







The relationship of neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) parameters with mortality in intensive care unit (ICU) patients

Selen Zeliha Mart Komurcu ¹ , Yakup Artik ^{2*} , Nevra Pelin Cesur ³ , Yavuz Uyar ⁴ ,
Yasemin Tuba Sutasis ¹ , Elcin Akduman Alasehir ⁵ , Ebru Kaya ¹ 

¹ Ministry of Health University of Health Science, Kanuni Sultan Süleyman Research and Training Hospital, 34303, Küçükçekmece, Istanbul, TURKEY

² Republic of Turkey, Ministry of Health, Health Institutes of Turkey (TUSEB), COVID-19 Diagnostic Center, Istanbul Provincial Directorate of Health, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, 34303, Istanbul, Küçükçekmece, TURKEY

³ Yildiz Technical University, Molecular Biology and Genetics Department, 34220, Esenler, Istanbul, TURKEY

⁴ Tekirdağ Namık Kemal University, Faculty of Medicine, Department of Medical Microbiology, 59100, Tekirdağ, TURKEY

⁵ Department of Medical Microbiology, Manisa Public Health Laboratory, Manisa, TURKEY

*Corresponding Author: ykp.artik@gmail.com

Citation: Mart Komurcu SZ, Artik Y, Cesur NP, Uyar Y, Sutasis YT, Akduman Alasehir E, Kaya E. The relationship of neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) parameters with mortality in intensive care unit (ICU) patients. ELECTR J MED DENT STUD. 2022;12(4):em0101. <https://doi.org/10.29333/ejmnds/12623>

ARTICLE INFO

Received: 17 Aug. 2022

Accepted: 01 Nov. 2022

ABSTRACT

The neutrophil/lymphocyte ratio (NLR) is generally accepted as an indicator of sub-clinical inflammation. In recent studies, it has been found that the NLR can be used in the calculation of morbidity and mortality. Within the scope of this study, the relationship between NLR and mortality in hospitalized patients between January 1, 2015, and August 31, 2019, was explained. Among the studies on NLR between these dates, the age range of 584 patients with normal and abnormal C-reactive protein (CRP) values ranged from 10 to 100, and the data of 272 female and 312 male patients were analyzed. In this study, while evaluating the academic contributions of the NLR and CRP data obtained with the retrospective approach to the literature in the cases of intensive care unit (ICU) patients. Age, NLR, CRP, IgG, and IgG percent levels of exitus group patients were significantly higher than non-exitus group ($p < 0.05$). Lymphocyte level of non-exitus group (lymphocyte 1.26 ± 1.04) was significantly higher ($p < 0.05$) than exitus group (age, mean \pm SD 68.70 \pm 16.69, NLR 17.48 \pm 25.80, CRP 167.27 \pm 114.10, IgG 0.38 \pm 0.60, IgG percent 2.56 \pm 5.15, and neutrophile 12.50 \pm 9.68). We hypothesize that the data evaluated together with the immature granulocyte count will help and benefit the intensive care specialists in their evaluation reports for the patient.

Keywords: neutrophil, lymphocyte, CRP, immature granulocyte, ICU

INTRODUCTION

Nowadays, the actual focus is the improving clinical outcomes of patients with critical illness in intensive care unit (ICU). Their C-reactive protein (CRP) levels are higher than the normal patients because of the severe inflammation reactions within their bodies. Thus, their mortality rate is high and critical which is approaching 35% among patients with expected stays of more than three days in ICU [1]. Therefore, there are many parameters to evaluate the immune system response properly. Antibodies play a critical role in the immune system and protection against viral and bacterial infections within the body.

Leukocytes are classified into two main groups: granulocytes and nongranulocytes (agranulocytes). The granulocytes, mainly which include neutrophils, eosinophils, and basophils, have granules in their cell cytoplasm and also have a multilobed nucleus. Leukocytes and granulocytes involved in certain autoimmune diseases and in immediate-type hypersensitivity [2].

The term granulocyte includes neutrophil, eosinophil, basophil, mast cells, dendritic cells, monocyte-macrophages, and phagocytes while lymphocytes consist of natural killer cells and some cells specialized under the "T" and "B" lymphocyte groups [2]. Especially, neutrophilic granulocytes are very effective in inflammatory reactions and the immune system. While the granulocytes are called innate immunity, leukocytes are termed in the acquired immune system [3].

Throughout a person life, innate immune system is observed predominantly. If an antigen across the body barriers, it first encounters with innate defense system (granulocytes). This innate response is often triggered by recognizing general characteristics found in large groups of microorganisms. In other words, this response is not specific to a single microorganism. In the presence of a microorganism that crosses body barriers, eicosanoids and some cytokines are secreted from damaged or infected cells, and these stimuli mediate the formation of the first response by the immune system against infection, called inflammation [4]. The four main symptoms of inflammation are described as fever, redness, pain and swelling. The cause of the redness in the

Table 1. Some baseline characteristics of patient groups and difference analysis results

	Non-exitus (n=286)	Exitus (n=298)	p-value
Age: mean±SD	57.13±21.44	68.70±16.69	0.000 ^a
Gender: n (%)			
Female	125 (43.7)	147 (49.3)	0.100 ^b
Male	161 (56.3)	151 (50.7)	
Neutrophile	11.65±7.43	12.50±9.68	0.800 ^a
Lymphocyte	1.26±1.04	1.15±1.17	0.006 ^a
NLR	13.36±13.08	17.48±25.80	0.029 ^a
CRP	122.38±103.90	167.27114.10	0.000 ^a
IgG	0.30±0.72	0.38±0.60	0.005 ^a
IgG percent	1.84±3.17	2.56±5.15	0.001 ^a

Note. ^aMann Whitney U test; ^bFischer's exact test; & SD: Standard deviation

damaged area is the enlargement of the blood vessels. Neutrophils migrate to the heavily damaged area with the effect of both the enlargement of the blood vessels and the molecules called leukotrienes found in the secreted cytokines. Neutrophils constitute approximately 50-60% of leukocytes in the blood [5]. Neutrophils are named as "neutrophils" because their granules do not tend to bind to the dyes used in histological examination. Neutrophils are produced in the bone marrow and then pass into the bloodstream [6].

Lymphocytes, like neutrophils, are produced in the bone marrow, but unlike granulocytes, they can fulfill their functions after going through a maturation process [7]. The lifespan of lymphocytes can range from a few weeks to several years. This period is considerably longer compared to neutrophils.

The neutrophil/lymphocyte ratio (NLR) is an indicator that is calculated using the neutrophil and lymphocyte values in the whole blood test, and its popularity is increasing day by day. NLR is generally accepted as an indicator of sub-clinical inflammation [8-10]. This study will focus mainly on short-term mortality predicting with the important parameters as CRP, NLR, age, and gender on ICU patients. So rapid and predictive results could be obtained, a significant criterion for the clinician in the assessment of severity of illness of ICU patients and likelihood of survival of the critically ill.

MATERIAL AND METHOD

The results obtained from the samples taken from the ICU between January 1, 2015, and August 31, 2019 (retrospective file scan) by examining the HSYS (public health system of Turkish Ministry of Health) records of the patients. In this study, hemogram and biochemical analysis parameters are analyzed for research purposes, as follows:

- (1) CRP,
- (2) neutrophil,
- (3) lymphocyte, and
- (4) immatur granulocyte count are "IG".

The files were examined within the scope of the research by dividing these parameter values in the hemogram into groups such as age and genders. The process of leaving the hospital was evaluated as ex and outpatient exit. The data obtained as a result of the evaluation were prepared in accordance with the statistical methodology.

Table 2. Spearman's rho correlation analysis results for mortality related factors

	r	p
Age	0.266**	0.000
Gender	-0.056	0.174
Neutrophile	0.010	0.800
Lymphocyte	-0.114**	0.006
NLR	0.090	0.029
CRP	0.214**	0.000
IgG	0.144**	0.005
IgG percent	0.175**	0.001

Note. *p<0.05 & **p<0.01

Statistical Methods

Age and mortality parameters described with frequency analysis, whereas scale parameters were described with means and standard deviations. Fischer's exact test was used for gender differences between patient groups. Kolmogorov Smirnov test was used for normality of scale parameters. Since all parameter distributions were non-normal, nonparametric tests were used.

Mann Whitney U test was used for differences of scale parameters. Spearman's rho test was used for correlation between parameters, and binary logistic regression analysis was used for multivariate analysis. SPSS 17.0 for analysis at 95% confidence interval with 0.05 significance level.

RESULTS

272 were female and 216 were male of the patients. The results in **Table 1** were obtained when they were divided into two groups as exitus and non-exitus. There was no difference between the two groups in terms of gender. Age factor was found to be significantly higher in the group with exitus compared to the nonexitus group (p=0.000). Age, NLR, CRP, IgG, and IgG percent levels of exitus group patients were significantly higher than non-exitus group (p<0.05). Lymphocyte level of non-exitus group was significantly higher (p<0.05) than exitus group (**Table 1**).

Spearman's rho correlation analysis results showed that age, CRP, NLR, IgG, and IgG percent parameters had positive and significant correlation with mortality, whereas lymphocyte has significant and negative correlation with mortality (p<0.05) (**Table 2**).

At multivariate level, effects of age and CRP on mortality at ICU were significant (p<0.05). However, effects of lymphocyte, NLR and IgG were insignificant (p>0.05). Since IgG and IgG percent parameters were cointegrated, and same parameters, IgG percent parameter was excluded from multivariate analysis (**Table 3**).

Both age and CRP means of exitus group were significantly higher (**Figure 1** and **Figure 2**).

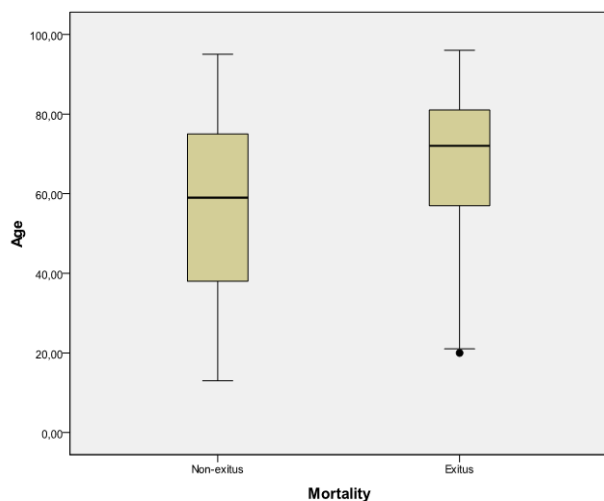
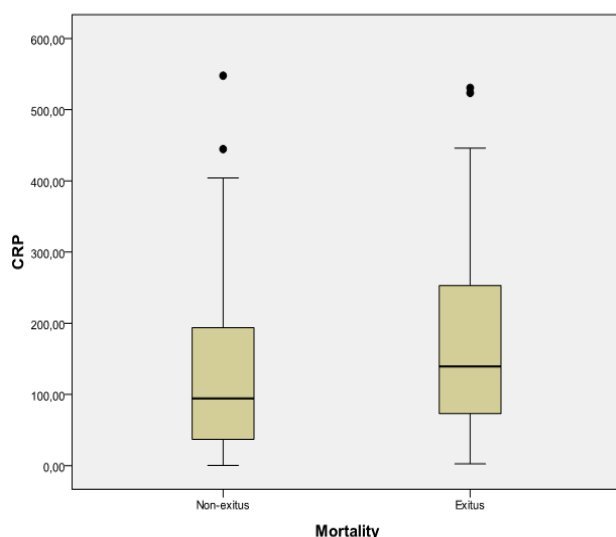
DISCUSSION

Today, laboratory tests play a very important role in the diagnosis of diseases, determination of prognosis and selection of medical treatments to be applied. The most important medical decision tool that can guide clinicians during the evaluation of laboratory tests is the reference

Table 3. Binary logistic regression analysis results for mortality related factors

	B	SE	Wald	P-value	OR	95% CI for OR	
						Lower	Upper
Age	0.034	0.006	31.740	0.000	1.035	1.023	1.047
Lymphocyte	0.019	0.096	0.037	0.847	1.019	0.843	1.231
NLO	0.007	0.006	1.380	0.240	1.007	0.995	1.020
CRP	0.002	0.001	5.027	0.025	1.002	1.000	1.004
IgG	0.204	0.173	1.389	0.239	1.227	0.873	1.723
Constant	-2.625	0.460	32.514	0.000	0.072		

Note. SE: Standard error & CI: Confidence interval

**Figure 1.** Age distribution of patient groups and differences (Source: Authors)**Figure 2.** CRP distribution of patient groups and differences (Source: Authors)

interval. The reference interval refers to the range of numbers obtained from a population of reference individuals using a number of statistical methods, in which the measurement results for that test can be considered normal.

There are many studies in the literature investigating the relationship of NLR value with different clinical conditions. However, due to the fact that the reference intervals in blood parameters vary depending on both age and gender, the

differences between the measurement methods also affect the measurement results, and the differences between the populations have an effect on the reference values, studies in which reference intervals are determined for male and female genders in different age groups are quite difficult and limited.

The mortality rate among patients admitted to the ICU depends on many factors such as the underlying cause, age, duration of mechanical ventilation, and the severity of the disease. Mortality rates have been reported to range from 14% to 41.1% worldwide [11]. There are many factors affecting mortality in the ICU. When these factors are examined, NLR is accepted as an indicator of sub-clinical inflammation. Inflammation is a body's process for fighting against things that harm it, like infections, injuries, and toxins, in an attempt to heal itself. When something damages your cells, your body releases chemicals that trigger a response from your immune system.

In the present study, not only NLR values of intensive care patients, but also hemogram tests and age, NLR, CRP, and IgG value analyzes were performed. In particular, considering the importance of NLR in mortality, there are many studies in the literature investigating the relationship between NLR values and some diseases. It has been reported that NLR values in community-acquired pneumonia are higher than 13 in hospitalized patients, NLR values are higher than 18 in patients followed in the ICU, and mortality rate is quite high in patients with NLR values of 23 or higher [12]. In addition, it has been reported that the prognosis is worse in patients with metastatic prostate cancer with an NLR value above five, and NLR values may be useful in making the decision for immunotherapy [5]. There are many studies in the literature investigating the relationship of NLR value with different clinical conditions. However, studies in which reference intervals in blood parameters vary depending on both age and gender and other biochemical analyzes are very limited.

The aim of this study is to make sense of the mortality relationship between NLR and CRP values. While the non-exitus group showed significantly higher ratio of lymphocyte, as expected, exitus patients demonstrated high level of NLR, CRP, and IgG. Additionally, most of the exitus patients are observed in older ages [13]. The most mortality is observed in patients with high CRP value. CRP level is very effective on immune system of the body which is adversely effective on it. CRP is usually measured in milligrams of CRP per liter of blood (mg/L). Normal CRP levels are typically below 3.0 mg/L [4]. However, not only in ICU patients this level is significantly higher but also lymphocyte is observed in lower rates. In a study conducted on a population of 1,070 people without any health problems or complaints, it was reported that there is a strong correlation between diabetes and hypertension, which includes chronic inflammatory processes, and NLR values above 2.57 [14].

In a study conducted in Turkey, it was reported that a NLR value above 3.5 was significantly correlated with the diagnosis of acute appendicitis in childhood acute appendicitis with a suitable clinical picture [15]. Inflammation is a body's process for fighting against things that harm it, like infections, injuries, and toxins, in an attempt to heal itself. When something damages your cells, your body releases chemicals that trigger a response from your immune system. NLR is accepted as an indicator of sub-clinical inflammation [10]. Thus, this study is important because the comparison of mean laboratory values between hospital exitus and non-exitus patients will be useful

to reveal statistically importance in differences of little clinical relevance and predictive power.

Author contributions: **SZMK:** provided support on academic consultancy and administrative process management throughout the entire research process and in the analysis of results; **YA:** provided support on academic consultancy and administrative process management throughout the entire research process and in the analysis of results, designed the figures; & **NPC, YU, YTS, EAA, & EK:** provided support on throughout the entire research process and in the analysis of results. All authors have agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Acknowledgements: The authors would like to thank to all COVID-19 Diagnostic Center staff for their devoted efforts during the entire pandemic period.

Ethical statement: The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital No: 2021.05.163, Subject No: KAEK/2021.05.163.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. Rocker G, Cook D, Sjøkvist P, et al. Clinician predictions of intensive care unit mortality. *Crit Care Med.* 2004;32(5):1149-54. <https://doi.org/10.1097/01.CCM.0000126402.51524.52> PMID:15190965
2. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy.* 2001;102(1):5-14.
3. Cervera L, González-Fernández C, Arizcun M, Cuesta A, Chaves-Pozo E. Severe natural outbreak of *cryptocaryon irritans* in gilthead seabream produces leukocyte mobilization and innate immunity at the gill tissue. *Int J Mol Sci.* 2022;23(2):937. <https://doi.org/10.3390/ijms23020937> PMID:35055122 PMCid:PMC8780452
4. Aydın I, Agilli M, Aydın FN, et al. Farklı yaş gruplarında nötrofil/lenfosit oranı referans aralıkları [Reference ranges of neutrophil/lymphocyte ratio in different age groups]. *Gülhane Tıp Dergisi [Gulhane Med J].* 2015;57:414-8. <https://doi.org/10.5455/gulhane.166398>
5. Duffy BK, Gurm HS, Rajagopal V, Gupta R, Ellis SG, Bhatt DL. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. *Am J Cardiol.* 2006;97(7):993-6. <https://doi.org/10.1016/j.amjcard.2005.10.034> PMID:16563903
6. Schmid-Schönbein GW. Analysis of inflammation. *Annu Rev Biomed Eng.* 2006;8:93-131. <https://doi.org/10.1146/annurev.bioeng.8.061505.095708> PMID:16834553
7. Tsujimura A, Kawamura N, Ichimura T, Honda K-I, Ishiko O, Ogita S. Telomerase activity in needle biopsied uterine myoma-like tumors: Differential diagnosis between uterine sarcomas and leiomyomas. *Int J Oncol.* 2002;20(2):361-5. <https://doi.org/10.3892/ijo.20.2.361> PMID:11788902
8. Tian X. *The halberd at red cliff: Jian'an and the three Kingdoms.* Cambridge, MA: Harvard University Asia Center; 2018. <https://doi.org/10.1163/9781684170920>
9. Tezcan MA. The relationship between primary spontaneous pneumothorax and neutrophil/lymphocyte ratio. *Turk Thorac J.* 2019;20:194. <https://doi.org/10.5152/TurkThoracJ.2019.194>
10. Jilma B, Blann A, Pernerstofer T, et al. Regulation of adhesion molecules during human endotoxemia: No acute effects of aspirin. *Am J Respir Crit Care Med.* 1999;159(3):857-63. <https://doi.org/10.1164/ajrccm.159.3.9805087> PMID:10051263
11. ten Boekel E, Vroonhof K, Huisman A, van Kampen C, de Kieviet W. Clinical laboratory findings associated with in-hospital mortality. *Clin Chim Acta.* 2006;372(1-2):1-13. <https://doi.org/10.1016/j.cca.2006.03.024> PMID:16697361
12. de Jager CPC, Wever PC, Gemen EFA, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PloS One.* 2012;7(10):e46561. <https://doi.org/10.1371/journal.pone.0046561> PMID:23049706 PMCid:PMC3462173
13. Senyurt O, Kaygusuz K, Avci O, Isbir AC, Ozdemir Kol I, Gursoy S. Yoğun bakım hastalarında hemogram parametrelerinin mortaliteyle ilişkisi [Relationship between hemogram parameters and mortality in intensive care patients]. *GAKD J.* 2018;24(4):165-71.
14. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med.* 2012;5(1):2. <https://doi.org/10.1186/1755-7682-5-2> PMID:22281066 PMCid:PMC3277482
15. Narci A, Tuncer AA, Cetinkursun S. Çocukluk çağı apendisitlerinde nötrofil/lenfosit oranının tanısal değeri [Diagnostic value of neutrophil/lymphocyte ratio in childhood appendicitis]. *Kocatepe Tıp Dergisi [Med J Kocatepe].* 2009;10:5-7.