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Assessment of Micro-R/Macro-R values and other hemogram parameters for the diagnosis of early neonatal sepsis

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ABSTRACT

Aim: Neonatal sepsis is a systemic condition that results in hemodynamic and clinical findings. We aimed to determine the role of hemogram parameters in the diagnosis of early neonatal sepsis.

Material and Method: This retrospective study was conducted with 126 neonates hospitalized in Kastamonu Training and Research Hospital Neonatal Intensive Care Unit between March 2018 to March 2022. There were 65 term neonates diagnosed with early neonatal sepsis in the patient group. In the control group, there were 61 term neonates who underwent hemogram within the first 72 hours (postnatal period) due to physiological jaundice and did not receive any antibiotic treatment. The assessment was made by comparing the hemogram parameters of these groups.

Results: The Macro-R value, white blood cell count, absolute neutrophil count, monocyte count, immature erythrocyte count and percentage, immature granulocyte count and percentage and neutrophil-lymphocyte ratio were found to be significantly higher in the patient group than in the control group ($p<0.05$). Macro R, white blood cell count, absolute neutrophil count, immature erythrocyte count and percentage, immature granulocyte count and neutrophil/lymphocyte ratio had high sensitivity and specificity for the diagnosis of early neonatal sepsis.

Conclusion: We think that these simple and easily accessible parameters have potential value in the diagnosis of ENS if they are used together with the clinical symptoms of ENS.

Keywords: Early neonatal sepsis, Macro R, immature granulocyte

INTRODUCTION

Neonatal sepsis is a systemic condition that results in hemodynamic and clinical findings due to viral, bacterial or fungal causes. It causes significant morbidity and mortality and is the third leading cause of neonatal death after prematurity and delivery complications (1,2). In fact, according to a large-scale meta-analysis study, the mortality rate due to sepsis in neonates is 15% (3).

The term of early neonatal sepsis (ENS) is used for sepsis cases in which clinical signs appear in the first 72 hours of life. Its incidence is 1-5 per 1000 live births (4,5). Fetal distress, low APGAR score and postnatal neonatal resuscitation are among the main causes that increase the risk of ENS (6).

The clinical findings of neonatal sepsis constitute a very broad picture, none of which is specific to sepsis. This makes the early diagnosis of ENS very difficult. The gold standard method used for diagnosis is blood culture. However, besides the low positivity rate of this method, its late results cause the treatment to be delayed (7). For this reason, many studies have been carried out on laboratory tests that are easily accessible, will give rapid results and enable the early diagnosis of ENS but no definitive laboratory test has yet been found.

In our study, we aimed to determine the effects of hemogram parameters such as Micro-R, Macro-R, immature granulocyte (IG), neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), which are easily accessible and fast-resulting laboratory tests in the early diagnosis of ENS. We also aimed to contribute to the literature with our findings.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 09.03.2022, Decision No: 2022-KAEK-29). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study was conducted with 126 neonates hospitalized in Kastamonu Training and Research Hospital Neonatal Intensive Care Unit between March 2018 and March 2022. In the patient group, there were 65 term neonates diagnosed with early neonatal sepsis by detecting growth in the blood culture in the first 72 (postnatal) hours. In the control group, there were 61 term neonates who underwent hemogram within the first 72 hours of the postnatal period due to physiological jaundice and who did not receive any antibiotic treatment.

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Neonates without hemogram data at the time of first admission were excluded from the study. Demographic data and data on laboratory tests were accessed through the hospital information system. Pre-treatment hemogram parameters belonging to the first admission time of the patients were calculated with an automatic hematological analyzer (XN-1000-Hematology-Analyzer-Sysmex Corporation, Japan). The Micro-R, Macro-R, NLR, IG and other hemogram parameters of the two groups were compared.

Statistical Analysis

Data were analyzed with the "Statistical Package for Social Sciences 25.0 for Windows" (SPSS Inc., Chicago, USA). In descriptive statistics, categorical variables were expressed as numbers and percentiles. Numerical variables were expressed as median (25 Percentiles, 75 Percentiles) values. Since the results did not show normal distribution, Mann Whitney U test was performed to compare the data between the patient and control groups. The chi-square test was used to determine whether there was a significant difference in terms of demographic data. The independent t test was performed to determine whether there was a significant difference between the PLR and NLR measurements.

Area Under Curve (AUC), cut-off, sensitivity and specificity values were determined by Receiver Operating Characteristic (ROC) analysis and Youden's index was used. A value of $p<0.05$ was considered statistically significant. G*Power Version 3.1.7 was used for calculating the power level and effect size of the study. Accordingly, it was determined that the study had a power of 90% and an effect size of around 0.45.

RESULTS

In our study, there was no statistically significant difference between the demographic data of the patient (n=65) and control (n=61) groups. (p>0.05) (Table 1).

Table 1. Demographic data of the patient and control groups

	Patient Group	Control Group	p
Gender n (%)			0.865
Boy	41 (63.1)	38 (62.2)	
Girl	24 (36.9)	23 (37.8)	
Type of Delivery			0.822
C/S n (%)	55 (84.6)	51 (83.6)	
NSVY n (%)	10 (15.4)	10 (16.4)	
Gestational Week	39.06±1.22	38.73±1.27	0.605
Birth weight (grams)	3080.16±420.92	3065.64±437.08	0.724

* Chi square test

There was a significant difference between the groups in terms of Macro-R, white blood cell (WBC) count, immature erythrocyte (NRBC) count and percentage, absolute neutrophil count (ANC), monocyte count and IG count and percentage ($p<0.05$). The hemogram parameters of the groups were compared in Table 2.

Our data showed that there was a significant difference (t= -4.32, p=0.01) between the groups in terms of NLR rate. Accordingly, the NLR rate in the patient group was significantly higher than in the control group. There was no significant difference between the groups in terms of PLR rate (t=-1.12, p=0.26).

ROC curve analysis of cut-off values of hemogram parameters was determined to predict the diagnosis of early neonatal sepsis (Figure 1). ROC curve analysis results of hemogram parameters that have specific importance in predicting the diagnosis are shown in Table 3.

Table 2. Comparison of hemogram parameters of the control and patient groups

	Median (IQR)		p
	Control (n:61)	Patient (n:65)	
WBC	11.43 (9.93; 15.06)	16.7 (14.8; 21.8)	<0.001*
MCV	97.7 (93.5; 103.5)	101.3 (97.6; 105.8)	0.16
MCHC	34.9 (33.6; 36.1)	34.1 (32.6; 35.2)	0.31
RDW_SD	57.6 (51.8; 63.3)	60.4 (57.5; 67.1)	0.10
RDW_CV	15.7 (14.8; 17.2)	16.7 (15.8; 18.6)	0.13
PDW	10.0 (9.1; 10.9)	10.7 (9.6; 11.7)	0.34
NRBC	0.01 (0.00; 0.13)	0.10 (0.01; 1.25)	0.007*
NRBC%	0.1 (0.00; 0.67)	0.50 (0.15; 7.3)	0.013*
NEUT	4.37 (2.76; 8.68)	10.36 (7.09; 14.6)	<0.001*
MONO	1.46 (1.03; 1.79)	1.78 (1.27; 2.28)	0.017*
NEUT%	40.2 (27.2; 58.8)	59.8 (44.5; 68.7)	0.001*
LYMPH%	43.7 (27.2; 53.8)	28.9 (18.9; 34.7)	0.001*
EOS%	3.25 (1.47; 5.12)	1.9 (0.95; 3.4)	0.028*
IG	0.11 (0.06; 0.28)	0.30 (0.19; 0.86)	0.001*
IG%	1.0 (0.6; 2.02)	2.0 (1.0; 4.0)	0.006*
MacroR%	8.3 (5.3; 13.3)	12.5 (8.7; 17.6)	0.009*
Micro R%	1.7 (1.3; 2.5)	1.4 (1.1; 1.9)	0.67

*Mann Whitney U test WBC: Wight blood cell, MCV:Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin consantration, RDW: Red cell distribution width, PDW: Platelet distribution width, NRBC:Nucleated red blood cell, NEUT: Nötrophil, MONO: Monocyte, LYMPH: Lymphocyte, EOS: Eosinophil, IG: Immature granulocyte

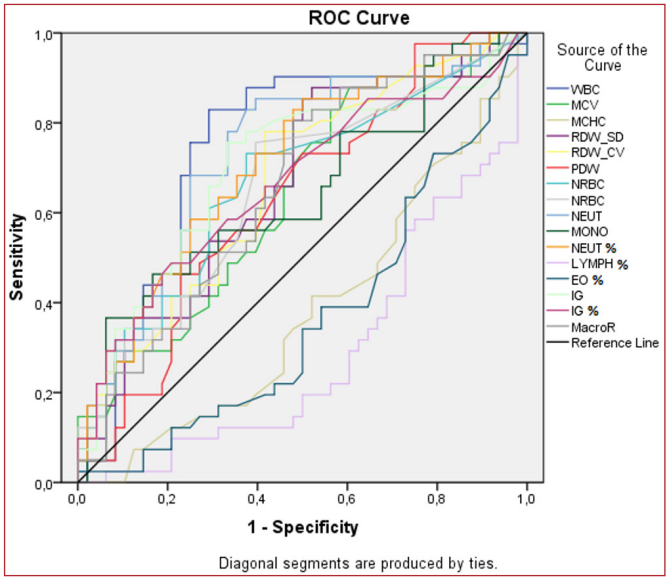

Figure 1. ROC curve analysis of the hemogram parameters of neonates with ENS

Table 3: ROC curve analysis of the hemogram parameters of neonates with ENS

	Cut-off	AUC	95% CI	p	Sensitivity %	Specificity %
WBC	14.4	.746	0.63-0.85	.000	82	70
MCV	96.6	.637	0.52-0.75	.027	87	39
RDWSD	55.2	.666	0.55-0.77	.007	87	47
RDWCV	15.7	.670	0.55-0.78	.006	78	58
PDW	10.05	.631	0.51-0.74	.034	73	50
MacroR	7.75	.655	0.54-0.76	.012	80	50
NRBC#	0.35	.668	0.55-0.78	.007	73	62
NRBC%	0.15	.658	0.54-0.77	.031	75	60
NEUT#	5.43	.733	0.62-0.84	.000	85	60
NEUT%	40.1	.709	0.60-0.81	.001	85	50
IG#	0.19	.701	0.58-0.81	.001	75	66
IG%	2.15	.664	0.54-0.77	.008	48	79
NLR	1.17	.698	0.53-0.79	.014	71	69

DISCUSSION

Neonatal sepsis causes an average of 1.5-2 million infant deaths per year (8). By using a sensitive and specific diagnostic test, it is possible to reduce treatment delays and prevent incorrect treatments. In this way, ENS-related outcomes can be improved (9). In our study, we examined the changes in hemogram parameters, which is a simple and easily accessible diagnostic test for ENS. Accordingly, we concluded that the Macro-R value, WBC, NRBC count and percentage, ANC and monocyte count, IG count and percentage, and NLR were significantly higher in neonates diagnosed with ENS than in neonates who did not diagnosed with ENS.

We found that WBC and ANC were significantly higher in the patient group compared to the control group. Consistent with our study, Yorulmaz et al. (10) concluded that the WBC and ANC were significantly higher in neonates with ENS. Similarly, Yalınbaş et al. (11) stated that high levels of WBC and ANC were associated with ENS. On the other hand, Smith et al. (12) reported that low WBC and ANC might be associated with ENS. Saboohi et al. (13) also stated that low WBC and ANC were important findings that could be used in the diagnosis of ENS. Philip et al. (14) concluded that WBC<5000/mm³ had 94% specificity and 50% sensitivity for the diagnosis of ENS. All these results made us think that low or high WBC and ANC alone may not be sufficient data for the diagnosis of ENS.

IG in peripheral blood means active bone marrow response against bacterial infections (15). In our study, we found that the IG count and percentage was significantly higher in neonates in the patient group than in the control group. We concluded that IG count above 0.19 cut-off value and IG percentage above 2.15 cut-off value had high sensitivity and specificity in predicting the diagnosis of ENS. Gungor et al. (16) determined that an increase in the percentage of IG was a strong finding in the prediction of serious bacterial infection. However, they found that the 0.35 cut-off value for the IG percentage had a sensitivity of 75.4% and a specificity of 76% in predicting the diagnosis of ENS. According to these results, we think that the presence of findings suggestive of sepsis in the neonates and an increase in the count or percentage of IG in the blood may be a warning for ENS.

According to different studies (17,18), the increase in the NRBC count and percentage is strong evidence that the neonate has gone through hypoxia. In our study, we found that the NRBC count and percentage was significantly higher in the neonates with ENS. In our opinion, this finding shows that a neonate with ENS may experience a hypoxic process with infection.

Macro-R is the hemogram parameter that shows the percentage of microcytic erythrocytes with sizes larger than 120fL in peripheral blood. Meanwhile micro-R indicates the percentage of microcytic erythrocytes smaller than 60fL. These parameters, which are new in use, are often used to narrow down the etiologies of anemia (19). In our study, we demonstrated that the Macro-R values of neonates in the patient group were significantly increased compared the control group. Also we determined that there was no significant difference between the groups in terms of Micro-R values. Based on this finding, we think that the risk of anemia and jaundice may be higher in newborns with ENS, since the production of macrocytic erythrocytes in the bone marrow is increased in newborns with ENS and these erythrocytes are more sensitive to hemolysis.

Neutrophils play an important role in the host's immune response in acute and chronic infections. This is thought to be a simple indicator of the NLR inflammatory response (20). Zhang et al. (21) concluded that C-reactive protein (CRP), procalcitonin and NLR values were significantly higher in neonates with sepsis. Accordingly, they stated that NLR was more specific and sensitive than CRP in predicting ENS. Similarly, Alkan et al. (22) demonstrated that NLR was significantly higher in neonates with proven sepsis compared to neonates with suspected sepsis and NLR was a more reliable parameter than CRP in predicting sepsis. Can et al. (23) stated that the high NLR was significant in neonates with ENS and expressed the 6.76 value as the cut-off value. In accordance with the literature, we found that the NLR value was significantly higher in neonates with ENS than in the control group. However, we concluded that if the NLR value of 1.17 was taken as the cut-off value, it had a sensitivity of 71% and a specificity of 69% in the prediction of ENS.

Our study has several limitations. First of these is that our study was conducted retrospectively. The lack of knowledge of neonates' exposure to any antibiotic in the antepartum period and maternal risk factors that may affect hemogram parameters are the other main limitations of the study. Other limitations are that our study was conducted in a single center and the patient group was small..

CONCLUSION

We demonstareted that Macro-R, WBC count, ANS, NRBC, IG and NLR were significantly higher in neonates with ENS compared to neonates in the control group. We also demonstrated that these parameters had sufficient sensitivity and specificity for predicting the diagnosis of ENS. We think that these simple and easily accessible parameters have potential value in the diagnosis of ENS if they are used together with the clinical symptoms of ENS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 09.03.2022, Decision No: 2022-KAEK-29).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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