

## A STUDY TO DETERMINE THE ROLE OF HEMATOLOGICAL PROFILE, SCORING SYSTEM, AND CRP IN EARLY DIAGNOSIS OF NEONATAL SEPSIS

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### ABSTRACT

**Objective:** The objective of the study was to study the hematological parameters according to Rodwell's Hematological Scoring System (HSS) in neonatal sepsis, to evaluate the efficacy of hematological parameters in the diagnosis of neonatal sepsis, and also to correlate the levels of C-reactive protein (CRP) with degree of neonatal sepsis. Neonatal sepsis is the most important cause of morbidity and mortality, especially among low-birth-weight and preterm babies in developing countries. According to the WHO, out of 4 million neonatal deaths all over the world annually, over 35% are due to infections in neonates and 99% of them occur in developing countries. The incidence of neonatal sepsis in India according to the data from the National Neonatal Perinatal Database (NNPD, 2002-03) is 30/1000 live births. The incidence is 10 times higher in infants with birth weight <1000 g.

**Methods:** The present study was carried out in Guru Gobind Singh Medical College and Hospital, Faridkot (Punjab) located in the northern part of India over a period of 1 year on all the neonates with clinical suspicion of sepsis admitted in Neonatal Intensive Care Unit (NICU).

**Results:** When distributed according to HSS, majority (37%) of neonates had score  $\geq 5$  followed by 33% with score 3 or 4 and 30% had score  $\leq 2$ . In the present study, among 37 neonates with HSS score  $\geq 5$ , 89.18% were CRP positive and 10.82% were CRP negative, followed by 33 with score  $\leq 2$  out of which 42.42% were CRP positive and 57.58% were CRP negative and 30 had score 3 or 4 among them 80% were CRP positive and 20% were CRP negative. Majority of them 76 (76.00%) showed either increased or decreased levels of polymorphonuclear neutrophils count (PMN) count and 24 (24.00%) showed PMN count within normal range. Among 76 neonates with increased or decreased levels of PMN count, majority (63.00%) showed neutrophilia, while only (13.00%) showed neutropenia. In this study, more than half of the neonates 59 (59.00%) had shown raised levels of immature PMN count. Forty-seven percent had shown an increased I: T ratio and 53% had normal I: T ratio. Only 9% of the neonates admitted to NICU with clinical suspicion of sepsis had an increased I: M ratio. Morphological degenerative changes were seen in 65 out of 100 neonates. In CRP-positive neonates, these degenerative changes were seen in 77.46% of neonates, while in CRP-negative neonates, only 31.07% showed these changes. Among 100 neonates, 77 (77.00%) had normal platelet count and 23 (23.00%) had shown decreased platelet count.

**Conclusion:** HSS helps effectively to make choices with respect to wise utilization of anti-microbial treatment which will be life sparing, give early cure, reduce mortality, shorten the hospital stay, and as well as will minimize the risk of emergence of resistant organisms due to misuse of antibiotics as well.

**Keywords:** Sepsis, Hematological, Rodwell.

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### INTRODUCTION

Neonatal sepsis is the most important cause of morbidity and mortality, especially among low birth weight and preterm babies in developing countries [1]. According to the WHO, out of 4 million neonatal deaths all over world annually, over 35% are due to infections in neonates and 99% of them occur in developing countries [2]. The incidence of neonatal sepsis in India according to the data from the National Neonatal Perinatal Database (NNPD, 2002-03) is 30/1000 live births [3]. The incidence is 10 times higher in infants with birth weight <1000 g [4].

The infection can be acquired from mother through transplacental route, ascending infection, during passage through an infected birth canal, or exposure to infected blood at delivery [5].

Diagnostic criterias for pediatric organ dysfunction have been published by Goldstein *et al.* in Pediatric Critical Care Medicine 2005. Neonatal septic shock is defined as sepsis with cardiovascular organ dysfunction despite fluid resuscitation. Cardiovascular dysfunction is defined differently in children than adults:

- Hypotension (<2 SD below normal age).
- Need for vasoactive drugs to maintain blood pressure in normal range.

Or is defined as any two of the following:

- Unexplained metabolic acidosis (>5.0 mEq/L), increased arterial lactate (>2 times upper limit of normal), oliguria (<0.5 mL/kg/hr), prolonged capillary refill (>5 s), core to peripheral temperature gap >3°C [6].

This life-threatening condition is treatable if diagnosed early but unfortunately, the early signs and symptoms are often non-specific thereby making it difficult to establish an early clinical diagnosis. As a result of this uncertainty, antibiotics are often started on the slightest clinical suspicion of sepsis. This approach is effective in fighting against the acute infections but increases the risks of antibiotic side effects and the emergence of drug-resistant organisms in neonatal units [7-9] Therefore, the early detection of neonatal sepsis is a vexing problem. A definite diagnosis is made by blood culture. However, the procedure is time consuming (takes 48-72 h) [10,11], and yield is low (87.3%) [10-13].

Various studies have shown that hematological parameters are simple, quick, and cost-effective tools in the early diagnosis of neonatal sepsis. For early diagnosis of neonatal septicemia, a Hematological Scoring System (HSS) of Rodwell was formulated in 1988 and is preferred which is based on normal values defined by Manroe *et al.* in 1979 [14]. This

HSS used seven hematological parameters to predict the occurrence of neonatal sepsis.

The parameters used were total leukocyte count (TLC), total polymorphonuclear neutrophils count (PMN), immature: total neutrophils ratio (I: T ratio), immature: mature neutrophils ratio (I:M ratio), immature PMN count, degenerative changes in PMN, and platelet count.

Each of the parameters was given a score of 1 in case of abnormality exception being that if no mature PMN was seen on peripheral blood film, the score of 2 was given to total PMN count rather than 1. Total score obtained ranges from minimum being 0 and maximum being 8.

Hematological Scoring System (Formulated by Rodwell et al.)			
S. No.	Criteria	Abnormality	Score
1.	TLC	≤5000/μL	1
		≥5000/at birth	1
		≥5000/at 12-24 h	1
		≥s h0/day 2 onwards	1
2.	Total PMN count	1800-5400/μL	0
		No mature PMN seen	2
		Increased/Decreased	1
3.	Immature PMN count	600/mm <sup>3</sup>	0
		Increased	1
4.	I: T ratio	0.120	0
		Increased	1
5.	I: M ratio	≤:M	0
		≥:M	1
6.	Degenerative changes in PMN	Toxic granulation/	1
		cytoplasmic vacuolation	
7.	Platelet count	<150,000/mm <sup>3</sup>	1

#### Interpretation of Hematological Scoring System (Formulated by Rodwell et al.)

Score	Interpretation
≤n	Sepsis is very unlikely
3 or 4	Sepsis is suspected
≥e	Sepsis is very likely

Accordingly, the interpretation was as follows:

- Score ≤2: Sepsis is unlikely
- Score 3 or 4: Sepsis is suspected
- Score ≥5: Sepsis or infection is very likely [15].

C-reactive protein (CRP) has been used as an acute phase reactant to diagnose and follow the course of infection in neonates. Its advantages include its very low serum levels in normal infants, a rapid rise after 12-24 h of sepsis, and a massive rise thereafter as long as inflammatory stimuli persists followed by immediate fall of serum level as soon as inflammation subsides making it suitable for diagnosis and follow-up of neonatal sepsis [16].

The present study is undertaken to evaluate the role of hematological profile in early diagnosis of neonatal sepsis because this is a simple test which can be done within a short period of time span before putting the neonate on antibiotic therapy.

#### METHODS

The present study was carried out in Guru Gobind Singh Medical College and Hospital, Faridkot (Punjab), located in the northern part of India over a period of 1 year on all the neonates with clinical suspicion of sepsis admitted in the neonatal intensive care unit (NICU) with the aim to find the role of hematological profile, scoring system, and CRP in patients with neonatal sepsis. The study was conducted after obtaining written permission from the parents of the newborns. Using all the aseptic precautions, blood sample was collected from the peripheral vein by the pediatrician before starting antibiotic treatment. 2 ml of

blood was collected in plain vial as well as ethylenediaminetetraacetic acid (EDTA) vial. Plain vial was used for CRP estimation and EDTA for hematological profile. The blood collected in EDTA vial was analyzed by an automated hematology analyzer and peripheral blood smear was made and HSS scoring was done.

#### Inclusion criterion

Neonates within the age group of 0-28 days who were clinically having signs and symptoms of septicemia (According to Systemic Inflammatory Response Syndrome criteria of Goldstein et al.) [6].

#### Exclusion criterion

Newborns with ages above 28 days have inborn errors of metabolism and hemolytic jaundice.

#### RESULTS AND DISCUSSION

A total of 100 neonates were taken in this study comprising 53.00% males and 47.00% females. The respondents were divided into two groups on the basis of age. The first group comprised neonates falling in the age group 0-7 days and other group being 7-28 days. The first group comprised 66.00% of the cases whereas other had 34.00% of the cases. Chi-square test reveals that there is a statistically significant difference between the age and sex distribution of the participants in the study as shown in Table 1.

#### Statistical analysis

X <sup>2</sup>	DF	p-value	Significance
10.240	1	<0.05	Significant

Table 2 shows the rural and urban area distribution of neonates. Sixty seven out of 100 neonates (67.00%) were from rural areas, followed by 33 neonates (33.00%) from urban areas. Chi-square test reveals that there is a statistically significance difference between rural and urban distribution of the neonates in the study.

#### Statistical analysis

X <sup>2</sup>	DF	p-value	Significance
11.560	1	<0.05	Significant

Table 3 shows that respiratory distress was the chief complaint in the majority of cases 61 (53.51%), followed by fever and lethargy. Many of them presented with more than one complaint.

Above table shows the distribution of the neonates according to their birth history. Nearly three fourth of them (73.00%) were prematurely delivered. Chi square reveals p value is less than 0.05 therefore it is statistically significant.

**Table 1: Distribution of neonates according to age and sex (n=100)**

Age Group (in days)	Males		Females		Total	
	No. of males	%age	No. of females	%age	No. of respondents	%age
0-7	36	36.00	30	30.00	66	66.00
7-28	17	17.00	17	17.00	34	34.00
Total	53	53.00	47	47.00	100	100.00

**Table 2: Rural and urban area distribution of neonates (n=100)**

Area	Number of cases	Percentage
Rural	67	67.00
Urban	33	33.00
Total	100	100.00

Table 4 depicts the distribution of neonates according to HSS. 37 cases (37.00%) out of 100 have a score  $\geq 5$ , followed by 33 cases (33.00%) with a score  $\leq 2$  and 30 cases (30.00%) with a score 3 or 4.

Table 5 shows the correlation between HSS and CRP value. 37 cases had HSS score  $\geq 5$  out of which 33 cases (89.18%) had positive CRP value. In respondents having score 3 or 4, CRP value was positive in 24 (80.00%) of the cases. In neonates with HSS score  $\leq 2$ , 58.00% of the cases had negative CRP.

Our study showed that the majority of the neonates (85 cases) had normal TLC whereas only 15 had TLC in abnormal range. Chi-square reveals that the p value is less than 0.05, so the results are statistically significant.

About 76% of cases had shown either increased or decreased levels of PMN count. No neonate showed a complete absence of mature PMN. Furthermore, majority of the neonates presented with neutrophilia (63.00%), while only 13 neonates had neutropenia. The results are statistically significant as  $p < 0.05$ .

Furthermore, it was seen that more than half of the neonates, that is 59.00%, had shown raised levels of immature PMN count and also seen is that among 100 neonates, 53 neonates (53.00%) had I: T ratio less than or equal to 0.120 whereas 47 neonates (47.00%) had an increased I:T ratio.

Table 6 shows that among 100 neonates, 91 (91.00%) had normal I:M ratio and 9 (9.00%) had shown increased I:M ratio. Chi-square reveals the  $p < 0.05$ , that is, results are statistically significant.

**Statistical analysis**

X <sup>2</sup>	DF	p-value	Significance
67.240	1	<0.05	Significant

**Table 3: Distribution of neonates according to chief complaints (n=114)**

Chief complaints	Number of cases	Percentage
Respiratory distress	61	53.51
Fever	13	11.41
Lethargy	10	08.77
Cyanosis	07	06.14
Hypothermia	06	05.26
Poor Feeding	14	12.28
Seizures	03	02.63
Total	114*	100.00

\*Multiple responses were obtained

**Table 4: Distribution of neonates according to scoring of hematological scoring system (n=100)**

Score	Interpretation	Number of cases	Percentage
$\leq e$	Sepsis is very unlikely	33	33.00
3 or 4	Sepsis is suspected	30	30.00
$\geq 0$	Sepsis is very likely	37	37.00

**Table 5: Distribution of neonates according to C-reactive protein and hematological scoring system score (n=100)**

Hematological scoring system score		C-reactive protein			
Score	No. of respondents	CRP Positive		CRP Negative	
		Cases	%age	Cases	%age
$\leq a$	33	14	42.00	19	58.00
3 or 4	30	24	80.00	06	20.00
$\geq 0$	37	33	89.18	04	10.82

Our study depicted that among 100 neonates admitted to Neonatal to (NICU) with clinical suspicion of sepsis degenerative changes such as cytoplasmic vacuolation and toxic granulation were seen in 65 cases (65.00%) neonates while 35 cases (35.00%) did not show any degenerative changes in PMN as shown in Table 7.

In addition, it was observed that among 100 neonates taken in this study, 23 cases (23.00%) had normal platelet count and 77 cases (77.00%) had shown decreased platelet count. Statistical analysis showed that the results are statistically significant.

Our study showed that among 100 neonates, 71 (71.00%) had positive CRP value and remaining 29 (29.00%) had negative CRP value. Chi-square reveals a statistical significant difference in CRP count.

Table 7 shows distribution of neonates according to degenerative changes and CRP value. Among 71 neonates with positive CRP value, degenerative changes were seen in 56 (78.87%) neonates, while they were absent in 15 (21.13%) neonates. Furthermore, out of 29 neonates with negative CRP values, 20 (68.97%) had normal neutrophil morphology, while 09 (31.03%) showed degenerative changes.

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection. Clinical manifestations include hemodynamic instability, hypoxemia, and various signs of acute inflammatory state [17]. Early-onset infections occur during 1<sup>st</sup> week of life and are most commonly associated with maternal to fetal transmission. Late-onset infections are contracted from the environment and occur after the 1<sup>st</sup> week of life [18]. Neonatal sepsis is the single most important cause of neonatal death in developing country.

The present study comprised 100 neonates, aged between 0 and 28 days. Male preponderance was noted with male: female ratio of 1.2:1. This is in concordance with a study conducted by Khair et al., in 2010 on the role of HSS in the early diagnosis of neonatal septicemia. In their study, male: female ratio was 1.4:1 [19].

The respondents were divided on the basis of time of presentation as early-onset sepsis, that is, 0–7 days and late-onset sepsis, that is, 7–28 days. It was deduced that the majority of neonates 66 (66.00%) presented themselves with sepsis in the first 0–7 days of life and 34 (34.00%) presented between 7 and 28 days. The results of the study conducted by Supreetha et al. were similar. They found out that out of 110 neonates admitted to NICU with clinical suspicion of sepsis, 82 (74.50%) had presentation between 0 and 7 days and 28 (25.50%) had late presentation [20].

Venkatarao et al. did a study on 40 neonates out of which 30 were from rural areas and 10 of them were from urban areas. Thus similar results were seen to the present study [21].

**Table 6: Distribution of neonates according to HSS (I: M ratio)**

I: M ratio	Number of cases	Percentage
<0.3	91	91.00
>0.3	09	09.00
Total	100	100.00

**Table 7: Distribution of neonates according to degenerative changes and CRP count**

Degenerative changes	CRP		Total
	Positive (%age)	Negative (%age)	
Degenerative changes			
Present	56 (78.87)	09 (31.03)	65
Absent	15 (21.13)	20 (68.97)	35
Total	71 (100.00)	29 (100.00)	100

The major chief complaint in our study was respiratory distress 61 (53.50%), followed by poor feeding 14 (12.28%), fever 13 (11.40%), and lethargy 10 (8.77%) which is in concordance with the study performed by Farhadi *et al.* in 2011 which revealed that overall most common chief complaint was respiratory distress, followed by poor feeding, fever, and lethargy [22].

Among 100 neonates, 73 (73.00%) were prematurely delivered and the rest 27 (27.00%) were delivered at full term. Labib *et al.* in 2013 found almost parallel results among 40 cases of which 68.6% of neonates were prematurely delivered and 31.4% were delivered full term [23]. Whereas in contrast, another study conducted by Mayuga and Isleta in 2005 showed that 57% of term neonates developed sepsis [5].

In our study, distribution of neonates according to HSS was done of which the majority (37.00%) had score  $\geq 5$ , followed by 33.00% with score  $\leq 2$  and 30.00% with score 3 or 4. These findings are in concordance with the study done by Makkar *et al.* in 2014, among 110 cases in which 47% had hematological score  $\geq 5$ , 29% had a score either 3 or 4, and remaining 24% had score  $\leq 2$  [24].

In the present study, among 37 neonates with HSS score  $\geq 5$ , 89.18% were CRP positive and 10.82% were CRP negative, followed by 33 with score  $\leq 2$  out of which 42.42% were CRP positive and 57.58% were CRP negative and 30 had score 3 or 4 among them 80% were CRP positive and 20% were CRP negative.

In the present study, on evaluating each of the seven parameters of HSS, it was found that TLC was within the normal range in 85% of the neonates. These results are in concordance with the study conducted by Mayuga and Isleta in 2005 among 100 neonates in which TLC was within the normal range in the majority (84%) and only a small percentage (16%) had TLC levels  $<5000$  or  $>25000$  at birth [5]. The results were also comparable with study done by Farhadi *et al.* in 2014 [22]. Concordance was also seen in another study performed in India on the utility of hematological parameters in the detection of neonatal sepsis by Duhan *et al.* in 2016 in which among 34 neonates with probable sepsis, 22 had TLC within the normal range and 7 had increased levels, while 5 had TLC on lower side [25].

In the present study, more than three-fourth of the neonates, 76 (76.00%), had shown either increased or decreased levels of PMN count, while 24 (24.00%) had shown PMN count within normal range. The results obtained were similar with the study published by Duhan *et al.* in 2016 who evaluated that among 34 neonates with probable sepsis, 79.40% had either increased or decreased PMN levels, and rest 20.60% had normal PMN levels [25]. Furthermore, majority of neonates with altered PMN count had neutrophilia (63.00%) while only 13 of the 100 neonates showed neutropenia.

In a recent study by Pramana *et al.* in 2016 on diagnosis accuracy of HSS in early identification of neonatal sepsis, it was seen that of 21 cases with proven sepsis, 14 (67%) had raised immature PMN count [26]. In our study, more than half of the neonates 59 (59.00%) had shown that raised levels of immature PMN count parallel results were seen in a study conducted by Duhan *et al.* in 2016 and found that among 34 neonates with probable sepsis, 18 (52.9%) neonates had increased levels of immature PMN count and 16 (47.1%) had normal immature PMN count [25].

In this study, 53 neonates (53.00%) had normal I: T ratio while 47 (47.00%) had increased I: T ratio. A study done by Mayuga and Isleta in 2005 also showed similar results and found that among 100 neonates, 83 of them had I: T ratio within the normal range and 17 of them shown raised I: T ratio [5]. However, dissimilar results were obtained by Duhan *et al.* in 2016 in which among 34 neonates with probable sepsis 20 (58.8%) had increased I: T ratio and 14 (41.2%) had shown I: T within the normal range [25].

In 91.00% of neonates in our study, normal I: M ratio was seen and only 09.00% had shown increase in I: M ratio. Comparable results were seen by Mayuga and Isleta in 2005 and found that among 100 neonates, 90 of them had shown I: M ratio within normal range, and 10 of them had raised I: M ratio [5]. Another study conducted by Duhan *et al.* in 2016 showed contradictory results and found that among 34 neonates with probable sepsis, 14 had normal I: M ratio and 20 had increased I: M ratio [25].

In this study, morphological degenerative changes were seen in 65 out of 100 neonates admitted to NICU with clinical suspicion of sepsis while 35 revealed normal neutrophil morphology. Out of 71 neonates with positive CRP count, 77.46% showed the degenerative changes while 22.54% showed normal morphology. Furthermore, among 29 neonates with negative CRP count, 68.96% had normal morphology of neutrophils while 31.04% showed degenerative changes which were similar to the study results by study conducted by Liu *et al.* [27] Results were discordant with the study conducted by Khair *et al.* on role of HSS in early diagnosis of neonatal septicemia. Their study revealed that degenerative changes in neutrophil had no significant association with neonatal sepsis [19].

In the present study, among 100 neonates, 77 (77.00%) had decreased platelet count and 23 (23.00%) had shown normal platelet count. Similar results were obtained by Arif *et al.* in the study on thrombocytopenia and bacterial sepsis in neonates done in 2011. The results showed that out of 85 neonates admitted with clinical suspicion of sepsis 71 (83.50%) had thrombocytopenia while 14 (16.50%) had normal platelet count [28]. Concordance was also obtained with the study done by Saleem *et al.* in 2014. In their study among 170 neonates, 75.6% of them showed decreased platelet count and rest of them had platelet count within normal range [29]. Results obtained were different from the study conducted by Duhan *et al.* in 2016. They found out that among 34 neonates with probable sepsis, 70.6% of them had normal platelet count and 29.4% had shown decreased platelet count [25].

The study revealed that among 100 neonates, 71 (71.00%) had positive CRP count, and the remaining 29 (29.00%) had negative CRP count. Similar results were obtained by Hissamuddin *et al.* in 2015 on validity of CRP for the diagnosis of neonatal sepsis. They found out that among 147 neonates with suspected neonatal sepsis, CRP done at the time of admission was positive in 94 cases (63.9%) and negative in 53 cases (36.1%) while CRP done after 72 h of the first one was 100 (68%) positive and 47 (32%) negative [30]. The results obtained were quite similar to the results obtained in our study. Another study conducted by Saleem *et al.* in 2014 showed similar results. In their study among 170 neonates, 81.7% of them showed increased CRP levels [29]. Results differed from the study by Duhan *et al.* in 2016 which revealed that among 34 neonates with probable sepsis, 44.1% had shown positive CRP count and 55.9% had shown negative CRP count [25].

Thus, the results of our study highlighted that even though there are several methods available for the rapid detection of microorganisms in blood cultures of newborn infants using automated blood culture system, DNA probe, fluorometric detection systems, etc., still HSS can be employed as a useful test to distinguish the infected from then on infected infants. It has high sensitivity and specificity, the certainty of sepsis being present with higher scores. Furthermore, the combination of HSS with other tests such as CRP increases its diagnostic accuracy as well which can be deduced from the observations of the current study.

## CONCLUSION

HSS is a simple, feasible, quick, cost-effective tool which can be used as screening test for providing a working diagnosis of neonatal sepsis. This working diagnosis may aid clinicians in identifying sepsis and instituting proper antibiotic therapy. In the present study, the association of sepsis was found to be significant ( $p < 0.05$ ) with age and sex, birth history, rural and urban distribution, TLC, total PMN count, immature PMN count, I: M ratio, and thrombocytopenia. The majority of



the neonates with altered levels of PMN had neutrophilia. Furthermore, CRP value correlated more with a higher score of hematological scoring system that is higher the score more is the CRP positivity.

Hence, it can be safely concluded that the hematological scoring system (HSS) helps effectively to make choices with respect to wise utilization of anti-microbial treatment which will be life sparing, give early cure, reduce mortality, shorten the hospital stay, and as well as will minimize the risk of emergence of the resistant organism due to misuse of antibiotics as well.

#### AUTHORS CONTRIBUTION

Dr. Sahil Chhabra, developing concepts for research, designing study, literature search, data acquisition, analysis and conclusion, and manuscript preparation. Dr. Arnav KR Roychoudhury, data analysis and conclusion, manuscript preparation, editing, and reviewing. Dr. Prerna Chhabra, data analysis and reviewing. Dr. Rupali, Data acquisition, statistical analysis, and guarantor.

#### CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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