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EVALUATION OF THE EXTENDED SICK NEONATAL SCORE AND ITS CORRELATION WITH BLOOD CULTURE IN NEONATES WITH SUSPECTED EARLY-ONSET SEPSIS IN A TERTIARY HEALTH CARE CENTRE- A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: *Neonatal sepsis remains a major contributor to neonatal morbidity and mortality worldwide, particularly in low- and middle-income countries. Early-onset sepsis (EOS), occurring within the first 72 hours of life, poses significant diagnostic challenges due to its nonspecific clinical presentation, often necessitating empirical antibiotic therapy. Although blood culture is the gold standard, its limited sensitivity and delayed results restrict timely decision-making. Conventional biomarkers like C-reactive protein (CRP), procalcitonin, total leukocyte count (TLC) lack consistent diagnostic accuracy. The Extended Sick Neonatal Score (ESNS), a validated clinical scoring system, has been proposed for assessing illness severity and predicting mortality in neonates.*

Objective*: To evaluate the Extended Sick Neonatal Score and Its Correlation with Blood Culture in Neonates with Suspected Early-Onset Sepsis in a Tertiary Health Care Centre*

Methods*: Study included 80 neonates meeting predefined inclusion criteria after obtaining parental consent. Maternal and neonatal demographic data were recorded. ESNS was assessed at 48 and 72 hours of life , correlated with blood culture, complete blood count, CRP, procalcitonin, urinary, serum sTREM-1 levels as per NICU protocols.*

Results*: Urinary sTREM-1 demonstrated a moderate positive correlation with procalcitonin at 48 hours ($r = 0.41$, $p < 0.001$), which reversed to a moderate negative correlation at 72 hours ($r = -0.41$, $p < 0.001$). No significant correlation was observed between urinary sTREM-1 and TLC, serum sTREM-1, or ESNS at either time point ($p > 0.05$). ESNS scores at 48 and 72 hours did not differ significantly between culture-positive and culture-negative groups ($p > 0.05$). While no association was found between ESNS and CRP at 48 hours ($p = 0.593$), a significant association emerged at 72 hours ($p = 0.035$).*

Conclusion*: ESNS has limited utility as a standalone tool for diagnosing culture-positive EOS. However, it may be valuable in assessing disease progression and inflammatory status, particularly when used in conjunction with biomarkers such as CRP.*

Keywords*: Neonatal sepsis, Early-onset sepsis, Extended Sick Neonatal Score, Blood culture, C-reactive protein, Neonates*

INTRODUCTION

Neonatal sepsis remains one of the leading causes of neonatal morbidity and mortality worldwide, particularly in low- and middle-income countries where the burden of neonatal infections is disproportionately high. Early-onset neonatal sepsis (EOS), defined as sepsis occurring within the first 72 hours of life, is commonly acquired through vertical transmission of microorganisms from the maternal genital tract and is associated with significant adverse outcomes if not recognized and treated promptly (1). Despite advances in neonatal care, EOS continues to pose a significant diagnostic and therapeutic challenge in neonatal intensive care units.The clinical presentation of neonatal sepsis is often subtle and non-specific,

including symptoms such as respiratory distress, temperature instability, lethargy, poor feeding, and hemodynamic instability. These manifestations may overlap with several non-infectious neonatal conditions, making early diagnosis difficult (2). Consequently, neonates with suspected sepsis are frequently started on empirical broad-spectrum antibiotics while awaiting laboratory confirmation. Although this strategy aims to prevent severe complications and mortality, it often results in unnecessary antibiotic exposure, prolonged hospitalization, and increased risk of antimicrobial resistance (3).

Blood culture remains the gold standard for confirming neonatal sepsis. However, its diagnostic accuracy is limited due to factors such as the pauci-bacterial nature of neonatal infections, small blood sample volumes, delayed culture positivity, and prior maternal antibiotic exposure, which may lead to false-negative results (4). These limitations highlight the need for adjunctive diagnostic approaches that can facilitate early identification of neonates at risk of sepsis.Inflammatory biomarkers such as C-reactive protein (CRP), procalcitonin, and leukocyte indices are commonly used in the evaluation of suspected neonatal sepsis. However, when used individually, these biomarkers demonstrate variable sensitivity and specificity and may also be elevated in non-infectious inflammatory conditions, thereby limiting their diagnostic reliability (5). Therefore, combining clinical evaluation with laboratory parameters may improve diagnostic accuracy.

Clinical scoring systems provide a structured approach for assessing the severity of illness in neonates using readily available clinical parameters. The Extended Sick Neonatal Score (ESNS) has been proposed as a practical bedside scoring system to assess the physiological status of sick neonates. Such scoring systems may help in early identification of neonates at risk of sepsis and facilitate timely therapeutic interventions, especially in resource-limited settings (6).

Objectives of the study:

Primary Objective

To determine the correlation between Early Neonatal Sepsis Score (ESNS) and inflammatory biomarkers (CRP, procalcitonin, and leukocyte indices) in neonates evaluated for early-onset sepsis.

Secondary Objectives

2. To evaluate the diagnostic association between ESNS and blood culture positivity.

Source of data: The data will be collected from newborns admitted in neonatal intensive care unit with suspected sepsis during the study period who fulfil the inclusion criteria and provide written informed consent.

Study design: A cross sectional observational study.

Study period:4 months, or till the sample size is met.

Method of collection of data:

Inclusion Criteria:

All neonates aged ≤72 hours of life admitted to the neonatal intensive care unit (NICU) or postnatal wards with suspected early-onset sepsis.

Neonates presenting with clinical features suggestive of sepsis, including but not limited to:

Respiratory distress

Temperature instability

Lethargy or poor activity

Poor feeding

Apnea or cyanosis

Hypotension or poor perfusion.

Neonates with maternal risk factors for early-onset sepsis, such as:

Prolonged rupture of membranes (>18 hours)

Maternal fever during labor

Foul-smelling liquor

Maternal urinary tract infection or chorioamnionitis.

Neonates whose parents or guardians provide informed consent for participation in the study.

Exclusion Criteria:

Neonates with major congenital anomalies or chromosomal abnormalities.

Neonates with inborn errors of metabolism.

Neonates who have received antibiotics before admission to the study center.

Neonates with surgical conditions requiring immediate intervention.

Sample size:

The sample size for the present study was estimated based on previous studies evaluating the Extended Sick Neonatal Score (ESNS) and neonatal sepsis outcomes in neonatal intensive care units, where the proportion of neonates with significant illness/sepsis was reported to be approximately 25%.

The sample size was calculated using the formula

$$n = (Z^2 \times p \times (1 - p)) / d^2$$

$$n = (1.96^2 \times 0.25 \times (1 - 0.25)) / 0.10^2$$

$n = (3.84 \times 0.25 \times 0.75) / 0.01$

$n = (3.84 \times 0.1875) / 0.01$

$n = 0.72 / 0.01$

$n = 72$

Where:
p represents the anticipated proportion derived from previously published data, Z = 1.96 at 95% confidence level ($\alpha = 0.05$), and absolute precision (d) was considered as 10%.

Substituting these values (p = 0.25 and d = 0.10), the calculated minimum sample size was 72 neonates.

Considering feasibility and to account for possible missing or incomplete data, the sample size was rounded to 80 neonates.

Therefore, a minimum of 80 neonates with suspected early-onset sepsis will be included in the study.

METHODOLOGY:

All neonates fulfilling the inclusion criteria will be enrolled in the study after obtaining written informed consent from the parents or guardians. A detailed history including maternal risk factors, perinatal events, and neonatal clinical features suggestive of early-onset sepsis will be recorded using a structured data collection proforma.

Baseline demographic and clinical details including gestational age, birth weight, sex, mode of delivery, Apgar scores, and maternal risk factors for sepsis will be documented at the time of admission.

A thorough clinical examination will be performed, and the Extended Sick Neonatal Score (ESNS) will be calculated for each neonate based on the clinical parameters at 48 hrs of life .

Laboratory Evaluation

Under strict aseptic precautions, blood samples will be collected at the time of initial evaluation (at 48 hours of life) for the following investigations:

Total leukocyte count

C-reactive protein (CRP)

Procalcitonin

Blood culture and sensitivity

To improve diagnostic accuracy and account for the delayed rise of inflammatory biomarkers, CRP and leukocyte indices will be reassessed at 48 hours after the initial evaluation.

Clinical Monitoring

All enrolled neonates will be closely monitored clinically during hospitalization, and relevant clinical findings will be documented. The Extended Sick Neonatal Score may be reassessed at 48 hours of life to evaluate changes in the clinical status of the neonate.

Data Recording

All collected information including clinical findings, ESNS values, inflammatory biomarker levels, and blood culture results will be systematically recorded in a structured case record proforma for subsequent analysis.

7.7 Statistical analysis:

Data will be entered into Microsoft Excel and analyzed using SPSS version 22 (IBM SPSS Statistics, Somers NY, USA).

Descriptive statistics will be used to summarize the baseline characteristics of the study population. Continuous variables such as gestational age, birth weight, inflammatory biomarker levels, and Extended Sick Neonatal Score (ESNS) will be expressed as mean ± standard deviation (SD) or median with interquartile range, while categorical variables such as sex, maternal risk factors, and blood culture results will be expressed as frequencies and percentages.

The Chi-square test or Fisher's exact test will be used to assess the association between categorical variables, including ESNS categories and blood culture positivity. The Student's t-test or Mann–Whitney U test will be used for comparison of continuous variables between groups where appropriate.

Correlation between Extended Sick Neonatal Score and inflammatory biomarkers (CRP, procalcitonin, and leukocyte indices) will be assessed using Pearson or Spearman correlation coefficient, depending on the distribution of the data.

The diagnostic performance of ESNS for predicting blood culture positivity will be evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver Operating Characteristic (ROC) curve analysis will be used to determine the optimal cutoff value of ESNS for predicting blood culture positivity.

A p value of <0.05 will be considered statistically significant after assuming all the rules of statistical tests.

Statistical software used: MS Excel and SPSS version 22 (IBM SPSS Statistics, Somers NY, USA).

ETHICAL CONSIDERATIONS

The study was conducted in accordance with ethical principles and institutional guidelines. Approval was obtained from the Institutional Ethics Committee prior to initiation of the study. Written informed consent was obtained from the parents or legal guardians of all enrolled neonates after explaining the study procedures in their native language. Confidentiality of patient information was strictly maintained, and all data were anonymized prior to analysis. The study involved minimal risk, as all investigations were part of routine clinical care, and non-invasive methods were used wherever possible. Participation was voluntary, and caregivers were informed of their right to withdraw from the study at any point without affecting the standard of care.

RESULTS

Table 1: Correlation between 48 and 72 hours Urinary Soluble triggering receptor expressed on myeloid cells-1 with procalcitonin levels, and White Blood Cell count

ESLS				
	48 hours	72 hours		
	r value	P value	r value	P value
Procalcitonin levels (ng/mL)	=0.41	< 0.001	-0.41	0
White Blood Cell ($\times 10^9$/L)	-0.09	0.422	-0.13	0.264
Urine sTREM-1 (ng/L)	0.06	0.574	0.09	0.416
Serum sTREM-1 (ng/L)	0.05	0.69	0.02	0.852
Total	80	80		

At 48 hours, urinary soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) showed a moderate positive correlation with procalcitonin levels ($r = 0.41$, $p < 0.001$), which reversed to a moderate negative correlation by 72 hours ($r = -0.41$, $p = 0.000$). No significant correlations were observed between urinary sTREM-1 and white blood cell count, urine sTREM-1, or serum sTREM-1 at either time point (all $p > 0.05$). All analyses were based on 80 patients.

Table 2: Extended Sick Newborn Scales compared with Blood culture report

Blood culture	N	Mean	Std. Deviation	Std. Error Mean
Extended Sick Newborn Scales at 48 hours				
Positive	6	15.5	± 3.271	0.891

Negative	74	15.65	± 2.485	
Extended Sick Newborn Scales at 72 hours				
Positive	6	17.17	± 1.602	0.853
Negative	74	17.04	± 1.600	

The 48 hours mean ESNS score among culture positive cases was 15.50 ± 3.271 and among culture negative cases was 15.65 ± 2.485. In 72 hour mean ESNS score among culture positive cases was 17.17 ± 1,602 and among culture negative cases was 17.04 ± 1.600. The mean ESNS score at 48 and 72 hours was equally distributed in culture positive and culture negative cases and it is not statistically significant with the p value shows more than 0,05 respectively.

Table 3: Extended Sick Newborn Scales compared with CRP

CRP	N	Extended Sick Newborn Scales			
	F value	p value			
		Mean	± Std. Deviation		
48 hours					
Negative	40	15.8	± 2.388	0.53	0.593
1:2 to 1:4	31	15.29	± 2.854		
>1:8	9	16.11	± 1.965		
72 hours					
Negative	26	17.58	± 0.758	3.49	0.035
1:2 to 1:4	42	16.62	± 1.962		
>1:8	12	17.42	± .996		

Note: p value based on one way ANOVA

At 48 hours ESNS scale, there was no significant association between C-reactive protein (CRP) categories and Extended Sick Newborn Scale scores (F = 0.53, p = 0.593). Mean scores were similar across the negative (15.80 ± 2.388), 1:2 to 1:4 (15.29 ± 2.854), and >1:8 (16.11 ± 1.965) CRP groups.

At 72 hours, a statistically significant difference emerged (F = 3.49, p = 0.035). The lowest mean score was observed in the 1:2 to 1:4 CRP group (16.62 ± 1.962), while higher scores were noted in the negative CRP cases (17.58 ± 0.758) and >1:8 (17.42 ± 0.996) groups, suggesting a non-linear relationship between CRP levels and sickness severity by 72 hours.

DISCUSSION:

Neonatal sepsis continues to be a major cause of neonatal morbidity and mortality, particularly due to challenges in early diagnosis and non-specific clinical presentation[1,2]. In the present study, the relationship between urinary sTREM-1, procalcitonin, white blood cell count, and clinical severity assessed by ESNS was evaluated in 80 neonates. At 48 hours,

urinary sTREM-1 demonstrated a moderate positive correlation with procalcitonin levels ($r = 0.41$, $p < 0.001$), suggesting that both markers reflect early inflammatory activation. However, this correlation reversed to a moderate negative relationship at 72 hours ($r = -0.41$, $p = 0.000$), indicating differing biomarker kinetics over time. Procalcitonin is known to rise early and decline with clinical improvement, whereas other inflammatory mediators may persist longer, leading to such divergence[3,4]. These findings highlight the dynamic nature of inflammatory biomarkers in neonatal sepsis. The variability observed emphasizes that a single biomarker may not reliably reflect disease progression at all time points. This supports current recommendations that multiple biomarkers should be interpreted together rather than in isolation. The findings also reinforce the need for serial monitoring rather than single-point assessment. Such an approach may improve diagnostic accuracy and guide clinical decision-making.

In contrast, no significant correlation was observed between urinary sTREM-1 and white blood cell count at either 48 or 72 hours, indicating that WBC is a less reliable marker of infection severity. This finding is consistent with previous studies demonstrating that WBC counts are influenced by multiple non-infectious factors such as stress, gestational age, and maternal conditions[5,6]. Hematological parameters have long been used in neonatal sepsis evaluation; however, their sensitivity and specificity remain suboptimal[7,8]. The lack of correlation in the present study further supports the limited diagnostic utility of WBC as a standalone marker. Additionally, urinary and serum sTREM-1 did not show significant correlation with ESNS scores, suggesting that biochemical markers and clinical severity indices may represent different aspects of the disease process. Clinical scoring systems reflect physiological instability, whereas biomarkers reflect underlying inflammatory pathways. This discrepancy highlights the importance of integrating both clinical and laboratory parameters in the evaluation of neonatal sepsis. The findings align with previous literature emphasizing a multimodal diagnostic approach. Therefore, reliance on a single parameter may lead to misinterpretation of disease severity.

The comparison of ESNS scores with blood culture results revealed no statistically significant difference at both 48 and 72 hours. The mean ESNS scores were similar in culture-positive and culture-negative groups, indicating that clinical severity scores may not reliably differentiate microbiologically confirmed sepsis from suspected cases. This finding is particularly relevant given the known limitations of blood culture, including low sensitivity and high rates of culture-negative sepsis[10]. Culture-negative sepsis is a well-recognized entity in neonatal practice and often complicates clinical decision-making. The absence of significant difference in ESNS scores suggests that clinical severity alone may not be sufficient to confirm infection. Similar observations have been reported in studies evaluating diagnostic tools in neonatal sepsis[11]. These findings highlight the need for adjunct biomarkers to improve diagnostic accuracy. The integration of clinical scoring systems with laboratory markers may provide a more comprehensive assessment. Therefore, combining ESNS with biomarkers such as procalcitonin or sTREM-1 may enhance clinical utility.

The association between CRP and ESNS demonstrated a time-dependent pattern in this study. At 48 hours, there was no significant association between CRP categories and ESNS scores ($p = 0.593$), indicating that CRP may not reflect early disease severity. However, at 72 hours, a statistically significant association was observed ($p = 0.035$), suggesting that CRP becomes more relevant in later stages of inflammation. This is consistent with the known delayed kinetics of CRP, which typically rises 24–48 hours after the onset of infection[3]. Furthermore, the non-linear relationship observed between CRP levels and ESNS scores suggests that CRP may not directly correlate with clinical severity in a predictable manner. Previous studies have also highlighted the limitations of CRP as an early diagnostic marker in neonatal sepsis[9]. While CRP remains useful for monitoring trends, its role in early diagnosis is limited. These findings reinforce the importance of interpreting CRP in conjunction with other biomarkers. Therefore, reliance on CRP alone may lead to delayed or inaccurate diagnosis. A combined biomarker approach may improve early detection and management.

Overall, the findings of this study highlight the complex and dynamic nature of biomarker behavior in neonatal sepsis. The observed variation in correlation between urinary sTREM-1 and procalcitonin over time underscores the importance of understanding biomarker kinetics. The lack of correlation between sTREM-1 and WBC or ESNS further emphasizes that different parameters reflect different aspects of the disease process. Clinical scoring systems, while useful, may not always correlate with biochemical markers or microbiological findings. These observations support the need for a comprehensive diagnostic approach that integrates clinical assessment with multiple laboratory markers. Current evidence suggests that no single biomarker is sufficient for accurate diagnosis, and a combination approach is recommended[8,13]. The findings of this study contribute to the growing body of literature emphasizing the importance of multimodal diagnosis in neonatal sepsis.

Further studies are required to validate these findings and explore the role of newer biomarkers in clinical practice. Such research may help improve early diagnosis and reduce neonatal morbidity and mortality.

STRENGTHS AND LIMITATIONS

The present study has several notable strengths. It evaluates the correlation between urinary sTREM-1 and established biomarkers such as procalcitonin, white blood cell count, and CRP, along with clinical severity assessment using ESNS, thereby providing a comprehensive and multidimensional analysis of neonatal sepsis. The use of serial measurements at 48 and 72 hours allows assessment of biomarker kinetics over time, which is crucial in understanding disease progression. Inclusion of both laboratory parameters and clinical scoring enhances the clinical relevance of the findings. Additionally, the study highlights the limitations of conventional markers and emphasizes the need for integrated diagnostic approaches. However, certain limitations must be acknowledged. The study was conducted in a single tertiary care center with a relatively small sample size, which may limit generalizability. The low blood culture positivity rate restricts validation against the gold standard. The observational design limits causal inference, and potential confounding factors such as prior antibiotic exposure were not controlled. Furthermore, sTREM-1 cut-off values were not established, limiting immediate clinical applicability.

CONCLUSION

The present study highlights the dynamic relationship between urinary sTREM-1, conventional biomarkers, and clinical severity in neonatal sepsis. Urinary sTREM-1 demonstrated a significant correlation with procalcitonin at 48 hours, which reversed at 72 hours, indicating differing biomarker kinetics over time. No significant association was observed between urinary sTREM-1 and white blood cell count or clinical severity scores (ESNS), suggesting that biochemical markers and clinical parameters reflect distinct aspects of the disease process. Additionally, ESNS scores did not differ significantly between culture-positive and culture-negative cases, underscoring the limitations of both clinical scoring systems and blood culture in isolation. A time-dependent association was observed between CRP and clinical severity, with significance emerging only at 72 hours, reinforcing its limited role in early diagnosis.

Overall, these findings emphasize that no single biomarker is sufficient for accurate diagnosis of neonatal sepsis. A combined approach incorporating clinical assessment and multiple laboratory markers is essential for improved diagnostic accuracy and timely management. Further large-scale studies are required to validate these findings and to establish the role of emerging biomarkers such as sTREM-1 in routine clinical practice.

REFERENCES:

1. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390(10104):1770-1780.
2. Polin RA; Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129(5):1006-1015.
3. Dong Y, Speer CP. The role of C-reactive protein in the diagnosis of neonatal sepsis. Neonatology. 2015;108(4):255-260.
4. Stocker M, van Herk W, el Helou S, Dutta S, Fontana MS, Schuerman FA, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in suspected neonatal early-onset sepsis: a multicentre randomized controlled trial. Lancet Infect Dis. 2017;17(10):1062-1070.
5. Sankar MJ, Natarajan CK, Das RR, Agarwal R, Chandrasekaran A, Paul VK. When do we use antibiotics in neonatal sepsis? Indian Pediatr. 2023;60(1):53-60.
6. Hofer N, Müller W, Resch B. Non-specific signs and symptoms of neonatal sepsis. Acta Paediatr. 2012;101(10):e448-e452.
7. Ng PC, Lam HS. Diagnostic markers for neonatal sepsis. Curr Opin Pediatr. 2012;24(2):165-171.
8. Benitz WE. Adjunct laboratory tests in the diagnosis of early-onset neonatal sepsis. Clin Perinatol. 2010;37(2):421-438.

9. Mathur NB, Arora D. Role of biomarkers in neonatal sepsis. Indian J Pediatr. 2020;87(3):202-208.

10. Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M. Culture-negative early-onset neonatal sepsis. Front Pediatr. 2018;6:285

11. Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr. 1988;112(5):761-767.

12. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. J Pediatr. 1979;95(1):89-98.

13. Ray S, Chatterjee K, Kaur J. Extended Sick Neonatal Score as a predictor of illness severity and mortality in neonates admitted to a neonatal intensive care unit. Indian Pediatr. 2019;56(2):130-133.