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Hematological scoring system: 'An early predictor of neonatal sepsis'

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Abstract
Neonatal Sepsis is a clinical syndrome resulting from pathophysiologic effects in the 1st month of life. Hematological scoring system (HSS) is the scoring system that includes 7 hematological parameter into account and assigns a score which helps in early diagnosis and treatment of sepsis. Aims and Objectives. To assess the importance of hematological parameters in the early diagnosis of neonatal sepsis, compare the variables with blood culture and assess the most sensitive and specific variables in diagnosing neonatal sepsis. Material and method. This is a prospective study done on 105 neonates admitted in NICU of CSSH Meerut from Dec 2020 to Aug 2022 with suspicion of sepsis. Results. HSS was seen to have high sensitivity (>98%) when compared with blood culture, it identified sepsis in > 95% of neonates. Among all parameters of HSS, immature PMN count show highest sensitivity (93%) followed by IT PMN ratio (91%) which also showed high specificity (94%) and positive predictive value. Platelet count was found to have lowest sensitivity but high specificity and high positive predictive value.
Conclusion: Hematological scoring system can be considered as a simple, reliable, quick and cost effective test for the early diagnosis of neonatal sepsis. This test helps treating physician to diagnose the neonatal sepsis as early as possible and start the appropriate therapy to prevent sepsis related mortality and morbidity.

Keywords: hematological scoring, neonatal sepsis, clinical syndrome

Introduction

Neonatal septicemia is a clinical syndrome resulting from pathophysiologic effects of local and systemic infection in the 1st month of life. Septicemia usually consists of bacteremia with a constellation of sign and symptoms caused by microorganisms or their toxic products in the circulation. [1] It comprises of various systemic infections such as septicemia, pneumonia, meningitis, arthritis, osteomyelitis and urinary tract infections. Superficial infections such as oral thrush, conjunctivitis are not included under neonatal sepsis [2]. Neonatal septicemia is a leading cause of mortality and morbidity during the neonatal period, especially, among LBW and preterm babies in developing countries [3]. Globally of 130 million babies born every year, about 4 million babies die in first 4 week of life. Most neonatal deaths (99%) arise in low- income and middle-income countries, and about half occur at home. In poor communities, many babies who die are unnamed and unrecorded, indicating the perceived inevitability of their deaths. [4] The reported incidence of neonatal sepsis in the developed countries varies from 1 to 10 per 1000 live births. In the developed countries mortality due to sepsis has increased by approximately 13.7% each year over the past 2 decades but early diagnosis of neonatal sepsis is difficult due to its non-specific clinical presentation. Nonetheless, the reported incidence of neonatal sepsis according to the data from National Neonatal Perinatal Database (NNPD) is 30 per 1000 live births. The NNPD network comprising of 18 tertiary care neonatal units across India found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths [5].

On the basis of clinical criteria alone, it is very difficult to diagnose neonatal sepsis because of non-specific and variable sign and symptoms. According to the National Neonatology forum, neonatal sepsis can be of two type [6] –

a. Proven sepsis: newborn with clinical picture suggestive of sepsis and isolation of pathogen from blood, CSF (cerebrospinal fluid), urine or other body fluids or autopsy evidence of sepsis.
b. Probable sepsis: newborn with clinical picture suggestive of sepsis with one or more of the following criteria:

1. Predisposing factors like maternal fever, foul smelling liquor or prolonged rupture of membrane>12hrs, gastric polymorph count of more than 6/HPF.
2. Positive sepsis screen with two of the following four parameters
   - Total leukocyte count < 5000/ cumm.
   - Band cell to total neutrophil ratio of ≥ 0.2
   - CRP ≥ 0.6 mg/dl
   - Micro-ESR≥15mm AEFH (at the end of first hour)
3. Radiological evidence of pneumonia.

Various cheap but reliable laboratory tests have been evaluated for the diagnosis of systemic infection in neonates. The complete blood count (CBC) with the various neutrophil parameters and C-reactive protein (CRP) are the most frequently used.

Blood culture is still considered to be the 'gold standard' for diagnosis of septicemia; however, its accuracy has been questioned because of spurious positive results due to contamination and negative blood cultures in fatal generalized bacterial infections. The yield of a positive blood culture ranges from 8-73% as shown in various studies. Moreover, the technique of blood culture is time consuming and demands a well-equipped laboratory which is not available in most of the community hospitals[6]. Therefore, the need is for a test that is cheap, easily performed with quick availability of reports [7].

Hematological scoring system

HSS is the screening test for diagnosing sepsis given by Dr. Rodwell include seven hematological parameter into account and assigns a score. [8] The total score thus ranges from 0-8, and it has been suggested that if the total score is less than 2, sepsis is very unlikely and if the score is more than 5 the likelihood of sepsis is very high. It has high sensitivity and specificity, the certainly of sepsis being present with higher score. [9] HSS can be employed as a useful test to distinguish the infected from the non-infected infants. The current study was undertaken to assess the significance of the hematological scoring system (HSS) for early detection of neonatal sepsis in high risk infants. [10]

Hence the present study is aimed to evaluate the usefulness of various parameters of CBC as an early indicator of neonatal septicemia because this is a simple bed-side test which can be done within a short time before putting the neonate on antibiotic therapy.

Material and Methods

Study Type and Place: This is a prospective observational study which includes 105 neonates (<28 days of age) who were suspected for neonatal sepsis and admitted in neonatal intensive care unit and has been conducted in the Central Laboratory at Subharti Medical College and associated Chhatrapati Shivaji Subharti Hospital meerut, Uttar Pradesh India.

Duration of the study was between December 2020 to August 2022.

Inclusion Criteria. All neonates (28 days of age) with signs and symptoms of clinical suspected septicemia.

Exclusion Criteria. Neonates with gross congenital anomalies and Neonates with history of previous antibiotic therapy.

Hematological investigation

- Peripheral smear manual method
- Automated methods

Microbiological investigation

- Blood culture

Biochemical investigation

- Determination of C-reactive protein

(whenever available, although CRP is a biochemical investigation but it is done in microbiology section in our laboratory)

Table 1: Hematological scoring system. [10]

Hematological Scoring System		
Criteria	**Abnormality**	**Score**
Total WBC Count	≤ 5000/cumm > 25000/cumm at birth > 30000/cumm at 12-24 Hr > 21000 day 2 Onward	1
Total PMN Count	No mature Neutrophil Increased or Decreased count (1800-5400/cumm)	2 1
Immature PMN Count	> 600/cumm	1
I:T PMN Ratio	> 0.2	1
I:M PMN Ratio	> 0.3	1
Degenerative changes in PMNs	Present (Toxic granules or cytoplasmic vacuolations)	1
Platelet count	<150000/cumm	1

Table 2: scoring system interpretation (9,10)

Score	Interpretation
≤2	Sepsis is very unlikely
3– 4	Sepsis is suspected
≥5	Sepsis or infection is more likely
Score ≤2 was interpreted as unlikely of sepsis; scores 3–4: Possibility of sepsis and≥5 infection or sepsis is more likely. Obtained minimum scoring is 0 and maximum scoring 8	

Statistical Analysis The data are reported depending on their distribution. Frequencies are expressed in percentages. Sensitivity and specificity test performed. Chi-square test was used to ascess differences in categoric variables between groups. A p-value of <0.05 is taken as being of significant for all statistical tests. Data entry and data analysis of quantitative data has been done using appropriate statistical software package. (SPSS, version 21.0 for windows)

Results

This prospective observational study included total of 105 neonates. Out of 105 neonates male patients were 64% and female patients were 36%. The diagnosis of sepsis was made when the blood culture was positive. Neonates were classified as having probable infection when there was strong clinical history or presence of 2 risk factors for infection and when the blood culture was negative.

Neonates were taken as no sepsis when there was no clinical history or risk factors for infection and negative blood culture**.**

Table 3: clinical group distribution

Categories	Clinical feature	Blood culture	Total no. of cases
Group-1 (Sepsis)	Yes	Positive	55
Group-2 (Probable infection)	Yes >2 risk factor	Negative	10
Group-3 (No sepsis)	Yes < 2 risk factor	Negative	40

Clinical scoring system based classification, babies were classified into different groups: sepsis, probable infection and normal infants or no sepsis (table- 3).

Neonates with positive blood culture were kept in **Sepsis** group. **Probable infection** included neonates when showing strong clinical history as presence of >2 risk factors for infection with negative blood culture. Neonates with no clinical history and <2 risk factors and with negative blood culture were taken as **No sepsis or normal infants**.

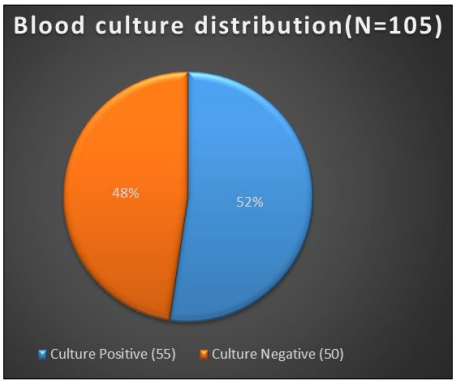

Fig 1: Distribution according to Blood culture (N=105)

The gold standard test for diagnosis of **sepsis** is positive blood culture.

Table 4: bacteriological profile in blood culture positive cases (N=55)

Gram negative organism	Number of cases
Klebsiella pneumonia	14 (25.4%)
Pseudomonas aeruginosa	03 (5.4%)
Citrobacter koseri	02 (3.6%)
Streptococcus hemolyticus	(7.2%)
Burkholderia cepacia complex	02 (3.6%)
Total	25
Gram positive organism	number of cases
Coagulase negative staphylococcus	24 (43.6%)
Staphylococcus aureus	03 (5.4%)
Enterococcus faecalis	02 (3.6%)
total	29
Fungus	Number of cases
Candida papsilosis	1

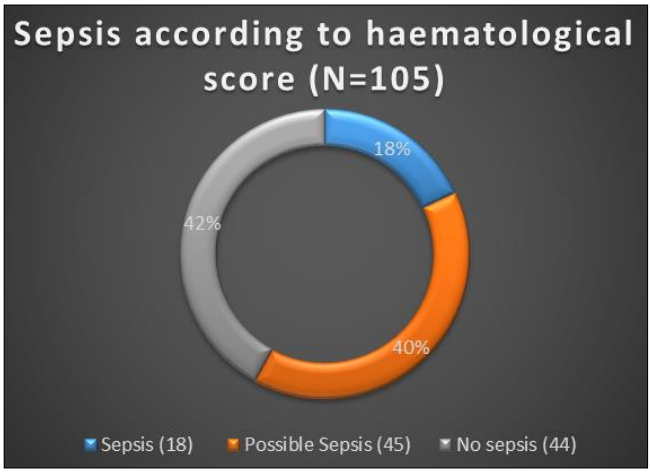

Fig 2: Sepsis distribution According to HSS

According to HSS 18% were in very likely sepsis, 40% in possible sepsis and 42% in no sepsis, group.

Table 5: Comparison of Blood culture with Hematological score

Blood culture (N=105)	Hematological score (N=105)		
	Very likely (%) (score: ≥ 5)	Possible sepsis (%) (score: 3-4)	No sepsis (%) (score:0-2)
Positive: 55 (52.4%)	18 (32.7%)	36 (65.4%)	01 (1.9%)
Negative :50 (47.6%)	0 (0%)	7 (14%)	43 (86%)

The chi-square statistic is 76.2388 with df= 1 and CI = 95%. The *p*-value is < .00001. The result is significant at *p* < .05

Patients in very likely and possible sepsis group which had positive blood culture consists 98.1% patients according to HSS. Whereas 1.9% of the neonates which come in no sepsis group, according to the HSS had positive blood culture. No patient in very likely sepsis group had negative culture report. But 14% of the patients in possible sepsis group had negative blood culture.

Table 6: HSS parameters - Statistical Incidence

Parameters	Sensitivity	Specificity	PPV	NPV
Total WBC(µl)	58%	87%	88%	58%
ANC	83%	66%	68%	81%
Immature PMNs Count	93%	86%	87%	92%
I/T PMNs Ratio	91%	94%	94%	90%
I/M PMNs Ratio	52%	94%	94%	50%
Degenerative Changes in PMNs	61%	96%	96%	58%
Platelet Count	55%	94%	94%	52%

Highest sensitivity is seen with immature polymorph nuclear cell count (93%), immature to total polymorph ratio (91%) and absolute polymorph count (83%). Immature to mature PMNs ratio has lowest sensitivity (52%) and high specificity (94%).

Immature to mature PMNs ratio, degenerative changes and platelet count have lower sensitivity, low NPV. Degenerative changes (Toxic granules, cytoplasmic vacuolation) in polymorphs, platelet count and Immature to mature polymorphs ratio have the highest specificity and high PPV.

I/T PMN ratio, I/M polymorphs ratio, immature polymorphs count, toxic granules, cytoplasmic vacuolations in polymorphs and platelet count have high PPV. Immature to Total PMNs (I/T PMNs) ration has a good sensitivity and excellent specificity and PPV. Immature to Mature PMNs (I/M PMNs) ratio have lower sensitivity but have High specificity and PPV. Immature PMN count and I:T PMN ratio and absolute polymorphs had higher NPV as compared to other parameters.

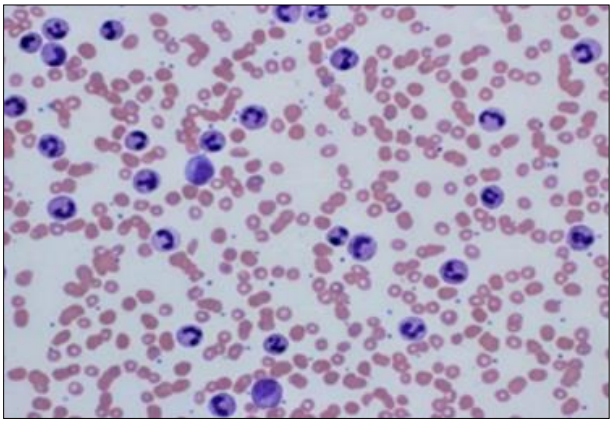

Fig 3: Leishman stain, neutrophilic leucocytosis, 40X

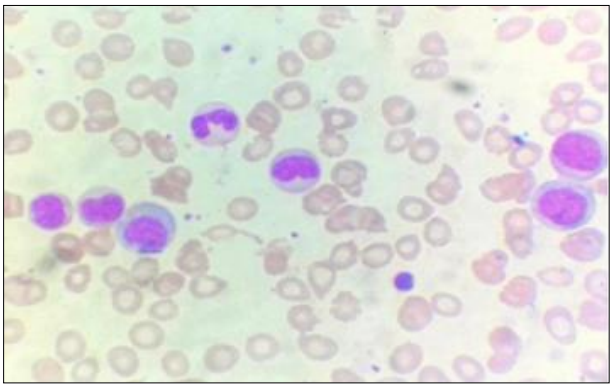

Fig 4: Leishman stain, Immature forms, 100X

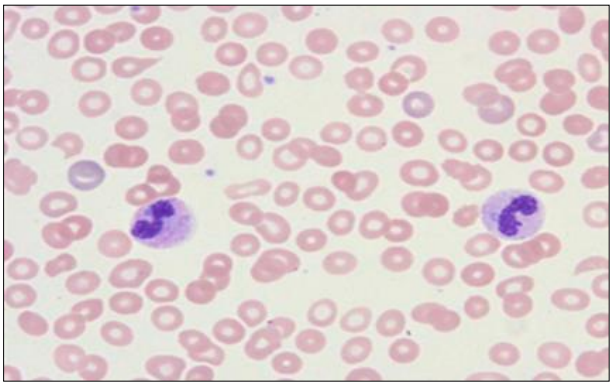

Fig 5: Neutrophils shows cytoplasmic vacuolations, 100X

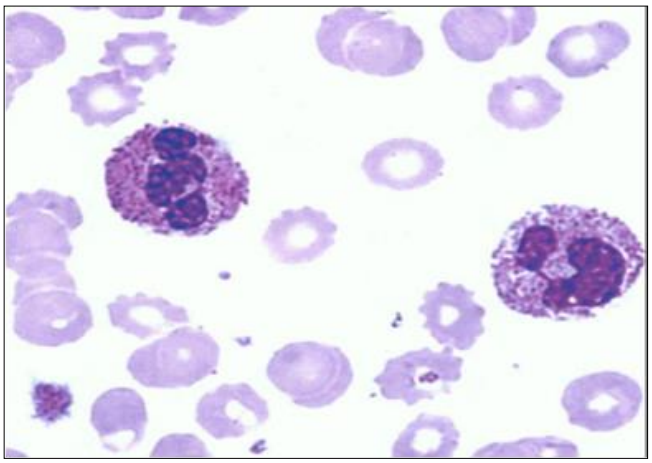

Fig 6: Leishman stain, toxic granules in neutrophils, 100X

Discussion

In newborn medicine neonatal sepsis is a very common challenge. Due to the immature development of the body Early diagnosis of neonatal sepsis is common problem faced by clinician because rapid deterioration is seen in undiagnosed sepsis in absence of proper treatment. There are various clinical and hematological parameters to combat this problem by which we can detect sepsis and start treatment on early basis. In our study we followed the HSS given by Rodwell *et al*, as 7 parameters for early detection of neonatal sepsis. But due to delay in final report we can use HSS for early diagnosis which is helpful for the clinician to start treatment and prevent and decrease neonatal mortality rate.

The prospective study done by Majumdar A *et al* [11], Makkar M *et al* [12] shows male predominance which correlate with our study. Neonates present with LOS are less susceptible than the EOS groups. There is low level of IgG and low defence mechanism in preterm and LBW neonates as described by Debroy A *et al* [13] and Makkar M *et al* [12] which also correlates with our study.

It was found similar when compared to other recent studies. Patient with higher HSS had increased chance of sepsis. Whereas sepsis is least likely with HSS score of less than two.

A prospective study done by Bhalodia MJ. *et al* [1] (2017) included 150, out of which all 48 cases which were culture-positive showed HSS ≥5. HSS among the culture-negative cases, 25 cases had score 0-2 whereas 77 cases had score 3-4. ANC showed high sensitivity (91%), and TLC showed high specificity (92.1%). Platelet count showed high NPV (58%) and least PPV (56%). Whereas in our study immature PMNs and I:T ratio are most specific parameter, degenerative changes showed high specificity.

In an another prospective study by Munazza Saleem [14] (2014) which included 170 newborns, HSS were assessed as incorporating increase or decrease in TLC,. Blood culture and CRP estimation were also included in study. HSS score of more than 3 was considered as positive. The hematological scoring system had sensitivity of 90%, specificity of 74.5%, PPV was 65.9% and NPV value was 93.2%. The individual parameter like thrombocytopenia had a sensitivity of 61% and specificity of 82%. But in our study HSS has shown the Sensitivity = 98.1% and Specificity = 86%. Platelet count as an parameter shows sensitivity of 55% and specificity 94%.

In a prospective study by Supreetha MS *et al* [15] (2015), out of 110 infants, 74.5% infants had EOS and 25.45% infants had LOS whereas in our study 80% infants had EOS and 20% had LOS. Preterm infants (60.8%) were more prone to neonatal septicemia which were predominant in our study. These results correlates with the results of our study.

Aparna *et al* [08] and Monika L *et al* [16] showed high sensitivity and high negative predictive value in total PMN count and similar findings are noted by our study also with additional findings such as high specificity and PPV also seen in I:T PMNs ratio.

Study conducted by Haider Shirazi *et al* [17] (2010) included total 138 infants which were evaluated for sepsis, out of which 48 were confirm sepsis by the positive blood culture test. Acenetobacter, Klebsiella pneumonia were the commonest organism isolated. While in our study out of 105 infants 55 were culture positive and Coagulase negative staphylococcus and Klebsiella pneumonie are commonest organism.

Platelet count was not a good predictor of sepsis in our study which is similar in the study by Duhan A *et al*. [13] Increased I:M PMNs ratio had good sensitivity in identifying sepsis which was similar to the study done by Debroy A *et al* [13] and Aparna s *et al*. [8]

Immature PMN count is an most excellent parameter of sepsis which correlates with study done by Manoj Maruti *et al* [9] and Narasimha *et al*. [8]

CRP is an average predictor of neonatal sepsis but it is shown significant with study previously done by Manucha V *et al*. [18] and Patel U *et al*. [19] which is significant in our study too.

The accuracy of diagnosis of sepsis in neonates is quite obvious by hematological scoring system. HSS can be used as a screening test in diagnosing sepsis but the interpretation and procedure of the test needs specific protocol to improve the sensitivity and specificity of this.

Conclusion

Though Blood culture is considered gold standard test but the results of our study indicate that Hematological scoring system can be effectively and reliably rule out Sepsis Neonatarum because it overlaps with other conditions due to non-specific symptoms.

Hematological scoring system can be considered as a simple, reliable, quick and cost effective test for the early diagnosis of neonatal sepsis. In our study results Total leucocyte count and total PMN counts followed by Immature PMNs and I/T Ratio are the most sensitive parameters in early diagnosis of neonatal sepsis.

This test helps treating physician to diagnose the neonatal sepsis as early as possible and start the appropriate therapy to prevent sepsis related mortality and morbidity. This test also helps to avoid unnecessary institution of antibiotics and development of their resistance in future.

Seven parameters included in HSS can provide sufficient information in determining the probability of sepsis in neonates. This scoring system can be taken as simple, less time consuming and cost friendly routine screening procedure that can be done anywhere even at small setup like primary health center.

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I pay tribute to My Parents, My Brother and My wife for lifting me up till this phase of life. I thank them for their love, trust, patience, support and bearing all kind of stress to make me what I am.

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