

## STUDY OF THE HEMATOLOGICAL SCORING SYSTEM AND CRP LEVELS IN CASES OF NEONATAL SEPSIS AT A TERTIARY CARE CENTRE: A COMPARATIVE STUDY

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### Abstract

**Background:** Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection. The current study is undertaken to study the hematological parameters in the early diagnosis of neonatal septicemia using Rodwell's scoring system (HSS). The objective is to study the correlation between HSS and CRP levels in cases of neonatal sepsis. **Materials and Methods:** Case-control study was carried out on babies with clinical features of sepsis. **Result:** The sensitivity and specificity of CRP for the diagnosis of sepsis were 68.9% and 47.3%. The sensitivity and specificity of HSS for diagnosis of sepsis, at a cut-off of 3 was 76.4% and 62.2%. A significant association was seen between CRP levels and HSS scoring. HSS (at a cut-off value of 3) is a sensitive marker for the diagnosis of sepsis. **Conclusion:** Combining the estimation of CRP with HSS may provide an even more effective tool to be used as a screening method for neonatal sepsis.

## INTRODUCTION

Neonatal sepsis is a clinical disease defined by systemic manifestations of infection along with bacteremia in the first month of life. It is more common in developing countries compared with developed countries. Despite improved antibiotic therapy and care, neonatal sepsis is associated with a mortality rate ranging from 13 to 60%. Even with major advances in neonatology in the past few decades, bacterial sepsis is still one of the most important causes of morbidity and mortality in this age group worldwide; particularly in the developing countries. Early detection of bacterial sepsis is difficult for a variety of reasons. For starters, early warning signs and symptoms are commonly vague and non-specific, and early detection is essential for decreasing the case fatality rate.<sup>[1]</sup>

Microbiological culture results are usually not available until at least 48-72 hours after the specimen arrives at the laboratory, and culture results can have a high percentage of false negatives.<sup>[2]</sup> The antibiotic therapy is usually initiated based on clinical suspicion

which can result in overtreatment ultimately leading to the emergence of multi-drug resistant organisms. In addition, the high cost of antibiotics overburdens the already underprivileged parents.

Neonatal sepsis is classified as early onset when it occurs within the first 72 hours of life and late-onset when it occurs after 72 hours.<sup>[3]</sup> Early-onset sepsis is caused by organisms prevalent in the maternal genital tract, labor room, or operating theatre 4,5 while late-onset sepsis usually results from nosocomial or community-acquired infection.<sup>[4,5]</sup>

The immature immune system, the decreased phagocytic activity of the white blood cells and incompletely developed skin barriers make newborns particularly susceptible to sepsis.<sup>[6-8]</sup> Common risk factors for neonatal sepsis have been identified as prolonged rupture of fetal membranes, maternal peripartum pyrexia, obstructed labor, prematurity and low birth weight, and birth asphyxia.<sup>[9-11]</sup>

Newborns, especially premature are prone to serious infections by organisms and the signs of these infections may be absent or minimal and hard to detect. As a result, fatal septicemia might develop

with little warning.<sup>[12]</sup> Aggressive approach to diagnosis and management is the principle determinant of the prognosis. Therefore, there is a need for a test that is cheap, easily performed with quick availability of reports.

Commonly requested tests are complete blood counts and CRP. Sepsis generally results in neutropenia, leukocytosis, and thrombocytopenia. Immature neutrophils are released into the circulation leading to a left shift.<sup>[13-16]</sup>

Changes in various components of blood count and blood picture make it one of the dependable early aids to the diagnosis and management of neonatal sepsis. Rodwell suggested a comprehensive scoring system using blood counts and blood picture.<sup>[17]</sup> The diagnostic usefulness of Rodwell's hematological scoring system and its individual components have been extensively studied and found invaluable.<sup>[18-20]</sup>

C-reactive protein was first described by Tillet and Francis in 1930. They concluded that it's a protein that aids in complement binding to foreign or injured cells in response to inflammation and peaks after fifty hours.<sup>[21]</sup> CRP synthesis is a non-specific reaction to disease and cannot be used to diagnose septicemia alone. CRP, in addition to clinical signs of the disease, gives a good indication of septicemia diagnosis.<sup>[22]</sup>

The current study is undertaken to study the hematological parameters in the early diagnosis of neonatal septicemia using Rodwell's scoring system and also to correlate them with findings of C-reactive protein (CRP) levels; as these can be performed quickly before putting the neonate on antibiotic therapy, and can be used for early diagnosis of neonatal sepsis and may help in preventing the morbidity and mortality.

The objective of the study is to analyze the performance evaluation of the hematological scoring system for the diagnosis of neonatal sepsis. Present study was also aim to assess the correlation between hematological parameters in the hematological scoring system, peripheral smears, and CRP levels in cases of neonatal sepsis.

## MATERIALS AND METHODS

**Study Design:** Prospective, Observational, Comparative (Case-Control), Clinical study

**Study Population:** All clinically suspected cases of neonatal sepsis were included in the study.

**Study Duration:** August 2019 to December 2021

**Study Participants:** 222 (148 cases and 74 controls)

**Inclusion Criteria:** Neonates with clinical signs or history suggestive of sepsis.

**Exclusion Criteria:** Neonate whose mother was not ready to give consent and interview. Neonates with known congenital anomalies or disorders. Neonates with hemolytic jaundice.

**Control Group:** Neonates who show no clinical signs of sepsis were selected as the control group.

**Methodology:** The study was conducted in a tertiary care centre. A total of 222 subjects were included after they satisfied the eligibility criteria. Blood was collected from the neonates within 24 hours of their admission to the hospital, before the administration of antibiotics. A detailed history, complete general & systemic examination, and probable diagnosis were noted on a predesigned proforma. Complete Blood Counts (CBCs), Peripheral Blood Smears (PBS), and CRP levels were performed on the samples collected from the neonates. Hematological findings were analyzed according to the Hematological Scoring System (HSS) of Rodwell et.al and the score was computed as follows [Table 1]:

## RESULTS

Neonates suspected to have sepsis admitted to the NICU of the Hospital were studied. The present study included 222 neonates. The final observations and results were given below. During the study period, 148 neonates were eligible based on the selection criteria, while 74 neonates were selected as the control group, and were included in the study. The ratio of cases to controls in the study was 2:1

### Gender distribution

The study showed 58.8% male and 41.2% female babies in the cases group whereas a similar result (56.8% males and 43.2% female babies) was noted in the control population. The male-to-female ratios for both cases and controls were 1.43 and 1.31 respectively.

### Age distribution

The average gestational age was 36.34 weeks and 37.34 weeks for the cases and controls respectively. In this study, the commonest age group was 1 to 5 days with 83.8% of the neonates (for the cases), whereas for the controls, 81.8% of cases belonged to the age group of 6 to 10 days ( $p < 0.01$ ). The average ages for both the cases and control population were 3.97 and 7.93 days respectively.

### Birth weight

The mean birth weight of the babies in the present study was 2.14 Kg with the prevalence of low birth (<2500 grams) as 68.3%. In the present study, a total of 94 cases (63.51%) cases were early onset sepsis while 54 cases (36.49%) were late onset sepsis.

### Mode of delivery

The rate of cesarean section was higher in cases of sepsis as compared to controls (61.5% vs 40.5%;  $p < 0.01$ ).

### Risk Factor

In the neonates with sepsis, 62.2% of the neonates showed prematurity. In contrast to this, in the control group, only 18.9% of the neonates were premature. Risk factors associated with the development of neonatal sepsis were pre-maturity (62.2% vs 18.9%;  $p < 0.01$ ) and PROM (27% v/s 6.8%;  $p < 0.01$ ). [PROM – Premature rupture of membranes, PPRM – Preterm premature rupture of membranes]

### Clinical Presentations

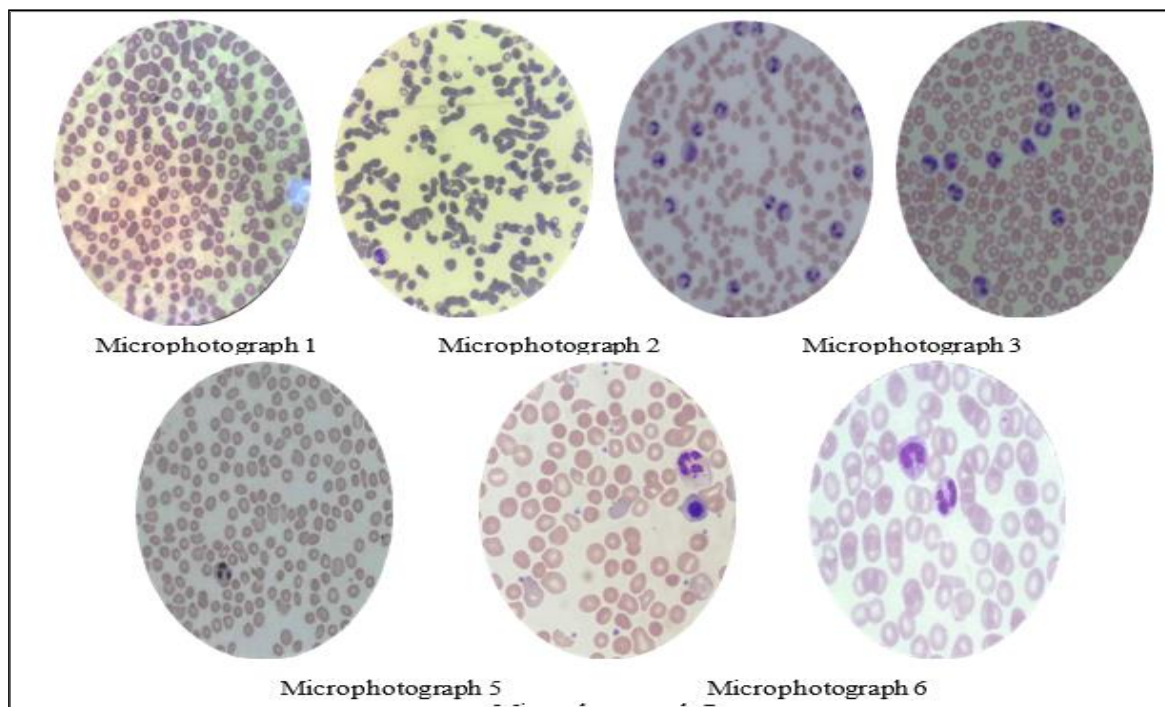
In the present study, for the neonates with sepsis, poor feeding tendency was the commonest complaint present in 54.72% of the neonates respectively. In the case of controls, the most common presenting complaint was jaundice, seen in 64.86% of the neonates. Quite a few neonates showed overlapping symptoms.

### Peripheral smear findings

Neutrophilia was the most common finding, for both cases and controls present in 88.51% and 64.86% of cases and control respectively.

### Microphotographs of peripheral smear findings

We analyze the peripheral blood smear of the cases by using the Leishman stain as shown in [Figure 1]. Microphotographs 1 and 2 showing leucopenia {40X}, Microphotograph 3 showing neutrophilia and leukocytosis {40 X}, Microphotograph 4 showing neutrophilia with the presence of band forms {40X}, Microphotograph 5 showing thrombocytopenia {100X}, Microphotograph 6 showing nucleated RBCs (Normoblasts) {100X}, Microphotograph 7 showing degenerative changes in neutrophils – Cytoplasmic vacuolations {100 X}.



**Figure 1: Microphotographs of peripheral smear findings on different resolutions.**

### CRP Levels among cases and controls

On comparing cases and controls we found that the sensitivity and specificity of CRP for diagnosis of sepsis were 68.9% and 47.3% respectively while overall accuracy was 61.7%.

### Hematological Score

A significant association of all the hematological scoring parameters was observed with the development of sepsis except total leucocyte count, degenerative changes on peripheral smear and platelet count. We also found that there was good sensitivity and NPV was seen with TNC, and IMC. Good specificity and PPV was seen with degenerative changes and I: M ratio. IMC and TNC had overall good accuracy.

Mean total leucocyte count, total neutrophil count, immature neutrophil count, Immature: Mature

Neutrophil Ratio, Immature: Total Neutrophil Ratio (I: T) and number of nucleated RBCs were significantly higher among sepsis cases as compared to the controls. The mean platelet counts were lower in cases as compared to the controls.

### Comparison between CRP levels and hematological scores

A significant association was seen between CRP levels and HSS scoring ( $p < 0.01$ ). Out of the 81 cases with low HSS score (labelled as sepsis unlikely), 61 cases also had low CRP values (75.3%). Similarly, out of 14 cases with high HSS score (labelled as sepsis very likely) 9 cases had high CRP values (64.3%). [(Figure 2, Table 3 (a) and 3 (b)).

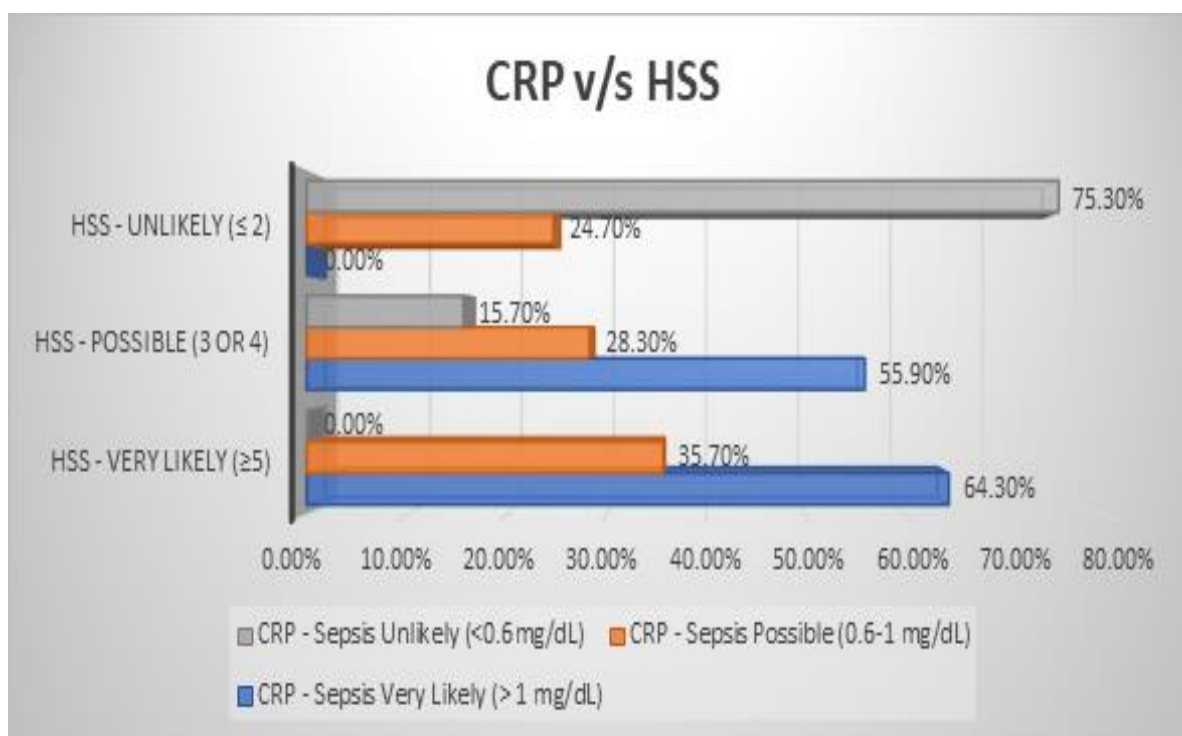


Figure 2: Comparison between CRP and HSS

Table 1: Hematological Scoring System (HSS) by Rodwell et al.:

Criteria	Abnormalities	Score
Total Leucocyte Count (TLC)	≤5000/μl ≥25000 at birth ≥30000-12-24 hrs ≥ 21000 days 2 onwards	1
Total Neutrophil Count (TNC)	1800-5400 No mature PMN seen Increased/Decreased	0 2 1
Immature Neutrophil Count (IMC)	< 600 > 600 (Increased)	0 1
Immature: Total Neutrophils Ratio (I: T)	< 0.120 > 0.120(Increased)	0 1
Immature: Mature Neutrophil Ratio(I:M)	< 0.3 ≥ 0.3(Increased)	0 1
Degenerative changes In Neutrophils	Toxic granules / cytoplasmic vacuolations	1
Platelet Count	≤ 150000/μl	1

CRP scores-based analysis was done as shown in [Table 2].

Table 2: The CRP levels and score were analyzed and interpreted as follows

CRP Levels	Score	Interpretation
≤ 0.6 mg/dL	≤ 2	Sepsis is unlikely
0.6-1 mg/dL	3 or 4	Sepsis is possible
≥ 1 mg/dL	≥ 5	Sepsis or infection is very likely

All the data was noted down in a pre-designed study proforma and analyzed.

Table 3: (a) Association of CRP levels with hematological scoring system

CRP	HSS			Total
	Very Likely (≥5)	Possible (3 or 4)	Unlikely (≤ 2)	
Sepsis Very Likely (> 1 mg/dL)	9 64.3%	71 55.9%	0 0.0%	80 36.0%
Sepsis Possible (0.6-1 mg/dL)	5 35.7%	36 28.3%	20 24.7%	61 27.5%
Sepsis Unlikely (<0.6mg/dL)	0 0.0%	20 15.7%	61 75.3%	81 36.5%
Total	14 100.0%	127 100.0%	81 100.0%	222 100.0%

p- value <0.01



**Table 3(b): Association of CRP levels with parameters of hematological scoring system**

HSS Parameters	CRP- Sepsis Interpretation			Total	p-value
	Very Likely (n-80)	Possible (n-61)	Unlikely (n-81)		
TLC	56	39	27	122	<0.01
	70.0%	63.9%	33.3%	55.0%	
TNC	78	50	50	178	<0.01
	97.5%	82.0%	61.7%	80.2%	
IMC	68	35	29	132	<0.01
	85.0%	57.4%	35.8%	59.5%	
I/T ratio	47	22	10	79	<0.01
	58.8%	36.1%	12.3%	35.6%	
I/M ratio	15	4	0	19	<0.01
	18.8%	6.6%	0.0%	8.6%	
Degenerative Changes	2	1	0	3	0.68
	2.5%	1.6%	0.0%	1.4%	
Platelet Count	45	30	20	0	<0.01
	56.3%	49.2%	24.7%	42.3%	
nRBCs	19	6	0	25	<0.01
	23.8%	9.8%	0.0%	11.3%	

A significant association of all the HSS parameters was observed with CRP levels ( $p < 0.01$ ) except for that of degenerative changes on the peripheral smear ( $p = 0.68$ ).

## DISCUSSION

Neonatal sepsis is a life-threatening emergency, and any delay in treatment could lead to death. Diagnosis of sepsis is a great challenge facing neonatologists in NICUs.<sup>[23-25]</sup>

**Gender Distribution:** We found that there is a male predominance in neonatal septicemia has suggested a sex-linked factor in host susceptibility which is also shown by other studies.<sup>[26]</sup>

**Sepsis & Birth Weight:** In our study mean birth weight was 2.14 Kg and the prevalence of low birth was seen in 68.3%, other supportive studies have shown similar trend.<sup>[27]</sup> According to Barbara J. Stoll et al., the rate of infection is inversely proportional to birth weight.<sup>[29]</sup>

**Type of Sepsis:** In our study, we found that most of the cases with early onset (EOS) while the rest were late onset (LOS). A similar trend was seen in literature.<sup>[28]</sup>

**Sepsis & C-reactive protein (CRP):** In our study, we found that the sensitivity and specificity of CRP for the diagnosis of sepsis were 68.9% and 47.3% respectively, while PPV and NPV were 72.3% and 43.2% respectively with an overall accuracy of 66.1%. A list of other studies in our support was given in bibliography.<sup>[30-34]</sup>

**Sepsis & Hematological Scoring System (HSS):** In the present study, the Sensitivity and specificity of HSS for diagnosis of sepsis at a cut-off of 3 was 76.4% and 62.2% while PPV and NPV were 80.1% and 56.8% with an overall accuracy of 71.6%. We found a similar trend among other studies in the literature.<sup>[35-38]</sup>

In the present study, good sensitivity and NPV was seen with TNC, IMC. Good specificity and PPV was seen with degenerative changes and I: M ratio. IMC and TNC had overall good accuracy. Dulay et al,<sup>[39]</sup> in 2008 in their study found that WBC count and

absolute neutrophil count (ANC) were not significant. In contrast, the associations with absolute band count (ABC), hematocrit, hemoglobin, bandemia, lymphocytes and I/T ratio were significant. Narasimha A et al.<sup>16</sup> found that an abnormal immature to total neutrophil ratio (I: T), followed by an abnormal immature to mature neutrophil ratio (I: M), were the most sensitive indicators in the diagnosis of neonatal sepsis. They concluded that the hematological scoring system (HSS) is a simple, quick, cost-effective screening tool for early diagnosis of neonatal sepsis. Supreetha MS et al,<sup>[40]</sup> in a similar study, observed that the PMN ratio (94%) was highly sensitive followed by Immature: Total PMN count (91%) in identifying infants with sepsis. Total leucocyte count (TLC) (94%) followed by platelet counts (75%) were highly specific tests helpful in diagnosing sepsis. Bhalodia MJ et al,<sup>[36]</sup> observed that total leukocyte count showed high specificity (74.5%) but least sensitivity (66.7%). ANC showed high specificity (92.1%) but least sensitivity (45.8%). I:T ratio showed high specificity (92.1%) and high sensitivity (91.6%). I: M ratio showed high specificity (94.2%) and high sensitivity (93.7%). Brijin Mary V et al,<sup>[37]</sup> in their study observed that raised I: T neutrophil ratio, raised I:M neutrophil ratio, and platelet count gives a significant p value in the assessment of neonatal sepsis.

**C-reactive protein & Hematological scoring system (HSS):** A significant association was seen between CRP levels and HSS scoring ( $p < 0.01$ ). Out of the 81 cases with low HSS score (labelled as sepsis unlikely), 61 cases also had low CRP values (75.3%). Similarly, out of 14 cases with high HSS score (labeled as sepsis very likely) 9 cases had high CRP values (64.3%).

We also observed a significant association of all the HSS parameters with CRP levels ( $p < 0.01$ ) except for that of degenerative changes on the peripheral smear ( $p = 0.68$ ).

Bhalodia MJ et al.<sup>[36]</sup> in their study aimed to analyze the diagnostic utility of hematological scoring system (HSS) and its correlation with C-reactive protein. Out of 150 cases, all 43 (89.6%) C-reactive protein (CRP) reactive cases showed hematological score  $\geq 5$  and 54 (70.1%) cases with score 3–4 showed CRP reactive. All 25 cases with score 0–2 showed CRP nonreactive. This result was statistically significant ( $P < 0.001$ ). Godbole R et al.<sup>38</sup> also observed a significant association between CRP and HSS. Cases with HSS of  $\geq 5$ , have mean CRP value of  $1.83 \pm 0.79$  mg/dL, cases with HSS of 3-4, have a mean CRP of  $1.26 \pm 0.56$  mg/dL, whereas mean CRP was  $0.35 \pm 0.21$  mg/dL in cases with HSS of 0-2.

## CONCLUSION

HSS and all its hematological parameters showed a good correlation with CRP levels. We thus conclude that, raised HSS, in the absence of blood culture, points positively towards the diagnosis of neonatal sepsis with good accuracy. HSS is thus an important tool in the armamentarium available for screening for neonatal sepsis. Present study thus recommends that high HSS ( $>3$ ) with or without another sepsis screen parameter should be used as an early marker of neonatal sepsis. As a result, unnecessarily exposing newborns to antibiotic therapy can be avoided. Combining the estimation of CRP with HSS may provide an even more effective tool to be used as a screening method for neonatal sepsis.

### Limitations of the study

The main limitation of this study is that we did not consider cultures such as blood, urine, CSF and surface culture to determine sepsis. Further, this study was also limited by its lack of serial measurements of CRP and hematological parameters.

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