Utility of Hematological Parameters in Early Diagnosis of Neonatal Sepsis in Comparison to C-Reactive Protein

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Abstract

Background Neonatal sepsis is the most common cause of neonatal mortality and morbidity. As neonatal sepsis presents with subtle symptoms and signs, decision to start empirical antibiotics is most often based on risk profile. Hematological parameters and C-reactive protein (CRP) are routinely done as a part of sepsis screening, but isolation of microorganism on blood culture is the gold standard for diagnosis of sepsis.

Methodology One-hundred neonates with suspected sepsis were studied and their hematological parameters, hematological scoring system (HSS), and CRP were correlated to blood culture.

Results Among the study population, immature to total neutrophil count (I:T) ratio had the best sensitivity (94.1%) and negative predictive value (83.3%), followed by HSS with a sensitivity of 64.7% and negative predictive value of 68.4%, whereas CRP was more specific (75.9%).

Conclusion HSS and CRP are good predictors of diagnosis of neonatal sepsis. I:T ratio had the best sensitivity and negative predictive value.

Keywords
► neonatal sepsis
► C-reactive protein
► I:T ratio
► hematological scoring system

Introduction

Neonatal septicemia refers a systemic infection in the infants in the first 28 days of life.[1] It is often challenging to diagnose neonatal sepsis due to the subtle nature of presenting symptoms at various gestational ages.[2] Most important factor about neonatal sepsis is that most of the cases are preventable with appropriate antibiotic therapy and aggressive supportive care.

Neonatal sepsis is the most common cause of neonatal mortality and morbidity. It accounts for 26% of all neonatal deaths worldwide.[3] In India, 11 to 24 neonates out of 1,000 neonates die due to neonatal sepsis.[4] Malnutrition, lower socioeconomic status, unhygienic delivery conditions, poor health infrastructure, and traditional and cultural practices in community are some of the important causes of high mortality in developing countries.[5] Neonatal sepsis can be classified into two categories based on onset of signs and symptoms of sepsis. When the signs and symptoms occur within 72 hours of life, it is termed as early onset neonatal sepsis (EONS). Whereas if the signs and symptoms occur after 72 hours of life, it is termed as late onset neonatal sepsis

(LONS). In the Indian subcontinent, the distinction between EONS and LONS is blurred.[6] Signs and symptoms of neonatal sepsis are often vague and subtle. Hence, it is challenging for the treating pediatrician to confirm the diagnosis and the appropriate line of management. Also, over-treating the neonate with empirical broad-spectrum antibiotics results in emergence of resistant strains of bacteria. It also has an effect on the neonatal health, as many of the antibiotics have their own adverse effects. Moreover, a child who is supposed to live his/her first few hours of life in his/her mother's arms will be separated from the mother and shifted to neonatal intensive care unit (NICU) for further medical management. Hence, it is necessary to recognize the onset of sepsis and treat appropriately. The gold standard for diagnosis of neonatal sepsis is isolation of the microorganism in blood culture. But the time that is required for the culture to be reported as positive is long enough for the infection to spread and cause fatal consequences. Also, the yield of positive culture is low.[7,8] Hence, an effective screening test is necessary to predict the presence of sepsis in the neonate. Sepsis screening in cases of suspected neonatal sepsis includes total leucocyte count (TLC), absolute neutrophil count, immature to total neutrophils ratio (I:T ratio), micro-erythrocyte sedimentation rate and C-reactive protein (CRP). A hematological scoring system (HSS) is designed to score the various hematological parameters and predict the presence of sepsis.[9,10]

Materials and Methodology

We conducted a cross-sectional analytical study with a total of 100 cases, which included neonates admitted to NICU, Department of Paediatrics, Justice K S Hegde Medical Hospital, Mangalore, during the study period from January 2019 to June 2020. Neonates with signs and symptoms of sepsis and risk factor for developing sepsis were included in the study. Neonates with major life-threatening congenital anomalies were excluded from the study. The hematological parameters, CRP, and blood culture were sent as a part of sepsis screening for all the neonates admitted with suspicion of neonatal sepsis. The hematological parameters included TLC, absolute neutrophil count, immature neutrophil count (INC), I:T ratio, immature: mature neutrophil ratio, platelet count, and peripheral smear examination. Serum CRP estimation was done by quantitative nephelometry method. Blood culture was processed by BACTEC method. HSS was used to calculate the score and predict the presence of sepsis. The obtained data was then tabulated and analyzed using SPSS software version 22. The individual hematological parameters, HSS, and CRP were compared to the gold standard test that is blood culture.

Results

Among the 100 neonates studied, the males were predominant compared to females, with a male to female ratio of 1.6:1. Majority of the neonates presented with early onset neonatal sepsis (91%). Most of the neonates were delivered by normal vaginal delivery, were term, and were appropriate for gestational age. A wide range of clinical presentations were noted and are shown in ►Fig. 1 that included risk factor for neonatal sepsis as well as signs or symptoms of neonatal sepsis. In the study population, blood culture was positive in 17 neonates. The most common organism isolated in blood culture was *Staphylococcus aureus*. *Klebsiella pneumoniae*, *Pantoea agglomerans*, *Pseudomonas species*, *Serratia marcescens* and *Streptococcus agalactiae* were the other isolated organism (►Fig. 2). The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of the tests are tabulated in ►Table 1. Out of all the hematological parameters studied, I:T ratio had the highest sensitivity and NPV, followed by HSS. In addition, we noted that INC values were significantly correlated with the presence of
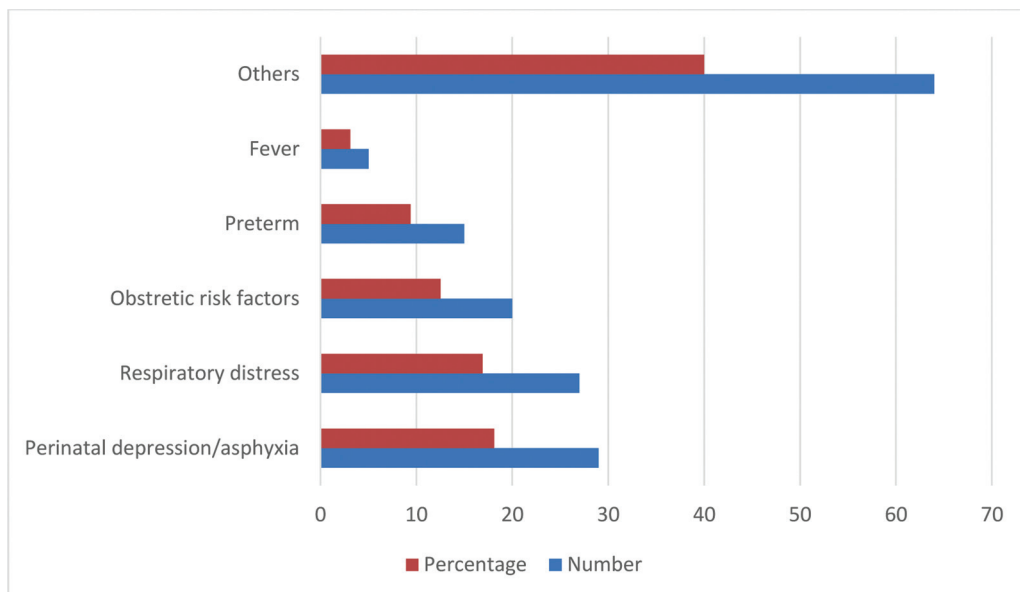

Fig. 1 Distribution of clinical presentation/risk factors in the study population.
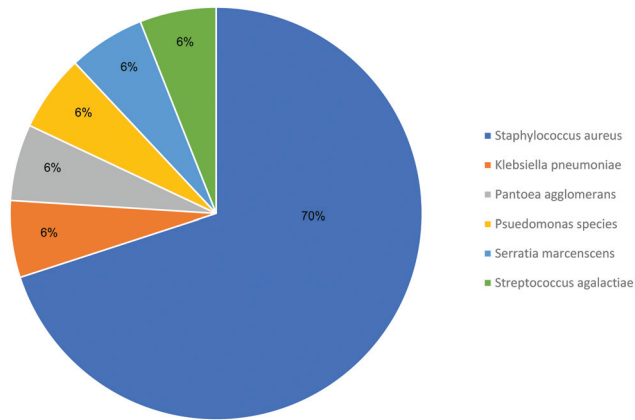
Fig. 2 Distribution of microorganisms isolated on blood culture.

neonatal sepsis. The presence of schistocytes, nucleated red blood cell (nRBC), and shift to left in neutrophils (leucoerythroblastic blood picture) can be seen in ►Figs. 3 and 4 that is the common finding seen in neonatal sepsis.

Discussion

In our study, we found that among the various hematological parameters analyzed, I:T ratio was a better predictor of neonatal sepsis. Similar results were noted in other studies conducted by Nayana and Sreenivas,[11] Nayak et al,[12] and Makadia and Shah[13] (►Table 2).

However, no single test was sufficient to diagnose neonatal sepsis. We also analyzed diagnostic utility of other parameters CRP, TLC, and HSS in neonatal sepsis.

In this study, CRP had a sensitivity of 47.1%, specificity of 75.9%, NPV of 87.5%, and a PPV of 28.6%. These results are comparable with Nayak et al. The discordance on comparing with study performed by Makadia and Shah[13], Jeyaganguli et al,[14] and Saboohi et al[15] may be due to variation in selected study population.

In this study, TLC had a sensitivity of 35.3%, specificity of 77.1%, NPV of 85.3%, and a PPV of 24%. These results are comparable with studies performed by Nayak et al[12] and Makadia and Shah.[13]
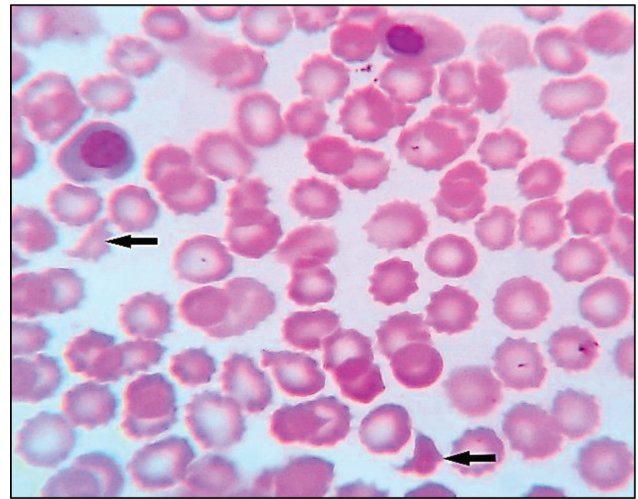

Fig. 3 Peripheral smear showing hemolysis suggested by schistocytes (arrows) and nucleated red blood cells.
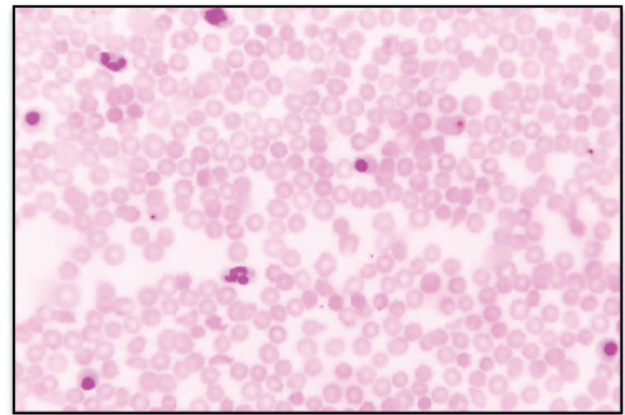

Fig. 4 Peripheral smear showing leucoerythroblastic blood picture.

In this study, HSS had a sensitivity of 64.7%, specificity of 15.7%, NPV of 68.4%, and a PPV of 13.6%. The obtained sensitivity and NPV of HSS are comparable with similar other studies performed on neonatal sepsis by Nayak et al[12] and Makadia and Shah.[13]

Table 1 Sensitivity, specificity, PPV, and NPVs of hematological parameters and CRP

Blood parameters	Sensitivity	Specificity	PPV	NPV
TLC	35.3	77.1	24.0	85.3
Platelets	29.4	97.6	71.4	87.0
I:T ratio	94.1	46.0	17.0	83.3
I:M ratio	58.8	36.1	15.9	81.1
ANC	41.2	59.0	17.1	83.1
P/S (toxic changes)	47.1	65.1	21.5	85.7
HSS	64.7	15.7	13.6	68.4
CRP	47.1	75.9	28.6	87.5

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; HSS, hematological scoring system; I:M ratio; immature: mature neutrophil ratio; I:T ratio; immature to total neutrophil count; NPV, negative predictive value; PPV, positive predictive value; TLC, total leucocyte count.

Table 2 Comparison of test having good sensitivity and NPV with other studies

Study	Year	Diagnostic tool with highest sensitivity and NPV
Nayana and Sreenivas[11]	2016	I:T ratio
Nayak et al[12]	2018	I:T ratio and INC
Makadia and Shah[13]	2020	I:T ratio
Present study	2020	I:T ratio

Abbreviations: I:T ratio; immature to total neutrophil count; INC, immature neutrophil count; NPV, negative predictive value.

In this study, I:T ratio had a sensitivity of 94.1%, specificity of 46%, NPV of 83.3%, and a PPV of 17%. These results are comparable with studies performed by Nayak et al[12] and Sundarapandian et al.[16]

In addition, a few other studies showed that nRBC count is also increased in neonatal sepsis.[12,17] nRBC count in a term neonate is said to increase in hypoxia, severe anemia, acute stress, and sepsis. In neonatal sepsis, nRBC count is increased due to release of cytokines and is independent of hypoxia.[18,19]

Conclusion

HSS, I:T ratio, and CRP are a good tool to diagnose neonatal sepsis at early stages and have a faster turnaround time than the gold standard test, blood culture. However, combination of above parameters would give better predictive value for neonatal sepsis. The study also found significant correlation of INC with blood culture. Therefore, further larger multi-centered prospective studies are required for validation of INC as a predictor of diagnosis of neonatal sepsis.

References

1 Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev 2014;27(01):21–47

2 Narasimha A, Harendra Kumar ML. Significance of hematological scoring system (HSS) in early diagnosis of neonatal sepsis. Indian J Hematol Blood Transfus 2011;27(01):14–17

3 Lawn JE, Cousens S, Zupan JLancet Neonatal Survival Steering Team. Four million neonatal deaths: when? where? why?. Lancet 2005;365(9462):891–900

4 Jaswal RS, Kaushal RK, Goel A, Pathania K. Role of C-reactive protein in deciding duration of antibiotic therapy in neonatal septicemia. Indian Pediatr 2003;40(09):880–883

5 Patel U, Patel VK, Patel NP, Verma J, Ratre BK, Verma SP. C-reactive protein and other hematological parameters for diagnosis of neonatal sepsis. Int J Med Res Rev. 2014;2(04):311–318

6 Sundaram V, Kumar P, Narang A. Bacterial profile of early versus late onset neonatal sepsis in a North Indian tertiary care centre: heading towards a change. J Pediatr Infect Dis 2009; 4:241–245

7 Arif S, Ehsan A, Arif M, Hussain J, Bano R. Early diagnosis of neonatal sepsis through hematological and biochemical markers. Gomal J Med Sci 2012;11:178–182

8 Gengaimuthu K, Karthikeyan V. Towards an ideal neonatal sepsis screen panel - a review. Indian J Child Health (Bhopal) 2017; 4:614–618

9 Saleem M, Shah KI, Cheema SM, Azam M. Hematological scoring system for early diagnosis of neonatal sepsis. JRMC 2014;18(01): 68–72

10 Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr 1988;112 (05):761–767

11 Nayana NS, Sreenivas N. Neonatal septicemia- a smooth technique of diagnosis in developing countries. Int J Res Med Sci 2016; 4:2305–2308

12 Nayak R, Ali SR, Nisha TG. Diagnostic utility of haematological parameters and C-reactive protein in early detection of neonatal septicaemia in developing countries. Indian Journal of Pathology and Oncology. 2018;5(01):112–117

13 Makadia KD, Shah P. A study of hematological changes in neonatal sepsis. Annals of Pathology and Laboratory Medicine. 2020;7(05): 236–240

14 Jeyaganguli D, Velvizhi G, Sucilathangam G, Revathy C. Diagnostic value of C - reactive protein and hematological markers in neonatal sepsis. Int J Curr Microbiol Appl Sci 2018;7(03): 722–727

15 Saboohi E, Saeed F, Khan RN, Khan MA. Immature to total neutrophil ratio as an early indicator of early neonatal sepsis. Pak J Med Sci 2019;35(01):241–246

16 Sundarapandian S, Chinnakannan S, Ahmed S, Das RR. Serial serum C-reactive protein in the diagnosis of neonatal sepsis: a cross-sectional Study. Indian Journal of Neonatal Medicine and Research. 2017;5(02):10–15

17 Supreetha MS, Alva SR, Shivendra VS, Kariappa TM. Evaluation of neonatal septicaemia using hematological parameters. Int J Recent Sci Res 2015;6(02):2775–2778

18 Dulay AT, Buhimschi IA, Zhao G, et al. Nucleated red blood cells are a direct response to mediators of inflammation in newborns with early-onset neonatal sepsis. Am J Obstet Gynecol 2008;198(04): 426.e1–426.e9

19 Xanthou M. Leucocyte blood picture in ill newborn babies. Arch Dis Child 1972;47(255):741–746