DOI: 10.7860/JCDR/2021/50366.15483

Original Article

Pathology Section

Diagnostic Utility of C-Reactive Protein and Permutation Combination of Quantitative and Qualitative Haematological Parameters in Neonatal Sepsis

SAPNA SHREYAS DESHPANDE[1], MOHASIN JAKIRHUSAIN HALGALE[2], RAVINDRA VILAS RAMTEKE[3]

ABSTRACT

Introduction: Neonatal sepsis at times is subclinical and lacks specific symptoms. The C-Reactive Protein (CRP) which is an acute phase reactant protein is thought to be an alternative biomarker to blood culture. Haematological parameters of sepsis are indirect biomarkers of infection. Authors found it worthwhile to discern efficacy of haematological parameters obtained by such three part haematology analysers in diagnosis of neonatal sepsis, when used in their pure form or with peripheral blood smear or with CRP, in isolation or in their combinations.

Aim: To find out the diagnostic utility of combinations of haematological parameters as obtained by three part differential automated haematology analyser and peripheral blood smear along with CRP in neonatal sepsis.

Materials and Methods: This observational and analytical study of diagnostic test outcome was carried out over a period of 12 months from January-December 2016 in Rajarshi Chhatrapati Shahu Maharaj Medical College and Chhatrapati Pramilaraje Rugnalaya, Kolhapur, Maharashtra, India, with special reference to clinical profile, blood culture, qualitative and quantitative haematological parameters and CRP. The statistical analysis included calculating diagnostic utility of isolated and combination of parameters and performing Chi-square test to study difference in frequency of occurrence and significance of association.

Results: There were 104 cases of neonatal sepsis out of which culture proven sepsis was seen in 73 (70.2%) cases while probable sepsis was seen in 31 (29.8%) cases. There were 32 (30.8%) fatalities. With parallel method with OR values, combination of haemoglobin, platelet parameters and White Blood Cells (WBC) parameters as obtained by analyser and peripheral blood smear exhibited sensitivity of 98.6%, specificity and Positive Predictive Value (PPV) of 100%, Negative Predictive Value (NPV) of 96.9% and Diagnostic Accuracy (DA) of 99%. This was surpassed by combination of CRP and all these parameters to attend values of 100%. Combination of all haematological parameters obtained purely by analyser showed these values to be 89%, 100%, 79.5% and 92.3%. Immature to Total WBC (I:T) ratio and platelet count influenced clinical outcome of fatality.

Conclusion: The liberal use of combination of haematological parameters is rewarding in supporting diagnosis of neonatal sepsis. The same was obtained by purely using analyser which showed remarkable diagnostic utility suitable for resource poor settings.

Keywords: Biomarkers, Infection, Screening score, 3 Part differential haematology analyser

INTRODUCTION

Incidence of neonatal sepsis in India amounts to 17000/100000 live births with a case fatality ranging from 25-65% [1]. Neonatal sepsis at times is subclinical and lacks specific symptoms and signs. This calls for augmentation of clinical diagnosis with biomarkers of sepsis. Though considered as gold standard, blood culture may not be available in moderate clinical set up, is labour intensive, time consuming and delays the diagnosis [2]. The quest for alternative biomarkers continues. The CRP which is an acute phase reactant protein is thought to be an alternative biomarker to blood culture. It is considered to be a late marker of neonatal sepsis which possesses remarkable specificity and PPV [3]. It is being said that culture positive cases with raised CRP need prolonged antibiotic therapy and NPV of serial CRP is 100% when used in deciding duration of antibiotic therapy [4].

Haematological parameters of sepsis are indirect biomarkers of infection. They can be obtained by cost effective means like automated complete blood count and peripheral blood smear examination. The basic three part automated haematology analyser adorns most of the public health as well as private clinical set ups. The objective of the present study was to find out the efficacy of haematological parameters obtained by such analysers in diagnosis of neonatal sepsis, when used in their pure form. Restricting to biomarkers from haematology analyser, thus, obviates the need for doing and examining peripheral blood smear in absence of experienced technician or pathologist. The main objective was to focus on contemplating this possibility.

MATERIALS AND METHODS

This observational and analytical study of diagnostic test outcome was carried out over a period of 12 months from January-December 2016 in Rajarshi Chhatrapati Shahu Maharaj Medical College and Chhatrapati Pramilaraje Rugnalaya, Kolhapur, Maharashtra, India. Institutional Ethical Committee approval was obtained (IEC no. ECR/703/Inst/MH/2015/RR-20). Consecutive cases of 104 neonates with neonatal sepsis which were prospectively registered during the period from January - December 2016 were enrolled in the study. Informed consent was taken from the parents of the neonates.

Inclusion criteria: The neonates admitted in neonatal intensive care unit with clinical suspicion of sepsis were included in the study.

Exclusion criteria: The neonates with hyaline membrane disease, transient tachypnea of newborn or hypoxia induced encephalopathy were excluded from the study.

The study population was evaluated thoroughly for clinical course, gestational age, birth weight and age of onset of sepsis. The details of maternal conditions were noted. Maternal and foetal risk factors were studied diligently.

Study Procedure

Under all aseptic precautions 5 mL of intravenous blood was collected with a disposable 5 mL syringe. It was distributed as follows, 1 mL each in Ethylenediamine Tetra-acetic Acid (EDTA) and plain microtainer and 3 mL in brain heart infusion broth for following investigations:

1. Complete blood count on three part differential automated haematology analyser (Councell-23 Plus).
2. Peripheral blood smear, stained with Leishman stain and reported with special reference to I:T ratio, Absolute Neutrophil Count (ANC) calculated from their differential count on smear and total WBC count on analyser and Toxic Granules (TG).
3. The CRP by slide latex agglutination qualitative method.
4. Blood culture on vial of brain heart infusion broth, incubated at 37°C for 24 hours. Subculture was carried out on blood and MacConkey's agar and incubated aerobically overnight at 37°C. The identification of organisms was carried out as per standard protocols. If the original smears showed fungal structures, the blood sample was plated on Sabouraud's agar.

Based on blood culture positivity, cases were classified as proven and probable neonatal sepsis and were compared with each other for calculating diagnostic utility. The positive blood culture was considered as gold standard for diagnosis of sepsis.

Following is the list of haematological parameters studied with mention of values decided as abnormal.

Haemoglobin (Hb) <14 g/dL, Total Leucocyte Count (TLC) <5000/cmm or >20,000/cmm, ANC <1800/cmm, I:T ratio (I:T) ≥0.2, Platelet Count (PC) <1,50,000/cmm, Mean Platelet Volume (MPV) >11.5 fL, Platelet Distribution Width (PDW) > 13.5% and presence of TG on peripheral blood smear [5-9].

The data was analysed to find out the clinical profile of neonatal sepsis, its risk factors, outcome profile, haematological profile, and diagnostic utility of various parameters including CRP and haematological parameters in isolation and in various combinations. Here combinations were studied with "OR" values. The diagnostic utility of conventional septic screen score with combination of either pure haematological parameters (TLC, ANC, I:T ratio, TG, PC) or those with CRP was carried out with "AND" values. The score was considered satisfactory when three or more criteria were fulfilled.

STATISTICAL ANALYSIS

Sensitivity, Specificity, PPV, NPV and DA were calculated with appropriate formulae. For calculation of diagnostic utility of various combinations of test "Parallel" method was used with "AND" and "OR" values. The p-value was calculated by Chi-square test to study frequency of occurrence.

RESULTS

There were 104 cases of neonatal sepsis of with 61 (58.7%) males and 43 (41.3%) females with Male:Female ratio as 1.4:1. In 73 (70.2%) cases blood culture was positive. These cases were classified as proven sepsis. While 31 (29.8%) cases did not yield organisms on culture and were classified as probable sepsis.

Clinical profile of neonatal sepsis was as follows: The early onset sepsis which presented within three days of birth was seen in 67 (64.4%) neonates while late onset sepsis which presented between 4-30 days was seen in 37 (35.6%) neonates. Early onset sepsis was statistically more common than late onset sepsis with p-value=0.066. The sepsis was more common in low birth weight neonates with weight less than 2500 grams (n=84, 80.8%) than in those with normal birth weight (more than or equal to 2500 grams) with p-value=0.028 (n=20, 19.2%). A higher frequency of sepsis was noted in preterm neonates (n=72, 69.2%) as compared to full term neonates (n=32, 30.8%) with p-value=0.011. There was no statistically significant influence of type of delivery on occurrence of sepsis (p-value=0.72) with 43 (41.3%) neonates being delivered as by caesarean section as against 61 (58.7%) being delivered with normal vaginal route.

The maternal risk factors for neonatal sepsis were premature rupture of membranes, pregnancy induced hypertension, prolonged labour, both these complications seen concurrently with number of cases being-10 (9.61%), 8 (7.69%), 7 (6.73%) and 6 (5.76%), respectively. Foetal factors consisted of low birth weight, prematurity, meconium aspiration, twin pregnancy and prolonged hospitalisation (n=84 (80.76%), 72 (69.23%), 9 (8.65%), 4 (3.84%) and 2 (1.92%) cases, respectively.

The culture proven sepsis was significantly more associated with low birth weight with p-value=0.02. The early onset sepsis was significantly more associated with prematurity (p-value=0.01).

There occurred 32 fatalities (30.8%), 27 of these were associated with preterm birth. Thirty deaths were seen in neonates with low birth weight. The blood culture positivity was a feature of 29 fatal cases. Preterm birth, low birth weight and positive blood culture were significantly associated with mortality with p-value=0.02. Type of delivery, gender of neonate and time of onset of sepsis did not affect the fatality significantly with p-values of 0.74, 0.92 and 0.54. The abnormalities of sepsis screen parameters that mattered in fatal cases were raised I:T ratio and thrombocytopenia with p-value <0.05.

Of the 73 culture positive cases, gram negative organisms were grown in 29 (39.7%) cases, the gram positive organisms were seen in 21 (28.8%) cases and *Candida* was noted in 23 (31.5%) cases. The gram negative organisms included *Klebsiella pneumoniae* (n:13), *E. coli* (n=6) and *Acinetobacter* (n=6) and *Pseudomonas aeruginosa* (n=4). The gram positive organisms consisted of coagulase negative *Staphylococcus* (n=4), methicillin resistant coagulase negative *staphylococci* (n=10), *Staphylococcus aureus* (n=6),) and *Streptococci* (n=1).

Haematological and CRP profile of cases of neonatal sepsis is summarised as [Table/Fig-1].

Sr. No.	Haematological parameters	Proven sepsis (n=73)	Probable sepsis (n=31)
1	Anaemia (Hb <14 gm%) (n=22)	18 (24.7%)	4 (12.9%)
2	Leucopenia (TLC<5000/cumm) or Leucocytosis (TLC>20000/cumm) (n=47)	36 (49.3%)	11 (35.5%)
3	ANC (<1800/cumm) (n=22)	16 (21.9%)	6 (19.4%)
4	Thrombocytopenia (Platelet count<1.5lacs) (n=62)	45 (61.6%)	17 (54.8%)
5	Raised PDW (>13%) (n=50)	37 (50.7%)	13 (41.9%)
6	Increased MPV (>11.5 fL) (n=28)	20 (27.4%)	8 (25.8%)
7	I:T ratio (≥ 0.2) (n=55)	49 (67.1%)	6 (19.4%)
8	Toxic granules present (n=50)	43 (58.9%)	7 (22.6%)
9	CRP (>6 mg/L) (n=70)	53 (72.6%)	17 (54.8%)

[Table/Fig-1]: Summarisation of haematological profile and CRP in neonatal sepsis. ANC: Absolute neutrophilic count; PDW: Platelet distribution width; MPV: Mean platelet volume; I:T ratio: Immature to total neutrophil ratio; CRP: C-reactive protein

In proven sepsis, there was one case which only showed raised CRP and succumbed to death. There were 33 cases which showed three or more conventional haematological parameters of sepsis to be abnormal. Forty two cases fulfilled three or more sepsis screen criteria with combinations with CRP with overlap of cases. There occurred seven deaths in these cases. In probable sepsis six cases fulfilled three or more sepsis screen haematological criteria and six more cases showed three point sepsis screen positivity when CRP was considered. One case having only thrombocytopenia as an abnormality had a mortality. This particular neonate was born of

twin delivery. In three cases haematological parameters and CRP was normal.

The diagnostic utility of individual haematological parameters and CRP in neonatal sepsis is depicted in [Table/Fig-2].

It can be seen from [Table/Fig-2] that CRP showed highest sensitivity and haemoglobin had highest specificity. The overall diagnostic utility with highest PPV, NPV and DA was exhibited by I:T ratio.

Sr. No.	Test	Sensitivity %	Specificity %	PPV %	NPV %	DA %
1	Hb	25	87	82	33	43.27
2	TLC	49	65	77	35	53.85
3	ANC	22	81	73	30	39.42
4	I:T ratio	67	81	89	51	71.15
5	Toxic granules	59	77	86	45	64.42
6	Platelet count (PC)	62	45	73	33	56.73
7	PDW	51	58	74	33	52.88
8	MPV	27	74	71	30	41.34
9	CRP	78	42	76	45	67.31

[Table/Fig-2]: Diagnostic utility of individual haematological parameters and CRP in neonatal sepsis.
Hb: Haemoglobin; TLC: Total leucocyte count; ANC: Absolute neutrophil count; I:T ratio: Immature to total neutrophil ratio; PDW: Platelet distribution width; MPV: Mean platelet volume; CRP: C-reactive Protein

The diagnostic utility of various combinations of conventional pure haematological septic screen parameters or those including CRP; necessitating positivity of three or more such parameters for diagnosis of culture proven neonatal sepsis was calculated. The results are shown in [Table/Fig-3].

Sr. No.	Combination of parameters	Sensitivity %	Specificity %	PPV %	NPV %	DA %
1	TLC+ANC+I:T	13.7	100	100	33	39.4
2	TLC+ I:T+TG	19.2	100	100	34.4	43.3
3	TLC+ANC+TG	11	100	100	32.2	37.5
4	ANC+ I:T+TG	10	100	100	32	36.5
5	TLC+I:T+PC	16.5	100	100	33.7	41.3
6	TLC+ ANC+PC	5	93.5	66.7	29.6	31.7
7	TLC+TG+PC	16.5	87.1	75	30.7	37.5
8	3 or More haematological parameters	45.2	80.6	84.6	38.5	55.7
9	CRP+TLC+ANC	16.4	83.9	70.6	29.9	36.5
10	CRP+TLC+I:T	21.9	16.1	8.1	38.1	20.2
11	CRP+TLC+TG	23.3	93.5	89.5	34.1	44.2
12	CRP+ANC+I:T	9.6	29	12	24.1	15.4
13	CRP+TLC+PC	20.5	90.3	83.4	32.6	41.4
14	CRP+ANC+PC	3	93.5	50	29	29.8
15	CRP+I:T+PC	37	12.9	8	50	29.8
16	CRP+TG+PC	23.2	90.3	85	33.3	43.3
17	3 or MORE parameters with CRP	57.5	67.7	80.8	40.4	60.6

[Table/Fig-3]: Diagnostic utility of combination of 3 or more conventional septic screen parameters in neonatal sepsis.
TLC: Total leucocyte count; ANC: Absolute neutrophil count; I/T ratio: Immature to total neutrophil ratio; TG: Toxic granules; PC: Platelet count; CRP: C-reactive protein

It can be seen from [Table/Fig-3] that specificity and PPV of sepsis screen parameters except for combinations involving CRP and I:T ratio was in the range of 87.1-100% and 66.7-100%. The overall sensitivity, NPV and DA of the whole group was not very satisfactory. The frequency of occurrence of CRP with combinations with single or multiple parameters of sepsis showed significant difference in proven and probable sepsis group (p-value <0.05) except for combination of CRP+TLC+I:T ratio. Similarly pure combinations of haematological sepsis screen were studied for difference in frequency of occurrence. It was significant with p-value <0.05 in combinations of TLC+TG+PC, TLC+ANC+PC and combination of any three or more haematological parameters of sepsis screen.

Diagnostic utility of combinations of CRP with haematological parameters with OR values is seen as [Table/Fig-4].

Sr. No.	Combination of parameters	Sensitivity %	Specificity %	PPV %	NPV %	DA %
1	CRP/TLC/I:T	95.9	100	100	91.2	97.1
2	CRP/TLC/ANC	84.9	70.9	87.3	66.6	80.7
3	CRP/I:T/ANC	94.5	100	100	88.6	96.2
4	CRP/TLC/PC	90.4	90.3	95.6	80	90.4
5	CRP/I:T/ PC	98.6	93.5	97.3	96.7	97.1
6	CRP/ANC/PC	89	93.5	97	78.3	90.4
7	CRP/PC/MPV	87.7	93.5	96.9	76.3	89.4
8	CRP/PC/PDW	95.8	90.3	95.8	90.3	94.2
9	CRP/MPV/PDW	93.2	90.3	95.8	84.8	92.3
10	CRP/TLC/Hb	89.9	100	100	79.48	92.3
11	CRP/Hb/PC	89	96.7	98.5	78.9	91.3
12	CRP/Hb/MPV	87.7	96.8	98.4	76.9	90.4
13	CRP/Hb/PDW	95.9	96.8	98.6	90.9	96.2
14	CRP/TLC/PC/Hb	91.7	100	100	83.8	94.2
15	CRP/TLC/I:T/ANC	95.8	100	100	91.1	97.1
16	CRP/PC/MPV/ PDW	95.8	93.5	97.3	90.6	95.2
17	CRP/PC/MPV/ PDW/Hb	95.8	96.7	98.5	90.9	96.2
18	CRP/TLC/PC/ MPV/PDW/Hb	97.2	96.7	98.6	93.7	97.1
19	All parameters	100	100	100	100	100

[Table/Fig-4]: Diagnostic utility of combinations of CRP with haematological parameters with OR values.
CRP-C: Reactive protein; TLC: Total leucocyte count; I/T ratio: Immature to total neutrophil ratio; ANC: Absolute neutrophil count; PC: Platelet count; MPV: Mean platelet volume; PDW: Platelet distribution width; Hb: Haemoglobin

The best 3 point combinations with CRP had TLC, I:T ratio or PC in common. Almost similar utility was shown by combination of CRP with all analyser parameters. This was surpassed only by combination of CRP with all haematological parameters. The utility of combination of pure haematological parameters is noted in following table [Table/Fig-5]. The best combinations of pure haematological parameters in terms of diagnostic utility were those including WBC parameters like TLC, I:T ratio and TG; only to be surpassed by combination of all haematological parameters.

Sr. No.	Combination of parameters	Sensitivity %	Specificity %	PPV %	NPV %	DA %
1	TLC/I:T/TG	95.89	100	100	91.2	97.1
2	TLC/I:T/ANC	86.3	100	100	75.6	90.4
3	TLC/ANC/TG	82.2	100	100	70.5	87.5
4	TLC/ANC/PC	83.6	93.6	96.8	70.7	86.5
5	TLC/ANC/MPV	67.1	96.8	98	55.6	76
6	TLC/ANC/PDW	76.7	93.6	96.6	63	81.7
7	I:T/TG/PC	90.4	93.6	97.1	80.6	91.4
8	I:T/TG/MPV	86.3	93.6	96.9	74.4	88.5
9	I:T/TG/PDW	90.4	93.6	97.1	80.6	91.4
10	PC/MPV/PDW	76.7	87	93.3	61.3	79.8
11	TLC/I:T/Hb	90.4	100	100	81.6	93.3
12	TLC/ANC/Hb	64.4	100	100	54.4	75
13	TLC/TG/Hb	87.7	100	100	77.5	91.4
14	I:T/ANC/Hb	80.8	100	100	68.9	86.8

15	I:T/TG/Hb	89	96.8	98.5	79	91.4
16	ANC/TG/Hb	74	100	100	62	81.7
17	TLC/PC/Hb	86.3	96.9	98.4	75	89.4
18	TLC/MPV/Hb	78.1	96.8	98.3	65.2	83.7
19	TLC/PDW/Hb	86.3	100	100	75.6	90.4
20	I:T/PC/Hb	89.	96.8	98.5	79	91.4
21	I:T/MPV/Hb	84.9	96.8	98.41	73.2	88.5
22	I:T/PDW/Hb	89	96.8	98.5	76	91.4
23	ANC/PC/Hb	78.1	100	100	66	84.6
24	ANC/MPV/Hb	57.5	100	100	50	70.2
25	ANC/PDW/Hb	75.3	100	100	63.3	82.7
26	TG/PC/Hb	82.2	96.8	98.4	69.8	86.5
27	TG/MPV/Hb	71.2	96.8	98.1	58.8	78.9
28	TG/PDW/Hb	83.6	96.8	98.4	71.4	87.5
29	TLC/PC/Hb	76.7	100	100	64.5	83.7
30	PC/MPV/PDW/Hb	87.1	96.7	98.3	69.7	86.5
31	TLC/I:T/ANC/TG	95.9	100	100	91.2	97.1
32	TLC/PC/MPV/PDW/Hb	89	100	100	79.5	92.3
33	All parameters	98.6	100	100	96.9	99

[Table/Fig-5]: Diagnostic utility of combinations of haematological parameters with OR value.
TLC: Total leucocyte count; I:T ratio: Immature to total neutrophil ratio; TG: Toxic granules; ANC: Absolute neutrophil count; PC: Platelet count; MPV: Mean platelet volume; PDW: Platelet distribution width; Hb: Haemoglobin

DISCUSSION

Much is being said about of haematological parameters and CRP as a biomarker of neonatal sepsis in terms of their utility, accessibility, simplicity of estimation, cost effectiveness and ability to provide early diagnosis [3,10].

In a study by Rudwell RL et al., described haematological scoring system consisting of seven haematological parameters of neonatal sepsis [5]. These were TLC, ANL, I:T ratio, PC and severe degenerative changes in neutrophils and micro Erythrocyte Sedimentation Rate (ESR). Abnormalities in each of these parameters were scored as 1. The likely hood of sepsis was 31% when the scores were equal to or more than 3 and with score less than 3 the possibility of sepsis could be completely ruled out. Other studies used this scoring system in its pure form or its modification in assessing neonatal sepsis, some which augmented it with CRP [2,6,11-14].

The conventional haematological sepsis screen criteria of three or more parameters for diagnosis of sepsis yielded DA of 55.7% and with CRP it rose to 60.6% in present study. This seems too modest to be a result of an exercise. Interestingly, there were eight mortalities in cases showing less than 3 criteria of neonatal sepsis, two of these cases showed single abnormality in the form of raised CRP and thrombocytopenia in one case each. This implies that an exercise of using septic screen score with rigid criteria necessitating abnormalities of multiple parameters to be present to diagnose sepsis does not seem to be suitable for confirming cases of neonatal sepsis.

It can be inferred from present study that the best diagnostic utility was offered by combinations including CRP. A very liberal combination of all parameters including CRP could effectively pick up all cases of culture positive sepsis with best utility parameters. The diagnostic utility of pure combination of haematological parameters was also remarkable with 99% DA. This was followed by wholesome combination of WBC parameters.

Particularly impressive was the utility of wholesome combination of those parameters which can be exclusively obtained by 3 part automated haematology analyser with DA of 92.3%, PPV and specificity 100% and sensitivity of 89%.

The liberal use of combination of parameters with "OR" values was meant for finding out ability of these biomarkers in acting at par or to match the performance of blood culture to prove the sepsis. The magnitude to which it can be done is reflected in their diagnostic utility. Interestingly fair number of cases of probable sepsis with negative blood culture showed abnormal results for one or more of conventional biomarkers of sepsis (n=27, 87%).

Four of such cases succumbed to death. This implies that clinical suspicion of sepsis was valid at least in 87% of these cases though it cannot be corroborated with blood culture. If we duly considered two cases with raised PDW to be indicative of sepsis almost 93.5% cases of probable sepsis group confirmed clinical suspicion of neonatal sepsis.

The strength of present study lies in its very elaborate and comprehensive assessment of haematological biomarkers both with septic screen score, in their pure forms, in various liberal combinations including those with CRP in finding out their diagnostic utility. The cost effectiveness and accessibility of this exercise is also worth considering.

Limitation(s)

The major drawback of present study was that it did not involved serial estimations of parameters which would have enlightened us on response to antibiotic treatment. These parameters were not tested in normal age matched neonates on ethical grounds.

CONCLUSION(S)

The combinations of various haematological parameters as obtained by analyser when used liberally increase the diagnostic utility and can act as alternative to sepsis scoring systems. It can obviate the need for estimation of CRP and further need of peripheral blood smear which needs expertise of pathologist. The almost ubiquitous availability of 3 part analysers makes such an attempt very accessible.

REFERENCES

[1] Murthy S, Godinho MA, Guddattu V, Lewis LES, Nair NS. Risk factors of neonatal sepsis in India: A systematic review and meta-analysis. PLoS One. 2019;14(4):e0215683.
[2] Makkar M, Gupta C, Pathak R, Garg S, Mahajan NC. Performance evaluation of hematologic scoring system in early diagnosis of neonatal sepsis. J Clin Neonatol. 2013;2(1):25-29.
[3] Shah BA, Padbury JF. Neonatal sepsis: An old problem with new insights. Virulence. 2014;5(1):170-78.
[4] Jaswal RS, Kaushal RK, Goel A, Pathania K. Role of C-reactive protein in deciding duration of antibiotic therapy in neonatal septicaemia. Indian Pediatrics. 2003;40(9):800-83.
[5] Rudwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr. 1988;112(5):761-67.
[6] Nabi SN, Basak AK, Kamruzzaman M, Pervez AF, Musharraf M, Sultana N, et al. Performance of haematological parameters in early diagnosis of clinically suspected neonatal sepsis. Mymensingh Med J. 2019;28(1):193-99.
[7] Sorsa A. Diagnostic significance of white blood cell count and C-reactive protein in neonatal sepsis; Asella referral hospital, South East Ethiopia. Open Microbiol J. 2018;12:209-17.
[8] 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(1):241-46.
[9] Harmansyah H, Alasiry E, Daud D. Absolute neutrophil count as predictor of early onset sepsis. Clin Med Res. 2015;4(3):87-91.
[10] Lacey A, Shakya H. Role of sepsis screening in early diagnosis of neonatal sepsis. Journal of Pathology of Nepal. 2017;7(1):1103-10.
[11] Khair KB, Rahman MA, Sultana T, Roy CK, Rahman MQ, Ahmed AN. Early diagnosis of neonatal septicemia by hematologic scoring system, C-reactive protein and serum haptoglobin. Mymensingh Med J. 2012;21(1):85-92.
[12] Manucha V, Rusia U, Sikka M, Faridi MM, Madan N. Utility of haematological parameters and C-reactive protein in the detection of neonatal sepsis. J Paediatr Child Health. 2002;38(5):459-64.

[13] Patel U, Patel VK, Patel NP, Verma J, Ratre BK, Verma SP. To evaluate C-Reactive Protein and other hematological parameters for diagnosis of neonatal sepsis. Int J Med Res Rev. 2014;2(4):311-18.

[14] Pruthvi D, Kulkarni PR, Jamkhandi UR, Inamdar SS. Haematological parameters in neonatal sepsis in a tertiary care centre study. J Evid Based Med Healthc. 2021;8(13):751-54.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, D.Y. Patil Medical College, Kolhapur, Maharashtra, India.
2. Assistant Professor, Department of Pathology, R.C.S.M. Government Medical College, Kolhapur, Maharashtra, India.
3. Professor and Head, Department of Pathology, R.C.S.M. Government Medical College, Kolhapur, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Mohasin Jakirhusain Halgale,
816/3, Plot No. 6, Karande Mala, Devane Colony, Opp. Sriram Residency,
Kolhapur-416003, Maharashtra, India.
E-mail: mohsinhalgale@yahoo.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 17, 2021
- Manual Googling: Sep 28, 2021
- iThenticate Software: Sep 30, 2021 (6%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 16, 2021**
Date of Peer Review: **Aug 15, 2021**
Date of Acceptance: **Sep 29, 2021**
Date of Publishing: **Oct 01, 2021**