The role of the complete blood cell count and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in newborn infection

Inbox ×

Asian Biomedicine <em@editorialmanager.com>
to me

Tue, Apr 27, 8:20 PM

Dear Dr. Utomo,

I would be very grateful if you would review a manuscript entitled "The role of the complete blood cell count and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in newborn infection" for Asian Biomedicine.

If not, I would be grateful if you would recommend alternative reviewers who could.

The abstract is as follows:
Background: The peripheral blood cells and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio is an simple suggestible biological marker that has been reported to show disease severity in different disease.
Objective: The aim of this study was to determine the diagnostic importance, specificity and sensitivity of peripheral blood cells and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in neonatal infections and discriminating between different patient groups.
Methods: The study consisted of newborn patient group and control group. The study consisted of 232 newborns patients between 2016-2018 years with the diagnosis and suspicion of infection.
Sensitivity, specificity and likelihood ratio of the these characteristics were calculated by using the Receiver Operating Characteristic Curve analysis.
Results: Neutrophil to lymphocyte ratio was higher in patients with neonatal sepsis than in other patients. Neutrophil to lymphocyte ratio was statistically significant in the neonates who were diagnosed with neonatal sepsis and fever only due to dehydration and/or poor feding (p<0.001). Lymphocyte to monocyte ratio was statistically significant in neonatal sepsis and neonates with viral infection (p=0.003).
Conclusions : Neutrophil to lymphocyte ratio may be useful in the diferential diagnosis of neonatal sepsis from other newborn with infection.

I note your expertise in the field. Would you please help us to get this manuscript suitably reviewed?

If you accept to review this manuscript, please click this link: https://www.editorialmanager.com/abm/l.asp?i=72514&l=ZX6HFPQU *

If you decline to review this manuscript, please click this link: https://www.editorialmanager.com/abm/l.asp?i=72515&l=SA7D1W3G *

If this links above do not work, please go to https://www.editorialmanager.com/abm/. Your User Name is Martono Utomo and your password: https://www.editorialmanager.com/abm/l.asp?i=72516&l=EI20FXA2.

The manuscript reference is ABM-D-19-00260R2.

The quality of our journal depends on good reviewing, so I hope you can help with the process. Ideally, I would appreciate receiving your review in 21 days. However, I can offer you more time if needed. You may submit your comments online at the URL indicated above. There you will find spaces for confidential comments to the editor, comments for the author and a report form to be completed.

With best regards,

Robin James Storer, PhD
Coeditor in chief

Thank you for agreeing to review

Inbox ×

Asian Biomedicine <em@editorialmanager.com>
to me

Tue, Apr 27, 8:26 PM

May 18 Tue

Review Due
When Tue May 18, 2021 (CST)
Who Asian Biomedicine*
Add to calendar »

Agenda
Tue May 18, 2021
No earlier events
All day Review Due
No later events

Dear Dr. Utomo,

Thank you for agreeing to review manuscript ABM-D-19-00260R2 for Asian Biomedicine.

I am grateful that you will review a paper entitled "The role of the complete blood cell count and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in newborn infection" for our journal and appreciate your expertise.

To download the paper now, please click this link: https://www.editorialmanager.com/abm/l.asp?i=72519&l=QEEI2VX1 *

I would appreciate receiving your review by May 18, 2021. Please let me know if you require an extension.

You may submit your comments online at https://www.editorialmanager.com/abm/. Your User Name is Martono Utomo and your password: https://www.editorialmanager.com/abm/l.asp?i=72520&l=BM50U3NA.

You can also submit your comments using this link: https://www.editorialmanager.com/abm/l.asp?i=72521&l=HGXMPGZG

There you will find spaces for confidential comments to the editor, comments for the author and a report form to be completed.

With kind regards,

Robin James Storer, PhD
Coeditor in chief
Asian Biomedicine

*If clicking the link above does not open an Editorial Manager window, your email program may have inserted some spaces and/or line markers into the link. Please open a browser window manually and copy and paste the entire link from the email into the url address box. The link starts with the letters "http" and ends with the letters "rev=X" (where X represents a number such as 0,1,2, etc.) Note that the end of the link may be shown on a different line in this email, and may be shown in a different color than the beginning of the link. The entire link must be copied and pasted into the browser in order for the correct Editorial Manager window to be displayed. After copying the link into the url address box, you must also remove any spaces and line markers (e.g. > or >>) by using the delete or backspace keys on your keyboard.

Thank you for the review of ABM-D-19-00260R2

Inbox ×

Asian Biomedicine <em@editorialmanager.com>
to me

Mon, May 3, 8:43 PM

Ref.: Ms. No. ABM-D-19-00260R2
The role of the complete blood cell count and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in newborn infection
Asian Biomedicine

Dear Dr. Utomo,

Thank you very much for taking time to review this manuscript. We are very grateful for your expert opinion.

You can access your review comments and the decision letter (when available) by logging onto the Editorial Manager site at:

https://www.editorialmanager.com/abm/
username: Martono Utomo
password: https://www.editorialmanager.com/abm/l.asp?i=73336&l=BZWG1ZP8

Kind regards,

Robin James Storer, PhD
Coeditor in chief
Asian Biomedicine

Asian Biomedicine

The role of the complete blood cell count and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in newborn infection

--Manuscript Draft--

Manuscript Number:	ABM-D-19-00260R2
Full Title:	The role of the complete blood cell count and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in newborn infection
Article Type:	Brief Communication
Keywords:	Infection, neutrophil, lymphocyte, monocyte, sepsis, newborn
Manuscript Region of Origin:	TURKEY
Abstract:	Background: The peripheral blood cells and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio is an simple suggestible biological marker that has been reported to show disease severity in different disease. Objective: The aim of this study was to determine the diagnostic importance, specificity and sensitivity of peripheral blood cells and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in neonatal infections and discriminating between different patient groups. Methods: The study consisted of newborn patient group and control group. The study consisted of 232 newborns patients between 2016-2018 years with the diagnosis and suspicion of infection. Sensitivity, specificity and likelihood ratio of the these characteristics were calculated by using the Receiver Operating Characteristic Curve analysis. Results: Neutrophil to lymphocyte ratio was higher in patients with neonatal sepsis than in other patients. Neutrophil to lymphocyte ratio was statistically significant in the neonates who were diagnosed with neonatal sepsis and fever only due to dehydration and/or poor feding ($p<0.001$). Lymphocyte to monocyte ratio was statistically significant in neonatal sepsis and neonates with viral infection ($p=0.003$). Conclusions : Neutrophil to lymphocyte ratio may be useful in the diferential diagnosis of neonatal sepsis from other newborn with infection.
Response to Reviewers:	Answers for Editor's comments: *The text was revised according to based on the STARD guidelines. * The abstract was revised according to reviwer and STARD recommendations. *The manuscript was revised according to Auther guidelines (especially sections 7 and 8). Answers for Reviewer' comments: INTRODUCTION *Manuscript was revised according to reviwer recommendations. *The aim of study was clearly explained. *Previously study reported that NLR has been increased more culture positive sepsis tna negative sepsis. There are very few studies on this subject in newborns. *I have written a few sentences about the hematological changes of the newborn. Physiological changes occur in the peripheral blood cells in newborns in the first few days of life. Normally, the neutrophil count increases in this period and decreases afterwards. Infectious diseases of the newborn may have contributed to this physiological changes. The decrease in neutrophil count may be related to the normal physiological response or another disorder (such as infection). Really, this also can be difficult to interpret. There is an increase in the number of studies on this subject. METHODS *I revised methods section. *Blood samples and blood cultures were taken from all newborns immediately after hospitalization. *In this study, the first blood results during hospitalization were used for evaluation diagnostic. *Patient information was obtained from the hospital electronic record system. *All newborn suspected of infection were included in the study. *The control group consisted of newborns who stay in the birth room after delivery or refer to the outpatient department, with a whole blood count result for any reason, but

	without any disease signs and symptoms according to on the history, physical examination or tests, and who were accepted as normal/healthy. *I want to clarify what is the reference standard that was used to calculate the sensitivity and specificity and the AROC curves? Is it culture confirmed sepsis? **Unfortunately, no assessment has been made. Patients with neonatal sepsis were divided into early onset sepsis and late onset sepsis. And the assessments were made accordingly. *In the ROC curve, there are points corresponding to various combinations of sensitivity and 1-specificity values. Since both the sensitivity and the specificity of the test to be high, the selected cut-off value should be the lowest 1-specificity point versus the highest sensitivity value. One way to find this point is to calculate likelihood ratio (LR). The cut-off limit of the maximum value for LR was found From the obtained coordinates table and the calculation was made from “LR = sensitivity / (1-specificity)” formula. *The comparison of the numerical data with the control group was evaluated by the Independent T test and the Mann-Whitney U test. Mann Whitney U test was used for non parametric conditions. T test was used for parametric conditions. Chi-square Fisher exact test was used to evaluate categorical data. RESULTS AND DISCUSSION *The LMR and NLR are higher in the neonatal sepsis vs the other groups, but the viral infection group and the fever with no infection group have a high ratio. Could this be due to time of sample collection? Please discuss in the revised Discussion **There was no seasonal difference in patients with viral infection and fever compared to other diseases. This was stated in the discussion. *Table 5. What is the comparison for the p values reported in table 5 - there appears to be no reference group to which the AROC values are compared. Or is it a test of whether the AROC is significantly better (or in the case of some parameters, worse) than chance? **The values compared here are statistically significant. P values are given in tables 3 and 4. The results of the ROC analysis of the values that are significant here are given in Table 5. *Table 3 and 4 results are given as median ± IQR.

THE ROLE OF THE COMPLETE BLOOD CELL COUNT AND NEUTROPHIL TO LYMPHOCYTE, LYMPHOCYTE TO MONOCYTE AND PLATELET TO LYMPHOCYTE RATIO IN NEWBORN INFECTIONS

Abdullah Kurt M.D.[a], Merve Sezen Tosun M.D.[b], Nilgün Altuntaş M.D.[c]

[a] **Professor Dr**, Department of Pediatrics Division of Neonatology, Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkey. E-mail: drabdullahkurt@yahoo.com

[b]**Assistant doctor**, Department of Pediatrics, Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkey. Orcid ID: 0000-0001-7033-2690, E-mail: mervesezenn@gmail.com

[c]**Associate professor**, Department of Pediatrics Division of Neonatology, Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkey. Orcid ID: 0000-0002-1478-7786, E-mail: nilgunaltuntas@hotmail.com

Running head: Neonatal infections and complete blood cell

Article category : Brief communication

Number of Authors:3, Number of Words:2360, Number of Tables;5, Number of Figures;3, Number of References:30.

- Approval was obtained from the **local ethics committee** for the study
- **Conflict of Interest**: No conflict of interest was declared by the authors.
- **Financial Disclosure**: The authors declared that this study has received no financial support.

Corresponding author
Prof Dr Abdullah Kurt M.D.
Department of Pediatrics Division of Neonatology, Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Yeni Batı Mah. 2026 cad. 2367 sokak No:4 Batıkent Yenimahalle
Ankara, Turkey.
Orcid ID:0000-0002-4430-444X
Phone: +90 312 587 20 00
My phone : 90 533 331 73 29
Fax: +90 312 587 37 75
E mail-1: abdullahkurt@ybu.edu.tr
E mail-2: drabdullahkurt@yahoo.com

ABSTRACT

Background: The peripheral blood cells and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio is an simple suggestible biological marker that has been reported to show disease severity in different disease.

Objective: The aim of this study was to determine the diagnostic importance, specificity and sensitivity of peripheral blood cells and neutrophil to lymphocyte, lymphocyte to monocyte and platelet to lymphocyte ratio in neonatal infections and discriminating between different patient groups.

Methods: The study consisted of newborn patient group and control group. The study consisted of 232 newborns patients between 2016-2018 years with the diagnosis and suspicion of infection.

Sensitivity, specificity and likelihood ratio of the these characteristics were calculated by using the Receiver Operating Characteristic Curve analysis.

Results: Neutrophil to lymphocyte ratio was higher in patients with neonatal sepsis than in other patients. Neutrophil to lymphocyte ratio was statistically significant in the neonates who were diagnosed with neonatal sepsis and fever only due to dehydration and/or poor feding ($p<0.001$). Lymphocyte to monocyte ratio was statistically significant in neonatal sepsis and neonates with viral infection ($p=0.003$).

Conclusions: Neutrophil to lymphocyte ratio may be useful in the diferential diagnosis of neonatal sepsis from other newborn with infection.

Key-words: Infection, neutrophil, lymphocyte, monocyte, sepsis, newborn

INTRODUCTION

Neonatal sepsis is one of the causes of mortality and morbidity of the newborns in the first month of life (1, 2). The diagnosis of neonatal sepsis is defined by evaluating with the clinical

and laboratory findings. Although the blood culture is the gold standard for the diagnosis of neonatal sepsis, it is a disadvantage for early diagnosis that the culture results cannot be taken before 24-48 hours and false negative and positive results can be obtained. The diagnosis of neonatal sepsis are used in various laboratory biomarkers such as interleukins (IL), tumor necrosis factor (TNF), C-reactive protein (CRP), procalcitonin (PCT) and immunoglobulins (3, 4). One of the important causes of infection risk in neonates is the qualitative and quantitative deficiency of neutrophils. Neutropenia associated with neonatal sepsis adversely affects prognosis (2, 5, 6, 7, 8, 9). Záhorec et al (10) recommended use of the neutrophil lymphocyte count ratio (NLR) for the first time as a marker of infection (4). In adult recent study by Loonen et al (11) reported that NLR had a diagnostic characteristic in the patients with culture-positive sepsis compared to patients without (culture negative or clinical sepsis). Loonen et al (11) show that the NLR was a mean of 23.0 ± 15.0 in patients with positive blood cultures and in the group with negative cultures was a mean of 12.2 ± 9.1 [($p < 0.001$) (AUC values for the NLR was 0,770 (95% CI 0.662–0.879)]. They reported that NLR might be promising, rapid outcome (11). In a adult Jager et al (12) reported that significant differences between patients with positive and negative blood cultures were detected with respect to the NLR (20.9 ± 13.3 vs. 13.2 ± 14.1; $P < 0.0001$). Also sensitivity, specificity, positive and negative predictive values were highest for the NLCR (77.2%, 63.0%, 67.6% and 73.4%, respectively and AUC values for the NLR (0.73; 0.66 to 0.81). Jager et al (12) suggested that NLR is a better predictor of bacteremia than CRP, white blood cell count (WBC) and neutrophil count (12). In later studies, peripheral blood count parameters were used in the diagnosis and prognosis of many different disease groups (13, 14). Physiological changes occur in the peripheral blood cells in newborns in the first few days of life (15, 16). Normally, the neutrophil count increases in this period and decreases afterwards (15, 16). Infectious diseases of the newborn may have contributed to this physiological changes. The decrease in neutrophil count may be related to the normal

physiological response or another disorder (such as infection). The aim of this study was to determine the diagnostic importance, specificity and sensitivity of peripheral blood cells and NLR, lymphocyte to monocyte (LMR) and platelet to lymphocyte ratio (PLR) in neonatal infections.

METHODS

Study design

*Patients:*The study consisted of patients who were admitted to neonatal intensive care unit (NICU) of the Ankara Yıldırım Beyazıt University Yenimahalle Training and Research Hospital between 2016-2018 years with the diagnosis and/or suspicion of infection. Patient information was obtained from the hospital electronic record system. The study was performed retrospectively. Postnatal age, gender, birthweight, gestational week, and hospital stay were recorded. Peripheral complete blood count (CBC) parameters (WBC, lymphocyte, monocyte, neutrophil, platelet count), CRP, culture (blood, urine) results were examined during the hospitalization. Neutrophil: lymphocyte, lymphocyte:monocyte and platelet:lymphocyte ratios were calculated. The study consisted of newborn patient group and control group. The control group consisted of newborns who stay in the birth room after delivery or refer to the outpatient department, with a whole blood count result for any reason, but without any disease signs and symptoms according to on the history, physical examination or tests, and who were accepted as normal/healthy.

Patients who were unable to access the file information or had incomplete information, patients with genetic disease, metabolic disease, congenital heart disease and perinatal asphyxia were excluded from the study. Local ethics committee approval was obtained for the study.

Diagnoses: All newborn suspected of infection were included in the study. The neonatal patient group was divided into 6 subgroups according to their final diagnosis. It was supported by

clinical, microbiology, serology and or radiology. The study groups were composed of disease in neonatal sepsis, pneumonia, urinary tract infection, focal infection and viral infection.

Neonatal sepsis is a clinical syndrome in an infant 28 days of life or younger, manifested by systemic signs of infection and/or isolation of a bacterial pathogen from the bloodstream.

Blood samples and blood cultures were taken from all newborns immediately after hospitalization. Patients with neonatal sepsis consisted of patients with blood culture positive and blood culture negative patients with clinical sepsis. Patients with neonatal sepsis were divided into early-onset sepsis and late-onset sepsis. Early-onset sepsis is defined as the onset of symptoms before 4 days of age. Late-onset sepsis is defined as the onset of symptoms at ≥4 days of age. Other neonatal infection groups consisted of patients without signs of sepsis or systemic infection and blood culture positivity. In this study, STARD reporting rules were used.(17).

Statistical analysis: Patient group data were evaluated with SPSS 19 package program. Kolmogrov simirnov test was used for normal distribution of data. The comparison of the numerical data with the control group was evaluated by the Independent T test and the Mann-Whitney U test. The comparison of the categorical data with the control group was evaluated by the Chi-square test. Sensitivity, specificity and likelihood ratio (LHOR) were calculated by using the Receiver Operating Characteristic Curve (ROC) analysis. In the ROC curve, there are points corresponding to various combinations of sensitivity and 1-specificity values. Since both the sensitivity and the specificity of the test to be high, the selected cut-off value should be the lowest 1-specificity point versus the highest sensitivity value. One way to find this point is to calculate LHOR. The cut-off limit of the maximum value for LHOR was found From the obtained coordinates table and the calculation was made from “LHOR = sensitivity / (1-specificity)” formula. $p<0.05$ was considered statistically significant.

RESULTS

A total of 232 newborns were included in the study for 155 newborns in the neonatal patient group and 77 healthy newborns in the control group for 2 years. The 232 patients included in this study for two years included 0.7 % (about 30.100 newborn) of the total admitted to the neonatology outpatient clinic of our hospital. The study included 57 patients with neonatal sepsis, 44 patients with pneumonia, 18 patients with urinary tract infection, 12 patients with focal infection and 9 patients with viral infection. Study data were compared with healthy newborn.

Neonatal sepsis: Culture-positive sepsis (proven sepsis): Consisted of 22 patients whose clinical and laboratory findings were consistent with sepsis and the causative agent was demonstrated. Clinical sepsis: It was composed of 35 patients whose clinical and laboratory findings were consistent with sepsis but agent could not be demonstrated.

Pneumonia: There were 44 patients according to clinical, laboratory and radiological findings of pneumonia.

Urinary tract infections: Consisting of 18 patients according to urine culture and clinical or laboratory findings.

Focal infections: Fifty-one patients according to clinical and laboratory findings such as omphalitis, pyoderma, cellulitis, conjunctivitis, and focal infection were detected.

Viral infections: These patients were admitted to the NICU with mild respiratory distress, runny nose, mild fever, and poor feeding. Radiological examinations, CRP values and culture results were evaluated as normal. In these patients, pneumonia, bacterial infections and sepsis were excluded and only supportive treatment was given. This group consisted of 9 patients diagnosed with upper respiratory tract infection due to clinical findings. However, in our hospital conditions, viral tests could not be performed in order to show the possible agent of viral infections in these patients.

Fever (no infection): Newborns who had only fever and > 10% weight loss during their referral were hospitalized for suspicion of sepsis. This group consisted of 15 patients who did not have growth of organism any culture and who were not clinical and laboratory findings of sepsis.

Control group: A total of 77 healthy newborn were consisted to admit the neonatology outpatient clinic (table 1).

There was no statistically significant difference between the neonatal patient group and the control group in terms of demographic characteristics ($p > 0.05$, table 2).

In this study, WBC, neutrophil and monocyte counts were statistically significant in the newborn with neonatal sepsis according to control group ($p<0.001$, $p<0.001$, $p=0.016$ respectively, table 3). NLR was higher in patients with neonatal sepsis than in other patients. NLR was statistically significant in the neonates who were diagnosed with neonatal sepsis and fever only due to dehydration and/or poor feeding ($p<0.001$, $p=0.001$, respectively). LMR was statistically significant in neonatal sepsis and neonates with viral infection ($p=0.004$, $p=0.01$, respectively).

In our study, patients with neonatal sepsis were evaluated as early onset sepsis (EOS) and late onset sepsis (LOS). Peripheral blood count results in the EOS and LOS are shown in table 4. WBC, neutrophil, monocyte, platelet counts and NLR, LMR and PLR were statistically significant in the EOS ($p<0.001$, $p<0.001$, $p=0.002$, $p<0.001$, $p<0.001$, $p=0.005$, $p=0.001$, respectively). The distinguishing feature of these tests was higher in the EOS than in other patient groups. Neutrophil counts, NLR and LMR were statistically significant in the LOS ($p=0.009$, $p=0.004$, $p=0.045$, respectively).

ROC analysis was performed for NLR and LMR with WBC, neutrophil, monocyte in patients with neonatal sepsis and sensitivity, specificity and likelihood ratio are shown in table 5 and figure 1, 2, 3.

Discussion

In our study, peripheral complete blood count results were high specificity and low sensitivity in exclusion of sepsis in patients with neonatal sepsis. These effects are more marked in EOS than LOS. Likelihood ratio for WBC, neutrophil count and NLR were 10.2, 30.8, 11.5 respectively. These have high specificity values. Platelet counts were not effective in the diagnosis of neonatal sepsis.

Peripheral complete blood count help differential diagnosis of neonatal sepsis in newborns (1, 2, 18, 19, 20). WBC, absolute neutrophil counts (ANC) and the ratio of immature to total neutrophils (I:T) use in the diagnosis of neonatal sepsis. In the literature, the diagnosis of neonatal sepsis has been reported that low WBC values (<5000 mm^3) is more important. Although WBC, ANC, and I:T ratio are commonly used in the diagnosis of neonatal sepsis, it may have significant limitations in diagnosis. Christensen et al (20) reported that there was no change in CBC in the first hours of sepsis in neonates with EOS. In their study showed that it was a poor indicator (20). Therefore, all these tests are not specific for the diagnosis of sepsis (2, 8, 21, 22, 23, 24). In contrast, there are studies reported that peripheral blood count results are useful in the diagnosis of sepsis (9, 18). Murphy et al (18) showed that sterile blood culture and two normal I:T ratios were 100% negative predictive values in the diagnosis of the EOS. Philip et al (9) showed that neutropenia was more predictive of neonatal sepsis than neutrophilia.

WBC may be normal or very mildly low or accompanied by leukopenia in neonatal infections with *Enterovirus*, *HSV (Herpes simplex virus 1 and 2)* and *HPeV (Human parechoviruses*) (25). In our study, WBC, neutrophil counts were statistically significant in patients who presented with fever without infection (p=0.003, p=0.001, respectively). Monocyte counts were statistically significant in patients with neonatal sepsis, pneumonia, focal infection and viral infection (p=0.016, p=0.025, p=0.009, p=0.014, respectively). Also, patients the highest the

number of monocytes were newborns with viral infectious. There was no seasonal difference in patients with viral infection and fever without infection compared to other diseases.

Manzoni et al (26) reported that thrombocytopenia is not an organism-specific marker of sepsis. Low platelet counts should not be associated with any infectious agent (or agent group) in preterm newborns. Platelet counts can be used as a pre-diagnostic test for neonatal sepsis but are not very specific to neonatal sepsis. However, platelet counts can help in monitoring the treatment prognosis (1, 2, 25, 26, 27).

Peripheral blood count rates are used for diagnostic in different age and diseases groups in pediatrics. (28, 29, 30). Naess et al (28) in their study, reported that NLR was a more useful diagnostic tool than other blood tests used to identify patients with septicemia. They reported that NLR and monocyte to lymphocyte (MLR) could be useful in the differential diagnosis of bacterial infection among patients hospitalized for fever (28). Warimwe et al (29) reported that MLR which is easily derived from routine peripheral complete blood counts in children diagnosed with malaria is an effective method for demonstrating the immune status of the individual against *Plasmodium falciparum* infection. Mentis et al (30) reported that cerebrospinal fluid neutrophil count and NLR were statistically significant in the diagnosis of meningitis according to blood tests. NLR has contributed to the diagnosis of meningitis (30).

In our study, patients with neonatal sepsis, we think that peripheral blood count results and rates can be used in the diagnosis of neonatal sepsis according to other disease groups. LMR and WBC, neutrophil, monocyte counts had high specificity values in the EOS. These results can be used safely in distinguishing EOS from other disease groups. In our study in the patients with fever without sepsis, NLR, WBC and neutrophil counts were statistically significant compared to the control group. However, in these patients was detected dehydration as a result of poor feeding. We believe that increases of the WBC, neutrophil and NLR are related to dehydration due to relative neutrophilia in these patients.

The limitations of the study are those newborns with infectious diseases were included in our study while those with other disorders were excluded. However, considering the physiological changes in the peripheral blood count in the first few days of newborns, it can be difficult to determine the level of this infections effect. Further studies are therefore required.

Conclusion the number of WBC, neutrophils and monocytes is important for the diagnosis of neonatal sepsis. Neutrophil to lymphocyte ratio may be a more useful diagnostic test to identify patients with septicemia than other commonly used diagnostic tests. These results have reliable high specificity and LHOR values. NLR has high specificity and LHOR values. It can be used in the diagnosis of neonatal sepsis.

Author contributions

Dr. Kurt conceptualized the idea for this study and designed the study, and acquired the data and interpreted findings, and wrote the first draft of the manuscript, revised and approved the final manuscript as submitted.

Dr. Tosun conceptualized the study, interpreted the data, revised and approved the final manuscript as submitted.

Dr. Altuntaş supported the data collection, supported carried out data collection and, drafted the initial paper and approved the final manuscript as submitted.

Conflicts of interest

None

References

1. Sharma D, Farahbakhsh N, Shastri S, Sharma P. Biomarkers for diagnosis of neonatal sepsis: a literature review. J Matern Neonatal Med. 2018; 31(12): 1646-1659.

2. Chauhan N, Tiwari S, Jain U. Potential biomarkers for effective screening of neonatal sepsis infections: An overview. Microb Pathog 2017;107:234-242.

3. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am 2004; 51: 939-959.

4. Khassawneh M, Hayajneh WA, Kofahi H, Khader Y, Amarin Z, Daoud A. Diagnostic markers for neonatal sepsis: comparing C-reactive protein, interleukin-6 and immunoglobulin M. Scand J Immunol 2007; 65: 171-175.

5. Shiffer CA. Granulocyte transfusion therapy. Curr Opin Hematol 1999; 6: 3-7.

6. Dale DC, Liles WC. Return of granulocyte transfusion. Curr Opin Pediatr 2000; 12: 18-22.

7. Calhoun DA, Christensen RD. Recent advances in the pathogenesis and treatment of nonimmune neutropenias in the neonate. Curr Opin Hematol 1998; 5: 37-41.

8. Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood cell count in early-onset neonatal sepsis. Pediatr Infect Dis J. 2012; 31: 799-802.

9. Philip AG, Hewitt JR. Early diagnosis of neonatal sepsis. Pediatrics 1980; 65: 1036-1041.

10. 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: 5-14.

11. Loonen AJ, de Jager CP, Tosserams J, et al. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. PLoS One 2014;9: e87315.

12. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care 2010; 4: R192.

13. Hu YX, Xu XX, Shao Y, et al. The prognostic value of lymphocyte-to-monocyte ratio in retinopathy of prematurity. Int J Ophthalmol 2017; 10: 1716-1721.

14. Daglar HK, Kirbas A, Kaya B, Kilincoglu F. The value of complete blood count parameters in predicting preterm delivery. Eur Rev Med Pharmacol Sci 2016 ; 20:801-805.

15. Schmutz N, Henry E, Jopling J, RD Christensen. Expected ranges for blood neutrophil concentrations of neonates: The Manroe and Mouzinho charts revisited. J Perinatol 2008;28:275-281.

16. Lambert RM, Baer VL, Wiedmeier SE, Henry E, Burnett J, Christensen RD. Isolated elevated blood neutrophil concentration at altitude does not require NICU admission if appropriate reference ranges are used. J Perinatol 2009;29:822-825.

17. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, LijmerJG Moher D, Rennie D, de Vet HCW, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, For the STARD Group. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies.

18. Murphy K, Weiner J. Use of leukocyte counts in evaluation of early-onset neonatal sepsis. Pediatr Infect Dis J 2012; 31:16-19.

19. Rozycki HJ, Stahl GE, Baumgart S. Impaired sensitivity of a single early leukocyte count in screening for neonatal sepsis. Pediatr Infect Dis J 1987; 6:440-442.

20. Christensen RD, Rothstein G, Hill HR, et al. Fatal early onset group B streptococcal sepsis with normal leukocyte counts. Pediatr Infect Dis 1985; 4: 242-245.

21. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells, J. Pediatr 1979; 95:89-98.

22. Gerdes JS. Clinicopathologic approach to the diagnosis of neonatal sepsis. Clin Perinatol 1991;18: 361-381.

23. Polin RA. Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics 2012;129:1006-1015.

24. Hornik CP, Benjamin DK, Becker KC, et al. Use of the complete blood cell count in late-onset neonatal sepsis. Pediatr Infect Dis J 2012; 31: 803-807. 2010

25. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev 2014; 27:21-47.

26. Manzoni P, Mostert M, Galletto P, et al. Is thrombocytopenia suggestive of organism-specific response in neonatal sepsis? Pediatr Int 2009;51: 206-210.

27. Guida JD, Kunig AM, Leef KH, McKenzie SE, Paul DA. Platelet count and sepsis in very low birth weight neonates: is there an organism-specific response? Pediatrics 2003; 111:1411-1415.

28. Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. Infection 2017; 45: 299-307.

29. Warimwe GM, Murungi LM, Kamuyu G, et al. The ratio of monocytes to lymphocytes in peripheral blood correlates with increased susceptibility to clinical malaria in Kenyan children. PLoS One 2013; 8:e57320.

30. Mentis AF, Kyprianou MA, Xirogianni A, Kesanopoulos K, Tzanakaki G. Neutrophil-to-lymphocyte ratio in the differential diagnosis of acute bacterial meningitis. Eur J Clin Microbiol Infect Dis 2016 ;35 :397-403.

Table Legend

Table 1: The diagram to report flow of participants through the study

Table 2: Patient demographic characteristics

Table 3: Comparison of neutrophil:lymphocyte ratio, lymphocyte:monocyte ratio, platelet:lymphocyte ratio and peripheral complete blood count parameters between neonatal patient group and control group

Table 4: Comparison of neutrophil:lymphocyte ratio, lymphocyte:monocyte ratio, platelet:lymphocyte ratio and peripheral complete blood count parameters between neonatal sepsis group and control group

Table 5: Receiver operating characteristic analysis results for NLR, LMR, PLR and peripheral blood count in patients with neonatal sepsis

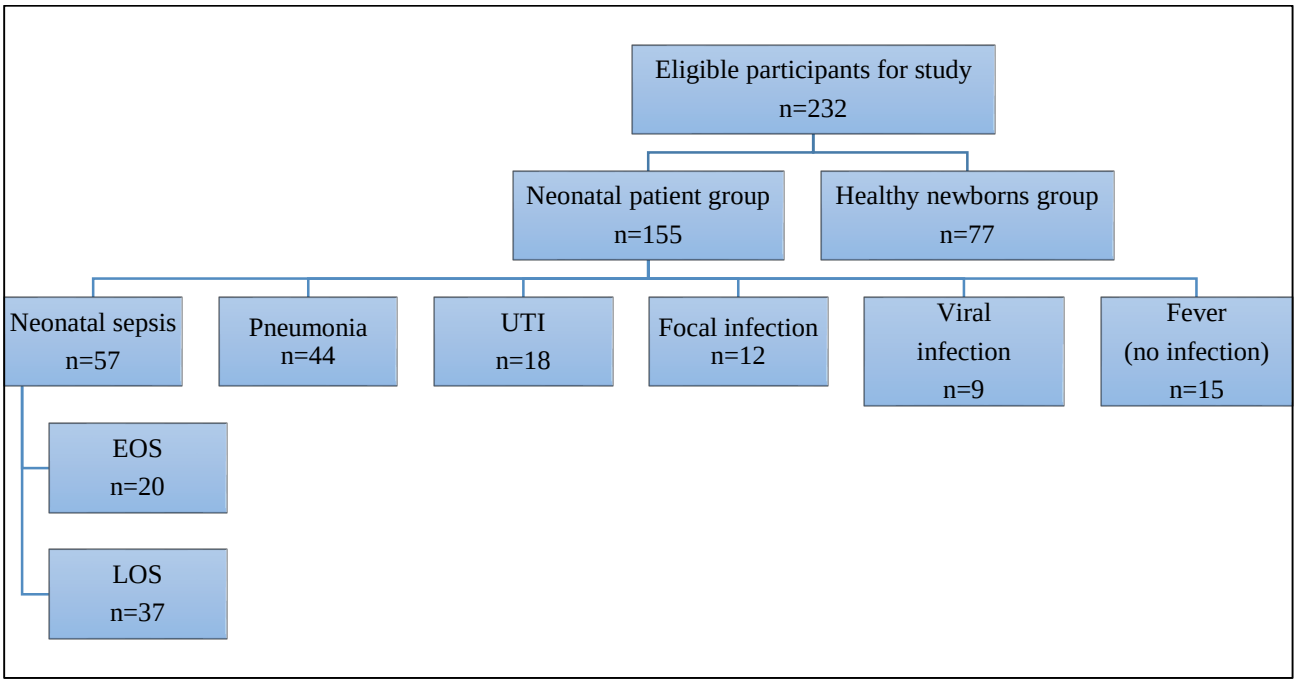
Figure Legend

Figure 1: Graph of Receiver operating characteristic analysis for NLR, LMR and white blood cell, neutrophils and monocytes in neonatal sepsis

Figure 2: Graph of Receiver operating characteristic analysis for NLR, LMR, PLR and white blood cell, neutrophils, monocytes, platelet counts in early onset sepsis

Figure 3: Graph of Receiver operating characteristic analysis for NLR, LMR and neutrophils counts in late onset sepsis

Table 1



(**UTI**: Urinary tract infection **EOS**: Early onset sepsis, **LOS**: Late onset sepsis)

Table 2

	Neonatal patient group	*Healthy newborns*	*P value*
Gender (n. %)	*Female:* 65 (41.9) *Male:* 90 (58.1)	*Female:* 34 (44.2) *Male: 4*3 (55.8)	p*= 0.77
Form of birth (n. %)	*Normal vaginal route:* 97 (62.6) *Cesarean section:* 58 (37.4)	*Normal vaginal route:41(53.2)* *Cesarean section:36 (46.8)*	p*= 0.20
Gestational week (weeks) *(Mean±SD) (Min.-Max.)*	38.8±1.13 (37-42)	38.7±1.06 (37-41)	p**= 0.63
Birth weight (grams) *(Mean±SD) (Min.-Max.)*	3397±468 (1830-4850)	3362±372 (2400-4050)	p***= 0.57
Postnatal age (days) *(Mean±SD) (Min.-Max.)*	14.4±9.6 (1-28)	12.2±8.5 (1-28)	p**= 0.14
Total (n)	155	77	

*:Chi-square test. **:Mann-Whitney test. ***: Independent t test

Table 3

	Neonatal patient group n=155 Median±IQR						***Healthy newborns group*** n=77 Median±IQR
	Neonatal sepsis (n=57)	Pneumonia (n=44)	UTI (n=18)	Focal infection (n=12)	Viral infection (n=9)	Fever (*no infection)* (n=15)	
WBC ($\times 10^9$/L)	***14.2**±8.82	11.10±5.59	11.57±5.53	13.85±11.8	10.2±4.10	***13.90**±6.80	10.12±4.84
Lymphocytes ($\times 10^9$/L)	3.97±2.58	4.98±2.76	4.66±2.68	5.26±3.58	4.56±2.30	3.73±1.30	4.53±1.52
Neutrophils ($\times 10^9$ /L)	***7.61**±8.35	3.33±3.63	4.46±4.20	4.0±9.24	3.94±2.26	***8.41**±5.90	3.38±3.13
Monocytes ($\times 10^9$/L)	***1.41**±1.06	***1.28**±1.21	1.39±0.94	***1.75**±1.17	***1.64**±1.77	1.05±0.94	1.21±0.67
Platelets ($\times 10^9$/L)	297.0±171.0	373.5±151.5	356.0±223.5	326.0±179.75	368.0±137.5	320.0±152.0	321.0±162.0
NLR	***1.95**±2.12	0.69±0.93	0.97±0.87	1.12±1.34	1.02±1.32	***1.80**±1.75	0.81±0.87
LMR	***2.79**±2.03	3.31±3.42	4.28±4.02	2.65±3.30	***1.60**±3.71	3.52±3.32	3.97±3.09
PLR	69.25±48.96	72.6±52.29	62.78±58.90	59.77±33.91	77.31±66.21	78.40±50.73	77.90±38.76
CRP (< 0.5 mg per 100 ml, normal)	0.58±1.69	0.10±0.54	0.09±1.10	0.45±13.64	0.33±0.59	1.5±3.11	-
Hospital stay (day)	9.0±3.0	9.0±3.0	10.0±4.0	10.0±4.75	6.0±3.0	8.0±3.0	-

*: *p* values from Independent T test / Mann–Whitney test for comparison with the healthy newborns (control group) and significant differences are marked by (p* < 0.05),
, (**WBC**: White blood cell. **NLR**: Neutrophil/lymphocyte ratio. **LMR**: Lymphocyte/monocyte ratio. **PLR**: Platelet/lymphocyte ratio. **CRP**:C-reactive protein, **UTI**: Urinary tract infection, IQR: Interquartile range)

Table 4

	Neonatal sepsis group n=57 Median±IQR		*Healthy newborns group* n=77 Median±IQR	**p* value**	**p** value**
	EOS (n=20)	LOS (n=37)			
WBC ($\times 10^9$/L)	***18.8**±11.27	13.1±6.57	10.12±4.84	<0.001*	0.51
Lymphocytes ($\times 10^9$/L)	4.79±1.81	3.84±2.75	4.53±1.52	0.614	0.57
Neutrophils ($\times 10^9$ /L)	***11.87**±7.98	***5.41**±7.28	3.38±3.13	<0.001*	0.009**
Monocytes ($\times 10^9$/L)	***1.68**±0.99	1.35±0.86	1.21±0.67	0.002*	0.359
Platelets ($\times 10^9$/L)	***252.5**±113.0	338.0±157.5	321.0±162.0	<0.001*	0.515
NLR	***2.39**±1.76	***1.49**±2.18	0.81±0.87	<0.001*	0.004**
LMR	***2.74**±1.64	***2.84**±3.33	3.97±3.09	0.005*	0.045**
PLR	***55.50**±34.87	81.29±51.27	77.90±38.76	0.001*	0.477

*: *p* Mann–Whitney test comparison with the healthy newborns (control group) for EOS and and significant differences are marked by ($p^* < 0.05$),

**: *p* Mann–Whitney test comparison with the healthy newborns (control group) for LOS and and significant differences are marked by ($p^{**} < 0.05$),

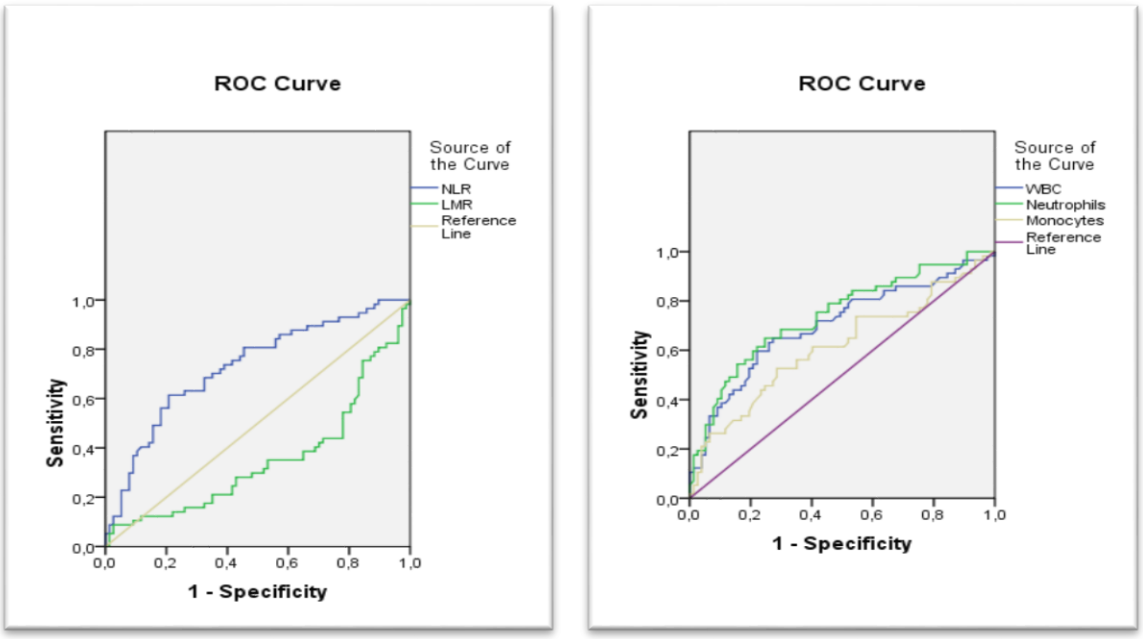
(**WBC**: White blood cell. **NLR**: Neutrophil/lymphocyte ratio. **LMR**: Lymphocyte/monocyte ratio. **PLR**: Platelet/lymphocyte ratio, **EOS**: Early onset sepsis, **LOS**: Late onset sepsis, IQR: Interquartile range).

Table 5

	Variables	Sensitivity (%)	Specificity (%)	LHOR	AUC ROC	95% Confidence Interval	Cutoff value	P value
Neonatal sepsis								
	WBC ($\times10^9$/L)	10.5	98.7	8.1	0.700	0.608-0.793	≥23.39	<0.001*
	Neutrophils ($\times10^9$ /L)	15.8	98.7	12.1	0.739	0.653-0.825	≥14.17	<0.001*
	Monocytes ($\times10^9$/L)	21.1	96.1	5.4	0. 613	0.514-0.712	≥ 2.04	0.025*
	NLR	8.8	98.7	6.7	0.729	0.643-0.816	≥ 4.79	<0.001*
	LMR	5.3	98.7	4.05	0.353	0.256-0.450	≥10.92	0.004*
Early onset sepsis								
	WBC ($\times10^9$/L)	40	96.1	10.26	0.861	0.773-0.950	≥20.35	<0.001*
	Neutrophils ($\times10^9$ /L)	40	98.7	30.8	0.902	0.836-0.967	≥14.0	<0.001*
	Monocytes ($\times10^9$/L)	10	98.7	7.7	0.725	0.594-0.856	≥2.77	0.002*
	Platelets ($\times10^9$/L)	5	94.8	0.96	0.236	0.118-0.354	≥525.5	<0.001*
	NLR	15	98.7	11.55	0.845	0.763-0.928	≥4.79	<0.001*
	LMR	100	2.6	1.02	0.295	0.181-0.410	≥1.24	0.005*
	PLR	80	7.8	0.86	0.268	0.145-0.390	≥37.72	0.001*
Late onset sepsis								
	Neutrophils ($\times10^9$ /L)	5.4	98.7	4.16	0.651	0.542-0.760	≥14.5	0.009*
	NLR	5.4	98.7	4.16	0.667	0.559-0.774	≥4.94	0.004*
	LMR	8.1	98.7	6.24	0.384	0.263-0.505	≥10.92	0.045*

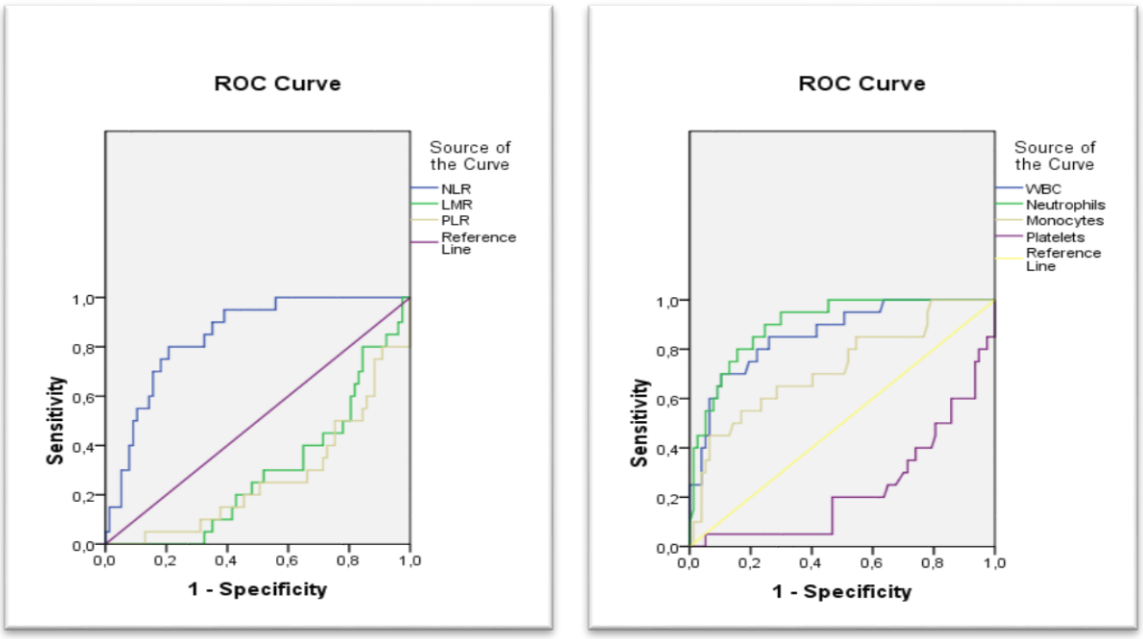
p* values from Independent T test / Mann–Whitney test for comparison with the healthy newborns (control group) and significant differences are marked by (p* < 0.05). **(LHOR: likelihood ratio**;** AUC: Area under curve; ROC: the receiver operating characteristic curve; **WBC**: White blood cell. **NLR**: Neutrophil/lymphocyte ratio. **LMR**: Lymphocyte/monocyte ratio

Figure 1



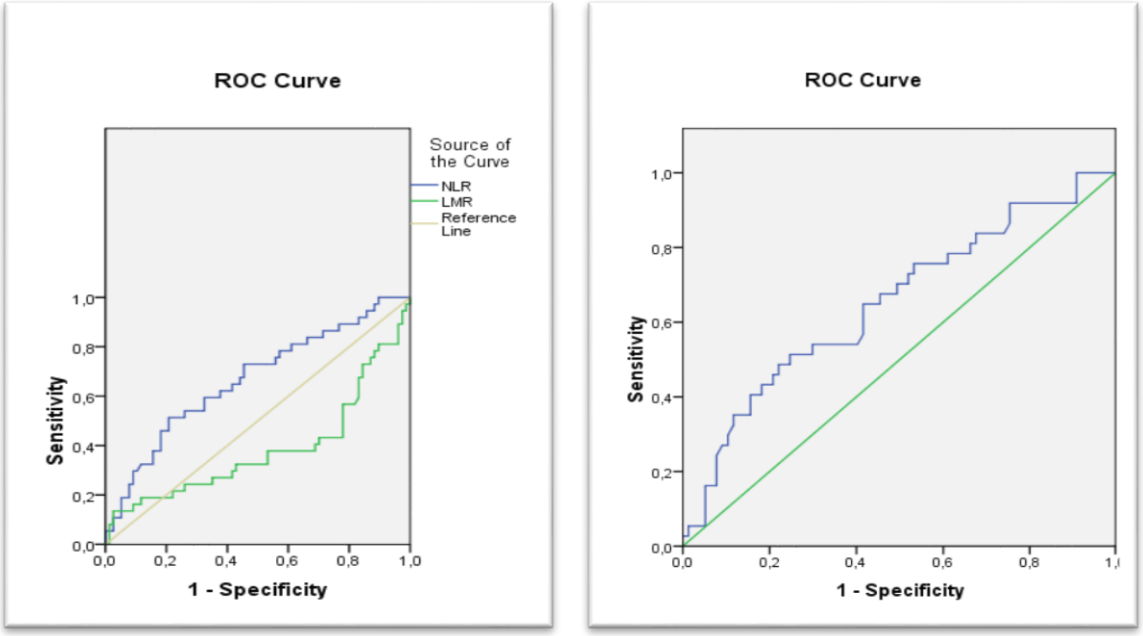
(**WBC**: White blood cell, **NLR**: Neutrophil/lymphocyte ratio, **LMR**: Lymphocyte/monocyte ratio)

Figure 2



(**WBC**: White blood cell, **NLR**: Neutrophil/lymphocyte ratio, **LMR**: Lymphocyte/monocyte ratio, **PLR**: Platelet/lymphocyte ratio)

Figure 3



(**NLR**: Neutrophil/lymphocyte ratio, **LMR**: Lymphocyte/monocyte ratio)