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ORIGINAL RESEARCH ARTICLE

DIAGNOSIS OF TWO TYPES OF NEONATAL SEPSIS USING A PRETESTED AND VALIDATED HEMATOLOGICAL SCORING SYSTEM AMONG THE NEONATES BORN IN A TERTIARY CARE HOSPITAL

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CONFLICT OF INTEREST: NIL

Background: preterm , low birth weight, and perinatal infections are some of the notable causal factors associated with early (EONS) and late-onset (LONS) subtypes. Early diagnosis is vital, in order to increase the survival rates among the newborn babies . In order to detect the subtypes for an early intervention Hematological scoring systems (HSS) has emerged as a lifesaving boon for early diagnosis of both EONS and LONS.

Objective: To ascertain the diagnostic efficiency of the modified hematological scoring system in detection of early and late onset neonatal sepsis.

Methods: In this prospective observational study, (n-100 neonates) were enrolled over 12 months. Clinical data and hematological parameters (including total White Blood Cell count, neutrophil count, immature-to-total neutrophil ratio, platelet count, and other relevant markers) were recorded at admission. The scoring system was applied, and its performance was analyzed by comparing the score with blood culture confirmation as the reference standard. Data were stratified by sepsis onset (early vs. late) and various parameters determining diagnostic efficiency such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results: Out of 100 newborn babies that were assessed – 50 belonged to early clinical sepsis and 50 had late clinical sepsis. Also in the second group, more severe hematological abnormalities—elevated IT ratios, abnormal PMN counts, and increased immature PMNs were seen. Degenerative PMN changes were more common in EONS. Klebsiella pneumoniae was the strongest and powerful pathogen determining the infectivity rate in both groups, and a thrombocyte count ≤150,000/mm³ remained the most reliable diagnostic marker with an accuracy of 81.7%.

Conclusion: This multifaceted index will serves as an important requisite in timely screening as well as confirming the provisional diagnosis for both the types of neonatal sepsis.

INTRODUCTION

Sepsis among newborn babies is one of the reigning causes of morbidity and mortality worldwide. Its presentation is often non-specific, and early diagnosis is of paramount importance for prompt treatment to improve outcomes. Globally, three million annual newborn diagnosed with sepsis have occurred out of which India has the highest number of incidental clinical sepsis (17,000/ 1,00,000 live births) [1]. The killing power of sepsis among newborn babies ranges between 25% to 65% in India [2, 3].

The key presenting factors of neonatal sepsis often range from evident signs to severe systemic involvement. Some of the commonly presented clinical diagnoses include septic shock, pneumonia, meningitis, osteomyelitis, arthritis and urinary tract infections[4]. Accurate and timely diagnosis is crucial for initiating immediate antibiotic treatment, which is imperative for improving outcomes.

Identification of risk factors has effectively helped in bringing down the cases of neonatal sepsis. When the trends were observed it was noted this disease frequently occurred in developing nations, driven by numerous contributing factors. These include low birth weight, premature birth, suboptimal APGAR scores at delivery, and socioeconomic challenges. Other important predisposing factors encompass premature rupture of membranes (PROM), acute and chronic maternal infections, Group B Streptococcal carriage, as well as complicated and complex infections like foul-smelling amniotic fluid or meconium-stained liquor [5]. In terms of understanding the culture and causal agents it was seen that, infections were predominantly caused by Gram-negative organisms like Klebsiella spp, Escherichia coli, and Acinetobacter. Other causal agents included Grampositive organisms like Staphylococcus aureus and coagulase-negative Staphylococci [6].

Though laboratory tests such as cultures are considered the gold standard since it easily detects upto 30-75% cases. The time required to diagnose may exceed upto 72hrs by which the cases could have progressed rapidly and complications would have developed easily [7].

In response to these challenges, a rapid screening tool, called as the Hematologic Sepsis Index was developed. This index utilizes various hematological tests to enable early diagnosis and timely intervention, thereby reducing neonatal morbidity and mortality. However, due to repeating pattern of parameters, such as band count and immature-to-mature ratios, a Modified Hematological Sepsis Scoring System (HSS) also called as Modified Hematological Sepsis Index was introduced. [8,9,14]

The Modified Hematological Sepsis Index is scored as likelihood of sepsis: ≤2, Sepsis unlikely 3–4, Probable Septic infection ≥5. The variables that constitute the index are as follows:

Absolute Neutrophil Count:

Neutropenia, an inconsequential indicator of sepsis, results from increased neutrophil consumption at infection sites and endothelial adhesion. In the Modified Hematological Sepsis Index it occupies greater diagnostic significance, scored at two points [8,9].

Total WBC count

CBC parameters gain diagnostic relevance for early-onset sepsis (EOS) after the initial 4 hours. While leukocyte count fluctuations are common in sepsis, the fluctuating values makes it challenging in accepting the reliability [10,14]

Platelet Count:

Decreased Platelet count with disseminated intravascular coagulation (DIC) and the harmful effects of endotoxins, leads decreased platelet levels. One of the most notable signs in Neonatal Sepsis [11,14]

Immature Cells:

Bone marrow releases immature cells, that are elevated if the newborn shows any signs of sepsis.

Toxic Granules and Döhle bodies

Toxic granules, formed during the promyelocyte phase of neutrophil maturation, enhance bacterial destruction by acidifying phagosomes to an optimal pH (5.5). The production of toxic granules is increased remarkably in late onset neonatal sepsis. Neutrophilic vacuoles, commonly seen with toxic granules, are key indicators of sepsis, while Döhle bodies are frequently associated with bacterial infections. [12] [14].

Nucleated RBCs:

Immature erythrocytes are produced in response to hypoxia, stress, and erythropoietin release during sepsis. Since, this factor is included with the preexisting factors, it will be resourceful in limited settings[13].

Since, there are few studies focused on the usage of modified Hematological scoring index together in dual diagnosis of both early and late onset neonatal sepsis. The following study was done.

METHODOLOGY

The study was conducted in the Department of Pathology over a one-year period from January 12, 2023, to January 12, 2024. Preterm and Term Neonates showing signs and symptoms of any of the two types of sepsis, samples were collected and evaluated . Exclusion criteria included cases without consent to participate, post term neonates, non-availability of blood culture samples, neonates with congenital anomalies affecting blood parameters, neonates diagnosed with pathological jaundice and those who received prior antibiotic treatment before sample collection were not included in the study. Based on the diagnostic timestamp for Sepsis, they were categorized as

- Early-Onset Neonatal Sepsis (EONS): Sepsis diagnosed within the first 72 hours of life.
- Late-Onset Neonatal Sepsis (LONS): Sepsis diagnosed after 72 hours of life.

As per study conducted by Baruwal S et al [14]

Using, Sensitivity 90.48% Where, Z = 1.96 in 95%CI d = precision i.e. 0.10., P=0.35

$N= Z^2$ x Sensitivity(1-Sensitivity)/d2 X P

=1.96x1.96x0.9048 (1-0.9048)/0.1x0.1x0.35

=3.84x0.08613696/0.0035 =0.330765926/0.0035 =94.5 i.e. 94

round off to **100 neonates**

After a comprehensive review by Institutional Ethics Committee (IEC), Ethical clearance was obtained. Parents were detailed on various tests that had to be performed and line of action in regards to combating sepsis, after which a written consent was obtained before the neonates were included in the study.

Protocol

- Choice of the patients: After garnering information from the parents or guardians of the affected newborns based on the inclusion criteria, newborns were chosen and the entire process was documented.

- Sample Collection: Following strict aseptic protocols, 2 ml of venous blood was collected from neonates clinically suspected of sepsis and meeting the inclusion criteria. Under sample processing, 1ml blood was used for culture and identifying sensitivity and resistance.

- Hematological Study: The remaining 1 ml of blood was treated with EDTA as an anticoagulant and set aside for detailed hematological analysis.

After Collecting blood samples,

- An ml of blood was inoculated into blood culture bottles (Bact/ALERT Pediatric Aerobic Bottles).Principle:
    - A liquid emulsion sensor at the bottom, separated by a selectively permeable membrane, detects CO_2 from microbial growth. The CO_2 diffuses across the membrane, triggering a reaction that lowers pH, signaling bacterial presence. The system's algorithm analyzes the rate of CO_2 concentration change to detect microbial growth.
- Sub culturing:
    - Bottles producing an alert signal were processed further:
        - Blood was subculture onto Blood Agar and MacConkey Agar plates.
        - The growth was isolated observing the protocols
        - Segregated growth was further studied in detail Antimicrobial susceptibility testing was performed using commonly used antibiotics in the institution.
- Negative Reporting:
    - Bottles that did not produce an alert signal within 5 days were reported as culture-negative.

Procedure for Hematological Study

- Leucocyte and Platelet Count:
    - White blood cells and platelets were measured and analyzed using the BeneSphere 5-part hematology analyzer H51.
    - Results were verified through manual cross-checking to ensure accuracy.
- Preparation of Peripheral Smears:
    - Peripheral blood smears were prepared and stained using the Jenner-Giemsa stain.
- Microscopic Examination:
    - The following parameters were assessed on the stained smears:
        - Differential leucocyte count (DLC)
        - Absolute neutrophil count (ANC)
        - Immature-to-mature neutrophil ratio
        - Presence of nucleated red blood cells (nRBCs)

The index as outlined in **Table 1**, was utilized to determine the score for each blood sample.

- Calculation of Immature-to-Total (IT) Neutrophil Ratio:

- This variablederived by dividing the total count of immature neutrophils by the total neutrophil count.
- Assessment of Nucleated RBCs (nRBCs):
  - The presence of nucleated RBCs was evaluated, using a cutoff value of 5% for the analysis.

Parameter	Score: 0	Score: 1	Score: 2
Total WBC count	5,000–25,000/mm³	25,000–30,000/mm³ (or <5,000)	>30,000/mm³
Immature-to-Total (IT) Ratio	<0.2	0.2–0.4	>0.4
Thrombocyte count	>150,000/mm³	100,000–150,000/mm³	<100,000/mm³
Micro-ESR	<15 mm	15–20 mm	>20 mm
Nucleated RBC (nRBC)	<5%	Not applicable	≥5%
Degenerative Changes in PMNs	Absent	Mild	Moderate/Severe

Table 1 Modified Hematological Sepsis Scoring System (MHSSS)

Upon admission, Demographics (age, gender, birth weight, gestational age), and clinical signs were recorded. After initial assessment, Hematological standards to be evaluated were procured and analyzed from the samples and neonates were classified as EONS or LONS based on the lead time.

After classifying the neontaes as EONS or LONS, A modified scoring system (range 0–10) was applied based on results of the above parameters. Each parameter was assigned a score, and a cumulative score obtained was used to grade the level indicated a positive predictive value for sepsis.

Statistical Analysis

Data were cleaned, entered and analyzed using IBM Statistical Package for Social Sciences (SPSS) ver 27. Mean values, standard deviations, and proportions were calculated.

- Comparisons: Differences between the sepsis groups (EONS and LONS) were assessed using t-test.
- Diagnostic efficiency evaluated by using Sensitivity, specificity, PPV, and NPV of the HSS.

RESULTS

Table 1. Clinical Variables and Patient Demographics

Parameter	*EONS (n = 50)*	*LONS (n = 50)*
Age at onset (days)	2.1 ± 0.6	7.8 ± 3.4
Gestational Age (weeks)	36.5 ± 2.8	35.2 ± 3.1
Weight of neonate (grams)	2500 ± 450	2300 ± 400
Hospital Residence time(days)(mean±SD)	17.46 ± 17.48	19.00 ± 15.48
Outcome (deaths)	30(60%)	38(76%)

EONS occurs earlier (2.1 ± 0.6 days) than LONS (7.8 ± 3.4 days) and is associated with slightly higher gestational age (36.5 ± 2.8 weeks vs. 35.2 ± 3.1 weeks) and birth weight (2500 ± 450 grams vs. 2300 ± 400 grams). Hospital stays are longer in LONS (19.00 ± 15.48 days) compared to EONS (17.46 ± 17.48 days), and mortality is notably higher in LONS (76% vs. 60%). Male predominance is observed in both groups, slightly higher in EONS (75%) than LONS (65%). These differences highlight the increased severity and vulnerability in LONS cases.

Table 2 "Distribution of Organisms in Blood Cultures for Early and Late-Onset Sepsis

Blood Culture Isolated Organism	Early Onset Sepsis (n=50)	% (Early)	Late Onset Sepsis (n=50)	% (Late)
Klebsiella pneumoniae	20	40%	14	28%
Pseudomonas aeruginosa	5	10%	8	16%
Acinetobacter	3	6%	10	20%
CONS	15	30%	8	16%
MRSA	2	4%	0	0%
B streptococci	0	0%	2	4%
Streptococcus pneumoniae	1	2%	0	0%
Staphylococcus aureus	2	4%	2	4%
Escherichia coli	0	0%	4	8%
Enterobacter	1	2%	1	2%
Salmonella	0	0%	1	2%
Stenotrophomonas	1	2%	0	0%

Klebsiella pneumoniae is the most commonly isolated organism in both EONS (40%) and LONS (28%), indicating its prominence in neonatal sepsis across both onset groups. Followed by Coagulase-Negative Staphylococci (CONS) as the second most frequent pathogen in EONS (30%), which appears significantly higher than in LONS (16%). *Streptococcus pneumoniae* and *Stenotrophomonas* are only seen in EONS, albeit at a very low frequency (2% each). Additionally, *Escherichia coli*, *B streptococci*, and *Salmonella* are uniquely isolated in LONS at lower frequencies (8%, 4%, and 2%, respectively).

Table 3. Hematological Scoring System Parameters

Variable	EONS (n=50)(%)	LONS (n=50)(%)
IT ratio > 0.2	15 (30)	32 (64)
PMN count < 1,800/mm³ or > 5,400/mm³	10 (20)	20 (40)
IM ratio ≥ 0.3	12 (24)	23 (46)
Immature PMN count > 500/mm³	5 (10)	16 (32)
Leukopenia ≤ 5,000/mm³ or leukocytosis ≥ 30,000/mm³	9 (18)	10 (20)
Degenerative changes in PMN	8 (16)	2 (4)
Thrombocyte count ≤ 150,000/mm³	17 (34)	31 (62)
Total score >5 within 24 hrs >5 within > 24 hrs	 38(76%) 0	 0 41(82%)
Total score (Mean ± SD)	8.1± 5.3	14± 7.2

LONS exhibits more severe hematological abnormalities compared to EONS, with IT Ratio > 0.2 being more common (64% vs. 30%) and abnormal PMN counts twice as frequent (40% vs. 20%). Elevated IM ratio (46%) and Immature PMN Count > 500/mm³ (32% vs. 10%) are significantly higher in LONS, while degenerative changes in PMN are predominantly observed in EONS (16%). Thrombocytopenia is markedly higher in LONS (62% vs. 34%), indicating greater platelet consumption or destruction. Additionally, 82% of LONS cases surpass the score threshold

beyond 24 hours, highlighting its progressive nature. The mean total score is significantly elevated in LONS (14 ± 7.2) compared to EONS (8.1 ± 5.3), emphasizing the greater severity of late-onset sepsis.

Table 4 Comparison of Mean ± SD Scores Between EONS and LONS for Hematological Parameters"

VARIABLE	EONS (MEAN ± SD)	LONS (MEAN ± SD)	T-VALUE	P-VALUE
IT RATIO > 0.2	0.6 ± 0.4	1.3 ± 0.6	-5.10	< 0.001
PMN COUNT < 1,800/MM³ OR > 5,400/MM³	0.4 ± 0.4	0.8 ± 0.6	-3.65	0.010
IM RATIO ≥ 0.3	0.5 ± 0.3	0.9 ± 0.7	-4.12	0.003
IMMATURE PMN COUNT > 500/MM³	0.2 ± 0.2	0.6 ± 0.5	-6.23	< 0.001
LEUKOPENIA ≤ 5,000/MM³ OR LEUKOCYTOSIS ≥ 30,000/MM³	0.4 ± 0.3	0.4 ± 0.5	-0.54	0.605
DEGENERATIVE CHANGES IN PMN	0.3 ± 0.2	0.1 ± 0.2	4.78	0.002
THROMBOCYTE COUNT ≤ 150,000/MM³	0.7 ± 0.5	1.2 ± 0.7	-5.90	< 0.001

The comparison reveals significant hematological differences between EONS and LONS. The mean IT ratio is notably higher in LONS (1.3 ± 0.6) compared to EONS (0.6 ± 0.4) with strong statistical significance (p-value < 0.001). Similarly, PMN count abnormalities (0.8 ± 0.6 vs. 0.4 ± 0.4) and IM ratio elevations (0.9 ± 0.7 vs. 0.5 ± 0.3) are significantly more pronounced in LONS (p-values of 0.010 and 0.003, respectively). Immature PMN counts are markedly elevated in LONS (0.6 ± 0.5) compared to EONS (0.2 ± 0.2), showing strong significance (p-value < 0.001). In contrast, leukopenia or leukocytosis displays no meaningful variation between EONS and LONS. Degenerative changes in PMN are more prominent in EONS (0.3 ± 0.2 vs. 0.1 ± 0.2, p-value = 0.002), while thrombocyte counts are significantly lower in LONS (1.2 ± 0.7 vs. 0.7 ± 0.5, p-value < 0.001). These findings underscore the greater severity and distinct pathological differences in LONS compared to EONS.

Table 5. Diagnostic Efficiency of the Hematological Scoring index

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
IT ratio > 0.2	80	62.5	72.7	71.4	72.5
Neutrophil count 1,800/mm³- 5,400/mm³	60	50	60.0	50.0	54.2
IM ratio ≥ 0.3	70	55	66.0	59.5	63.3
Immature PMN count > 500/mm³	55	37.5	50.0	42.9	47.5
Leukopenia ≤ 5,000/mm³ or leukocytosis ≥ 30,000/mm³	62	45	56.0	51.4	53.3
Degenerative changes in PMN	45	75	64.3	66.7	65.0
Thrombocyte count ≤ 150,000/mm³	84	75	80.8	78.9	81.7

Thrombocyte Count ≤ 150,000/mm³ demonstrates the highest diagnostic accuracy (81.7%), supported by excellent sensitivity and specificity, making it the most reliable parameter for neonatal sepsis. *Degenerative Changes in PMN* has high specificity but lower sensitivity, achieving moderate accuracy (65%). Finally, *Immature PMN Count > 500/mm³* performs weakest, with poor sensitivity, specificity, and accuracy (47.5%). While *Thrombocyte Count* is the most robust parameter, others may require complementary diagnostics for improved reliability.

DISCUSSION

EONS occurs earlier (2.1 ± 0.6 days) than LONS (7.8 ± 3.4 days) and is associated with slightly higher gestational age (36.5 ± 2.8 weeks vs. 35.2 ± 3.1 weeks) and birth weight (2500 ± 450 grams vs. 2300 ± 400 grams). Hospital stays are longer in LONS (19.00 ± 15.48 days) compared to EONS (17.46 ± 17.48 days), and mortality is notably higher in LONS (76% vs. 60%). Male predominance is observed in both groups, slightly higher in EONS (75%) than LONS (65%).. Similar to study by **Bulkowstein et al** [15]: where on studying the characteristics of EONS and community-acquired LONS in infants under 3 months, higher rates of prematurity (42.9% vs. 17.0%), premature rupture of membranes (22.9% vs. 1.9%), and mortality (20.0% vs. 5.3%) in EONS was noted and Longer hospital stays in EONS (23.3 ± 25.1 days) compared to LONS (10.3 ± 8.6 days). These differences highlight the increased severity and vulnerability in LONS diagnosis.

In our study *Klebsiella pneumoniae* was the most prevalent and recurring isolated organism in both EONS (40%) and LONS (28%), indicating its prominence in neonatal sepsis across both onset groups. Similar to the studies done by **Turkmen MK et al [16], Aksoy et al [17]** and **Ozkan et al [18]** in Turkey, and also **Boghossian NS et al [19]** in her study says Klebsiella, streptococcus were the common causative organisms of neonatal sepsis.

In our study, Thrombocytopenia was markedly higher in LONS (62% vs. 34%), indicating greater platelet consumption or destruction. Additionally, 82% of LONS cases surpass the score threshold beyond 24 hours, highlighting its progressive nature. The mean total score is significantly elevated in LONS (14 ± 7.2) compared to EONS (8.1 ± 5.3), emphasizing the greater severity of late-onset sepsis. **Ogundare et al [20]** in a Nigerian hospital found similar lower mean platelet count in EONS compared to LONS. Reason identified was low birth weight and perinatal asphyxia were significant risk factors for EONS, and delivery outside the health facility for LONS. **Sofouli et al [21]** developed and validated a sepsis prediction score (SPS) using clinical and laboratory parameters, including platelet count and CRP and found that a score ≥ 3 could predict sepsis with good sensitivity, specificity, and accuracy in both retrospective and prospective cohorts of suspected LONS. Similar to our study where 41 (82%) easily presented with score of >5 after 24 hours in LONS.

The comparison reveals significant hematological differences between EONS and LONS. Immature PMN counts were markedly elevated in LONS (0.6 ± 0.5) compared to EONS (0.2 ± 0.2), showing strong association. Similarly **Makkar et al [22] in his paper** evaluated HSS and found immature PMN count to be the most sensitive and I:M PMN ratio the most specific indicator of sepsis, also it was seen that HSS had higher sensitivity and specificity in preterm neonates. These findings underscore the greater severity and distinct pathological differences in LONS compared to EONS [22].

Thrombocyte Count ≤ 150,000/mm³ demonstrates the highest diagnostic accuracy (81.7%), supported by excellent sensitivity and specificity, making it the most reliable parameter for neonatal sepsis. Moderate diagnostic accuracy, was seen in *IT Ratio > 0.2* and *IM Ratio ≥ 0.3* establishing them as on e of the dependable indicators. Similarly, in other study by **Pramana et al [23]** concluded that the Hematological Scoring Index has a sensitivity of 80.9%, specificity of 92.7%, and accuracy of 88.7% with a cut-off score ≥ 5 making it a reliable and good diagnostic tool. Other studies by **Adhikari et al [24]** evaluated a Modified HSS incorporating nucleated RBC and increased weightage for neutropenia. According to this study, mostly all culture positive samples of suspected neonatal sepsis showed the scoring of >5 confirming the tool is reliable, acceptable and feasible. Their study reported a sensitivity of 96.83% and specificity of 90.48% for nucleated RBC. **Shalini et al [25]** also noted the significance of nucleated RBC in neonatal sepsis and presented with similar findings in her study.

CONCLUSION

The study highlights distinct clinical and immunological profiles for early- and late-onset neonatal sepsis. Although both forms share common pathogens, differences in clinical presentation and hematological responses suggest unique underlying mechanisms and disease progressions. The findings imply that late-onset sepsis tends to follow a more severe course, which reinforces the importance of prompt and specialized diagnostic strategies. Moreover, the evaluation of hematological markers proves crucial, as specific parameters emerge as reliable indicators for early detection and risk assessment. These insights advocate for the development of tailored clinical approaches to enhance early intervention and improve neonatal outcomes.

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