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Research Article
Protein

Study of the hematological scoring system and C-reactive protein (CRP) in determining Neonatal sepsis

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Background: Laboratory sepsis markers play an important role in the assessment of a neonate with clinical signs of a probable infection with. C - reactive protein (CRP), Blood culture (BC), Hematological Scoring System (HSS) are three well-identified parameters designated for the investigation of Neonatal Sepsis or infection. **Material and Methods:** The current study was a prospective hospital-based cross-sectional study carried out at the Department of Pathology, MIMER Medical College, Talegaon (D), Maharashtra, India. Neonates with features suggestive of sepsis and Neonates with recent maternal infection were included in the study. Sensitivity, specificity, Positive Predictive Values (PPVs) and Negative Predictive Values (NPVs) were calculated for each parameter. **Results:** A total of 40 neonates suspected of having sepsis were enrolled in the current study. In the current study, blood culture was positive in 10 cases (25%), out of which 6 (60%) were Gram-positive and 4 (40%) were Gram-negative, whereas 30 cases were found to be negative for blood culture. The mean CRP levels in positive culture cases were 85.7±17, whereas, in the negative culture case, the mean CRP Levels were 38.7±23, whereas the mean value in control was 5.88±0.72. **Conclusion:** HSS is a simple, easy, cheap, and rapid adjunct for the diagnosis of clinically suspected cases of neonatal sepsis. C-reactive protein values correlate well with HSS in predicting sepsis. However, C-reactive protein does not have any advantage over HSS, either as a single test or in combination.

Keywords: Neonatal sepsis, C - reactive protein (CRP), Blood culture (BC), Hematological Scoring System (HSS)

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Introduction

Neonatal sepsis is defined as an aggressive bacterial infection occurring in the first 4 weeks of life. The incidence of neonatal sepsis varies from 11-24.5 /1000 live births in India [1]. The clinical pointer of sepsis in new-born infants is usually non-specific. Because of the high morbidity and mortality which is related to neonatal sepsis [2,3,4], antibiotic therapy is started soon after the commencement of the symptoms before the diagnosis is long-established by blood culture. The use of effective antimicrobial therapy has evidently reduced neonatal mortality. However, there is a need for a rapid test that can identify infected neonates at the time of initial valuation thus sparing the uninfected ones from redundant antibiotic therapy. The current practice of starting empirical antibiotic therapy in all neonates showing infection-like symptoms results in their exposure to adverse drug effects, nosocomial complications, and in the emergence of resistant strains. [5].

Sepsis results from the complex interaction between the invading microorganism and the host immune, inflammatory, and coagulation response. [6,7] Inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-15, IL-18, MIF) and growth factors (IL-3, CSFs), and their secondary mediators, including nitric oxide, thromboxanes, leukotrienes, platelet-activating factor, prostaglandins, and complement, cause activation of the coagulation cascade, the complement cascade, and the production of prostaglandins, leukotrienes, proteases, and oxidants. [8]

Laboratory sepsis markers represent a helpful tool in the evaluation of a child with clinical signs and complement the evaluation of a neonate with a potential infection. During the last decades' efforts were done to improve laboratory sepsis diagnosis and a variety of the above-mentioned markers and more were studied with different success. Despite the promising results for some of them, the current evidence suggests that none of them can consistently diagnose 100% of infected cases.

C - reactive protein (CRP), Blood culture (BC), Hematological Scoring System (HSS) are three well-identified parameters indicated for analysis of Neonatal Sepsis or infection.

C-reactive protein (CRP) is the most extensively studied acute phase reactant so far and despite the ongoing rise (and fall) of new infection markers it Still remains the preferred index in many neonatal intensive care units. C-reactive protein was first described in 1930 by Tillet and Francis at Rockefeller University [10]. C-reactive protein is an acute phase and an inflammatory marker that is synthesized in the liver in response to inflammatory cytokines. The level of C-reactive protein rises rapidly with a peak level in 6 hours, even up to thousands of folds during an acute response. It has a short half-life of 19 hours, so the level falls rapidly once the source is removed [11,12,13]. Thus, the CRP level is also a useful marker in determining the duration of antibiotic therapy. These features distinguish CRP from other acute-phase proteins and with the availability of rapid assay method, it has potential importance in diagnosing neonatal sepsis. Unlike blood culture, the CRP level is not affected by prior antibiotic therapy [14,15,16], so it may be particularly useful in developing countries like India, where a significant number of neonates may have been given antibiotics by local doctors before presentation at the hospital.

Blood Culture is considered the Gold Standard in detecting Neonatal Infections. But still, the consequences of Blood Culture get affected by blood volume, usage of pre-natal antibiotics, level of bacteremia and laboratory facilities. Hence, its rate of positivity is relatively low. Also, in the case of Sample volume, the mentioned minimal blood volume for blood culture in new-borns is only 1ml. However, in most cases, the sample volume collected is found to be only 0.5ml.In low-colony count bacteremia, around 60% of blood cultures will be falsely negative with 0.5 ml sample volumes. Multiple blood culture could benefit the augmentation of this test, but past studies conducted in the neonatal period have shown that diagnostic tests like blood culture are time-consuming as well as show conflicting results [17,18].

Hematological Scoring System (HSS) can improvise the diagnostic accuracy of the complete blood cell count as the screening test for neonatal sepsis. But it is challenging to interpret peripheral smears and hemogram parameters in the neonatal period because they vary considerably with the day of life and the gestational age (preterm or otherwise).

Low values of white blood cells, low values of absolute neutrophil counts and high immature/ total ratio are related to early onset of sepsis in infants. High or low white blood cell counts, high absolute neutrophil counts, high immature /total ratio and

Low platelet counts are related to the late onset of sepsis. Though all of these mentioned parameters are linked with sepsis or infection, all of these values separately have low sensitivities. Monroe devised a criterion that used three parameters of total PMN count, immature PMN count and I: T ratio, whereas in this hematologic scoring system.

Here, the current study undertake the study to evaluate the performance of the hematological scoring system (HSS) of Rodwell et al. (1988) in 110 neonates for the early detection of sepsis in high-risk infants, which should improve the diagnostic accuracy of the complete blood cell count as a screening test [19,20].

The present study was conducted to review the role of HSS and CRP as a diagnostic parameter in neonatal infections. The purpose was to obtain a range of tests that are fast, efficient, feasible and practically possible for laboratories with small setups in the developing as well as developed countries for diagnosis of neonatal sepsis.

Material and Methods

Type of study: The current study was a prospective hospital-based cross-sectional study carried out at the Department of Pathology during months of March and April 2019.

Sample size: A total of 40 neonates suspected of having sepsis were enrolled in the current study

Inclusion criteria:

- Neonates with clinical features suggestive of sepsis.
- Neonates with recent maternal infections.

Exclusion criteria:

- Intraventricular hemorrhage
- Meconium aspiration
- Pneumothorax
- Those who underwent surgery
- Birth asphyxia
- Antibiotic therapy prior to admission

Study procedure

Relevant maternal and neonatal histories were recorded in designed and pretested proforma. Blood samples (2 mL) were collected from the peripheral venous puncture within 24 hours of admission before the initiation of antibiotic therapy.

Under complete aseptic conditions, 0.5-1 ml of the blood sample was obtained. Sepsis workup involved complete blood counts along with hematological score (Rodwell's) and microbial culture. Uncorrected WBC count, platelet count was measured using 5 part fully automated analyzer. Neutrophils were classified as band forms when there was no nuclear segmentation or when the width of the nucleus at any constriction was not less than one-third the widths at its widest portion. Band forms together with less mature cell forms were classified as immature Polymorphonuclear (PMN) leukocytes. Using these values, I: M and I: T ratios were computed. Immature neutrophils include promyelocyte myelocyte, metamyelocyte and band form. The hematological findings were analyzed according to the Haematologic Scoring System (HSS) of Rodwell's et al,[20] which includes.

- White Blood Cell (WBC) count and it's differential.
- Platelet count, N-RBCs (To correct total WBC's count).
- Assessment of degenerative and toxic changes in PMNs.

The HSS assigns a score of one for each of the seven criteria found to be significantly associated with sepsis with one exception. An abnormal total PMN count is assigned a score of 2 instead of 1 as shown in the [Table 1]. Sensitivity, specificity, positive and negative predictive values will be evaluated for each of the seven criteria of HSS. Blood Culture and CRP estimation were done as per the standard protocol.

Diagnosis

Proven (definitive) sepsis

Blood culture positive cases with either positive clinical signs or positive septic screen. Following parameters

Were considered significant in septic screen:

Total WBC: ≤ 5000 cells/c.mm.

I/T Ratio: ≥ 0.2

CRP: ≥ 6mg/l

Band cells: ≥ 20%.

Platelet count ≤ 1, 50,000 cells/mm.3

Considered as a positive septic screen if any two or more of the above criteria are met.

Probable sepsis

If the septic screen was positive or clinically symptomatic but blood culture negative.

No sepsis

Sepsis screen, as well as blood culture, are negative and baby is asymptomatic

Statistical Analysis

The data obtained were tabulated on Microsoft excel spreadsheets and analyzed. The data were expressed in terms of Mean±SD and percentages. Sensitivity, specificity, Positive Predictive Values (PPVs) and Negative Predictive Values (NPVs) were calculated for each parameter.

Table 1: Haematologic scoring system (HSS).

Hematological scoring system		
Criteria	**Abnormality**	**Score**
Total leukocyte count (cells/cumm)	<5000	1
	>20,000	
ANC (cells/cumm)	<1800	1
Immature neutrophil count (cells/cumm)	<1200	1
I:T	≥0.2	1
I:M	≥0.3	1
Platelet count (cells/cumm)	<150,000	1
Degenerative changes in neutrophils	Toxic granules cytoplasmic vacuoles	1
I: T – Immature to total neutrophils ratio; I: M – Immature to mature neutrophils ratio		
ANC – absolute neutrophil count		

Results

In the current study, blood culture was positive in 10 cases (25%), out of which 6 (60%) were Gram-positive and 4 (40%) were Gram-negative, whereas 30 cases were found to be negative for blood culture. If the bacteriological profile of the culture is assumed to be the standard outcome, 10 cases are labeled as the definitive sepsis cases. *Klebsiella Pneumonia, Pseudomonas, Enterococcus, Staphylococcus aureus,*and *E. coli* were the infections observed in the positive culture (Table 2).

Table 2: Distribution of cases in accordance with the culture positivity (n=40).

Culture	Number
Positive	10 (25%)
Gram-Positive	6 (60%)
Gram-Negative	4 (40%)
Negative	30
Total	40

The mean CRP levels in positive culture cases were 85.7±17, whereas, in the negative culture cases, the mean CRP Levels were 38.7±23, whereas the mean value in control was 5.8±0.72, which further indicates the positive culture cases under proven sepsis category (Table 3).

Table 3: Mean CRP levels at 72 hours for the diagnosis of neonatal sepsis (n=40).

Mean Value of Control (n =20)	Mean Value of Cases (n=40)		Reference
	Positive Culture (n=10)	Negative Culture (n=30)	
5.88±0.72	85.9±1.27	38.37±2.31	0-6 mg/L

The commonest age in the cases was 6-10 days and ≤5 days in both the positive and negative culture cases. 6 (60%) of positive culture cases were under 6-10 days while 13 (43.3%) of cases were ≤ 5 days (Table 4).

Table-4: Age-wise distribution of Culture results (n=40)

Age (in Days)	Culture sensitivity	
	Positive	Negative
≤ 5 Days	3 (30%)	13 (43.3%)
6-10 Days	6 (60%)	13 (43.3%)
11-15 Days	-	2 (6.66%)
16+ Days	1 (10%)	2 (6.66%)

Based on Rodwell's scoring system, neonates could be classified as sepsis to be unlikely Score Interpretation ≤ 2 Sepsis is unlikely in 4 cases, possible in 11 cases and very likely in 25 cases (Table 5 and Table 6).

Table 5: HSS Profile of Neonates (N=40)

Score	Interpretation	Cases
≤ 2	Sepsis is unlikely	4
3 or 4	Sepsis is possible	11
≥ 5	Sepsis is very likely	25

Table 6: Interpretation of HSS

HSS	Positive Culture	Negative Culture	Total
≤ 2	0	4	4
3 or 4	0	11	11
≥ 5	10	15	25

The current study showed 10 neonates with positive culture, of which all of them had a HSS of ≥6 (Table 7). The sensitivity, specificity, PPV and NPV of HSS with cut-off score of 6 in predicting sepsis was 33.3%, 56.6%, 62.5%, 100%. Similarly, the

Sensitivity, specificity, PPV and NPV of HSS with cut-off score of 5 in predicting sepsis was 33.3%, 40%, 40%, 100%. , the sensitivity, specificity, PPV and NPV of HSS with cut-off score of 4, 3 and 2 in predicting sepsis was 33.3%, 30%, 32.2%, 33.3%, 13.3%, 27%, 33.3%, 6.66%, 25% (Table 8).

Table 7: Diagnostic Accuracy of HSS.

HSS	Positive Culture	Negative Culture	Total
≥6	10	6	16
<6	-	17	17
≥ 5	10	15	25
<5	-	12	12
≥ 4	10	21	31
<4	-	9	9
≥3	10	27	37
<3	-	4	4
≥2	10	29	39
<2	-	2	2
Total	10	30	40

Table 8: Diagnostic accuracy of different haematological scores.

HSS	Sensitivity	Specificity	PPV	NPV
HSS > 6	33.3%	56.6	62.5	100
HSS > 5	33.3%	40	40	100
HSS > 4	33.3%	30%	32.2	100
HSS > 3	33.3%	13.3	27	100
HSS > 2	33.3%	6.66%	25	100

Out of the 10 positive cultured samples from the neonates, 3 had normal I: T Ratio and 7 had increased I: T Ratio. The Sensitivity, Specificity, PPV, and NPV of increased I: T Ratio in predicting sepsis was observed to be 70%, 100%, 100%, 90.0%. The number of neonates that had increased PMN count was 10, with Sensitivity, Specificity, PPV, and NPV of increased PMN Count in predicting sepsis was observed to be 100%, 13.3%, 27.77, 100%. In the current study, 7 neonates had increased I: T Ratio with Sensitivity, Specificity, PPV, and NPV of increased I: T Ratio in predicting sepsis was observed to be 70%, 100%, 100%, 90.0%. The number of neonates with increased Total WBC Count was found to be 10 with Sensitivity, Specificity, PPV, and NPV of Total WBC Count in predicting sepsis were observed to be 100%, 30%, 32.25%, 100%. The number of neonates with immature PMN Count was 10 with Sensitivity, Specificity, PPV, and NPV of immature PMN Count in predicting sepsis was observed to be 100%, 13.3%, 27.77%, 100%. Degenerative changes were observed in 10 neonates with Sensitivity, Specificity, PPV, and NPV Of Degenerative Changes in predicting sepsis was observed to be 100%, 13.3%, 27.77, 100%. The reduction in platelet count was observed in 10 patients with Sensitivity, Specificity, PPV, and NPV of platelet count was observed to be 100%, 43.3%, 37.03%, 100% (Table 9 and Table 10).

Table 9: Diagnostic accuracy of different haematological parameters in predicting sepsis.

Characteristics	I: T Ratio	Positive Culture	Negative Culture	Total
I:T: PMN Ratio	Normal	3	30	33
	Increased	7	0	7
Total PMN Ratio	Normal	-	-	-
	Increased	10	30	40
I:M PMN Ratio	≤ 0.3	-	24	26
	≥ 0.3	10	6	16
Immature PMN Count	Normal	-	4	4
	Increased	10	26	36
Total WBC Count	Normal		9	9
	Increased	10	21	31
Degenerative Changes	Present ≥3	10	26	36
	Absent	-	4	4
Platelet Count	Reduced ≤100,000/ µL	10	17	27
	Normal>100,000/ µL	-	13	13

Table 10: Association of the individual haematological parameters with neonatal sepsis.

Parameters	Sensitivity	Specificity	PPV	NPV
I:T Ratio	70%	100%	100%	90.0%
Total PMN Ratio	100%	-		-
I:M PMN Ratio	100%	80%	62.5%	92.30%
Immature PMN Count	100%	13.3%	27.77	100%
Total WBC Count	100%	30%	32.25	100%
Degenerative Changes	100%	13.3%	27.77	100%
Platelet Count	100%	43.3%	37.03	100%

In table 11, HSS values were compared with the mean values of CRP values, the association between the two parameters represented the significant relationship. 10 cases of the positive culture with the mean CRP value of 85.9±1.27 had an HSS of ≥5, whereas 4 cases of the negative group with the mean CRP value of 7.52±2.34 had HSS of 0-2, 11 cases of the negative group with the mean CRP of 25.21±3.21 had HSS of 3-4, lastly 15 cases of the negative group with the mean CRP of 56.24±3.81 had HSS of ≥5.

Table 11: Haematological score in comparison with CRP value.

HSS	C Reactive Protein (Mean Value)		Total cases
	Positive	Negative	
0-2	0	7.52±2.34	4
3-4	0	25.21±3.21	11
≥5	85.9±1.27	56.24±3.81	15
Total	10	30	40

Figure 1 represented Leucocytosis with degenerative changes and band forms. Immature polymorphs include promyelocyte, myelocyte, metamyelocytes, and band forms. Band cell is described as a PMN in which the nucleus is indented by more than one-half, but in which, the isthmus between the lobes is wide enough to reveal two distinct margins with nuclear material in between. Vacuolization, toxic granulations, and Dohle bodies comprise of degenerative changes.

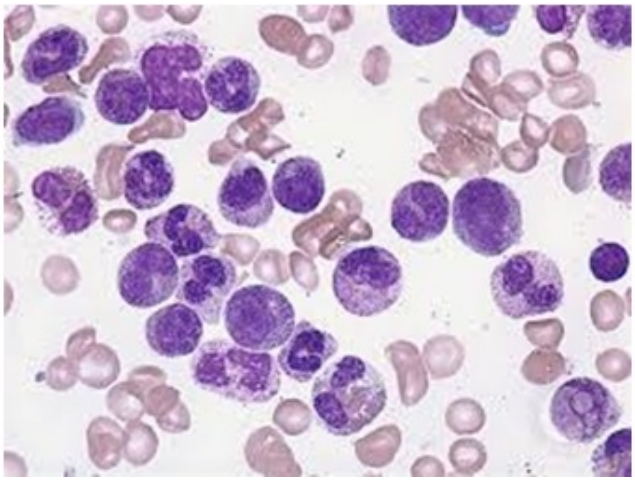

Fig-1: Leucocytosis with degenerative changes and band forms.

Toxic granulations represent the cytoplasmic alterations in peripheral blood neutrophils in response to bacterial infection and have been found to be of greater use in differentiating localized from generalized infection or the development of complications (Figure 2).

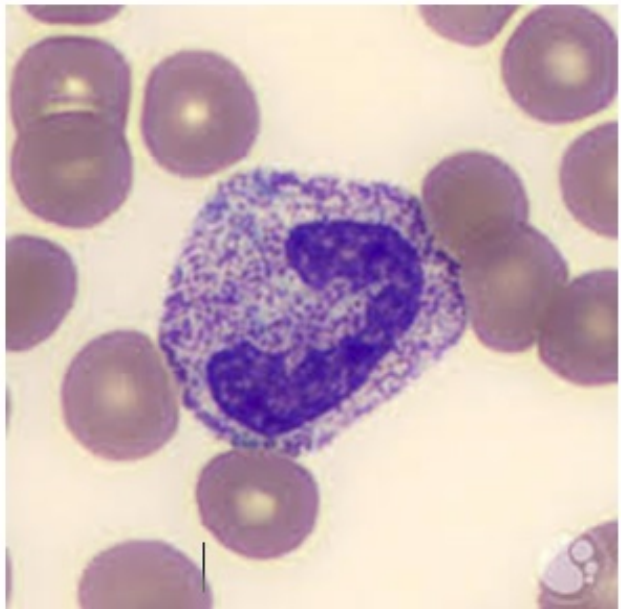

Fig-2: Toxic granulation in neutrophils.

Discussion

Neonatal sepsis is a serious and potentially life-threatening condition. In developing countries like India, neonatal sepsis is the major cause of morbidity and mortality in new-born. Risk is increased very much again because of non-institutional delivery and poor postnatal follow-up. However early diagnosis and treatment are vital for a favorable outcome. Early diagnosis is a difficult task and based mainly on clinical suspicion. No doubt, blood culture is still the gold standard but because of its non-availability in most peripheral setups, high cost, more chances of contamination and delayed results, a need for more convenient, cost-effective test protocol whose results are available in time is felt. C-reactive protein can fill up this time gap, as this is an important indirect test to diagnose neonatal sepsis. C-reactive protein has some practical advantages: it can be done in all those neonates who are on prior antimicrobial therapy. Despite all this still, it is recommended to rely on both clinical correlations and laboratory findings for confirmed diagnosis [15]. The bacteria isolated from the subject's blood culture were *Klebsiella Pneumonia, Pseudomonas, Enterococcus, Staphylococcus aureus,* and *E. Coli*.

A previous study also reported about the most commonly observed etiology associated with neonatal sepsis were Gram-Negative bacteria [21]. Bacteria entering the circulation trigger the body's immune response. The cell membrane and wall contain phosphocholine which can activate the

Complement system. An activated complement system induces granulocyte, phagocyte, and proinflammatory cytokine production. C-reactive protein is an acute-phase protein synthesized along with the activation of proinflammatory cytokines. The same thing will happen to granulocyte which is also a component of white blood cells [22]. The wide variability in diagnostic values of CRP may have been influenced by sample characteristics, study design, sample size, inclusion criteria, and differences in CRP cut-off points. C-reactive protein levels increase 24 to 48 hours after clinical manifestations appear. In the current study, the mean values of CRP were compared with the positive culture cases and negative culture cases with that of the control cases. The overall comparison was further linked to the reference range. Jave DL [23] stated that monitoring of CRP over time may be used to in determining the response of the treatment after the primary diagnosis. They were discharged home after 5 days of intravenous antibiotic therapy. Jin Cherdze and colleagues [24,25] concluded in their study that quantitative CRP is a rapid, sensitive diagnostic marker for the identification of sepsis in preterm infants. In the current study, it was observed that CRP is a good indicator of neonatal sepsis as the quantitative status of CRP helped in the identification of neonatal sepsis and also in deciding the line of management of the patient.

The common age distribution in the current study was between 6-10 days and ≤5 days in both the positive and negative culture cases. 6 (60%) of positive culture cases were under 6-10 days while 13 (43.3%) of cases were ≤ 5 days. Several studies reported age to be significantly associated with neonatal sepsis [26,27,28]. Based on Rodwell's scoring system, neonates were classified as sepsis to be unlikely in 4 cases, possible in 11 cases and very likely in 25 cases. In the current study considering all four parameters i.e. sensitivity, specificity, positive predictive value and negative predictive value, I: T PMN ratio and degenerative changes were the most reliable tests for diagnosing sepsis. An abnormal I: M PMN ratio was highly sensitive in identifying sepsis. Degenerative changes in neutrophils were not found to be a very sensitive indicator of sepsis. Thrombocytopenia was consistently associated with poor prognosis. These findings were in comparison with other studies [29-32]. The higher the score, the greater was the likelihood of sepsis. A score ≤2 suggests that sepsis was unlikely.

Protein sepsis markers, such as CRP, should be used in concert with clinical signs and findings to make the diagnosis of neonatal sepsis and formulate a plan for management [33, 34]. CRP has been used to monitor response to infection and to assist in ruling out an infection. Most of these studies have been done in children, term, or near-term neonates using the lower CRP level cutoffs of <8 mg/dL or <10 mg/dL [35]. The Committee of Fetus and Newborn of the American Academy of Pediatrics (AAP) in their statement on infants with suspected or proven sepsis have expressed agreement in the utility of inflammatory biomarkers [36]. Although other biomarkers such as PCT may also be used, CRP has been described as a later but more specific marker of infection

The major limitations of the present study were the small size of the subjects. A similar study with a large sample size might be able to provide a more comprehensive outcome on the role of HSS and CRP in neonatal sepsis.

Conclusion

HSS is a simple, quick, cost-effective tool that can be used as a screening test for early diagnosis of neonatal sepsis. It may aid the clinicians in identifying sepsis and to institute proper antibiotic therapy. Unnecessary exposure of infants to antibiotic therapy can thus be avoided. A hematological score can be obtained by a complete blood count and examination of a peripheral blood smear, thus permitting an objective assessment of hematological changes that occur in a neonate suspected of sepsis. Similarly, it would be fair to say that the estimation of CRP in the diagnosis of neonatal sepsis have emerged and evolve rapidly over the last few years. Combining the estimation of CRP with HSS appears to provide a far more effective tool to be used as a screening method for neonatal sepsis.

What does the study add to the existing knowledge?

The current study aims to highlight the significant role and association between HSS and CRP in the diagnosis of neonatal sepsis. C-reactive protein values correlate well with HSS in predicting sepsis. However, C-reactive protein along with HSS does promise to establish a more effective tool to be used in the screening of neonatal sepsis.

Author's contribution

All the authors, **Dr. Chandrahas Ramesh Godbole**, **Dr. Sneha Ramdas Joshi,** and **Dr. Janice Jaison** contributed equally in the conduct of the study and in the preparation of the manuscript.

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