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Original Article

Paediatrics Section

Significance of Serum Inflammatory Markers in Predicting Bacterial Meningitis amongst Neonates with Sepsis

APARAJITA RAGHAV[1], AJAY KUMAR[2], PRATIMA ANAND[3], GARIMA YADAV[4], RANI GERA[5]

ABSTRACT

Introduction: Neonatal meningitis in developing countries is 0.8-6.1 per 1000 live births with mortality of 40-85% had morbidity. Since, the clinical signs and symptoms of meningitis are non-specific and like those seen in sepsis, Cerebrospinal Fluid (CSF) examination via Lumbar Puncture (LP) is essential to establish the diagnosis of meningitis. Performing a LP has its own set of complications. The need for lumbar puncture can be averted and early optimal antibiotic can be instituted if serum inflammatory markers are found to be a good predictor of meningitis in suspected neonatal sepsis.

Aim: To investigate the role of serum inflammatory markers, to predict bacterial meningitis amongst neonates with sepsis and to determine the cut-off values for these markers to predict bacterial meningitis amongst neonates with sepsis.

Materials and Methods: This was a cross-sectional observational study done over a period of 17 months in the paediatric wards in a tertiary care centre. All neonates presenting with clinical suspicion of sepsis were enrolled. The blood samples were collected for serum inflammatory markers and CSF examination was done as indicated (American Academy of Paediatrics, AAP guidelines). CSF examination findings and serum inflammatory markers were then statistically analysed to determine the significance in predicting bacterial meningitis in neonatal sepsis. A total of 234 neonates were selected as per laboratory investigations for enrollment in the study. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±Standard deviation (SD) and median. Diagnostic tests were used to calculate sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

Results: A total 234 neonates with features suggestive of sepsis and in whom C-Reactive Protein (CRP) >10 mg/L, Erythrocyte Sedimentation Rate (ESR) >15 mm, White Blood Cell (WBC) <4000 cells/mm^3, Absolute Neutrophil Count (ANC) <1800/mm^3 and in whom LP was recommended as per the AAP guidelines were included in the study. A 222 (94.87%) neonates were in the age group 1-10 days. A total of 134 (57.3%) study subjects were males. No significant association of ANC, WBC, ESR and CRP was seen with meningitis (p-value >0.05). Receiver Operator Curve (ROC) for all the four parameters were constructed, they showed performance was non-significant.

Conclusion: Based on the current single site study results, it is implicated that diagnosis and management of neonatal meningitis should be solely based on LP since serum inflammatory markers are poor discriminators for meningitis. Future studies should evaluate the diagnostic parameters from other inflammatory markers like Immature to Total Neutrophil (IT) ratio and micro ESR, which, if proven to be of diagnostic value, can reduce the time to initiate management and avert the need for LP in neonatal meningitis.

Keywords: Cerebrospinal fluid, C-reactive protein, India, Neonatal septicaemia

INTRODUCTION

Sepsis in neonates is characterised by varied signs and symptoms. The diagnosis of neonatal sepsis and meningitis continues to be a challenge. Early diagnosis and management of neonatal sepsis is associated with improved neonatal outcomes. The incidence of neonatal sepsis is 30 per 1000 live births [1]. Sepsis accounts for about 30-50% of neonatal deaths in developing countries [2]. In India, case fatality rate of sepsis among neonates ranges between 25-65% [3,4]. Meningitis is defined as acute inflammation of the meninges, subarachnoid spaces and brain vasculature resulting in infection [5]. The incidence of meningitis in neonatal sepsis has varied from 0.3-3% in various studies with late onset sepsis found to be fairly associated with meningitis with a percentage ranging from 3-30% [6-8]. The incidence of neonatal meningitis in developing countries is 0.8-6.1 per 1000 live births with mortality of 40-85% [9]. It is associated with long term neurological outcomes [10].

Since, the clinical signs and symptoms of meningitis are non-specific and like those seen in sepsis, CSF examination via LP is essential to establish the diagnosis of meningitis [5]. CSF culture is the gold standard for the diagnosis of meningitis. The AAP [11,12] recommends performing LP in infants with a positive blood culture and/or a basis of clinical course or laboratory data (including raised inflammatory markers for which no threshold is given) that strongly suggest bacterial sepsis or in infants who deteriorate despite antimicrobial therapy. Performing a LP has number of complications such as spinal haematoma, spinal abscess, and cerebral herniation [13]. The LP can be traumatic at times causing delay in diagnosis. Sometimes parents might give negative consent for the procedure. If LP is delayed and infants are exposed to empiric broad spectrum of antibiotics, alteration of CSF results can occur. Hence, it becomes important to perform the LP timely [14]. Therefore, if serum inflammatory markers are found to have reasonable diagnostic accuracy to predict meningitis, appropriate antibiotics in optimal dosage can be administered, without waiting for the lumbar puncture examination results, which could possibly reduce neonatal morbidity and mortality.

The studies on association and prediction of meningitis by serum inflammatory markers are few, and are either retrospective or cross-sectional in design, done on limited number of study participants [15-20]. Moreover, there is even more paucity of literature from the resource constraint low-middle-income countries, where this study would be important for clinical decision making in diagnosing neonatal meningitis. Hence, this study was done with the objective to investigate the role of serum inflammatory markers to predict bacterial meningitis amongst neonates with sepsis and to determine cut-off values of serum inflammatory markers to predict the occurrence of bacterial meningitis amongst neonates with sepsis.

MATERIALS AND METHODS

This present study was a cross-sectional observational study done over a period of 17 months from November 2018 to March 2020 in the paediatric wards in a tertiary care centre. Ethical clearance was obtained from the Institutional Ethics Committee. (S.No IEC/VMMC/SJH/Thesis/October/2018/06 dated 30th October 2018). Informed consent was obtained from parents.

Inclusion criteria: All neonates presenting with features of sepsis, serum inflammatory markers e.g., serum CRP, serum ESR, WBC and ANC were taken, and LP performed as per the AAP guidelines and then CSF examination findings were analysed with serum inflammatory markers to determine whether serum inflammatory markers could predict bacterial meningitis.

Exclusion criteria: Neonates with cardiorespiratory insufficiency, with congenital anomalies such as spina bifida, anencephaly and other neural tube defects and neonates with traumatic LP were excluded from the study.

Sample size: The study by Goldfinch CD et al., observed Area under the ROC curve (AUC) for culture positive and probable culture-negative meningitis as 0.43 for CRP [16]. Taking this value as reference, δ as 0.07 and 5% level of significance, using the formula:

$$n=\frac{1\text{-AUC}}{2}\left(\frac{Z_{\alpha/2}}{\delta}\right)$$

The calculated sample size was 224.

In this study, 1100 neonates were identified during the study period who presented to the hospital with features of sepsis and in whom LP was recommended according to the AAP guidelines [12]. Blood investigations comprised of Complete Blood Count (CBC), ESR, CRP, blood culture and sensitivity and blood dextrose and LP for CSF cytology, biochemistry, were performed. Out of these neonates, 234 neonates with CRP >10 mg/L, ESR >15 mm in first hour, WBC <4000 cells/mm^3, ANC <1800 cells/mm^3 were included in the study and their serum investigations were analysed to predict bacterial meningitis based on the ROC curves. Based on the CSF results, the neonates were categorised as: (i) Confirmed culture positive meningitis: defined by CSF culture result that identified a bacterium that is not a contaminant; (ii) Culture negative meningitis: diagnosed based on CSF cell counts, glucose, and proteins; and (iii) No evidence of meningitis [21]. The outcome measures were taken in terms of length of hospital stay (>21 days) and mortality. Clinicians were blinded to the cut-offs and median values of serum markers as a diagnostic criterion for meningitis. The serum markers were however used to decide the initiation of antibiotics and other clinical management.

STATISTICAL ANALYSIS

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Diagnostic tests were used to calculate sensitivity, specificity, NPV and PPV. The p-value was calculated using Chi-square and Fischer's-Exact test for categorical variables and t-test and Mann-Whitney test for continuous variables. ROC curve was used to find out cut-off point of various parameters for predicting meningitis. McNemar's test were used to compare sensitivity and specificity. A p-value of <0.05 were considered as statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Of the 234 enrolled neonates, mean age at presentation (in days) for study subjects was 4.52±4.5 with median (IQR) of 4 (1.25-5). Baseline characteristics are depicted in [Table/Fig-1].

The laboratory values of inflammatory markers and outcomes are depicted in [Table/Fig-1].

S. No.	Variable	Meningitis (n=208)	No meningitis (n=26)	p-value
1.	**Day of life of clinical symptoms**			
	1 to 10 days	197 (88.7%)	25 (11.3%)	0.765*
	11 to 10 days	6 (85.7%)	1 (14.3%)	
	21 to 30 days	5 (100%)	0 (0%)	
	Mean±SD	4.51±4.62	4.52±4.55	
	Median (IQR) and range	4 (2 to 5)	4 (1.25 to 5)	0.845#
2.	**Gender**			
	Males	125 (60%)	9 (34.6%)	0.012$
	Females	83 (40%)	17 (65.4%)	
3.	**ANC (per cubic mm)**			
	<500	7 (87.5%)	1 (12.5%)	0.785*
	501 to 1000	102 (87.2%)	15 (12.8%)	
	1001 to 1500	85 (90.4%)	9 (9.6%)	
	1501 to 1800	14 (93.3%)	1 (6.7%)	
	Mean±SD	1018.9±275	969.7±285.9	
	Median IQR	1000 (880 -1150)	998 (780-1100)	0.308#
4.	**WBC (per cubic mm)**			
	1100 to 2000	19 (76%)	6 (24%)	0.076*
	2001 to 3000	72 (92.3%)	6 (7.7%)	
	3001 to <4000	117 (89.4%)	14 (10.6%)	
5.	**CRP (mg per L)**			
	11 to 20	67 (91.78%)	6 (8.2%)	0.029*
	21 to 30	84 (87.50%)	12 (12.5%)	
	31 to 40	20 (80%)	5 (20%)	
	41 to 50	35 (97.2%)	1 (2.78%)	
	51 to 60	2 (50%)	2 (50%)	
6.	**ESR (mm)**			
	16 to 25	101 (90.18%)	11 (9.82%)	0.168*
	26 to 35	69 (84.1%)	13 (15.99%)	
	>35	38 (95%)	2 (5%)	
7.	Positive blood culture	92 (95.8%)	4 (4.12%)	0.005$
	Positive meningitis	92	0	
	Negative meningitis	0	4	
8.	Deaths	26 (12.5%)	0 (0%)	0.112$

[Table/Fig-1]: Baseline characteristics.
p-value calculated using. *t-test; chi-square test and Fischer-Exact test
#t-test and Mann-Whitney test

No significant association was seen in the outcome with meningitis (p-value >0.05). None of the patients without meningitis expired, however, 26 (12.50%) of patients with meningitis expired during the hospital stay. Five out of 208 (2.4%) of patients with meningitis Left Against Medical Advice (LAMA). None of the patients without meningitis went LAMA, however difference between the meningitis and non-meningitis group was not statistically significant.

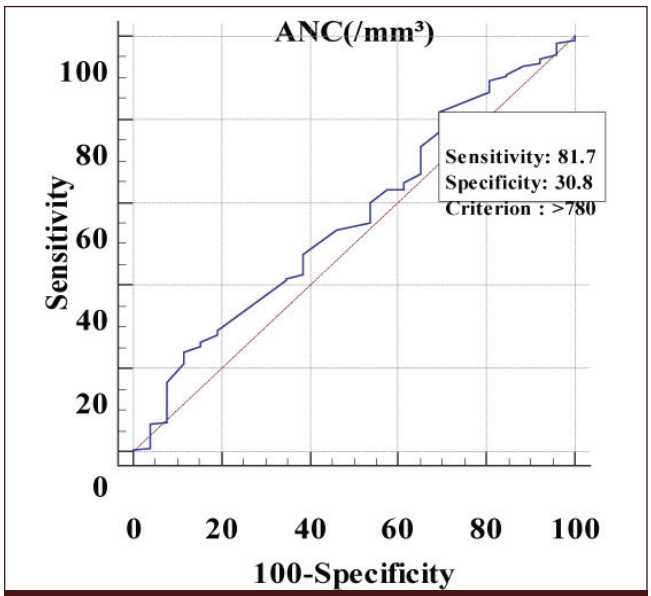
None of the parameters had significant discriminatory power to predict meningitis. Interpretation of the area under the ROC curve showed that the performance of ANC (/mm³) (AUC 0.561; 95% CI: 0.495 to 0.626), WBC(/mm³) (AUC 0.52; 95% CI: 0.454 to 0.586), CRP (mg/l) (AUC 0.527; 95% CI: 0.461 to 0.592) and ESR (mm) (AUC 0.502; 95% CI: 0.436 to 0.568) was non-significant. Highest PPV was found in CRP (mg/l) (91.90%) and highest NPV was found in WBC (/mm³) (28.60%) [Table/Fig-2-6].

For predicting meningitis	ANC (/mm³)	WBC (/mm³)	CRP mg/L	ESR (mm)
Area under the ROC curve (AUC)	0.561	0.52	0.527	0.502
Standard error	0.0599	0.0694	0.0585	0.0605
95% Confidence interval	0.495 to 0.626	0.454 to 0.586	0.461 to 0.592	0.436 to 0.568
p-value	0.30*	0.76*	0.64*	0.97*
Cut-off	>780	>1800	≤21	>30
Sensitivity (95% CI)	81.73% (75.8-86.7%)	92.79% (88.4-95.9%)	32.69% (26.4-39.5%)	31.25% (25.0-38.0%)
Specificity (95% CI)	30.77% (14.3-51.8%)	23.08% (9.0-43.6%)	76.92% (56.4-91.0%)	53.85% (33.4-73.4%)
PPV (95% CI)	90.4% (85.3-94.2%)	90.6% (85.9-94.2%)	91.9% (83.2-97.0%)	84.4% (74.4-91.7%)
NPV (95% CI)	17.4% (7.8-31.4%)	28.6% (11.3-52.2%)	12.5% (7.8-18.6%)	8.9% (5.0-14.5%)
Diagnostic accuracy	76.07%	85.04%	37.61%	33.76%

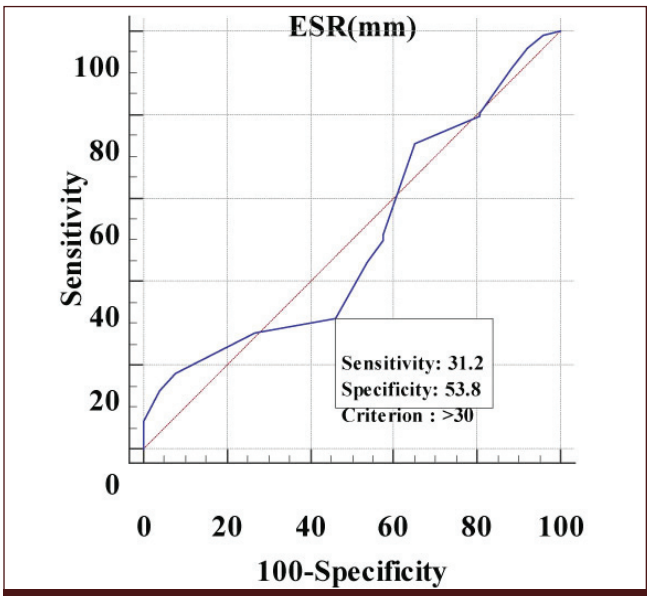
[Table/Fig-2]: Receiver operating characteristic curve of ANC, WBC, CRP and ESR for predicting meningitis.
*p-value calculated using ANOVA test

DISCUSSION

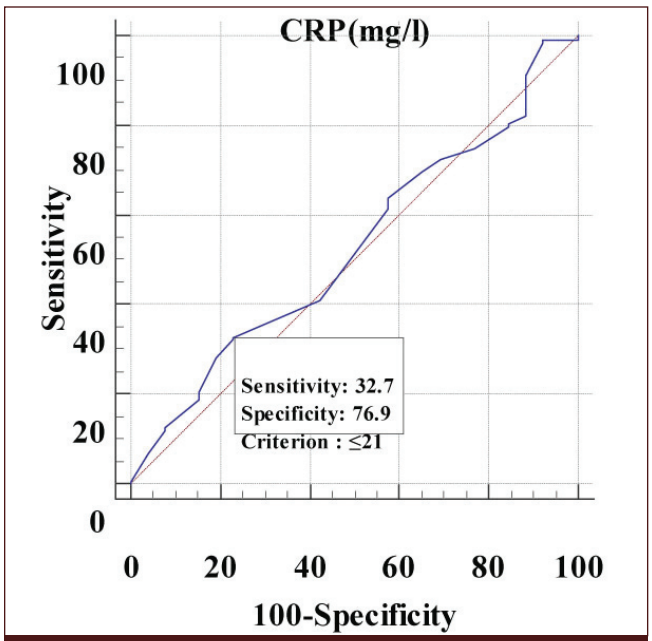
Since neonates have higher chances of acquiring sepsis, in the current study, the participants included neonates in contrast to most of the studies conducted worldwide where the study population included were children up till one year of age. In present study, majority of the patients (94.87%) belonged to the age group 1-10 days with mean value of age (in days) of study subjects was 4.52±4.5 with median (IQR) of 4 (1.25-5). In this study, no significant association was seen in the distribution of age with meningitis (p-value >0.5). Majority of patients had meningitis of which 88.7% patients belonged to the age group 1-10 days. Like the present study, Siakwan FD et al., also included 97 newborns in the study



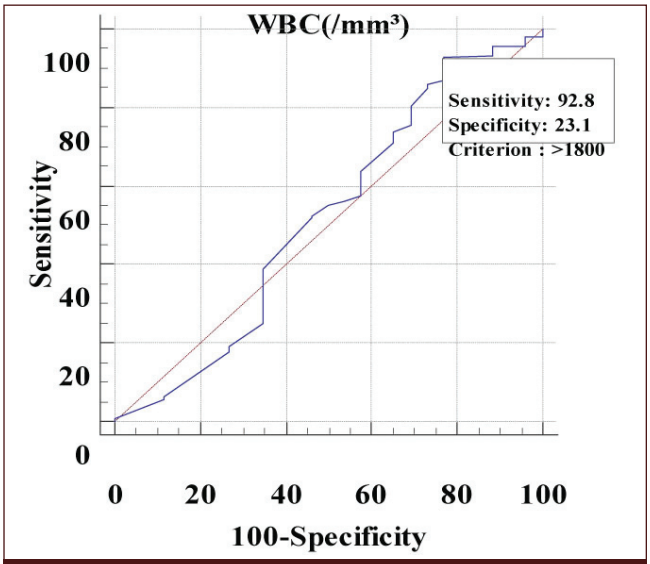
[Table/Fig-3]: Receiver operating characteristic curve of ANC for predicting meningitis.



[Table/Fig-5]: Receiver operating characteristic curve of ESR for predicting meningitis.



[Table/Fig-4]: Receiver operating characteristic curve of CRP for predicting meningitis.



[Table/Fig-6]: Receiver operating characteristic curve of WBC for predicting meningitis.

with culture negative Early Onset Sepsis (EOS). The neonates with meningitis in study by Siakwan FD et al., had mean gestational age of 37±4 weeks while with no meningitis the mean gestational age was 38±4 weeks [15]. Goldfinch CD et al., included infants <6 months with 63% infants were <3 days of age with median gestational age 38.4 weeks (30-40.3) [16]. Blauw D et al., included infants younger than 90 days of age. The median age was 12.5 days (IQR 6-27days) with median gestational age 29±5 weeks [17]. Bonsu BK et al., included infants between 0 days- 89 days. The rates of bacteremia and meningitis was the highest, 42% in infants less than 29 days of age [18].

In the present study, 57.3% (134/234) of neonates were males and significant association was seen in the distribution of gender with meningitis (p-value <0.5). Proportion of patients with meningitis was 40% females (83/208) which was significantly lower than proportion of males (60%; 125/208). Similarly, in study by Siakwan FD et al., Blauw D et al., and Cruz AT et al., 51%, 60.2% and 56% of study population were males, respectively [15,17,19]. In either of the studies no interpretation on the association of gender with meningitis was given.

In this study, blood culture was positive in 96 (41.03%) out of 234 patients. Significant association was seen in the distribution of blood culture with meningitis (p-value <0.5). Proportion of patients with meningitis was 84.06% of blood culture negative patients which was significantly lower than 95.83% of blood culture positive patients. In study by Cruze AT et al., out of 24 infants with meningitis, 11 had blood culture positive bacteremia. No association was seen in the distribution of blood culture with meningitis [19]. In study by Siakwan FD et al., all the 97 study subjects taken were culture negative EOS, 11 subjects were diagnosed as meningitis. Out of these 11 neonates, only 1 neonate was CSF culture proven meningitis [15].

In the current study where ANC and WBC is counted as a component of CBC had poor predictive value, study by Cruz AT et al., found that CBC parameters had poor accuracy in distinguishing febrile infants 60 days or younger with or without invasive bacterial infections although ANC had the highest sensitivity hence it was concluded that meningitis should be investigated and treated in children if clinically suspected, regardless of the CSF, CRP, or peripheral blood results [19]. This study supports these studies whereas decision to establish the diagnosis and treat meningitis should solely be based on CSF results.

In the present study, the sensitivity of WBC was 92.79%, and specificity was 23.08% to predict meningitis, similar study by Cruz AT et al., found that the sensitivity of WBC was 56% and specificity was 62% in age group 0-28 days with 11.6×10^3 cells/µL as WBC threshold and in age group 29-60 days, with 9×10^3 cells/µL WBC as threshold sensitivity was 65% and specificity was 47%. No CBC parameters reliably distinguished between infants with and without Invasive Bacterial Infections (IBIs) thus, the WBC count was found to have a poor discriminatory value [19]. In contrast to present findings in a study conducted by Bonsu BK et al., it was found that median peripheral WBC count for children with acute bacterial meningitis was 9500 cells/mm^3 and the median WBC count of 15,524 cells/mm^3 for children with bacteremia alone which differed significantly (p-value< 0.001). The highest sensitivity of WBC for meningitis was at WBC < 5,000 or ≥ 15,000 cells/mm^3 and was 60%. The PPV and NPV at WBC <5,000/mm^3 or ≥15,000/mm^3 for detecting meningitis was 0.7% and 99.8%, respectively. It was found that bacterial meningitis was more prevalent than bacteremia in a peripheral WBC count below 5000 cells/mm^3. Infants with bacterial meningitis were seven times more likely than those with bacteremia to have peripheral WBC counts below 5000cells/mm^3 [18].

In this study, no association of CRP with meningitis was seen. Like low sensitivity (32.69%) of CRP reported in the current study, in another study by Blauw D et al., it was found that CRP was significantly higher in neonates with bacterial infection than in neonates with viral infection (p-value=0.01). The study concluded that an increased CRP was indicative of meningitis [17]. In contrast to these studies, in another study by Siakwan FD et al., it was found that AUC for CRP at 12 and 24 Hours Of Life (HOL) was 0.52 (95% CI:0.37-0.67) and 0.63 (95% CI:0.44-0.82) and using a cut-off value of CRP >40 mg/L at 12 HOL had sensitivity, specificity, PPV and NPV 70%, 45%, 16.7% and 90%, respectively. At cut-off value of CRP >40 mg/L at 24 HOL, sensitivity, specificity, PPV and NPV were 72.7%, 28%, 12.9% and 87.5%, respectively in diagnosing meningitis in culture negative EOS. It was concluded that CRP >40 mg/L and I/T ratio >0.3 or their combination lack sufficient sensitivity, specificity and predictive values for them to be used as screening tests for meningitis in culture negative sepsis [15]. In another study by Golfinch CD et al., it was found that median CRP value in culture positive meningitis was 33.7 and in culture negative meningitis was 37.4. The AUC for CRP was 0.43 (95% CI 0.36-0.51). At threshold of 30 mg/L, the sensitivity of CRP was 51.2% and specificity was 33.8%. Hence, it was concluded that peripheral inflammatory marker such as CRP and immature to total neutrophil ratio (ITR) either individually or in combination have poor test performance in diagnosing culture positive and probable culture negative meningitis [16]. So, for CRP there have been mixed studies with some of them supporting that CRP can predict bacterial meningitis and some supporting that meningitis cannot be predicted based on serum CRP.

In the current study, ESR did not have the significant discriminatory power to predict meningitis and had low sensitivity and specificity to detect meningitis, however in a study by Sanaei D et al., which was conducted on paediatric age group between 28 days and 14 years, it was seen that in a cohort of 50 patients with meningitis, combination of low CSF lactate, ANC, ESR, and serum-CRP could reasonably rule out the bacterial meningitis [20].

None of the inflammatory parameters included in present study (serum CRP, serum ESR, WBC and ANC) could reliably be used to predict meningitis in neonates with sepsis. The strength of this study was its large sample size, study subjects were neonates which are the most susceptible population to sepsis and meningitis and included the commonly used serum inflammatory markers, considering all the four markers in a single study.

Limitation(s)

It is a single site study and micro ESR and ITR should have been included in the study, however, authors could not include them since these investigations were not done in their set-up.

CONCLUSION(S)

Based on the current single site study results, it is implicated that diagnosis and management of neonatal meningitis should be solely based on LP since serum inflammatory markers

are poor discriminators for meningitis. Future studies should evaluate the diagnostic parameters from other inflammatory markers like IT ratio and micro ESR, which, if proven to be of diagnostic value, can reduce the time to initiate management and avert the need for LP in neonatal meningitis.

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PARTICULARS OF CONTRIBUTORS:
1. Student, Department of Paediatrics, Vardhman Mahavir Medical College, New Delhi, India.
2. Professor, Department of Paediatrics, Vardhman Mahavir Medical College, New Delhi, India.
3. Chief Medical Officer, Department of Paediatrics, Vardhman Mahavir Medical College, New Delhi, India.
4. Senior Resident, Department of Paediatrics, Vardhman Mahavir Medical College, New Delhi, India.
5. Professor, Department of Paediatrics, Vardhman Mahavir Medical College, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Ajay Kumar,
Professor, Department of Paediatrics, VMMC and Safdarjung Hospital,
New Delhi-110029, India.
E-mail: drajayk70@yahoo.co.in

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