrest rhythm (n/%)				**<0.001**
	Asystole	64 (35%)	119 (65%)	
	PEA	27 (52%)	25 (48%)	
	VT/VF	41 (77%)	12 (23%)	
Laboratory parameters				**<0.001**
	Hemoglobin (g/dL)	13.13 ± 0.23	12.23 ± 0.22	**<0.001**
	RDW (%)	15.48 ± 0.21	16.14 ± 0.20	**0.001**
	Platelet count (K/μL)	218.18 ± 8.90	234.72 ± 13.90	0.969
	Lymphocyte count (K/μL)	5.13 ± 0.31	4.14 ± 0.48	**<0.001**
	Neutrophil count (K/μL)	13.61 ± 4.95	58.67 ± 48.84	0.102
	Urea (mg/dL)	61.29 ± 3.78	85.82 ± 5.05	**<0.001**
	Creatinine (mg/dL)	1.57 ± 0.81	2.10 ± 0.14	**0.044**
	Lactate (mmol/L)	7.04 ± 0.32	6.88 ± 0.36	0.365
PLR measurements				
	PLR value	109.81 ± 15.76	170.85 ± 19.83	**<0.001**
	PLR quartiles (n/%)			**<0.001**
	First	48 (67%)	24 (33%)	
	Second	28 (39%)	44 (61%)	
	Third	32 (44%)	40 (56%)	
	Fourth	24 (33%)	48 (67%)	
NLR		5.91 ± 14.83	29.06 ± 26.52	**0.001**

Abb.: PEA: pulseless electrical activity, VT: ventricular tachycardia, VF: ventricular fibrillation, RDW: red cell distribution width, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio

Table 1: Demographic and laboratory parameters of cardiac and non-cardiac arrest distinction.

Evaluation of factors affecting the 30-day mortality after cardiopulmonary arrest

The factors affecting the 30-day mortality after cardiopulmonary arrest are shown in Table 2. There were no significant differences between groups according to age, gender, arrest location and rhythm,

reason for arrest, and laboratory parameters except for platelet count, and PLR and NLR measurements. The platelet levels were higher in the surviving group than in the deceased group (p=0.040).

	Surviving (n=35)	Deceased (n=253)	p
Age (year)	64.79 ± 2.99	69.40 ±0.89	0.129
Gender (Male/Female)(n)	18/17	124/129	0.858
Arrest location (n/%)			0.261
Hospital	20 (11%)	169 (89%)	
Non-hospital	15 (15%)	84 (85%)	
Arrest rhythm (n/%)			0.411
Asystole	19 (10%)	164 (90%)	
PEA	7 (13%)	45 (87%)	
VT/VF	9 (17%)	44 (83%)	
Reason for arrest			0.285
Cardiac	13 (10%)	119 (90%)	
Non-cardiac	22 (14%)	134 (86%)	
CPR duration (minute)	22.64 ± 2.22	15.83 ±0.15	0.093
Laboratory parameters			
Hemoglobin (g/dL)	12.58 ± 0.52	12.66 ± 0.17	0.672
RDW (%)	15.83 ± 0.43	14.85 ± 015	0.870
Platelet count (K/µL)	245.41 ± 15.60	224.52 ± 9.44	0.040
Lymphocyte count (K/µL)	4.50 ± 0.68	4.61 ± 0.32	0.879
Neutrophil count (K/µL)	10.90 ± 1.52	41.42 ± 29.84	0.154
Urea (mg/dL)	70.79 ± 9.42	74.69 ± 3.53	0.571
Creatinine (mg/dL)	1.45 ± 0.13	1.91 ± 0.99	0.141
Lactate (mmol(L)	6.71 ± 0.89	6.99 ± 0.25	0.324
PLR measurements			
PLR value	121.07 ± 23.51	145.43 ± 14.43	0.278
PLR quartiles (n/%)			0.108
First	3 (4%)	69 (96%)	
Second	12 (17%)	60 (83%)	
Third	10 (14%)	62 (86%)	
Fourth	10 (14%)	62 (86%)	
NLR	5.02 ± 5.38	20.27 ± 20.77	0.665

Abb.: PEA: pulseless electrical activity, VT: ventricular tachycardia, VF: ventricular fibrillation, RDW: red cell distribution width, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, CPR: cardiopulmonary resuscitation

Table 2: Factors affecting the 30-day mortality after cardiopulmonary arrest.

Evaluation of factors related to the PLR quartiles

The evaluation of the factors related to the PLR quartiles during admission to the emergency room are shown in Table 3. As the mean age increased, the PLR also increased. Similarly, as the PLR increased, the possibility of arrest in the hospital also increased (p<0.001). There were no significant relations between the PLR quartiles and gender, arrest rhythm, and CPR duration (p=0.964 for gender, p=0.186 for arrest rhythm, and p=0.683 for CPR duration). As the mean PLR value increased, the mean hemoglobin and lactate levels also decreased, whereas the RDW, urea, and creatinine levels also increased. There were no significant correlations between the PLR quartiles and the neutrophil count.

ROC analysis

The sensitivities and specificities of the PLR values used to distinguish the cardiac and non-cardiac arrest patients as well as the ROC data for the PLRs and NLRs are shown in Figure 1.

The sensitivities, specificities, +LR, -LR, PPVs, and NPVs of the PLRs and NLRs were 80.13%, 42.2%, 140%, 48%, 64.0% and 62.3%, and 49.7%, 73.5%, 187%, 68.0%, 68.8% and 55.4%, respectively. ROC analysis showed that the cut-off values for the PLR and NLR yielded the best sensitivities and specificities, which were 31.04 and 3.82, respectively. The area under the curve (AUC) for the PLR was 61.7% and the AUC for the NLR was 61.0%. Youden's index for the PLR was 0.223, and Youden's index for the NLR was 0.232.

	Quartile 1 (n=72)	Quartile 2 (n=72)	Quartile 3 (n=72)	Quartile 4 (n=72)
Age (year)	66.08 ± 15.21	67.40 ± 17.73	68.55 ± 14.06	72.87 ± 10.93[a,b,c]
Gender (Male/Female)(n)	36/36	35/37	37/35	38/34
Arrest location (n/%)				
Hospital	35 (19%)	38 (20%)	54 (29%)	62 (32%)
Non-hospital	37 (37%)	34 (34%)	18 (18%)	10 (11%)
Arrest rhythm				
Asystole	46 (25%)	40 (22%)	45 (25%)	52 (28%)
PEA	9 (17%)	15 (29%)	15 (29%)	13 (25%)
VT/VF	17 (32%)	17 (32%)	12 (23%)	7 (13%)
CPR duration	29.33 ± 17.33	25.77 ± 14.59	27.34 ± 17.14	27.38 ± 15.60
Laboratory parameters				
Hemoglobin (g/dL)	13.00 ± 2.82	12.73 ± 3.03	12.90 ± 2.73	11.84 ± 2.69[x,y,z]
RDW (%)	15.74 ± 2.91	15.20 ± 2.36	16.00 ± 2.40[d]	16.53 ± 2.07[e,f]
Neutrophil count (K/µL)	16.22 ± 7.00	7.44 ± 7.39	112.98 ± 86.10*	1.84 ± 6.26*
Urea (mg/dL)	58.48 ± 40.35	58.26 ± 41.70	78.00 ± 55.11[#]	100.70 ± 68.45*
Creatinine (mg/dL)	1.55 ± 1.03	1.62 ± 1.11	1.98 ± 1.38	2.29 ± 2.13[$,€]
Lactate (mmol/L)	8.00 ± 4.29	7.66 ± 4.88	6.35 ± 3.38[¤]	5.65 ± 3.28[β,µ]

Abb.: PEA: pulseless electrical activity, VT: ventricular tachycardia, VF: ventricular fibrillation, RDW: red cell distribution width, PLR: platelet-to-lymphocyte ratio, CPR: cardiopulmonary resuscitation

[a]p=0.002 vs quartile 1, [b]p=0.037 vs quartile 2, [c]p=0.060 vs quartile 3, [x]p=0.006 vs quartile 1, [y]p=0.033 vs quartile 2, [z]p=0.036 vs quartile 3, [d]p=0.019 vs quartile 2, [e]p=0.003 vs quartile 1, [f]p<0.001 vs quartile 2, *p<0.001 vs quartile 1 and 2, [#]p=0.014 vs quartile 2, [$]p=0.004 vs quartile 1, [€]p=0.015 vs quartile 2, [¤]p=0.019 vs quartile 1, [β]p<0.001 vs quartile 1, [µ]p=0.008 vs quartile 2

Table 3: Factors related to the PLR quartiles during admission to the emergency room.

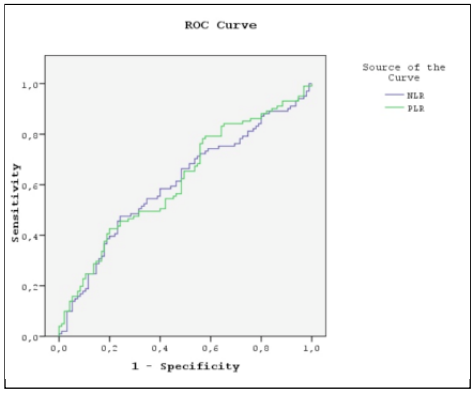

Figure 1: Figure 1. ROC curve used to distinguish cardiac arrests from non-cardiac arrests.

Discussion

The identification of the etiology of CPA provides an important contribution to the management

of cardiac arrest. In this study, we found that some hematological parameters including RDW, lymphocyte count, NLR and PLR can be used to distinguish cardiac and non-cardiac arrest.

While 80% of CPA occurs due to cardiac causes, 20% occurs due to non-cardiac causes. Non-cardiac causes usually include respiratory problems (e.g. pneumonia and pulmonary embolism), cerebrovascular events (e.g. intracranial hemorrhage and stroke), and metabolic disorders (e.g. acute or chronic renal failure and electrolyte disturbances)[2,3]. In our study, 47% of the arrests were due to cardiac causes, whereas 53% had a non-cardiac etiology. The most common etiology of cardiac arrests was myocardial infarction, whereas the most common cause of non-cardiac arrests was pulmonary disease. In terms of types of arrhythmia, while asystole is considered to be the most deadly rhythm and was the most common rhythm in the non-cardiac arrest group (65%), ventricular fibrillation (VF)/ventricular tachycardia (VT) was the most common rhythm in the cardiac arrest group (77%). PEA was similar in both groups, and these results were consistent with the literature[16].

Numerous studies have investigated the effectiveness of hematological CBC parameters in the prediction of disease severity and prognostic risk. The prognostic values of RDW, MPV, WBC, NLR, and PLR have recently been investigated as predictors for major adverse cardiovascular outcomes[6,17,18].

A large area of research concerns the examination of CBC parameters as prognostic tests. A positive correlation was found between the acute phase reactants and proinflammatory proteins and an elevated platelet count in nonspecific inflammatory conditions[19]. Increased platelet counts may indicate underlying inflammation because several inflammatory mediators stimulate megakaryocytic proliferation and produce relative thrombocytosis. Activated platelets release inflammatory mediators into the local microenvironment[20,21].

Recent studies have shown that patients with coronary artery disease (CAD) have increased platelet and monocyte aggregates in their bloodstream, which was associated with plaque instability, worse in-hospital outcomes, and an increased risk of future cardiac events[22,23].

NLR and PLR are novel inflammatory biomarkers used as prognostic factors in various diseases[24,25]. PLR has been proposed to be a pro-thrombotic and inflammatory marker[26]. Azab et al.[27] reported that higher PLR values were associated with increased long-term mortality in non-ST elevated myocardial infarction (non-STEMI) patients. Recently, various studies(24-28) and a meta-analysis(29) showed significant relations between NLR and an increased risk of all-cause mortality and cardiovascular events. In a study conducted on the acute coronary syndrome, Suliman et al.[30] found that a higher NLR was associated with a higher 30-day in-hospital mortality.

Jilma et al.[9] investigated changes in the subtypes of CBC after inflammation and found a 300% increase in neutrophils, a 96% increase in monocytes and an 85% reduction in lymphocytes 4-6 hours after inflammation. Various studies have confirmed the significance of RDW as a predictor of mortality both in the general population and in patients with various diseases such as peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), kidney failure and infectious diseases[31,32].

The hematocrit value has been shown to be the most important determinant of blood viscosity in many studies[33,34]. Soylu et al.[17] found significant elevations in the hematocrit level and erythrocyte counts in patients with the coronary slow flow phenomenon compared with patients who had normal coronary blood flow. Another study reported by Cho et al.[35] showed that the combined use of NLR and hemoglobin provided valuable information for early risk identification in patients with myocardial infarction. Saygitov et al.[36] found blood urea nitrogen (BUN) to be a more significant risk factor for the acute coronary syndrome (ACS) outcome compared with creatinine. In addition, serum creatinine was shown to be an independent predictor of coronary heart disease mortality in normotensive and normal-weighted survivors of a myocardial infarction.

When CBC parameters are examined on the basis of disease, the situation is similar. Celik et al.[37] studied pulmonary embolism (PE) and found that RDW, NLR, and PLR values in the PE group were higher than in the non-PE group. However, only RDW was found to be an independent predictor of PE. They found that PLR was elevated in patients with PE depending on the extent of inflammation. In another study,[38] PLR, like NLR, is the first parameter used in determining inflammation in acute exacerbationCOPD. In the literature, there are increasing quantities of data that describe the link between RDW and prognosis in patients with stable coronary artery disease (SCAD)[39].

In our study, we investigated the usability of hematological parameters in distinguishing cardiac

and non-cardiac arrest, unlike the diagnostic and prognostic uses of parameters that are reported in the literature. According to our results, the PLR and NLR were significantly higher in the non-cardiac arrests. The cause of this increase in the non-cardiac arrest group is probably the etiologies associated with diseases characterized by inflammation including renal failure, pulmonary thromboembolism, respiratory disorders, and cerebrovascular events. Similarly, in accord with the literature RDW, urea and creatinine levels were higher in the non-cardiac arrest group. However, unlike in the literature, none of hematological parameters we evaluated had an effect on 30-day mortality except for platelet count, PLR and NLR measurements.

We found that PLR and NLR were higher in patients with non-cardiac arrest admitted to the emergency room. The identification of etiology is very important for treatment and follow-up because the underlying cardiac and non-cardiac pathologies play an important role in prognosis. Therefore, identification and analysis of these parameters, in addition to other specific clinical parameters, is recommended because they help in planning treatment.

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