GEVHER NESIBE JOURNAL OF MEDICAL & HEALTH SCIENCES | ISSN 2717-7394

Arrival Date: 28.08.2022 | **Published Date:** 31.01.2023 | **Vol:** 8, **Issue:** 1 | **pp:** 1-7 | **Doi Number:** http://doi.org/10.5281/zenodo.7599300

INVESTIGATION OF THE EFFECT OF NEUTROPHIL/LYMPHOCYTE RATIO ON MORTALITY IN LATE-ONSET NEONATAL SEPSIS

GEÇ NEONATAL SEPSİSTE NÖTROFİL/LENFOSİT ORANININ MORTALİTE ÜZERİNDEKİ ETKİSİNİN BELİRLENMESİ

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ABSTRACT

Objective: Neonatal Sepsis (NS) is a term used to define any systemic bacterial infection in the first month of life. NS continues to be a major factor for morbidity and mortality in newly born babies both in developed and developing countries. The selection of tests for early diagnosis of sepsis and the acceleration of the initiation of the treatment process are of critical importance in reducing morbidity and mortality. This study aimed at determining the significance of Neutrophil/Lymphocyte Ratio (NLR) and its relationship with mortality in preterm or full-term babies born with sepsis.

Method: The study retrospectively included inpatient preterm and full-term babies with late-onset NS who were treated between January 2012 and January 2014 at the Neonatal Intensive Care Unit (NICU) of Zekai Tahir Gynaecology Training and Research Hospital. Those who did not have any clinical conditions or laboratory findings indicating sepsis such as jaundice were included in the control group. The variables studied in the groups were maternal age, maternal clinical diseases, maternal infections, and prepartum and postpartum problems during treatment.

Results: The NLR values of the groups were compared with respect to infection. The patient group was found to have higher Neutrophil (p=0,005), NLO (p<0,001), Haemoglobin (p<0,001), Platelet (p=0,001), MPV (p=0,002), CRP (p<0,001) and IL-6 (p=0,004) values, and a lower Lymphocyte (p=0.004) value than the control group (p<0.05). No significant correlation was found between patient mortality and NLR (p>0.05).

Conclusion: As a result of the analyses performed in our study, it was determined that NLR is important in the early diagnosis of neonatal late onset sepsis. However, it was found that NLR had no effect on predicting mortality.

Keywords: Neonatal, Sepsis, Neutrophil/Lymphocyte Ratio, Mortality.

ÖZET

Amaç: Neonatal sepsis (NS) yaşamın ilk ayında herhangi bir sistemik bakteriyel enfeksiyonu tanımlamak için kullanılan terimdir. NS, hem gelişmiş hem de gelişmekte olan ülkelerde halen yenidoğan bebeklerin morbidite ve mortalite için önemli bir faktör olmaya devam etmektedir. Sepsiste erken tanıya yönelik tetkiklerin seçimi ve bu tetkiklerin tedavi sürecine başlamayı hızlandırması morbidite ve mortaliteyi azaltabilmek için kritik önemi bulunmaktadır. Bu çalışmada sepsis ile doğan preterm veya term bebeklerde Nötrofil/Lenfosit Oranının (NLO) önemini ve mortalite ile arasındaki ilişkiyi belirlemeyi amaçladık.

Metod: Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi Yenidoğan Yoğun Bakım Ünitesinde Ocak 2012 ile Ocak 2014 yılları arasında yatarak tedavi gören geç başlangıçlı neonatal sepsisi gelişen preterm ve term bebekler retrospektif olarak değerlendirildi. Sarılık veya yenidoğan geçici takipnesi gibi tanılarla yatırılmış olan, sepsis kliniği ve sepsis laboratuvar bulguları olmayan hastalar kontrol grubu olarak seçilmiştir. Gruplara ait üzerinde inceleme yapılan değişkenler ise maternal yaş, maternal klinik hastalıklar, maternal enfeksiyon, doğum öncesi ve doğum sonrası takipteki sorunlardır.

Bulgular: Çalışmada NLO değerlerinin her iki grupta enfeksiyon açısından karşılaştırılması yapıldı. Hasta grubunda yer alanların kontrol grubunda yer alanlara göre Nötrofil (p=0,005), NLO (p<0,001), Hemoglobin (p<0,001), Platelet (p=0,001) ve MPV (p=0,002), CRP (p<0,001) ve IL-6 (p=0,004) değerlerinin yüksek; Lenfosit (p=0,010), değerlerinin ise düşük olduğu saptandı (p<0,05). Hastalardaki mortalite ile NLO arasında anlamlı bir ilişki olmadığı gözlendi (p>0,05).

Sonuç: Çalışmamızda yapılan analizler sonucunda NLO'nın neonatal geç sepsisin erken tanısında önemli olduğu saptandı. Fakat NLO'nun mortaliteyi öngörmede etkisinin olmadığı saptanmıştır.

Anahtar Kelimeler: Yenidoğan, Sepsis, Nötrofil Lenfosit Oranı, Mortalite

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Bu makaleye atıf yapmak için / Cite this article: Değirmencioğlu H. (2023). Investigation of the Effect of Neutrophil/Lymphocyte Ratio on Mortality in Late-Onset Neonatal Sepsis. *Gevher Nesibe Journal of Medical & Health Sciences,* 8(1), 1-7. http://doi.org/10.5281/zenodo.7599300

INTRODUCTION

Neonatal sepsis (NS) may cause various morbidity and mortality beyond the neonatal period (Shane-Sanchez, 2017) and a major global public health problem (Qazi-Stoll, 2009). NS is reported to develop in approximately 2202/100,000 live births with a mortality rate between 11 and 19% (Fleischman-Struzek et al., 2018). Early diagnosis and treatment of late-onset NS in particularly premature babies can decrease related serious complications and mortality. Symptoms of NS include pneumonia, tachycardia, respiratory distress, alimentation and temperature intolerance These symptoms of NS, however, may be confused with other unspecific causes other than infection and make it difficult to diagnose (Shane-Sanchez, 2017). Blood culture has been recognised as gold standard test for the certain diagnosis of NS (Goldstein et al, 2005). However, blood culture usually requires a long waiting time to obtain a result and the rate of growth in a blood culture may be too low because of the inadequate volume of blood drawn, contamination in the blood culture, or any antibiotics given previously to the patient (Lamy et al., 2016; Scheer et al., 2019).

Additional more accurate laboratory values that would clarify uncertainties may be needed for an early diagnosis of NS. For this reason, various biomarkers of the blood in circulation that can be useful for diagnosis have been investigated in many studies (Sharma et al., 2018). Systemic inflammatory response syndrome triggered by sepsis is caused by a severe infectious state and inflammation plays an important role in the onset and progression. White blood cells and their sub-populations are of vital importance in the immune system's defence against a pathogenic infection. Many previous clinical trials have identified the numbers of neutrophils and lymphocytes obtained from a whole blood count and the neutrophil/lymphocyte ratio (NLR) are the early markers could predict sepsis (de Pablo et al., 2014; Djordjevic et al., 2018;Martins et al., 2019). Since the numbers of both neutrophils and lymphocytes are included in the calculation, NLR is considered more stable than absolute neutrophil or absolute lymphocyte amounts (Dirican et al., 2015). NLR attracted great attention for its potential to be a new risk factor for NS (Liu et al., 2016; Hwang et al., 2017;Huang et al., 2020). However, most of the designed researches to study the relation between NLR and NS have been conducted with adult cases (Djordjevic et al., 2018). The information on the relationship between NLR and NS has generally been obtained from studies with small sample sizes (Omran et al., 2018; Can et al., 2018; Alkan et al., 2018; Lee, 2019). For this reason, this study aimed at assessing the possible association between NLR and late-onset NS in a comparatively large neonatal cases and whether NLR had any significant role in predicting mortality.

MATERIALS AND METHODS

The study retrospectively included inpatient preterm and full term babies at ≤40 weeks of birth with late-onset NS who were treated between January 2012 and January 2014 at the Neonatal Intensive Care Unit (NICU) of Zekai Tahir Gynaecology Training and Research Hospital. A local ethics committee approval was obtained for the study. A total of 170 newborns (with evidenced late-onset NS n=85 and controls=85) were included into this study and their medical and laboratory data were obtained and analysed retrospectively. Patients with any or any combination of following underlying problems were excluded from the study: 1)- Cases of early sepsis, 2)- Cases of uncertain and clinical sepsis and 3)- Other cases such as hematologic diseases, congenital malformations and congenital heart diseases.

In addition to laboratory results showing high levels of C-Reactive Protein (CRP) or Interleukin-6 (IL-6), at least three of the following should be present for the diagnosis of clinical sepsis: Bradycardia (<100/min.), tachycardia (>200/min.), hypotension, hypotonia, seizures, apnea, tachypnea, cyanosis, respiratory distress, skin discolouration, impaired perfusion, feeding difficulty, agitation, and restlessness. Patients with culture positivity were considered to have evidenced sepsis. Those who had clinical NS and whose culture subsequently turned out positive were considered to have evidenced late-onset NS and were included in the study. Patients who were bedded in the NICU but did not have NS were included in the control group.

The absolute neutrophil and absolute lymphocyte values of those with clinical NS, which were obtained from patient files, were proportioned to obtain an NLR value. From the whole blood count data, the White blood cell (WBC) and Platelet (PLT) counts, Mean Platelet Volume (MPV), Haemoglobin (HB), CRP and IL-6 values were recorded. The NLRs obtained from the data were then compared with demographic characteristics, other infection parameters and mortality relationships in both groups.

Hemogram measurements were performed using a Cell-Dyn 3700 automatic haemocytometer (Abbott, II.). CRP levels were measured on a Roche Modular P analyser (Roche kit, Roche Diagnostics, Mannheim, Germany) using a Tina-quant CRP (Latex) high sensitivity turbidimetric assay in line with the manufacturer's instructions. IL-6 levels were measured on an IMMULITE 2000 analyser (Siemens Diagnostic Product Corporation, Los Angeles, CA) using an IL-6 solid phase chemiluminescent enzyme immunometric assay.

The SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages and continuous measurements as means and standard deviations (as medians and minimums-maximums when necessary). Chi-square and Fisher Exact tests were used for comparisons of categorical propositions. Parameters studied were tested for normal distribution using the Kolmogorov-Smirnov test. In paired group analyses, independent samples t-test was used for parameters showing normal distribution and Mann Whitney-U test for parameters not showing normal distribution. Based on the mortality variable of the patients in the sepsis group, the sensitivity and specificity values of NLR were calculated and a cut-off value was found based on the area under the ROC curve. Statistical significance was set at 0.05 in all tests.

RESULTS

The number of patients who were born by way of a caesarean section was higher in the NS group (Table 1, p<0.001). The two groups did not differ significantly with respect to gender, mother's age, birth week or birth weight (Table 1, p>0.05).

Table 1. Demographic characteristics of patients

	Sepsis (n=85)	**Control (n=85)**	**p[b]**
	n (%)	**n (%)**	
Delivery type			
Caesarean section	44 (51,8)	20 (23,5)	**<0.001***
Gender			
Male	45 (52,9)	45 (52,9)	1.000
	Sepsis (n=85)	**Control (n=85)**	**p[a]**
	Mean±SD	**Mean±SD**	
Mother's age	27.5±6.2	27.6±6.2	0.823
Birth week	36.9±2.1	35.6±4.5	0,346[,a]
Birth weight	1966±634.1	2080±891.5	0,567[,a]

**p<0,001, a: Mann Whitney u test, b: Chi-square & Fisher exact test*

The patients in the NS group had statistically significantly higher Neutrophil (p=0,005), NLO (p<0,001), haemoglobin (p<0,001), CRP (p<0,001), IL-6 (p=0,004), Platelet (p=0,001), and MPV (p=0,002) values, and a lower Lymphocyte (p=0.010) value than the control group (Table 2, p<0.05).

Table 2. Laboratory parameters of the sepsis and control groups

	Sepsis (n=85)	**Control (n=85)**	**p**
Neutrophils	7.6±4.7	6.1±5.2	**0,005**[,b]**
Lymphocytes	4.49±1.7	7.5±6.8	**0,010*[,b]**
NLR	1.82±1.1	1.3±1.5	**<0,001**[,b]**
WBC	13.1±5.6	13.7±8.5	0,493[b]
HB	17.8±2.2	16.4±2.6	**<0,001**[,a]**
Plt	259.100±75.300	219.100±84.800	**0,001**[,a]**
MPV	8.15±0.7	7.75±0.9	**0,002**[,a]**
CRP	20.1±27.7	1.57±1.7	**<0,001**[,b]**
IL-6	108.5±230.7	13.7±10.3	**0,004**[,b]**

**p<0,05; **p<0,001 a: Independent samples t-test; Mean±SD, b: Mann Whitney u test*

NLR: Neutrophil Lymphocyte Ratio, WBC: white blood cells, HB: haemoglobin, Plt: platelet count, MPV: mean platelet volume, CRP: C-reactive protein, IL-6: interleukin-6

In the sepsis group of patients, 75 (89,3%) had respiratory distress syndrome, 14 (16,7%) a twin sibling, 2 (2,4%) Intrauterine Growth Retardation, 5 (6,0%) Preeclamptic Mother Baby, 11 (13,1%) Intracranial Haemorrhage, 1 (1,2%) Early Membrane Rupture, and 7 (8,3%) Necrotizing Enterocolitis (Figure 1).

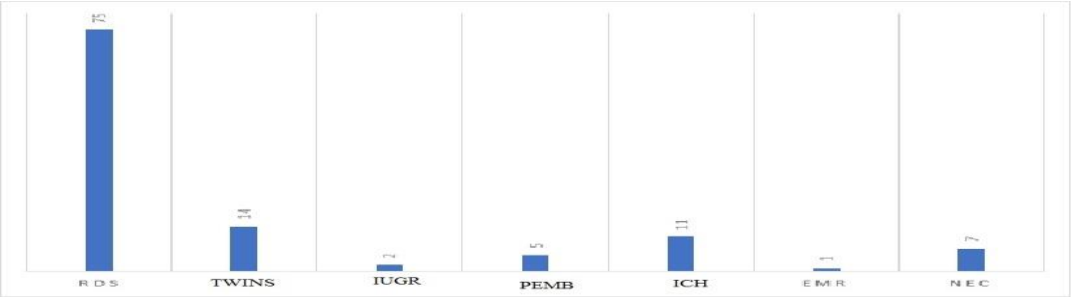

Figure 1. Values of variables in sepsis group

RDS: respiratory distress syndrome, IUGR: intrauterine growth restriction, PEMB: preeclamptic mother's baby, ICH: intracranial hemorrhage, EMR: early membrane rupture, NEC: nectorizing enterocolitis.

The patients in the sepsis group had 43.5% Staphylococcus epidermidis growth and 17.6% Klebsiella pneumoniae growth in their blood cultures. In Table 3, the diagnostic testing performance of the NLR values of the patients in the sepsis group was reviewed with respect to mortality using the ROC Curve test. The analysis showed that the NLR diagnostic testing performance of the patients in the late-onset NS group was not statistically significant (Table 3, P<0.05).

Table 3. Diagnostic testing performance of patients' NLR values with respect to mortality

	NLR-Mortality relationship
AUC 95%-Cl (%)	0.502 (0.391-0.613)
Cut-off	>0.73
Sensitive (%) 95%-Cl (%)	76.56 (64.3-86.2)
Spesitive 95%-Cl (%)	5.0 (0.1-24.9)
PPV 95%-Cl (%)	72.1 (68.5-75.3)
NPV 95%-Cl (%)	6.3 (0.9-32.1)
p	0.977*

**p<0.05*
AUC: Area Under Curve, PPV: Pozitive Predictive Value, NPV: Negative Predictive Value

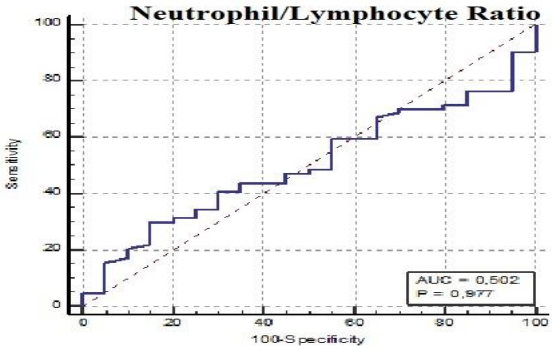

Figure 2. Receiver operating characteristic (ROC) curves used to predict NLR-mortality relationship

DISCUSSION

NS is one of the major serious diseases that threaten life throughout the neonatal period. Globally, 2.76 million children died in their newborn period and 15.2% of these deaths was due to NS in 2015 (Mukhopadhyay-Puopolo, 2012). Early diagnosis of NS is critical for initiation therapeutic

interventions, which has been shown to reduce life-threatening serious complications and mortality rates. At present, criteria for NS diagnosis are mostly based on clinical symptoms, but these symptoms are not specific (Mukhopadhyay-Puopolo, 2012). Growth in blood culture is the gold standard for the diagnosing NS, but obtaining the results takes at least 48 hours. Moreover, blood culture may be affected by many factors such as giving concurrent antimicrobial treatment to the mother, drawing insufficient volume of blood and contamination, and may turn out to be insensitive (Iroh Tam-Bendel, 2017). Due to these negative factors, identifying new fast, accurate and specific biomarkers is thought to be of critical importance.

Some studies have shown that increases in MPV are associated with NS. An increase in MPV shows that the amount of young platelets in circulation has increased because platelets become smaller in size as they get older, which suggests that platelet production and/or platelet degradation has increased (Castle-Patriek, 1990;Becchi et al., 2006). Some researchers have argued that MPV may be useful as an indicator of invasive bacterial infections and septicaemia (Van der Lelie-Van Dem Barae, 1983). In a study investigating the relationship between MPV and NS, the MPV values were found significantly higher in evidenced sepsis cases than in clinical sepsis cases (Oncel et al., 2012). Consistent with other studies, our study has also shown that MPV values were significantly higher in evidenced late-onset NS.

Late onset bloodstream infections in neonates may be hospital or community acquired after birth with highest incidence between postpartum day 10 and 22 (Vergnano et al., 2011;Boghossian et al., 2013). These infections are more likely to be coagulase-negative staphylococci (CNS) such as Staphylococcus epidermidis are the most common (53.2-77.9%) microorganisms found in blood cultures (Dong-Speer, 2015). Consistent with other studies (Bizzarro MJ, 2015, Dong Y, 2014), the late onset NS patients in our study mostly had Staphylococcus epidermidis growth (43.5%) in their blood cultures.

NLR reflects changes in the numbers of neutrophils and lymphocytes. NLR has been seen as a new risk factor that can be used in the diagnosis of NS. Sepsis has been shown to result in increased amounts of neutrophils and decreased amounts of lymphocytes due to pathogenic microorganism infections; thus, sepsis patients may have a higher NLR (Drewry et al., 2014;Shen et al., 2017). Studies have reported that NLR may be a useful early marker for NS and cases with increased NLRs may be at greater risk of poor prognosis (Ni et al., 2019, Alkan et al., 2018). As in other studies, the relationship between NLR and NS was also observed to be statistically significant in our study.

Our study has various limitations. One of them is that the sample studied was relatively large. Moreover, NLR was measured only at a single point in time. We think that a series of NLR measurements and its variations in neonatal sepsis will provide more information about the relationship between them and be useful for more detailed investigation of the dynamic correlation between them. There is a need for further studies with larger samples and a series of NLR measurements to show the relationship between NLR and mortality.

The present study has shown that there is a significant association between NLR and presence of NS. The results have shown that NLR has a potential value in prediction of neonatal sepsis risk. The analyses performed in our study led to a conclusion that NLR has no effect in predicting mortality.

Conflict of interest

The authors report no actual or potentialconflicts of interest.

Funding

This study did not receive any specific grant or funding.

Authors Contributions

Plan, design: HD; Material, methods and data collection: HD; Data analysis and comments: HD; Writing and corrections: HD

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