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Diagnostic Accuracy of Platelet to Lymphocyte Ratio for Early Onset Neonatal Sepsis Keeping Blood Culture as Gold Standard

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Abstract

Objective: To compare the sensitivity and specificity of the platelet to lymphocyte ratio (PLR) in diagnosing neonatal sepsis when comparing it to blood culture as gold standard. **Study Design:** Prospective observational study. **Place and Duration of Study:** Department of Pediatrics, Combined Military Hospital, Sialkot from January – June 2024. **Methodology:** A total of 180 patients were included in the study further divided into Group-A and Group-B as culture positive and negative based on culture results sent at admission to the NICU. Platelet to lymphocyte ratio was calculated on the blood panel sent at the time of admission before starting anti-biotics. Primary variables observed were sensitivity and specificity of PLR in diagnosing early onset sepsis compared with blood culture results as gold standard. **Results:** The overall diagnostic parameters of PLR when compared to the gold standard blood culture results showed sensitivity of 91.7%, specificity of 91.3%, with a positive predictive value of 98.6%, negative predictive value of 61.8% with a diagnostic accuracy of 91.6%. **Conclusion:** We conclude that PLR provides good sensitivity and specificity of 91.7% and 91.3% with a diagnostic accuracy of 91.1% for early onset neonatal sepsis.

Key Words: Accuracy, blood, culture, diagnosis, lymphocyte, neonatal, platelet, sepsis

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 in the developing world is more than the projected prevalence worldwide with around 45-50 per 1000 live births in South-East Asia, especially in countries like Pakistan, Indian and Bangladesh.[3] This is attributed to poor ante-natal facilities and non-availability of well-maintained pediatric intensive care units (PICU).[4] Diagnosis of neonatal sepsis requires confirmation of microorganisms in blood cultures to tailor treatment strategies accordingly. The availability of blood culture in our medical setups and the time of result availability causes a constraint in early diagnosis of the condition. In low income countries where the facility cannot be provided in all pediatric setups, alternate, cost-effective and robust methods need to be employed to diagnose neonatal sepsis with acceptable accuracy.[5]

Early onset neonatal sepsis occurs in the first 72 hours after birth and requires diagnostic options which can reliably diagnose or segregate suspicious cases till the time results of more sensitive and specific tests arrive.[6] Recent studies have proposed other laboratory parameters in helping diagnose neonatal sepsis which are easy and generally available. Two of the methods are the

neutrophil lymphocyte ratio (NLR) and the platelet lymphocyte ratio (PLR). The PLR ratio is based on the principle of thrombocytosis and its relative increase in inflammatory conditions like sepsis and when titrated with lymphocytes, studies have indicated that a higher PLR ratio is strongly suggestive of neonatal sepsis.[7] Same principle is used for the NLR ratio for inflammatory and septic conditions. The parameter does not require expensive investigations and can be calculated with a simple blood complete picture or a peripheral blood film giving early insight into segregating patients with a high suspicion of neonatal sepsis early in the treatment phase to prevent any complications.[8] While the marker looks promising, comparing it to the gold standard methods for sensitivity and specificity for diagnostic accuracy needs to be determined in our setups for further recommendation and addition in standard diagnostic guidelines for better patient outcomes.

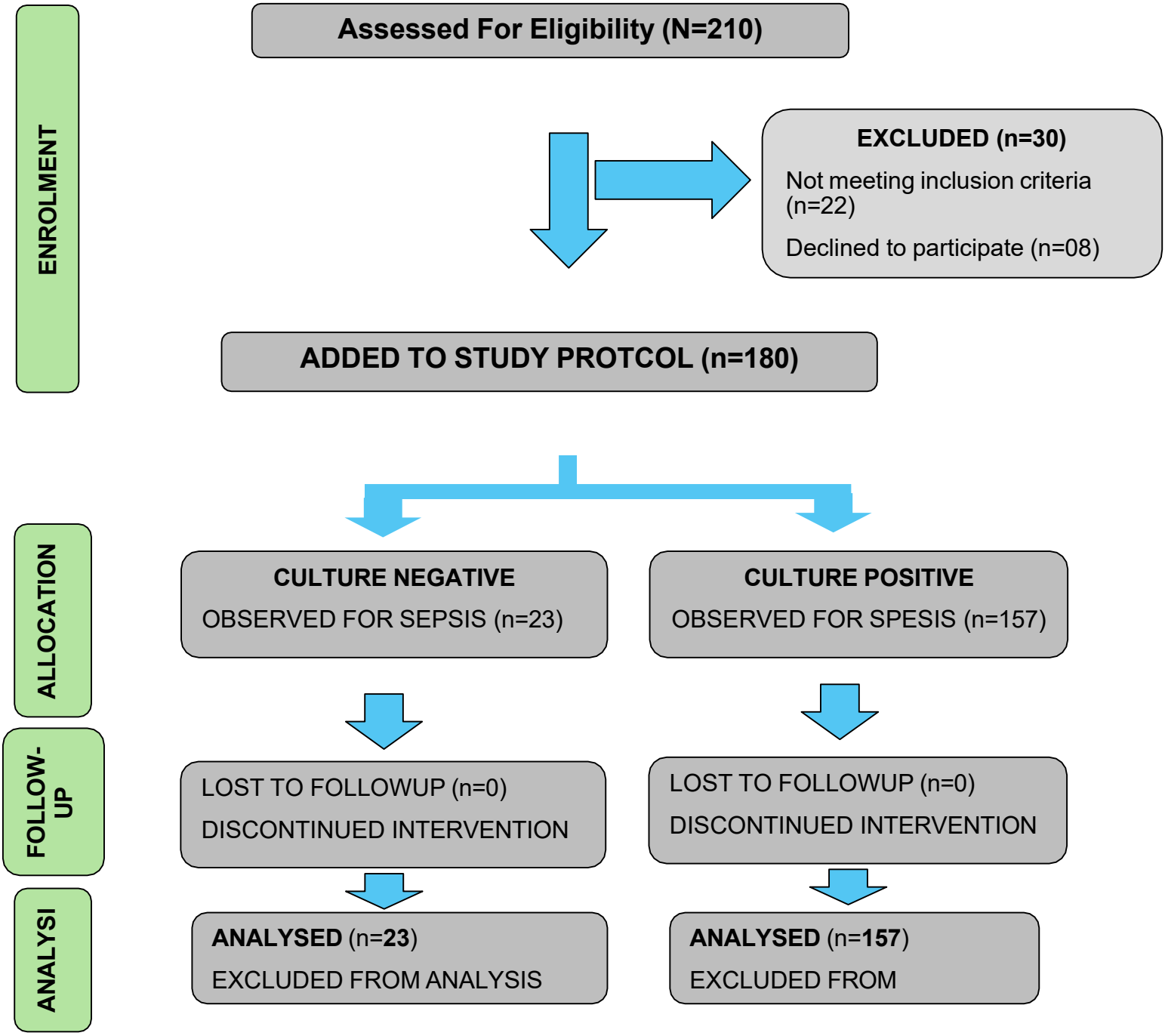
Methodology

This prospective observational study was carried out at the Department of Pediatrics, Combined Military Hospital, Sialkot from January – June 2024 after approval from the ethical review board vide letter no. The sample size was calculated keeping the confidence interval at 95%, margin of error at 5% with the anticipated diagnostic specificity of the PLR ratio at 94.7% versus 100% for diagnostic blood culture.[9] Minimum sample size according to WHO calculator came out to be 141 patients. We included 180 patients in the final study protocol keeping margin for lost to follow-up and inconclusive results for the diagnostic tests. **Inclusion criteria** included all in-hospital born neonates, till 72 hours of birth shifted to the NICU with suspicion of early onset neonatal sepsis clinically. **Exclusion criteria** included all out of hospital born neonates, patients with admission after 72 hours after birth, patients with critical cardiac congenital abnormalities, patients lost to follow-up and non-consent of parents or next of kin to be included in the study.

The study method included all patients as per the inclusion criteria furnished. A written informed consent was taken from parents or next of kin of all patients to be included in the study protocol and all ethical concerns were addressed. After admission into the NICU for all patients with a post-birth age less than 72 hours suspected for early neonatal sepsis, demographic data including age, weight, gender, gestational age, mode of delivery were endorsed by a pediatric resident on duty unaware of the study protocol on a proforma. Vitals were recorded by the nursing staff including mean arterial pressure, heart rate, respiratory rate, temperature and random blood sugar. Neonates were added into the protocol for suspicion of early onset neonatal sepsis using the following 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).[10] According to the protocol, presence of two or more variables were considered as patients being candidates to be further evaluated for neonatal sepsis. The differential leucocyte count (DLC), absolute lymphocyte count (ALC) and platelet count (PC) were obtained, and PLR was calculated and recorded within an hour of admission in the NICU. Blood cultures taken from two separate intravenous sites were taken before the start of anti-biotic regimens in all patients to be compared with the PLR and compare variables of study. The calculated values and blood reports received were 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. Patients were designated as culture negative or positive if organisms were isolated on culture samples sent at the time of admission and divided into Group-A for culture positive and Group-B for culture negative patients. Cut-off values of PLR and outcome variables were segregated for confirmed and unconfirmed cases on the basis of culture being negative or positive as the gold standard. PLR recorded at the time of admission was then co-related with the culture results and analyzed for sensitivity and specificity

in diagnosing early onset neonatal sepsis. Receiver operator characteristics (ROC) curve was used to find the suitable cut-off value with the maximum sensitivity and specificity for the condition. Primary variables observed were sensitivity and specificity of PLR in diagnosing early onset sepsis compared with blood culture results as gold standard. 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 PLR 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.

Figure-I: Phases of the Study



Results

A total of 210 patients were assessed for the study with 180 patients added to the final study protocol which met the inclusion criteria. Based on culture results, all patients were divided into the culture positive group (Group-A) (n=157) and culture negative group (Group-B) (n=23). Mean age of patients between both groups was 40.43±15.52 hours versus 40.83±15.05 hours (p=0.910). Gender distribution revealed 103 (65.6%) males and 54 (34.4%) females in Group-A versus 17 (73.9%) males and 06 (26.1%) females in Group-B (p=0.430). Gestational age in the study group showed pre-term neonates being 129 (82.2%) in Group-A versus 14 (60.9%) in Group-B and 28 (17.8%) versus 09 (39.1%) at term between both groups (p=0.018). Weight distribution revealed extremely low birth weight in 07 (4.5%) versus 03 (13.0%), very low birth weight in 94 (59.9%) versus 19 (82.6%), low birth weight in 46 (39.3%) versus 04 (4.3%) and normal birth weight in 10 (6.4%) versus 00 (0%) patients between both groups (p=0.014). Maternal risk factors reported in the last trimester with a causal link to early onset neonatal sepsis showed vaginitis in 45 (28.7%) versus 10 (43.5%) patients, urinary tract infection in 44 (28.0%) versus 09 (39.1%) patients and early membrane rupture was reported in 37 (23.6%) versus 01 (4.3%) patients (Table-I).

Receiver operative characteristics (ROC) for PLR revealed a strong diagnostic strength of the test with area under the curve at 0.933, asymptotic significance <0.001 with a suitable cut-off value for PLR for early onset neonatal sepsis being 44.0 having a sensitivity of 91.1% with a specificity of 95.7% for the value (Table-II). The overall diagnostic parameters of PLR when compared to the gold standard blood culture results showed sensitivity of 91.7%, specificity of 91.3%, with a positive predictive value of 98.6%, negative predictive value of 61.8% with a diagnostic accuracy of 91.6% (Table-III).

Table 1: Demographic Characteristics of the Study Group (N=180)

Variable	**Culture positive group-a (n=157)**	**Culture negative group-b (n=23)**	**P value**
Mean age (hours)	40.43±15.52	40.83±15.05	**0.910**
Gender			
Male	103 (65.6%)	17 (73.9%)	**0.430**
Female	54 (34.4%)	06 (26.1%)	
Gestational age			
Pre-term	129 (82.2%)	14 (60.9%)	**0.018**
Term	28 (17.8%)	09 (39.1%)	
Weight At Birth			
Extremely low birth weight (<1000 gram)	07 (4.5%)	03 (13.0%)	**0.014**
Very low birth weight (<1500 grams)	94 (59.9%)	19 (82.6%)	
Low birth weight (<2500 grams)	46 (39.3%)	04 (4.3%)	

Normal birth weight	10 (6.4%)	00 (0%)	
Maternal risk factors (last trimester)			
Vaginits	45 (28.7%)	10 (43.5%)	**0.099**
Urinary tract infection	44 (28.0%)	09 39.1%)	
Early membrane rupture	37 (23.6%)	01 (4.3%)	

Table 2: ROC Curve Characteristics for Early Onset Neonatal Sepsis Using PLR as a Diagnostic Marker (N=180)

AUC	Asymptotic significance	Upper bound	Lower bound
0.933	<0.001	0.971	0.895

Table 3: Sensitivity, Specificity, PPV And NPV Of PLR For Early Onset Neonatal Sepsis Versus Blood Culture (N=180)

	Blood Culture Findings	
	Early onset Neonatal Sepsis positive	Early onset Neonatal Sepsis negative
PLR positive for early onset neonatal sepsis	144 (91.7%)	02 (8.7%)
PLR negative for early onset neonatal sepsis	13 (8.3%)	21 (91.3%)
Sensitivity= True Positive/ (True Positive +False Negative) = **91.7%** **Specificity**= True Negative / (True Negative +False Positive) = **91.3%** **Positive Predictive Value**= True Positive/ (True Positive+ False Positive) = **98.6%** **Negative Predictive Value**= True Negative/ (True Negative +False Negative) = **61.8%** **Diagnostic Accuracy**= (True Positive +True Negative)/All Patients = **91.6%**		

Discussion

Our study concluded that PLR is a good and reliable biomarker for detection of early onset neonatal sepsis due to strong diagnostic accuracy complimented by high sensitivity and specificity. Zhang et al carried out a similar study comparing PLR with culture results and reported sensitivity and specificity of more than 90% in their study which is in line with results of our study as well.[11] Not only did they compare PLR to culture results but also NLR (neutrophil lymphocyte ratio) with similar results for sensitivity and specificity. This is very promising since both these biomarkers are cost-effective, easy to calculate giving strong prediction for early onset neonatal sepsis. A meta-analysis by El-Bai et al also concluded a strong diagnostic accuracy of PLR for early onset neonatal sepsis reporting sensitivity and specificity at ranges between 88-93% and specificity between 91-94% when comparing different studies.[12]

Demographic results of our study also showed important findings. While age and gender distribution were statistically comparable between both groups, birth weight was associated with a statistically significant association between early onset sepsis and positive culture results which isolation of organisms. A study by Kostlin et al reported a strong causal link between birth weight

and neonatal sepsis with very low birth weight being the most commonly affected.[13] A study on the same done on the local level by Shahzad et al showed that low birth weight neonates had a 83% increased chance of having neonatal sepsis than their normal counterparts.[14] In context, gestational age is also important since pre-term neonates are low birth weight in majority of the cases and pre-term birth is linked to poor immunity leading to increased chances of neonatal sepsis.[15] It is also well documented and reported that early neonatal sepsis is strongly associated with transmission of infection from affected mothers. Major risk factors reported are chorioamnionitis, early rupture of membranes, vaginitis and persistent urinary tract infections in the last trimester. These findings have been corroborated by our results as well but our study found the link to be clinically significant but it was not statistically significant.[16]

Local studies done in Pakistan on the subject show that PLR is a good biomarker for early diagnosis of neonatal sepsis. When comparing with other markers for diagnosis, NLR has been shown to be equally effective and sometimes providing a higher sensitivity than PLR for diagnosis of early onset neonatal sepsis.[17] Nevertheless, PLR shows excellent diagnostic accuracy around 91% which are also in line with a study done by Ashour et al.[18] These conclusive results and comparison to local studies concludes that PLR should be considered and used as an early marker for early neonatal sepsis in susceptible neonates with clinical signs suggesting infection. Not only is it cost-effective but can be performed and interpreted by doctors of all experience levels helping to incorporate this as a strong diagnostic tool in NICUs to be used by house officers, residents and consultants for segregating patients and designing more tailored treatment regimens for the best possible patient care.

Recommendations

The study recommends PLR to be a cost-effective, easy, and effective method in detecting early onset neonatal sepsis with good reliability and strong diagnostic power

Conclusion

We conclude that PLR provides good sensitivity and specificity of 91.7% and 91.3% with a diagnostic accuracy of 91.1% for early onset neonatal sepsis.

Limitations

The limitations are that the study is single center only. Secondly, since this marker is based on inflammatory responses to disease, undiagnosed inflammatory conditions other than neonatal sepsis can affect the results which were controlled by the study team using a strict inclusion criterion for keeping confounding factors at minimum

Conflict Of Interest

None

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