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Original Article

Sepsis Screen Parameters in Blood Culture Positive Neonatal Sepsis

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Abstract

Background
Neonatal sepsis is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first 28 days of life. Although, Positive blood culture is the gold standard for the diagnosis of neonatal septicemia, definitive culture results take at least 48–72 h, resulting in treatment delay. Hence certain rapid diagnostic tests such as C-reactive protein, micro erythrocyte sedimentation rate, total white blood cell count, absolute neutrophil count, and immature/total neutrophil count ratio collectively termed as the "Sepsis Screen" is used. The aim of this research is to study the relation between sepsis screen parameters and blood culture proven neonatal sepsis and to assess the clinical profile of neonates with culture-proven sepsis.

Materials and Methods
This was a descriptive observational study conducted on 97 clinically suspected neonatal sepsis cases in the neonatal intensive care unit. Sepsis screen tests were evaluated for sensitivity, specificity, positive predictive value and negative predictive value. The culture results were correlated with sepsis screen tests and p-value<0.05 was considered significant.

Results
Early-onset sepsis was seen in 47.4% cases, while late-onset sepsis accounted for 52.6% cases. Immature to total neutrophil ratio was the single best reliable sepsis screen test with a high specificity, PPV, and negative predictive values of 93.8%, 85.7%, and 88.4% respectively.

Conclusion
Most of the individual sepsis screen parameters showed statistical correlation with blood culture status, yet Immature to total neutrophil ratio had highest sensitivity, specificity, positive predictive value and proved to be a sensitive and responsive indicator of neonatal sepsis.

Keywords: *Blood culture, Neonate, Sepsis*

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Introduction

Neonatal sepsis is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first 28 days of life. This includes the systemic infections of the newborn including septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and newborn urinary tract infection [1]. Of the 130 million babies born each year globally, about 4 million die during the neonatal period.

The major direct causes of neonatal mortality are premature birth (28 %), severe infection (26 %), and birth asphyxia (23 %) [2] .Incidence of culture positive sepsis in hospital based reports from South Asia is 15.8 per 1000 live births. It is also critical that the diagnosis is made early and care begun within the shortest possible time frame to avoid significant morbidity and mortality [3].

Systemic Inflammatory Response Syndrome (SIRS) is the systemic response to the invasion and infection in neonates, which may present as a refusal to take feeds, hypo or hyperthermia, etc. Since these signs and symptoms of sepsis and systemic inflammatory response syndrome in neonates are variable and subtle, it makes neonatal sepsis clinically indistinguishable from certain non-infectious diseases like respiratory distress syndrome. So the laboratory investigations play a vital role in arriving at a diagnosis.

Although, Positive blood culture is the gold standard for the diagnosis of neonatal septicemia, definitive culture results take at least 48–72 h, resulting in treatment delay. Hence, certain rapid diagnostic tests such as C-reactive protein (CRP), micro erythrocyte sedimentation rate (micro-ESR), total white blood cell (WBC) count, absolute neutrophil count (ANC), and immature/total neutrophil count ratio collectively termed as the "Sepsis Screen" is used [4]. This study is conducted to evaluate the relation between sepsis screen parameters and blood culture proven neonatal sepsis and to assess the clinical profile of neonates with culture-proven sepsis.

Materials and Methods

The hospital based descriptive observational study was conducted in the neonatal intensive care unit, intermediate care nursery of Nobel Medical College Teaching Hospital, Biratnagar from June 2021 to May 2022 .Ethical approval for the study was obtained from the Institutional Ethical review board of Nobel Medical College Teaching Hospital. All clinically suspected cases of neonatal sepsis admitted in NICU, nursery were included.Neonates who had already received antibiotics outside before admission, neonates who died before workup was complete, neonates who underwent surgery,congenital anomalies like tracheoesophageal fistula, lobar agenesis, malrotation of the gut, complex heart diseases, neural tube defects were excluded.

Cases were categorized into 0- 72 hours (early-onset) or >3 days (late-onset) sepsis based on the day of presentation. A detailed history and clinical findings were recorded in the Proforma and screened with a septic parameter with predetermined cut-off values and at the same time, blood culture was sent. The culture results were correlated with the sepsis screen tests.

The calculated sample size was 97 and convenient purposive sampling method was used . The sample size was calculated by the formula $N=Z^2pq/d^2$ where Z is the standard normal deviation (usually set as 1.96),d=degree of accuracy required (we take 10% error), p=proportion in the targeted population estimated to have a particular characteristic and q= 1-p.

Data was entered in SPSS 20.0 software and analyzed. Descriptive statistics were used for analysis. Statistical analysis such as sensitivity, specificity, predictive value were calculated wherever necessary and p-value<0.05 was considered significant.

Results

This is a hospital based descriptive observational study conducted among 97clinically suspected neonatal sepsis cases in the neonatal intensive care unit. Early-onset sepsis was seen in 46 (47.4%) cases; while late-onset sepsis accounted for 51(52.6%). 32 (33%) cases were blood culture-positive. Higher proportions of culture-positive babies were male 23(71.9%), preterm 17 (53.1%), low birth weight 20(62.5%), inborn 18(56.25%), and those delivered spontaneously 27(84.4%). Gram-negative organisms formed the majority of the isolates as compared to Gram-positive organisms (53.2% vs. 46.8% respectively). Staphylococcus aureus and Escherichia coli were the commonest organisms isolated in 12(37.5%) and 06(18.75%) of culture positive cases respectively. Immature/Total neutrophil count (I/T ratio) was the single best reliable sepsis screen test with a high specificity, PPV, and negative predictive values of 93.8%, 85.7%, and 88.4% respectively which was acceptable with a p-value of <0.0001. Sepsis screen parameters such as CRP, I/T ratio, and micro-ESR were significantly associated with culture-proven sepsis. I/T ratio followed by CRP and micro-ESR had more sensitivity. Neutropenia followed by Leukopenia, micro-ESR, and I/T ratio had high specificity. When two or more sepsis screen parameters

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were considered together, the sensitivity, specificity, positive predictive value, and the negative predictive value was found 75%, 86.1%, 72.7%, and 87.5% respectively.

Table 1: Distribution of culture positivity in sepsis

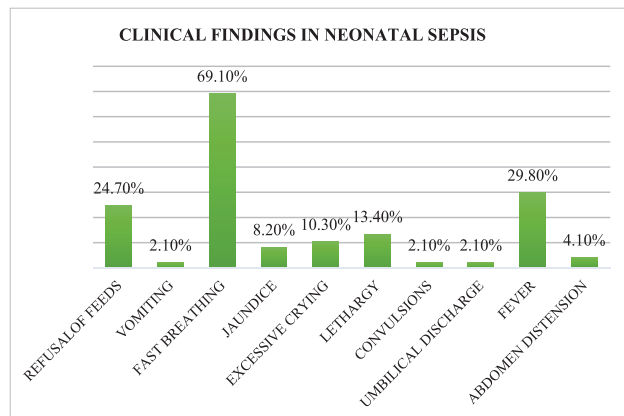| BLOOD CULTURE	EARLY ONSET SEPSIS	LATE ONSET SEPSIS	TOTAL
POSITIVE	17 (37%)	15 (29%)	32 (33%)
NEGATIVE	29 (63%)	36 (71%)	65 (67%)

Figure 1: Distribution of clinical finding in neonatal sepsis

Fig 1 shows clinical findings in neonatal sepsis. Among 97 septic cases, the commonest symptoms studied were Fast Breathing (69.1%), followed by fever (29.8%) and Refusal of feeds (24.7%). Other symptoms like Lethargy, Excessive crying, Jaundice, and Abdominal distension accounted for 13.4%, 10.3%, 8.2%, and 4.1% respectively. Whereas Umbilical discharges, Convulsions, and vomiting accounted for 2.1% each. The only Refusal of feeds was found to be statistically significant to culture-positive sepsis as shown in figure 1 above.

Table 2: Correlation of septic parameters with the blood culture

SCREENING PARAMETERS	CULTURE POSITIVE	CULTURE NEGATIVE	TOTAL	P VALUE
CRP POSITIVE	20(62.5%)	24(36.9%)	44(45.4%)	0.01*
LEUCOPENIA (<5000/cumm)	4(12.5%)	3(4.6%)	7(7.2%)	0.1
NEUTROPENIA (<1750/cumm)	4(12.5%)	1(1.5%)	5(5.2%)	0.2
MICRO ESR	9(28.1%)	4(6.1%)	13(13.4%)	0.002*
I/T RATIO >0.2	24(75%)	4(6.1%)	28(28.9%)	0.001*
TWO OR MORE TESTS POSITIVE	24(75%)	9(13.8%)	33(34%)	0.001*

*P-value<0.05 is significant

Table 3: Sensitivity, specificity, positive predictive accuracy, and negative predictive accuracy of sepsis screen parameters

Screening Parameters	Sensitivity	Specificity	Ppv	Npv
CRP Positive	62.5%	63%	45.5%	77.4%
Leucopenia	12.5%	95.4%	57.1%	68.9%
Neutropenia	12.5%	98.5%	80%	69.6%
Micro Esr	28.1%	93.8%	69.2%	72.6%
I/T Ratio >0.2	75%	93.8%	85.7%	88.4%
Two Or More Tests Positive	75%	86.1%	72.7%	87.5%

Discussion

In this descriptive study, of the 97 neonates with signs and symptoms of sepsis, 32 (33%) were culture positive and 65 (67%) were culture negative. This isolation rate (33%) is comparable with the 39.66% isolation by Sahoo MR et al [5]. Much lower rate of culture positivity was shown by Yadav NS et al (16.9%) [6]. Higher rates of culture positivity of about 48% by Lakhey A and Shakya H [7], 63% by Hassan et al[8] and 60% by Sonawane et al [9] were also reported in their study.

The incidence of late-onset sepsis was more when compared to the early onset of sepsis. Maximum culture-positive cases were seen in neonates with EOS 17 (37.0%) as compared to neonates with LOS 15 (29%) in the present study. This could be due to ascending infection following rupture of membranes or through the infected birth canal or at the time of resuscitation of the newborn in the labor room. Immature immunological responses of the neonates in the first week of life make them more susceptible to infections in this period.

Similar observations were made in the studies by Shrestha S et al (84.08%), Sahoo MR et al (69.45%) [5]. However, increased LOS compared to EOS has been reported in the studies done by Yadav NS et al (71.2%) [6]. The lower incidence of LOS in this study cannot be explained by a single factor.A single CRP value has a sensitivity of 62.5% and a negative predictive value of 22.6% which is comparable to the observation made by other studies. The differences in the results of this parameter shown by the different studies are due to variations in the diagnostic criteria, and different methods of CRP estimation and different cutoff value used in the qualitative test.

In the present study, Leucopeniai.e Total WBC counts < 5,000 cells/cmm was taken as the diag-

nostic criteria for detecting neonatal septicemia. Altered WBC count in this study was seen in 7 neonates of whom 4 had proven sepsis with 12.5% sensitivity, 57.1% PPV, 68.9% NPV, and 95.4% specificity. Leucopenia had a low sensitivity, and a low positive predictive value but, a very high specificity comparable to the observation made by Hassan et al[8]. In different studies, the differences in the outcome of this parameter may be due to variations in the time of blood sampling, the severity of the infection, the diagnostic criteria followed, the age of the neonates, and the decreased sensitivity of the test after the first week of life.

Absolute neutrophil count (ANC) had the highest specificity, the positive predictive value of 98.5% and 80% respectively among the sepsis screen tests studied, which was different from the observations seen in another study. ANC varies considerably in the immediate neonatal period and normal reference ranges are available from Monroe's chart. ANC below 1750 per cubic mm is believed to be the best predictor of sepsis, while neutrophilia does not correlate well. I/T ratio >0.2 is a useful marker of infection and the ratio less<0.2 makes infection unlikely.

In this study, the I/T ratio had sensitivity and specificity, PPV, and negative predictive values of 75%, 93.8%, 85.7%, and 88.4% respectively which was acceptable with a p-value of <0.0001. Different studies have shown variable results in this parameter, which may be due to variation in the blood sampling time, the severity of infection, the age of the neonates, the diagnostic criteria followed, and the reduced sensitivity of this test after the first week of life as observed by different authors in their study.

Micro-ESR had very low sensitivity (28.1%) and positive predictive value (69.2%), but a higher specificity (93.8%) and negative predictive value (72.6%) in detecting septicemia in the study.

However, in this study the timing of sample collection was variable due to various factors like financial constraint and delayed parental decision regarding NICU admission. When two or more sepsis screen tests were combined, the sensitivity and the positive predictive values decreased to 75% and 72.7%% respectively, while the specificity and the negative predictive values increased to 86.1% and 87.5% respectively, and was found to be statistically significant in detecting septicemia. Similar observations were made by the other authors [6,8].

Conclusion

Most of the individual sepsis screen parameters showed statistical correlation with blood culture status, yet I/T ratio had highest sensitivity, specificity, positive predictive value and proved to be a sensitive and responsive indicator of neonatal sepsis. But it is neither 100% sensitive nor 100% specific to have relied upon as a sole marker.

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Conflict of interest: None.

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