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Sensitivity and Specificity of the Neutrophil Lymphocyte Ratio (NLR) in Diagnosing Late Onset Neonatal Sepsis in NICU Patients

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ABSTRACT

Objective: To compare the sensitivity and specificity of the neutrophil lymphocyte ratio in diagnosing late onset neonatal sepsis in NICU patients at a tertiary care center

Study Design and Setting: Prospective observational study at Department of Pediatrics, Combined Military Hospital, Lahore from February 2024-July 2024

Methodology: After admission into the NICU for suspected late onset neonatal sepsis, complete blood count, C-reactive protein and blood cultures were sent before changing or starting broad spectrum anti-biotic therapy for 350 patients included in the study. Primary variables observed were sensitivity and specificity of the neutrophil lymphocyte ratio in diagnosing late onset sepsis once co-related with the culture results.

Results: Blood panel parameters showed mean absolute neutrophil count to be 5928.19796.05/mm^3 versus 7032.80166.02/mm^3 between the suspected and confirmed patients' groups ($p<0.001$). Similarly, mean absolute lymphocyte count was 2745.32394.53/mm^3 versus 3223.60278.90/mm^3 between both groups ($p<0.001$). Median value for NLR was 1.70 (1.00) versus 2.20 (1.00) between the suspected and confirmed culture groups ($p<0.001$). Assessment of receiver operating characteristics (ROC) for NLR when compared with suspected and confirmed sepsis showed area under the curve being 0.644 (CI=95%) with sensitivity of 74.6%, specificity of 55.6%, positive predictive value being 57.3% and negative predictive value being 73.3% with a cut-off value for NLR being 2.05.

Conclusion: We conclude that neutrophil lymphocyte ratio with a cut-off value of 2.05 is a reliable method to diagnose late onset neonatal sepsis with good sensitivity.

Key Words: Lymphocyte ratio, neonatal, neutrophil, sepsis

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INTRODUCTION

Neonatal sepsis is the leading cause of neonatal morbidity and mortality worldwide.[1] The estimated prevalence for neonatal sepsis is 1-10 per 1000 live births worldwide.[2] The prevalence is considerably higher in the developing world with around 45-50 per 1000 live births in South-East Asia.[3] Neonatal sepsis refers to bacteremia or infection in the bloodstream in neonates less than 28 days post-birth. It constitutes a varied clinical presentation with majority of the neonates affected in the first and second week of life.[4] Various factors contribute as causative and risk factors for the development of neonatal sepsis. The causes increasing susceptibility after birth include neonatal factors including low birth weight, birth asphyxia, prematurity and maternal factors include poor maternal health, smoking, mode of delivery, delivery environment, ante-natal care given and maternal infection especially in the last trimester.[5]

Early onset neonatal sepsis refers to infections during the first week of life and late onset neonatal sepsis are infection from the first week to the 90 days post-birth.[6] Developing countries face a dilemma in the diagnosis of neonatal sepsis due to lack of resources and paucity of diagnostic panels

except for a few large centers of excellence already constrained with the patient load. Various investigations have been proposed to reliably diagnose the condition, but their sensitivity and specificity as sole markers have been questionable. Total leucocyte count, C-reactive protein (CRP), absolute neutrophil count have all been used as panel markers for diagnostic purposes, but their use remains questioned in neonates.[7] The use of blood culture for the diagnoses poses the limitation of delayed time required for results and early intervention required in neonates suspected of infection.[6] Procalcitonin as a sepsis marker has gained widespread acceptance but its high cost and limited availability in our demographic area restricts its use in each case under suspicion.[8]

The **neutrophil-to-lymphocyte ratio (NLR)** plays a crucial role in diagnosing neonatal sepsis. This inflammatory biomarker measures the balance between the innate and adaptive immune systems. Recent literature revealed that NLR is significantly higher in neonates with sepsis compared to healthy controls. Additionally, NLR was higher in septic neonates than in those suspected of sepsis but with negative blood cultures. Integrating NLR into clinical practice can aid in early diagnosis, potentially improving outcomes.

Restoring immune system balance may serve as an attractive therapeutic target. While certain markers including CRP can aid and augment the diagnosis. The sole credibility of the score need to be assessed for its recommendation. The association is also strong with bacterial infections than viral pathogens. It has also been linked to balance between the integrity of the immune system and is very sensitive to changes in normal homeostasis. High NLR values are thought to signify a systemic inflammatory response and poor immune competence, both of which are critical in the pathophysiology of sepsis. Studies have demonstrated that NLR can be a valuable predictive marker for sepsis severity and mortality risk. For instance, research has shown that an elevated NLR is linked to higher mortality rates and prolonged hospital stays, suggesting that it may serve as an adjunctive tool in clinical settings for assessing patient prognosis.

Moreover, NLR's utility in sepsis extends to its potential role in guiding therapeutic interventions and monitoring disease progression, offering a cost-effective and readily accessible parameter for clinicians. However, while NLR is a promising biomarker, it is essential to consider its limitations, such as variability due to pre-existing conditions or other inflammatory diseases, which can affect neutrophil, and lymphocyte counts independently of sepsis. Furthermore, the interpretation of NLR should be integrated with other clinical parameters and diagnostic tools to enhance its accuracy and reliability.

Neutrophil lymphocyte ratio (NLR) has been advocated to be increased in neonates in cases of inflammation and infection.[9] It is simple, cost effective and literature has shown reliable results in diagnosing late onset sepsis when co-related with culture specimen results retrieved later. We aim to incorporate this useful parameter in our diagnostic protocol by assessing its sensitivity and specificity in diagnosing late onset neonatal sepsis in our NICUs.

METHODOLOGY:

This prospective observational study was carried out at the Department of Pediatrics, Combined Military Hospital Lahore from Feb 2024-July 2024 after approval from the ethical review board vide letter no. 501/2024. The sample size was calculated keeping the confidence interval at 95%, margin of error at 5% with the population prevalence of suspected neonatal sepsis in our demographic setup to be 29.5%. Minimum sample size according to WHO calculator came out to be 320 patients. We included 320 patients in the final study protocol.

Inclusion criteria included all in-hospital born neonates presenting to the NICU from the ward or high dependency unit suspected of late onset neonatal sepsis after 7 days of birth

Exclusion criteria included all out of hospital born neonates, those with congenital abnormalities, those suspected of sepsis <7 days after birth, neonates already on broad spectrum antibiotics and non-consent of parents or next of kins to be included in the study.

The study method included all patients as per the inclusion criteria furnished. After admission into the NICU for suspected late neonatal sepsis, complete blood count, C-reactive protein and blood cultures were sent before changing or starting broad spectrum anti-biotic therapy. Neonates were added into the protocol for suspicion of late onset neonatal sepsis using the fetal inflammatory response syndrome criteria (FIRS) standardized and proposed by Haque1.[11] This included clinical variables (Heart rate >180 or <100, resp rate >60, altered mental status, lethargy, glucose intolerance with BSR >10 mmol/l and feeding intolerance), hemodynamic variables of low blood pressure and systolic pressure less than 65 mmHg, tissue perfusion variables (capillary refill time >3 sec, plasma lactate >3 mmol/l) and inflammatory variables (leukocytosis TLC >34, CRP>10, low platelet count <100,000 and immature neutrophils in the peripheral blood film). Presence of two or more of the criteria were regarded as suspected neonatal sepsis as per the study protocol. The differential leucocyte count, absolute lymphocyte count (ALC) and absolute neutrophil count (ANC) were obtained and NLR was calculated and recorded at the time of admission in all subjects. The diagnostic criteria and blood panel was endorsed by the resident pediatrics on duty on a non-descript proforma unaware of the study protocol and submitted at the end shift to the consultant on duty. The patients were divided in the final analysis into the suspected and confirmed neonatal sepsis groups if the cultures were negative or positive respectively.

The type of organism isolated was also recorded and respective NLR recorded at the time of admission was then co-related with the culture results and analyzed for sensitivity and specificity in diagnosing late onset neonatal sepsis with the cut-off value.

Primary variables observed were sensitivity and specificity of the neutrophil lymphocyte ratio in diagnosing late onset sepsis once co-related with the culture results. Maternal and neonatal demographic variables were also recorded including mode of delivery, fetal weight on admission and gestational age at delivery. Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. Independent samples t-test was used to compare statistically significant means. Median values were compared using the Mann-Whitney U test. Chi-square test was used to compare frequency variables. Cut-off value for NLR was done using AUC (area under curve) using ROC (receiver operating characteristics). A p value of 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0

RESULTS:

A total of 320 were analyzed in the study protocol for diagnosis of late neonatal sepsis. Once the report of culture was received, they were assigned into the suspected culture negative group (n=142) and confirmed culture positive group (n=178). Mean age of patients in both groups was 14.862.46 days versus 14.962.46 days (p=0.704). Gender distribution was 139 (78.1%) males and 39 (21.9%) females in the suspected versus 96 (67.6%) males and 46 (32.4%) females in the confirmed neonatal sepsis group (p=0.035). Gestational age showed 151 (84.4%) patients as pre-term in the suspected versus 127 (89.4%) in the confirmed group (p=0.225). Weight at birth revealed normal birth weight in 54 (30.3%) versus 07 (4.9%) patients, low birth weight in 81 (45.5%) versus 85 (59.9%) patients, very low birth weight in 36 (20.2%) versus 40 (28.2%) patients and extremely low birth weight in 07 (3.9%) and 10 (7.0%) patients in the suspected versus confirmed neonatal sepsis group respectively (p<0.001). Maternal parameters showed mode of delivery to be vaginal in 15 (8.4%) patients versus 09 (6.3%) patients and caesarian section in 163 (91.6%) versus 133 (93.7%) patients (p=0.481) (Table-I).

Blood panel parameters showed mean absolute neutrophil count to be 5928.19796.05/mm^3 versus 7032.80166.02/mm^3 between the suspected and confirmed patients' groups (p<0.001). Similarly, mean absolute lymphocyte count was 2745.32394.53/mm^3 versus 3223.60278.90/mm^3 between both groups (p<0.001). Median value for NLR was 1.70 (1.00) versus 2.20 (1.00) between the suspected and confirmed culture groups (p<0.001) (Table-II).

Assessment of receiver operating characteristics (ROC) for NLR when compared with suspected and confirmed sepsis showed area under the curve being 0.644 (CI=95%) with sensitivity of 74.6%, specificity of 55.6%, positive predictive value being 57.3% and negative predictive value being 73.3% (Table-III and IV).

DISCUSSION:

We aimed to carry out this study to find an easy, convenient, and cost effective solution for diagnosing late neonatal sepsis. Any blood marker or panel that is easily available and helps to identify possible patients at the risk of developing the condition would be helpful in our resource constrained setup since it would allow only the patients at risk to undergoing advanced blood panel and investigations.

Neonatal sepsis is characterized by a systemic inflammatory response syndrome resulting from the introduction of specific or suspected pathogens into the bloodstream and the continuous generation of toxins, leading to pathological inflammation and dysfunction of organ systems. Neutrophils play a vital role in the innate immune response in sepsis by releasing inflammatory cytokines, chemokines, and regulatory cytokines, as well as by phagocytosing invading pathogens and eliminating them through various antimicrobial peptides, proteases, and oxidants.

The identification of neutrophil extracellular traps (NETs) in recent times has revealed a novel mechanism in the immune system's defense against pathogen invasion. Nevertheless, the excessive production of inflammatory cytokines and the formation of NETs contribute to heightened inflammation and tissue injury. Our study found that the second week of life was the time where majority of the neonates were admitted with clinical suspicion of neonatal sepsis. This is in line with studies carried out by Mukopadhyay et al who also concluded the median age of presentation to be the second week of life.[12] There was a pre-dominantly male pre-disposition in our study and needs further studies to see whether gender is associated with an increased risk of late onset neonatal sepsis. Our study found that even though pre-term infants were more prone to develop the disease, there was no statistically significant co-relation once both groups of suspected and the confirmed neonatal sepsis were compared. There was a significant co-relation between the birth weight at presentation to develop neonatal sepsis. Studies done by Kostlin et al and Pan et al concluded very low birth weight to be associated with the highest incidence of late onset neonatal sepsis,[6,13] Similar findings were concluded in our study with the age group being the most severely affected. The higher incidence is attributed to the increased chance of infection due to insertion of central venous lines, arterial lines and lumbar punctures done for diagnostic and therapeutic purposes. These chances are especially increased in low resources centers where disinfection and NICU care is hampered. Total and differential leukocyte counts are commonly utilized as cost-effective and readily accessible markers of the inflammatory response. The Neutrophil-to-Lymphocyte Ratio (NLR) is indicative

Table-1: Demographic Characteristics (n=320)

Variable	Suspected Neonatal Sepsis (n=142)	Confirmed After Culture (n=178)	P Value
Mean Age (Days)	14.86+2.46	14.96+2.46	0.704
Gender			
Male	139 (78.1%)	96 (67.6%)	0.035
Female	39 (21.9%)	46 (32.4%)	
Gestational Age			
Pre-Term	151 (84.4%)	127 (89.4%)	0.225
Term	27 (15.2%)	15 (10.6%)	
Weight At Birth			
Extremely Low Birth Weight (<1000 Gram)	07 (3.9%)	10 (7.0%)	<0.001
Very Low Birth Weight (<1500 Grams)	36 (20.2%)	40 (28.2%)	
Low Birth Weight (<2500 Grams)	81 (45.5%)	85 (59.9%)	
Normal Birth Weight	54 (30.3%)	07 (4.9%)	
Mode Of Delivery			
Vaginal	15 (8.4%)	09 (6.3%)	0.481
Caesarian	163 (91.6%)	133 (93.7%)	

Table-2 Blood Panel Parameters between Both Groups (n=320)

Variable	Suspected Neonatal Sepsis (n=142)	Confirmed After Culture (n=178)	P Value
Mean Absolute Neutrophil Count (/MM3)	5928.19+796.05	7032.80+166.02	**<0.001**
Mean Absolute Lymphocyte Count (/MM3)	2745.32+394.53	3223.60+278.90	**<0.001**
Median NLR	1.70 (1.00)	2.20 (1.00)	**<0.001**

Table-3 AUC and ROC Characteristics (n=320)

Area	STD Error	Asymptotic Sig	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.664	0.030	0.000	0.604	0.724

Table-4 Sensitivity, Specificity, PPV and NPV of NLR for Late Onset Neonatal Sepsis (n=320)

Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
74.6%	**55.6%**	**57.3%**	**73.3%**

of fluctuations in neutrophil and lymphocyte levels.

Numerous research endeavors have established the NLR as a dependable tool for assessing inflammation and as a prognostic indicator across various medical conditions such as ischemic stroke, cerebral hemorrhage, major adverse cardiac events, and solid tumors. In recent times, the NLR has garnered significant interest as a novel risk factor that holds promise for aiding in the diagnosis of sepsis. Sepsis, characterized by heightened neutrophil counts and reduced lymphocyte counts due to pathogenic microbial invasion, is associated with elevated NLR levels in affected individuals. Extensive epidemiological inquiries and meta-analyses have provided evidence suggesting that NLR could serve as a valuable predictive marker for sepsis, with patients exhibiting elevated NLR levels facing an increased likelihood of an unfavorable prognosis.

When talking about the co-relation of neutrophil lymphocyte ratio (NLR) and diagnosing late onset neonatal sepsis, we found a sensitivity of 74.6% and a specificity of 55.6%. When assessing for a suitable cut-off value, we found that a value of 2.05 was associated with the most suitable sensitivity and minimum false positives. This was in-line with findings in studies done by Sumitro et al and Bai et al. Varal et al also concluded a cut-off value of 2.12 which was in line with our findings as well.[14-16] They concluded that

neonates above the cut-off has twice the chance of being diagnosed with the disease than the ones below it. Local studies done by Naseer et al and Al Nady et al also found NLR to be a good screening tool in resource constrained setups to be utilized for suspicion in patients with specific cut-off values in conjunction with the CRP values.[17,18]

The Neutrophil-to-Lymphocyte Ratio (NLR) is a prominent biomarker in sepsis management, valued for its simplicity and cost-effectiveness, but its utility is often compared to other key biomarkers such as C-Reactive Protein (CRP), Procalcitonin (PCT), and Lactate. NLR, reflecting the ratio of neutrophils to lymphocytes in the blood, provides insight into the balance between systemic inflammation and immune response, with elevated levels indicating heightened inflammatory activity and potentially worse outcomes. However, CRP, an acute-phase protein produced in response to inflammation, offers a more direct measure of systemic inflammatory activity. Although CRP levels rise significantly in sepsis and correlate with disease severity, it lacks specificity as it can be elevated in various inflammatory conditions beyond sepsis. Procalcitonin, a peptide precursor of calcitonin, offers a more specific marker of bacterial infection, distinguishing sepsis from non-bacterial inflammatory processes. Elevated PCT levels are associated with more severe infections and poorer outcomes, making it a valuable tool for identifying bacterial sepsis, though it is typically more expensive and less accessible compared to NLR. Lactate, a marker of tissue hypoperfusion and metabolic distress, is crucial in assessing the severity of sepsis and the need for resuscitation. High lactate levels are closely linked to increased mortality risk and provide direct insight into the physiological impact of sepsis, unlike NLR which primarily reflects inflammatory response rather than tissue perfusion. In clinical practice, the combined use of NLR with CRP, PCT, and lactate can offer a comprehensive evaluation of sepsis, with each biomarker contributing unique and complementary information. While NLR provides an accessible and cost-effective measure of systemic inflammation, CRP and PCT enhance diagnostic specificity, and lactate offers critical insights into tissue perfusion and severity. Integrating these biomarkers can improve diagnostic accuracy and guide more effective management strategies for sepsis.

The neutrophil-to-lymphocyte ratio (NLR) is emerging as a valuable biomarker for diagnosing neonatal sepsis, often outperforming traditional markers like C-reactive protein (CRP) and neutrophil counts alone. NLR offers a pooled sensitivity of 79% and specificity of 91% for sepsis diagnosis, indicating its reliability. While CRP has been shown to have a maximum sensitivity and specificity of 84.3% and 46.1% for sepsis, its takes longer to elevate, while NLR can rise rapidly following infection, allowing for earlier detection. Combining NLR with CRP enhances diagnostic accuracy, making it a promising tool in clinical settings. The neutrophil-to-lymphocyte ratio (NLR) is increasingly recognized as a potential biomarker for neonatal sepsis due to its ability to reflect the balance between the innate and adaptive immune responses. Despite its promise, the use of NLR in clinical settings is hindered by several drawbacks. One significant limitation is that NLR is often measured at a single time point, which may not capture the dynamic nature of sepsis progression.[19] This static assessment can lead to misinterpretation of a patient's condition, particularly in cases where the clinical status may change rapidly. Additionally, many studies investigating NLR are cross-sectional, which restricts their ability to predict future outcomes and may introduce biases that affect the reliability of the findings.[20] Furthermore, the diagnostic accuracy of NLR can be questioned since its association with sepsis is frequently based on clinical features rather than confirmed blood cultures. This reliance on clinical diagnosis can lead to overdiagnosis or underdiagnosis of sepsis, especially in neonates where symptoms may be subtle. Another challenge is the variability in the cut-off values for NLR across different studies, which complicates the standardization of its use in clinical practice. This inconsistency can lead to confusion among healthcare providers regarding what constitutes a clinically significant NLR, ultimately affecting decision-making in the management of neonatal sepsis.

CONCLUSION:

Authors Contribution:
Zunaira Zulfiqar: Conception, design, analysis and interpretation of data and drafting of article
Unaiza Syed: Conception, design, analysis and interpretation of data and drafting of article
Syed Arsalan Hassan: Conception, design, analysis and interpretation of data and drafting of article
Nabeera Hayat: Conception, design, analysis and interpretation of data and drafting of article
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