ORIGINAL RESEARCH

Role of serial c-reactive protein in early diagnosis of neonatal sepsis- A prospective study in tertiary care hospital

Archana Agrawal [1] , Abhishek Singh [2]* , Surabhi kumari [3], Neha Singh[4]

[1]Associate professor, Department of Pediatrics, LLRM Medical college, Meerut, UP, INDIA
[2]Professor, Department of Pediatrics, LLRM Medical college, Meerut, UP, INDIA
[3]Junior resident Department of Pediatrics, LLRM Medical college, Meerut, UP, INDIA
[4]Professor Department of Pathology, LLRM Medical college, Meerut, UP, INDIA

***Corresponding author:**
Dr Abhishek Singh
Professor, Dept of pediatrics, LLRM medical college, Meerut, UP

Received: 22 May 2023 Accepted: 25 June, 2023

ABSTRACT

Introduction: Neonatal sepsis (NS) is leading cause of mortality and morbidity in neonates specially in developing countries and early diagnosis and treatment is key in reduction of its complication.
Objective: To evaluate accuracy of serial C-Reactive Protein in comparison to blood culture in early diagnosis of neonatal sepsis
Study design: prospective cohort study.
Setting: Tertiary neonatal intensive care unit of government hospital in western UP
Participants: All neonates admitted with suspicion of sepsis from July 2021 to June 2022
Intervention: Serial CRP on admission, at 12,24 and 48 hours was sent along with blood culture on admission of all the study participants.Results: Amongst 250 neonates CRP was positive in 205 patients at least on 1 occasion whereas 131 neonates were culture positive. Diagnostic accuracy of the 12 hours, 24 hours and 48 hours CRP were 50.8%, 58.4% and 65.2% to diagnose sepsis, respectively. The area under curve (AUC) of the 48-hour CRP levels was 0.826 ($p<0.001$), 48hour CRP was a significant predictor of neonatal sepsis.
Conclusion: CRP may be used as screening test to determine newborn sepsis since it is widely accessible, affordable, and generates results quickly. Overall, serial CRP at 12, 24 and 48 hours are a useful early marker in predicting the neonatal sepsis and among them 48 hours CRP has the highest predictive capacity.

Abbreviations used-NS- neonatal sepsis, EOS- early onset sepsis, Los- late onset sepsis, Lbw- low birth weight

INTRODUCTION

Neonatal sepsis (NS) is defined as a systemic inflammatory response syndrome in the presence or following a suspected or established infection with or without associated bacteremia, documented by a positive blood culture during the first 28 days of life[(1,2).] It includes various systemic infection of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection.

The term 'neonatal sepsis' is used to denote a condition of bacterial, viral or fungal origin associated with hemodynamic changes and other clinical manifestations[(3)]. Despite several researches and advances in the medical field, the prevention of neonatal deaths due to sepsis is challenging. Early diagnosis and prompt initiation of treatment is one of the most crucial aspect for reduction of neonatal mortality related to NS. Blood culture although being gold standard for diagnosis of NS the high specificity come at the cost of low sensitivity, increased turn around time causing delayed diagnosis, resources and cost constraints and false negativity are other limiting factors. Sepsis screen is therefore widely used to diagnose NS and decide management while awaiting culture results if facilities are available for the same. Although newer diagnostic methods like procalcitonin and other biomarkers are published as early diagnostic methods again cost, and availability at hospitals with limited resources is limiting factor. CRP has been widely used traditionally in bundle of sepsis screen. CRP being an acute phase reactant protein synthesized by liver within 4-6 hours of infection or inflammation, then rises attaining peak level in next 24-72 hours, can remain elevated for days in presence of infection. While a single CRP measurement can provide initial information, serial CRP measurements offer advantages in terms of diagnostic accuracy, capturing the dynamics of CRP elevation over time and treatment monitoring too[(4–6)].

We therefore conducted this study to compare diagnostic accuracy of serial CRP vs. blood culture in early diagnosis of NS.

METHODS

Ethical clearance from our institutional ethical committee was taken and an informed consent was taken from the guardian of each newborn prior to the enrolment in our study.Participants: All neonates who got admitted with suspicion of sepsis with or without risk factors for sepsis in NICU in LLRM Medical College from July 2021 to June 2022.Study Design: prospective observational studySample Size:Based on the findings of similar study by Gupta et al,(7) assuming a sensitivity &specificity of 86.7% and 42%of CRP in diagnosing the neonatal sepsis, which has a prevalence of 17% in India and at 95% confidence level, 10% margin of error, a sample size of 256 was required(8).

INCLUSION CRITERIA

All neonates who were admitted in the NICU with signs or symptoms of sepsis with or without risk factors for sepsis.

EXCLUSION CRITERIA

Babies with any of the following excluded:
1.Babies born with any major congenital anomalies
2.Babies require any surgical intervention
3.Babies who had suffered from birth asphyxia
4. Birth weight less than 1500 grams, extremely premature (less than 32 weeks of gestation)
5. Babies already on antibiotics.

Intervention: After written informed consent from the patient's parents, detailed history, demographic data was recorded and clinical examination findings and laboratory findings were noted on pre-designed proforma. 1-2 mL of blood was collected under all aseptic precautions and inoculated into a blood culture bottle containing 5 mL of Brain Heart infusion broth (BACTEC). Identification of bacteria and antibiotic sensitivity testing was done by standard bacterial methods as per the CLSI guidelines [(9)]. 1ml fresh sample was sent for CRP at 12 hours of admission, if any fibrin clot was found then it was centrifuged, lipaemic and hemolyzed samples were discarded. CRP estimation was done by Latex Agglutination Card test and was reported as positive if agglutination particles were detected and negative if no particles seen. Samples positive for CRP were further subjected to CRP estimation using Automated Clinical Chemistry Analyses (ERBA Diagnostics Mannheim GmbH- Germany). Samples were collected at 24 and 48 hours too for CRP estimation. Additional sampling like hemogram was done initially and later if required. CRP more than 10mg/L was termed as positive. Mean levels of CRP were calculated, sensitivity, specificity, positive predictive value and negative predictive values were calculated. ROC curves were constructed to access diagnostic accuracy of CRP in diagnosing neonatal sepsis at different time intervals.

RESULTS: 256 was required sample size but we could enroll 250 participants in specified time interval. Out of 250, Majority of patients were preterm n=139, low birth weight (LBW) n= 196, and intramural n= 163 and male patients n= 137 (table 1). The mean birth weight of the Babie was 2.13 kg. Mean duration of admission was 9.12 days with Std dev 5.12 days. Almost similar distribution of gestational age, weight, gender was seen in patients with blood culture positive status. Similarly, majority of them were having eos.

66% of patients had early onset sepsis. 131 patient yielded positive blood culture and diagnosed to have confirmed sepsis. CRP was positive in 200, 205 and 202 patients at 12, 24 and 48 hours of admission. CRP levels at 12 hours, 24 hours and 48 hours reported a sepsis positivity rate of 80%, 82% and 80.8%, respectively. Confirmed blood culture positive sepsis rate was in 52% of cases, n=131.

Table 1: Distribution of neonates as per gestation, age at admission, gender, birth weight and inborn/outborn

	n	%
Term	111	44.40
Preterm	139	55.60
Age of admission<72hr	165	66.0
Age of admission >72 hr	85	34.0
Male	137	54.8
female	114	45.2
Birth weight		
1.5-2kg	109	43.6
2-2.5kg	87	34.8
2.5-3kg	54	21.6
intramural	163	65.2
extramural	87	34.8

The range of CRP at 12hr, 24hr and48 hr were 0.10-118.00, 0.30-120.50 and 0.10-135.00. (table 2, fig 1)

Table 2: Mean and median levels of CRP at 12,24 and 48 hrs. of admission.

	Mean	Median	Std. Deviation	Minimum	Maximum
CRP(12h)	37.45	32.55	24.72	0.10	118.00
CRP(24h)	38.99	36.50	26.25	0.30	120.50
CRP(48h)	35.57	30.35	29.32	0.10	135.00

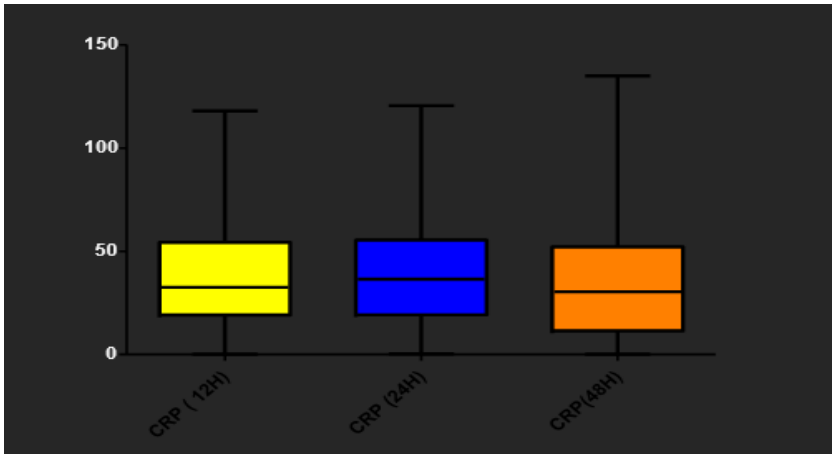

Figure 1: Box plot shows the details of CRP at 12hr,24hr and48 hr

Demographic profile of neonates with positive blood culture: The percentage of Preterm and Term neonates with culture positive was 60.48% and 39.52%. The percentage of <72hr and ≥72hr age on admission was 68.55% and 31.45%. The percentage of male and female was 45.97% and 54.03%. The percentage of Intramural and /Extramural was 60.48% and 39.52%. The percentage of 1.5-2.0 kg, 2-2.5 kg and 2.5-3.0 kg birth weight were 58.06%, 21.77%. and 20.16%, respectively. E. coli and klebsiella were most frequently grown organism in both early as well as late onset neonatal sepsis.

Diagnostic accuracy of CRP in predicting the sepsis:

The 12 hours CRP levels had a sensitivity, specificity, PPV and NPV values of 79.4%, 19.3%, 52% and 46% to diagnose sepsis, respectively and it rose significantly with passing time with maximum levels at 48 hours. The 48 hours CRP levels had a sensitivity, specificity, PPV and NPV values of 93.9%,33.6%, 60.9% and 83.3% to diagnose sepsis (positive blood culture), respectively.

Table 3 sensitivity, specificity, PPV, NPV and accuracy of serial CRP

CRP	Sensitivity/	specificity	PPV	NPV	Accuracy
12 hours	79.4	19.3	52	46	50.8
24 hours	88.5	25.2	56.6	66.7	58.4
48 hours	93.9	33.6	60.9	83.3	65.2

Diagnostic accuracy of the 12 hours, 24 hours and 48 hours CRP was were 50.8%, 58.4% and 65.2% to diagnose sepsis, respectively.

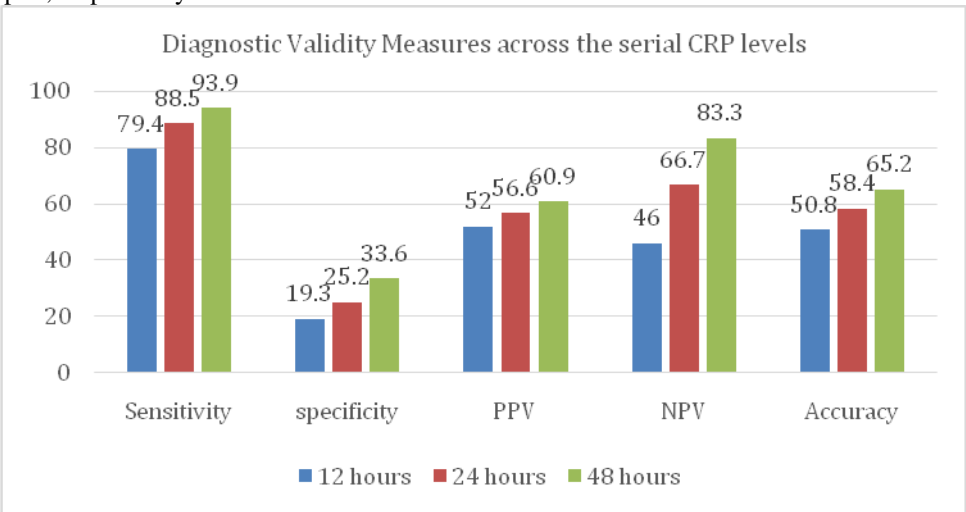

Figure 2 Diagnostic validity measures across serial CRP levels

ROC curves for identifying best cut-offs to predict the sepsis:

The AUC of the 12-, 24- and 48-hours CRP levels was 0.605 (p-0.003), 0.736 (p<0.001), 0.826 (p<0.001) respectively. CRP across all time intervals was significant predictor of neonatal sepsis with maximum sensitivity and septicity at 48 hours. (Figure 2).

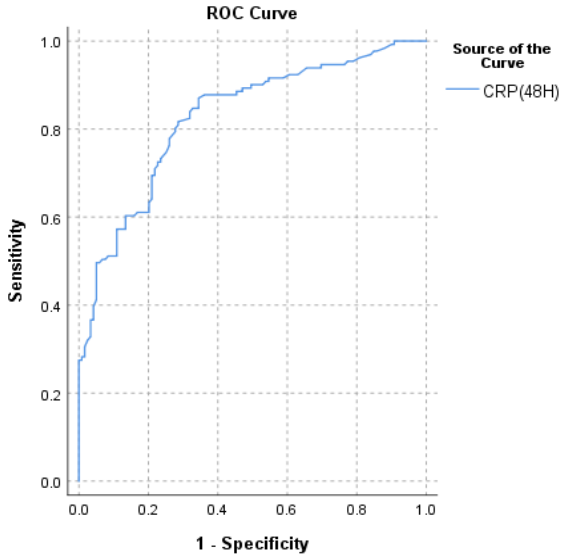

Figure 3: ROC curve for CRP at 48 hr. in NS.

CRP and blood culture: The mean CRP wassignificantly higher in Culture positive as compared to Culture negative at12hr, 24hr and 48hr.

CRP vs outcome:
Mortality rate among probable sepsis was 18.8%,47 out of 250 patients expired.There was a significant association between the CRP positivity at 12, 24 and 48 hours and the neonatal mortality. 23% of the neonates who were CRP positive for sepsis at 12 hours died while 2% of the CRP negative neonates died. 22% of the neonates who were CRP positive for sepsis at 24 hours died while 4.4% of the CRP negative neonates died. 22.3% of the neonates who were CRP positive for sepsis at 48 hours died while 4.2% of the CRP negative neonates died. (table 4). Also, there was a significant association between the blood culture positivity and the neonatal mortality. 32.8% of the neonates who were blood culture positive for sepsis died while 3.4% of the CRP blood culture negative neonates died.

Table 4: CRP status vs patient outcome as discharge and death

			Outcome		
			expired	**discharged**	**p value**
CRP (12H)	positive	Frequency	46	154	0.006
		Percentage	23.0%	77.0%	
	negative	Frequency	1	49	
		Percentage	2%	98%	
Total		Frequency	47	203	
		Percentage	18.8%	81.2%	
CRP (24H)	negative	Frequency	45	160	0.006
		Percentage	22.0%	78.0%	
	Frequency	47	2	43	
	Percentage	18.8%	4.4%	95.6%	
Total		Frequency	47	203	
		Percentage	18.8%	81.2%	
CRP (48H)	positive	Frequency	45	157	0.006
		Percentage	22.3%	77.7%	
	negative	Frequency	2	46	
		Percentage	4.2%	95.8%	
Total		Frequency	47	203	
		Percentage	18.8%	81.2%	

DISCUSSION

Neonatal sepsis is a frequent, serious bacterial bloodstream illness that mostly affects newborns and has a high fatality rate.[10,11] The blood culture is the standard test for newborn sepsis. The drawbacks of time-consuming and erroneous negative findings, however, place a limit on it.[12] Thus, there has been a continuous and rigorous search for a bio-marker which can assist in the early prediction and diagnosis of the neonatal sepsis. This in-turn will enable earlier intervention in the neonates, ultimately reducing the morbidity and mortality associated with the sepsis among the neonates. The present study was conducted among 250 neonates who were having probable sepsis and admitted at the NICU ward of the pediatrics department at a tertiary care institute at Meerut, India to explore the capability of the serum CRP levels measured serially at 12, 24 and 48 hours to predict neonatal sepsis.

Demography

Majority of the neonates included in our study were males (54.8%). This is in line with findings of most of previous studies. [13–16]

In the present study, majority of the neonates were of preterm delivery (55.6%), which is in line with the findings of Monga et al (52%).[13]Jethani et al included female neonates as the majority (55%).[17] Also proportion of preterm patients was more compared to term in both probable as well as culture positive sepsis explaining immature immune system in preterm babies. It was also observed that probable and culture positive sepsis rate was inversely proportional to birth weight and it increased with decreasing birth weight and maximum in age group of 1.5-2kg (58%).

Sepsis

Among the neonates included in our study, the sepsis positivity rate, by blood culture, was 52.4%. This was similar to the sepsis rate reported by Monga et al (47%). [13]In contrast, Sodani et al and Bunduki et al and Ganesan et al reported a lower culture positivity rate of sepsis (36% ,30.3% and 25% respectively) in their study.[14,18,19] Singhal et al reported it much lower almost 10%.[15]

Incidence of Early onset sepsis and LOS was almost similar in our study with a bias towards eos, (51.8% and 48.2% respectively) mostcommon Bacteria isolated was Escherichia coli in both types of sepsis. Similar to our study, Singhal et al and Kaur et alreported klebsiella as the most common organism cultured (34% & 63.4%).[15,20] Monga et al reported high proportion of gram positive bacteria (27/47) among the culture positive sepsis cases than the gram negative bacteria (20/47).[13] Previous study from our own center in 2016 reported E.coli as most commonly grown organism in EOS. [21]

According to CRP levels

Aim of our study was to evaluate role of serial CRP in early diagnosis of neonatal sepsis. Studies in the past have reported widely ranging sensitivities and specificities of CRP ranging from 29 - 100% and from 6 to 100%, respectively. [22,23] In our study, CRP levels at 12 hours, 24 hours and 48 hours reported a sepsis positivity rate of 80%, 82% and 80.8%, respectively. Monga et al and Sodani et al study from Jaipur reported a slightly lower CRP sepsis positivity rate ours (70% & 68%)[13,14]. In contrast, Bunduki et al and Singhal et al reported a much lower CRP sepsis positivity rate of 41.2% and 47%.(15,24) However, these past studies did not undertake serial CRP measures, but only at one point of time.

The mean CRP levels of the neonates included in our study at 12 hours, 24 hours and 48 hours are 35.72, 38.45 and 35.62 mg/L, respectively. This was very similar to the CRP levels reported among the suspected sepsis neonates by Monga et al (34.7 mg/L) and Ganesan et al (33.33 mg/l).[13,18] Celik et al reported a differential CRP levels of 13.6 to 18.2 mg/ml.[16]

Diagnostic accuracy

Sensitivity of CRP levels were assessed at 48 hours>24 hours>12 hours in our study. CRP levels at the admission had sensitivity and specificity of 66.7% and 12.07% in Mehar et al, lower than our study at 12 hours.[25] While the sensitivity of CRP measures reported in our study at 24 (88.5%) and 48 hours (93.9%) was found to be higher than many other above mentioned studies[13,16,17,20] specificity found in our study (19.3%-33.6%) was lower than Monga et al (43.4%), Jethani et al (65%), Kaur et al (43.1%) Celik et al (97%). Bunduki et al and Singhal et al reported both sensitivity (95.7%) and specificity (82.4%) and (90.6% and 86.5% respectively) to be higher than our findings.(15,24)In our study, the overall diagnostic accuracy of the 12 hours, 24 hours and 48 hours CRP was were 50.8%, 58.4% and 65.2% to diagnose sepsis, respectively. Monga et al reported a diagnostic accuracy of 63% for CRP among the included neonates in predicting the neonatal sepsis.[13]Sodani et al and Jethani et al reported a higher diagnostic of 69% and 75.3% for CRP, than our study.[14,17] Kaur et al reported accuracy lower (55%). [20]

ROC curves

Among the serum levels of CRP measured serially, the 48 hours CRP was found to have the highest AUC of 0.826 and hence the highest predictive capacity. The ideal 48-hour CRP cut-off to predict sepsis is 26.05. A CRP level of >26.05 can predict neonatal sepsis with a sensitivity of 81.7% and specificity of 71.4%. Singhal et al reported an AUC of 0.83 for CRP to predict sepsis, similar to our findings.[15] Ganesan et al reported an AUC of 0.748 and CRP cut-off of 13.50 for predicting the neonatal sepsis with a sensitivity of 80% and specificity of 65.7%, which similar to our findings.[18]Bunduki et al reported the highest predictive capacity with an AUC of 0.948.[24]

Because of the lack of established cut-off values for sepsis indicators and the non-specific clinical

presentation, the identification of newborn sepsis continues to be a problem for both the laboratory and the physicians who treat the condition. [18] CRP as a sepsis indicator shall be measured in newborns whose infectious status is unknown.

Although CRP levels rises within hours of infection its sensitivity is known to be lowest during the early stages of infection.

Benitz et al. [5] performed serial CRP for 3 days 24 hr apart along with blood culture on day 1 in suspected neonates of sepsis and found that the sensitivity in the diagnosis of culture-proven early-onset sepsis increased from 35% at the initial sepsis workup to 79% after 8–24 h, and 89% for the higher of two levels obtained after 8–48 h after the initial workup. But they reported a decrease in specificity from 90% to 74%for CRP levels during the same duration with negative predictive value of 98% emphasizing role of serial CRP to rule and rule out sepsis as a diagnosis in neonates. Pourcyrous et al. [27] evaluated serial CRP levels in a large series of 689 investigations for neonatal sepsis in 489 neonates, and determined CRP at the initial sepsis evaluation and 12 and 24 h later of which 187 tested positive on blood culture. They reported a higher sensitivity for any of the three CRP values taken later compared to the first value (74 vs. 55%). Thus, the sensitivity increases to a great extent with serial determinations 24–48 h after the onset of symptoms. In coherence with the above studies, we found a rising sensitivity, and decreasing speficity of CRP in diagnosing neonatal sepsis in performing serial evaluations. Although our sensitivity crossed 90% diagnostic accuracy remained limited to 65% maximum thus emphasizing again the importance of thorough clinical examination, and performing complete sepsis screen along with gold standard blood culture.

Studies have suggested that serial CRP levels may also be useful for identification of infants who do not have a bacterial infection and can be used as a guide to monitor response to antibiotic treatment in NS.[28]A repeat CRP 24–48 h after the initiation of antibiotic therapy has been reported to carry a 99% negative predictive value in accurately identifying, in ruling out infants without sepsis.

- Strength of our study was large cohort of 250 patients with prospective study design, representative sample as it studied intramural as well as extra mural babies, and EOS and LOS both. Limitation of our study was we did not consider other sepsis screen parameters like I:T ratio, procalcitonin levels, micro ESR or platelet indices. Other morbidity following sepsis were not assessed which might also vary according to the sepsis status

CONCLUSION

CRP is a screening test that may be used to determine newborn sepsis since it is widely accessible, affordable, and generates results quickly. Overall, serial CRP at 12, 24 and 48 hours are a useful early marker in predicting the neonatal sepsis and among them 48 hours CRP has the highest predictive capacity but not specific enough to recommend it as a sole investigation. Thus, CRP may be used as a supplementary investigation in determining the neonatal sepsis and empirical therapy started till the time culture reports are available. However, further, multi-centric studies from the diagnostic accuracy perspective of CRP or to include it in a scoring criterion to diagnose sepsis needs to be conducted to verify our findings and improve the generalizability.

Acknowledgement of financial support- NONE

Ethical considerations: Ethical approval from institutional ethical committee was obtained prior to begin the study.

Consent: Ours being prospective study design involving infants a wellinformed, written consent in local language was obtained and nature and possible consequences of the study had been fullyexplained to parents of the infant getting admitted in NICU. Participants who consented forstudy were enrolled. Privacy rights of participants were maintained during study.

References

1. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med. 2018 Mar;6(3):223–30.
2. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2005 Jan;6(1):2–8.
3. Agnche Z, YenusYeshita H, AbdelaGonete K. Neonatal Sepsis and Its Associated Factors Among Neonates Admitted to Neonatal Intensive Care Units in Primary Hospitals in Central Gondar Zone, Northwest Ethiopia, 2019. Infect Drug Resist. 2020;13:3957–67.
4. Noor MK, Shahidullah M, Mutanabbi M, Barua C, Mannan MA, Afroza S. Comparison between CRP and IL-6 as early markers of neonatal sepsis. Mymensingh Med J MMJ. 2008 Jul;17(2 Suppl):S72-76.
5. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. Pediatrics. 1998 Oct;102(4):E41.
6. Couto RC, Barbosa JAA, Pedrosa TMG, Biscione FM. C-reactive protein-guided approach may shorten length of antimicrobial treatment of culture-proven late-onset sepsis: an intervention study. Braz J Infect Dis Off Publ Braz Soc Infect Dis. 2007 Apr;11(2):240–5.
7. Gupta D, Dayal D, Yadav D, Kumar D, Singh D. Current Scenario of Neonatal Sepsis in West U.P. Pediatr Rev Int J Pediatr Res. 2018 Dec 31;5:609–16.

8. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform. 2014 Apr;48:193–204.
9. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement. CLSI document M100-S18. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.
10. Xu L, Li Q, Mo Z, You P. Diagnostic value of C-reactive protein in neonatal sepsis: A meta-analysis. Eur J Inflamm. 2016 Aug 1;14(2):100–8.
11. Moorman JR, Delos JB, Flower AA, Cao H, Kovatchev BP, Richman JS, et al. Cardiovascular oscillations at the bedside: early diagnosis of neonatal sepsis using heart rate characteristics monitoring. Physiol Meas. 2011 Nov;32(11):1821–32.
12. Delanghe JR, Speeckaert MM. Translational research and biomarkers in neonatal sepsis. Clin Chim Acta Int J Clin Chem. 2015 Dec;451(Pt A):46–64.
13. Monga N. Correlation of C-Reactive Protein and Blood Culture in Neonatal Sepsis. Indian J Neonatal Med Res. 2018;6.
14. Gupta A, Rajput D, Sodani S, Mutha A. Comparison of CRP with blood culture in the diagnosis of neonatal septicaemia. Indian J Microbiol Res [Internet]. 2021 Jan 15 [cited 2023 Jul 3];7(4):327–9. Available from: https://www.ijmronline.org/article-details/12893
15. Singhal A, Rati* R, Jaggi N. C-reactive protein as a diagnostic marker of neonatal sepsis in association with blood culture a retrospective study at a tertiary care hospital. Indian J Microbiol Res [Internet]. 2021 Dec 15 [cited 2023 Jul 3];8(4):291–6. Available from: https://www.ijmronline.org/article-details/15426
16. Celik IH, Demirel FG, Uras N, Oguz SS, Erdeve O, Biyikli Z, et al. What are the cut-off levels for IL-6 and CRP in neonatal sepsis? J Clin Lab Anal. 2010;24(6):407–12.
17. Jethani S, Bhutani N, Yadav A. Diagnostic utility of combined immature and total neutrophil counts along with C-reactive protein in early detection of neonatal sepsis: A cross-sectional study. Ann Med Surg 2012. 2022 May;77:103589.
18. Ganesan P, Shanmugam P, Sattar SBA, Shankar SL. Evaluation of IL-6, CRP and hs-CRP as Early Markers of Neonatal Sepsis. J Clin Diagn Res JCDR [Internet]. 2016 May [cited 2023 Jul 3];10(5):DC13–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4948389/
19. Bunduki GK, Adu-Sarkodie Y. The usefulness of C-reactive protein as a biomarker in predicting neonatal sepsis in a sub-Saharan African region. BMC Res Notes. 2020 Apr 1;13(1):194.
20. Kaur S, Singh K. Early-Onset Neonatal Sepsis: Role of C-Reactive Protein, Micro-ESR, and Gastric Aspirate for Polymorphs as Screening Markers. Int J Pediatr. 2021;2021:1544553.
21. Tomar P, Garg A, Gupta R, Singh A, Gupta NK, Upadhyay A. Simultaneous Two-site Blood Culture for Diagnosis of Neonatal Sepsis. Indian Pediatr. 2017 Mar 15;54(3):199–203.
22. Hengst JM. The role of C-reactive protein in the evaluation and management of infants with suspected sepsis. Adv Neonatal Care Off J Natl Assoc Neonatal Nurses. 2003 Feb;3(1):3–13.
23. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology. 2012;102(1):25–36.
24. Bunduki GK, Adu-Sarkodie Y. The usefulness of C-reactive protein as a biomarker in predicting neonatal sepsis in a sub-Saharan African region. BMC Res Notes. 2020;13(1):194.
25. Mehar V, Malhotra A, Mehta P, Thakur K, Malik R. Role of serial C-reactive protein measurements for determination of the duration of empirical antibiotic therapy in suspected neonatal sepsis. Indian J Child Health [Internet]. 2020 Sep 27 [cited 2023 Jul 3];388–92. Available from: https://mansapublishers.com/index.php/ijch/article/view/2544
26. M P, Hs B, Sb K, V B, Sp W. Significance of serial C-reactive protein responses in neonatal infection and other disorders. Pediatrics [Internet]. 1993 Sep [cited 2023 Jul 3];92(3). Available from: https://pubmed.ncbi.nlm.nih.gov/8361798/
27. Ehl S, Gering B, Bartmann P, Högel J, Pohlandt F. C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. Pediatrics. 1997 Feb;99(2):216–21.
28. von Dach E, Albrich WC, Brunel AS, Prendki V, Cuvelier C, Flury D, et al. Effect of C-Reactive Protein-Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia: A Randomized Clinical Trial. JAMA. 2020 Jun 2;323(21):2160–9.