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Neutrophil-Lymphocyte Ratio as a Mortality Predictive Paramater In Patıents Wıth Out-of-Hospital Cardiac Arrest

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Abstract

Introduction: Cases of gunshot injuries among trauma patients admitted in the emergency room are fatal cases in Turkey as much as all over the world. It is perhaps the most complex group among trauma patients. Because the route of the bullet fragment, how much damage it causes on its way and which organ or organs will be harmed cannot be understood immediately so long-term follow-up may be required.

Case report: A 48-year-old civilian male patient brought to our hospital after gunshot injury. It was found that he was injured with pellets in many parts of his body. He was not operated on to prevent possible bleeding and to remove the pellets. Instead, vital signs were followed.

Results and Conclusion: Most of the patients who are injured by guns die. The most important reason for this is acute and large amount of bleeding. In this article, we will present a patient who has been exposed to multiple pellet shots but survived.

Key words: Emergency Service,Gunshot injury, multiple injury, trauma

Introduction

The rates of out-of-hospital cardiac arrests (OHCA) increase every passing day[1], while the corresponding survival rates display regional differences. The survival rate is around 10% percent in Europe, 6% percent in North America, 11% percent in Australia and 2% in Asia[2]. In patients with return of spontaneous circulation (ROSC), the systemic ischemia/reperfusion injury leads to development of a systemic inflammatory response and thereby, a sepsis-like condition[1,3], which is called post-cardiac arrest syndrome (PCAS) ensues.

PCAS is composed of 4 major components including post-cardiac cerebral injury, myocardial injury, systemic ischemia reperfusion response and persistent precipitating pathology[4]. Despite all the improvements in care after cardiac arrest, the majority of mortalities occur in the first 24-hours after the cardiac arrest[5]. Unfortunately, the prognostic factors, which can be utilized in this critical period, are not well defined[1] .

According to the studies performed in recent years, prominent changes have been found to occur in the white blood cell (WBC) subtypes following stress. Galus reported that lymphocytopenia can develop in infectious conditions[6] and Jilma *et al.* determined increases in neutrophil counts and decreases in lymphocyte and monocyte counts following inflammation[7].

Zahorec proposed a new parameter, which he called "neutrophil to lymphocyte stress factor". It was indicated that the ratio of the peripheral neutrophils to lymphocytes (NLR) was a better indicator of prognosis in comparison to the total WBC counts[8]. In recent years, studies performed on acute coronary syndrome, acute decompansed heart failure and pulmonary embolism revealed that NLR was associated with mortality[9-12]. In this current study, we also aimed to investigate the association of NLR with early mortality in OHCA patients with return of spontaneous circulation (ROSC).

Methods

Study Setting

This retrospective study was conducted in an emergency department of a regional academic hospital in Konya providing services with 1096 beds. This emergency department provides services to an approximate 300,000 patients per year. All the OHCA patients with ROSC between January 1st and 31st of December were included in the study. Resuscitations were performed on all patients according to the recommendations of the American Heart Association Cardiopulmonary Resuscitation Guideline of 2010.

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Table 1. Demographics and laboratory findings of the study population.

Age, years, median (IQR)	73(19)
Sex, no(%)	
Male	44(48.4)
Female	47(51.6)
Presence of witness, n (%)	
Witnessed	65 (71)
Bystander CPR, n(%)	
Done	3 (3.2)
Arrest rhythm, n(%)	
Asystole	52(57.1)
PEA	29(31.9)
VT/VF	10(11)
Cause of arrest, n(%)	
Cardiac	37 (40.6)
Noncardiac	54 (59.4)
Hemoglobin,gr/dl, median (IQR)	12.7(3.6)
Neutrophil, K/UL, median (IQR)	8.6(8.3)
Lymphocyte, K/UL, median(IQR)	2.8(5.2)
NLR, median(IQR)	3.05(9.8)
Platelet, K/UL, median(IQR)	208.000(128.500)
Urea, mg/dl, median(IQR)	65(55)
Creatinine, mg/dl, median(IQR)	1.37(1.51)
Arterial lactate, mmol/L, median(IQR)	6.2(3.9)
24-h mortality, n (%)	51 (56.1)
14-day mortality, n(%)	75(82.4)

IQR: Interquartile range, CPR: cardiopulmonary resuscitation, PEA: pulseless electrical activity, VF: ventricular fibrillation, VT: ventricular fibrillation, NLR: neutrophil lymphocyte ratio

Prehospital patient data were obtained from the records of the 112-Emergency Medical System, which is the nationwide official emergency service in Turkey. All the laboratory data were acquired by the survey of the laboratory findings, which were obtained from the blood specimens obtained on patient admission.

Participitants and The Data Collection

The study population was defined as OHCA patients with ROSC. The exclusion criteria comprised patient age of under 18, a medical history of hematological disease, cancer and cirrhosis and traumatic and toxicological causes of OHCA. The age, gender, the presence of witness, bystander CPR and the arrest rhythms of the patients were recorded.

Among the laboratory data, the WBC, hemoglobin, neutrophil, lymphocyte counts, lactate and creatinine values were recorded. NLR values were calculated and the 24-hour and the 14-day mortalities of the patients were recorded. Local ethics committee approval was obtained for the study and is compatible with the Helsinki declaration.

Statistical analysis

Statistical analysis was performed using the SPSS v.15.0 for Windows. Both visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods were used to determine if the data was normally distributed. Descriptive variables were expressed as mean ± SD for data that were normally distributed, and as median and interquartile range (IQR) for variables that were not normally distributed. The chi-square or Fisher's exact test was used to compare the categorical values.

The clinical and laboratory characteristics of the deceased and surviving patients in the first 24-hours were compared with the Mann Whitney U-test. The cause of arrest was classified as cardiac and non-cardiac arrest according to the etiology. These two groups were also compared by the Mann-Whitney U-test. Two groups were formed according to the median values of the NLR and their clinical and laboratory features were compared with the Mann Whitney U-test and the Fisher's exact test.

The effect of the NLR median values on the survival of the ROSC patients was evaluated with the log rank test.

Table 2. Analysis of factors associated with 24-h mortality

	Death within 24-h (n=51)	24–h survivors (n=40)	p
Age,years, median(IQR)	72 (21)	76.5 (15)	0.31
Sex			0.26
Male, n (%)	22(43.1)	22(55)	
Female, n (%)	29(56.9)	18(45)	
Arrest rhythm, n(%)			0.06
Asystole	34(66.7)	18(45)	
PEA	13 (25.5)	16(40)	
VT/VF	4(7.8)	6(15)	
Cause of arrest, n(%)			0.16
Cardiac	24(47.1)	13 (32.5)	
Noncardiac	27 (52.9)	27 (67.5)	
Hemoglobin,gr/dl, median (IQR)	12.3(3.4)	13.1(5)	0.47
Neutrophyl, K/UL, median (IQR)	7.1 (5.7)	11.2(7.1)	0.004
Lymphocyte, K/UL, median(IQR)	4.1(5.4)	2.0(3.8)	0.1
NLR, median(IQR)	1.27 (3.8)	5.6(12.8)	0.004
Platelet, K/UL, median(IQR)	205.000 (119.000)	203.000(146.000)	0.76
Urea, mg/dl, median(IQR)	57.5 (75.5)	65.5 (46.7)	0.69
Creatinine, mg/dl, median(IQR)	1.37 (1.3)	1.37 (1.7)	0.98
Arterial Lactate, mmol/L, median(IQR)	6.3 (3.8)	4.6 (4.8)	0.04

IQR: Interquartile range, PEA: pulseless electrical activity, VF: ventricular fibrillation, VT: ventricular fibrillation, NLR: neutrophil lymphocyte ratio

The Kaplan-Meier survival estimates were calculated. The univariate and the multivariate Cox regression models were utilized to evaluate the independent associations of the NLR values with the 24-hour mortality. Age, sex, arrest rhythm on admission, lactate and creatinine were included in this model. Utility of the NLR in 24-hour mortality in ROSC patients was evaluated via receiver operating characteristic (ROC) curves: the cut-off value was determined using the Youden's index. A p value of < 0.05 was considered statistically significant.

Results

Between the 1st of January and 31st of December in 2013, 191 OHCA cases were surveyed. It was determined that 115 (60.2% percent) of these patients returned to spontaneous circulation. 24 patients from this group were excluded by the exclusion criteria and a total of 91 patients were included in the study. The median (interquartile range) age of the patients was 73 (19), and 44 (48,4% percent) of the patients were males. The basal characteristics of the patients have been presented in Table-1.

Hypothermia never been applied to a patient. 34% percent (31) of the patients administered percutaneous coronary intervention. 43.9% percent (40) of the patients survived for more than 24 hours, and in the group who survived less than 24 hours, significant differences were found in neutrophil counts, NLR, lactate levels and arrest rhythm on admission (p<0,05). (Table-2). No significant differences were detected with regard to age, gender, neutrophil, lymphocyte, platelet counts and levels of hemoglobin, lactate and creatinine

Table 3. Performance parameters of neutrophil / lymphocyte ratio as a predictor of mortality

Performance parameters	95 % Confidence interval
Sensitivity	52.0 (37,4 - 66,3)
Specificity	80.0 (64,4 - 90,9)
Positive predictive value	76.5 (64.2-86.1)
Negative predictive value	56.1 (41.9-74.2)
Positive likelihood ratio	2.60 (1,3 - 5,1)
Negative likelihood ratio	0.60 (0,4 - 0,8)
Receiver operator characteristic curve area	0.68 (0.57-0.77)

between the cases of arrest due to cardiac and non-cardiac causes (p>0,05). The performance characteristics of the NLR to predict the 24-hour mortality were calculated (Table-3). The cut-off value of the mortality obtained by the ROC curve was ≤ 1,55. (Sensitivity: specificity: AUC 0.68 CI% 0.57-0.77, p=0.02) (Figure 1).

Two groups were formed according to the NLR median values lower and higher than 3.05. Significant differences were found with regard to the 24-hour and 14-day survivals, platelet counts and urea levels between these two groups (p<0,05) (Table-4). In the 1. group with lower NLR, the survival rate calculated with the Kaplan Meier curve was significantly lower (Log Rank 5.07 p=0.02) (Figure 2). It was determined with the multivariable Cox regression model, that the NLR being lower than 3.05 was a predictive parameter of the 24-hour mortality independent of age, gender, lactate levels, creatinine and the arrest rhythm on admission (Hazard Ratio: 0.34 (0.15-0.79), p=0.01).

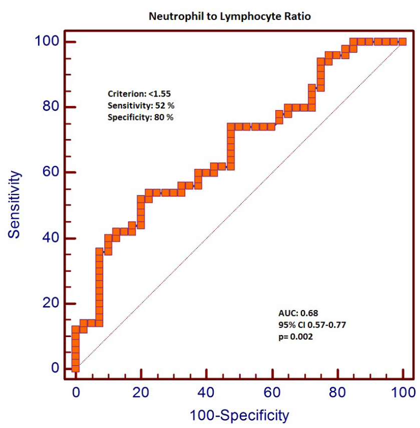
Discussion

This was a retrospective study evaluating the prognostic value of the NLR in OHCA patients with ROSC. According to the data which we obtained from this study and opposite to the previous observations, a low NLR level was found as an indicator of 24-hour mortality independent of the age, gender, arrest rythm on admission, lactate and creatinine levels.

The beginning phase of the inflammation is called SIRS (Systemic Inflammatory Response Syndrome), which could be either caused by a pathogen or by the tissue degradation products[13-14]. Besides the infectious causes, SIRS can develop following sepsis, trauma, surgery and resuscitation. The main role of SIRS is played by the WBC[8]. Jilma *et al.* investigated the changes in WBC subtypes following inflammation and they revealed a 300% increase in neutrophils, 96% decrease in monocytes and 85% decrease in lymphocytes in 4 to 6-hours after inflammation[7]. Zahorec reported that neutrophilia and lymphocytopenia developed in 90 oncological patients who required intensive care treatment, but also underlined that the neutrophil to lymphocyte ratio was a more predictive parameter. He mentioned that this ratio was a reliable parameter with regard to reflecting the intensity of the stress and for evaluating and monitoring the systemic inflammatory response[8]. In studies performed in recent years, high NLR levels were found to be associated with mortality in acute decompensated heart failure, acute coronary syndrome and pulmonary embolism[9-12].

The compensatory anti-inflammatory response syndrome (CARS) defined in 1996 was described as a loss of systemic efficacy of the immune system by its re-organization from an inflammatory stage to haematopoesis[15]. Conquy has defended the hypothesis that the CARS is an adaptation mechanism to suppress the excessive inflammatory response[13]. CARS occurs in immunocompromised patients or during the endotoxin intolerance phase of the SIRS or sepsis[13-14]. Endotoxin intolerance is defined as an attenuated responsiveness to lipopolysaccharides following the first exposure to endotoxin[16]. This has been reported to be a protective mechanism against the destructive effects of pro-inflammatory processes, yet it is also mentioned that it is associated with nosocomial infections and mortality by causing immunosuppression[16-18]. In this process, the aim is to avoid the detrimental effects of the neutrophils and monocytes against the host via receptor-based changes in monocytes, neutrophils and lymphocytes. It has been reported that the apoptosis rates are increased in leukocytes in endotoxin intolerance leading to leukopenia[14,16,17]. It has also been underlined that the survival lengths of the neutrophils and their sensitivity to apoptosis are important factors in determining the severity of the inflammatory response[19]. The likely cause of the endotoxemia in post-resuscitative patients is the increase in permeability in the intestinal mucosa following ischemia/reperfusion injury and the subsequent translocation of bacteria and endotoxins[18].

In PCAS, the systemic ischemia reperfusion response is characterized with systemic inflammatory immune respons-



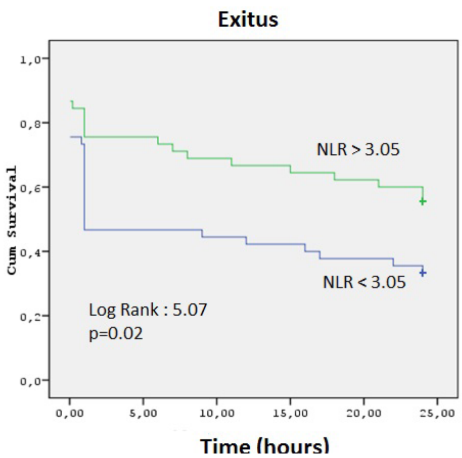


Table 4. Patients characteristics according to median of neutrophil / lymphocyte ratio

	NLR<3.05 (n=46)	NLR≥3.05 (n=45)	p
Age, years, median (IQR)	72(19)	75(15)	0.09
Sex, n (%)			0.34
Male	20 (43.5)	24 (53.3)	
Female	26 (56.5)	21 (46.7)	
Arrest rhythm, n(%)			0.43
Asystole	28 (60.9)	24 (53.3)	
PEA	13 (28.2)	16 (35.6)	
VT/VF	5 (10.9)	5 (11.1)	
Cause of arrest, n(%)			0.07
Cardiac	23 (%50)	14 (31.1)	
Noncardiac	23 (%50)	31 (68.9)	
Hemoglobin, median (IQR)	12.7 (3.2)	12.7 (3.8)	0.80
Platelet, K/UL, median (IQR)	172.000 (149.800)	243.000 (108.000)	0.008
Urea, mg/dl, median (IQR)	52.5 (48.5)	73 (83)	0.009
Creatinine, mg/dl, median (IQR)	2.0 (1.75)	3.0 (2.0)	0.09
Arterial lactate, mmol/L, median (IQR)	3.5 (0.75)	3.1 (1.0)	0.13
24-h mortality	31 (67.4)	20 (44.4)	0.02
14-day mortality	42 (91.3)	33 (73.3)	0.02

NLR: neutrophil lymphocyte ratio, IQR: Interquartile range, PEA: pulseless electrical activity, VF: ventricular fibrillation, VT: ventricular fibrillation

es, perturbed vasoregulation, increased coagulation, adrenal suppression and immunosuppression[20].

The mainstay of these results was obtained by the study of Adrie *et al.* performed in 2002. According to the results of this study, increase in plasma cytokines, presence of plasma endotoxins in 50% percent of cases, and dysregulation of cytokine synthesis were determined in patients resuscitated successfully, and it was also stated that these features were also seen in severe sepsis, and thus, the PCAS may be a sepsis-like syndrome[17-18].

In our results, we found the NLR to be lower in OHCA patients with ROSC, contrary to the usual responses in SIRS. We think that this result may be a consequence of the endotoxin intolerance or CARS subsequent to an immunodepression with as yet an unknown pathophysiology. According to our view, this result may reflect the severity of immune-paralysis and the inflammation occuring in PCAS. Low NLR level is an independent indicator of the 24-hour mortality independent of the important prognostic markers such as lactate, creatinine, age, gender and the arrest rhythm on admission.

The majority of the mortalities in PCAS patients occur in the first 24-hours and the prognostic factors which can be utilized in this period are not well known[1]. At this point, it may be possible to use NLR as a marker, which may also lead to the development of different treatment choices. For instance, Vasileiou *et al.* demonstrated that the erythropoietin improves survival following cardiac arrest in their experimental study, and proposed that the likely causes of their results may be explained by the erythropoietin-reduction of ischemia reperfusion injury, apoptosis and inflammation[21].

In previous studies, CRP and procalcitonin levels were found to be elevated due to the systemic inflammation subsequent to ischemia reperfusion response in PCAS, and they were also found to be associated with short and long-term mortality[22-23]. In comparison to these markers, NLR can be obtained cheaper and faster in daily practice and it is a parameter with easier accesibility.

Limitations

This study has some limitations. First of all, this study is a single-center retrospective study performed by the survey of hospital records. Some biases are unavoidable to the retrospective character of the study. Secondly, Bystander CPR was only done in %3. 69.2% (45) of the witnesses of the arrest has witnessed an emergency call system. Therefore bystander CPR ratio is low. Third, due to the low number of cases and due to low survival rates, the associations of the NLR with long term mortality and neurological sequelae were not investigated. Prospective studies with higher numbers of cases are needed.

Conclusion

A low NLR level is an independent indicator of the 24-hour mortality in PCAS, indepedent of the age, gender, creatinine, lactate and arrest rhythms on admission. It is a laboratory parameter, which can be obtained cheaply and easily, and it may help for development of novel treatment choices in cardiopulmonary resuscitation and postresuscitation care.

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